Infectious Agents and Cancer

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Genetic susceptibility association between viral infection and colorectal cancer risk: a two-sample Mendelian randomization analysis

Gen Li[1], Siyu Wang[1], Jianli Ma[1] and Shanshan Liu[1*]

Abstract

Background The genetic susceptibility association between viral infection and the risk of colorectal cancer (CRC) has not been established.

Methods We conducted two-sample Mendelian randomization (MR) analysis using genome-wide association study (GWAS) data. In addition to traditional MR methods, we employed several other approaches, including cML, ConMix, MR-RAPS, and dIVW, to comprehensively assess causal effects. Sensitivity analyses were also performed to ensure the robustness of the results.

Results After sensitivity analysis, presence of SNPs linked to increased susceptibility to cold sores infection was found to decrease the risk of CRC (OR: 0.73, 95% CI: 0.57–0.93, $P=0.01$). In subgroup analysis, presence of SNPs linked to increased susceptibility to viral hepatitis (OR: 0.89, 95% CI: 0.81–0.98, $P=0.02$) and infectious mononucleosis (OR: 0.91, 95% CI: 0.84–0.98, $P=0.02$) were associated with a decreased risk of colon cancer, while measles virus (OR: 1.41, 95% CI: 1.07–1.85, $P=0.01$) was associated with an increased risk of colon cancer. Presence of SNPs linked to increased susceptibility to herpes zoster (OR: 1.26, 95% CI: 1.05–1.52, $P=0.01$) was associated with an increased risk of rectal cancer, while infectious mononucleosis (OR: 0.809, 95% CI: 0.80–0.98, $P=0.02$) was associated with a decreased risk.

Conclusion The study provides the first evidence of the genetic susceptibility associations between different viral infections and CRC, enhancing our understanding of the etiology of CRC.

Keywords Mendelian randomization, Viral infections, Colorectal cancer, GWAS

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Introduction

Colorectal cancer (CRC) is the third most common cancer and the fourth leading cause of cancer-related deaths worldwide [1]. While screening has reduced the incidence and mortality of CRC, it is often constrained, particularly in resource-limited settings [2–4]. Thus, identifying risk factors for CRC effectively could alleviate the global burden of CRC and prove to be an attractive strategy [5].

Recent studies suggest that viral infections may play a potential role in the development of CRC [6]. Viruses such as cytomegalovirus and human papillomavirus (HPV16, HPV18) have been found to have a higher prevalence in tumor-associated colorectal tissues [7]. Meta-analysis indicates a statistically significant presence of HPV infection levels in CRC tumor tissues [8]. Laghi et al. revealed viral infections present in 81-89% of CRC tissues, with viral infection being predominant [9]. However, different studies have observed inconsistent results. For instance, serum positivity rates indicating viral infection based on antibody titers did not show significant differences between CRC cases and healthy controls [7]. Additionally, the potential contamination or infection and the timeline of CRC development are often unclear, and observational studies cannot avoid unknown confounders. Therefore, there is an urgent need for more evidence to explore the risk relationship between viral infections and CRC.

Genome-wide association studies (GWAS) have identified genetic variations associated with a wide range of cancers, and Mendelian randomization (MR) based on GWAS provides a method for causal inference in epidemiology [10]. Because genetic variations are fixed at birth, MR results are less susceptible to confounding effects and avoid some limitations of observational studies [11]. MR studies identifying risk factors have been widely applied in CRC [12, 13]. However, research on the risk effects of viral infections on CRC is still lacking.

Therefore, this study employed two-sample Mendelian randomization (MR) to assess the genetic susceptibility association of various viruses including herpes simplex virus, hepatitis virus, rubella virus, measles virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and human immunodeficiency virus (HIV) on CRC. Additionally, considering the high heterogeneity of gastrointestinal tumors, we further analyzed the genetic susceptibility association between viral infections and CRC subtypes.

Materials and methods

Study design

The overall research process was illustrated in Fig. 1A. This study adhered to the three major assumptions of MR and utilized the traditional two-sample analysis method, with viral infections as exposure and CRC and its subtypes as outcomes, to assess the genetic susceptibility

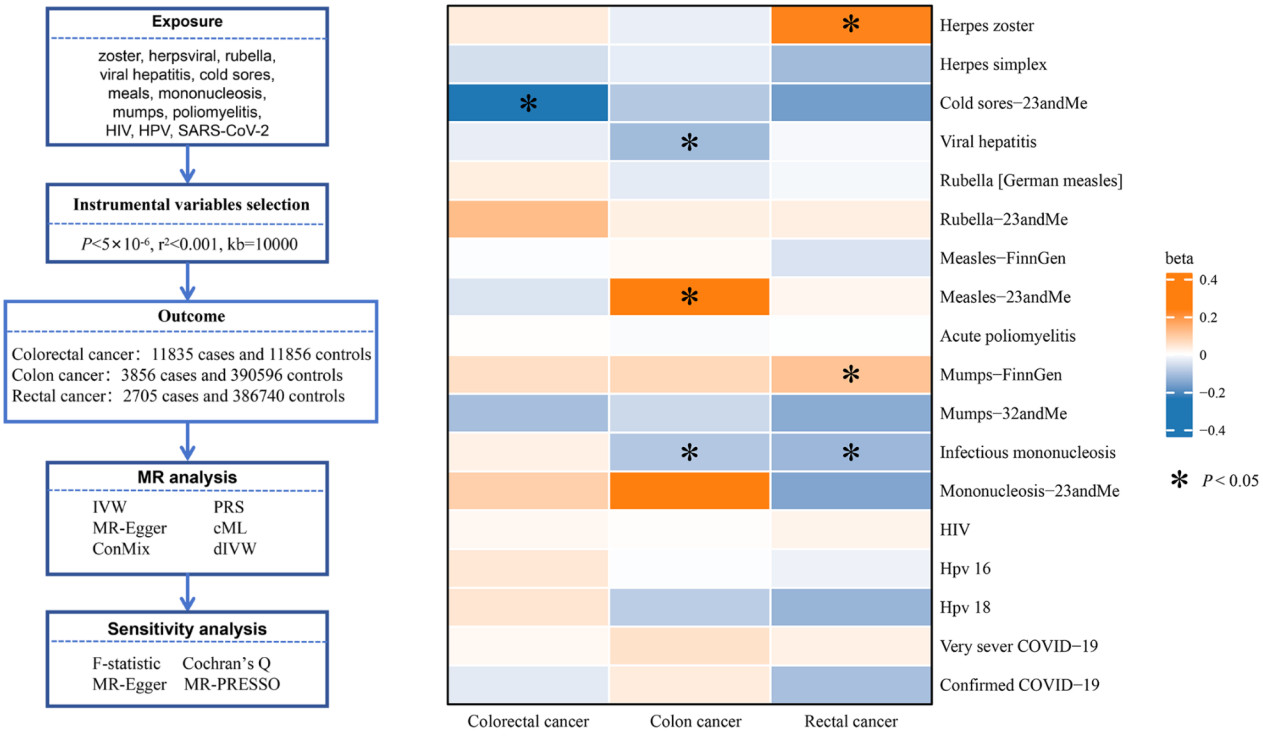

Fig. 1 **A**: Research flowcharts. **B**: Preliminary analysis of risk effects

association of viral infections on CRC risk. This study followed MR standardization reporting guidelines (Supplementary STROBE-MR checklist).

Viral GWAS source

The studied viruses included herpes simplex virus, hepatitis virus, rubella virus, measles virus, poliovirus, Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), human papillomavirus (HPV16, HPV18), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and mumps virus. Summary statistics for virus GWAS were obtained from 23andMe [14] and the r10 version of the FinnGen database [15].

The GWAS analysis from 23andMe was based on self-reported infection history questionnaires. Herpes simplex virus included 25,108 cases of cold sores and 63,332 controls from 23andMe [14], while the FinnGen dataset included 3,723 cases of herpes simplex virus infection and 396,378 controls, and 5,488 cases of herpes zoster infection and 396,378 controls [15]. Hepatitis infection data were obtained from FinnGen, including 2,320 cases and 409,861 controls. Poliovirus data were also from FinnGen, including 396 cases and 409,849 controls [15]. Rubella virus data were derived from 23andMe, with 12,000 cases and 71,597 controls [14], and from FinnGen, with 1,041 cases and 396,378 controls [15]. Measles virus data were obtained from 23andMe, with 38,219 cases and 47,279 controls [14], and from FinnGen, with 351 cases and 396,378 controls [15]. Mumps virus data were derived from 23andMe, with 31,227 cases and 68,446 controls [14], and from FinnGen, with 827 cases and 400,974 controls [15]. Infectious mononucleosis (EBV infection) data were obtained from 23andMe, with 17,457 cases and 68,446 controls [14], and from FinnGen, with 2,979 cases and 400,974 controls [15]. HPV infection data were sourced from the study by Shure et al., including 1,388 individuals of European ancestry [16]. COVID-19 data were obtained from the COVID-19 Host Genetics Initiative (HGI) r7 release (https://www.covid19hg.org/), including 13,769 cases and 1,072,442 controls [17]. Additionally, the FinnGen dataset included 2,856 confirmed COVID-19 cases and 405,232 controls [15].

Outcome GWAS sources

CRC GWAS data were obtained from the study by Huyghe et al., including 11,835 cases of European ancestry and 11,856 controls [18]. Additionally, subgroup analyses for rectal cancer and colon cancer were conducted using large GWAS summary statistics from the Pan-UK Biobank (https://pan.ukbb.broadinstitute.org/), which included 3,856 colon cancer cases and 390,596 controls, and 2,705 rectal cancer cases and 386,740 controls. The generalized mixed model association test framework was used for multi-ancestry analysis of 7,228 phenotypes, including 16,131 GWAS, adjusted for age, sex, age*sex, age^2, age^2*sex, and the first 10 principal components [19].

Genetic factors that may influence infection and outcome risk

To further investigate the genetic factors that may increase the risk of viral infections and cancer, we analyzed 1,400 blood metabolites (GWAS ID: GCST90199621-GCST90201020). The GWAS for these metabolites adjusted for age, sex, time since last meal or drink, genotyping batch, and the top ten genetic principal components. Linear regression was performed on the metabolites and metabolite ratios [20]. Due to the inability to obtain sufficient SNPs at the significance threshold of 5×10^{-8}, we used a more lenient significance threshold of 1×10^{-5}. For all metabolite analysis results, only those where all MR directions remained consistent were included in the subsequent mediation analysis. We employed the traditional two-step method, the coefficient product test, to assess the overall effects of metabolites, viral infections, and outcomes.

Mendelian randomization analysis

In the MR analysis, we could not obtain enough instrumental variables (IVs) based on the significance threshold ($P<5\times10^{-8}$). Therefore, we relaxed the threshold to $P<5\times10^{-6}$, with genetic variants clustered at $r^2<0.001$ within a 10,000 kb physical window. Additionally, IVs with an F-statistic less than 10 were filtered out to avoid weak instrument bias. The F-statistic was calculated as $(\text{beta/se})^2$ [21]. In the traditional MR analysis, inverse-variance weighted (IVW) was used as the primary method. Besides, we employed multiple MR methods to evaluate risk associations, including constrained maximum likelihood-based MR (cML), contamination mixture (ConMix), robust adjusted profile score (MR-RAPS), and debiased inverse-variance weighted method (dIVW) [22–25]. For single instrumental variables, the Wald ratio method was used to evaluate causal effects. Additionally, considering the directionality in MR analysis, we employed the Steiger method to ensure the correct analysis direction [26].

In the sensitivity analysis, Cochran's Q statistic was used to assess heterogeneity, with a P-value ≤ 0.05 indicating the presence of heterogeneity [27]. We used MR-Egger and Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) to evaluate the presence of horizontal pleiotropy [28, 29]. When horizontal pleiotropy was detected, MR-PRESSO was employed to remove outlier SNPs [29].

Results

The genetic susceptibility association between viral infections and colorectal cancer

After extracting exposure-related IVs, the results showed that all IVs had F-values greater than 10, indicating that the current analysis did not suffer from weak instrument bias (Table S2). In all analyses, eight causal associations were identified after filtering with the Steiger method (all $P<0.05$) (Fig. 1B). Tables S3-S8 display the causal effects and sensitivity analyses for all viral infections and outcomes.

For CRC, in the 23andMe cohort, the IVW method indicated that presence of SNPs linked to increased susceptibility to cold sores significantly reduced risk of CRC (OR: 0.73, 95% CI: 0.57–0.93, $P=0.01$) (Table S3) (Fig. 2). Additionally, various MR methods showed consistent effect directions (beta < 0) (Figure S1), suggesting that the current results provide a consistent risk estimate. In the sensitivity analysis, no pleiotropic associations were identified (Table S4).

The genetic susceptibility association between viral infections and colon cancer

For colon cancer, according to the IVW method (Fig. 3), presence of SNPs linked to increased susceptibility to viral hepatitis reduced the risk of colon cancer (OR: 0.89, 95% CI: 0.81–0.98, $P=0.02$) (Table S5). Presence of SNPs linked to increased susceptibility to infectious mononucleosis also reduced the risk of colon cancer (OR: 0.91, 95% CI: 0.84–0.98, $P=0.02$) (Table S5). In the 23andMe cohort, presence of SNPs linked to increased susceptibility to measles virus increased the risk of colon cancer (OR: 1.41, 95% CI: 1.07–1.85, $P=0.01$) (Table S5). However, this effect was not significant in FinnGen, but the direction of effect remained consistent. Furthermore, for the above analyses, all MR methods obtained consistent risk estimates (Figure S2). In sensitivity analysis, no significant pleiotropic interference was found (Table S6).

The genetic susceptibility association between viral infections and rectal cancer

For rectal cancer, in the FinnGen cohort, the IVW method showed that presence of SNPs linked to increased

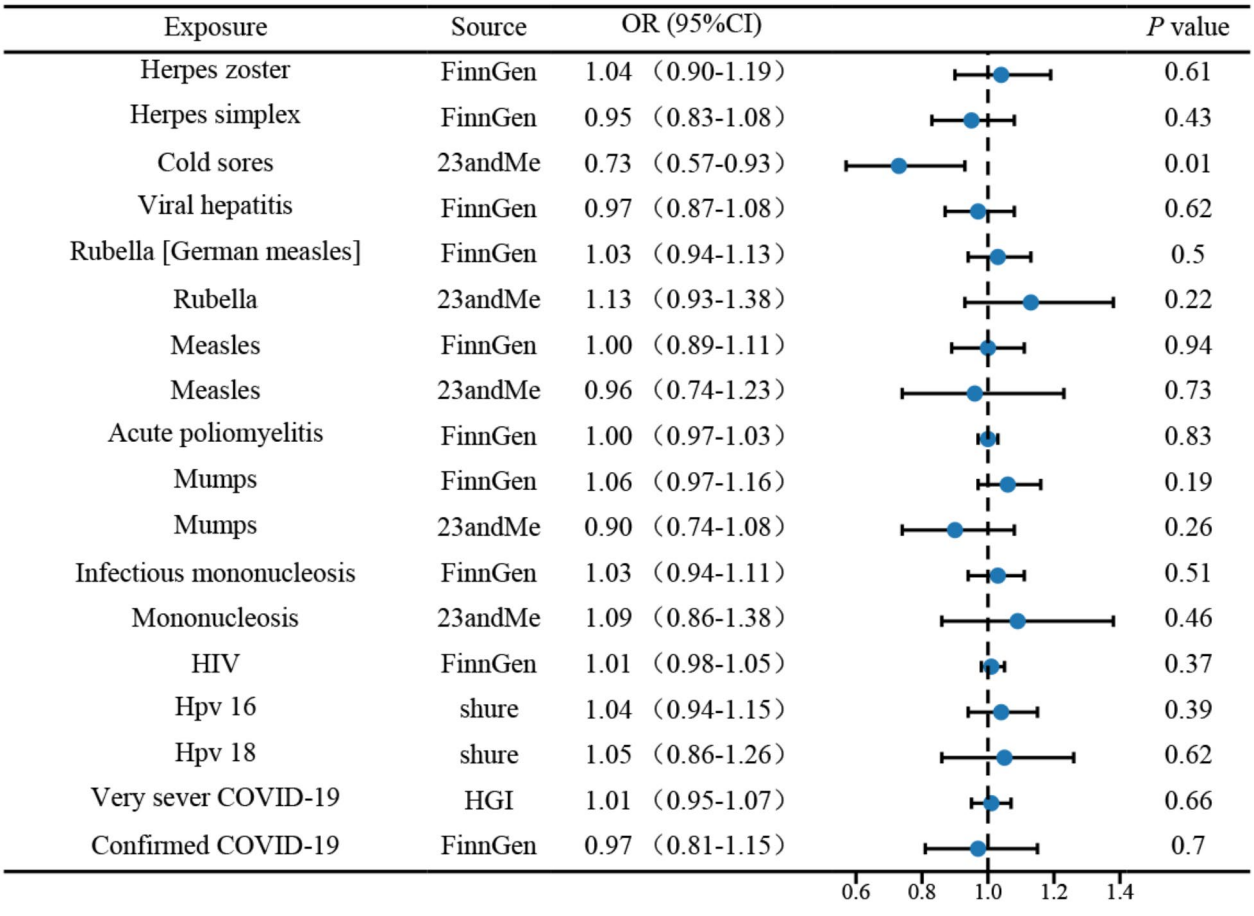

Fig. 2 Genetic susceptibility association between viral infections and colorectal cancer risk

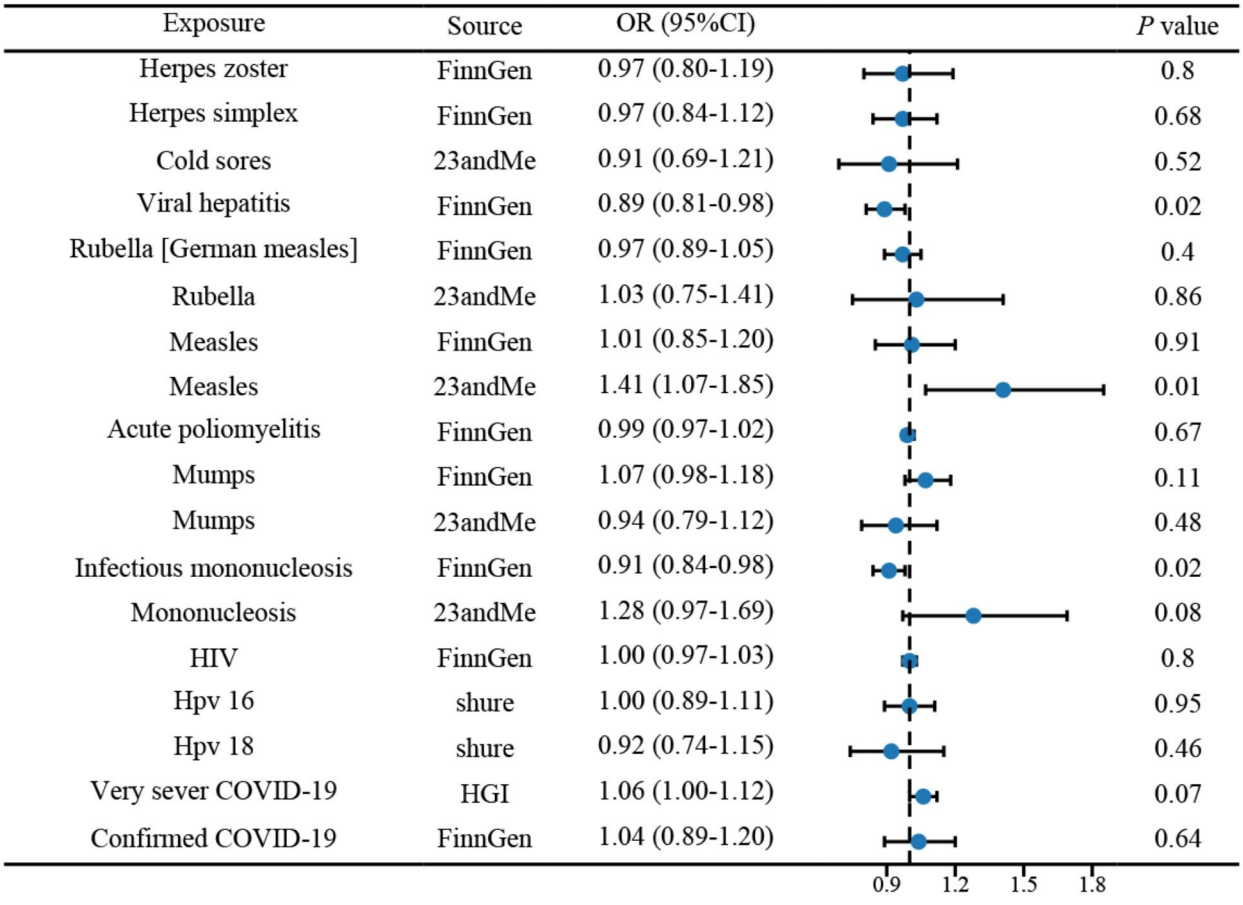

Fig. 3 Genetic susceptibility association between viral infections and colon cancer risk

susceptibility to herpes zoster virus increased the risk of rectal cancer (OR: 1.26, 95% CI: 1.05–1.52, P=0.01), while presence of SNPs linked to increased susceptibility to infectious mononucleosis reduced the risk of rectal cancer (OR: 0.809, 95% CI: 0.80–0.98, P=0.02). Presence of SNPs linked to increased susceptibility to mumps virus increased the risk of rectal cancer (OR: 1.12, 95% CI: 1.01–1.24, P=0.03) (Fig. 4) (Table S7). However, this effect did not remain consistent between FinnGen and 23andMe. Except for herpes zoster, most MR methods for other phenotypes provided the same direction of risk, but most MR analyses for herpes zoster virus remained consistent (Figure S3). In sensitivity analysis, no significant evidence of pleiotropy was found (Table S8).

Genetic susceptibility to blood metabolites, viral infection, and outcomes

After summarizing all consistent MR direction results, the current consistent estimates were only present for rectum cancer. In the genetic susceptibility analysis of zoster and rectum cancer, we found that presence of SNPs linked to increased susceptibility to X-23,997 levels decreased the risk of zoster infection (OR: 0.88, 95% CI: 0.77–0.99, P=0.035) and rectum cancer (OR: 0.84, 95% CI: 0.72–0.99, P=0.036). Presence of SNPs linked to increased susceptibility to the ratio of cysteinylglycine to taurine decreased the risk of zoster infection (OR: 0.90, 95% CI: 0.83–0.98, P=0.020) and rectum cancer (OR: 0.85, 95% CI: 0.74–0.97, P=0.014). In the genetic susceptibility analysis of EBV and rectum cancer, presence of SNPs linked to increased susceptibility to cortisone levels decreased the risk of EBV infection (OR: 0.79, 95% CI: 0.65–0.95, P=0.014) and rectum cancer (OR: 0.82, 95% CI: 0.68–0.99, P=0.036). Presence of SNPs linked to increased susceptibility to phenylpyruvate levels decreased the risk of EBV infection (OR: 0.84, 95% CI: 0.71–0.99, P=0.038) and rectum cancer (OR: 0.86, 95% CI: 0.75–0.99, P=0.034) (Table S9). However, significant mediators were not identified in the mediation analysis (Table S10). Nevertheless, the current results still provide some reference for the genetic susceptibility to viral infection and rectum cancer.

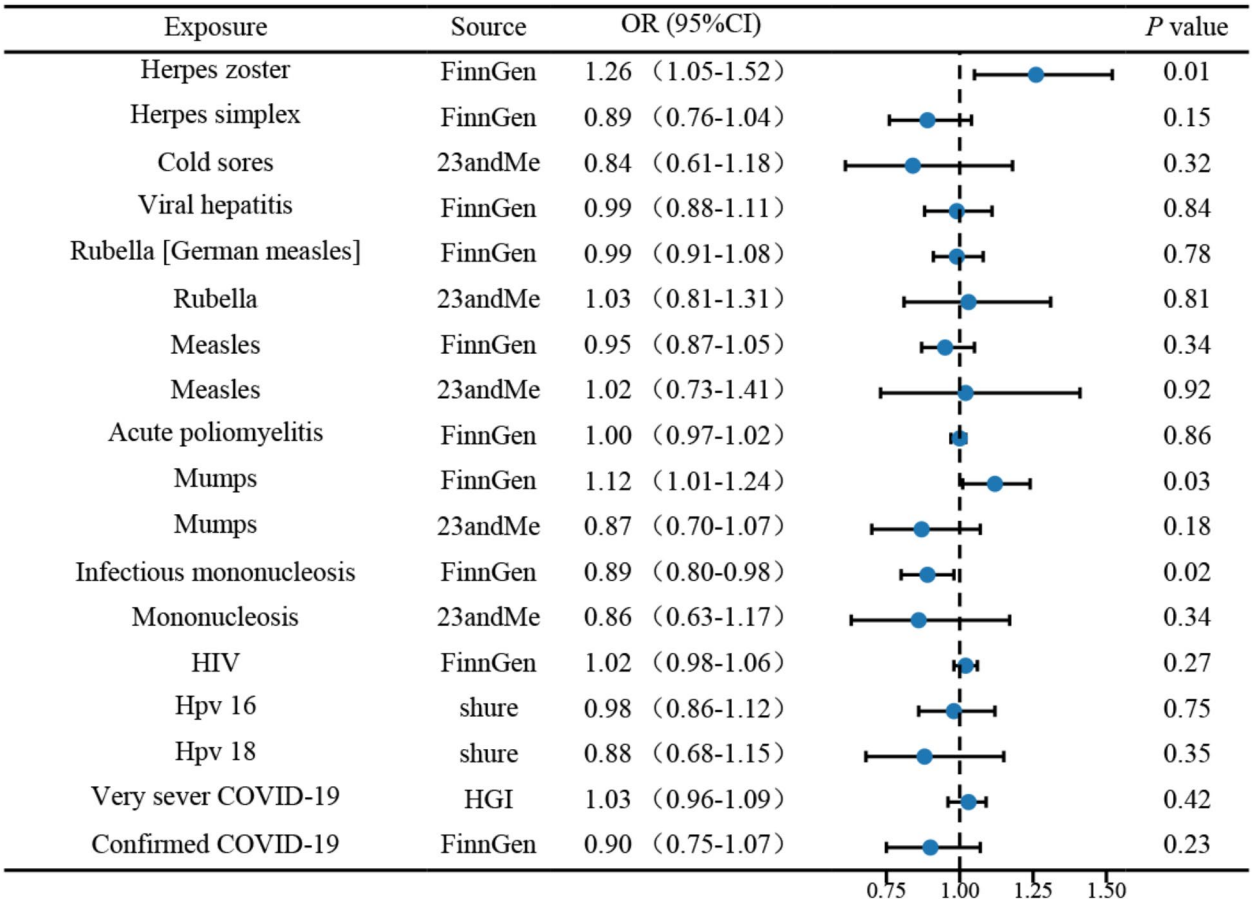

Fig. 4 Genetic susceptibility association between viral infections and rectal cancer risk

Discussion

In this study, we assessed the genetic susceptibility association between viral infections and CRC, identifying potential susceptibility factors. Indeed, conflicting views persist regarding the genetic susceptibility to viral infections and CRC risk, making causal inference challenging due to limitations such as small sample sizes and inherent biases. Therefore, we utilized MR to elucidate these relationships. The results revealed potential genetic associations between herpes zoster virus, infectious mononucleosis, mumps, viral hepatitis, and CRC and its subtypes.

Our results indicated that presence of SNPs linked to increased susceptibility to cold sores decreases the risk of CRC (OR=0.73, P=0.01), although this association was only observed in the 23andMe dataset. In herpes zoster virus infection, there were no definitive results indicating the causal estimate of all herpes zoster viruses on CRC risk. In the case of herpes zoster virus infection, there were no clear results indicating a causal estimate of all herpes zoster viruses for CRC risk. In the FinnGen cohort, herpes zoster is primarily caused by varicella-zoster virus (VZV), while cold sores is mainly caused by herpes simplex virus (HSV) in 23andMe. A similar trend was observed in FinnGen's herpes simplex virus infection (OR=0.95), indicating that presence of SNPs linked to increased susceptibility to HSV may reduce the risk of CRC. Due to the neurotropic nature of HSV, studies have confirmed its ability to selectively infect and destroy tumors within the central nervous system while preserving normal neurons [30]. The deletion of the g34.5 gene in HSV infection affects the activity of the mammalian protein GADD 34. When infected, this leads to an upregulation of the protein, which in turn inhibits protein synthesis. Additionally, infected cells perceive the damage caused by viral infection and enter a programmed cell death pathway rather than attempting repair or continued survival [31, 32]. Previous studies have demonstrated that targeted HSV therapy can effectively infect and kill CRC cells, and inhibit liver metastasis [33]. Therefore, our MR results further reinforce these previous findings.

Considering the heterogeneity of gastrointestinal tumors, in subgroup analyses, we found that presence of SNPs linked to increased susceptibility to hepatitis virus infection reduced the risk of colon cancer. Unlike

previous studies suggesting that chronic hepatitis virus infection increases the risk of chronic inflammatory bowel disease or adenomatous polyps, thereby increasing the risk of CRC [34], this association is often attributed to the sustained role of inflammatory mechanisms in the long-term development of CRC. However, Song et al. found that chronic hepatitis reduces CRC liver metastasis and prolongs survival time [35]. Similar trends were also observed in the study by Qiu et al. [36]. Furthermore, hepatitis viruses may enhance the cytotoxicity of cytotoxic T lymphocytes [37], which could explain some potential connections. However, it is still unclear to differentiate between infection status and infection type, and specific mechanisms exploration is lacking. Therefore, additional validation is needed for the current associations.

For measles virus, there was a similar trend between FinnGen and 23andMe, but the results from FinnGen were not significant. Measles virus infection may induce human immune suppression, such as lymphocyte depletion and peripheral lymphocyte silence [38], which could result in the body's inability to mount effective antitumor immune responses. Additionally, the poliovirus receptor-like 4 (PVRL4), which is a receptor for measles virus, is significantly upregulated in colorectal cancer [39], providing some suggestive associations. However, observational studies supporting this are currently lacking.

For herpes zoster, presence of SNPs linked to increased susceptibility to VZV infection increased the risk of rectal cancer (OR=1.26, P=0.01). However, presence of SNPs linked to increased susceptibility to VZV decreased the risk of colon cancer (OR=0.97, P=0.80). Although this difference is not statistically significant, the opposing trend suggests that intestinal site heterogeneity may influence the direction of VZV's effect on outcomes. VZV replicates readily in CD8 cells and triggers inflammation [40]. Observational studies has reported that high levels of CD8 cells reduce the risk of colon cancer (OR=0.42, P=0.012), but increase the risk of rectal cancer (OR=1.13, P=0.753) [41]. Therefore, the infective properties of VZV on colorectal cancer may be influenced by the immune infiltration characteristics of sub-site anatomy. Additionally, VZV may increase cancer risk, but lacks specificity for anatomical sites [42]. Therefore, our study suggests a sub-site-specific effect of VZV on cancer risk. Subsequent research is also needed to explore the exact mechanisms. Additionally, we found in the FinnGen cohort that presence of SNPs linked to increased susceptibility to mumps may increase the risk of rectal cancer, albeit with a weak statistical effect, and this causal effect was not validated in the 23andMe dataset. This effect is consistent in CRC and colon cancer. This indicates that the association between mumps and rectal cancer risk warrants further investigation.

In infectious mononucleosis, EBV infection simultaneously reduces the risk of both colon and rectal cancer. Large-scale cohort studies have shown that EBV reduces the standardized incidence rate of rectal cancer (SIR=0.90, 95% CI: 0.65–1.22) [43]. Similar to a study conducted in Germany, these studies all indicate that EBV increases the risk of hematological malignancies, while EBV infection appears to reduce the risk of digestive system tumors [43, 44]. Although these findings may not be statistically significant, these large-scale studies consistently demonstrate the same trend. Collectively, these studies suggest that EBV infection may reduce the risk of colon or rectal cancer.

Finally, we identified several blood metabolites associated with the risk of viral infections and colorectal cancer. Similar studies support our findings. We found that the Cysteinylglycine to taurine ratio reduced the risk of viral infections and rectal cancer. Cysteine plays a crucial role in cellular redox regulation. Miranti et al. demonstrated that cysteine reduces the risk of esophageal cancer [45], and can serve as a target against SARS infection [46]. Cortisone has anti-inflammatory properties, reducing the risk of viral infection and cancer [47, 48]. Phenylpyruvate is a metabolic product of phenylalanine and may play a role in inducing apoptosis in cancer [49]. Additionally, phenylpyruvate may inhibit viral replication by suppressing viral protease activity [50]. Although specific mediating mechanisms have not yet been identified, these findings suggest that exploring factors that may increase the risk of persistent chronic infection and cancer progression will be beneficial for disease control.

Our study has several strengths. Firstly, it encompasses a large number of virus GWAS and, for the first time, explores the causal association between viral infections and CRC. Secondly, we aggregated the latest GWAS data from the FinnGen r10 release, which has a larger sample size. Thirdly, our study is limited to European populations, thus avoiding ethnic bias. However, there are still limitations to the current study. Firstly, the applicability of the results requires validation through extensive prospective studies. Secondly, despite the use of MR-Egger and MR-PRESSO, it is still not possible to completely avoid some potential pleiotropy, which is a common limitation of GWAS studies. Lastly, although we stratified by anatomical site, the current study was unable to stratify by some common characteristics such as gender and age. In addition, the current study provides an association between susceptibility to viral infection and colorectal cancer risk. More in-depth research is needed to explore the direct risk association between viral infections and colorectal cancer.

Conclusion

Our study investigated the genetic susceptibility association between viral infections and CRC risk. We found that presence of SNPs linked to increased susceptibility to HSV may reduce the risk of CRC, while presence of SNPs linked to increased susceptibility to VZV increases the risk of rectal cancer. In sub-site stratification, presence of SNPs linked to increased susceptibility to viral hepatitis and EBV infection were associated with a decreased risk of colon cancer, while measles virus increased the risk of colon cancer. Additionally, presence of SNPs linked to increased susceptibility to EBV infection was found to decrease the risk of rectal cancer.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13027-024-00602-6.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

Authors' contributionsGen Li conceived the study and conducted the main analysis. Gen Li, Siyu Wang, and Jianli Ma participated in data collection. Shanshan Liu revised the final manuscript. All authors have informed consent for the manuscript.

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The funders had no role in the study design, data collection, analysis, interpretation, manuscript preparation, or the decision to submit the manuscript for publication.

Data availability

Availability of data and materialsAll data were from open access GWAS large data. FinnGen's GWAS data are derived from the latest released r10 version (https://www.finngen.fi/en/access_results). The GWAS data for the 23andMe cohort were sourced from previous studies [15]. COVID-19 data were obtained from HGI's r7 version (https://www.covid19hg.org/). Data on 1400 blood metabolites can be obtained from the GWAS catalog website (https://www.ebi.ac.uk/gwas/) (GWAS ID: GCST90199621-GCST90201020).

Declarations

Consent to participate

This research has been conducted using published studies and consortia providing publicly available summary statistics. All original studies have been approved by the corresponding ethical review board, and the participants have provided informed consent. In addition, no individual-level data was used in this study. Therefore, no new ethical review board approval was required.

Ethics approval

Due to such a re-analysis of previously collected and published data, no additional ethics approval was needed.

Competing interests

The authors declare no competing interests.

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References

1. Sung H, et al. Global Cancer statistics 2020: GLOBOCAN estimates of incidence and Mortality Worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
2. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2008;149(9):627–37.
3. Zauber AG, et al. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. Ann Intern Med. 2008;149(9):659–69.
4. Holme Ø, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA. 2014;312(6):606–15.
5. Gupta S, et al. Challenges and possible solutions to colorectal cancer screening for the underserved. J Natl Cancer Inst. 2014;106(4):dju032.
6. A VSS, Sinha S, Donakonda S. Virus-host interaction analysis in colorectal cancer identifies core virus network signature and small molecules. Comput Struct Biotechnol J. 2022;20:4025–39.
7. Chen H, et al. Viral infections and colorectal cancer: a systematic review of epidemiological studies. Int J Cancer. 2015;137(1):12–24.
8. Ibragimova MK, Tsyganov MM, Litviakov NV. Human papillomavirus and colorectal cancer. Med Oncol. 2018;35(11):140.
9. Laghi L, et al. JC virus DNA is present in the mucosa of the human colon and in colorectal cancers. Proc Natl Acad Sci U S A. 1999;96(13):7484–9.
10. Smith GD, Ebrahim S. Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol. 2003;32(1):1–22.
11. Evans DM, Davey Smith G. Mendelian randomization: New Applications in the coming age of hypothesis-free causality. Annu Rev Genomics Hum Genet. 2015;16:327–50.
12. Nimptsch K, et al. Prospective and mendelian randomization analyses on the association of circulating fatty acid binding protein 4 (FABP-4) and risk of colorectal cancer. BMC Med. 2023;21(1):391.
13. Papadimitriou N, et al. Separating the effects of early and later life adiposity on colorectal cancer risk: a mendelian randomization study. BMC Med. 2023;21(1):5.
14. Tian C, et al. Genome-wide association and HLA region fine-mapping studies identify susceptibility loci for multiple common infections. Nat Commun. 2017;8(1):599.
15. Kurki MI, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. Nature. 2023;613(7944):508–18.
16. Suhre K, et al. Connecting genetic risk to disease end points through the human blood plasma proteome. Nat Commun. 2017;8:14357.
17. The COVID-19. Host Genetics Initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic. Eur J Hum Genet. 2020;28(6):715–8.
18. Huyghe JR, et al. Discovery of common and rare genetic risk variants for colorectal cancer. Nat Genet. 2019;51(1):76–87.
19. Bycroft C, et al. The UK Biobank resource with deep phenotyping and genomic data. Nature. 2018;562(7726):203–9.
20. Chen Y, et al. Genomic atlas of the plasma metabolome prioritizes metabolites implicated in human diseases. Nat Genet. 2023;55(1):44–53.
21. Yuan C, et al. Causal association between colorectal cancer and Alzheimer's disease: a bidirectional two-sample mendelian randomization study. Front Genet. 2023;14:1180905.
22. Xue H, Shen X, Pan W. Constrained maximum likelihood-based mendelian randomization robust to both correlated and uncorrelated pleiotropic effects. Am J Hum Genet. 2021;108(7):1251–69.
23. Burgess S, et al. A robust and efficient method for mendelian randomization with hundreds of genetic variants. Nat Commun. 2020;11(1):376.
24. Yu K, et al. Assessment of bidirectional relationships between brain imaging-derived phenotypes and stroke: a mendelian randomization study. BMC Med. 2023;21(1):271.
25. Ye T, Shao J, Kang H. Debiased Inverse-Variance Weighted Estimator in Two-Sample Summary-Data Mendelian Randomization. 2019.
26. Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. PLoS Genet. 2017;13(11):e1007081.

27. Bowden J, et al. A framework for the investigation of pleiotropy in two-sample summary data mendelian randomization. Stat Med. 2017;36(11):1783–802.
28. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol. 2015;44(2):512–25.
29. Verbanck M, et al. Detection of widespread horizontal pleiotropy in causal relationships inferred from mendelian randomization between complex traits and diseases. Nat Genet. 2018;50(5):693–8.
30. Yazaki T, et al. Treatment of human malignant meningiomas by G207, a replication-competent multimutated herpes simplex virus 1. Cancer Res. 1995;55(21):4752–6.
31. Roizman B, Markovitz N. Herpes simplex virus virulence: the functions of the gamma (1)34.5 gene. J Neurovirol. 1997;3(Suppl 1):S1–2.
32. Chou J, et al. Mapping of herpes simplex virus-1 neurovirulence to gamma 134.5, a gene nonessential for growth in culture. Science. 1990;250(4985):1262–6.
33. Kooby DA, et al. Oncolytic viral therapy for human colorectal cancer and liver metastases using a multi-mutated herpes simplex virus type-1 (G207). Faseb j. 1999;13(11):1325–34.
34. Chiba T, Marusawa H, Ushijima T. Inflammation-associated cancer development in digestive organs: mechanisms and roles for genetic and epigenetic modulation. Gastroenterology. 2012;143(3):550–63.
35. Song E, et al. Rare occurrence of metastatic colorectal cancers in livers with replicative hepatitis B infection. Am J Surg. 2001;181(6):529–33.
36. Qiu HB, et al. HBV infection decreases risk of liver metastasis in patients with colorectal cancer: a cohort study. World J Gastroenterol. 2011;17(6):804–8.
37. Tordjmann T, et al. Perforin and granzyme B lytic protein expression during chronic viral and autoimmune hepatitis. Liver. 1998;18(6):391–7.
38. Avota E, Gassert E, Schneider-Schaulies S. Measles virus-induced immunosuppression: from effectors to mechanisms. Med Microbiol Immunol. 2010;199(3):227–37.
39. Delpeut S et al. Measles Virus enters breast and Colon cancer cell lines through a PVRL4-Mediated macropinocytosis pathway. J Virol, 2017. 91(10).
40. Fouladseresht H, et al. Increased frequency of HLA-A*02 in patients with atherosclerosis is associated with VZV seropositivity. Arch Physiol Biochem. 2021;127(4):351–8.
41. Berntsson J, et al. The clinical impact of tumour-infiltrating lymphocytes in colorectal cancer differs by anatomical subsite: a cohort study. Int J Cancer. 2017;141(8):1654–66.
42. Tayyar R, Ho D. Herpes Simplex Virus and Varicella Zoster Virus infections in Cancer patients. Viruses, 2023. 15(2).
43. Hjalgrim H, et al. Risk of Hodgkin's disease and other cancers after infectious Mononucleosis. J Natl Cancer Inst. 2000;92(18):1522–8.
44. Roderburg C et al. The Association between Infectious Mononucleosis and Cancer: a cohort study of 24,190 outpatients in Germany. Cancers (Basel), 2022. 14(23).
45. Miranti EH, et al. Prospective study of serum cysteine and cysteinylglycine and cancer of the head and neck, esophagus, and stomach in a cohort of male smokers. Am J Clin Nutr. 2016;104(3):686–93.
46. Alghamdi YS, et al. Unveiling the multitargeted potential of N-(4-Aminobutanoyl)-S-(4-methoxybenzyl)-L-cysteinylglycine (NSL-CG) against SARS CoV-2: a virtual screening and molecular dynamics simulation study. J Biomol Struct Dyn. 2023;41(14):6633–42.
47. Montes A, Figueras A, Novoa B. Nodavirus Encephalopathy in turbot (Scophthalmus maximus): inflammation, nitric oxide production and effect of anti-inflammatory compounds. Fish Shellfish Immunol. 2010;28(2):281–8.
48. Sakamoto N, et al. Inhibitory effects of heparin plus cortisone acetate on endothelial cell growth both in cultures and in tumor masses. J Natl Cancer Inst. 1987;78(3):581–5.
49. Guo Y, et al. Design, synthesis and structure-activity relationship of a focused library of β-phenylalanine derivatives as novel eEF2K inhibitors with apoptosis-inducing mechanisms in breast cancer. Eur J Med Chem. 2018;143:402–18.
50. Trivedi J, Ghosh P, Mitra D. N-p-Tosyl-L-phenylalanine chloromethyl ketone (TPCK) inhibits HIV-1 by suppressing the activity of viral protease. Biochem Biophys Res Commun. 2020;527(1):167–72.

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