

RESEARCH LETTERS

HLA Heterozygosity Influences Colorectal Cancer Risk and Survival Outcome



The diversity of HLAs is critical for effective immune responses against pathogens and cancer. HLA class I molecules present endogenous antigens to eliminate infected or cancerous cells, while HLA class II molecules present exogenous antigens to helper CD4⁺ T cells, stimulating antibody production. Polymorphisms in HLA genes, particularly in the peptide-binding cleft, create diverse antigen-binding affinities, suggesting evolutionary selection pressure to maintain diversity as a defense against pathogen adaptation.¹ One mechanism by which HLA diversity is maintained is through heterozygote advantage,² where individuals with 2 different alleles at a genetic locus have higher fitness compared with those with 2 identical alleles. Particular attention has been focused on the role of HLA heterozygote advantage in colorectal cancer (CRC).^{3–5} Our prior study of 5406 patients with CRC and 4635 controls found that HLA class I and/or II alleles may be associated with higher tumor-infiltrating lymphocytes and reduced risk of CRC.⁴ Here, we expand on this work by analyzing 183,626 participants (84,907 CRC cases and 98,689 controls) from the International Colorectal Cancer GWAS Collaborative, including the United States, Europe, and Australia; United Kingdom and Europe; and Asia (Supplementary Table 1). HLA class I and class II alleles were imputed from germline genotype data, and the number of heterozygous genotypes at HLA class I (*A*, *B*, *C*) and HLA class II (*DPB1*, *DQB1*, *DRB1*) loci were quantified. Logistic regression estimated the risk of CRC, and Cox proportional hazards regression assessed overall survival (OS) and CRC-specific survival (CS) in 20,332 CRC cases (Supplementary Methods). To account for multiple hypothesis testing, we applied a Bonferroni correction, adjusting the statistical significance threshold to $P < .0063$ (.05/8 independent tests).

Our meta-analysis demonstrated that HLA heterozygosity is associated with significantly reduced CRC risk and longer survival. Compared with individuals with 0 or 1 heterozygous alleles across HLA class I and class II loci, those with 2–5 heterozygotes had a 10% reduced odds of CRC (odds ratio [OR], 0.90; $P = .004$), and those with all heterozygous genotypes at class I and class II loci were at lower odds of CRC (OR, 0.89; $P = .002$) (Figure 1A). For HLA class I, individuals who carried 2 or 3 heterozygous genotypes were at 10% lower risk of CRC (2 heterozygotes: OR, 0.89; $P = .003$; 3 heterozygotes: OR, 0.91; $P = .004$) (Supplementary Table 2). Among 20,322 CRC cases, a higher number of heterozygous genotypes was associated with better OS in a dose-response relationship ($P_{\text{trend}} = .008$ for class II, $P_{\text{trend}} = .029$ for class I/II combined) (Supplementary Table 3). Interestingly, early stage (I and II) CRC cases with all 6 heterozygous loci exhibited a 41% lower risk of dying from CRC (hazard ratio, 0.59; $P = .025$) (Figure 1B). However, this was not

observed in patients with locally advanced or metastatic disease. Although our primary finding for CRC risk remained statistically significant after multiple testing correction, the survival analysis P values (.008–.025) did not meet this stringent threshold, but are still strongly suggestive of an association.

These findings are consistent with the hypothesis that HLA heterozygosity enhances immune surveillance by means of presenting a broader antigenic peptide repertoire to T cells. Prior studies revealed the complementary roles of HLA class I and II genotypes on the oncogenic mutational landscape and immunoediting during tumor development,^{6,7} influencing both CD8⁺ and CD4⁺ T-cell responses. Our work explores the less-studied impact of germline HLA heterozygosity, which is distinct from the common somatic loss of heterozygosity. Analyzing germline HLA zygosity rather than individual alleles offers a key advantage in a multi-ethnic study, allowing examination of HLA variability across ancestry groups without the complexity of comparing highly population-specific alleles. Our prior analysis found an association between HLA class I and II heterozygosity and higher levels of tumor-infiltrating lymphocytes,⁴ suggesting a mechanistic role in CRC development. Furthermore, a study of esophagogastric adenocarcinoma demonstrated that germline HLA class I homozygosity reduced immunogenic peptide repertoires,⁸ supporting HLA heterozygote advantage in enhancing immune surveillance against cancer.

Our analysis revealed a dose-response relationship between HLA heterozygosity and improved OS, but not CS. This suggests that HLA heterozygosity may influence OS through mechanisms beyond exclusively cancer-specific mortality. We found that patients with early-stage CRC and greater HLA class I and II heterozygosity exhibited significantly better CS, likely because increased HLA diversity allows the immune system to recognize and respond to a wider range of tumor antigens, especially when tumor burden is low. Conversely, advanced-stage CRC patients did not experience such benefit, possibly due to factors like somatic HLA loss, immune exhaustion, or reduced tumor infiltration. Notably, a different trend was observed in the Asian cohort, where HLA class I heterozygosity was associated with worse OS and CS. This finding may be influenced by the small sample size and variability in HLA allele frequencies specific to the Asian population. The Asian cohort's limitation of including only male

Abbreviations used in this paper: CRC, colorectal cancer; CS, colorectal cancer-specific survival; OR, odds ratio; OS, overall survival.



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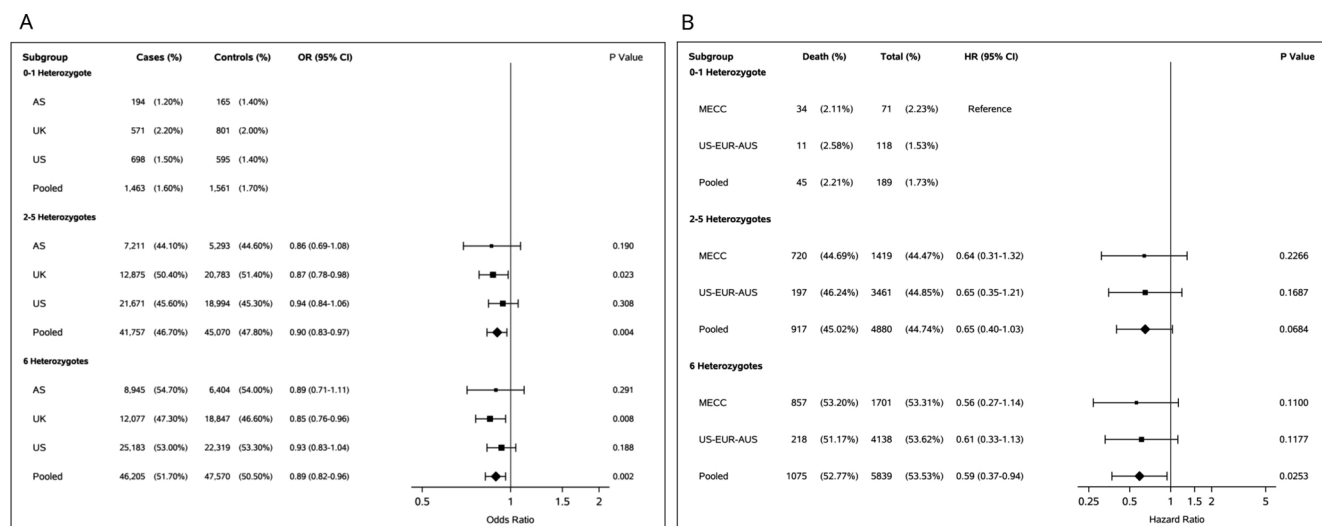


Figure 1. Associations between HLA class I and II heterozygosity and CRC risk and outcome. (A) HLA class I and II heterozygosity and CRC risk. (B) HLA class I and II heterozygosity and CRC-specific survival in patients with stage I and II disease. AS, Asia-based consortium; UK-EUR, United Kingdom and Europe-based consortium; US-EUR-AUS, United States, Europe, and Australia-based Consortium.

patients may further contribute to these differences. However, we cannot rule out that this observation is due to chance.

Despite robust statistical power, our study has limitations. Our findings, primarily from individuals of European and Asian ancestry, have limited generalizability. The lack of comprehensive treatment information, including immunotherapy, precluded analysis of the effect of HLA heterozygosity on treatment responses. Incomplete survival information for some data sets, especially the Asia-based consortium, may also give rise to potential bias. A higher proportion of stage I/II cases also constrained our stage-specific results, highlighting the need for larger samples of advanced-stage patients to better understand the influence of HLA heterozygosity on outcomes.

Using the largest data set of HLA genotypes from patients with CRC across multiple continents, we unveiled the important relationship between germline HLA diversity and both CRC risk and prognosis. Our findings demonstrate that increased HLA heterozygosity is associated with reduced CRC risk and potentially better clinical outcomes, particularly in early-stage patients. These results highlight potential for incorporating HLA diversity into polygenic risk scores and prognostic models to improve CRC risk prediction and prognostication. Future research should focus on understanding the mechanisms by which HLA diversity influences CRC development and progression to inform the targeted immunoprevention and immunotherapies that leverage this diversity to improve CRC outcomes.

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at <https://doi.org/10.1053/j.gastro.2025.10.020>.

References

1. Penn DJ, et al. *Proc Natl Acad Sci U S A* 2002; 99:11260–11264.
2. Doherty PC, et al. *Nature* 1975;256:50–52.
3. Liu Z, et al. *Front Genet* 2021;12:675860.
4. Tsai YY, et al. *Front Immunol* 2023;14:1268117.
5. Wang QL, et al. *Ebiomedicine* 2023;92:104588.
6. Marty Pyke R, et al. *Cell* 2018;175:416–428.e413.
7. Marty R, et al. *Cell* 2017;171:1272–1283.e1215.
8. Garcia-Marquez MA, et al. *J Immunother Cancer* 2024; 12:e007268.

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Data Availability

Summary statistics for the full set of Asian and European genome-wide association studies are available through the GWAS catalog (GCST90129505). Individual-level genotype data are available via dbGaP (phs001415.v1.p1, phs001315.v1.p1, phs001078.v1.p1, phs001903.v1.p1, phs001856.v1.p1, and phs001045.v1.p1 for CCFR, CORECT, CORSA_2 and GECCO), the European Genome-Phenome Archive (accession numbers EGAS00001005412 for NSCCG, EGAS00001005421 for COIN), UK Biobank (<http://www.ukbiobank.ac.uk>), and THL Biobank (for Finnish data). Access to the remaining individual-level data require application through oversight committees or specific contacts, as detailed for CCFR (www.coloncfr/collaboration.org), QUASAR2, SCOT, CORGI (LP1), Scotland Phase 1, Scotland Phase 2, SOCCS, DACHS, Croatia (access.crc.gwas.data@outlook.com), CORSA_1 (gecco@fredhutch.org), Generation Scotland controls (access@generationscotland.org), and Asian cohorts (Aichi1, Aichi2, Korea and Shanghai cohorts; see <https://swhs-smhs.app.vumc.org/> or contact Dr. Zheng at wei.zheng@vanderbilt.edu). Germline genotype data are available in dbGaP for the MECC study (https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001045.v1.p1; https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001856.v1.p1; https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001903.v1.p1).