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Genetic variants associated with circulating C-reactive protein levels and colorectal cancer survival: Sex- and lifestyle factors- specific associations

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Abbreviations: BMI=Body Mass Index, CCFR= Colon Cancer Family Registry, CI=Confidence Interval, CPS II= Cancer Prevention Study II, CRC=Colorectal Cancer, CRP=C-Reactive Protein, DACHS= Darmkrebs: Chancen der Verhütung durch Screening, DALS= Diet, Activity, and Lifestyle Study, EDRN= Early Detection Research Network, EPIC=European Prospective Investigation into Cancer, GWAS= Genome-Wide Association Studies, HPFS=Health Professionals Follow-up Study, HR=Hazard Ratio, ICD= International Classification of Diseases, ISACC= International Survival Analysis in Colorectal Cancer Consortium, LD=Linkage Disequilibrium, MCCS= Melbourne Collaborative Cohort Study, NHGRI-EBI=National Human Genome Research Institute-European Bioinformatics Institute, NHS= Nurses' Health Study, PCA=Principal Components Analysis, PHS= Physicians' Health Study, PLCO= Prostate, Lung, Colorectal, and Ovarian Study, QC=Quality Control, SNP= Single Nucleotide Polymorphism, UKB= UK Biobank, VITAL= VITamins And Lifestyle Study, WHI= Women's Health Initiative.

Novelty and Impact: This is the first study evaluating the gene-environment interactions of C-reactive protein level-related genetic variants with sex and lifestyle factors in relation to colorectal cancer-specific mortality. We found evidence of a statistically significant interaction

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between variant rs1933736 at *FRK* gene and sex. Women with C (vs. T) allele of variant rs1933736 were associated with increased colorectal cancer-specific mortality, while an inverse association was observed for men.

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Abstract

Elevated blood levels of C-reactive protein (CRP) have been linked to colorectal cancer (CRC) survival. We evaluated genetic variants associated with CRP levels and their interactions with sex and lifestyle factors in association with CRC-specific mortality.

This study included 16,142 CRC cases from the International Survival Analysis in Colorectal Cancer Consortium. We identified 618 common single nucleotide polymorphisms (SNPs) associated with CRP levels from the NHGRI-EBI GWAS Catalog. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between SNPs and CRC-specific mortality adjusting for age, sex, genotyping platform/study, and principal components. We investigated their interactions with sex and lifestyle factors using likelihood ratio tests.

Of 5,472 (33.9%) deaths accrued over up to 10 years of follow-up, 3,547 (64.8%) were due to CRC. No variants were associated with CRC-specific mortality after multiple comparison correction. We observed strong evidence of interaction between variant rs1933736 at *FRK* gene and sex in relation to CRC-specific mortality (corrected $P_{interaction}$ = 0.0004); women had higher CRC-specific mortality associated with the minor allele (HR = 1.11, 95% CI = 1.04 to 1.19) whereas an inverse association was observed for men (HR = 0.88, 95% CI = 0.82 to 0.94). There was no evidence of interactions between CRP-associated SNPs and alcohol, obesity or smoking.

Our study observed a significant interaction between sex and a CRP-associated variant in relation to CRC-specific mortality. Future replication of this association and functional annotation of the variant are needed.

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Introduction

Chronic inflammation is strongly associated with colorectal cancer (CRC) through several mechanisms [1]. C-reactive protein (CRP) is a sensitive marker of chronic low-grade inflammation. Increasing evidence has shown associations of elevated CRP levels with higher CRC risk and worse prognosis [2-6]. Although the mechanisms underlying these relationships are incompletely understood, germline genetic variants are thought to play an important role.

Genome-wide association studies (GWAS) have been successful in identifying genetic variants associated with CRP levels [7, 8], and have facilitated investigations of the role of CRP-related variants in CRC incidence [9, 10]. Slattery et al. and Nimptsch et al. reported several genetic variants in *CRP* gene associated with the risk of colon or rectal cancer. However, few studies evaluated the association between CRP-related variants and CRC prognosis.

Additionally, CRP concentrations are positively associated with several prognostic factors of CRC such as sex, obesity, smoking, as well as excessive alcohol consumption [11-20]. CRC patients who were smokers, obese, heavy drinkers, or males were shown to have worse survival outcomes [16-18, 20]. To further evaluate the interactions between CRP-related genetic variants and these environmental factors in relation to CRC mortality can help to improve our understanding of the relationship between CRP-associated genetic variants and CRC mortality, and to identify populations at differential risk of CRC death and provide insights into underlying mechanisms of progression and prognosis.

In this consortium study, we examined CRP-related variants in relation to CRC survival and whether these associations differed according to sex and lifestyle factors among patients diagnosed with CRC.

Method

Study population

This study included individuals diagnosed with incident, invasive CRC from the International Survival Analysis in Colorectal Cancer Consortium (ISACC), a consortium of case-control studies, cohort studies, and clinical trials from around the world. The following 14 ISACC studies were included: the Colon Cancer Family Registry (CCFR) [21], Cancer Prevention Study II (CPSII) [22], Darmkrebs: Chancen der Verhütung durch Screening (DACHS) [23], Diet, Activity, and Lifestyle Study (DALS) [24], Early Detection Research Network (EDRN) [25], European Prospective Investigation into Cancer (EPIC) [26], Health Professionals Follow-up Study (HPFS) [27], Melbourne Collaborative Cohort Study (MCCS) [28], Nurses' Health Study (NHS) [29, 30], Physicians' Health Study (PHS) [31], Prostate, Lung, Colorectal, and Ovarian Study (PLCO) [32], UK Biobank (UKB) [33], VITamins And Lifestyle Study (VITAL) [34], Women's Health Initiative (WHI) [35]. Study-specific details are described in the Supplementary Table 1.

Demographic and epidemiologic factors were collected using self- or interviewer-administered questionnaires at enrollment according to study-specific protocols. A multistep data harmonization process was conducted centrally using an iterative process to reconcile the differences of the protocols and data collection instruments across studies, as described previously [36]. Briefly, within each study, all exposure information, including age at diagnosis, sex, body mass index (BMI), ever smoking, alcohol consumption, was collected by in-person or phone interviews, self-administered structured questionnaires, or both with the reference time for cohort studies as the time of enrollment. For this study, we restricted the population to CRC cases who all had available data on genotyping, epidemiologic factors, and CRC survival outcomes, and were of European genetic ancestry. The final study population for the analysis of CRP-levels related gene variants and CRC mortality consisted of 16,142 CRC cases after

excluding cases with non-European ancestry or extreme low BMI (BMI<18.5 kg/m^2). For the analyses of gene x environment interactions, we only included individuals with complete data of the specific lifestyle factor (i.e., BMI, ever smoking, and alcohol consumption).

Genotype data

Details of genotyping and quality control (QC) methods have been reported previously [37]. Briefly, genomic DNA was extracted from blood or buccal samples using conventional methods. Genotyping was performed using several platforms (Supplementary Table 1). All genotype data underwent standardized QC procedures, such as exclusion of samples and variants with low call rates (<98%), variants in regions with chromosomal anomalies, samples with discrepant self-reported vs. genetic sex, and variants departing from Hardy–Weinberg Equilibrium ($P < 10^{-4}$). To investigate population structure, PLINK (v1.9) was used for principal components analysis (PCA) [38]. We restricted analyses to participants of European genetic ancestry based on PCA. The first three eigenvectors explained 46% of the genetic variation and thus were used as covariates in analysis. Variants were phased using SHAPEIT2 and imputed to the Haplotype Reference Consortium panel using the University of Michigan Imputation Server [39-41]. Genotype probabilities were converted to allelic dosages after imputation.

A total of 781 single nucleotide polymorphisms (SNPs) associated with CRP levels were identified from the National Human Genome Research Institute-European Bioinformatics Institute (NHGRI-EBI) GWAS catalog (October 30, 2020), of which 651 have minor allele frequency >5% in European ancestry. Among those common CRP-related SNPs, 618 were directly genotyped or imputed in our dataset and, therefore, included in analysis (Supplementary Table 2).

Definitions of covariates

Age at diagnosis was ascertained via cancer registries and/or medical records. BMI defined as weight/height^2 was categorized as normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese ($\geq$ 30 kg/m^2). Ever smoking was defined as a binary variable (yes for smokers and former smokers; no for never smokers). Alcohol consumption was categorized as nondrinker (≤1 g/day), moderate drinker (1.01-28 g/day), and heavy drinker (> 28 g/day). A joint variable of study and genotyping platform was created.

Ascertainment of survival outcomes

All study participants were followed up for vital status. For CCFR, CPSII, DACHS, DALS, EDRN, EPIC, MCCS, UKB, and VITAL, date and cause of death were ascertained through linkages to the National Death Index or cancer registries, which link to death certificates. For HPFS, NHS, PHS, PLCO, and WHI, date and cause of death were obtained via active follow-up and verified by death certificates and/or medical records. We computed person-time of follow-up for each participant from the diagnosis of CRC to the date of death, last date of contact, or the end of follow-up. Participants who died from causes other than CRC were censored at the time of death. We used the International Classification of Diseases-9 (ICD-9) or ICD-10 (depending on year of linkage) to define CRC-specific deaths (ICD-9: 153.0-153.4, 153.6-153.9, or 154.0-154.1; ICD-10: C18.0-20.0 or C26.0).

Statistical methods

Statistical analyses were conducted using individual-level data. To evaluate the association of each CRP-related SNP with CRC mortality, we used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Variants were analyzed as continuous variables assuming log-additive effects. We adjusted for age at diagnosis, sex, a joint variable of study and genotyping platform, and the first three principal components.

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Violations of the proportional hazards assumption were evaluated by Schoenfeld residuals [42]. Age at diagnosis (continuous), sex, and the joint variable of study/genotyping platform violated the proportional hazards assumption. To resolve this, models were stratified by age categories (<50, 50-59, 60-69, 70-79, and 80+ years), sex and study/genotyping platform. We used likelihood ratio tests to assess multiplicative gene-environment interactions between CRP-related SNPs and sex, obesity, smoking, or alcohol consumption. Sub-analyses stratifying by these factors were also conducted for SNPs with statistically significant interactions.

To account for multiple comparisons, Pearson correlation coefficients were computed to determine the correlations between every pair of SNPs within the same chromosome, and principal components analysis was performed to obtain the effect number of independent tests (M_{eff_G}). M_{eff_G} of 556 was used for type I error control in Bonferroni correction in single-SNP survival analysis, with $P_{corrected}$ <0.05 considered statistically significant [43]. All statistical tests and *P*-values were two-sided. All analyses were conducted using R 3.6.0.

Results

Participant characteristics are presented in Table 1. Study-specific characteristics are presented in Supplementary Table 1. The mean (standard deviation) age at diagnosis across studies was 66.4 (9.8) years, and 50.3% of participants were male. After a median of 4.7 years (interquartile range = 2.3 to 7.7 years) of follow-up since diagnosis, 5,472 (33.9%) deaths accrued, 3,547 (64.8%) of which were due to CRC.

The main effects of 618 SNPs were not significantly associated with CRC mortality after multiple comparison correction (Supplementary Table 2). One variant, rs4148191 at *ABCG5* gene, was borderline significantly associated with higher CRC-specific mortality (HR = 1.18, 95% CI = 1.08 to 1.29; $P_{corrected}$ = 0.08).

We observed strong evidence of interaction between variant rs1933736 (MAF = 0.42) at *FRK* gene and sex in relation to CRC-specific mortality (corrected $P_{interaction}$ = 0.0004); women had higher CRC-specific mortality associated with the minor allele (HR = 1.11, 95% CI = 1.04 to 1.19) whereas an inverse association was observed for men (HR = 0.88, 95% CI = 0.82 to 0.94) (Table 2 and Supplementary Table 3). The overall association of this variant with CRC-specific mortality was not significant (HR = 0.99, 95% CI = 0.94 to 1.04; $P_{corrected}$ >0.99). There was no evidence of statistically significant interactions between CRP-associated SNPs and alcohol, obesity or smoking in association with CRC-specific mortality (Supplementary Table 4, 5, and 6).

Discussion

To our knowledge, this is the first study evaluating the gene-environment interactions of CRP level-related genetic variants identified by GWAS catalog with sex and lifestyle factors in relation to CRC-specific mortality. We found evidence of a statistically significant interaction between rs1933736 at *FRK* gene and sex. Women with C (vs. T) allele of variant rs1933736 were associated with increased CRC-specific mortality, while an inverse association was observed for men.

Few studies have reported associations of CRP-related variants and CRC survival. Slattery et al. investigated four CRP-related variants, rs1205, rs1417938, rs1800947, and rs3093075, selected based on linkage disequilibrium (LD) (r^2 >0.90) and minor allele frequency > 4%. They did not observe association of these variants with colon or rectal cancer mortality [10]. The variant rs1800947 was the only one that was also investigated by our study, and our results were

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consistent (Supplement Table 2). There is limited evidence for the influence of CRP-related variants on CRC incidence. Slattery et al. reported association of rs1205 with colon cancer incidence and association of rs3093075 with rectal cancer incidence, while no associations of rs1417938 and rs1800947 were observed [10]. Nimptsch et al. analyzed five tagging SNPs to cover variations in CRP gene common to European population, and reported that two CRP-related variants, rs1205 and rs11308864, were associated CRC incidence, while rs1800947, rs3093077 and rs2808630 were not associated with CRC risk [9].

Although no associations were observed for CRP-related SNPs and CRC-specific mortality, we observed an interaction between sex and the variant rs1933736. This genetic variant locates at the intronic region of the gene *FRK,* which is known to negatively regulates cell proliferation and positively regulates PTEN protein stability and may function as a tumor suppressor. Han et al reported that C allele of variant rs1933736 was associated with decreased CRP level [44]. The mechanism of the interaction is unclear. Although we cannot rule out that the interaction may be due to chance, one possible explanation could be the difference in sex hormones-binding globulin levels between women and men. CRP concentrations are higher in women than men and it is possible that CRP level-related variants have stronger impact on CRP concentrations in women as compared to men [19, 45]. Cross-sectional studies also suggested an inverse association between sex hormone-binding globulin and CRP in men and women [46-49]. In addition, Ruth et al. reported a variant rs1890426 at gene *FRK*, which is in high LD with the variant rs1933736 (r^2=1), was positively associated with sex hormone-binding globulin levels in men while no association was observed in women of European ancestry [50], which further supports this hypothesis.

Our study has several strengths. First, our large sample size facilitated examination of gene-environment interactions. Second, we standardized and harmonized environmental data, and thus bias attributable to heterogeneity in the definitions of environmental variables is likely to be minimal. Moreover, we had a relatively long follow-up period and cause of death was verified, reducing information bias.

We acknowledge some limitations. First, we only analyzed 618 out of 651 CRP-related SNPs identified by GWAS catalog due to lack of data. Thus, some influential SNPs may have been omitted. Second, we had some missing data on smoking and alcohol consumption slightly reducing our ability to exam those factors. However, the proportions of missing data (2.9% for smoking and alcohol consumption) were small and unlikely to bias our results. In addition, our findings have not been replicated due to lack of a replication cohort. Lastly, although our sample size was large for our main analysis, some stratified analyses for rare variants may be underpowered. Although we used conservative approach to correct for multiple comparisons in our GxE analysis, it is possible that our finding on the interaction between SNP rs1933736 and sex may be due to chance.

In summary, we found that 618 CRP-associated variants were not associated with CRC-specific mortality after correcting for multiple comparisons. However, we observed an interaction between the variant rs1933736 and sex. Although further validation is needed, these findings may provide novel insights for strategies of improving CRC prognosis in population subgroups. Validation in additional populations and investigation of the biological function of this SNP in relation to CRC are needed.

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Conflict of Interest: The authors declare no potential conflicts of interest.

Data Availability Statement
The summary statistics of the 618 common CRP-related SNPs analyzed in this study are listed in Supplementary Table 2. Further data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Statement
All participants provided written or oral informed consent, and studies were reviewed and approved by their respective institutional review boards or ethics committees.

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Novelty and Impact:

Chronic inflammation is strongly associated with colorectal cancer (CRC). C-reactive protein (CRP) is a sensitive marker of this type of inflammation, and may be associated with poor prognosis. In this large genetic study, the authors found that none of over 600 CRP-associated SNPs were associated with CRC-specific mortality. However, they did identify a genetic variant of the FRK gene that may affect levels of CRP. This variant was associated with increased CRC mortality in women, while it showed the opposite effect in men. These findings may provide novel insights for improving CRC prognosis.

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Table 1. Baseline characteristics of Study Participants[a]

Variables		Number of colorectal cancer cases, N (%) (n=16142)	Number of colorectal cancer deaths, N (%) (n=3547)
Age at diagnosis, years, mean (SD)		66.4 (9.8)	66.6 (10.0)
Age at diagnosis, years			
	<50	890 (5.5)	197 (5.6)
	50-59	2598 (16.1)	591 (16.7)
	60-69	6267 (38.8)	1296 (36.5)
	70-79	5146 (31.9)	1147 (32.3)
	80+	1241 (7.7)	316 (8.9)
Male		8125 (50.3)	1798 (50.7)
Body Mass Index			
	Normal	5189 (32.1)	1137 (32.1)
	Overweight	7041 (43.6)	1494 (42.1)
	Obese	3912 (24.2)	916 (25.8)
Ever smoker			
	No	6940 (43.0)	1527 (43.1)
	Yes	8732 (54.1)	1897 (53.5)
	Missing	470 (2.9)	123 (3.5)
Alcohol consumption			
	Nondrinker (0-1 g/day)	5580 (34.6)	1350 (38.1)
	Moderate drinker (1.01-28 g/day)	7643 (47.3)	1561 (44.0)
	Heavy drinker (>28 g/day)	2449 (15.2)	553 (15.6)
	Missing	470 (2.9)	83 (2.3)

SD = Standard Deviation

[a] Age at diagnosis, sex, body mass index, ever smoking, and alcohol consumption, were measured by in-person or phone interviews, structured questionnaires, or both with the reference time for cohort studies as the time of enrollment.

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Table 2. HR and 95% CI for the association between SNP rs1933736 and CRC-specific mortality, stratified by sex

SNP	Gene	CA/RA	CAF	HR (95% CI)[a] Female	HR (95% CI)[a] Male	$P_{interaction}$	Corrected $P_{interaction}$[b]
rs1933736	*FRK*	C/T	0.42	1.11 (1.04, 1.19)	0.88 (0.82, 0.94)	8.00×10^{-7}	0.0004

SNP = Single-Nucleotide Polymorphisms; CA = Coded Allele; RA = Reference Allele; CAF = Coded Allele Frequency; HR = Hazard Ratio; CI = Confidence Interval; CRC = Colorectal Cancer.

[a] Adjusted for age at diagnosis categories, genotyping platform/study, and the first three principal components.

[b] *P* values were adjusted using Bonferroni method using M_{eff_G}.

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