Genetically Predicted Circulating C-Reactive Protein Concentration and Colorectal Cancer Survival: A Mendelian Randomization Consortium Study

Xinwei Hua[1,2], James Y. Dai[1,2], Sara Lindström[1,2], Tabitha A. Harrison[1], Yi Lin[1], Steven R. Alberts[3], Elizabeth Alwers[4], Sonja I. Berndt[5], Hermann Brenner[4,6,7], Daniel D. Buchanan[8,9,10], Peter T. Campbell[11], Graham Casey[12], Jenny Chang-Claude[13,14], Steven Gallinger[15], Graham G. Giles[16,17,18], Richard M. Goldberg[19], Marc J. Gunter[20], Michael Hoffmeister[4], Mark A. Jenkins[17], Amit D. Joshi[21,22], Wenjie Ma[22,23], Roger L. Milne[16,17,18], Neil Murphy[20], Rish K. Pai[24], Lori C. Sakoda[1,25], Robert E. Schoen[26], Qian Shi[27], Martha L. Slattery[28], Mingyang Song[22,23,29,30], Emily White[1,2], Loic Le Marchand[31], Andrew T. Chan[30,32,33], Ulrike Peters[1,2], and Polly A. Newcomb[1,2]

ABSTRACT

Background: A positive association between circulating C-reactive protein (CRP) and colorectal cancer survival was reported in observational studies, which are susceptible to unmeasured confounding and reverse causality. We used a Mendelian randomization approach to evaluate the association between genetically predicted CRP concentrations and colorectal cancer–specific survival.

Methods: We used individual-level data for 16,918 eligible colorectal cancer cases of European ancestry from 15 studies within the International Survival Analysis of Colorectal Cancer Consortium. We calculated a genetic-risk score based on 52 CRP-associated genetic variants identified from genome-wide association studies. Because of the non-collapsibility of hazard ratios from Cox proportional hazards models, we used the additive hazards model to calculate hazard differences (HD) and 95% confidence intervals (CI) for the association between genetically predicted CRP concentrations and colorectal cancer–specific survival, overall and by stage at diagnosis and tumor location. Analyses were adjusted for age at diagnosis, sex, body mass index, genotyping platform, study, and principal components.

Results: Of the 5,395 (32%) deaths accrued over up to 10 years of follow-up, 3,808 (23%) were due to colorectal cancer. Genetically predicted CRP concentration was not associated with colorectal cancer–specific survival (HD, −1.15; 95% CI, −2.76 to 0.47 per 100,000 person-years; $P = 0.16$). Similarly, no associations were observed in subgroup analyses by stage at diagnosis or tumor location.

Conclusions: Despite adequate power to detect moderate associations, our results did not support a causal effect of circulating CRP concentrations on colorectal cancer–specific survival.

Impact: Future research evaluating genetically determined levels of other circulating inflammatory biomarkers (i.e., IL6) with colorectal cancer survival outcomes is needed.

[1]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Washington. [2]University of Washington, Seattle, Washington. [3]Division of Medical Oncology, Mayo Clinic, Rochester, Minnesota. [4]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany. [5]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland. [6]Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany. [7]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany. [8]Department of Clinical Pathology, Colorectal Oncogenomics Group, The University of Melbourne, Parkville, Victoria, Australia. [9]University of Melbourne Center for Cancer Research, Victorian Comprehensive Cancer Center, Parkville, Victoria, Australia. [10]Genomic Medicine and Family Cancer Clinic, The Royal Melbourne Hospital, Parkville, Victoria, Australia. [11]Department of Population Science, American Cancer Society, Atlanta, Geogia. [12]Center for Public Health Genomics, University of Virginia, Charlottesville, Virginia. [13]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany. [14]University Medical Center Hamburg-Eppendorf, University Cancer Center Hamburg, Hamburg, Germany. [15]Lunenfeld Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada. [16]Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Victoria, Australia. [17]Center for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia. [18]Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia. [19]West Virginia University Cancer Institute, Morgantown, West Virginia. [20]Nutrition and Metabolism Section, International Agency for Research on Cancer, World Health Organization, Lyon, France. [21]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Harvard University, Boston, Massachusetts. [22]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts. [23]Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts. [24]Department of Laboratory Medicine and Pathology, Mayo Clinic, Scottsdale, Arizona. [25]Division of Research, Kaiser Permanente Northern California, Oakland, California. [26]Department of Medicine and Epidemiology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania. [27]Department of Health Science Research, Mayo Clinic, Rochester, Minnesota. [28]Department of Internal Medicine, University of Utah, Salt Lake City, Utah. [29]Department of Nutrition, Harvard T.H. Chan School of Public Health, Harvard University, Boston, Massachusetts. [30]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts. [31]Epidemiology Program, University of Hawaii Cancer Center, Honolulu, Hawaii. [32]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts. [33]Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Current address for X. Hua: Clinical and Translational Epidemiology Unit and Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts.

Corresponding Author: Polly A. Newcomb, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, M4-B402, Seattle, WA 98109. E-mail: pnewcomb@fredhutch.org

Cancer Epidemiol Biomarkers Prev 2021;30:1349–58

doi: 10.1158/1055-9965.EPI-20-1848

Introduction

Chronic inflammation plays an important role in colorectal cancer development and progression (1). Elevated level of inflammation after colorectal cancer diagnosis may lead to increased expression of proinflammatory mediators and promote tumor growth and progression (2).

C-reactive protein (CRP) is an abundant acute-phase protein produced mainly by hepatocytes in response to pro-inflammatory cytokines (3). Observational studies of colorectal cancer outcomes have reported positive associations between prediagnostic and preoperative concentrations of CRP and larger tumor size, metastases, and survival (4–8). These studies, however, may have been subject to bias as most were unadjusted or insufficiently adjusted for potential confounders and factors related to inflammation and survival, such as adiposity, use of NSAIDs, and smoking. Furthermore, disease progression itself could lead to enhanced tumor-associated inflammation and elevated concentrations of circulating pro-inflammatory markers. Thus, reverse causation is also a potential source of bias.

Most studies of CRP and colorectal cancer only had a single measurement of CRP, which may not represent lifelong levels of chronic inflammation. Mendelian randomization uses inherited germline genetic markers known to be associated with the risk factor of interest, in this case circulating CRP concentrations. These genetic variants can serve as non-modifiable markers of long-term susceptibility to chronic inflammation. Because of the natural random assortment of alleles during gamete formation, genetic variants are not affected by environmental factors that occur after conception and are non-modifiable by disease progression (9). Over the last of 15 years, genome-wide association studies (GWAS) have accumulated robust evidence on genetic variants associated with various inflammatory biomarkers, including CRP (10, 11). "Mendelian randomization" has become a common approach for observational studies of inflammatory biomarkers in association with cancer risk, providing a way to minimize reverse causality and residual confounding. However, Mendelian randomization studies of inflammatory biomarkers and cancer survival are scarce (12).

In this study, we aimed to test the association of genetically predicted concentrations of CRP with colorectal cancer–specific survival using a Mendelian randomization approach. As a secondary aim, we evaluated stage- and tumor site–specific associations between genetically predicted circulating CRP concentration and colorectal cancer survival. To achieve this, we used the existing data on germline genetic variants and epidemiological and clinical factors from the International Survival Analysis in Colorectal Cancer Consortium (ISACC).

Materials and Methods

Study sample

We included individuals diagnosed with incident, invasive colorectal cancer from ISACC, a consortium consisting of clinical trials, case–control, and cohort studies from North America, Europe, and Australia. Of the 26,282 eligible ISACC participants who had GWAS and survival data available (**Fig. 1**), we excluded individuals whose GWAS data did not pass QC (n = 1,154), whose epidemiologic data were not available (n = 217), and those with non-European

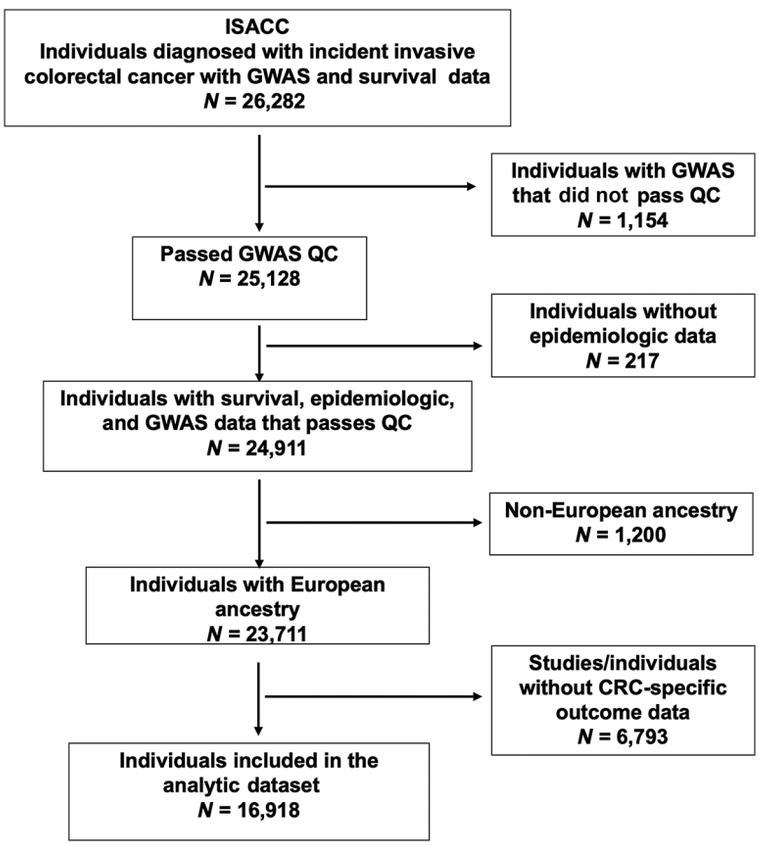

Figure 1.
Study sample diagram. Of the 26,282 eligible ISACC participants with both GWAS and survival data, we further excluded individuals based on GWAS QC, genetic ancestry, availability of epidemiologic data, and disease-specific survival outcomes, leaving a total of 16,918 subjects included in the analysis.

ancestry ($n = 1,200$) for this analysis. Further exclusion of studies and individuals without data on colorectal cancer–specific survival outcome ($n = 6,793$) resulted in a total of 16,918 subjects included in these analyses from the following 15 studies: Colon Cancer Family Registry (CCFR; ref. 13), Cancer Prevention Study-II (CPS-II; ref. 14), German Darmkrebs: Chancen der Verhütung Durch Screening (DACHS; ref. 15), Diet Activity and Lifestyle Study (DALS; ref. 16), Early Detection Research Network (EDRN; ref. 17), European Prospective Investigation into Cancer (EPIC; ref. 18), Health Professionals Follow-up Study (HPFS; ref. 19), Melbourne Collaborative Cohort Study (MCCS; ref. 20), Nurses' Health Study (NHS; ref. 21), North Central Cancer Treatment Group (NCCTG) N9741 randomized trial (ClinicalTrials.gov Identifier: NCT00003594; ref. 22), Physician's Health Study (PHS; ref. 23), Prostate, Lung, Colorectal, and Ovarian Study (PLCO; ref. 24), UK Biobank (UKB; ref. 25), VITamins And Lifestyle Study (VITAL; ref. 26), and Women's Health Initiative (WHI; ref. 27). Study-specific details are summarized in Supplementary Table S1. All studies were approved by their respective Institutional Review Boards and participants provided written informed consent.

Ascertainment of environmental variables and survival outcomes

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 to define epidemiologic and clinicopathological variables in the same way across studies, as described previously (28). Information on cancer diagnosis, such as age at diagnosis, tumor location (proximal, distal colon, or rectum), and stage at diagnosis [local: American Joint Committee of Cancer (AJCC) stage I; regional: AJCC stage II/III; or distant: AJCC stage IV], was obtained from cancer registries and/or medical records.

All study participants were followed for vital status. Date and cause of death were ascertained through linkages to the National Death Index or cancer registries (CCFR, CPSII, DACHS, DALS, EPIC, MCCS, UKB, VITAL) or via active follow-up with dates/cause of death verified by the review of death certificates and/or medical records (HPFS, NHS, PHS, PLCO, WHI, N9741). Time to event was defined as days between colorectal cancer diagnosis and death, last date of contact, or the end of study follow-up. To evaluate 10-year colorectal cancer–specific survival, we censored cases at 10 years from the date of colorectal cancer diagnosis. Cases who died from causes other than colorectal cancer within 10 years from diagnosis 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 colorectal cancer–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).

Genotyping, quality control, and imputation

Details of genotyping and quality control (QC) methods have been reported previously (29–33). Briefly, genomic DNA was extracted from blood or buccal samples using conventional methods. Genotyping was performed using multiple platforms (Supplementary Table S1). All genotype data underwent standardized QC procedures, including the exclusion of samples and SNPs with low call rates (<98%), chromosomal anomalies, samples with discrepancies in self-reported and genetically determined sex, and SNPs out of Hardy–Weinberg Equilibrium. To investigate population structure, we used Plink (v1.9) to conduct principal components analysis (PCA). We restricted our analytic sample to participants with estimated European ancestry based on the PCA due to the low numbers of participants of other ancestries (detailed in Supplementary Methods). We imputed genotypes to infer unobserved genotypes and increase the density of genetic variants. All samples were first phased using SHAPEIT2 (34) and imputed to the Haplotype Reference Consortium (HRC) panel (35) using the University of Michigan Imputation Server (36).

Selection of instrumental variables

The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) is the largest GWAS of circulating CRP concentrations to date, analyzing 204,402 individuals of European descent (11). It reported 48 lead genetic variants from the HapMap GWAS and four additional variants from the 1000 Genome GWAS that were associated with CRP at the genome-wide statistical significance ($P < 5 \times 10^{-8}$). Together these 52 SNPs explained 6.5% of the variance in circulating CRP (11).

We also searched for, but did not identify additional variants from the NHGRI-EBI GWAS Catalog (ref. 37; downloaded on 03/09/20) that met the following criteria: (i) association with CRP at a genome-wide statistical significance level ($P < 5 \times 10^{-8}$); (ii) study population of European ancestry; (iii) not in LD ($R^2 < 0.3$) with previously selected SNPs; and (iv) available information on effect sizes and standard errors.

We included the 52 variants as instrumental variables in our Mendelian randomization analyses. The imputation quality (r^2) of all 52 CRP-associated SNPs in our data was greater than 0.8. We then calculated a 52-SNP genetic-risk score (GRS; ref. 38) by taking the sum of the number of risk (CRP-increasing) alleles for each of the 52 genetic variants weighted by the β coefficients reported by the CHARGE study (11). The β coefficients represent the change in the natural log-transformed CRP per copy increment in the risk allele (**Table 1**).

Statistical analysis

The genetic variants selected as an instrumental variable in a Mendelian randomization analysis need to meet three assumptions: (i) they are robustly associated with the exposure ("relevance"), (ii) they do not share a common cause with the outcome ("exchangeability"), and (iii) they affect the outcome only through the exposure ("exclusion restriction").

We first verified the "relevance" assumption by evaluating the association between GRS and post-diagnosis circulating CRP concentrations in a subset of colorectal cancer cases from Seattle CCFR ($n = 285$) whose CRP levels were measured in between one to three years after diagnosis to rule out active treatment effects (39). We estimated the proportion of variance (R^2) explained by the 52 genetic variants and calculated the F statistic, a measure of instrument strength, based on R^2, the sample size (n), and the number of instruments (k) as described in the formula: $F = \frac{R^2}{R^2+1} * \frac{n-k-1}{k}$. A strong instrumental variable is defined as having $F \geq 10$ (40).

For the second "exchangeability" assumption, we examined several epidemiologic and clinicopathological factors that may confound the CRP-survival association, including smoking, body mass index (BMI), NSAID use, tumor location, and stage at diagnosis. Each was assessed for association with the GRS. BMI was statistically significantly associated with the GRS, and therefore it was included as an additional adjustment variable in the following Mendelian randomization analysis. No other variables were statistically significantly associated with GRS.

The "exclusion restriction" assumption was assessed in a series of sensitivity analyses. We used MR-Egger regression to assess the

Table 1. Associations of SNPs with circulating CRP concentrations and with colorectal cancer–specific survival in ISACC.

				Ligthart et al. SNP–CRP associations			ISACC SNP-survival associations		
rs	chr: pos[a]	Count/ Alternative allele	Count allele freq	beta[b]	se	*P*	HD[c] (per 100,000 person year)	se	*P*
rs2293476	1:40036847	C/G	0.23	0.030	0.004	8.27E−13	0.124	3.44E−06	0.72
rs1805096	1:66102257	G/A	0.62	0.104	0.004	2.17E−183	−0.121	2.99E−06	0.68
rs4129267	1:154426264	C/T	0.61	0.088	0.004	1.20E−129	−0.474	2.91E−06	0.10
rs2794520	1:159678816	C/T	0.66	0.182	0.004	4.17E−523	−0.049	3.17E−06	0.88
rs10925027	1:247612562	T/C	0.40	0.036	0.004	4.25E−21	−0.759	2.92E−06	0.01
rs1260326	2:27730940	T/C	0.41	0.073	0.004	2.72E−92	0.278	2.95E−06	0.35
rs13409371	2:113838145	A/G	0.39	0.048	0.004	5.07E−36	−0.209	2.91E−06	0.47
rs13233571	7:72971231	C/T	0.88	0.057	0.005	2.95E−25	−0.180	4.22E−06	0.67
rs4841132	8:9183596	G/A	0.92	0.065	0.006	2.00E−25	0.442	5.40E−06	0.41
rs10778215	12:103537266	T/A	0.52	0.033	0.004	1.86E−20	−0.222	2.87E−06	0.44
rs7310409	12:121424861	G/A	0.60	0.137	0.004	2.54E−299	0.105	2.88E−06	0.71
rs340005	15:60878030	A/G	0.63	0.030	0.004	1.01E−15	0.352	2.92E−06	0.23
rs10521222	16:51158710	C/T	0.95	0.104	0.011	2.06E−22	−1.450	6.99E−06	0.04
rs2852151	18:12841176	A/G	0.40	0.025	0.004	1.36E−11	−0.002	2.94E−06	0.99
rs4420638	19:45422946	A/G	0.83	0.229	0.006	1.23E−305	−0.425	4.16E−06	0.31
rs1800961	20:43042364	C/T	0.97	0.112	0.011	4.63E−23	−0.742	8.51E−06	0.38
rs469772	1:91530305	C/T	0.81	0.031	0.005	5.54E−12	0.242	3.60E−06	0.50
rs12995480	2:629881	C/T	0.83	0.031	0.005	1.24E−10	0.329	3.92E−06	0.40
rs4246598	2:88438050	A/C	0.46	0.022	0.004	5.11E−10	−0.200	2.89E−06	0.49
rs9284725	2:102744854	C/A	0.24	0.027	0.004	7.34E−11	−0.434	3.36E−06	0.20
rs1441169	2:214033530	A/G	0.47	0.025	0.004	2.27E−11	−0.130	2.81E−06	0.64
rs2352975	3:49891885	C/T	0.31	0.025	0.004	6.43E−10	0.161	3.27E−06	0.62
rs17658229	5:172191052	C/T	0.04	0.056	0.010	5.50E−09	−0.274	6.67E−06	0.68
rs9271608	6:32591588	G/A	0.17	0.042	0.005	2.33E−17	0.094	4.15E−06	0.82
rs12202641	6:116314634	C/T	0.60	0.023	0.004	3.00E−10	0.187	2.94E−06	0.53
rs1490384	6:126851160	C/T	0.49	0.025	0.004	2.65E−12	0.175	2.83E−06	0.54
rs9385532	6:130371227	C/T	0.66	0.026	0.004	1.90E−11	−0.403	3.25E−06	0.21
rs1880241	7:22759469	A/G	0.51	0.028	0.004	8.41E−14	−0.313	2.90E−06	0.28
rs2710804	7:36084529	C/T	0.37	0.021	0.004	1.30E−08	0.298	2.91E−06	0.31
rs2064009	8:117007850	T/C	0.58	0.027	0.004	2.28E−14	−0.697	3.03E−06	0.02
rs2891677	8:126344208	T/C	0.54	0.020	0.004	1.59E−08	0.212	3.00E−06	0.48
rs643434	9:136142355	A/G	0.37	0.023	0.004	1.02E−09	−0.041	3.05E−06	0.89
rs1051338	10:91007360	G/T	0.30	0.024	0.004	2.27E−09	0.514	3.14E−06	0.10
rs10832027	11:13357183	A/G	0.67	0.026	0.004	4.43E−12	−0.394	2.96E−06	0.18
rs10838687	11:47312892	T/G	0.79	0.031	0.004	9.12E−13	0.016	3.39E−06	0.96
rs1582763	11:60021948	G/A	0.63	0.022	0.004	2.37E−09	−0.083	2.97E−06	0.78
rs7121935	11:72496148	G/A	0.62	0.022	0.004	5.28E−09	0.090	3.04E−06	0.77
rs11108056	12:95855385	C/G	0.58	0.028	0.004	5.42E−14	0.318	3.02E−06	0.29
rs2239222	14:73011885	G/A	0.37	0.035	0.004	9.87E−20	0.415	3.15E−06	0.19
rs4774590	15:51745277	G/A	0.62	0.022	0.004	2.71E−08	0.110	3.07E−06	0.72
rs1558902	16:53803574	A/T	0.40	0.034	0.004	5.20E−20	0.030	2.84E−06	0.92
rs178810	17:16097430	T/C	0.56	0.020	0.004	2.95E−08	−0.060	2.83E−06	0.83
rs10512597	17:72699833	C/T	0.80	0.037	0.005	4.44E−14	−0.048	3.87E−06	0.90
rs4092465	18:55080437	G/A	0.62	0.027	0.004	3.11E−10	−0.154	3.11E−06	0.62
rs12960928	18:57897803	C/T	0.26	0.024	0.004	1.91E−09	−0.296	3.34E−06	0.38
rs2315008	20:62343956	G/T	0.68	0.023	0.004	5.36E−10	0.118	3.11E−06	0.70
rs2836878	21:40465534	G/A	0.73	0.043	0.004	7.71E−26	0.289	3.10E−06	0.35
rs6001193	22:39074737	A/G	0.63	0.028	0.004	6.53E−14	−0.678	3.10E−06	0.03
rs75460349	1:27180088	A/C	0.98	0.086	0.014	4.50E−10	0.477	9.43E−06	0.61
rs1514895	3:170705693	G/A	0.30	0.027	0.004	2.70E−09	0.002	3.26E−06	0.99
rs112635299	14:94838142	G/T	0.98	0.107	0.017	2.10E−10	−2.150	1.22E−05	0.08
rs1189402	15:53728154	A/G	0.63	0.025	0.004	3.90E−09	0.474	3.20E−06	0.14

Abbreviations: ISACC, the International Survival Analysis in Colorectal Cancer Consortium; HD, hazards difference; se, standard error.

[a]Chromosome: position, hg19.

[b]Beta, SNP-specific coefficients for association with circulating concentrations of CRP obtained from Ligthart et al (11), per unit increase in natural log-transformed CRP (mg/L).

[c]Hazards difference for colorectal cancer–specific survival per unit increase in the count allele based on additive hazards model.

horizontal pleiotropic effect. The test of a non-zero intercept indicates whether there are averaged pleiotropic effects (41). We also restricted the instrumental variable to rs2794520 in the *CRP* gene to minimize the probability of horizontal pleiotropy. This variant itself explained 1.4% of the variance in circulating CRP (11).

We performed the Mendelian randomization analyses using a two-stage regression approach (42). Additive hazards model offers a flexible alternative for modeling associations on the hazard scale: A hazard difference (HD), unlike the hazard ratio (HR) from the Cox proportional hazards model, is a collapsible effect measure over strata of unmeasured and unknown confounders (42, 43). We used additive hazards models to calculate HD and 95% confidence intervals (CI) for the associations between CRP-associated GRS and colorectal cancer–specific survival. The R package "timereg" was used for fitting additive hazards models (44).

We also evaluated the association between genetically determined CRP-circulating concentration and colorectal cancer–specific survival using the inverse-variance weighted (IVW) method (45), MR-Egger regression (41), and the estimator from the weighted median approach (46) based on summary statistics on SNP-specific associations with colorectal cancer survival. In secondary analyses, we evaluated the associations between genetically predicted concentrations of CRP and colorectal cancer–specific survival according to tumor stage and location.

In the sensitivity analyses, Cox proportional hazards models were used for hypothesis testing. We also compared results with and without adjustment of BMI in addition to age at diagnosis, sex, genotyping platform, study, and the first nine principal components. All analyses were conducted using R version 3.6.0.

Currently, there is no available power calculation tool for survival outcomes in Mendelian randomization analysis, we first took a conservative approach treating colorectal cancer–specific survival as a binary outcome and used the methods described by Burgess (47). With a total of 16,916 colorectal cancer cases and 23% colorectal cancer–specific deaths occurring over up to 10 years follow-up, we have more than 85% power to detect an OR of 1.25 for the association between CRP and colorectal cancer–specific survival at a significance level of 0.05, assuming 5.9% variance of CRP explained by the genetic variance.

In addition, we ran a simulation using the additive hazards model for power calculation. With the number of colorectal cancer cases and 3,808 colorectal cancer–related deaths accrued over a 10-year follow-up, the population-averaged hazard was estimated to be $3{,}808/(16{,}918 \times 10) = 0.023$ per person $\times$ year. We have at least 83% power to detect a 25% difference in hazard (HD, 0.0058) for every 1 SD increase of CRP assuming 5.9% of the variance of CRP was explained by GRS. The R code for the simulation is included in the Supplementary Materials.

Results

We included 16,918 eligible colorectal cancer cases from ISACC in this study (**Fig. 1**). Study participants were diagnosed at a median of 67 years of age, and 49.7% were female. Over the maximum 10-year follow up, there were 5,395 (32%) deaths accrued with 3,808 (23%) due to colorectal cancer. Study-specific summaries are shown in Supplementary Table S1. SNP-specific associations with circulating CRP concentrations and colorectal cancer–specific survival are summarized in **Table 1**.

In evaluating the "relevance" assumption, we observed strong associations between the GRS and circulating CRP concentrations in a subset of the study participants ($n = 285$). A 1 U increase in GRS was associated with a 1.22 U increase in the natural log-transformed CRP (95% CI, 0.65–1.80; $P = 4.33 \times 10^{-5}$) and explained 5.9% of the variance of the natural log-transformed CRP concentrations. The estimated F statistic was 20.2, indicating a strong instrumental variable.

Among the 16,918 participants from ISACC, the distribution of the CRP-associated GRS calculated on the basis of individual-level data is shown in Supplementary Fig. S2. On basis of additive hazards model, we observed that 1 U increase in GRS was associated with 1.15 fewer deaths due to colorectal cancer per 100,000 patients each year (HD, −1.15; 95% CI, −2.76 to 0.47 per 100,000 person-year, **Table 2**). However, it did not reach statistical significance ($P = 0.16$). No

Table 2. Association between genetically determined CRP concentrations and colorectal cancer–specific survival.

	Additive hazards model		Cox proportional hazards model	
	HD (95% CI) per 100,000 person-years	*P*	HR (95% CI)	*P*
Using individual-level data				
52-SNP GRS				
Continuous[a]	−1.15 (−2.76–0.47)	0.16	0.90 (0.79–1.02)	0.10
By quartiles				
Q1 (2.05–3.06)	1.00 Ref		1.00 Ref	
Q2 (3.06–3.24)	0.31 (−0.87–1.49)	0.61	1.02 (0.93–1.12)	0.67
Q3 (3.24–3.41)	−0.52 (−1.71–0.68)	0.40	0.96 (0.88–1.05)	0.41
Q4 (3.41–4.08)	−0.73 (−1.87–0.41)	0.21	0.93 (0.85–1.02)	0.14
Using summary statistics				
IVW	−1.12 (−2.72–0.48)	0.17	0.90 (0.79–1.02)	0.10
MR-Egger	−1.29 (−3.68–1.11)	0.29	0.88 (0.72–1.06)	0.18
Weighted median	−0.77 (−3.02–1.47)	0.50	0.93 (0.77–1.11)	0.40

Note: All models adjusted for age at diagnosis, sex, body mass index, genotyping platform, study and principal components.
Abbreviations: CI, confidence interval; GRS, genetic-risk score; HD, hazard difference; HR, hazard ratio; IVW, inverse-variance weighted; MR, Mendelian randomization.
[a]Per one-unit increment in GRS.

associations between quartiles of GRS and colorectal cancer–specific survival were observed (**Table 2**). Results based on IVW, MR-Egger, and weighted median approaches using summary statistics were consistent with those based on individual GRS data (**Table 2**). Sensitivity analyses using Cox proportional hazards models for hypothesis testing showed similar null associations between GRS and colorectal cancer–specific survival (HR, 0.90; 95% CI, 0.79–1.02; $P = 0.10$, **Table 2**).

We further evaluated this association by stage at diagnosis and tumor location, and found no evidence of statistically significant association in these subgroup analyses using Cox proportional hazards models, whereas the additive hazards model did not converge due to limited number of events in subgroups (**Table 3**). Among individuals diagnosed with colon cancer, we observed a borderline significant association: 1 U increase in GRS was associated with improved colorectal cancer–specific survival (HR, 0.87; 95% CI, 0.75–1.00; $P = 0.06$; **Table 3**).

We plotted the SNP-specific associations with colorectal cancer–specific survival against coefficients of SNP–CRP associations (**Fig. 2**). After conducting MR-Egger regression analysis, we found that the intercept was not statistically significantly different from zero ($\beta_0 = 1.28 \times 10^{-7}$; 95% CI, -1.23×10^{-6} to 1.48×10^{-6}; $P = 0.85$) when using additive hazards models. This suggested no horizontal pleiotropic effect. The MR-Egger regression using Cox proportional hazards estimates (**Fig. 2B**) yielded similar results compared with the one using additive hazards models (**Fig. 2A**). We then restricted the instrumental variable to rs2794520 in the *CRP* gene and repeated the Mendelian randomization analysis. A null association with colorectal cancer survival was observed (additive hazards model: HD, −0.049 per 100,000 person-year; $P = 0.88$; Cox proportional hazards model: HR, 0.99; 95% CI, 0.94–1.04; $P = 0.60$).

Discussion

In this large Mendelian randomization study, we did not find evidence of an association between genetically predicted CRP-circulating concentration and colorectal cancer–specific survival in a cohort of individuals diagnosed with incident invasive colorectal cancer and followed up for survival. No associations were observed in subgroups defined by tumor stage at diagnosis and location. Our findings do not support a causal relationship between circulating CRP and colorectal cancer–specific survival.

Previous studies of CRP and colorectal cancer incidence and survival do not provide convincing evidence of causation. For colorectal cancer risk, meta-analyses of prediagnostic circulating CRP concentrations showed that a 1-unit change in natural logarithm CRP was associated with a 12% increased risk of developing colorectal cancer (48). Conversely, we showed in a large multi-consortium Mendelian randomization study with more than 30,400 cases and 22,800 controls no association between genetically determined CRP concentrations and colorectal cancer risk (49). For colorectal cancer–specific survival, results from observational studies of circulating CRP concentration were inconsistent. Some studies observed that circulating CRP concentration measured before surgery was not statistically significantly associated with survival after multivariable adjustment (7, 8). Other studies observed that elevated concentrations of pre-operative (4–6, 50) and post-treatment (51, 52) CRP were associated with worse colorectal cancer survival outcomes. However, the CRP measures in these studies were crude. Several of these studies used CRP ≥10 mg/L as the cutoff to dichotomize circulating CRP concentrations (4, 5, 50). Elevated CRP concentrations ≥10 mg/L are likely driven by acute inflammatory conditions other than chronic inflammation. Similarly, in our recent study, circulating concentration of CRP was no longer associated with colorectal cancer survival after we excluded colorectal cancer cases who had post-treatment CRP >10 mg/L (39).

In this study, we used genetic variants as proxies of circulating CRP concentrations that can help address potential biases due to residual confounding and reverse causality, but existing evidence on colorectal cancer survival outcomes is limited. Slattery and colleagues (53) evaluated four tag SNPs in the *CRP* gene in relation to colorectal cancer survival among 1,574 cases; however, none were statistically significantly associated with colorectal cancer–specific survival within 5 years after diagnosis. Another study with 421 colorectal cancer cases of East Asian ancestry showed that two SNPs from the *CRP* gene were associated with colorectal cancer survival: rs3093059 was associated with disease-free survival, whereas rs1205 was associated with colorectal cancer–specific survival (54). Although these two variants were

Table 3. Association between genetically determined CRP concentrations and colorectal cancer–specific survival, by subgroups.

			Cox proportional hazards model	
52-SNP GRS	**Total**	**Events[a]**	**HR (95% CI)[b]**	***P***
All	16,918	3,808	0.90 (0.79–1.02)	0.10
By stage at diagnosis[c]				
Local	3,341	142	0.50 (0.24–1.02)	0.06
Regional	6,420	1,177	0.92 (0.73–1.17)	0.51
Distant	1,845	1,387	0.97 (0.75–1.24)	0.79
By tumor location[d]				
Colon	12,000	2,791	0.87 (0.75–1.00)	0.06
Proximal	6,205	1,365	0.86 (0.69–1.07)	0.18
Distal	4,879	932	0.98 (0.75–1.29)	0.91
Rectum	4,729	974	1.02 (0.79–1.33)	0.85

Abbreviations: CI, confidence interval; GRS, genetic risk score; HR, hazard ratio; AJCC, American Joint Committee on Cancer.

[a]Death events due to colorectal cancer within up to 10-year follow-up.

[b]HRs represent per 1-U increase in GRS, and were adjusted for age at diagnosis, sex, body mass index, genotyping platform, study, and principal components; additive models do not converge in subgroup analysis.

[c]Stage at diagnosis was defined using SEER summary stage (local, AJCC stage I; regional, stage II–III; distant, stage IV).

[d]Proximal colon was defined as from the cecum through transverse colon; distal colon was from the splenic flexure to sigmoid colon; rectum included the rectosigmoid junction and rectum.

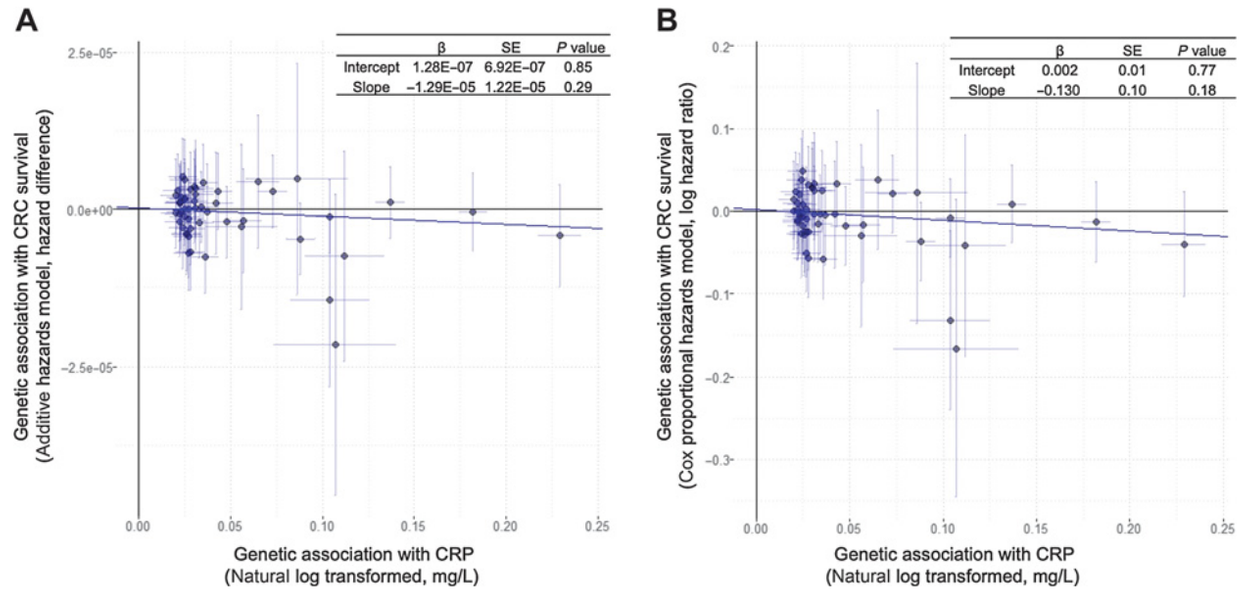

Figure 2.

Scatter plot of SNP-specific associations with colorectal cancer survival against coefficients of SNP–CRP associations among colorectal cancer cases from ISACC using (**A**) additive hazards models and (**B**) Cox proportional hazards models. The slope of the regression line provides an estimate of the association between genetically predicted circulating concentration of CRP and colorectal cancer survival; the intercept is an estimate of the average pleiotropic effect across all the genetic variants.

not included in our study, we evaluated rs2794520, at *CRP* locus that is in high LD with these two SNPs. The allele frequencies of these SNPs are twice as common in the East Asian population (ASN) compared with the European population (EUR): rs3093059 (ASN: 0.14; EUR: 0.07), rs2794520, and rs1205 (ASN: 0.60; EUR: 0.31). This could partially explain the different study findings.

There are some limitations when interpreting our study results. First, the restriction of our study sample to individuals diagnosed with colorectal cancer by design could be a potential source of selection bias (also known as collider bias) particularly if CRP is causally associated with increased risk of developing colorectal cancer. By conditioning on the collider-colorectal cancer risk (selecting only colorectal cancer cases into the study sample), it can induce an association between genetic variants and risk factors of colorectal cancer. However, evidence from our previous Mendelian randomization study suggests that CRP is not causally associated with colorectal cancer risk (49). To further address this potential selection bias, we evaluated the associations between the genetic variants with both potential confounders of CRP and colorectal cancer survival associations and common risk factors of colorectal cancer risk. BMI was identified as the only variable being statistically significantly associated with the GRS for CRP in our study sample and was adjusted for in all analyses. However, as BMI is an inheritable trait that shares some genetic susceptibilities with CRP, we also assessed whether there was potential bias due to BMI adjustment (55, 56) and compared main analysis with and without adjustment of BMI (Supplementary Table S2). We observed minimal changes due to BMI adjustment. Second, the 52-SNP GRS for CRP explained only less than 6% of the variance of the natural log-transformed CRP concentrations. The null results of our study cannot rule out a weaker causal effect of CRP on colorectal cancer–specific survival. Third, the genetic variants shown to be robustly associated with circulating CRP were identified from a GWAS based on study sample from the general population. The SNP–CRP associations may be different in a sample of colorectal cancer cases. Although we evaluated the "relevance" assumption in a subset of our study sample and observed a strong association between the CRP-associated GRS and post-diagnostic circulating CRP concentrations among colorectal cancer cases, the small sample size limited the statistical power to evaluate SNP-specific associations with CRP among colorectal cancer cases. In addition, our subgroup analyses had insufficient statistical power even though our main analysis was well powered. The limited number of events in subgroups also led to convergence issues when using the additive hazards model. Finally, because the study sample was limited to individuals with European ancestry, our findings may not be generalizable to other racial/ethnicity groups.

Our study also has many strengths. This is the first study that evaluates circulating biomarkers in relation to colorectal cancer survival using a Mendelian randomization approach. Our large sample size possessed adequate statistical power to detect associations with moderate effect sizes. Also, the well-characterized study sample with individual-level genotype data and detailed information on epidemiologic and clinic factors allowed us to compare study results with those based on summary statistics, to evaluate the "exchangeability" assumptions, and to conduct subgroup analysis by stage at diagnosis and tumor location; however, we were not able to account for several clinical prognostic factors for colorectal cancer survival, such as treatment, due to data availability. A subset of study participants had data on both genotypes and circulating CRP concentrations allowing us to evaluate the "relevance" assumption. By carefully examining the three assumptions, our Mendelian randomization study is less susceptible to confounding and reverse causality compared with observational studies.

In summary, our study did not find evidence of an association between genetically predicted circulating CRP concentration and colorectal cancer–specific survival, overall or in subgroups defined by stage at diagnosis or tumor location. Future research should be

conducted to determine whether other circulating inflammatory biomarkers, such as IL6, are associated with colorectal cancer survival outcomes to better understand chronic inflammation and disease progression among patients with colorectal cancer.

Authors' Disclosures

G. Casey reports grants from NIH during the conduct of the study, as well as grants from NIH outside the submitted work. G.G. Giles reports grants from National Health and Medical Research Council (Australia) during the conduct of the study. R.M. Goldberg reports grants from National Cancer Institute during the conduct of the study, as well as personal fees from Amgen, Taiho, AstraZeneca, Merck, Novartis, Genentech, Adaptimmune, and Bayer outside the submitted work. R.K. Pai reports personal fees from PathAI, Alimentiv Inc., Allergan, Eli Lilly, AbbVie, and Genentech outside the submitted work. L.C. Sakoda reports grants from National Cancer Institute during the conduct of the study, as well as grants from National Cancer Institute outside the submitted work. R.E. Schoen reports grants from NIH during the conduct of the study. Q. Shi reports personal fees from Regeneron Pharmaceuticals, Inc., Chugai Pharmaceutical Co., Ltd., Boehringer Ingelheim Pharmaceuticals, Inc., and Merck & Co.; grants from Roche/Genentech and BMS/Celgene; and personal fees from Yiviva Inc., Johnson & Johnson, and Amgen outside the submitted work. M.L. Slattery reports grants from National Cancer Institute during the conduct of the study. L. Le Marchand reports grants from NCI during the conduct of the study. A.T. Chan reports personal fees from Bayer Pharma AG, Pfizer Inc., and Boehringer Ingelheim outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

X. Hua: Conceptualization, software, formal analysis, visualization, methodology, writing–original draft. **J.Y. Dai:** Conceptualization, methodology, writing–review and editing. **S. Lindström:** Conceptualization, methodology, writing–review and editing. **T.A. Harrison:** Methodology, project administration, writing–review and editing. **Y. Lin:** Data curation, methodology, writing–review and editing. **S.R. Alberts:** Resources, data curation, writing–review and editing. **E. Alwers:** Data curation, writing–review and editing. **S.I. Berndt:** Resources, data curation, writing–review and editing. **H. Brenner:** Resources, data curation, writing–review and editing. **D. D. Buchanan:** Resources, data curation, writing–review and editing. **P.T. Campbell:** Resources, data curation, writing–review and editing. **G. Casey:** Resources, data curation, writing–review and editing. **J. Chang-Claude:** Resources, data curation, writing–review and editing. **S. Gallinger:** Resources, data curation, writing–review and editing. **G.G. Giles:** Resources, data curation, writing–review and editing. **R.M. Goldberg:** Resources, data curation, writing–review and editing. **M.J. Gunter:** Resources, data curation, writing–review and editing. **M. Hoffmeister:** Resources, data curation, writing–review and editing. **M.A. Jenkins:** Resources, data curation, writing–review and editing. **A.D. Joshi:** Methodology, writing–review and editing. **W. Ma:** Methodology, writing–review and editing. **R.L. Milne:** Resources, data curation, writing–review and editing. **N. Murphy:** Methodology, writing–review and editing. **R.K. Pai:** Resources, data curation, writing–review and editing. **L.C. Sakoda:** Resources, data curation, writing–review and editing. **R.E. Schoen:** Resources, data curation, writing–review and editing. **Q. Shi:** Resources, data curation, writing–review and editing. **M.L. Slattery:** Resources, data curation, writing–review and editing. **M. Song:** Methodology, writing–review and editing. **E. White:** Resources, data curation, writing–review and editing. **L. Le Marchand:** Resources, data curation, writing–review and editing. **A.T. Chan:** Resources, funding acquisition, writing–review and editing. **U. Peters:** Resources, supervision, funding acquisition, writing–review and editing. **P.A. Newcomb:** Resources, supervision, funding acquisition, writing–review and editing.

Acknowledgments

ISACC: The authors would like to thank all those at the ISACC Coordinating Center for helping bring together the data and people that made this project possible. This research was funded by in part through National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services (R01 CA176272) and the NIH/NCI Cancer Center Support grant P30 CA015704. Scientific Computing Infrastructure at Fred Hutch funded by ORIP grant S10OD028685. CCFR: The Colon CFR graciously thanks the generous contributions of their 42,505 study participants, dedication of study staff, and the financial support from the U.S. National Cancer Institute, without which this important registry would not exist. CCFR (www.coloncfr.org) is supported in part by funding from the National Cancer Institute (NCI), National Institutes of Health (NIH; award U01 CA167551). The CCFR Set-1 (Illumina 1M/1M-Duo) and Set-2 (Illumina Omni1-Quad) scans were supported by NIH awards U01 CA122839 and R01 CA143247 (to G. Casey). The CCFR Set-3 (Affymetrix Axiom CORECT Set array) was supported by NIH award U19 CA148107 and R01 CA81488 (to SBG). The CCFR Set-4 (Illumina OncoArray 600K SNP array) was supported by NIH award U19 CA148107 and by the Center for Inherited Disease Research (CIDR), which is funded by the NIH to the Johns Hopkins University, contract number HHSN268201200008I. The content of this article does not necessarily reflect the views or policies of the NCI, NIH, or any of the collaborating centers in the Colon Cancer Family Registry (CCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. government, any cancer registry, or the CCFR. SCCFR: The authors would like to thank the study participants and staff of the Seattle Colon Cancer Family Registry and the Hormones and Colon Cancer study (CORE Studies). [OFCCR ARCTIC]: Additional funding for the OFCCR/ARCTIC was through award GL201-043 from the Ontario Research Fund, award 112746 from the Canadian Institutes of Health Research through a Cancer Risk Evaluation (CaRE) Program grant from the Canadian Cancer Society (to S. Gallinger), and through generous support from the Ontario Ministry of Research and Innovation. [SCCFR (Illumina HumanCytoSNP (300k)]: The SCCFR Illumina HumanCytoSNP array was supported through NCI award R01 CA076366 (to P.A. Newcomb). [CCFR Set-1 and/or Set-2 scan (Illumina Human 1M, 1M-Duo, and/or Omni1-Quad)]: The CCFR Set-1 (Illumina 1M/1M-Duo) and Set-2 (Illumina Omni1-Quad) scans were supported by NIH awards U01 CA122839 and R01 CA143247 (to G. Casey). [CCFR Set-3 scan (Affymetrix Axiom CORECT Set array)]: The CCFR Set-3 (Affymetrix Axiom CORECT Set array) was supported by NIH award U19 CA148107 and R01 CA81488 (to SBG). [CCFR Set-4 scan (Illumina OncoArray 600K SNP array)]: The CCFR Set-4 (Illumina OncoArray 600K SNP array) was supported by NIH award U19 CA148107 (to SBG) and by the Center for Inherited Disease Research (CIDR), which is funded by the NIH to the Johns Hopkins University, contract number HHSN268201200008I. CPS-II: The authors thank the CPS-II participants and Study Management Group for their invaluable contributions to this research. The authors would also like to acknowledge the contribution to this study from central cancer registries supported through the Centers for Disease Control and Prevention National Program of Cancer Registries, and cancer registries supported by the National Cancer Institute Surveillance Epidemiology and End Results program. The American Cancer Society funds the creation, maintenance, and updating of the CPS-II cohort. This study was conducted with Institutional Review Board approval. DACHS: We thank all participants and cooperating clinicians, and everyone who provided excellent technical assistance. This work was supported by the German Research Council (BR 1704/6-1, BR 1704/6-3, BR1704/6-4, CH 117/1-1, HO 5117/2-1, HE 5998/2-1, KL 2354/3-1, RO 2270/8-1 and BR 1704/17-1), the German Federal Ministry of Education and Research (01KH0404, 01ER0814, 01ER0815, 01ER1505A, and 01ER1505B), the Interdisciplinary Research Program of the National Center for Tumor Diseases (NCT), Germany, and German Cancer Research Center. DALS: National Institutes of Health (R01 CA48998; to M.L. Slattery). EDRN: We acknowledge all contributors to the development of the resource at University of Pittsburgh School of Medicine, Department of Gastroenterology, Department of Pathology, Hepatology and Nutrition and Biomedical Informatics. This work is funded and supported by the NCI, EDRN Grant (U01 CA 84968-06). EPIC: Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization. EPIC is financially supported by the European Commission (DGSANCO) and the International Agency for Research on Cancer. The national cohorts are supported by Danish Cancer Society (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM; France); German Cancer Aid, German Cancer Research Center (DKFZ), Federal Ministry of Education and Research (BMBF), Deutsche Krebshilfe, Deutsches Krebsforschungszentrum and Federal Ministry of Education and Research (Germany); the Hellenic Health Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro-AIRCItaly and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (the Netherlands); ERC-2009-AdG 232997 and Nordforsk, Nordic Center of Excellence program on Food, Nutrition and Health (Norway); Health Research Fund (FIS), PI13/00061 to Granada, PI13/01162 to EPIC-Murcia, Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra, ISCIII RETIC (RD06/0020; Spain); Swedish Cancer Society, Swedish Research Council and County Councils of Skåne and Västerbotten (Sweden); Cancer Research

UK (14136 to EPIC-Norfolk; C570/A16491 and C8221/A19170 to EPIC-Oxford), Medical Research Council (1000143 to EPIC-Norfolk, MR/M012190/1 to EPICOxford, UK). Harvard cohorts (HPFS, NHS, and PHS): The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required. We would like to thank the participants and staff of the HPFS, NHS, and PHS for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data. HPFS is supported by the National Institutes of Health (P01 CA055075, UM1 CA167552, U01 CA167552, R01 CA137178, R01 CA151993, and R35 CA197735), NHS by the National Institutes of Health (R01 CA137178, P01 CA087969, UM1 CA186107, R01 CA151993, and R35 CA197735), and PHS by the National Institutes of Health (R01 CA042182). MCCS cohort recruitment was funded by VicHealth and Cancer Council Victoria. The MCCS was further supported by Australian NHMRC grants 509348, 209057, 251553, and 504711 and by infrastructure provided by Cancer Council Victoria. Cases and their vital status were ascertained through the Victorian Cancer Registry (VCR) and the Australian Institute of Health and Welfare (AIHW), including the National Death Index and the Australian Cancer Database. PLCO: The authors thank the PLCO Cancer Screening Trial screening center investigators and the staff from Information Management Services Inc. and Westat Inc. Most importantly, we thank the study participants for their contributions that made this study possible. Cancer incidence data have been provided by the District of Columbia Cancer Registry, Georgia Cancer Registry, Hawaii Cancer Registry, Minnesota Cancer Surveillance System, Missouri Cancer Registry, Nevada Central Cancer Registry, Pennsylvania Cancer Registry, Texas Cancer Registry, Virginia Cancer Registry, and Wisconsin Cancer Reporting System. All are supported in part by funds from the Center for Disease Control and Prevention, National Program for Central Registries, local states, or by the National Cancer Institute, Surveillance, Epidemiology, and End Results program. The results reported here and the conclusions derived are the sole responsibility of the authors. Intramural Research Program of the Division of Cancer Epidemiology and Genetics and supported by contracts from the Division of Cancer Prevention, National Cancer Institute, NIH, DHHS. Funding was provided by National Institutes of Health (NIH), Genes, Environment and Health Initiative (GEI) Z01 CP 010200, NIH U01 HG004446, and NIH GEI U01 HG 004438. UK Biobank: The authors thank all the participants and staff of UK Biobank for making such a wonderful resource available for research. This study has been conducted under Application Number 8614. VITAL is supported by National Institutes of Health (K05 CA154337). WHI: The authors thank the WHI investigators and staff for their dedication and the study participants for making the program possible. A full listing of WHI investigators can be found at http://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Short%20List.pdf. The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received January 1, 2021; revised February 17, 2021; accepted May 7, 2021; published first May 10, 2021.

References

1. Terzic J, Grivennikov S, Karin E, Karin M. Inflammation and colon cancer. Gastroenterology 2010;138:2101–14.
2. Klintrup K, Makinen JM, Kauppila S, Vare PO, Melkko J, Tuominen H, et al. Inflammation and prognosis in colorectal cancer. Eur J Cancer 2005;41:2645–54.
3. Ansar W, Ghosh S. C-reactive protein and the biology of disease. Immunol Res 2013;56:131–42.
4. Takasu C, Shimada M, Kurita N, Iwata T, Nishioka M, Morimoto S, et al. Impact of C-reactive protein on prognosis of patients with colorectal carcinoma. Hepatogastroenterology 2013;60:507–11.
5. Crozier JE, McKee RF, McArdle CS, Angerson WJ, Anderson JH, Horgan PG, et al. The presence of a systemic inflammatory response predicts poorer survival in patients receiving adjuvant 5-FU chemotherapy following potentially curative resection for colorectal cancer. Br J Cancer 2006;94:1833–6.
6. Koike Y, Miki C, Okugawa Y, Yokoe T, Toiyama Y, Tanaka K, et al. Preoperative C-reactive protein as a prognostic and therapeutic marker for colorectal cancer. J Surg Oncol 2008;98:540–4.
7. Chung YC, Chang YF. Serum C-reactive protein correlates with survival in colorectal cancer patients but is not an independent prognostic indicator. Eur J Gastroenterol Hepatol 2003;15:369–73.
8. Volkova E, Willis JA, Wells JE, Robinson BA, Dachs GU, Currie MJ. Association of angiopoietin-2, C-reactive protein and markers of obesity and insulin resistance with survival outcome in colorectal cancer. Br J Cancer 2011;104:51–9.
9. Davey Smith G, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? Int J Epidemiol 2003;32:1–22.
10. Dehghan A, Dupuis J, Barbalic M, Bis JC, Eiriksdottir G, Lu C, et al. Meta-analysis of genome-wide association studies in >80,000 subjects identifies multiple loci for C-reactive protein levels. Circulation 2011;123:731–8.
11. Ligthart S, Vaez A, Vosa U, Stathopoulou MG, de Vries PS, Prins BP, et al. Genome analyses of >200,000 individuals identify 58 loci for chronic inflammation and highlight pathways that link inflammation and complex disorders. Am J Hum Genet 2018;103:691–706.
12. Guo Q, Burgess S, Turman C, Bolla MK, Wang Q, Lush M, et al. Body mass index and breast cancer survival: a Mendelian randomization analysis. Int J Epidemiol 2017;46:1814–22.
13. Newcomb PA, Baron J, Cotterchio M, Gallinger S, Grove J, Haile R, et al. Colon Cancer Family Registry: an international resource for studies of the genetic epidemiology of colon cancer. Cancer Epidemiol Biomarkers Prev 2007;16:2331–43.
14. Calle EE, Rodriguez C, Jacobs EJ, Almon ML, Chao A, McCullough ML, et al. The American Cancer Society Cancer Prevention Study II Nutrition Cohort: rationale, study design, and baseline characteristics. Cancer 2002;94:2490–501.
15. Brenner H, Chang-Claude J, Seiler CM, Rickert A, Hoffmeister M. Protection from colorectal cancer after colonoscopy: a population-based, case–control study. Ann Intern Med 2011;154:22–30.
16. Slattery ML, Potter J, Caan B, Edwards S, Coates A, Ma KN, et al. Energy balance and colon cancer—beyond physical activity. Cancer Res 1997;57:75–80.
17. Amin W, Singh H, Dzubinski LA, Schoen RE, Parwani AV. Design and utilization of the colorectal and pancreatic neoplasm virtual biorepository: an early detection research network initiative. J Pathol Inform 2010;1:22.
18. Riboli E, Kaaks R. The EPIC Project: rationale and study design. European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol 1997;26:S6–14.
19. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. Epidemiology 1990;1:466–73.
20. Giles GG, English DR. The Melbourne Collaborative Cohort Study. IARC Sci Publ 2002;156:69–70.
21. Colditz GA, Manson JE, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. J Womens Health 1997;6:49–62.
22. Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004;22:23–30.
23. Christen WG, Gaziano JM, Hennekens CH. Design of Physicians' Health Study II–a randomized trial of beta-carotene, vitamins E and C, and multivitamins, in prevention of cancer, cardiovascular disease, and eye disease, and review of results of completed trials. Ann Epidemiol 2000;10:125–34.
24. Prorok PC, Andriole GL, Bresalier RS, Buys SS, Chia D, Crawford ED, et al. Design of the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial. Control Clin Trials 2000;21:273S–309S.
25. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779.

26. White E, Patterson RE, Kristal AR, Thornquist M, King I, Shattuck AL, et al. VITamins and lifestyle cohort study: study design and characteristics of supplement users. Am J Epidemiol 2004;159:83–93.
27. Group TWsHIS. Design of the Women's Health Initiative clinical trial and observational study. Control Clin Trials 1998;19:61–109.
28. Hutter CM, Chang-Claude J, Slattery ML, Pflugeisen BM, Lin Y, Duggan D, et al. Characterization of gene-environment interactions for colorectal cancer susceptibility loci. Cancer Res 2012;72:2036–44.
29. Peters U, Jiao S, Schumacher FR, Hutter CM, Aragaki AK, Baron JA, et al. Identification of genetic susceptibility loci for colorectal tumors in a genome-wide meta-analysis. Gastroenterology 2013;144:799–807.
30. Huyghe JR, Bien SA, Harrison TA, Kang HM, Chen S, Schmit SL, et al. Discovery of common and rare genetic risk variants for colorectal cancer. Nat Genet 2019; 51:76–87.
31. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, et al. The UK Biobank resource with deep phenotyping and genomic data. Nature 2018;562: 203–9.
32. Schmit SL, Edlund CK, Schumacher FR, Gong J, Harrison TA, Huyghe JR, et al. Novel common genetic susceptibility loci for colorectal cancer. J Natl Cancer Inst 2019;111:146–57.
33. Schumacher FR, Schmit SL, Jiao S, Edlund CK, Wang H, Zhang B, et al. Genome-wide association study of colorectal cancer identifies six new susceptibility loci. Nat Commun 2015;6:7138.
34. Delaneau O, Marchini J, McVean GA, Donnelly P, Lunter G, Marchini JL, et al. Integrating sequence and array data to create an improved 1000 Genomes Project haplotype reference panel. Nat Commun 2014;5:3934.
35. McCarthy S, Das S, Kretzschmar W, Delaneau O, Wood AR, Teumer A, et al. A reference panel of 64,976 haplotypes for genotype imputation. Nat Genet 2016; 48:1279–83.
36. Das S, Forer L, Schönherr S, Sidore C, Locke AE, Kwong A, et al. Next-generation genotype imputation service and methods. Nat Genet 2016;48: 1284–7.
37. Buniello A, MacArthur JAL, Cerezo M, Harris LW, Hayhurst J, Malangone C, et al. The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. Nucleic Acids Res 2019;47: D1005–d12.
38. Burgess S, Dudbridge F, Thompson SG. Combining information on multiple instrumental variables in Mendelian randomization: comparison of allele score and summarized data methods. Stat Med 2016;35:1880–906.
39. Hua X, Kratz M, Newcomb PA. Associations between post-treatment inflammatory biomarkers and survival among stage II–III colorectal cancer patients. Cancer Epidemiol Biomarkers Prev 2020;29:691.
40. Staiger DO, Stock JH. Instrumental variables regression with weak instruments. Mass., USA: National Bureau of Economic Research Cambridge; 1994.
41. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol 2015;44:512–25.
42. Tchetgen Tchetgen EJ, Walter S, Vansteelandt S, Martinussen T, Glymour M. Instrumental variable estimation in a survival context. Epidemiology 2015; 26:402–10.
43. Sjolander A, Dahlqwist E, Zetterqvist J. A note on the noncollapsibility of rate differences and rate ratios. Epidemiology 2016;27:356–9.
44. Scheike TH, Zhang MJ. Analyzing competing risk data using the R timereg package. J Stat Softw 2011;38.2.
45. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol 2013;37: 658–65.
46. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol 2016;40:304–14.
47. Burgess S. Sample size and power calculations in Mendelian randomization with a single instrumental variable and a binary outcome. Int J Epidemiol 2014;43: 922–9.
48. Zhou B, Shu B, Yang J, Liu J, Xi T, Xing Y. C-reactive protein, interleukin-6 and the risk of colorectal cancer: a meta-analysis. Cancer Causes Control 2014;25: 1397–405.
49. Wang X, Dai JY, Albanes D, Arndt V, Berndt SI, Bezieau S, et al. Mendelian randomization analysis of C-reactive protein on colorectal cancer risk. Int J Epidemiol 2019;48:767–80.
50. Li C, Xu Q, Chen L, Luo C, Ying J, Liu J. C-reactive protein (CRP) as a prognostic factor for colorectal cancer after surgical resection of pulmonary metastases. Bull Cancer 2017;104:232–6.
51. Cooney RV, Chai W, Franke AA, Wilkens LR, Kolonel LN, Le Marchand L. C-reactive protein, lipid-soluble micronutrients, and survival in colorectal cancer patients. Cancer Epidemiol Biomarkers Prev 2013;22:1278–88.
52. Matsubara D, Arita T, Nakanishi M, Kuriu Y, Murayama Y, Kudou M, et al. The impact of postoperative inflammation on recurrence in patients with colorectal cancer. Int J Clin Oncol 2020;25:602–13.
53. Slattery ML, Curtin K, Poole EM, Duggan DJ, Samowitz WS, Peters U, et al. Genetic variation in C-reactive protein in relation to colon and rectal cancer risk and survival. Int J Cancer 2011;128:2726–34.
54. Yang SH, Huang CJ, Chang SC, Lin JK. Association of C-reactive protein gene polymorphisms and colorectal cancer. Ann Surg Oncol 2011;18:1907–15.
55. Aschard H, Vilhjálmsson BJ, Joshi AD, Price AL, Kraft P. Adjusting for heritable covariates can bias effect estimates in genome-wide association studies. Am J Hum Genet 2015;96:329–39.
56. Aschard H, Guillemot V, Vilhjalmsson B, Patel CJ, Skurnik D, Ye CJ, et al. Covariate selection for association screening in multiphenotype genetic studies. Nat Genet 2017;49:1789–95.