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Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

A Comprehensive Study of the Effect on Colorectal Cancer Survival of Common Germline Genetic Variation Previously Linked with Cancer Prognosis

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Abstract

Background: Germline genetic variants may influence pathways of tumor progression common to multiple cancer types. Here, we investigated the association between survival after colorectal cancer diagnosis and 128 common genetic variants previously associated with prognosis in genome-wide association studies in different cancer types.

Methods: We studied survival outcomes in a large well-documented, prospective, population-based cohort (5,675 patients with colorectal cancer) with up to 20 years' follow-up.

Results: None of the 128 variants were significantly associated with overall or colorectal cancer–specific survival ($P < 5 \times 10^{-4}$, Bonferroni-corrected threshold). We observed suggestive evidence ($P < 0.05$) for eight variants (rs17026425, rs17057166, rs6854845, rs1728400, rs17693104, rs202280, rs6797464, and rs823920) in all colorectal cancer and two variants (rs17026425 and rs6854845) in rectal cancer that were concordant with previous reports.

Conclusions: Given good statistical power (>0.80 for 75% of variants), this study indicates that most previously reported variants associated with cancer survival have limited influence on colorectal cancer prognosis.

Impact: Although small effects cannot be excluded, clinically meaningful germline influences on patients with colorectal cancer as a group are unlikely.

Background

Colorectal cancer is the second leading cause of cancer-related deaths worldwide (1). However, current knowledge on germline genetic influences over colorectal cancer prognosis is sparse. There is evidence that shared germline genetic basis exists across multiple cancer types in several key regulatory pathways of cancer pathogenesis (2) and progression (3). Previous genome-wide association studies (GWAS) have identified a number of genetic loci that might be associated with prognostic outcomes for various cancers. These genetic variants may also influence survival outcomes of patients with colorectal cancer. Here, we report a large population-based study investigating the effects of published GWAS-identified variants associated with cancer prognosis on colorectal cancer survival.

Materials and Methods

We searched the NHGRI-EBI GWAS Catalog (https://www.ebi.ac.uk/gwas/ accessed in December 2018) to retrieve GWAS-identified variants ($P < 5 \times 10^{-5}$) associated with survival-related traits for patients of any types of cancer. Patients with colorectal cancer with available information on age at diagnosis, sex, American Joint Committee on Cancer (AJCC) stage, and GWAS data were included from the Study of Colorectal Cancer in Scotland (SOCCS). The MultiCentre Research Ethics committee for Scotland and other committees approved the study and written informed consent was obtained from all participants. Additional details on the study cohort and quality control measures on genotyping have been reported previously (4, 5). Patients with colorectal cancer were prospectively followed up until death or censored on July 1, 2017. We evaluated overall survival (OS) and colorectal cancer–specific survival (CSS) as outcomes. A Cox proportional hazards model was adopted to estimate the effect of each variant (under an additive genetic model) on survival outcomes adjusting for age, sex, and AJCC stage. We also performed stratified analyses by sex, AJCC stage, and tumor site. With the type I error at $\alpha < 5 \times 10^{-4}$ (a Bonferroni corrected threshold), we estimated the study power for variants of various minor allele frequencies (MAF) and effect sizes using the method proposed by Owzar and colleagues (6).

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Table 1. Summarized characteristics of the SOCCS cohort

Basic characteristics	CRC cases (n = 5,675)
Age at diagnosis (years)[a]	64.5 (54.6–71.6)
Sex	
Male	3,235 (57.0%)
Female	2,440 (43.0%)
Site	
Colon	3,392 (59.8%)
Rectum	2,201 (38.8%)
Colon and rectum	16 (0.3%)
Unknown	66 (1.2%)
AJCC stage	
I	1,005 (17.7%)
II	1,891 (33.3%)
III	1,995 (35.2%)
IV	784 (13.8%)
No. of all-cause deaths	1,918 (33.8%)
No. of CRC-related deaths	1,358 (23.9%)

Abbreviations: CRC, colorectal cancer; No., number.
[a]Median and quartiles in parentheses.

Results

A total of 5,675 colorectal cancer cases were included in this analysis and their basic characteristics are summarized in Table 1. A total of 128 genetic variants (linkage disequilibrium $r^2 < 0.2$) were identified from GWAS Catalog (details presented in Supplementary Table S1) and were included in the analysis. Power calculation indicated a power of at least 0.80 to detect a hazard ratio (HR) of 1.25 for 75% of the included variants (MAF > 0.1). Power estimates with various parameters are presented in Supplementary Table S2. In the overall analysis of all 5,675 patients with colorectal cancer, none of the included variants were significantly associated with either OS or CSS (at $P < 0.0005$). We observed eight variants (rs17026425, rs17057166, rs6854845, rs1728400, rs17693104, rs202280, rs6797464, and rs823920) with $P < 0.05$ in the same direction of effects with previous findings (Table 2); of them, three variants (rs17026425, rs17057166, and rs6854845) were previously reported to be associated with rectal cancer survival. In stratified analysis, the variant rs17026425 was statistically significantly associated with OS for male patients with colorectal cancer (HR = 1.37; 95% confidence interval, 1.15–1.62; $P = 3.3 \times 10^{-4}$). In addition, we observed two variants to be associated at $P < 0.05$ (rs17026425 and rs6854845) with OS in patients with rectal cancer. No statistically significant associations were found in other stratified analyses (Supplementary Tables S3–S5).

Discussion

Here, we studied all common variants previously reported to be associated with prognosis in different cancer types. Overall, our results do not support any associations between these variants and survival outcomes for patients with colorectal cancer. There are some suggestive signals that may merit further investigation in even larger datasets. For instance, we report a suggestive effect of rs17026425 in both overall and stratified analysis of patients with rectal cancer, which concords with a previous GWAS (7). Of note, neither our study nor the previous GWAS detected association of this variant with colon cancer survival, indicating that this potential effect may be specific to rectal cancer. The variant is an intron variant of *IQ motif containing M* (*IQCM*) gene and is located in the binding region of JUN/JUND transcription factors, which manifest higher expression in colorectal cancer (8). The *IQCM* gene itself is highly expressed in testis only, making results restricted to males only in our study even more intriguing.

Presented here, the study has sufficient power to detect 75% of previously reported survival variants, but failed to do so. Notably, 90% (19/21) of identified studies (Supplementary Table S1) have sample size below 5,675, which is required to detect effect of genetic variants with MAF of 10% and HR of 1.25, thus suggesting potential false-positive association as well as overestimation of real effects in original studies (winner's curse). Lack of pleiotropic and common effects across different cancers could also be behind the observed results, given the fact that variants reportedly associated with prognosis of other cancers except colorectal cancer showed mostly null effects in SOCCS. Our findings show poor reproducibility of results in the field and a pressing need for collaborative efforts, so as to aggregate larger colorectal cancer cohorts with genotype data to unravel the genetic architecture of colorectal cancer survival.

Table 2. Summarized results of genetic variants that are associated with colorectal cancer survival ($P < 0.05$) in SOCCS

Variant	Locus	Gene	GWAS outcome that variant was originally reported	Reported effect (HR)	MA	MAF	Estimates in SOCCS HR[a] (95% CI)	Estimates in SOCCS P	Power[b]
OS									
rs17026425	4q31.23	*IQCM*	Rectal cancer (OS)	5.06	A	0.079	1.16 (1.01–1.33)	0.039	1.00
rs17057166	5q33.3	*LINC01847*	Rectal cancer (DFS)	5.56	T	0.088	1.14 (1.00–1.29)	0.042	1.00
rs6854845	4q13.3	Intergenic	Rectal cancer (DFS)	3.31	T	0.119	1.14 (1.01–1.29)	0.040	1.00
rs1728400	16q24.1	Intergenic	Breast cancer (OS)	0.80	A	0.330	0.93 (0.87–0.99)	0.026	1.00
rs17693104	10q23.1	*SH2D4B*	Serous epithelial ovarian cancer (OS)	1.65	T	0.348	1.08 (1.01–1.15)	0.021	1.00
rs11138220	9q21.31	Intergenic	Rectal cancer (DFS)	2.76	G	0.131	0.88 (0.79–0.98)	0.016	1.00
CRC-specific survival									
rs17693104	10q23.1	*SH2D4B*	Serous epithelial ovarian cancer (OS)	1.65	T	0.348	1.09 (1.01–1.17)	0.031	1.00
rs202280	8q21.13	Intergenic	Serous epithelial ovarian cancer (OS)	2.00	G	0.038	1.14 (1.02–1.26)	0.018	1.00
rs6797464	3q26.2	*MECOM*	Osteosarcoma (OS)	1.80	A	0.119	1.18 (1.02–1.37)	0.030	1.00
rs823920	9q31.1	Intergenic	Pancreatic cancer (OS)	1.43	G	0.123	1.11 (1.00–1.23)	0.042	1.00
rs11138220	9q21.31	Intergenic	Rectal cancer (DFS)	2.76	G	0.131	0.85 (0.75–0.97)	0.016	1.00

Abbreviations: CRC, colorectal cancer; DFS, disease-free survival; MA, minor allele.
[a]HRs are estimated on the basis of minor alleles.
[b]Statistical power is estimated using originally reported effect sizes with type I error (α) at 0.0005.

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Disclosure of Potential Conflicts of Interest

M.G. Dunlop is a scientific advisory board member at Oxford Cancer Biomarkers. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: Y. He, S.M. Farrington, M.G. Dunlop, E. Theodoratou
Development of methodology: M.G. Dunlop
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y. He, F.V.N. Din, J.P. Blackmur, P. Vaughan-Shaw, S.M. Farrington, H. Campbell, M.G. Dunlop, E. Theodoratou
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. He, M. Timofeeva, X. Li, J.P. Blackmur, V. Svinti, M.G. Dunlop
Writing, review, and/or revision of the manuscript: Y. He, M. Timofeeva, X. Li, J.P. Blackmur, P. Vaughan-Shaw, S.M. Farrington, H. Campbell, M.G. Dunlop, E. Theodoratou
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.M. Farrington
Study supervision: H. Campbell, M.G. Dunlop, E. Theodoratou
Other (supervision of statistical analysis): M. Timofeeva

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