Published in final edited form as:
Gastroenterology. 2012 July ; 143(1): 51–4.e4. doi:10.1053/j.gastro.2012.04.052.

Association Between Colorectal Cancer Susceptibility Loci and Survival Time After Diagnosis With Colorectal Cancer

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Abstract

Genome-wide association studies have identified 16 germline single-nucleotide polymorphisms (SNPs) that are associated with colorectal cancer (CRC) incidence. We examined the relationship between these SNPs and survival of 2611 individuals with CRC, enrolled in 5 cohort studies. We used Cox regression analysis to associate SNPs with overall and CRC-specific survival times. The minor allele in rs4939827 (*SMAD7*) was associated with reduced overall survival (hazard ratio, 1.16; 95% confidence interval, 1.06–1.27; $P = .002$) and disease-specific survival (hazard ratio, 1.17; 95% confidence interval, 1.05–1.30; $P = .005$). Other SNPs were not associated significantly with survival. Common germline variations might be prognostic factors for patients with CRC. A variant in *SMAD7* could affect progression of CRC.

Keywords

Colon Cancer; Genetic; GWAS; Prognosis

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Conflicts of interest: The authors disclose the following: Dr Chan has received funding as an ad hoc consultant for Bayer Healthcare, Pfizer, and Millenium Pharmaceuticals.

Supplementary Material: Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2012.04.052

Recent genome-wide association studies (GWAS) have identified at least 16 single-nucleotide polymorphisms (SNPs) at 14 loci that are associated statistically significantly with risk of incident colorectal cancer (CRC).[1,2] Common genetic variation also may play a role in CRC prognosis. To date, however, most studies evaluating genetic variation in relation to CRC survival have focused on polymorphisms in candidate genes involved in putative pathways of action for cancer therapeutics,[3–5] mismatch repair,[6] or oncogenes (eg, cyclooxygenase-2 [*COX-2*][7]), and have reported null or only marginally significant associations that have been replicated inconsistently. A small number of studies have examined loci identified by GWAS for CRC susceptibility in relation to prognosis.[8–11] These studies also have yielded inconsistent results, but each were limited by small sample sizes. We therefore evaluated associations between 16 CRC susceptibility SNPs identified from prior GWAS and survival after CRC diagnosis, using genotype and survival information from 2611 men and women diagnosed with incident invasive CRC after enrolling in one of the following prospective cohort studies: the Health Professionals Follow-Up Study, the Nurses' Health Study, the Physicians' Health Study, the VITamins And Lifestyle study, and 2 subsets of the Women's Health Initiative (WHI1 and WHI2).

Characteristics of incident CRC cases enrolled in each of the included study populations are provided in Table 1. In total, 979 of 2611 (37%) CRC cases died during study follow-up, with the proportion of cases who died ranging from 32% in WHI2 to 49% in the Health Professionals Follow-Up Study, and with the proportion of deaths attributable to CRC ranging from 52% in the Physicians' Health Study to 78% in WHI2.

In meta-analyses of overall survival (OS) adjusted for age at diagnosis and sex, we observed a Bonferroni-adjusted statistically significant association with rs4939827 (18q21, *SMAD7*) (hazard ratio [HR], 1.16; 95% confidence interval [CI], 1.06-1.27; $P = .002$) consistent with a 16% increased risk of all-cause mortality per copy of the minor allele (*G*) (Table 2). After additional adjustment for stage at diagnosis, this association with rs4939827 was modestly attenuated (HR, 1.13; 95% CI, 1.01–1.25; $P = .03$). Rs4939827 also was associated with poorer disease-specific survival (DSS), with borderline significance after Bon-ferroni-adjustment for multiple comparisons (HR, 1.17; 95% CI, 1.05–1.30; $P = .005$). Associations with rs4939827 were similar across individual studies (P heterogeneity = .80 and .96 for OS and DSS, respectively) (Supplementary Figure 1). Prior studies of rs4939827 have indicated no association with overall survival,[9–11] although one study did find an association between rs4939827 and survival confined to women who were regular users of nonsteroidal anti-inflammatory drugs.[11] We found no significant difference in our observed associations with rs4939827 in analyses stratified by reported use of nonsteroidal anti-inflammatory drugs ($P_{interaction} = .97$ and .54 for OS and DSS, respectively). In our study, the association between rs4939827 and survival also did not appear to differ according to smoking history or body mass index, but there was a suggestive, albeit not statistically significant, difference according to family history of CRC: the HRs for OS were 1.18 (95% CI, 1.05–1.32; $P = .004$) for cases without family history compared with 1.01 (95% CI, 0.69–1.46; $P = .97$) for cases with a family history ($P_{interaction} = .78$).

In analyses adjusted for age, sex, and stage, we observed modest associations with OS for the minor alleles of rs10795668 (10p14) (HR, 1.14; 95% CI, 1.02–1.28; $P = .03$) and rs4925386/rs2151512 (20q13) (HR, 1.14; 95% CI, 1.02–1.29; $P = .03$). However, these associations were not statistically significant after Bonferroni adjustment. Other evaluated SNPs were not associated significantly with OS or DSS, consistent with previous studies.[9–11]

We assessed differences in our results according to tumor site (colon, rectum), sex, stage at diagnosis (I–II, III–IV), first-degree family history of CRC (absent, present), smoking

history (never, ever), body mass index (<30, ≥30 kg/m^2), and use of nonsteroidal anti-inflammatory drugs (no, yes). Although the number of individuals within each analysis was limited, results did not differ appreciably across these strata (not shown).

We calculated a risk score across all 16 SNPs by summing risk alleles as defined by the results from previous GWAS for CRC incidence; however, no association was evident per risk allele for OS (HR, 0.96; 95% CI, 0.91–1.01; $P = .13$) or DSS (HR, 0.98; 95% CI, 0.93–1.03; $P = .43$). When we instead calculated a risk score by summing risk alleles as defined by our findings in relation to survival, we did note significantly poorer OS (HR, 1.06; 95% CI, 1.02– 1.10; $P = .001$) and DSS (HR, 1.09; 95% CI, 1.04–1.13; $P < .001$) per risk allele. By using a risk score limited to the SNPs most strongly associated with survival in our analysis (rs4939827, rs10795668, and rs4925386/rs2151512), we also observed significantly poorer survival per risk allele (HR_{OS}, 1.13; 95% CI, 1.06 –1.20; $P < .001$; and HR_{DSS}, 1.14; 95% CI, 1.05–1.23; $P = .001$).

Recent genome-wide association studies have shown the importance of common genetic variation in mediating the risk of CRC.[1,2] Our findings provide support for a role of genetic variation in survival after CRC diagnosis. Specifically, the G allele in rs4939827, previously associated with lower risk of incident CRC,[1] was associated with poorer survival after CRC diagnosis. Rs4939827 is located in an intronic region of *SMAD7,* a downstream inhibitor of transforming growth factor-β1 (TGF-β1). The seemingly contrary associations of rs4939827 with decreased risk of incident CRC but poorer survival after CRC diagnosis may be owing to the pleiotropic functions of the TGF-β pathway. In normal epithelium, TGF-β1 appears to function as a tumor suppressor through induction of cell arrest and inhibition of cell proliferation[12]; however, once cells are resistant to TGF-β1-mediated proliferative inhibition (ie, in established tumors), TGF-β1 promotes metastasis by enhancing angiogenesis and extracellular matrix disruption and inhibiting infiltrating tumor immune cells.[12] Thus, although the functionality of rs4939827 is currently unknown, it is plausible that a variant in *SMAD7* that contributes to up-regulation of TGF-β1 could result in decreased cancer risk but poorer survival. The consistency of the association between this SNP and survival across each of our included cohorts and our prospective design add strength to this finding. Nonetheless, it is notable that most GWAS-identified susceptibility loci for CRC we evaluated were not associated with CRC survival. Thus, these findings also suggest that common genetic variants most associated with CRC survival may be distinct from those that underlie initial tumor development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors wish to acknowledge Patrice Soule and Hardeep Ranu for genotyping at the Dana-Farber Harvard Cancer Center High Throughput Polymorphism Core, under the supervision of Immaculata Devivo, as well as Carolyn Guo and Haiyan Zhang for programming assistance. The authors also wish to acknowledge Dave Duggan at TGen and Andrew Crenshaw at the Broad Institute for genotyping. The authors also thank the Health Professionals Follow-up Study, Nurses' Health Study, Physicians' Health Study, VITamins And Lifestyle study, and Women's Health Initiative investigators and staff for their dedication, and the study participants for making these programs possible. A full listing of Women's Health Initiative investigators can be found at: https://cleo.whi.org/researchers/SitePages/Write%20a%20Paper.aspx.

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Abbreviations in this paper

CI	confidence interval
CRC	colorectal cancer
DSS	disease-specific survival
GWAS	genome-wide association study
HR	hazard ratio
OS	overall survival
SNP	single nucleotide polymorphism
TGF-β1	transforming growth factor β1
WHI	Women's Health Initiative

Table 1

Characteristics of Colorectal Cancer Cases in Included Study Populations

	Health Professionals Follow-up Study (HPFS)	Nurses' Health Study (NHS)	Physicians' Health Study (PHS)	VITamins And Lifestyle study (VITAL)	Women's Health Initiative (subset 1) (WHI1)	Women's Health Initiative (subset 2) (WHI2)
Cases, n	268	367	281	281	451	963
Total deaths, n (% of cases)	130 (49)	151 (41)	128 (46)	94 (33)	166 (37)	310 (32)
CRC-specific deaths, n (% of deaths)	72 (55)	113 (75)	67 (52)	59 (63)	118 (71)	241 (78)
Median follow-up period, y (SE)[a]	6.5 (0.3)	7.7 (0.3)	13.9 (0.5)	4.4 (0.1)	6.7 (0.2)	4.2 (0.1)
% Female	0	100	0	47	100	100
Age at diagnosis, n (%)						
<65 y	55 (21)	118 (32)	92 (33)	51 (18)	87 (19)	149 (15)
65–69 y	36 (13)	79 (22)	43 (15)	59 (21)	87 (19)	205 (21)
70–74 y	55 (21)	81 (22)	37 (13)	90 (32)	133 (29)	248 (26)
75–79 y	56 (21)	61 (17)	43 (15)	67 (24)	96 (21)	199 (21)
≥80 y	66 (25)	28 (8)	66 (23)	14 (5)	48 (11)	162 (17)
Stage at diagnosis, n (%)						
I	74 (37)	80 (25)	57 (30)	58 (32)	111 (29)	241 (31)
II	38 (19)	107 (33)	61 (32)	47 (26)	136 (35)	255 (33)
III	55 (27)	82 (25)	50 (26)	45 (25)	72 (19)	152 (20)
IV	34 (17)	56 (17)	24 (13)	31 (17)	65 (17)	123 (16)
Unknown	67	42	89	100	67	192
Tumor site, n (%)						
Colon	177 (76)	282 (79)	198 (78)	211 (77)	437 (98)	678 (75)
Rectum	57 (24)	75 (21)	55 (22)	64 (23)	11 (2)	232 (25)
Unknown	34	10	28	6	3	53

SE, standard error.

[a]Calculated as the median time from diagnosis to censoring in cases who did not die during the study follow-up period.

Table 2

Association Between 16 Colorectal Cancer Susceptibility SNPs and Survival After Colorectal Cancer Diagnosis

Individual SNPs				Overall survival				CRC-specific survival			
SNP	**Position (nearest gene)**	**Minor allele**	**MAF**	**HR (95% CI)**	***P***	**Stage-adjusted HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**Stage-adjusted HR (95% CI)**	***P***
rs6691170	1q41	A[a]	0.37	0.92 (0.84–1.02)	.11	0.94 (0.82–1.09)	.43	0.92 (0.82–1.03)	.15	0.99 (0.86–1.14)	.89
rs6687758	1q41	G†	0.20	0.95 (0.83–1.08)	.42	0.98 (0.86–1.12)	.82	0.97 (0.84–1.12)	.68	1.06 (0.90–1.23)	.49
rs10936599	3q26	A	0.24	0.98 (0.86–1.13)	.82	0.93 (0.80–1.09)	.37	0.95 (0.81–1.11)	.51	0.90 (0.77–1.06)	.20
rs16892766	8q23 (*EIF3H*)	C[a]	0.09	1.06 (0.90–1.23)	.50	1.09 (0.91–1.31)	.34	1.10 (0.91–1.32)	.32	1.12 (0.83–1.52)	.46
rs6983267	8q24	A	0.47	1.01 (0.92–1.12)	.79	—		0.96 (0.85–1.07)	.43	—	
rs10795668	10p14	A	0.31	1.08 (0.98–1.19)	.15	1.14 (1.02–1.28)	.02	1.07 (0.95–1.20)	.27	1.14 (0.99–1.32)	.07
rs3802842	11q23	C[a]	0.31	0.96 (0.86–1.07)	.49	1.00 (0.89–1.12)	.97	0.94 (0.83–1.06)	.30	1.00 (0.88–1.15)	.96
rs7136702	12q13	A[a]	0.35	0.93 (0.84–1.03)	.15	0.89 (0.79–1.01)	.06	0.95 (0.84–1.08)	.43	0.91 (0.79–1.06)	.22
rs11169552[b]	12q13	A	0.25	1.03 (0.90–1.18)	.70	1.03 (0.88–1.20)	.70	0.97 (0.82–1.15)	.74	0.95 (0.82–1.11)	.54
rs4444235[c]	14q22 (*BMP4*)	G[a]	0.48	0.95 (0.86–1.05)	.34	1.04 (0.86–1.25)	.71	0.93 (0.82–1.06)	.28	—	
rs4779584	15q13 (*CRAC1/HMPS/GREM1*)	A[a]	0.20	1.06 (0.94–1.20)	.35	1.10 (0.95–1.27)	.19	1.08 (0.93–1.26)	.30	1.18 (1.00–1.41)	.06
rs9929218[b]	16q22 (*CDH1*)	A	0.30	1.06 (0.96–1.17)	.27	1.12 (0.99–1.26)	.07	1.06 (0.95–1.20)	.30	1.10 (0.96–1.26)	.19
rs4939827[b]	18q21 (*SMAD7*)	G	0.46	1.16 (1.06–1.27)	.002	1.13 (1.01–1.25)	.03	1.17 (1.05–1.30)	.005	1.16 (1.02–1.32)	.02
rs10411210	19q13 (*RHPN2*)	A	0.10	1.13 (0.91–1.40)	.26	1.09 (0.90–1.32)	.37	1.09 (0.87–1.38)	.45	1.11 (0.85–1.46)	.43
rs961253	20p12 (*BMP2*)	A[a]	0.37	0.98 (0.89–1.07)	.63	0.97 (0.85–1.11)	.68	0.94 (0.81–1.08)	.37	0.93 (0.78–1.11)	.41
rs4925386[bd]	20q13	A	0.30	1.02 (0.92–1.13)	.69	1.14 (1.02–1.29)	.03	0.99 (0.88–1.12)	.88	1.14 (0.97–1.29)	.13
Combined SNP scores											
Sum of all 16 “risk” alleles[e]				0.96 (0.93–0.99)	.02	0.96 (0.91–1.01)	.13	0.97 (0.94–1.00)	.05	0.98 (0.93–1.03)	.43
Sum of all 16 “survival” alleles[f]				1.04 (1.01–1.07)	.007	1.06 (1.02–1.10)	.002	1.06 (1.02–1.09)	.001	1.08 (1.04–1.13)	<.001
Sum of 3 alleles associated with survival[g]				1.09 (1.03–1.15)	.002	1.13 (1.06–1.20)	<.001	1.08 (1.02–1.16)	.01	1.14 (1.05–1.23)	.001

NOTE. All meta-analyses were adjusted for age. Analyses in the VITamins And Lifestyle study also were adjusted for sex. After Bonferroni correction for multiple comparisons, a *P* value less than .003125 was considered statistically significant in age-adjusted analyses.

MAF, minor allele frequency; —, significant heterogeneity was noted in meta-analysis of study-specific effect estimates.

[a]Minor allele associated with increased risk of incident CRC in prior GWAS.[1,2] (For other SNPs, the minor allele is associated with a reduced risk of incident CRC.)

[b] SNP was genotyped directly in all studies. Genotype for other SNPs was based on imputation (in VITamins And Lifestyle study and WHI2) or direct genotyping (Health Professionals Follow-Up Study, Nurses' Health Study, Physicians' Health Study, and WHI1).

[c] Meta-analysis excludes the Nurses' Health Study because of violation of the Hardy–Weinberg equilibrium.

[d] Genotype data on rs4925386 was used for the VITamins And Lifestyle Study, WHI1, and WHI2. Genotype data on rs2151512 was used for the Physicians' Health Study, Health Professionals Follow-Up Study, and the Nurses' Health Study.

[e] Risk alleles were defined by results from previous genome-wide association studies for colorectal cancer incidence.

[f] Survival alleles were defined by which allele was associated with poorer survival in individual SNP analyses.

[g] Sum of survival alleles for SNPs rs4939827, rs10795668, and rs4925386/rs2151512.