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No association between germline variation in catechol-*O*-methyltransferase and colorectal cancer survival in postmenopausal women

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Abstract

Objective—Sex-steroid hormones play a role in colorectal cancer (CRC) development, but little is known about their influence on tumor progression and metastasis. Because catechol-*O*-methyltransferase activity (*COMT*; 22q11.21) is an important component of estrogen-mediated carcinogenesis, we hypothesized that germline variation in *COMT* may be associated with CRC survival.

Methods—We identified 10 single-nucleotide polymorphisms (SNPs) that tagged variation across both isoforms of *COMT* in 2,458 women with CRC from the Nurses' Health Study (NHS), Postmenopausal Hormones Supplementary Study to the Colon Cancer Family Registry (PMH-CCFR), VITamins And Lifestyle (VITAL) Study, and Women's Health Initiative (WHI). All four studies participate in the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO).

Results—Over a median follow-up of 7 years across all studies, there were 799 deaths, including 566 from CRC. Accounting for multiple comparisons, no associations between the SNPs and CRC-specific or overall survival reached statistical significance, including the well-characterized Val108/158Met polymorphism (rs4680; hazard ratio per minor allele [HR], 1.04; 95% confidence interval [CI], 0.92–1.17 for CRC-specific survival and 1.01; 0.90–1.14 for overall survival).

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Conclusions—In this large study of women with CRC, we found no evidence that common inherited variation in *COMT* is associated with survival-time after diagnosis.

INTRODUCTION

Reproductive factors and postmenopausal hormone use are associated with the risk of developing colorectal cancer (CRC).[1–3] Estrogen-receptor methylation occurs in the colon as a part of the aging process, and receptor-expression loss correlates with carcinogenic progression.[4, 5] The association between endogenous and exogenous hormones and CRC survival is less clear.[6–9] Although few hormone-related genes have been found to be associated with CRC risk,[10, 11] genetic studies of survival may inform estrogen-mediated metastatic mechanisms.[12]

Catechol-*O*-methyltransferase (*COMT*; 22q11.21) is a key enzyme involved in the metabolism of catechol estrogens to methoxy estrogens.[13] Catechol estrogens have the potential to form depurinating DNA adducts,[14–16] and function in the development of estrogen-related cancers.[17] *COMT* has two major isoforms, a soluble cytoplasmic isoform (S-COMT) accounting for approximately 90% of enzyme activity, and a membrane-bound isoform (MB-COMT) encoded by 50 additional amino acids.[18] Both isoforms are expressed in the gut.[19]

A common nonsynonymous single-nucleotide polymorphism (SNP) at codon 108 of S-COMT and 158 of MB-COMT (Val108/158Met; rs4680), known to decrease enzyme activity, has been extensively characterized.[20, 21] Urinary[22] and blood[23] concentrations of estrogen-metabolites have been found to depend on Val108/158Met genotype, but not in all studies.[24] The more than 40 epidemiologic studies that have evaluated this variant with respect to breast cancer risk have been highly inconsistent,[25] and more comprehensive genotyping efforts suggest that *COMT* variants independent of Val108/158Met may be related to breast cancer risk.[26] Although polymorphism in this gene has also been linked to the risk of developing other hormonal cancers, including endometrial[27] and prostate,[28] the few previous studies of *COMT* genotype and CRC risk have reported no meaningful association.[29–31]

Little is known about whether catechol estrogens influence disease progression and metastasis. In studies of breast cancer, *COMT* genotype has been linked to advanced stage at diagnosis,[32] treatment-associated outcomes, such as fatigue and pain tolerance,[33] and disease-specific survival.[34] Not all studies, however, have observed this,[35] including one that found survival differences for a variant of *COMT* other than Val108/158Met.[36] In this first evaluation of *COMT* genotype and CRC survival, we captured common germline variation across the gene using data from four large epidemiologic studies in the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO).

METHODS

Survival cohorts and follow-up

Mortality information was ascertained for 2,458 genotyped women diagnosed with incident invasive CRC after age 50. These women were participants in either the: 1) Nurses' Health Study (NHS); 2) Postmenopausal Hormones Supplementary Study to the Colon Cancer Family Registry (PMH-CCFR); 3) VITamins And Lifestyle (VITAL) Study; or 4) Women's Health Initiative (WHI). Study-specific data collection procedures have been documented previously.[37–42] All participants provided informed consent and all studies were approved by their respective Institutional Review Boards.

Relevant prediagnostic exposures, such as body mass index (BMI), smoking status, and hormone therapy, were harmonized from study-specific baseline or follow-up questionnaires by members of a GECCO committee.[43] Tumor characteristics were abstracted from medical records and/or cancer registry linkages. Tumor site was classified using ICD 9 and ICD 10 codes, and stage at diagnosis was harmonized to approximate categorizations of SEER summary stage. Vital status, dates, and causes of death were determined from medical records, state death certificates, and/or National Death Index (NDI) linkage through mid-2008 for NHS, mid-2009 for WHI, and the end of 2009 for PMH-CCFR and VITAL.

COMT genotypes

Eleven tag-SNPs of *COMT* with minor allele frequency (MAF) ≥5% and linkage-disequilibrium (LD) threshold of r^2=0.8 were selected using the Genome Variation Server.[44] Study-specific genotyping procedures have been previously published[40, 41] and additional details are available in a similar survival analysis using the same samples.[12] WHI genotyped participants in two mutually exclusive sets (WHI1, WHI2). All 11 SNPs were directly genotyped in PMH-CCFR using a GoldenGate assay from Illumina (San Diego, CA). All but 2 SNPs were available from Illumina genome-wide arrays used by NHS, VITAL, WHI1, and WHI2. Missing genotypes were imputed with MaCH based on HapMap2.[45] We used a modest proxy for rs4646315 (rs4646312; r^2=0.3), but rs9332347 had no suitable proxy and was excluded.

Statistical analyses

Survival-time was calculated from the date of CRC diagnosis until the end of available follow-up or death from any cause (overall) or CRC (CRC-specific). Of 2,726 women 50 years old or older at diagnosis with available genotype, we excluded those missing survival-time (N=97, 5, 25, and 43 in NHS, VITAL, WHI1, and WHI2, respectively), and those missing stage (N=34, 2, 1, 5, 53 in NHS, PMH-CCFR, VITAL, WHI1, and WHI2, respectively). Hazard ratios (HR) and 95% confidence intervals (CI) per minor allele were calculated from proportional hazards regression using SAS 9.2. Single-SNP models were adjusted for age at diagnosis and race (PMH-CCFR) or principal components of ancestry (NHS, WHI1, WHI2, VITAL). We considered models with and without further adjustment for stage at diagnosis, as well as those additionally adjusted for prediagnostic BMI, smoking status, and hormone therapy.

In secondary exploratory analyses, we tested whether associations with CRC-specific and overall survival depended on BMI, smoking status, or postmenopausal hormone use prior to diagnosis by fitting SNP-interactions in single-SNP models that adjusted for age at diagnosis, race/ancestry, and stage at diagnosis. Estimates were pooled across studies using inverse variance-weighted random-effects meta-analysis. We report uncorrected *P*-values and Benjamini-Hochberg[46] false discovery rate (FDR)-corrected *P*-values that account for multiple comparisons, considering $P_{FDR} \leq 0.05$ statistically significant. Analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). All statistical tests were two-sided.

RESULTS

Of 2,458 women with CRC and available information on stage and survival-time, 799 died from any cause (566 from CRC) over a median follow-up of 7 years after diagnosis across all study samples (Table 1). PMH-CCFR had the narrowest age-range for study eligibility and accordingly included the youngest women. There were relatively few rectal cancers included in WHI1 by design. The observed MAF of evaluated SNPs ranged from 16–49%, which helped ensure a sufficient number of observed deaths for all possible genotypes.

No SNP-survival association reached statistical significance accounting for multiple comparisons for CRC-specific or overall survival (Table 2). Estimates further adjusted for prediagnostic BMI, smoking status, and hormone therapy were similar (not shown). None of the SNP-interactions with prediagnostic BMI, smoking status, and hormone therapy achieved statistical significance for CRC-specific or overall survival (not shown).

DISCUSSION

Aside from estrogen-receptor silencing via methylation,[4] little is known about the role of estrogen and its metabolites in promoting or inhibiting tumor cell proliferation in the colon and rectum. Catechol-*O*-methyltransferase inactivates estrogen-quinones responsible for oxidative DNA damage[47] and influences levels of pro-apoptotic estrogen-metabolites such as 2-hydroxyestrone[48] – both phenotypes that may be associated with *COMT* polymorphism.[49] Our findings, however, do not support the hypothesis that common germline variation in *COMT* is related to CRC survival in postmenopausal women. Furthermore, genetic associations with survival-time did not depend on prediagnostic BMI, smoking habits, and hormone usage, all factors that have been independently linked to *COMT* genotype in previous studies.[22, 23, 50–52]

Studies of *COMT* genotype and cancer risk and survival have been highly inconsistent. If at all, germline polymorphism in *COMT* likely explains only a small proportion of the variation in circulating hormone concentrations,[24] making it difficult to observe associations with downstream chronic disease outcomes. The large size of our study is its primary strength. Our meta-analysis had adequate statistical power to detect modest associations. Given MAFs as observed in our samples (16–49%), assuming 75% 5-year overall survival with 30% of deaths occurring over at most 20 years of follow-up for those homozygous for the major allele, we had approximately 90% statistical power to detect HRs per minor allele between 1.2 and 1.3 for α=0.05 under an additive model. At α=0.005, we had 90% power to detect HRs between 1.2 and 1.4 for this MAF range. Minimum-detectable HRs for CRC-specific survival were slightly higher. Lastly, whereas previous investigations of *COMT* genotype and cancer outcomes have focused only on the Val108/158Met polymorphism, our tagging approach captured common variation across the gene.

Information on treatment was not available from the epidemiologic studies included in this analysis. Because treatment tends to be homogenous by stage, our stage-adjusted and stage-stratified analyses, however, may have some ability to account for confounding and effect-modification by treatment. We considered only common SNPs with MAF≥5%; it remains unclear if rare variants of *COMT* are associated with CRC survival.

CONCLUSIONS

Our findings suggest that common SNPs in the gene for catechol-*O*-methyltransferase may be unrelated to estrogen-mediated metastatic mechanisms for CRC. More comprehensive studies that include men, measure more and rarer variants, and evaluate intermediate clinical outcomes such as treatment tolerance may still be informative.

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TABLE 1

Characteristics at diagnosis of 2,458 women diagnosed with CRC in the five genotyped study samples[a]

Characteristic	NHS (N = 260)		PMH-CCFR (N = 729)		VITAL (N = 129)		WHI1 (N = 430)		WHI2 (N = 910)	
No. of deaths from CRC/any cause	77/104		161/244		23/37		113/157		192/257	
Age at diagnosis (years), mean (SD)	69	(7)	64	(7)	71	(6)	71	(7)	72	(7)
White race, N (%)	260	(100)	674	(92)	129	(100)	430	(100)	910	(100)
BMI (kg/m^2), mean (SD)	25	(4)	28	(5)	28	(6)	28	(6)	28	(6)
Smoking status, N (%)										
Never	113	(44)	338	(46)	58	(46)	184	(43)	438	(49)
Former	114	(44)	282	(39)	58	(46)	212	(50)	392	(44)
Current	32	(12)	109	(15)	11	(9)	29	(7)	65	(7)
Postmenopausal hormone therapy[b], N (%)										
No	122	(52)	309	(44)	62	(53)	--	--	328	(56)
Yes	114	(48)	401	(56)	56	(47)	--	--	261	(44)
Tumor subsite, N (%)										
Proximal colon	132	(51)	352	(48)	71	(56)	283	(66)	462	(51)
Distal colon	72	(28)	251	(34)	31	(25)	135	(32)	216	(24)
Rectum	54	(21)	126	(17)	24	(19)	9	(2)	227	(25)
Stage, N (%)										
Localized	60	(23)	309	(42)	58	(45)	172	(40)	392	(43)
Regional	150	(58)	344	(47)	48	(37)	196	(46)	397	(44)
Distant	50	(19)	76	(10)	23	(18)	62	(14)	121	(13)

[a] Counts for other variables may not sum to total due to missing data.

[b] Prediagnostic use of estrogen-alone or estrogen plus progestin. Use approximately one year prior to diagnosis for PMH-CCFR, at baseline questionnaire for WHI2 and VITAL, in 1990 for NHS. Not available for WHI-OS.

Abbreviations: BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; PMH-CCFR, Postmenopausal Hormones Supplementary Study to the Colon Cancer Family Registry; NHS, Nurses' Health Study; OS observational study; SD, standard deviation; VITAL, VITamins And Lifestyle Study; WHI1, Women's Health Initiative Set 1; WHI2, Women's Health Initiative Set 2.

TABLE 2

Associations between *COMT* genotype and CRC-specific survival and overall survival after diagnosis.

											CRC-specific Survival						Overall Survival					
		N with CRC[c]			N Deaths[c]			N CRC Deaths[c]			Stage-adjusted[d]			Not Stage-adjusted[e]			Stage-adjusted[d]			Not Stage-adjusted[e]		
SNP (Alleles)[a]	MAF (%)[b]	AA	Aa	aa	AA	Aa	aa	AA	Aa	aa	HR (95% CI)	*P*	P_{FDR}	HR (95% CI)	*P*	P_{FDR}	HR (95% CI)	*P*	P_{FDR}	HR (95% CI)	*P*	P_{FDR}
rs4646310 (G>A)	19	1,603	774	78	513	262	24	363	181	22	1.13 (0.94, 1.36)	0.18	0.36	1.07 (0.92, 1.24)	0.38	0.54	1.06 (0.92, 1.21)	0.40	0.56	1.02 (0.86, 1.22)	0.81	0.90
rs2020917 (C>T)	27	1,278	1,011	168	417	326	55	297	230	39	0.93 (0.81, 1.07)	0.33	0.41	0.99 (0.87, 1.14)	0.90	0.90	0.96 (0.85, 1.07)	0.45	0.56	1.01 (0.90, 1.13)	0.92	0.92
rs933271 (T>C)	29	1,239	1,016	199	390	336	72	293	224	48	1.18 (0.96, 1.43)	0.11	0.36	1.14 (1.00, 1.29)	0.05	0.25	1.12 (0.98, 1.29)	0.11	0.36	1.05 (0.91, 1.21)	0.5	0.73
rs1544325 (G>A)	44	776	1,221	457	258	409	131	186	286	94	0.92 (0.81, 1.05)	0.22	0.37	0.92 (0.81, 1.05)	0.23	0.46	0.93 (0.83, 1.05)	0.24	0.40	0.94 (0.82, 1.08)	0.37	0.73
rs740603 (G>A)	48	645	1,277	532	222	412	164	150	303	113	0.97 (0.85, 1.11)	0.65	0.65	0.95 (0.81, 1.12)	0.58	0.73	0.97 (0.82, 1.14)	0.73	0.73	0.97 (0.80, 1.18)	0.75	0.90
rs4646312 (T>C)	41	601	836	291	185	279	90	146	195	63	0.90 (0.72, 1.11)	0.31	0.41	0.86 (0.70, 1.06)	0.15	0.46	0.95 (0.76, 1.18)	0.64	0.71	0.94 (0.79, 1.13)	0.51	0.73
rs4680 (G>A)	49	630	1,239	582	190	409	200	146	284	136	1.04 (0.92, 1.17)	0.55	0.61	1.01 (0.90, 1.14)	0.83	0.90	1.10 (0.99, 1.22)	0.08	0.36	1.08 (0.97, 1.19)	0.16	0.53
rs165774 (G>A)	31	1,123	1,119	212	357	376	63	235	281	47	1.17 (1.02, 1.35)	0.03	0.30	1.18 (1.03, 1.36)	0.02	0.20	1.09 (0.97, 1.23)	0.16	0.36	1.08 (0.95, 1.23)	0.24	0.60
rs174696 (T>C)	21	1,537	810	104	533	234	31	374	170	21	0.87 (0.73, 1.02)	0.09	0.36	0.87 (0.72, 1.07)	0.19	0.46	0.84 (0.71, 0.99)	0.04	0.36	0.85 (0.71, 1.02)	0.08	0.53
rs9332377 (C>T)	16	1,752	630	73	547	266	25	384	166	16	1.11 (0.95, 1.30)	0.17	0.36	1.10 (0.90, 1.36)	0.35	0.54	1.09 (0.96, 1.25)	0.18	0.36	1.11 (0.97, 1.27)	0.13	0.53

[a] rs4646312 used as a proxy for rs4646315, which was genotyped only in PMH-CCFR. All SNPs are in intronic regions, except rs4680 (Val108/158Met) of exon 4. Major allele > Minor allele.

[b] Observed MAF across all studies; does not include PMH-CCFR for rs4646312.

[c] "A" represents major allele, "a" represents minor allele. Counts may not sum to total of 2,458 due to missing data. Counts for imputed SNPs based on best-call.

[d] Meta-analysis HR per minor allele adjusted for age at diagnosis, race (PMH-CCFR) or principal components of ancestry (NHS, WHI1, WHI2, VITAL), and stage at diagnosis..

[e] Meta-analysis HR per minor allele adjusted for age at diagnosis, race (PMH-CCFR) or principal components of ancestry (NHS, WHI1, WHI2, VITAL).

Abbreviations: CI, confidence interval; *COMT*, catechol-O-methyltransferase; CRC, colorectal cancer; FDR, false discovery rate; HR, hazard ratio; MAF, minor allele frequency; NHS, Nurses' Health Study; PMH-CCFR, Postmenopausal Hormones Supplementary Study to the Colon Cancer Family Registry; SNP, single-nucleotide polymorphism; VITAL, VITamins And Lifestyle Study; WHI1, Women's Health Initiative Set 1; WHI2, Women's Health Initiative Set 2