Genetic Variation in Inflammatory Pathways Is Related to Colorectal Cancer Survival

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Abstract

Purpose: Prognosis of patients with colorectal cancer (CRC) is associated with systemic inflammation, and anti-inflammatory drugs can reduce both CRC incidence and mortality. Genetic variation in proinflammatory pathways can affect an individual's CRC risk. However, few studies have investigated the prognostic importance of this genetic variation in CRC patients.

Experimental Design: We investigated the association between CRC survival and genetic variation in proinflammatory pathways among patients from the Puget Sound Surveillance Epidemiology and End Results registry. Single-nucleotide polymorphisms were genotyped in five genes (PTGS-1, PTGS-2, MRP4, NFKB, and IκBβ). Vital status was ascertained through linkage to the National Death Index. Cox proportional hazards regression was used to calculate HRs and 95% confidence intervals (CI). The false discovery rate method of Benjamini and Hochberg was applied to address multiple testing.

Results: Four PTGS-1 variants were associated with CRC survival. One, G>A intron 9 (rs1213266), was associated with approximately 50% lower CRC mortality (HRAA/AG vs. GG = 0.48; 95% CI, 0.25–0.93). Three variants, including L237M, resulted in significantly elevated CRC mortality risk, with HRs ranging from approximately 1.5 to 2.0. Two variants in IκBβ, including R526Q, were significantly associated with CRC survival. Correction for multiple testing indicated that variants in both PTGS-1 and IκBβ are reproducibly associated with CRC survival.

Conclusion: Our findings suggest that genetic variation in proinflammatory pathways may be important for CRC prognosis. This investigation represents one of the first descriptions of the relationship between inherited polymorphisms and mortality in CRC patients and provides a starting point for further research.

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Introduction

Inflammation has consistently been associated with colorectal cancer (CRC) development and prognosis in clinic and population studies (1, 2). The role of inflammation in prognosis may be mediated through influences on processes crucial for tumor progression, including metastasis and invasion (3–5). Medications that inhibit inflammation such as nonsteroidal anti-inflammatory drugs (NSAID), which interact with the prostaglandin synthesis pathway, decrease the risk of colorectal neoplasia (6–8). Consistent with inflammation’s role not only in cancer development but also cancer progression, NSAIDs have also been associated in large, population-based studies with improved survival of patients with CRC (9–11).

The prostaglandin synthesis pathway is critical for regulation of inflammatory processes and plays a well-defined role in colorectal carcinogenesis (12, 13). Prostaglandin H synthases (COX-1 and COX-2) are pivotal enzymes in this pathway (14, 15); upregulation of prostaglandins results in cellular proliferation, angiogenesis, and increased cellular motility (16–18). The NFκB pathway represents another important proinflammatory pathway associated with CRC; NFκB is a transcription factor with multiple targets involved in inflammatory signaling and carcinogenesis, including prostaglandin synthases (19–22). The NFκB transcription factor plays a role not only in regulating cellular growth signals but also in regulating apoptosis and the survival of cancer cell populations (23, 24).

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Translational Relevance

The presence of common genetic variation can refine prediction of patient outcome for colorectal cancer (CRC) and help guide the management and risk assessment for individual patients. This study suggests that inflammatory pathway–associated genetic variation may possibly be useful for improving outcome prediction for CRC patients. These results improve our understanding of colorectal cancer progression, confirming that key cellular pathways involved in CRC incidence also play a role in disease progression. Identified genes provide a good starting point for further research and potential targets for CRC therapy, including pharmacogenetic research on COX inhibitors.

A study conducted in a Spanish population (25) investigated variation in 2 PTGS-2 (COX-2) single-nucleotide polymorphisms (SNP: -765 G>C and 3618 A>G) among 284 patients with CRC in relation to tumor characteristics and disease prognosis. 3618 A>G was found to be a prognostic indicator for patients with CRC, with carriers of the variant allele experiencing approximately 60% improved survival compared with wild-type patients. To our knowledge, this has been the only population study to date examining polymorphisms in genes involved in the prostaglandin synthesis pathway in relation to CRC survival. However, multiple studies have noted that variation in genes encoding both prostaglandin synthases and the NFkB transcription factor is associated with CRC risk (26–29). We therefore hypothesized that variation in these important inflammation-associated genes would affect the survival of patients with CRC.

We examined SNPs in genes involved in both the prostaglandin synthesis pathway (PTGS1 = COX-1, PTGS2 = COX-2, MRP4) and the NFkB pathway (NFkB, IkBβ) in relation to CRC survival among patients identified from the population-based Seattle Colon Cancer Family Registry. This investigation represents one of the first descriptions of the relationship between inherited genetic polymorphisms and survival after a diagnosis of CRC.

Materials and Methods

Study population

The Colon Cancer Family Registry (Colon CFR) is a 6-site international collaboration established to investigate the genetic epidemiology of CRC. This report describes the Seattle Colon CFR, where patients with incident, invasive CRC occurring from 1997 to 2002 from 3 counties in Western Washington State were ascertainment from the population-based Puget Sound Surveillance Epidemiology and End Results (SEER) Registry (30).

Patients with CRC from the Seattle Colon CFR who were genotyped as part of a Colon CFR-wide study of candidate SNPs were included in our survival analysis (31). No patients reported multiple primary tumors. The parent study used a case/unaffected sibling control design, selecting CRC cases from each Colon CFR study site who had unaffected siblings also enrolled in the Colon CFR.

SNP selection and genotyping

Selection of tagSNPs and SNP genotyping methods for the parent study have been published previously (31). Briefly, tagSNPs for PTGS-1, PTGS-2, MRP4, NFkB, and IkBβ were selected using Haploview Tagger and the following criteria: minor allele frequency (MAF) more than 5%, pairwise r² of more than 0.95, and distance from closest SNP of more than 60 bps. The 5′ and 3′ untranslated regions (UTR) for each gene were extended to include the most up- or downstream SNP within the linkage disequilibrium (LD) block (~10 kb upstream and 5 kb downstream). In regions of no or low LD, SNPs with an MAF more than 5% at a density of approximately 1 per kb were selected from either HapMap or dbSNP.

We investigated the following tagSNPs: 17 in PTGS-1, 8 in PTGS-2, 41 in NFkB, 9 in IkBβ, and 62 in MRP4. SNPs were genotyped on the Illumina platform in the laboratory of Dr. Duggan at Translational Genomics Research Institute (Phoenix, AZ). SNPs were excluded on the basis of the following criteria: GenTrain score of <0.4, 10% GC score of <0.25, ABT Dev of >0.1239, call rate of >0.95, or more than 2 P-P-C errors. Interplate and intraplate replicates were included, and SNPs were excluded from the analysis if there were more than 2 errors on the replicate genotypes. In addition, genotype data from 30 CEPH trios (Coriell Cell Repository) were used to confirm reliability and reproducibility of the genotyping. SNPs were excluded from the analysis if more than 3 genotypes were discovered to be discordant in comparison with the genotype from the International HapMap Project.

Outcome assessment

Vital status and date of death were ascertained for all cases through linkage to the National Death Index (NDI) records; causes of death were classified using ICD10 codes. The NDI identifies known deaths throughout the United States with a high degree of sensitivity, validity, and completeness (32, 33). The primary outcome of interest was mortality from CRC, assessed from underlying cause of death obtained from the NDI. Time to CRC mortality was evaluated from SEER-reported date of CRC diagnosis and NDI-recorded date of death. Patients alive at the time of their last known vital assessment were censored at that date, with the most recent vital status linkage occurring December 31, 2009. Patients dying of causes other than CRC were censored at their recorded date of death.

Tumor characteristics at the time of diagnosis, including stage and subsite, were obtained from Surveillance Epidemiology and End Results reports. Advanced disease was defined as CRC with distant metastasis (n = 61); nonadvanced disease included localized and regional stage disease (n = 362). Subsite of disease was categorized using ICD10.
Genetic Variation and Colorectal Cancer Prognosis

codes: proximal (C18.0-C18.5); distal (C18.6-18.7); and rectal (C19.9, C20.9, and C21.8). On the basis of established guidelines and 10 available MSI markers (34), cases were classified as MSI-stable if 0% of loci were unstable, MSI-low if less than 30% of loci were unstable, and MSI-high if 30% or more of loci were unstable, with unequivocal results for at least 4 markers required to characterize MSI status.

Statistical analyses

Cox proportional hazards regression models were used to calculate HRs and 95% CIs for the association between each SNP and CRC survival. Regression models assumed a dominant mode of inheritance; the number of events was not sufficient to evaluate unrestricted or log-additive models. Cox models included adjustment for sex, age at diagnosis, and self-reported White/non-White race; models additionally including the stage of disease at diagnosis were also run. In exploratory analyses, models were restricted to Caucasians (n = 381). Regression models were also run with all-cause mortality as an outcome. Results were considered statistically significant if the 2-sided value of \( P < 0.05 \).

To address the issue of conducting multiple tests within each gene, we applied the false discovery rate (FDR) control method of Benjamini and Hochberg (35, 36). The control of the FDR using the Benjamini and Hochberg (B&H) method takes a decidedly different approach from the more conservative family-wise error rate (FWER) methods, including the Bonferroni correction, balancing protection against false inference with the ability to detect true associations. The B&H method is a step-up method that requires listing the \( P \) values calculated from regression analyses in descending order from highest to lowest (i.e., values closer to 0 listed first). Once a FDR level has been predetermined, the B&H method takes into account both the total of number of tests done (i.e., number of SNPs tested) and the \( P \) values calculated for each test from regression models to calculate an adjusted \( P \) value for each test (i.e., each SNP). These adjusted \( P \) values are compared with the \( P \) values calculated directly from regression models, and a list of noteworthy SNPs at the FDR level chosen is identified. Instead of protecting against any type I error (i.e., one or more false positives), the B&H method allows for false positive results in the process of discovering true positives and guarantees that under repeated use, the long-run average of false positives will fall at or below some prespecified FDR level.

For example, if a FDR level (i.e., 25%) is chosen, the following equation is applied to each of the sequentially listed \( P \) values in a given gene, beginning from the least to most extreme (i.e., beginning at the bottom of the list of \( P \) values): \( \text{FDR} \times (P \text{ value order/total } P \text{ values}) \). At an FDR of 25%, the Benjamini-adjusted \( P \) value for the sixth ordered SNP of a list of 20 SNP \( P \) values in a given gene would be: \( 0.25 \times (6/20) = 0.08 \). If the \( P \) value for the \( n^{th} \) ordered value falls below the Benjamini-adjusted \( P \) value, all SNPs with \( P \) values equal to or less than that ordered value are considered noteworthy. Returning to the previous example, if the \( P \) value (calculated from Cox regression) for the sixth ordered SNP were less than 0.08, the first 6 \( P \) values (i.e., first 6 SNPs) would all be considered noteworthy at the FDR 25% level. Of these, we would expect that one quarter (less than 2) would be false positive but that the remaining three quarters (at least 4) are true positives.

This FDR method controls the number of false positives so that we have confidence that a certain percentage of the positive results reported are in fact true positives, recognizing at the same time that a certain percentage are false positives. We generated a list of noteworthy SNPs at both the FDR 50% and FDR 25% levels for the 5 genes investigated.

Results

After an average of 6.5 years (SD = 3.1 years) of follow-up after CRC diagnosis, 151 deaths from any cause were observed. Three quarters of the deaths among patients were due to CRC (n = 115). Patients’ ages at diagnosis ranged from 23 to 74, with approximately 10% of patients under the age of 40. A slightly larger proportion of deceased patients had microsatellite stable tumors and tumors located in the distal colon. As expected, patients diagnosed with localized tumors had much better overall survival compared with patients with advanced disease, with more than 30% of deceased patients being diagnosed with advanced disease, as compared with only 5% of patients who remained alive at the end of study follow-up (Table 1).

Genetic variation in both PTGS-1 (COX-1) and 1kb\textit{BK}β was associated with prognosis of patients with CRC. These 2 genes had more SNPs with values of \( P < 0.05 \) than expected by chance (more than 1 SNP for every 20 tested, detected as statistically significant). In addition, of the 5 genes tested, only PTGS-1 and 1kb\textit{BK}β had SNPs that were noteworthy. All SNPs noteworthy at the FDR 50% level are reported in Tables 2 and 3; SNPs noteworthy at the FDR 25% level are denoted in italics. The other 3 genes investigated did not include noteworthy SNPs; for illustrative purposes, \( P \) values calculated from Cox regression models and B&H-adjusted \( P \) values (at the FDR 50% level) for these 3 genes are presented in Supplementary Tables.

Four of the 17 SNPs in PTGS-1 were statistically significantly associated with CRC-specific mortality. The presence of the minor allele conferred an approximately 1.5 to 2 times greater risk of CRC mortality compared with the wild-type for 3 of the SNPs (rs10306155: G>\textit{C}, \textit{rs}4836885: A>G intron 8, L237M: C>A exon 7). In contrast, patients with the minor allele for rs1213266 (C>A exon 9) had approximately 50% lower mortality compared with wild-type patients (HR = 0.48; 95% CI, 0.25–0.93; Table 2). Correction for multiple testing confirmed that genetic variation in PTGS-1 was associated with CRC survival, with 6 SNPs; including all SNPs noted above with value of \( P < 0.05 \), were noteworthy at the FDR 25% level; the expectation is that one quarter of these SNPs (less than 2) are false positives but that the remaining 3 quarters (at least 4) may in fact be associated with CRC survival.
Two of the 9 SNPs in \(\text{IkB}\beta\) were statistically significantly associated with CRC mortality. Patients with the minor allele for rs1986055 (A > G intron 19) experienced less than half the mortality due to CRC compared with wild-type patients (HR = 0.39; 95% CI, 0.14–1.00; Table 3). Estimates for R524Q were imprecise because only one patient was observed to carry the minor allele. Correction for multiple testing also indicated that genetic variation in \(\text{IkB}\beta\) was associated with CRC survival, with 2 SNPs in \(\text{IkB}\beta\) noteworthy at the FDR 25% level.

When we restricted analyses to Caucasians only (\(n = 381\)), we obtained similar results to those reported here. For both PTGS-1 and \(\text{IkB}\beta\), all SNPs noteworthy when investigating CRC survival, except one, were also noteworthy when considering the outcome of death from any cause among patients. Effect estimates for the association between these SNPs and all-cause mortality were similar to those specific to CRC. For example, of the 4 SNPs in PTGS-1 that were statistically significantly associated with CRC-specific mortality, 3 were also statistically significantly associated with all-cause mortality (rs10306155: G > A intron 2, rs4836885: A > G intron 8, L237M: C > A exon 7; Table 2).

Adjustment for stage of disease at diagnosis attenuated the statistical significance of the associations for 3 of the SNPs in PTGS-1 (rs10306155: G > A intron 2, rs4836885: A > G intron 8, L237M: C > A exon 7), although 2 of these SNPs, rs10306155 (G > A intron 2) and L237M (C > A exon 7), remained marginally associated with CRC-specific mortality (HR = 1.48; 95% CI, 0.96–2.28; HR = 1.77; 95% CI, 0.91–3.45, respectively). For these SNPs, patients with the wild-type genotype were statistically significantly less likely than patients with the minor allele to present with advanced stage of disease at diagnosis. For both rs10306155 (G > A intron 2) and rs4836885 (A > G intron 8), approximately 13% of patients with the wild-type genotype presented with advanced disease, compared with approximately 19% of patients with the minor allele. For L237M, 14% of patients with the LL genotype presented with advanced tumors compared with 29% of patients with either the LM or MM genotype.

Adjustment for other tumor characteristics, including MSI status and tumor subsite, did not alter reported effect estimates, and the distribution of these tumor characteristics was similar between cases with and without the minor allele for all except L237M. Although approximately 36% and 30% of patients with the LL genotype presented with advanced tumors compared with rectal and distal tumors, respectively, only about 13% of patients with either the LM or MM genotype presented with distal tumors, and 50% presented with rectal tumors.

**Discussion**

This investigation is one of the first to explore the relationship between inherited genetic polymorphisms and CRC survival. Genetic variation in both PTGS-1 (COX-1) and \(\text{IkB}\beta\) was associated with an altered risk of mortality from CRC. Our confidence in these results is strengthened by the fact that specific polymorphisms in PTGS-1 and \(\text{IkB}\beta\) showed consistent statistical evidence of an association with CRC survival. Both genes had more SNPs with statistically significant associations than would be expected by chance; each gene had multiple SNPs that were noteworthy using the B&H FDR control method; and all of the statistically significant SNPs in both PTGS-1 and \(\text{IkB}\beta\) were also noteworthy SNPs at the FDR 25% level.
Table 2. Associations between PTGS-1 polymorphisms\(a\), CRC mortality, and all-cause mortality

<table>
<thead>
<tr>
<th>Common name</th>
<th>dbsNP ID</th>
<th>MAF (%)</th>
<th>Alive/ censored</th>
<th>CRC deaths</th>
<th>HR (95% CI) for CRC mortality</th>
<th>P</th>
<th>Alive Death from any cause</th>
<th>HR (95% CI) for all-cause mortality</th>
<th>P</th>
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<td>G&gt;A intron 9</td>
<td>rs1213266</td>
<td>15.2</td>
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<td>226</td>
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<td></td>
<td>49</td>
<td>20</td>
<td>0.71 (0.43–1.15)</td>
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<td>G&gt;A intron 2</td>
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<td>60</td>
<td>44</td>
<td>1.63 (1.13–2.36)</td>
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<td>A&gt;G intron 8</td>
<td>rs4836885(b,d)</td>
<td>70</td>
<td>34</td>
<td>1.62 (1.06–2.49)</td>
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<td>67</td>
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<td>1.47 (1.02–2.12)</td>
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<td>C&gt;A exon 7</td>
<td>L237M</td>
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<td>1.63 (1.06–2.49)</td>
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<td></td>
<td>30</td>
<td>20</td>
<td>1.22 (0.73–2.03)</td>
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</table>

Note: Results in italics were noteworthy at the FDR 25% level (6 SNPs for CRC-specific and 5 SNPs for all-cause mortality). Results in table above are adjusted for age, sex, and reported race at enrollment. MAF were calculated among unaffected siblings of cases.

\(a\)The SNPs were ‘noteworthy’ at an FDR 50% level when investigating both CRC-specific and all-cause mortality unless otherwise noted.

\(b\)SNPs are in high LD \(\left(r^2 = 0.93\right)\).

\(c\)SNPs are in high LD \(\left(r^2 = 0.87\right)\).

\(d\)SNPs are in high LD \(\left(r^2 = 0.95\right)\).

\(e\)SNPs are in high LD \(\left(r^2 = 0.91\right)\).

\(f\)SNPs are in high LD \(\left(r^2 = 0.95\right)\).

\(g\)SNP was not ‘noteworthy’ at the FDR 50% level for all-cause mortality.
Clinical Cancer Research

The majority of the SNPs identified have not been thoroughly characterized with respect to function, but at least 3 of the polymorphisms identified result in nonsynonymous coding amino acid changes. The presence of the minor allele (A allele) in L237M (rs3747811) in PTGS-1 results in a proline to leucine change at amino acid position 237; the presence of the minor allele (A allele) in P17L (rs3842787) in PTGS-1 results in a proline to leucine change at amino acid position 17; and the minor allele (A allele) in R524Q (rs6478565) of lkbkβ results in an arginine to glutamine change. The L237M polymorphism has been characterized previously as significantly altering protein expression levels. Multiple SNPs in PTGS-1 were observed to be in high LD ($r^2 = 0.91$); rs10306163 and rs3842798 ($r^2 = 0.95$). These SNPs can be grouped into 3 LD blocks in PTGS-1: bin 1 (rs10306155: G>A exon 2, rs4836885: A>G intron 8, and rs9299280: A>G intron 8), bin 2 (rs10306163: A>G intron 8, rs3842798: A>G exon 7), and bin 4 (rs6478565: A>G intron 8, rs4273915: G>C intron 7). Although this may represent some redundancy in the information for any of these given SNPs, at least 3 distinct SNPs with values of $P < 0.05$ and 4 SNPs noteworthy at the FDR 25% level would remain if only one SNP from each of these bins were included in our analyses; the inference that genetic variation in PTGS-1 (COX-1) is associated with CRC mortality would be unchanged. In addition, the observation of multiple noteworthy SNPs within one LD block provides stronger evidence that these particular regions of the prostaglandin synthase 1 gene may be associated with CRC prognosis.

It is biologically plausible that these genes, which influence inflammation, are involved in CRC survival. Prostaglandin synthase 2 (COX-2) expression has been linked to

### Table 3. Associations between lkbkβ polymorphisms, CRC mortality, and all-cause mortality

<table>
<thead>
<tr>
<th>Common name</th>
<th>dbSNP ID</th>
<th>MAF (%)</th>
<th>Alive/</th>
<th>CRC deaths</th>
<th>HR (95% CI) for CRC mortality</th>
<th>P</th>
<th>Alive/</th>
<th>Death from any cause</th>
<th>HR (95% CI) for all-cause mortality</th>
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<td>A&gt;C intron 19</td>
<td>rs11986055</td>
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<td>AA</td>
<td>281</td>
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<td>G&gt;A exon 15</td>
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<td>312</td>
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<td>0.77</td>
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NOTE: Results in italics were also noteworthy at the FDR 25% level (2 SNPs for CRC-specific and 3 SNPs for all-cause mortality). Results in table above are adjusted for age, sex, and reported race at enrollment.

MAF were calculated among unaffected siblings of cases.

The SNPs were noteworthy at an FDR 50% level when investigating both CRC-specific and all-cause mortality unless otherwise noted.

SNP was not noteworthy at the FDR 50% level for all-cause mortality.
Recent findings suggest that variation in genes involved in crucial inflammatory pathways may be important for disease progression and treatment responses. Future studies should also include more detailed treatment information. We were only able to consider first-line treatment data in our analysis; although these data did not alter observed associations, the examination of more detailed treatment information could shed light on potential interactions between inherited genetic variation and treatment responses. Finally, patients originated from a population-based cancer registry, but the design of the parent genetic association studies required that each patient with CRC had to have a sibling that was not affected by CRC to participate. The minor allele frequencies observed in this study population were higher than would be expected in a population that was not enriched with a first-degree family history of CRC. Although the direction of the potential bias introduced by this selection is difficult to predict, future studies should be conducted in true population-based samples to maximize generalizability.

Very little is known about the role of genetic variation in altering patient survival after a diagnosis of CRC. Our findings suggest that variation in genes involved in crucial inflammatory pathways may be important for disease prognosis. This study begins to shed light on potential interactions between inherited genetic variation and treatment responses.
PTGS-1 (COX-1) and IkBkβ should be top priority genes for inclusion in future studies of CRC outcomes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References


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