Introduction

Colorectal cancer (CRC) is the second most common cause of cancer-related death in the United States. Despite improvements in treatment modalities, the 5-year survival rate for CRC patients ranges from 10–90% [1]. This large variation in clinical outcome is due, in part, to the fact that CRC is a heterogeneous disease comprising discrete subsets that evolve through multiple different etiologies. Both germline and somatic genetic alterations can be involved in the malignant transformation of normal colon cells. Extensive investigations have identified somatic mutations in TP53 or KRAS that are involved in the progression of adenoma to CRC [2–5]. For germline mutations, high-penetrance changes in adenomatosis polyposis coli, mismatch repair, mothers against decapentaplegic homolog 4, bone morphogenetic protein receptor type IA and serine threonine kinase 11 genes have been reported to be associated with increased CRC susceptibility in 5% of the population [6] while the effects of combinations of low-penetrance variants remains largely elusive.

The completion of the Human Genome Project and the development of improved high-throughput genotyping techniques permit large scale interrogation of the genome, resulting in a better understanding of common polygenic disease. This progress has led to the common disease, common variant hypothesis, which
suggests that a number of allelic variants found in more than 1–5% of the population genetically influences the susceptibility to common heritable diseases [7]. In line with this model, candidate gene analysis and multi-stage genome wide association studies (GWAS) have identified numerous single nucleotide polymorphisms (SNPs) across several chromosomes that are associated with an increased risk of CRC development [8–10]. In a case-control study involving 1807 patients and 5511 controls, Haiman and colleagues noted that rs6983267 on chromosome 8q24, a genomic region that contains few genes, was significantly linked to a higher predisposition of CRC in individuals of different ethnicities [10]. Several later reports confirmed rs6983267 as a low-penetrance risk marker for CRC [9,12,13,16,17]. Given this consistent observation and the frequent amplification of this region in CRC [10], further analysis of SNPs within this gene-poor area revealed a second tightly linked variant, rs10505477, as well as three other SNPs on 8q24, rs10808556, rs7014346 and rs7013278, as low-penetrance variants that also influence carcinoma formation [10,13,14,15,17].

Besides the SNPs on 8q24, Tomlinson et al identified rs16892766 on 8q23.3 as an additional risk variant [15]. Likewise, Zanke and colleagues found an association between rs719275 on 9p24 and CRC [17]. Subsequent investigation of this site by Poynter et al showed that individuals with the A/A genotype had a moderate increased risk of CRC compared to C/C individuals in population-based but not clinic-based families [13]. On the 10p14 and 11q23 loci, rs10795668 and rs3092842 were respectively shown to be related to disease occurrence [14,15]. In addition, numerous other risk loci have been subsequently identified and mapped to 14q22.2 (rs4444235, BMP4) [18], 15q13 (rs4779584, rs10518, CRAC1) [11], 16q22.1 (rs9929218, CDH1) [18], 18q21 (rs4939827, rs12953717, rs4464148, SMAD7) [8], 19q13.1 (rs10411210, RPHN2) [18] and 20p11.23 (rs961253) [18].

Despite the increasing number of loci being identified to influence the risk of CRC development, to date, only a few studies have investigated the effects of these variants on disease outcome [19–22]. The findings of these studies however remained inconsistent on the relationship between these risk variants and CRC survival. Therefore, in the present study, we examined the prognostic significance of 11 CRC susceptibility SNPs at 6 CRC risk loci (rs6983267, rs10505477, rs7013278, rs7014346, rs719275, rs10795668, rs3092842, rs4779584, rs10518, rs4464148 and rs4939827, Table S1), using 583 patients with CRC from the prospective North Carolina (NC) Cancer Care Outcomes Research and Surveillance Consortium Study (CanCORS).

**Methods**

**Study Population and Follow-Up Information**

The study design of CanCORS has been described previously [23]. NC CanCORS assembled a prospective population-based cohort in 33 county areas of NC, USA. In this study, DNA samples from 383 eligible patients diagnosed with CRC between April 2003 and January 2005 were retrospectively genotyped. Patient demographics were obtained from a baseline patient survey. Detailed clinical information on primary site of tumor, American Joint Committee on Cancer (AJCC) stage and type of treatment provided were obtained from review of medical records and pathological reports of CRC diagnosis from the North Carolina Central Cancer Registry by trained abstractors within 6 months following diagnosis. Patients were followed up for a median of 3.5 years. Survival and mortality data was determined from a three-year phone survey of participants or next-of kin and further confirmed through ascertainment of death records through the social security death index (SSDI) using patients’ social security numbers. Mortality information or survival status was available for all patients genotyped in this study through the SSDI. Disease-free survival information was not available. This study was approved by the Institutional Review Board of the University of NC (IRB number: 04–08–60). Written informed consent was obtained from each participant.

**DNA Extraction and SNP Genotyping**

Buffy coat was prepared from a blood sample collected from each study participant. DNA was extracted fromuffy coat using Puregene kit (Qiagen, Valencia, CA, USA). In addition, DNA samples comprising of 94 European-Americans, 93 Han Chinese (Han people of Los Angeles) and 94 Mexican-Americans (Mexican-American community of Los Angeles) from Coriell (Coriell Institute for Medical Research, Camden, NJ, USA) as well as 86 African-Americans as previously described [24], were also used to confirm the reliability and reproducibility of the genotyping performed. All DNA samples were genotyped for 11 CRC susceptibility SNPs at 6 CRC risk loci using TaqMan allelic discrimination assays (Applied Biosystems, Foster City, CA, USA) (Table S1). In a total volume of 20 μL, reactions consisted of 2 μL of 10 ng/μL DNA, 0.5 μL of 20X TaqMan® SNP genotyping assays (Applied Biosystems), 10 μL of 2X TaqMan® Universal PCR Master Mix, No AmpErase UNG (Applied Biosystems) and 7.5 μL of water. PCR was performed with an initial denaturation step at 95°C for 10 min followed by 50 cycles of denaturation at 92°C for 15 s and annealing with extension at 60°C for 1 min. All PCR reactions were performed on a Bio-Rad Tetrad 2 Thermal Cycler (Bio-Rad, Hercules, CA, USA). The fluorescence intensities of the samples were measured before and after PCR using an Applied Biosystems 7500 Real-Time PCR System (Applied Biosystems). Data obtained was analyzed and genotypes assigned using 7300 System SDS Software, version 1.4 (Applied Biosystems). Genotype allocation was performed blinded to patients’ clinical data. Genotyping was successful in >96% of samples. For the samples from the four additional populations, all genotypes were in agreement with that reported in the Hapmap (www.hapmap.org). No discordance in genotype or allele frequencies was observed between the European-American or African-American patient samples with the respective European-Americans or African-Americans in the additional populations genotyped.

**Statistical Analysis**

All polymorphisms were examined for deviation from Hardy-Weinberg equilibrium (HWE) using χ² test. Clinical and biological variables were examined for associations with individual SNPs using Fisher’s Exact Test. Univariate and multivariate survival analyses were carried out using Cox regression analysis to evaluate associations between genetic variants and overall survival. Multivariate models were adjusted for age, ethnicity, gender, disease stage, site of tumor and treatment administered. For each SNP, the risk allele was defined as the allele previously established in the literature to confer a risk of CRC while the other allele was considered the protective allele. Homozygosity for the protective allele served as a reference genotype for regression analysis and was assigned a hazard ratio (HR) of 1.0. A P<0.05 was considered significant. Multiple correction was performed using the conservative Bonferroni method. All data was analyzed using SAS statistical analysis software version 9 (SAS Institute Inc, Cary, NC, USA).
Table 1. Demographic, Histopathological and Clinical Characteristics of Study Patients.

| Characteristics          | N (%)       |
|--------------------------|-------------|
| Patients                 | 583         |
| Age, years               | Median (range) 65.0 (26.0–93.0) |
| Gender                   | Male 304 (52.1) |
|                          | Female 279 (47.9) |
| Ethnicity                | European-American 472 (81.0) |
|                          | African-American 111 (19.0) |
| Stage                    | 1 161 (27.6) |
|                          | 2 160 (27.4) |
|                          | 3 165 (28.3) |
|                          | 4 68 (11.7) |
|                          | Missing 29 (5.0) |
| Tumor Site               | Colon 261 (44.8) |
|                          | Rectum 241 (41.3) |
|                          | Missing 81 (13.9) |
| Treatment - Surgery      | Yes 573 (98.3) |
|                          | No 8 (1.4) |
|                          | Missing 2 (0.3) |
| Treatment – Chemotherapy | Yes 297 (50.9) |
|                          | No 279 (47.9) |
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Table 1. Demographic, Histopathological and Clinical Characteristics of Study Patients.

Results

Patient Characteristics

Table 1 summarizes the baseline characteristics of patients in this study. The median age of patients was 65.0 years old and 47.9% were female. Among the 583 patients, 81.0% were European-Americans and 19.0% were African-Americans. At the time of diagnosis, the proportions of study participants classified to AJCC stages 1, 2, 3 and 4 were 27.6%, 27.4%, 28.3% and 11.7% respectively. In this cohort, the proportion of patients with colon cancer or rectal cancer was comparable. The majority of patients (98.3%) received surgical treatment while chemotherapy was administered to 50.9% of the study population.

Low-Penetrance CRC Susceptibility Genotypes

The distribution of genotypes in this patient cohort is presented in Table S2. For this group of patients, no deviation from HWE was detected among European- or African-American patients for any of the SNPs. The allele frequencies for all SNPs were similar to those previously reported in HapMap (www.hapmap.org). Genotype distributions varied between European- and African-American patients for all SNPs (P<0.05 except rs7014346 and rs3802842 (Table S2).

Relationships Between Low-Penetrance CRC Susceptibility SNPs and Clinicopathological Features of CRC Patients

No significant differences were observed between the SNPs with gender, tumor site, surgical intervention or chemotherapy administration (Table S2). For age of CRC diagnosis, apparent differences in genotype distribution were only found for rs10795660 (P=0.005; Table S2). It was observed that the prevalence of the A/A genotype for this SNP decreases in patients older than 50 years. In addition, stage of disease was significantly related to rs4464148 and rs4939827 genotypes (P<0.05; Table S2). C and T alleles, the risk allele for rs4464148 and rs4939827 respectively, were shown previously to be associated with an increased risk for CRC [8,21]. Surprisingly in the present study, more patients homozygous for the risk allele for both SNPs presented with earlier stage cancer (stages 1–2) at the time of diagnosis, suggesting that these alleles are protective (Table S2).

Discussion

The present study was performed to examine the prognostic significance of 11 common, low-penetrance genetic variants at 6 CRC loci that have been previously reported to predispose individuals to CRC [8–17]. Although we found marginal significance between two SNPs, rs7013278 and rs7014346 (HR = 2.20; 95% CI = 1.24–3.91; P=0.03; Table 2). This difference was not significant in a multivariate model (P=0.05; Table 2). In multivariate analysis, patients carrying two risk alleles (T/T) for rs7013278 had reduced survival compared with patients homozygous for the protective allele (C/C) (HR = 1.96; 95% CI = 1.08–3.52; P=0.01; Table 2). Likewise, patients homozygous for the CRC risk allele of rs7014346, A/A, showed inferior overall survival to G/G patients (HR = 1.96; 95% CI = 1.08–3.52; P=0.03; Table 2). The moderate level of significance for these two SNPs was not maintained upon correction for multiple testing. No additional significant association was observed between the rest of the SNPs studied and survival (Table 2).

Relationships Between Low-Penetrance CRC Susceptibility SNPs and Overall Survival

To test whether the germline variants underlie differences in overall survival in CRC patients, we performed both univariate and multivariate survival analyses. In univariate analysis, a significant difference in survival was only observed in patients with the A/C genotype compared to the A/A genotype for rs3802842 (P<0.05; Table 2). This difference was not significant in a multivariate model (P=0.05; Table 2). In multivariate analysis, patients carrying two risk alleles (T/T) for rs7013278 had reduced survival compared with patients homozygous for the protective allele (C/C) (HR = 2.20; 95% CI = 1.24–3.91; P=0.03; Table 2). Likewise, patients homozygous for the CRC risk allele of rs7014346, A/A, showed inferior overall survival to G/G patients (HR = 1.96; 95% CI = 1.08–3.52; P=0.03; Table 2). This moderate level of significance for these two SNPs was not maintained upon correction for multiple testing. No additional significant association was observed between the rest of the SNPs studied and survival (Table 2).
## Table 2. Associations between genotypes and overall survival of study patients.

| SNP and Genotype | Univariate | Multivariate* |
|------------------|------------|---------------|
|                  | Risk Allele | Hazard Ratio | 95% CI | P   | Hazard Ratio | 95% CI | P   |
| rs6983267        | T/T        | G            | 1.00   | –    | 1.00         | –      | –    |
|                  | G/T        | 0.85         | 0.51–1.41 | 0.53  | 1.07 | 0.59–1.93 | 0.83 |
|                  | G/G        | 1.17         | 0.71–1.92 | 0.54  | 1.35 | 0.73–2.51 | 0.35 |
| rs10505477       | G/G        | 1.00         | –        | –    | 1.00         | –      | –    |
|                  | A/G        | 0.90         | 0.55–1.48 | 0.68  | 1.14 | 0.64–2.06 | 0.66 |
|                  | A/A        | 1.21         | 0.74–1.98 | 0.46  | 1.38 | 0.74–2.55 | 0.31 |
| rs7013278        | C/C        | T            | 1.00   | –    | 1.00         | –      | –    |
|                  | C/T        | 0.94         | 0.63–1.40 | 0.76  | 1.06 | 0.66–1.71 | 0.81 |
|                  | T/T        | 1.55         | 0.94–2.56 | 0.08  | 2.20 | 1.24–3.91 | 0.01*|
| rs7014346        | G/G        | A            | 1.00   | –    | 1.00         | –      | –    |
|                  | A/G        | 0.89         | 0.60–1.31 | 0.50  | 1.04 | 0.67–1.64 | 0.84 |
|                  | A/A        | 1.33         | 0.78–2.27 | 0.29  | 1.96 | 1.08–3.52 | 0.03*|
| rs719725         | C/C        | A            | 1.00   | –    | 1.00         | –      | –    |
|                  | A/C        | 1.29         | 0.69–2.39 | 0.43  | 0.93 | 0.47–1.86 | 0.84 |
|                  | A/A        | 1.07         | 0.57–2.01 | 0.84  | 0.80 | 0.39–1.62 | 0.53 |
| rs10795668       | G/G        | A            | 1.00   | –    | 1.00         | –      | –    |
|                  | A/G        | 0.79         | 0.54–1.16 | 0.23  | 0.82 | 0.51–1.31 | 0.40 |
|                  | A/A        | 0.54         | 0.25–1.17 | 0.11  | 0.82 | 0.37–1.83 | 0.62 |
| rs3802842        | A/A        | C            | 1.00   | –    | 1.00         | –      | –    |
|                  | A/C        | 1.53         | 1.05–2.23 | 0.03* | 1.25 | 0.80–1.93 | 0.33 |
|                  | C/C        | 0.95         | 0.50–1.79 | 0.88  | 1.03 | 0.52–2.03 | 0.94 |
| rs10318          | C/C        | T            | 1.00   | –    | 1.00         | –      | –    |
|                  | C/T        | 1.10         | 0.74–1.64 | 0.63  | 1.20 | 0.73–1.90 | 0.59 |
|                  | T/T        | 0.50         | 0.12–2.03 | 0.33  | 0.62 | 0.15–2.55 | 0.50 |
| rs4779584        | C/C        | T            | 1.00   | –    | 1.00         | –      | –    |
|                  | C/T        | 0.92         | 0.63–1.34 | 0.65  | 0.72 | 0.45–1.14 | 0.16 |
|                  | T/T        | 1.02         | 0.52–1.98 | 0.96  | 1.01 | 0.46–2.22 | 0.98 |
| rs4464148        | T/T        | C            | 1.00   | –    | 1.00         | –      | –    |
|                  | C/T        | 0.78         | 0.54–1.15 | 0.21  | 0.74 | 0.48–1.16 | 0.19 |
|                  | C/G        | 0.95         | 0.50–1.80 | 0.87  | 1.39 | 0.67–2.90 | 0.38 |
| rs4939827        | C/C        | T            | 1.00   | –    | 1.00         | –      | –    |
|                  | C/T        | 0.90         | 0.60–1.34 | 0.59  | 0.82 | 0.52–1.30 | 0.40 |
|                  | T/T        | 0.82         | 0.50–1.36 | 0.44  | 0.81 | 0.45–1.48 | 0.50 |

*Potential confounding variables such as age, gender, ethnicity, stage, and treatment received were included in multivariate modeling

*Statistically significant at P < 0.05.

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Potential confounding variables such as age, gender, ethnicity, stage, and treatment received were included in multivariate modeling.
recurrence while our study and that by Tenesa et al [21] evaluated overall survival and overall mortality respectively.

This inconsistency in findings between reported studies is not surprising as the mechanisms by which these variants alter the risk of CRC is not fully understood and it is still unclear how they might influence tumor progression and patient survival. Currently, the potential functional effects of these SNPs have been most widely investigated for the variants at the 8 q24 gene locus. Since this locus is not known to encode for any gene, it was thus conceived that the variants found here may either lie within promoters or enhancer elements that can affect the transcription of genes outside this locus [10]. However, in a study using the UCSC Browser and VISTA Enhancer database, rs7013278 and rs7014346, which showed marginal significance in our study prior to Bonferroni correction, were not found in segments containing putative enhancers or in predicted regions of regulatory potential [25]. On the other hand, rs6983267 was found to lie within a putative enhancer element that binds TCF4, a transcription factor that interacts with β-catenin to activate the transcription of Wnt target genes, which are activated in most CRCs [26,27]. Additionally, some reports have shown that rs6983267 has a long range physical interaction with a promoter region of MYC in colorectal cancer cell lines [26,28]. Despite this, no association between the risk allele of rs6983267 and MYC expression levels has been found in normal and cancerous colon tissues [17,26,27]. Therefore, the functional consequence of rs6983267 remains uncertain.

For rs10795668 at 10 p14, rs3802842 at 11 q23 and rs4779584 at 15 q13, a systematic search by Niittymaki and colleagues failed to show any association of these SNPs with predicted enhancer or regulatory elements [29]. Further investigation using tumor samples again showed a lack of allelic imbalance between the risk allele of these SNPs with CRC, prompting the authors to conclude that these risk variants were unlikely somatically selected for neoplastic progression [29]. While the functional effects of these susceptibility SNPs remain to be further validated, the results of these functional studies to date support our finding that the susceptibility SNPs tested, their susceptibility risk allele and TaqMan® SNP genotyping assay identifiers. (DOCX)

Table S1 Chromosomal loci of low-penetration CRC susceptibility SNPs tested, their susceptibility risk allele and TaqMan® SNP genotyping assay identifiers. (DOCX)

Table S2 Distribution of patients’ clinicopathological characteristics according to genotypes for individual SNP. (DOCX)

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Author Contributions

Conceived and designed the experiments: JMH PO TOK CFM RSS HLM. Performed the experiments: JMH PO CAC MW. Analyzed the data: JMH PO. Wrote the paper: JMH PO. Performed statistical analyses: JAG.

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