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Genetic Basis for Colorectal Cancer Disparities

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Abstract

African Americans suffer the highest burden from colorectal cancer (CRC) in the USA. Studies have suggested that healthcare access and poorer utilization of preventive services may be playing more of a role in this disparity. However, African Americans also tend to develop CRC at younger ages and are more likely to have proximal cancers. This raises the possibility of higher genetic predisposition to CRC among African Americans and this has not been well studied. In this article, we reviewed possible genetic basis underpinning biological differences in CRC burden in the USA.

Keywords

Colorectal cancer; Disparities; Colonoscopy; Screening; Underserved; Ethnic minorities; Molecular biology; Genetics; Race-ethnicity

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer-related mortality among men and women in the USA [1••]. Although the incidence and mortality from CRC have been declining recently, significant disparities continue to be noted among different races [1••]. African Americans have been reported to have both the highest incidence and the highest mortality from the disease when compared to all other race-ethnicities. This disparity is likely due to multiple putative risk factors such as low socioeconomic status, high prevalence of obesity, poor health literacy, low insurance coverage, adoption of unhealthy dietary practices, poor compliance to medical care, and low screening utilization.

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Compliance with Ethical Standards

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However, studies have shown that even after controlling for most of these factors, racial differences persist [2]. Moreover, when compared to non-Hispanic whites, Hispanic Americans have lower burden of disease despite having comparable prevalence of these putative risk factors and even lower uptake of CRC screening as compared to African Americans [3]. Furthermore, African Americans are more likely to present with CRC at younger ages, have proximal tumors [4, 5], present at more advanced stages of disease and have lower survival from CRC [6]. These findings have made the possibility of biological differences hard to ignore. Although no definite genetic basis for the disproportionately higher burden from CRC among African Americans has been identified, there have been many studies examining different pathways for biological differences in predisposition to CRC among different race-ethnicities. Some of these are highlighted as follows:

Microsatellite Instability

Microsatellite instability (MSI) is caused by defective DNA mismatch repair and can be seen in 15 to 20 % of patients with sporadic CRC [7, 8]. Although a high frequency of MSI was previously reported among 22 African American patients with CRC [9], a more recent population-based study with prospective data collection from North Carolina by Carethers et al. [10•] found lower prevalence of MSI when compared with Caucasians. In that study, the authors examined CRC samples from 503 patients (45 % African Americans and 55 % Caucasians). MSI was demonstrated among 14 % of CRC from Caucasians, but only 7 % of African Americans had MSI. CD8+ T cell infiltration of colon cancer which is known to correlate positively with MSI tumors was also noted in this study (88.0/hpf in MSI tumors versus 30.4/hpf in tumors without MSI; $P<0.0001$), but there was no difference by race. The authors suggested that the lower MSI prevalence in the CRC of African Americans without a change in the CD8+ T cell infiltration may be contributing to the observed higher mortality from CRC among African Americans.

In another study, Sylvester et al. [11] evaluated the Microsatellite instability (MSI) status of 222 CRC from African Americans and 205 Caucasians. They also determined the mutations in Kras codons 12 and 13 and BRAF codon 600. The authors did not find any difference in MSI or BRAF mutation frequencies between African Americans and Caucasians. However, Kras mutation was higher among African Americans (34 versus 23 %, $P=0.048$) and was isolated to proximal colon cancers and primarily driven by mutations in codon 13. Although there was no difference in the receipt of chemotherapy, but African Americans with MSS/MSI-L had a 73 % increased risk of death. The authors suggested that this disparity in outcome may be due to differences in the distribution of factors influencing response to standard therapies.

Single Nucleotide Polymorphism in African American CRC tumors

Using whole exome and targeted sequencing, Guda et al. [12••] evaluated somatic mutations in 103 CRC from African Americans. The authors reported a discovery of 20 new genes which appears to be targeted for recurrent mutations among African Americans. Resequencing in 129 CRC from Caucasians was performed, and the authors were able to confirm that 15 genes were preferentially targeted in African Americans. Two of these genes ephrin type A receptor 6 (EPHA6) and folliculin (FLCN) were exclusive to African

Americans with mutation rates of 5.83 versus 0 % and 2.91 versus 0 %, respectively, when compared with Caucasians. This approach focused primarily on detecting genes with differential mutation rates between African Americans and Caucasians. In another study, Ashktorab et al. [13••] also used whole exome sequencing to analyze the CRC tumor samples from 12 African Americans and their freshly frozen matched normal tissue. Their approach primarily focused on evaluating differential mutations within known cancer pathways. The authors identified novel somatic mutations in genes that are known targets in CRC such as APC, BRAF, Kras, and PIK3CA. They also detected novel alterations in the Wnt pathway gene, APC, within its exon 15, of which mutations are highly associated with CRC. Taken together, these two studies identified novel mutations that may be playing a role in CRC among African Americans. This underscores the need for more studies targeting minorities in this field of research. The novel mutations reported in these two studies (Table 1) should be explored in future studies to enhance our understanding of race-specific cancer genes and mutations.

P53 Pathway Alterations

The tumor p53 protein regulates apoptosis, senescence, cell cycle arrest, and DNA damage response pathways. Katkoori et al. [14] assessed p53 mutations and performed genotyping for the codon 72 polymorphism in CRC from 137 African Americans and 236 Caucasians. The authors reported similar incidence of p53 mutations among African Americans (50 %) and Caucasian (54 %), but the homozygous Pro72 allele was higher in frequency among African Americans, 17 versus 7 % whereas the frequency of homozygous Arg72 allele was higher in Caucasians 36 versus 19 %, (*P* value=0.002). The authors reported that African Americans with the Pro/Pro phenotype had a twofold increased risk of death from CRC as compared to those with Arg/Arg or Arg/Pro phenotype. This findings was only limited to African Americans. This suggests that a higher frequency of the Pro/Pro phenotype of p53 in African Americans may be contributing to advanced stage of CRC presentation and poorer survival.

Arachidonic Acid Pathway

Cyclooxygenase (COX) and arachidonate lipoxygenase (ALOX) are enzymes that are thought to play a role in colorectal carcinogenesis by metabolizing arachidonic acid and forming certain lipid metabolites [15]. Goodman et al. [16] evaluated the relationship between CRC and polymorphisms in these two enzymes in the arachidonic acid pathway. The authors used hospital (n=229) and population-based (n=304) controls, and compared with 293 CRC cases from African Americans and Caucasians. There were no racial differences in the reported frequency of ALOX5 G-1752A polymorphism (*P* value=0.08) and ALOX5 G-1699A (*P* value=0.11) polymorphism among African Americans and Caucasians. The authors reported a reduced risk of CRC among Caucasians with A alleles at positions -1752 (OR=0.60; 95 % CI: 0.38–0.96) and -1699 (OR=0.56; 95 % CI: 0.35–0.88) of ALOX5. There was no association among African Americans, (OR=1.22; 95 % CI: 0.69-2.16) and (OR=1.18; 95 % CI: 0.68-2.05), respectively. The authors concluded that a haplotype containing ALOX5 G-1752A and G-1699A in a negative regulatory region of the promoter may differentially reduce CRC risk among Caucasians.

However, in another case control study involving only African Americans, Ashktorab et al. [17] evaluated the association between Cox-2 polymorphism and prevalence of adenoma among 72 cases with advanced adenoma and 146 polyp-free controls. The authors reported a significant 58 % reduced odds (*P* value=0.03) of adenoma prevalence with the heterozygous genotypes at the 5229 G>T polymorphism in intron 5 and a 61 % reduced odds (*P* value=0.01) with the 10935 A>G polymorphism in the 3′ flanking region downstream from the poly A signals. There was no association among patients with homozygous genotypes, (*P* value=0.91 and *P* value=0.68, respectively). Taken together, these case control studies suggest that allelic variants of the arachidonic pathway may be playing protective roles in CRC neoplasia development but the variants may differ by race.

Vitamin D Genetic Variations

There have been suggestions that low vitamin D level is associated with an increased risk of CRC [18, 19]. It has been postulated that vitamin D decreases CRC risk by inhibiting proliferation, being pro-apoptotic, and promoting differentiation. African Americans and Hispanics have been shown to have lower levels of vitamin D [20]. Pibiri et al. [21] reported that single nucleotide polymorphisms in vitamin D-related (VDR) genes could minimally affect CRC susceptibility in African Americans based on their study of 961 African American CRC cases and 838 healthy African American controls. In comparison to Hispanic Americans (a population with lower CRC risk when compared to Caucasians), Sarkissyan et al. [22] evaluated the association between VDR gene single nucleotide polymorphisms (SNPs) in VDR (FokI, BsmI, TaqI, and ApaI) and CRC risk. The authors compared 78 patients with CRC (cases) with 70 patients with polyps and 230 polyp-free controls. They reported a threefold increased odds of VDR-FokI FF genotype with CRC when compared with polyp-free controls. This FF genotype was the most common among African American participants (61 %) whereas the Ff genotype was the most common in Hispanic/Latino participants (49 %). The other three polymorphic variants of VDR (BsmI, TaqI, and ApaI) were not associated with CRC risk. The authors suggested that genetic variation of the VDR-FokI SNPs may influence CRC risk and contribute to CRC disparity. However, in a case–control study of 93 patients with colon polyp (cases) and 187 controls, Ashktorab et al. [23] reported that low levels of vitamin D rather than SNPs in the VDR gene were associated with prevalence of these precancerous lesions in African Americans.

IGF Pathway, Insulin Resistance, Inflammation, and Obesity

Obesity is associated with the activation of insulin-like growth factor (IGF), oxidative stress and inflammatory pathways that increase the risk of adenoma and CRC [24, 25]. Ochs-Balcom et al. [25] reported statistically significant association of IGF-1 with colorectal adenoma among African Americans. In another study, Jovov et al. [26] evaluated the gene expression of CRC from 43 African Americans matched by stage to 43 Caucasians and 40 normal colorectal tissues. They reported that major differences in gene expression occurred among those genes that were related to inflammation and immune response. These were DHX58, HLA-DQB1, IL27, IL33, PAK2, PROKR1, SAA2, TLR4, and ZNF234. The authors suggested that differences in tumor microenvironment may be playing a substantial role in CRC disparities. It appears that higher prevalence of chronic subclinical inflammation among African Americans may be contributing to the observed higher incidence of and poorer outcome from CRC.

MicroRNA

Dysregulation of microRNAs (miRNAs) could possibly lead to the development of cancer. Certain microRNA expression promotes CRC cell growth in vitro and in vivo by targeting tumor suppressor genes. An exploratory study by Li et al. [27] suggested that differences in microRNA expression levels especially miR-182 may contribute to decreased survival among African Americans with CRC. miR-182 has been reported previously to be associated with increased hepatic metastasis. The authors proposed that the potential mechanism of this poorer outcome may be due to epigenetic modulation of the miR-182 locus or defective mismatch repair. Further studies to elucidate biological pathways associated with differential expression of miRNAs by race are needed.

Fecal Microbes and Short Chain Fatty Acids

An emerging area of investigation into the differential burden of CRC among race-ethnicities is in composition and function of gut microbiota. It is well known that the risk of CRC is low among native Africans [28••] whereas African Americans suffer the highest burden from the disease in the USA [1••]. Ou et al. [29] performed microbiome analysis from fresh fecal samples from 12 healthy African Americans and 12 age- and sex-matched native Africans. The authors observed that the microbial composition in the two groups was very different. Bacteroides were the predominant microbes among African Americans whereas Prevotella was the dominant microbe among native Africans. Fecal secondary bile acid concentrations were higher in African Americans, but short-chain fatty acids (SCFA) were higher in native Africans. This suggests that African Americans have higher prevalence of microbiota and metabolites that promote carcinogenesis as compared with native Africans.

In an exploratory study in the USA, Hester et al. [30] investigated differences in microbes and SCFA levels in stool samples from Hispanic and non-Hispanic African American, American Indian, and White participants. The authors found that levels of acetate, butyrate, and total SCFAs were lower among African Americans when compared to all other race-ethnicities. Of note, butyrate is a gut microbiota metabolite with anti-proliferative characteristics. Furthermore, the Firmicutes/Bacteroidetes ratio was also significantly higher for African Americans than for Whites. Brim et al. [31] suggested that the differences in microbiota and subsequent predisposition to pre-cancerous lesions may be occurring at the sub-genus level [31], and even when SCFA is available through a favorable microbiota metabolic outcome, the host genetic makeup still influences their transportation in the colon. In many African Americans with colon neoplastic lesions, SLC5A8, a gene responsible for butyrate is silenced through methylation, thus preventing its transport and effect on colonocytes [32].

Clinical Relevance

At the present time, CRC screening and surveillance practices are based on the predisposition to CRC using established risk factors such as age, presence of inflammatory bowel disease, and family history of CRC [33]. The major determining factor for the onset of screening to prevent CRC or facilitate early detection of malignancy is the family history of CRC. This is even more intense for those with known syndromic hereditary CRC. For

example, if a patient has a family history of familial adenomatous polyposis (FAP) which is a germline mutation in the APC gene on long arm of chromosome 5, they are to undergo initial screening with flexible sigmoidoscopy at age 10 to 12 years and be treated with colectomy if they already developed carpets of adenomatous polyposis. For families with Lynch syndrome which is due to mutation in mismatch repair (MMR) genes, subjects are recommended to begin screening every 2 years from age 20 to 25 years or 10 years before the youngest case in the family. Thereafter, they should undergo yearly colonoscopy from age 40 years. Furthermore, first-degree relatives of patients with sporadic CRC should begin CRC screening at age 40 or 10 years earlier than the index case in that family whichever is earlier. This underscores the need to know the medical history of family members. However, studies have shown that African Americans are less likely to know their family history of cancer including CRC [34, 35]. The implication of this is that African Americans at the highest risk of developing CRC based on their genetic makeup are not being identified and, therefore, are not appropriately screened. This may be a substantial underlying factor driving the higher incidence and mortality from CRC among African Americans. There is a great need for increased awareness of CRC among African Americans and improved family discussions about the disease.

Conclusions

There is a need for more studies to elucidate the biologic basis for the disproportionately higher incidence and mortality from CRC among blacks. Efforts to improve family discussions about CRC will improve the identification of high-risk groups such as families with Lynch syndrome, FAP, and other inherited conditions which predispose to CRC. These individuals can then be targeted for appropriate risk-based screening strategies that can potentially reduce the burden of CRC.

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Table 1

Genes with novel mutations identified among African Americans through whole exome and targeted sequencing [12••, 13••]

From Guda et al. [12••]
EPHA6
FLCN
HTR1F
GPR149
ZNF862
ANKRD36
KIAA1551
EML6
WASH1
ATP8B2
CP
CPT1C
MAGEB10
CHD5
JAK1
CDK8
MGAT4C
ZNF717
TCEB3CL
WDR87
From Ashktorab et al. [13••]
APC
KRAS
ZNF568
CACNA1C
TEL02
SRMS