World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2022 July 7; 28(25): 2782-2801

DOI: 10.3748/wjg.v28.i25.2782

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Inflammation, microbiome and colorectal cancer disparity in African-Americans: Are there bugs in the genetics?

Sami Ahmad, Hassan Ashktorab, Hassan Brim, Franck Housseau

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Dabravolski SA, Belarus; Ogino S, United States
A-Editor: Gao W, China

Received: October 28, 2021
Peer-review started: October 28, 2021
First decision: December 26, 2021
Revised: January 27, 2022
Accepted: May 26, 2022
Article in press: May 26, 2022
Published online: July 7, 2022

Sami Ahmad, Franck Housseau, Department of Oncology, Johns Hopkins University, Baltimore, MD 21231, United States

Hassan Ashktorab, Department of Medicine, Howard University, Washington, DC 20060, United States

Hassan Brim, Department of Pathology, Howard University, Washington, DC 20060, United States

Corresponding author: Franck Housseau, PharmD, PhD, Associate Professor, Department of Oncology, Johns Hopkins University, CRB1 4M59 1650 Orleans street, Baltimore, MD 21231, United States. fhousse1@jhmi.edu

Abstract

Dysregulated interactions between host inflammation and gut microbiota over the course of life increase the risk of colorectal cancer (CRC). While environmental factors and socio-economic realities of race remain predominant contributors to CRC disparities in African-Americans (AAs), this review focuses on the biological mediators of CRC disparity, namely the under-appreciated influence of inherited ancestral genetic regulation on mucosal innate immunity and its interaction with the microbiome. There remains a poor understanding of mechanisms linking immune-related genetic polymorphisms and microbiome diversity that could influence chronic inflammation and exacerbate CRC disparities in AAs. A better understanding of the relationship between host genetics, bacteria, and CRC pathogenesis will improve the prediction of cancer risk across race/ethnicity groups overall.

Key Words: Inflammation; African-American; Population-specific genome wide association studies; Minorities health; Microbiome; Colorectal cancer

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Studies largely examine either variations in microbiome composition or host immunity polymorphisms, often using genome-wide association studies comprised of populations mainly of European ancestry. There is, thus, a pressing need for studies that include, recruit, and account for more widely diverse cohorts. Identification of population-associated polymorphisms driving host/microbiome interactions linked to colorectal cancer (CRC) disparity may reveal genes or pathways that could be targeted for patient-specific CRC interception strategies.

Citation: Ahmad S, Ashktorab H, Brim H, Housseau F. Inflammation, microbiome and colorectal cancer disparity in African-Americans: Are there bugs in the genetics? *World J Gastroenterol* 2022; 28(25): 2782-2801
URL: https://www.wjgnet.com/1007-9327/full/v28/i25/2782.htm
DOI: https://dx.doi.org/10.3748/wjg.v28.i25.2782

INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of death amongst cancer patients, an estimated 53000 of whom will die in the United States from CRC in 2021[1]. Strikingly, although total CRC mortality has decreased over the last two decades, particularly in older individuals (age 64 +), CRC incidence has increased in individuals under 50[1]. Recent studies showed early-onset CRC patients were more likely to be African-Americans (AAs), who bear the highest CRC incidence rate between 20-year-old and 44-year-old (7.9/100000) as compared to Caucasian Americans (CAs) (6.7/100000) and Asian-Pacific Islanders (6.3/100000)[2]. AAs commonly display more aggressive types of CRC as well, and are generally diagnosed at more advanced stages of the disease, exhibiting survival rates 7% below those of CAs (58% *vs* 65% 5-year survival)[3]. Such statistics must be interpreted cautiously, since the noted increase of early-onset CRC may result from recently recommended and adopted early colonoscopy (40-45 years old) screening campaigns. Nevertheless, there are multiple proposed influences on CRC disparities in AAs, including differences in health care and treatment access, comorbidities and tumor characteristics[4-8]. Socioeconomic status (SES) also weighs heavily on the late diagnoses and prevention campaign efficacy observed in AA populations[2,6,9]. Undoubtedly the source of CRC disparity is multifactorial, and a layered perspective is imperative to address the alarming rise of early onset CRC, an otherwise preventable disease when detected early.

Herein, we aim to elucidate novel biological factors that may also contribute to the AA disparities in CRC mortality. Specifically, in addition to the genetic influence on CRC pathogenesis, an accumulating body of evidence connects CRC to dysregulated interactions between mucosal innate immunity and the microbiome[10]. Indeed, sustained inflammation promoted by chronic colorectal dysbiosis is an established driver of CRC pathogenesis[11]. Related to this notion is a recent gut microbiome profiling study that found that, in addition to diminished overall species diversity, pro-inflammatory *Fusobacterium nucleatum (F. nucleatum)* and *Enterobacter* species were significantly more abundant in AA CRC patients as compared to a CA cohort[12]. The presence of *F. nucleatum* has also been linked to inflammation-associated microsatellite alterations found more prevalently in AA rectal tumors, a finding linked to worsened CRC prognosis[13-15]. Furthermore, genetic landscape and microbiome composition have been shown to influence the occurrence of proximal colorectal tumors[16], which are more difficult to detect and are diagnosed nearly four times more often in AA than in CA CRC patients[17]. Nearly 80% of sessile serrated polyps are found in the proximal colon, a phenomenon associated with microbial biofilms and *Fusobacteria*, plus the frequency of *BRAF* mutations, CpG island hypermethylation phenotype, and microsatellite instability that increases from the distal to the proximal region[16,18-22]. Altogether, there is emerging research on the genetically tuned relationships between mucosal innate immunity, the microbiome, and disparate CRC development, but a functional understanding of how said relationships impact CRC pathology remains incomplete[23]. Additionally, despite the evidence that mucosal innate immunity and the microbiome are intimately connected, this review highlights how minority health research currently evaluates their contribution to CRC risk in a largely separate fashion [24].

Accordingly, we propose an integrated concept whereby a differential mucosal inflammatory response to gut microbiota, influenced by host genetic ancestry, represents an underappreciated factor affecting population susceptibility to CRC. In support of this concept, a recent study found that the most differentially expressed genes (DEGs) between AA and CA CRC tumors were related to the regulation of inflammatory immunity[25]. More broadly, transcriptional regulation of inflammation was determined the most distinguishing DNA variation between African and European genetic ancestries[26]. Another study demonstrated that African genetic ancestry and level of African admixture (mixture with ancestral African genetic lineage) predicted a stronger inflammatory transcriptional response in macrophages infected with bacterial pathogens[27]. From this framework, one could theorize that in a CRC setting, the same bacterium or a community of bacteria may induce a differentially deleterious

inflammatory response based on a patient's immune-related genetic background. Positive ancestral selection of anti-pathogenic immunity providing survival benefit in endemic areas may, in a modern "westernized life style" context, exacerbate localized inflammation in the tumor micro-environment and, when compounded by SES and environmental factors, accelerate CRC progression into the more aggressive form seen in AA patients, whose self-reported race/ethnicity correlates with an elevated African admixture[28,29] (Figure 1).

Given that SES and a variety of environmental factors associated with CRC pathogenesis and disparities are commonly discussed elsewhere[2,9], we are limiting the scope of the present review to the nascent literature associating CRC first to genetic polymorphisms related to innate immunity, second to those related to the microbiome, and finally explore how they may conjointly contribute to CRC disparities in the AA population. We also emphasize that, by considering admixture and genetic ancestry rather than self-reported race, population-specific risk studies including microbiome genome-wide association studies (GWAS) can more accurately capture human genetic diversity, thereby increasing the likelihood of identifying clinically relevant CRC risk factors associated with African ancestry[30-34]. Furthermore, polymorphisms related to innate immunity as well as the microbiome and contributing to links between CRC risk and African ancestry may have been left undiscovered by the longstanding genetic homogeneity of genomic research cohorts, a problem we discuss in our closing remark. Although technically challenging, expanding GWAS to more diverse "multi-ancestry" cohorts will reveal novel linkages between the microbiome, inflammation, and CRC risk that can build predictive polygenic risk scores adaptable to an equally diverse patient base[35,36]. Crucially, functional evaluation of CRC risk variants associated with African ancestry may offer insights into the trend of aggressive, earlier onset CRC in AA patients, paving the way towards personalized prevention and precision medicine.

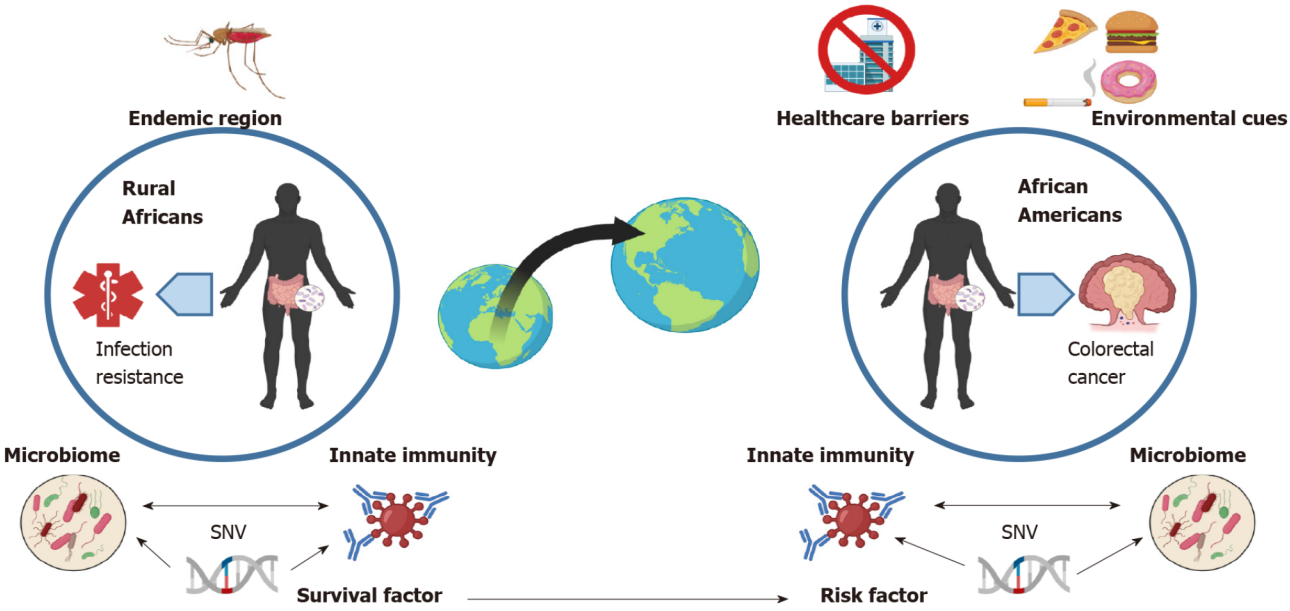
MUCOSAL INFLAMMATION, MICROBIOME, AND CRC

To better appreciate how host genetics may impact CRC risk between populations of different ancestral origins by modulating innate immunity or the microbiome, we will first highlight how mucosal inflammation and the gut microbiome interact to affect CRC pathogenesis. The human gut contains up to 10^{13} bacteria that play critical roles in immune, metabolic, cardiovascular, and neurological development [37]. The composition and functions of this bacterial community (microbiota) and its associated genome (microbiome) are highly dynamic and influenced by both environmental factors and host genetic background to maintain immunological and metabolic functionality[38]. Meanwhile, a tightly regulated physical separation between the immune system and commensal bacteria is necessary to limit a chronic inflammatory response to the microbiota[39,40]. The integrity of the intestinal barrier and its epithelium are therefore essential elements of healthy host-microbiota mutualism[40]. To establish a "demilitarized zone" and keep microbes at bay, the epithelium uses different mechanisms including tight junctions between epithelial cells, protective mucus production, and the expression of a complex arsenal of innate receptors that trigger bactericidal mediator secretion[41]. Nevertheless, a permissible level of contact or bacterial penetrance is necessary to facilitate metabolic exchanges and immunity maturation for homeostatic equilibrium between dense microbial flora and the host[39,40].

In the case of a high-fat diet, the cumulative alteration of bacterial metabolites can disrupt this equilibrium, thereby promoting carcinogenic dysbiosis and mucosal inflammation[42]. Diet is, thus, a critical environmental factor when connecting inflammation and the microbiome to CRC risk, especially when considering CRC disparities in AAs compared to Native Africans[43-45]. However, CRC as impacted by the genetic origins of host inflammatory response remains understudied. Inflammatory bowel disease (IBD), a model of perturbed micro-immune crosstalk and a known influencing factor of CRC etiology, can be a useful departure point for this line of inquiry[46]. In fact, multiple GWAS have linked higher risk of IBD, CRC[47-50], and microbiotic dysbiosis to host genetic variations, but surprisingly little is known about how CRC disparities may be compounded by the genetic regulation of host inflammatory response to gut bacteria[51].

There are, however, documented relationships between the genetic regulation of innate inflammatory immunity, the microbiome, and colon carcinogenesis. For example, adenomatous polyposis coli (Apc) $^{Min/+}$ mice knockout for toll-like receptor (TLR) 4 or its signaling adaptor partner myeloid differentiation primary response 88 demonstrated a decreased number of intestinal polyps[52]. Nucleotide-binding oligomerization domain leucine-rich repeat and pyrin domain containing 6 and nucleotide binding oligomerization domain containing protein 2 (NOD2) knockout mice were shown to develop colon tumors following colitis, and fecal microbiota transplantation from these mice into wild type recipients triggered similar tumorigenesis, which interestingly attributed carcinogenic causality to the microbiota [53,54]. In the case of lipocaline-2 knockout mice, *Alistipes spp.* commensals thrived and drove proximal colon tumorigenesis[55]. The nature of host genetic events can therefore drive different microbiome shifts impacting CRC and its anatomical pathogenesis (*i.e.*, distal *vs* proximal).

If inflammation is a mechanism connecting the microbiome and colorectal carcinogenesis, host genetic background, including immune-related single-nucleotide polymorphisms (irSNPs), could differ-



DOI: 10.3748/wjg.v28.i25.2782 **Copyright** ©The Author(s) 2022.

Figure 1 Immune-related variant may promote survival to pathogens in ancestral African environment but precipitate cancer in descendent African-Americans. Pathogens associated with endemic African regions (*e.g.*, malaria) are thought to pressure selection for specific immune-related genetic variants associated with pathogen resistance and survival of Native Africans (left). In the context of westernized diet and lifestyle, this genetic predisposition (represented herein by a single nucleotide variant), when associated with inflammatory regulation and inherited from African ancestors, may lead to altered interactions with bacteria or communities of bacteria of the gut microbiome, thereby precipitating the colon adenoma-carcinoma sequence in African-Americans (right). Higher inflammation associated with lack of exercise, high fat diet, and socio-economic status are thought to be predominant factors driving early colorectal cancer onset in African-Americans *via* their impact on shaping the gut microbiome and its interactions with the host genetic background. SNV: Single nucleotide variant. Created with Biorender.com.

entially regulate such associations based on ancestry. In humans, pattern recognition receptor polymorphisms are associated with both IBD and CRC risk[48]. GWAS have linked genetic loci to increased IBD risk and a variety of risk alleles affect immune response[56], including NOD2 or autophagy-related 16 like 1[57,58]. Such polymorphisms have been associated with microbial dysbiosis and an excessive inflammatory response[59,60]. Namely, Knights *et al*[59] found that among 474 individuals, NOD2 variants were associated with *Enterobacteriaceae* family enrichment, including *Escherichia coli*, a species notably enriched in IBD individuals. Also, Lavoie *et al*[60] described an increase of interleukin (IL)-17-producing CD4$^+$ T (*i.e.*, Th17) cells in the lamina propria of mice engineered to express the polymorphism T300A (rs2241880) in the *Atg16 L1* gene. Although Th17-based colitis was associated with an increase of *Bacteroides ovatus*, T300A did not directly induce the increase of *Bacteroides ovatus* but rather induced the increase of IL23p19, an important cytokine for maintaining the Th17 lineage[61]. Th17 cells and their canonical cytokine IL-17 are critical pro-inflammatory contributors to epithelial homeostasis and mucosal immunity by orchestrating anti-bacterial defense and epithelial repair and regeneration as well as regulating barrier permeability by controlling the expression of occludin proteins[62,63]. When dysregulated in a chronic setting, sustained IL-17 production may promote colon tumorigenesis[64,65]. Several studies have now identified IL-23/Th17 pathway-associated polymorphisms linked to IBD susceptibility and the gut microbiome profile[66-68]. Presumably, genetic regulation of Th17-driven inflammation may impact IBD and ensuing CRC risk *via* the extent or nature of colonic dysbiosis. In sum, these GWAS suggest that by influencing the extent or nature of colonic dysbiosis, genetic regulation of inflammation represents a risk factors for both IBD and CRC. Next, we review how genetic ancestry contributes to this phenomenon, and how it may exacerbate CRC disparity in AAs.

GEOGRAPHIC AND POPULATION-RELATED INNATE IMMUNITY DISPARITIES THAT MODULATE CRC RISK

The flow of genetic information across time and geography may contribute to current disparities in cancer incidence and progression[69]. Cancer is known to result from an accumulation of somatic genetic and epigenetic alterations that dysregulate the cell cycle but also depends on genetic background and polymorphisms that impact patient risk and predisposition[70,71]. Yet, few GWAS have implicated ancestral genetic variants in cancer predisposition amongst self-identified racial/ethnic

groups[72,73]. Many such polymorphisms regulate gene expression *via* epigenetic or post-translational modification mechanisms, which affect noncoding sequences like microRNA (miRNA) binding sites[74,75]. Yet, the biological and clinical significance of most polymorphisms associated with cancer disparities remains unknown[72]. Mechanistic associations between chronic inflammation and carcinogenesis could link ancestral genetic diversity to cancer, whereby immune-related genetic regulatory variants have the potential to differentially modulate CRC across populations[27].

In fact, a large fraction of population-associated polymorphisms impact gene expression related to inflammation and innate immunity, which, being likely essential for surviving life-threatening infections, evolved under stronger selection pressures than other traits[76,77]. For instance, human genome diversification *via* archaic human genome introgression (*i.e.*, admixture with Neanderthal genome) is a proposed adaptation of ancestral humans to infectious environments following "out of Africa" migration[77,78]. In non-African populations, Neanderthal-introgressed haplotypes reintroduced a splice variant (rs10774671) of the 2'-5'-oligoadenylate synthetase (*OAS*) *1* gene[79]. The *OAS* locus on chromosome 12 encodes three genes, *OAS1*, *OAS2* and *OAS3* that play an important role in virus defense. The elevated frequency of the Neanderthal-derived allele at the *OAS* locus was proposed to be the result of a positive selection in European and East Asian populations. This allele selection has a functional significance since it is associated with the production of a protein variant (OAS1 p46) characterized by higher enzymatic activity and improved resistance to West Nile virus and hepatitis virus C[80]. Therefore, the allele haplotype may provide a survival advantage to infectious agents in the non-African environment and represents an example of variety in baseline inflammation levels that may influence susceptibility to diseases like IBD and CRC in patients with insignificant African ancestry. Selection of genetic variants providing health and survival benefit in endemic areas may represent another means of adaptation and human genome diversification. In a cohort of 158 healthy individuals (distributed as European, Sub-Saharan African, and East-Asian), Barreiro *et al*[81] found that nucleotide diversity of the TLR family was shown to vary between African populations, suggesting pathogen-specific selection pressures. Specifically, the *TLR10/TLR1/TLR6* locus showed signs of recent positive selection amongst non-African populations. Furthermore, of all SNPs in this region, a high frequency *TLR1* single nucleotide variant (SNV) (non-synonymous T1805G variant) found in Europeans was the most significant population differentiator and was associated with a decrease in agonist-mediated nuclear factor-kappa B activation[81]. Although it is unclear if decreased TLR1-mediated immune response confers a selective advantage, it could potentially modulate otherwise harmful inflammatory responses to pathogens[82,83]. This finding suggested that a finely tuned balance between optimal defenses to pathogens and excessive inflammation may have been critical for evolutionary survival[78].

To investigate how ancestral immunity would impact pathogen response, Nédélec *et al*[27] studied interactions between macrophages and live bacteria (*Listeria* and *Salmonella*). Amongst the macrophages, they found that many of the DEGs; (30% of the 11914 genes analyzed) between AAs (n = 77) and CAs (n = 91) were involved in the regulation of the innate immunity. These results built off their previous findings that 9% of macrophage DEGs varied according to ancestry-associated regulation and that increased African ancestry could predict a stronger inflammatory response to infection[27]. Performing quantitative trait locus (QTL) analysis, the authors identified SNVs in 14% of DEGs or using alternative splicing between CA and AA individual-derived macrophages (either non-infected or infected with *Listeria* or *Salmonella*). A large fraction of DEGs were associated with expression QTL only in infected macrophages. In other words, SNVs in a significant fraction of inflammation-related genes were expressed in infected macrophages according to the level of African ancestry. Interestingly, the same authors also found that these DEGs included susceptibility genes previously reported by GWAS for rheumatoid arthritis, systemic sclerosis, or ulcerative colitis, all related to chronic inflammation and conditions with known AA disparity[78]. The interest of such a study, although performed on macrophages *in vitro*, is its illustration of the link between African genetic ancestry and inflammatory response to bacteria, one that could accelerate CRC by aggravating interactions between gut microbiota and the mucosal immune system. Reinforcing this concept is another GWAS that revealed that some of the most differentiating irSNPs between African and European populations were associated with genes regulating nuclear factor-kappa B or chemokine gene clusters[78]. Selected genetic variants may offer protection against infection in endemic regions for native/rural Africans but favor cancer development in descendants bearing the same variants in a western environment, a concept exemplifying the crossroad between host genetics and environmental factors that shapes cancer risk (Figure 1).

Regarding the possibility of a role of associations between irSNP and CRC risk into AA disparity, a recent study by Sanabria-Salas *et al*[33] studied links between pro-inflammatory *IL1B* haplotypes and CRC risk in patients from six Colombian cities. The authors associated the *IL1B* CGTC haplotype with CRC risk exclusively in patients from the coastal regions of Colombia who possessed the highest proportion of admixed African ancestry[33]. The same group has associated *IL1B* irSNPs (four SNPs -3737C/-1464G/-511T/-31C) with African ancestry and elevated cancer risk. The CGTC haplotype was most frequently found and highly expressed in AAs, establishing a functional link between *IL1B* irSNP and CRC risk[84]. Further studies, validating the connection between AA CRC patients and *IL1B* polymorphisms, will be required to confirm the *IL1B* SNP haplotype as a population-associated CRC risk marker; these findings nevertheless showcase a prime example of an exploitable connection

between ancestry-related inflammation and cancer risk disparity.

Next, a cancer genomic meta-analysis using 48 GWAS within the National Cancer Institute GAME-ON Network (64591 cancer and 74467 control patients) across five common cancer sites (ovarian, lung, breast, colorectal, and prostate) found that genetic variants associated with inflammation and innate immune response were relevant to CRC risk, including SH2B adapter protein 3 (*SH2B3*) (rs3184504, $P = 3.32 \times 10^{-5}$), a negative regulator of growth factors and cytokine-induced signaling (Table 1). Unfortunately, irSNP associations with race/ethnicity and geographic distributions were not evaluated[85]. In contrast, Wang *et al*[47] demonstrated the merit of accounting for population diversity in their analysis of associations between innate immunity pathways and CRC risk. In two large studies (discovery and validation cohorts) across five distinct ethnic groups (AA, CA, Japanese-American, Latino, and Native Hawaiian), they found that among more than 600 common variants associated with 37 innate immunity-related genes, a SNV in the second intron of peroxisome proliferator-activated receptor gamma (*PPARG*) (rs9858822) showed a statistically significant association with CRC in the AA population (Table 1). This variant, rare in other non-AA populations, was not previously reported. Importantly, a frequently reported *PPARG* variant rs1801282, inconsistently associated with CRC in other studies[86-88], was not detected in association with CRC in Wang *et al*[47]'s study that carefully controlled for population diversity, supporting the value of multi-ancestry SNP association studies. In another meta-analysis of 308 SNPs performed by Montazeri *et al*[89], 14 SNPs showed credible association with CRC including rs3802842, whose expression was associated with immune infiltration. Curiously, the *PPARG* rs9858822 polymorphism detected by Wang *et al*[47] failed as a positive SNP in this meta-analysis, a finding that warrants additional verification. However, such discrepancies between the multi-ethnic study of Wang *et al*[47] and European study of Montazeri *et al*[89] may highlight the issue of the underrepresented diversity when seeking genetic cancer risk. Population-associated risk may be missed, and alternatively discovered cancer risk may not be relevant for minorities.

Lastly, functional variants in the 3′-untranslated region (UTR) of inflammatory gene miRNA binding sites (miRSNPs) have been associated with CRC risk[75]. Four miRSNPs in the mannose binding lectin 2 (*MBL2*) gene 3′-UTR have been associated with increased CRC risk in the AA population. *MBL2* codes for mannose binding lactose protein, a pattern recognition receptor that binds a wide range of pathogen-expressed sugars, leading to their phagocytosis. Although not assessed in this study, the modulation of the interactions between the mucosal inflammation and the microbiome, *via* MBL2 expression, could be a mechanistic link between African ancestry and higher CRC risk[74]. irSNPs associated with CRC risk are summarized in Table 1.

Ultimately, linking chronic inflammation risk loci to positive selection *via* resistance to past infectious agents and population displacement should be done with caution, as the merits are still debated[78]. Physiological interfacing of the immune system with other biological systems (reproduction and organ development) may also explain positive selection in a manner distinct from past pathogen resistance [78]. Yet, considering the evidence of host innate immunity regulation by population-enriched irSNPS [27], it is reasonable to speculate that the mucosal inflammation associated with commensalism is differentially tuned according to the level of African ancestry and could therefore influence CRC disparities. This view is supported by disparity research in other cancers, such as the finding that *IL10* promoter SNPs enriched in AAs are also potential risk factors for prostate cancer development and progression [90]. Interestingly, one such *IL10* polymorphism (rs1800871) was associated with Proteobacteria load in the gut microbiome (Table 2), but a connection between rs1800871, proteobacteria, and prostate cancer remains to be established[90]. In breast cancer, Jenkins *et al*[91] demonstrated how the ancestral selection of immune variants in the African continent can predispose AA women to ancestry-related differences in tumor immunogenicity. Specifically, the status of a "Duffy-null" polymorphism-regulated atypical chemokine receptor 1 (*ACKR1*) allele linked West African genetic ancestry to tumor immune infiltration. Thus, for breast cancer, duffy antigen receptor for chemokines/ACKR1 polymorphism may serve as a biomarker for precision medicine and immunotherapy in patients bearing significant West African ancestry[91]. This result highlights the potential that ancestry-associated irSNPS have for cancer screening and clinical care when paired with functional analyses and elevating the importance of similar studies for CRC.

HOST GENETICS AND MICROBIOME INTERACTIONS' CONTRIBUTION TO CRC DISPARITY

While host genetics may impact mucosal inflammation and CRC risk, other factors, including environmental factors such as diet, lifestyle, and antibiotic exposure, undoubtedly influence CRC susceptibility and treatment response by shaping gut microbiome composition[51,92,93]. Notwithstanding such findings, we propose that the predominant reliance of the microbiome on environmental cues in healthy individuals may conceal host genetic contributions (including genetic ancestry and somatic mutations) in disease contexts (*e.g.*, CRC), driving the microbiome response to environmental fluctuations and defining, at least in part, differential susceptibility to cancer in AAs[94-96]. The numerous immune-related genetic variants that delineate chronic disease susceptibility between AAs and CAs (previously

Table 1 Immune-related single nucleotide polymorphism associated with colorectal cancer

Ref.	Size	Analysis	Gene	SNP	Function	Ethnicity	Comment
Montazeri *et al*[89], 2020	6149 CRC 7337 controls	Meta-analysis	*COLCA1/2*[1]	rs3802842 (11q23.1)	Immune infiltration of LP	Europeans	Confirmed by Lu *et al*[49], 2019[1]
			TGFB1, *SMAD7*, *SMAD7*	rs1800469, rs12953717, rs4464148	TGFB signaling inhibitor		
Law *et al*[50], 2019	34627 CRC 71379 controls	Meta-analysis	*HLA-C*	rs3131043 (6p21.33)	Adaptive immunity	Europeans	
			HLA-DRB1/DQA1	rs9271770 (6q21.33)	Adaptive immunity		
			COLCA1/2	rs3087967 (11q23.1)	Immune LP leukocytes		
			FUT2	rs12979278 (19q13.33)	Gut barrier		
Lu *et al*[49], 2019		GWAS	*NOD2*	rs2066847	Innate immunity	East Asians	Confirmed by Montazeri *et al*[89], 2020[2]
			GATA3	rs10795668 (10p14)	T cell transcription factor		
			SMAD7	rs7229639	TGFB signaling inhibitor		
			SMAD7	rs4939827	TGFB signaling inhibitor		
			COLCA1/2[2]	rs3802842 (11q23.1)	Immune infiltration of LP		
Sanabria-Salas *et al*[33], 2017	391 CRC	GWAS	*IL1B*	CGTC haplotype (2q14)	Inflammation	Columbian Africans	Association with AA admixture
Hung *et al*[85], 2015	15414 CRC 17688 controls	GWAS	*SH2B3*	rs3184504 (12q24)	Cytokine signaling	Europeans	Confirmed by Schumacher *et al*[135], 2015
Schumacher *et al*[135], 2015	18299 CRC, 19656 controls (Europeans), 2098 cases, 6172 controls (Asian 1), 2627 cases, 3797 controls (Asian 2)	Meta-analysis	*SH2B3*[3]	rs3184504 (12q24.12)	Cytokine signaling	Europeans/Asians	Confirmed by Hung *et al*[85], 2015[3]
			NOS1	rs73208120 (12q24.22)	ROS production		
Wang *et al*[47], 2013	2535 CRC, 3915 controls (discovery), 2153 CRC, 2630 controls (validation)	GWAS	*PPARG*	rs9858822	Monocyte activation	Multi-ethnic	High frequency in AA
Tsilidis *et al*[136], 2009	CLUE II cohort, 208 CRC, 381 controls	GWAS	*IL10*	rs1800896, rs1800890, rs3024496, rs3024498	Increased IL-10	ND	

[1]Confirmed by Lu *et al*[49].
[2]Confirmed by Montazeri *et al*[89].
[3]Confirmed by Hung *et al*[85].
AA: African-American; CRC: Colorectal cancer; GWAS: Genome-wide association studies; IL: Interleukin; LP: Lamina propria; ROS: Reactive oxygen species; SNP: Single nucleotide polymorphism; TGF: Transforming growth factor;

ND: Not determined; HLA: Human leukocyte antigen; FUT2: Fucosyltransferase 2; NOD2: Nucleotide binding oligomerization domain containing protein 2; GATA3: GATA binding protein 3; SH2B3: SH2B adapter protein 3; NOS1: Nitric oxide synthase 1; PPARG: Peroxisome proliferator-activated receptor gamma.

discussed) may then contribute to differential inflammatory responses to the microbiome dysbiosis and compound existing CRC disparities (Figure 2).

From this perspective, multiple metagenomic studies of fecal and mucosal samples have already found compositional and metabolomic differences between CRC and healthy patient microbiome[97-100]. Novel meta-analysis approaches combined these metagenome shotgun datasets across heterogeneous populations to explore relationships between the microbiome and CRC; associations were identified at both bacterial strain and gene levels[101-103]. A common core of 29 bacterial species was enriched in CRC cases, and choline metabolism was established as a reproducible biomarker of the CRC-associated microbiome[101,102]. While such findings are correlative and do not suggest causative links, several smaller studies have highlighted the role of specific bacteria[104-106] and microbial dysbiosis in triggering colorectal carcinogenesis in animal models[107]. However, microbiome GWAS (mGWAS) have not yet identified consistent associations between such carcinogenic bacteria and CRC risk[108]. Unfortunately, because population diversity was systematically underrepresented or not annotated in the metagenome datasets, it remains unknown how these results could translate into CRC risk factors or diagnostic biomarkers for specific racial/ethnic groups.

Meanwhile, several taxonomic and metagenomic studies have revealed an intriguing diversity in microbiome composition across racial/ethnic groups, but mechanistic understandings of associations between bacteria or groups of bacteria and race/ethnicity are sparse[34,109-113]. In particular, diversity of the microbiome is highly diet-driven. A study by O'Keefe *et al*[44] showed that a 2-wk food swap between AAs (received high fiber, low fat diet) and rural Africans (received low fiber, high fat diet) produced dramatic changes in mucosal biomarkers and a metabolome switch, illustrated by an increase in saccharolytic fermentation and anti-inflammatory butyrogenesis as well as suppression of secondary bile acid synthesis in AAs. In light of these results, it is critical that mGWAS take diet into consideration as a confounding factor, as its impact will inevitably interfere with the genetic/epigenetic influence on CRC risk[114]. Interestingly though, differences between CAs and AAs with respect to the mean alternate Healthy Eating Index (a measure of diet quality[115]) faded when adjusting for SES, implying that diet cannot entirely account for CRC disparities[116]. Multiple other factors besides diet are known to impact the composition and function of the microbiome, including smoking, alcohol consumption, as well as antibiotic exposure or metabolic condition such as diabetes or obesity, which are coincidentally also risk factors for CRC[117-119]. While these aspects of the microbiome biology have been extensively reviewed[120], we are paying much of our attention herein on the role of the host genetics and the ancestral genetic origin on the microbiome diversity and consequently CRC risk between ethnicities.

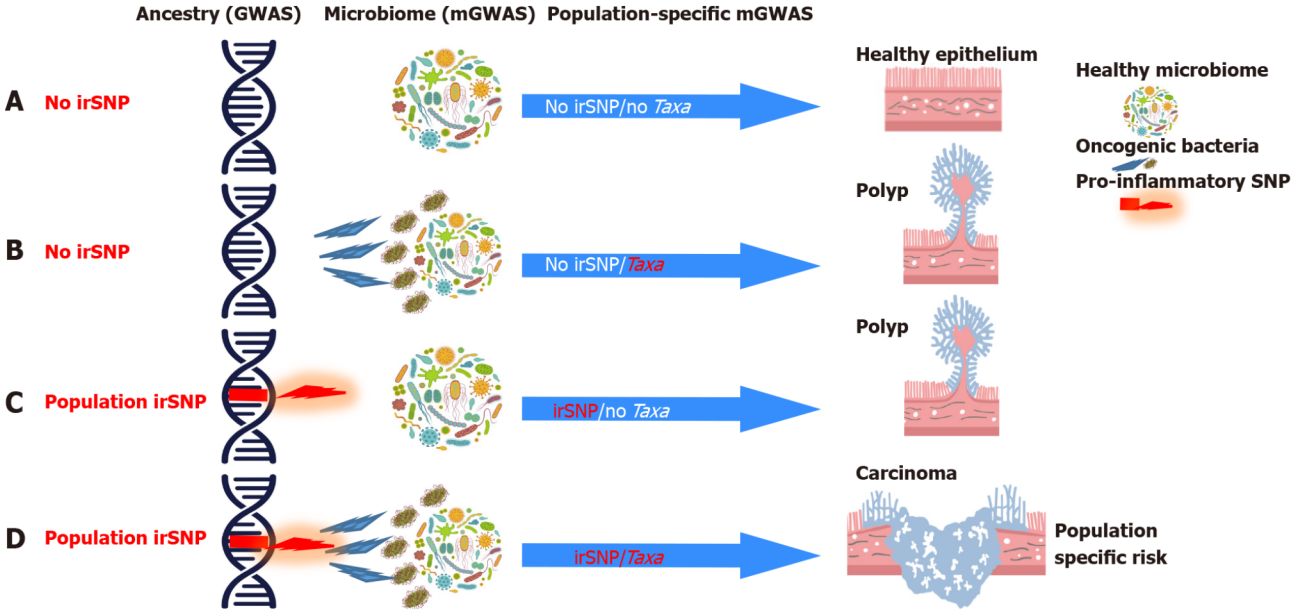
Interestingly, using the Healthy Life in an Urban Setting cohort and fecal 16S ribosomal RNA gene sequencing of over 2000 individuals, Deschasaux *et al*[110] found that microbiome diversity between racial/ethnic groups living in the same city was independent of metabolic health and only partially explained by SES, lifestyle, and diet factors. Yet, this finding was not always reproduced in other studies [45,111,121]. Overall, however, there is sufficient evidence to justify additional efforts to clarify if host genetics and population origins are taking part in shaping the microbiome[51,94]. The role of host genetic background has been suggested by mGWAS, which showed that SNPs such as rs4988235,

Table 2 Interactions of host genetics (metabolic and immune-related single nucleotide polymorphism) with gut bacteria

Ref.	Size	Analysis	Gene	SNP	Function	Bacteria	Ethnicity	Comment
Knights *et al*[59], 2014	474 IBD	16S RNA	*NOD2*	rs5743293, rs104895431, rs104895467, rs2068844, rs2068845, rs5743277, rs5743293	Innate immunity	*Enterobacteriaceae*	Europeans	IBD
Blekhman *et al*[122], 2015	93 (HMP)	Metagenomic	*LCT*	rs2304371, rs3754689	Metabolism	*Bifidobacterium*, *SMB53* (*Clostridiaceae*)	Multi-ethnic	NS
			GNA12	rs1182182	IBD			
Goodrich *et al*[123], 2016	1126	Fecal 16S rRNA	*CD36*	rs1360741	Immune-related	*Blautia*	Europeans	United Kingdom twins
Li *et al*[137], 2016	10523 IBD, 5726 IBD	Mucosal 16S rRNA	*SLC39A8*	rs13107325	Immune-related	*Composition*	ND	IBD
Bonder *et al*[68], 2016	1514	Metagenomic	*C11orf30-LRRC32*	rs2155219	IBD	*Coprococcus comes/Proteobacteria*		AA[1] PCa risk
			CCL2	rs3091315, rs3091316	Immune-related	*Methonobacteria*		
			DAP2	rs267939	Innate immunity	*Bifidobacterium*		
			IL23R	rs12141575	Immune-related	*Enterobacteriaceae/E. coli*		
			IL10	rs1800871[1]	Immune-related	*Proteobacteria/Sutterella*		
			MUC22	rs3873352	Barrier defense			
			NOD1	rs12669082	Innate immunity	*Enterobacteriaceae/E.coli*		
				rs41524946	Innate immunity	*Enteroba cteriaceae/E. coli*		
				rs55689059	Innate immunity	*Enterobacteriaceae/E. coli*		
				rs55841603	Innate immunity	*Enterobacteriaceae/E. coli*		
			NOD2	rs8056611, rs2357792,	Innate immunity	*Enterobacteriaceae/E. coli*		
			CD209	rs1010046	Innate immunity	*Bacteroidetes*		
Rühlemann *et al*[138], 2021	8956	16S rRNA/GWAS	*FUT2*	rs602662	Barrier defense	*Bacteroides* OTU97_27	Europeans	
			BLVRA	rs623108	Innate immunity	*Barnesiella spp*. OTU99_55		

[1]Studies include an analysis according to the population origins.

AA: African-American; GWAS: Genome-wide association studies; HMP: Human Microbiome Project; IBD: Inflammatory bowel disease; SNP: Single nucleotide polymorphism; ND: Not determined; NS: Not significant; PCa: Prostate cancer; rRNA: Ribosomal RNA; *E. coli*: *Escherichia coli*; FUT2: Fucosyltransferase 2; NOD2: Nucleotide binding oligomerization domain containing protein 2; LCT: Lactase; GNA12: Guanine nucleotide-binding protein alpha-12; CCL2: C-C motif chemokine ligand 2; IL: Interleukin; MUC22: Mucin 22; BLVRA: Biliverdin reductase.



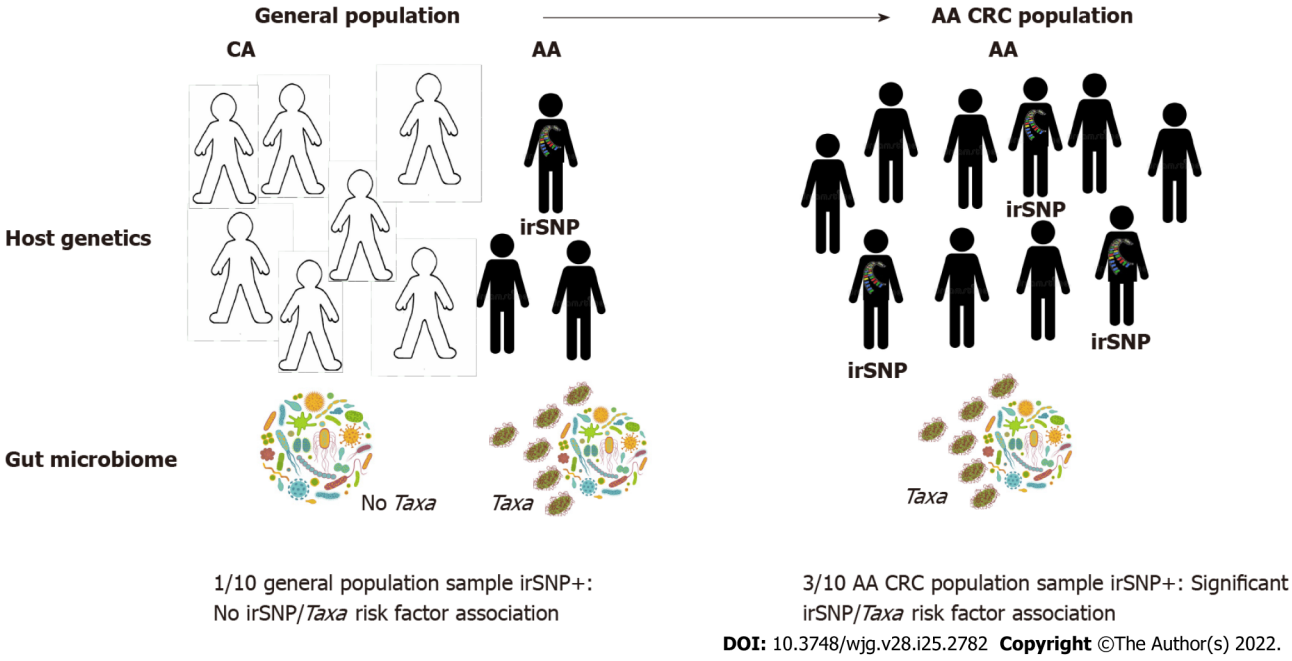
DOI: 10.3748/wjg.v28.i25.2782 **Copyright** ©The Author(s) 2022.

Figure 2 Interactions between host genetics and microbiome delineate colorectal cancer risk factors. Immune-related risk factors of colorectal cancer (CRC) may combine host genetics [including immune-related single-nucleotide polymorphisms (irSNPs)] and microbiome cues. The genetic regulation (irSNP) of bacteria (*Taxa*) recognition by the mucosal immunity may mediate the heterogeneity of CRC risk factors between populations which vary by the representation of irSNPs. A: Absence of irSNPs and pathogenic bacteria (no irSNPs/no *Taxa*) maintain healthy mucosal inflammation and gut barrier; B: Absence of irSNPs with enrichment of pathogenic bacteria (no irSNPs/*Taxa*) may lead to chronic inflammation that slowly promotes polyp formation; C: Presence of irSNP in absence of pathogenic bacteria may also lead to chronic inflammation that slowly promotes polyp formation; D: Combination of irSNP and pathogenic bacteria (dysbiosis) may trigger a smoldering chronic inflammatory response precipitating early progression of the adenoma-carcinoma sequence. Genome-wide association studies (GWAS) (irSNP as CRC risk) and microbiome GWAS (mGWAS) (bacteria as CRC risk) are poised to miss the association of the irSNP with CRC because of the necessity of a combined occurrence of irSNP and specific bacteria enrichment in the microbiota to increase the CRC risk. However, if the irSNP is linked to the genetic ancestry, population-specific microbiome GWAS will likely detect the association of irSNP and the bacteria as a CRC risk in the population carrying this genetic ancestry. CRC: Colorectal cancer; irSNPs: Immune-related single-nucleotide polymorphisms; GWAS: Genome-wide association studies; mGWAS: Microbiome genome-wide association studies.

associated with lactase persistence gene, contributed to microbiome composition[45,68,122,123]. A study performed with 416 twin pairs in the United Kingdom identified 26 "heritable" taxa, also suggesting that specific host genetic variants may participate in microbiome composition (Table 2)[124]. Notably, host genetic variants associated with microbiome composition were found to be enriched in immunity-related pathways[122]. Studies showing associations between metabolic and immune-related polymorphisms and microbiome composition are summarized in Table 2.

Finally, associations between the microbiome and somatic mutations in CRC have been described by Burns *et al*[95], who suggested that genetic determinants of the host and colon tumor mutations alter microbiome structure. The CRC mutanome could therefore help predict the composition and function of CRC-associated microbiomes and the clinical outcome or the response to therapies. To this end, of intrigue is the recent description by Ashktorab *et al*[125] and Brim *et al*[126] of genetic variation in tumor suppressor genes (*APC*), DNA mismatch repair genes, and other driver mutations (*KRAS* and *PIK3C*) in AAs with CRC, some of which were novel and not previously described in other populations. Loss of function mutations in *APC* were correlated with changes in 25 different microbial taxa, including an abundance of *Finegolia* or *Christensenellaceae*. Mutations in the zinc finger protein 717-coding gene were associated with an abundance of *Akkermansia* and *Verrucomicrobiaceae*, both colitis-associated species. Additionally, the same authors have isolated a novel *Streptococcus spp*. VT_162 from colon adenoma and CRC lesions in AAs[126]. Fecal *Streptococcus spp*. VT_162 was also confirmed in an advanced adenoma and CRC Chinese/Hong-Kong cohort[126]. An assessment of this bacterium's relative prevalence in CAs compared to AAs will be necessary. Whether CA genetic background is more restrictive, while AA genetic background is more permissive to this species is not yet established. It may be postulated that, as seen in IBD patients, host genetic background drives the nature of the microbiome and alters the CRC risk posed by procarcinogenic "driver" bacteria[48,51].

Although there is a lack of direct causative links between such bacteria and colon carcinogenesis or growth promotion, this evidence at least signals that CRC disparities in AAs may be related to differential host inflammatory responses to similar bacterial communities (inflammation-driven disparities) and/or the contribution of ancestry-related factors in shaping microbiome diversity (bacteria-driven disparities). The molecular pathological epidemiology (MPE) that aims at uncovering an interactive relationship between environmental features and disease subtypes to understand disease incidence and



DOI: 10.3748/wjg.v28.i25.2782 **Copyright** ©The Author(s) 2022.

Figure 3 Population-specific colorectal cancer microbiome genome-wide association studies to understand colorectal cancer disparities. Systemic underrepresentation of minorities in microbiome genome-wide association studies (mGWAS) may compromise the identification of microbiome-associated colorectal cancer (CRC) risks in African-Americans (AAs). Left: Associations between AA-enriched immune-related single-nucleotide polymorphisms (irSNPs) (pop-irSNPs) and gut bacteria (*Taxa*) may remain undetected in the global population if pop-irSNP and *Taxa* have too low frequency in the AA population and AAs are underrepresented. Right: If pop-irSNP and pathogenic bacteria are CRC risk factors in AA, they will be enriched in AA CRC patients compared to the general AA population (left), and mGWAS will detect the association between pop-irSNP and *Taxa* in AA CRC cohort. These features justify population-specific CRC mGWAS to detect additional CRC risk resulting from the interaction between ancestral irSNP and bacteria in minorities. CRC: Colorectal cancer; irSNPs: Immune-related single-nucleotide polymorphisms; mGWAS: Microbiome genome-wide association studies; AA: African-American; CA: Caucasian-American.

mortality will provide etiologic and pathogenic insights in CRC disparities[127,128]. However, discoveries made in healthy donors often remain inconsistent from one study to another, perhaps due to multiple confounding environmental factors between heterogeneous cohorts[45,129]. More likely culprits for the inconsistency seen in GWAS that seek to identify the impact of host genetics on microbiome diversity are the homogeneity in sampled cohorts and differences in experimental approaches including stool *vs* mucosa sampling, sequencing approaches, and annotations. Future GWAS must address such issues in order to identify associations between genetic background and the microbiome that can reliably be applied to the question of disparities.

CONCLUSION

CRC disparity is far from an exclusively biological phenomenon but rather involves a complex interplay of SES, environmental and genetic components that collectively impact CRC risk and prognostics. Although there is a growing understanding of this complexity, studies examining the influence on CRC pathogenesis from ancestry-specific interactions between host genetics and the commensal microbiome are lacking. Such work is nevertheless urgently needed to appropriately mitigate CRC on a population basis and especially to help address alarming new trends, such as early-onset CRC amongst AAs. To facilitate this line of investigation, we reviewed irSNPs identified in CRC mGWAS and proposed that some of such variants (and others yet to be discovered) may alter microbiome composition and/or differential inflammatory responses to bacteria, thereby impacting CRC risk in a manner associated with genetic ancestry. However, testing the functional significance of such variants will require systematic studies that can incorporate the microbiome, mucosal immunity, and host genetics. A recent investigation by DeStefano Shields *et al*[130], although not related to cancer disparity, offers a potential experimental blueprint. Researchers introduced the *BRAF*^{V600E} mutation to a Min$^{Apc\Delta716/+}$ murine model of distal colon polyposis, then colonized *BRAF* mutant and Min$^{Apc\Delta716/+}$ mice with *Enterotoxigenic Bacteroides fragilis*. Distal colon tumorigenesis was observed in Min$^{Apc\Delta716/+}$ mice following colonization, whereas *BRAF*^{V600E} Min$^{Apc\Delta716/+}$ mice developed proximal colon tumors associated with immune signature and microbiome alterations plus sensitivity to anti-programmed death ligand 1[130]. These results suggested that host gene/bacteria interactions may drive CRC risk and pathogenesis, and demonstrate how such interactions can be disentangled mechanistically using experimental models with clinical implications. In the nascent field of precision medicine and multidisciplinary big data integration, the rapidly

evolving MPE represents a successful model of integration of pathology, genomics, microbiome, immunology, epidemiology, and social science[127,128]. MPE will considerably improve precision medicine and prevention allowing, among other things, identifying SNPs that may impact microbiome and inflammation and serve as predictive markers. Genetic ancestry, however, remains to be integrated to this model to precisely address CRC disparities at the molecular level. Elucidating the mechanisms by which ancestry-associated variants impact CRC pathogenesis will be much more challenging, but models such as the one described by Lavoie *et al*[60], who used mice engineered to express the polymorphism T300A (rs2241880) in the *Atg16 L1* gene known to increase IBD risk in humans, represent a promising approach to identifying mechanisms that can lead to personalized interventions applicable to minorities.

Yet, without addressing biases in genomics science, the ability of GWAS to detect variants of significance for AAs (or other minorities in general) will remain stunted[131]. To date, cancer GWAS have examined cohorts predominantly composed of Caucasian individuals, an homogeneity that limits the appreciation of how genetic ancestry impacts cancer risk[101,102]. Critically, the lack of diverse representation in sampling cohorts results in the increased likelihood that, even if identified, cancer-associated variants may be of limited clinical significance for non-Caucasian populations. While commenting on this issue, Davis[131] recently argued that the current state of genomic medicine is inadequately equipped to confront current oncological trends of disparate incidence and mortality in inclusive fashion and advocated for a persistent push towards the prioritization of patient diversity. Such an agenda is not only more harmonious with the principles of ethical human subjects research but is also scientifically meritable, as studies that account for diversity have already revealed novel genomic data that may improve our understanding of cancer etiology[132]. Therefore, for powered GWAS to detect and discern associations between population-enriched irSNPs, the microbiome, and CRC, proper accounting of population diversity and sufficient cohort size (estimated at > 4000 individuals)[45], or even population-specific CRC studies will be essential (illustrated in Figure 3). Encouragingly, recent methodological frameworks for multi-ancestry cohort GWAS have already yielded ancestry-related cancer variant risk factors[133,134]. Moreover, the recent initiative of the National Cancer Institute: Genetic Association and Mechanism in Oncology (GAME-ON; https://epi.grants.cancer.gov), which regrouped genomic data from more than 33 GWAS across five different cancers (CRC, lung, breast, ovary, and oral), is an example of the benefit of data sharing that will help identifying through meta-analysis data cancer risk loci in understudied populations, especially since 40% of the samples are from African, Asian, and Hispanic backgrounds. However, our integrated concept for CRC genomic research proposes that to represent accurately and capture the contribution of irSNP/microbiome interactions to CRC disparities, such diversified host genomic data must be paired with microbiome data.

In sum, population-related irSNP that regulate mucosal inflammation may modify the microbiota and its interaction with colon epithelium. Alternatively, a population-related SNP not involved in immune regulation may also alter the microbiome and trigger procarcinogenic chronic inflammation. Finally, a combination of two SNPs impacting inflammation and the microbiome with minor effects on CRC pathogenesis may trigger a strong procarcinogenic bacteria/inflammation interaction when combined in an at-risk population (Figure 2). By hunting for and characterizing such genetic factors using the emerging genetic admixture and ancestry paradigms, we believe scientists and clinicians will have a precision tool that enables a clearer understanding of the association between CRC with AA populations and the increasing trend of early onset CRC, ultimately to better mitigate CRC outcome disparities.

FOOTNOTES

Author contributions: Ahmad S wrote the manuscript; Housseau F and Brim H contributed equally to the review's conception and oversight of the writing, with additional insight from Ashktorab H; and all authors have read and approve the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: United States

ORCID number: Sami Ahmad 0000-0001-5838-3137; Hassan Ashktorab 0000-0002-4048-4666; Hassan Brim 0000-0001-7055-2298; Franck Housseau 0000-0002-7028-3953.

S-Editor: Wang JJ

L-Editor: A
P-Editor: Wang JJ

REFERENCES

1 **Siegel RL**, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**: 145-164 [PMID: 32133645 DOI: 10.3322/caac.21601]
2 **Carethers JM**, Doubeni CA. Causes of Socioeconomic Disparities in Colorectal Cancer and Intervention Framework and Strategies. *Gastroenterology* 2020; **158**: 354-367 [PMID: 31682851 DOI: 10.1053/j.gastro.2019.10.029]
3 **Carethers JM**. Clinical and Genetic Factors to Inform Reducing Colorectal Cancer Disparitites in African Americans. *Front Oncol* 2018; **8**: 531 [PMID: 30524961 DOI: 10.3389/fonc.2018.00531]
4 **Polite BN**, Sing A, Sargent DJ, Grothey A, Berlin J, Kozloff M, Feng S. Exploring racial differences in outcome and treatment for metastatic colorectal cancer: results from a large prospective observational cohort study (BRiTE). *Cancer* 2012; **118**: 1083-1090 [PMID: 21800287 DOI: 10.1002/cncr.26394]
5 **Sanoff HK**, Sargent DJ, Green EM, McLeod HL, Goldberg RM. Racial differences in advanced colorectal cancer outcomes and pharmacogenetics: a subgroup analysis of a large randomized clinical trial. *J Clin Oncol* 2009; **27**: 4109-4115 [PMID: 19636001 DOI: 10.1200/JCO.2009.21.9527]
6 **Johnston FM**, Yeo HL, Clark C, Stewart JH 4th. Bias Issues in Colorectal Cancer Management: A Review. *Ann Surg Oncol* 2022; **29**: 2166-2173 [PMID: 34142287 DOI: 10.1245/s10434-021-10232-6]
7 **Ciccone G**, Prastaro C, Ivaldi C, Giacometti R, Vineis P. Access to hospital care, clinical stage and survival from colorectal cancer according to socio-economic status. *Ann Oncol* 2000; **11**: 1201-1204 [PMID: 11061620 DOI: 10.1023/a:1008352119907]
8 **Jepson C**, Kessler LG, Portnoy B, Gibbs T. Black-white differences in cancer prevention knowledge and behavior. *Am J Public Health* 1991; **81**: 501-504 [PMID: 2003635 DOI: 10.2105/ajph.81.4.501]
9 **Zavala VA**, Bracci PM, Carethers JM, Carvajal-Carmona L, Coggins NB, Cruz-Correa MR, Davis M, de Smith AJ, Dutil J, Figueiredo JC, Fox R, Graves KD, Gomez SL, Llera A, Neuhausen SL, Newman L, Nguyen T, Palmer JR, Palmer NR, Pérez-Stable EJ, Piawah S, Rodriquez EJ, Sanabria-Salas MC, Schmit SL, Serrano-Gomez SJ, Stern MC, Weitzel J, Yang JJ, Zabaleta J, Ziv E, Fejerman L. Cancer health disparities in racial/ethnic minorities in the United States. *Br J Cancer* 2021; **124**: 315-332 [PMID: 32901135 DOI: 10.1038/s41416-020-01038-6]
10 **Chen J**, Pitmon E, Wang K. Microbiome, inflammation and colorectal cancer. *Semin Immunol* 2017; **32**: 43-53 [PMID: 28982615 DOI: 10.1016/j.smim.2017.09.006]
11 **Dejea C**, Wick E, Sears CL. Bacterial oncogenesis in the colon. *Future Microbiol* 2013; **8**: 445-460 [PMID: 23534358 DOI: 10.2217/fmb.13.17]
12 **Farhana L**, Antaki F, Murshed F, Mahmud H, Judd SL, Nangia-Makker P, Levi E, Yu Y, Majumdar AP. Gut microbiome profiling and colorectal cancer in African Americans and Caucasian Americans. *World J Gastrointest Pathophysiol* 2018; **9**: 47-58 [PMID: 30283710 DOI: 10.4291/wjgp.v9.i2.47]
13 **Koi M**, Okita Y, Carethers JM. *Fusobacterium nucleatum* Infection in Colorectal Cancer: Linking Inflammation, DNA Mismatch Repair and Genetic and Epigenetic Alterations. *J Anus Rectum Colon* 2018; **2**: 37-46 [PMID: 30116794 DOI: 10.23922/jarc.2017-055]
14 **Devaraj B**, Lee A, Cabrera BL, Miyai K, Luo L, Ramamoorthy S, Keku T, Sandler RS, McGuire KL, Carethers JM. Relationship of EMAST and microsatellite instability among patients with rectal cancer. *J Gastrointest Surg* 2010; **14**: 1521-1528 [PMID: 20844976 DOI: 10.1007/s11605-010-1340-6]
15 **Carethers JM**, Koi M, Tseng-Rogenski SS. EMAST is a Form of Microsatellite Instability That is Initiated by Inflammation and Modulates Colorectal Cancer Progression. *Genes (Basel)* 2015; **6**: 185-205 [PMID: 25836926 DOI: 10.3390/genes6020185]
16 **Dejea CM**, Wick EC, Hechenbleikner EM, White JR, Mark Welch JL, Rossetti BJ, Peterson SN, Snesrud EC, Borisy GG, Lazarev M, Stein E, Vadivelu J, Roslani AC, Malik AA, Wanyiri JW, Goh KL, Thevambiga I, Fu K, Wan F, Llosa N, Housseau F, Romans K, Wu X, McAllister FM, Wu S, Vogelstein B, Kinzler KW, Pardoll DM, Sears CL. Microbiota organization is a distinct feature of proximal colorectal cancers. *Proc Natl Acad Sci U S A* 2014; **111**: 18321-18326 [PMID: 25489084 DOI: 10.1073/pnas.1406199111]
17 **Thornton JG**, Morris AM, Thornton JD, Flowers CR, McCashland TM. Racial variation in colorectal polyp and tumor location. *J Natl Med Assoc* 2007; **99**: 723-728 [PMID: 17668638]
18 **Park CH**, Han DS, Oh YH, Lee AR, Lee YR, Eun CS. Role of Fusobacteria in the serrated pathway of colorectal carcinogenesis. *Sci Rep* 2016; **6**: 25271 [PMID: 27125587 DOI: 10.1038/srep25271]
19 **Yu J**, Chen Y, Fu X, Zhou X, Peng Y, Shi L, Chen T, Wu Y. Invasive Fusobacterium nucleatum may play a role in the carcinogenesis of proximal colon cancer through the serrated neoplasia pathway. *Int J Cancer* 2016; **139**: 1318-1326 [PMID: 27130618 DOI: 10.1002/ijc.30168]
20 **DeDecker L**, Coppedge B, Avelar-Barragan J, Karnes W, Whiteson K. Microbiome distinctions between the CRC carcinogenic pathways. *Gut Microbes* 2021; **13**: 1854641 [PMID: 33446008 DOI: 10.1080/19490976.2020.1854641]
21 **Yang JF**, Tang SJ, Lash RH, Wu R, Yang Q. Anatomic distribution of sessile serrated adenoma/polyp with and without cytologic dysplasia. *Arch Pathol Lab Med* 2015; **139**: 388-393 [PMID: 25724036 DOI: 10.5858/arpa.2013-0523-OA]
22 **Yamauchi M**, Morikawa T, Kuchiba A, Imamura Y, Qian ZR, Nishihara R, Liao X, Waldron L, Hoshida Y, Huttenhower C, Chan AT, Giovannucci E, Fuchs C, Ogino S. Assessment of colorectal cancer molecular features along bowel subsites challenges the conception of distinct dichotomy of proximal *versus* distal colorectum. *Gut* 2012; **61**: 847-854 [PMID: 22427238 DOI: 10.1136/gutjnl-2011-300865]
23 **Polite BN**, Adams-Campbell LL, Brawley OW, Bickell N, Carethers JM, Flowers CR, Foti M, Gomez SL, Griggs JJ,

Lathan CS, Li CI, Lichtenfeld JL, McCaskill-Stevens W, Paskett ED. Charting the future of cancer health disparities research: A position statement from the American Association for Cancer Research, the American Cancer Society, the American Society of Clinical Oncology, and the National Cancer Institute. *CA Cancer J Clin* 2017; **67**: 353-361 [PMID: 28738442 DOI: 10.3322/caac.21404]

24 **Zheng D**, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. *Cell Res* 2020; **30**: 492-506 [PMID: 32433595 DOI: 10.1038/s41422-020-0332-7]

25 **Jovov B**, Araujo-Perez F, Sigel CS, Stratford JK, McCoy AN, Yeh JJ, Keku T. Differential gene expression between African American and European American colorectal cancer patients. *PLoS One* 2012; **7**: e30168 [PMID: 22276153 DOI: 10.1371/journal.pone.0030168]

26 **Quach H**, Rotival M, Pothlichet J, Loh YE, Dannemann M, Zidane N, Laval G, Patin E, Harmant C, Lopez M, Deschamps M, Naffakh N, Duffy D, Coen A, Leroux-Roels G, Clément F, Boland A, Deleuze JF, Kelso J, Albert ML, Quintana-Murci L. Genetic Adaptation and Neandertal Admixture Shaped the Immune System of Human Populations. *Cell* 2016; **167**: 643-656.e17 [PMID: 27768888 DOI: 10.1016/j.cell.2016.09.024]

27 **Nédélec Y**, Sanz J, Baharian G, Szpiech ZA, Pacis A, Dumaine A, Grenier JC, Freiman A, Sams AJ, Hebert S, Pagé Sabourin A, Luca F, Blekhman R, Hernandez RD, Pique-Regi R, Tung J, Yotova V, Barreiro LB. Genetic Ancestry and Natural Selection Drive Population Differences in Immune Responses to Pathogens. *Cell* 2016; **167**: 657-669.e21 [PMID: 27768889 DOI: 10.1016/j.cell.2016.09.025]

28 **Banda Y**, Kvale MN, Hoffmann TJ, Hesselson SE, Ranatunga D, Tang H, Sabatti C, Croen LA, Dispensa BP, Henderson M, Iribarren C, Jorgenson E, Kushi LH, Ludwig D, Olberg D, Quesenberry CP Jr, Rowell S, Sadler M, Sakoda LC, Sciortino S, Shen L, Smethurst D, Somkin CP, Van Den Eeden SK, Walter L, Whitmer RA, Kwok PY, Schaefer C, Risch N. Characterizing Race/Ethnicity and Genetic Ancestry for 100,000 Subjects in the Genetic Epidemiology Research on Adult Health and Aging (GERA) Cohort. *Genetics* 2015; **200**: 1285-1295 [PMID: 26092716 DOI: 10.1534/genetics.115.178616]

29 **Bryc K**, Durand EY, Macpherson JM, Reich D, Mountain JL. The genetic ancestry of African Americans, Latinos, and European Americans across the United States. *Am J Hum Genet* 2015; **96**: 37-53 [PMID: 25529636 DOI: 10.1016/j.ajhg.2014.11.010]

30 **Batai K**, Hooker S, Kittles RA. Leveraging genetic ancestry to study health disparities. *Am J Phys Anthropol* 2021; **175**: 363-375 [PMID: 32935870 DOI: 10.1002/ajpa.24144]

31 **Denny JC**. Chapter 13: Mining electronic health records in the genomics era. *PLoS Comput Biol* 2012; **8**: e1002823 [PMID: 23300414 DOI: 10.1371/journal.pcbi.1002823]

32 **Ruterbusch JJ**, Levin AM, Kittles R, Rybicki BA, Bock CH. Abstract A66: Admixture and fine mapping in African Americans identifies a susceptibility locus for prostate cancer on chromosome 7. *Cancer Epidemiol Biomarkers Prev* 2012; **21**: A66 [DOI: 10.1158/1055-9965.DISP12-A66]

33 **Sanabria-Salas MC**, Hernández-Suárez G, Umaña-Pérez A, Rawlik K, Tenesa A, Serrano-López ML, Sánchez de Gómez M, Rojas MP, Bravo LE, Albis R, Plata JL, Green H, Borgovan T, Li L, Majumdar S, Garai J, Lee E, Ashktorab H, Brim H, Margolin D, Fejerman L, Zabaleta J. IL1B-CGTC haplotype is associated with colorectal cancer in admixed individuals with increased African ancestry. *Sci Rep* 2017; **7**: 41920 [PMID: 28157220 DOI: 10.1038/srep41920]

34 **Nieves Delgado A**, Baedke J. Does the human microbiome tell us something about race? *Humanit Soc Sci Commun* 2021; **8**: 97 [DOI: 10.1057/s41599-021-00772-3]

35 **Gallagher S**, Hughes E, Wagner S, Tshiaba P, Rosenthal E, Roa BB, Kurian AW, Domchek SM, Garber J, Lancaster J, Weitzel JN, Gutin A, Lanchbury JS, Robson M. Association of a Polygenic Risk Score With Breast Cancer Among Women Carriers of High- and Moderate-Risk Breast Cancer Genes. *JAMA Netw Open* 2020; **3**: e208501 [PMID: 32609350 DOI: 10.1001/jamanetworkopen.2020.8501]

36 **Thomas M**, Sakoda LC, Hoffmeister M, Rosenthal EA, Lee JK, van Duijnhoven FJB, Platz EA, Wu AH, Dampier CH, de la Chapelle A, Wolk A, Joshi AD, Burnett-Hartman A, Gsur A, Lindblom A, Castells A, Win AK, Namjou B, Van Guelpen B, Tangen CM, He Q, Li CI, Schafmayer C, Joshu CE, Ulrich CM, Bishop DT, Buchanan DD, Schaid D, Drew DA, Muller DC, Duggan D, Crosslin DR, Albanes D, Giovannucci EL, Larson E, Qu F, Mentch F, Giles GG, Hakonarson H, Hampel H, Stanaway IB, Figueiredo JC, Huyghe JR, Minnier J, Chang-Claude J, Hampe J, Harley JB, Visvanathan K, Curtis KR, Offit K, Li L, Le Marchand L, Vodickova L, Gunter MJ, Jenkins MA, Slattery ML, Lemire M, Woods MO, Song M, Murphy N, Lindor NM, Dikilitas O, Pharoah PDP, Campbell PT, Newcomb PA, Milne RL, MacInnis RJ, Castellví-Bel S, Ogino S, Berndt SI, Bézieau S, Thibodeau SN, Gallinger SJ, Zaidi SH, Harrison TA, Keku TO, Hudson TJ, Vymetalkova V, Moreno V, Martín V, Arndt V, Wei WQ, Chung W, Su YR, Hayes RB, White E, Vodicka P, Casey G, Gruber SB, Schoen RE, Chan AT, Potter JD, Brenner H, Jarvik GP, Corley DA, Peters U, Hsu L. Genome-wide Modeling of Polygenic Risk Score in Colorectal Cancer Risk. *Am J Hum Genet* 2020; **107**: 432-444 [PMID: 32758450 DOI: 10.1016/j.ajhg.2020.07.006]

37 **Sommer F**, Bäckhed F. The gut microbiota--masters of host development and physiology. *Nat Rev Microbiol* 2013; **11**: 227-238 [PMID: 23435359 DOI: 10.1038/nrmicro2974]

38 **Sonnenburg ED**, Sonnenburg JL. The ancestral and industrialized gut microbiota and implications for human health. *Nat Rev Microbiol* 2019; **17**: 383-390 [PMID: 31089293 DOI: 10.1038/s41579-019-0191-8]

39 **Belkaid Y**, Harrison OJ. Homeostatic Immunity and the Microbiota. *Immunity* 2017; **46**: 562-576 [PMID: 28423337 DOI: 10.1016/j.immuni.2017.04.008]

40 **Hooper LV**, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. *Science* 2012; **336**: 1268-1273 [PMID: 22674334 DOI: 10.1126/science.1223490]

41 **Johansson ME**, Phillipson M, Petersson J, Velcich A, Holm L, Hansson GC. The inner of the two Muc2 mucin-dependent mucus layers in colon is devoid of bacteria. *Proc Natl Acad Sci U S A* 2008; **105**: 15064-15069 [PMID: 18806221 DOI: 10.1073/pnas.0803124105]

42 **Louis P**, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. *Nat Rev Microbiol* 2014; **12**: 661-672 [PMID: 25198138 DOI: 10.1038/nrmicro3344]

43 **Ocvirk S**, Wilson AS, Posma JM, Li JV, Koller KR, Day GM, Flanagan CA, Otto JE, Sacco PE, Sacco FD, Sapp FR,

Newton K, Brouard F, DeLany JP, Behnning M, Appolonia CN, Soni D, Bhatti F, Methé B, Fitch A, Morris A, Gaskins HR, Kinross J, Nicholson JK, Thomas TK, O'Keefe SJD. A prospective cohort analysis of gut microbial co-metabolism in Alaska Native and rural African people at high and low risk of colorectal cancer. *Am J Clin Nutr* 2020; **111**: 406-419 [PMID: 31851298 DOI: 10.1093/ajcn/nqz301]

44 **O'Keefe SJ**, Li JV, Lahti L, Ou J, Carbonero F, Mohammed K, Posma JM, Kinross J, Wahl E, Ruder E, Vipperla K, Naidoo V, Mtshali L, Tims S, Puylaert PG, DeLany J, Krasinskas A, Benefiel AC, Kaseb HO, Newton K, Nicholson JK, de Vos WM, Gaskins HR, Zoetendal EG. Fat, fibre and cancer risk in African Americans and rural Africans. *Nat Commun* 2015; **6**: 6342 [PMID: 25919227 DOI: 10.1038/ncomms7342]

45 **Rothschild D**, Weissbrod O, Barkan E, Kurilshikov A, Korem T, Zeevi D, Costea PI, Godneva A, Kalka IN, Bar N, Shilo S, Lador D, Vila AV, Zmora N, Pevsner-Fischer M, Israeli D, Kosower N, Malka G, Wolf BC, Avnit-Sagi T, Lotan-Pompan M, Weinberger A, Halpern Z, Carmi S, Fu J, Wijmenga C, Zhernakova A, Elinav E, Segal E. Environment dominates over host genetics in shaping human gut microbiota. *Nature* 2018; **555**: 210-215 [PMID: 29489753 DOI: 10.1038/nature25973]

46 **Terzić J**, Grivennikov S, Karin E, Karin M. Inflammation and colon cancer. *Gastroenterology* 2010; **138**: 2101-2114.e5 [PMID: 20420949 DOI: 10.1053/j.gastro.2010.01.058]

47 **Wang H**, Taverna D, Stram DO, Fortini BK, Cheng I, Wilkens LR, Burnett T, Makar KW, Lindor NM, Hopper JL, Gallinger S, Baron JA, Haile R, Kolonel LN, Henderson BE, Newcomb PA, Casey G, Duggan D, Ulrich CM, Le Marchand L. Genetic variation in the inflammation and innate immunity pathways and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev* 2013; **22**: 2094-2101 [PMID: 24045924 DOI: 10.1158/1055-9965.EPI-13-0694]

48 **Turpin W**, Goethel A, Bedrani L, Croitoru Mdcm K. Determinants of IBD Heritability: Genes, Bugs, and More. *Inflamm Bowel Dis* 2018; **24**: 1133-1148 [PMID: 29701818 DOI: 10.1093/ibd/izy085]

49 **Lu Y**, Kweon SS, Tanikawa C, Jia WH, Xiang YB, Cai Q, Zeng C, Schmit SL, Shin A, Matsuo K, Jee SH, Kim DH, Kim J, Wen W, Shi J, Guo X, Li B, Wang N, Zhang B, Li X, Shin MH, Li HL, Ren Z, Oh JH, Oze I, Ahn YO, Jung KJ, Conti DV, Schumacher FR, Rennert G, Jenkins MA, Campbell PT, Hoffmeister M, Casey G, Gruber SB, Gao J, Gao YT, Pan ZZ, Kamatani Y, Zeng YX, Shu XO, Long J, Matsuda K, Zheng W. Large-Scale Genome-Wide Association Study of East Asians Identifies Loci Associated With Risk for Colorectal Cancer. *Gastroenterology* 2019; **156**: 1455-1466 [PMID: 30529582 DOI: 10.1053/j.gastro.2018.11.066]

50 **Law PJ**, Timofeeva M, Fernandez-Rozadilla C, Broderick P, Studd J, Fernandez-Tajes J, Farrington S, Svinti V, Palles C, Orlando G, Sud A, Holroyd A, Penegar S, Theodoratou E, Vaughan-Shaw P, Campbell H, Zgaga L, Hayward C, Campbell A, Harris S, Deary IJ, Starr J, Gatcombe L, Pinna M, Briggs S, Martin L, Jaeger E, Sharma-Oates A, East J, Leedham S, Arnold R, Johnstone E, Wang H, Kerr D, Kerr R, Maughan T, Kaplan R, Al-Tassan N, Palin K, Hänninen UA, Cajuso T, Tanskanen T, Kondelin J, Kaasinen E, Sarin AP, Eriksson JG, Rissanen H, Knekt P, Pukkala E, Jousilahti P, Salomaa V, Ripatti S, Palotie A, Renkonen-Sinisalo L, Lepistö A, Böhm J, Mecklin JP, Buchanan DD, Win AK, Hopper J, Jenkins ME, Lindor NM, Newcomb PA, Gallinger S, Duggan D, Casey G, Hoffmann P, Nöthen MM, Jöckel KH, Easton DF, Pharoah PDP, Peto J, Canzian F, Swerdlow A, Eeles RA, Kote-Jarai Z, Muir K, Pashayan N; PRACTICAL consortium, Harkin A, Allan K, McQueen J, Paul J, Iveson T, Saunders M, Butterbach K, Chang-Claude J, Hoffmeister M, Brenner H, Kirac I, Matošević P, Hofer P, Brezina S, Gsur A, Cheadle JP, Aaltonen LA, Tomlinson I, Houlston RS, Dunlop MG. Association analyses identify 31 new risk loci for colorectal cancer susceptibility. *Nat Commun* 2019; **10**: 2154 [PMID: 31089142 DOI: 10.1038/s41467-019-09775-w]

51 **Hall AB**, Tolonen AC, Xavier RJ. Human genetic variation and the gut microbiome in disease. *Nat Rev Genet* 2017; **18**: 690-699 [PMID: 28824167 DOI: 10.1038/nrg.2017.63]

52 **Rakoff-Nahoum S**, Medzhitov R. Regulation of spontaneous intestinal tumorigenesis through the adaptor protein MyD88. *Science* 2007; **317**: 124-127 [PMID: 17615359 DOI: 10.1126/science.1140488]

53 **Hu B**, Elinav E, Huber S, Strowig T, Hao L, Hafemann A, Jin C, Wunderlich C, Wunderlich T, Eisenbarth SC, Flavell RA. Microbiota-induced activation of epithelial IL-6 signaling links inflammasome-driven inflammation with transmissible cancer. *Proc Natl Acad Sci U S A* 2013; **110**: 9862-9867 [PMID: 23696660 DOI: 10.1073/pnas.1307575110]

54 **Couturier-Maillard A**, Secher T, Rehman A, Normand S, De Arcangelis A, Haesler R, Huot L, Grandjean T, Bressenot A, Delanoye-Crespin A, Gaillot O, Schreiber S, Lemoine Y, Ryffel B, Hot D, Nùñez G, Chen G, Rosenstiel P, Chamaillard M. NOD2-mediated dysbiosis predisposes mice to transmissible colitis and colorectal cancer. *J Clin Invest* 2013; **123**: 700-711 [PMID: 23281400 DOI: 10.1172/JCI62236]

55 **Moschen AR**, Gerner RR, Wang J, Klepsch V, Adolph TE, Reider SJ, Hackl H, Pfister A, Schilling J, Moser PL, Kempster SL, Swidsinski A, Orth Höller D, Weiss G, Baines JF, Kaser A, Tilg H. Lipocalin 2 Protects from Inflammation and Tumorigenesis Associated with Gut Microbiota Alterations. *Cell Host Microbe* 2016; **19**: 455-469 [PMID: 27078067 DOI: 10.1016/j.chom.2016.03.007]

56 **Davies JM**, Abreu MT. The innate immune system and inflammatory bowel disease. *Scand J Gastroenterol* 2015; **50**: 24-33 [PMID: 25523553 DOI: 10.3109/00365521.2014.966321]

57 **Hugot JP**, Chamaillard M, Zouali H, Lesage S, Cézard JP, Belaiche J, Almer S, Tysk C, O'Morain CA, Gassull M, Binder V, Finkel Y, Cortot A, Modigliani R, Laurent-Puig P, Gower-Rousseau C, Macry J, Colombel JF, Sahbatou M, Thomas G. Association of NOD2 Leucine-rich repeat variants with susceptibility to Crohn's disease. *Nature* 2001; **411**: 599-603 [PMID: 11385576 DOI: 10.1038/35079107]

58 **Ebbo M**, Crinier A, Vély F, Vivier E. Innate lymphoid cells: major players in inflammatory diseases. *Nat Rev Immunol* 2017; **17**: 665-678 [PMID: 28804130 DOI: 10.1038/nri.2017.86]

59 **Knights D**, Silverberg MS, Weersma RK, Gevers D, Dijkstra G, Huang H, Tyler AD, van Sommeren S, Imhann F, Stempak JM, Vangay P, Al-Ghalith GA, Russell C, Sauk J, Knight J, Daly MJ, Huttenhower C, Xavier RJ. Complex host genetics influence the microbiome in inflammatory bowel disease. *Genome Med* 2014; **6**: 107 [PMID: 25587358 DOI: 10.1186/s13073-014-0107-1]

60 **Lavoie S**, Conway KL, Lassen KG, Jijon HB, Pan H, Chun E, Michaud M, Lang JK, Gallini Comeau CA, Dreyfuss JM, Glickman JN, Vlamakis H, Ananthakrishnan A, Kostic A, Garrett WS, Xavier RJ. The Crohn's disease polymorphism, *ATG16L1* T300A, alters the gut microbiota and enhances the local Th1/Th17 response. *Elife* 2019; **8** [PMID: 30666959

DOI: 10.7554/eLife.39982]

61 **Harrington LE**, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM, Weaver CT. Interleukin 17-producing CD4+ effector T cells develop *via* a lineage distinct from the T helper type 1 and 2 lineages. *Nat Immunol* 2005; **6**: 1123-1132 [PMID: 16200070 DOI: 10.1038/ni1254]

62 **Lee JS**, Tato CM, Joyce-Shaikh B, Gulen MF, Cayatte C, Chen Y, Blumenschein WM, Judo M, Ayanoglu G, McClanahan TK, Li X, Cua DJ. Interleukin-23-Independent IL-17 Production Regulates Intestinal Epithelial Permeability. *Immunity* 2015; **43**: 727-738 [PMID: 26431948 DOI: 10.1016/j.immuni.2015.09.003]

63 **Stockinger B**, Veldhoen M. Differentiation and function of Th17 T cells. *Curr Opin Immunol* 2007; **19**: 281-286 [PMID: 17433650 DOI: 10.1016/j.coi.2007.04.005]

64 **Grivennikov SI**, Wang K, Mucida D, Stewart CA, Schnabl B, Jauch D, Taniguchi K, Yu GY, Osterreicher CH, Hung KE, Datz C, Feng Y, Fearon ER, Oukka M, Tessarollo L, Coppola V, Yarovinsky F, Cheroutre H, Eckmann L, Trinchieri G, Karin M. Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth. *Nature* 2012; **491**: 254-258 [PMID: 23034650 DOI: 10.1038/nature11465]

65 **Wang K**, Kim MK, Di Caro G, Wong J, Shalapour S, Wan J, Zhang W, Zhong Z, Sanchez-Lopez E, Wu LW, Taniguchi K, Feng Y, Fearon E, Grivennikov SI, Karin M. Interleukin-17 receptor a signaling in transformed enterocytes promotes early colorectal tumorigenesis. *Immunity* 2014; **41**: 1052-1063 [PMID: 25526314 DOI: 10.1016/j.immuni.2014.11.009]

66 **Bank S**, Andersen PS, Burisch J, Pedersen N, Roug S, Galsgaard J, Ydegaard Turino S, Brodersen JB, Rashid S, Kaiser Rasmussen B, Avlund S, Bastholm Olesen T, Hoffmann HJ, Andersen Nexø B, Sode J, Vogel U, Andersen V. Polymorphisms in the Toll-Like Receptor and the IL-23/IL-17 Pathways Were Associated with Susceptibility to Inflammatory Bowel Disease in a Danish Cohort. *PLoS One* 2015; **10**: e0145302 [PMID: 26698117 DOI: 10.1371/journal.pone.0145302]

67 **Newman WG**, Zhang Q, Liu X, Amos CI, Siminovitch KA. Genetic variants in IL-23R and ATG16L1 independently predispose to increased susceptibility to Crohn's disease in a Canadian population. *J Clin Gastroenterol* 2009; **43**: 444-447 [PMID: 19276991 DOI: 10.1097/MCG.0b013e318168bdf0]

68 **Bonder MJ**, Kurilshikov A, Tigchelaar EF, Mujagic Z, Imhann F, Vila AV, Deelen P, Vatanen T, Schirmer M, Smeekens SP, Zhernakova DV, Jankipersadsing SA, Jaeger M, Oosting M, Cenit MC, Masclee AA, Swertz MA, Li Y, Kumar V, Joosten L, Harmsen H, Weersma RK, Franke L, Hofker MH, Xavier RJ, Jonkers D, Netea MG, Wijmenga C, Fu J, Zhernakova A. The effect of host genetics on the gut microbiome. *Nat Genet* 2016; **48**: 1407-1412 [PMID: 27694959 DOI: 10.1038/ng.3663]

69 **Yeyeodu ST**, Kidd LR, Kimbro KS. Protective Innate Immune Variants in Racial/Ethnic Disparities of Breast and Prostate Cancer. *Cancer Immunol Res* 2019; **7**: 1384-1389 [PMID: 31481520 DOI: 10.1158/2326-6066.CIR-18-0564]

70 **Quan B**, Qi X, Yu Z, Jiang Y, Liao M, Wang G, Feng R, Zhang L, Chen Z, Jiang Q, Liu G. Pathway analysis of genome-wide association study and transcriptome data highlights new biological pathways in colorectal cancer. *Mol Genet Genomics* 2015; **290**: 603-610 [PMID: 25362561 DOI: 10.1007/s00438-014-0945-y]

71 **Wallace TA**, Prueitt RL, Yi M, Howe TM, Gillespie JW, Yfantis HG, Stephens RM, Caporaso NE, Loffredo CA, Ambs S. Tumor immunobiological differences in prostate cancer between African-American and European-American men. *Cancer Res* 2008; **68**: 927-936 [PMID: 18245496 DOI: 10.1158/0008-5472.CAN-07-2608]

72 **Özdemir BC**, Dotto GP. Racial Differences in Cancer Susceptibility and Survival: More Than the Color of the Skin? *Trends Cancer* 2017; **3**: 181-197 [PMID: 28718431 DOI: 10.1016/j.trecan.2017.02.002]

73 **Yuan J**, Hu Z, Mahal BA, Zhao SD, Kensler KH, Pi J, Hu X, Zhang Y, Wang Y, Jiang J, Li C, Zhong X, Montone KT, Guan G, Tanyi JL, Fan Y, Xu X, Morgan MA, Long M, Zhang R, Sood AK, Rebbeck TR, Dang CV, Zhang L. Integrated Analysis of Genetic Ancestry and Genomic Alterations across Cancers. *Cancer Cell* 2018; **34**: 549-560.e9 [PMID: 30300578 DOI: 10.1016/j.ccell.2018.08.019]

74 **Zanetti KA**, Haznadar M, Welsh JA, Robles AI, Ryan BM, McClary AC, Bowman ED, Goodman JE, Bernig T, Chanock SJ, Harris CC. 3'-UTR and functional secretor haplotypes in mannose-binding lectin 2 are associated with increased colon cancer risk in African Americans. *Cancer Res* 2012; **72**: 1467-1477 [PMID: 22282660 DOI: 10.1158/0008-5472.CAN-11-3073]

75 **Karimzadeh MR**, Zarin M, Ehtesham N, Khosravi S, Soosanabadi M, Mosallaei M, Pourdavoud P. MicroRNA binding site polymorphism in inflammatory genes associated with colorectal cancer: literature review and bioinformatics analysis. *Cancer Gene Ther* 2020; **27**: 739-753 [PMID: 32203060 DOI: 10.1038/s41417-020-0172-0]

76 **Lazarus R**, Vercelli D, Palmer LJ, Klimecki WJ, Silverman EK, Richter B, Riva A, Ramoni M, Martinez FD, Weiss ST, Kwiatkowski DJ. Single nucleotide polymorphisms in innate immunity genes: abundant variation and potential role in complex human disease. *Immunol Rev* 2002; **190**: 9-25 [PMID: 12493003 DOI: 10.1034/j.1600-065x.2002.19002.x]

77 **Barreiro LB**, Quintana-Murci L. From evolutionary genetics to human immunology: how selection shapes host defence genes. *Nat Rev Genet* 2010; **11**: 17-30 [PMID: 19953080 DOI: 10.1038/nrg2698]

78 **Brinkworth JF**, Barreiro LB. The contribution of natural selection to present-day susceptibility to chronic inflammatory and autoimmune disease. *Curr Opin Immunol* 2014; **31**: 66-78 [PMID: 25458997 DOI: 10.1016/j.coi.2014.09.008]

79 **Sams AJ**, Dumaine A, Nédélec Y, Yotova V, Alfieri C, Tanner JE, Messer PW, Barreiro LB. Adaptively introgressed Neandertal haplotype at the OAS locus functionally impacts innate immune responses in humans. *Genome Biol* 2016; **17**: 246 [PMID: 27899133 DOI: 10.1186/s13059-016-1098-6]

80 **Green R**, Wilkins C, Thomas S, Sekine A, Hendrick DM, Voss K, Ireton RC, Mooney M, Go JT, Choonoo G, Jeng S, de Villena FP, Ferris MT, McWeeney S, Gale M Jr. Oas1b-dependent Immune Transcriptional Profiles of West Nile Virus Infection in the Collaborative Cross. *G3 (Bethesda)* 2017; **7**: 1665-1682 [PMID: 28592649 DOI: 10.1534/g3.117.041624]

81 **Barreiro LB**, Ben-Ali M, Quach H, Laval G, Patin E, Pickrell JK, Bouchier C, Tichit M, Neyrolles O, Gicquel B, Kidd JR, Kidd KK, Alcaïs A, Ragimbeau J, Pellegrini S, Abel L, Casanova JL, Quintana-Murci L. Evolutionary dynamics of human Toll-like receptors and their different contributions to host defense. *PLoS Genet* 2009; **5**: e1000562 [PMID: 19609346 DOI: 10.1371/journal.pgen.1000562]

82 **Ness RB**, Haggerty CL, Harger G, Ferrell R. Differential distribution of allelic variants in cytokine genes among African Americans and White Americans. *Am J Epidemiol* 2004; **160**: 1033-1038 [PMID: 15561982 DOI: 10.1093/aje/kwh325]

83 **Bidwell J**, Keen L, Gallagher G, Kimberly R, Huizinga T, McDermott MF, Oksenberg J, McNicholl J, Pociot F, Hardt C, D'Alfonso S. Cytokine gene polymorphism in human disease: on-line databases. *Genes Immun* 1999; **1**: 3-19 [PMID: 11197303 DOI: 10.1038/sj.gene.6363645]

84 **Chen H**, Wilkins LM, Aziz N, Cannings C, Wyllie DH, Bingle C, Rogus J, Beck JD, Offenbacher S, Cork MJ, Rafie-Kolpin M, Hsieh CM, Kornman KS, Duff GW. Single nucleotide polymorphisms in the human interleukin-1B gene affect transcription according to haplotype context. *Hum Mol Genet* 2006; **15**: 519-529 [PMID: 16399797 DOI: 10.1093/hmg/ddi469]

85 **Hung RJ**, Ulrich CM, Goode EL, Brhane Y, Muir K, Chan AT, Marchand LL, Schildkraut J, Witte JS, Eeles R, Boffetta P, Spitz MR, Poirier JG, Rider DN, Fridley BL, Chen Z, Haiman C, Schumacher F, Easton DF, Landi MT, Brennan P, Houlston R, Christiani DC, Field JK, Bickeböller H, Risch A, Kote-Jarai Z, Wiklund F, Grönberg H, Chanock S, Berndt SI, Kraft P, Lindström S, Al Olama AA, Song H, Phelan C, Wentzensen N, Peters U, Slattery ML; GECCO, Sellers TA; FOCI, Casey G, Gruber SB; CORECT, Hunter DJ; DRIVE, Amos CI, Henderson B; GAME-ON Network. Cross Cancer Genomic Investigation of Inflammation Pathway for Five Common Cancers: Lung, Ovary, Prostate, Breast, and Colorectal Cancer. *J Natl Cancer Inst* 2015; **107** [PMID: 26319099 DOI: 10.1093/jnci/djv246]

86 **Theodoropoulos G**, Papaconstantinou I, Felekouras E, Nikiteas N, Karakitsos P, Panoussopoulos D, Lazaris ACh, Patsouris E, Bramis J, Gazouli M. Relation between common polymorphisms in genes related to inflammatory response and colorectal cancer. *World J Gastroenterol* 2006; **12**: 5037-5043 [PMID: 16937502 DOI: 10.3748/wjg.v12.i31.5037]

87 **Landi S**, Moreno V, Gioia-Patricola L, Guino E, Navarro M, de Oca J, Capella G, Canzian F; Bellvitge Colorectal Cancer Study Group. Association of common polymorphisms in inflammatory genes interleukin (IL)6, IL8, tumor necrosis factor alpha, NFKB1, and peroxisome proliferator-activated receptor gamma with colorectal cancer. *Cancer Res* 2003; **63**: 3560-3566 [PMID: 12839942]

88 **Koh WP**, Yuan JM, Van Den Berg D, Ingles SA, Yu MC. Peroxisome proliferator-activated receptor (PPAR) gamma gene polymorphisms and colorectal cancer risk among Chinese in Singapore. *Carcinogenesis* 2006; **27**: 1797-1802 [PMID: 16513680 DOI: 10.1093/carcin/bgl001]

89 **Montazeri Z**, Li X, Nyiraneza C, Ma X, Timofeeva M, Svinti V, Meng X, He Y, Bo Y, Morgan S, Castellví-Bel S, Ruiz-Ponte C, Fernández-Rozadilla C, Carracedo Á, Castells A, Bishop T, Buchanan D, Jenkins MA, Keku TO, Lindblom A, van Duijnhoven FJB, Wu A, Farrington SM, Dunlop MG, Campbell H, Theodoratou E, Zheng W, Little J. Systematic meta-analyses, field synopsis and global assessment of the evidence of genetic association studies in colorectal cancer. *Gut* 2020; **69**: 1460-1471 [PMID: 31818908 DOI: 10.1136/gutjnl-2019-319313]

90 **Abbas M**, Mason T, Ibad A, Khraiwesh M, Apprey V, Kanaan Y, Wilson B, Dunston G, Ricks-Santi L, Brim H. Genetic Polymorphisms in IL-10 Promoter Are Associated With Smoking and Prostate Cancer Risk in African Americans. *Anticancer Res* 2020; **40**: 27-34 [PMID: 31892550 DOI: 10.21873/anticanres.13923]

91 **Jenkins BD**, Martini RN, Hire R, Brown A, Bennett B, Brown I, Howerth EW, Egan M, Hodgson J, Yates C, Kittles R, Chitale D, Ali H, Nathanson D, Nikolinakos P, Newman L, Monteil M, Davis MB. Atypical Chemokine Receptor 1 (*DARC/ACKR1*) in Breast Tumors Is Associated with Survival, Circulating Chemokines, Tumor-Infiltrating Immune Cells, and African Ancestry. *Cancer Epidemiol Biomarkers Prev* 2019; **28**: 690-700 [PMID: 30944146 DOI: 10.1158/1055-9965.EPI-18-0955]

92 **Cho I**, Blaser MJ. The human microbiome: at the interface of health and disease. *Nat Rev Genet* 2012; **13**: 260-270 [PMID: 22411464 DOI: 10.1038/nrg3182]

93 **Gopalakrishnan V**, Helmink BA, Spencer CN, Reuben A, Wargo JA. The Influence of the Gut Microbiome on Cancer, Immunity, and Cancer Immunotherapy. *Cancer Cell* 2018; **33**: 570-580 [PMID: 29634945 DOI: 10.1016/j.ccell.2018.03.015]

94 **Xu F**, Fu Y, Sun TY, Jiang Z, Miao Z, Shuai M, Gou W, Ling CW, Yang J, Wang J, Chen YM, Zheng JS. The interplay between host genetics and the gut microbiome reveals common and distinct microbiome features for complex human diseases. *Microbiome* 2020; **8**: 145 [PMID: 33032658 DOI: 10.1186/s40168-020-00923-9]

95 **Burns MB**, Montassier E, Abrahante J, Priya S, Niccum DE, Khoruts A, Starr TK, Knights D, Blekhman R. Colorectal cancer mutational profiles correlate with defined microbial communities in the tumor microenvironment. *PLoS Genet* 2018; **14**: e1007376 [PMID: 29924794 DOI: 10.1371/journal.pgen.1007376]

96 **Thyagarajan S**, Zhang Y, Thapa S, Allen MS, Phillips N, Chaudhary P, Kashyap MV, Vishwanatha JK. Comparative analysis of racial differences in breast tumor microbiome. *Sci Rep* 2020; **10**: 14116 [PMID: 32839514 DOI: 10.1038/s41598-020-71102-x]

97 **Yu J**, Feng Q, Wong SH, Zhang D, Liang QY, Qin Y, Tang L, Zhao H, Stenvang J, Li Y, Wang X, Xu X, Chen N, Wu WK, Al-Aama J, Nielsen HJ, Kiilerich P, Jensen BA, Yau TO, Lan Z, Jia H, Li J, Xiao L, Lam TY, Ng SC, Cheng AS, Wong VW, Chan FK, Yang H, Madsen L, Datz C, Tilg H, Wang J, Brünner N, Kristiansen K, Arumugam M, Sung JJ. Metagenomic analysis of faecal microbiome as a tool towards targeted non-invasive biomarkers for colorectal cancer. *Gut* 2017; **66**: 70-78 [PMID: 26408641 DOI: 10.1136/gutjnl-2015-309800]

98 **Zeller G**, Tap J, Voigt AY, Sunagawa S, Kultima JR, Costea PI, Amiot A, Böhm J, Brunetti F, Habermann N, Hercog R, Koch M, Luciani A, Mende DR, Schneider MA, Schrotz-King P, Tournigand C, Tran Van Nhieu J, Yamada T, Zimmermann J, Benes V, Kloor M, Ulrich CM, von Knebel Doeberitz M, Sobhani I, Bork P. Potential of fecal microbiota for early-stage detection of colorectal cancer. *Mol Syst Biol* 2014; **10**: 766 [PMID: 25432777 DOI: 10.15252/msb.20145645]

99 **Baxter NT**, Ruffin MT 4th, Rogers MA, Schloss PD. Microbiota-based model improves the sensitivity of fecal immunochemical test for detecting colonic lesions. *Genome Med* 2016; **8**: 37 [PMID: 27056827 DOI: 10.1186/s13073-016-0290-3]

100 **Zackular JP**, Rogers MA, Ruffin MT 4th, Schloss PD. The human gut microbiome as a screening tool for colorectal cancer. *Cancer Prev Res (Phila)* 2014; **7**: 1112-1121 [PMID: 25104642 DOI: 10.1158/1940-6207.CAPR-14-0129]

101 **Thomas AM**, Manghi P, Asnicar F, Pasolli E, Armanini F, Zolfo M, Beghini F, Manara S, Karcher N, Pozzi C, Gandini S, Serrano D, Tarallo S, Francavilla A, Gallo G, Trompetto M, Ferrero G, Mizutani S, Shiroma H, Shiba S, Shibata T, Yachida S, Yamada T, Wirbel J, Schrotz-King P, Ulrich CM, Brenner H, Arumugam M, Bork P, Zeller G, Cordero F,

Dias-Neto E, Setubal JC, Tett A, Pardini B, Rescigno M, Waldron L, Naccarati A, Segata N. Metagenomic analysis of colorectal cancer datasets identifies cross-cohort microbial diagnostic signatures and a link with choline degradation. *Nat Med* 2019; **25**: 667-678 [PMID: 30936548 DOI: 10.1038/s41591-019-0405-7]

102 **Wirbel J**, Pyl PT, Kartal E, Zych K, Kashani A, Milanese A, Fleck JS, Voigt AY, Palleja A, Ponnudurai R, Sunagawa S, Coelho LP, Schrotz-King P, Vogtmann E, Habermann N, Niméus E, Thomas AM, Manghi P, Gandini S, Serrano D, Mizutani S, Shiroma H, Shiba S, Shibata T, Yachida S, Yamada T, Waldron L, Naccarati A, Segata N, Sinha R, Ulrich CM, Brenner H, Arumugam M, Bork P, Zeller G. Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer. *Nat Med* 2019; **25**: 679-689 [PMID: 30936547 DOI: 10.1038/s41591-019-0406-6]

103 **Dai Z**, Coker OO, Nakatsu G, Wu WKK, Zhao L, Chen Z, Chan FKL, Kristiansen K, Sung JJY, Wong SH, Yu J. Multi-cohort analysis of colorectal cancer metagenome identified altered bacteria across populations and universal bacterial markers. *Microbiome* 2018; **6**: 70 [PMID: 29642940 DOI: 10.1186/s40168-018-0451-2]

104 **Wu S**, Rhee KJ, Albesiano E, Rabizadeh S, Wu X, Yen HR, Huso DL, Brancati FL, Wick E, McAllister F, Housseau F, Pardoll DM, Sears CL. A human colonic commensal promotes colon tumorigenesis *via* activation of T helper type 17 T cell responses. *Nat Med* 2009; **15**: 1016-1022 [PMID: 19701202 DOI: 10.1038/nm.2015]

105 **Arthur JC**, Perez-Chanona E, Mühlbauer M, Tomkovich S, Uronis JM, Fan TJ, Campbell BJ, Abujamel T, Dogan B, Rogers AB, Rhodes JM, Stintzi A, Simpson KW, Hansen JJ, Keku TO, Fodor AA, Jobin C. Intestinal inflammation targets cancer-inducing activity of the microbiota. *Science* 2012; **338**: 120-123 [PMID: 22903521 DOI: 10.1126/science.1224820]

106 **Kostic AD**, Chun E, Robertson L, Glickman JN, Gallini CA, Michaud M, Clancy TE, Chung DC, Lochhead P, Hold GL, El-Omar EM, Brenner D, Fuchs CS, Meyerson M, Garrett WS. Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. *Cell Host Microbe* 2013; **14**: 207-215 [PMID: 23954159 DOI: 10.1016/j.chom.2013.07.007]

107 **Tomkovich S**, Dejea CM, Winglee K, Drewes JL, Chung L, Housseau F, Pope JL, Gauthier J, Sun X, Mühlbauer M, Liu X, Fathi P, Anders RA, Besharati S, Perez-Chanona E, Yang Y, Ding H, Wu X, Wu S, White JR, Gharaibeh RZ, Fodor AA, Wang H, Pardoll DM, Jobin C, Sears CL. Human colon mucosal biofilms from healthy or colon cancer hosts are carcinogenic. *J Clin Invest* 2019; **129**: 1699-1712 [PMID: 30855275 DOI: 10.1172/JCI124196]

108 **Knippel RJ**, Drewes JL, Sears CL. The Cancer Microbiome: Recent Highlights and Knowledge Gaps. *Cancer Discov* 2021; **11**: 2378-2395 [PMID: 34400408 DOI: 10.1158/2159-8290.CD-21-0324]

109 **Brooks AW**, Priya S, Blekhman R, Bordenstein SR. Gut microbiota diversity across ethnicities in the United States. *PLoS Biol* 2018; **16**: e2006842 [PMID: 30513082 DOI: 10.1371/journal.pbio.2006842]

110 **Deschasaux M**, Bouter KE, Prodan A, Levin E, Groen AK, Herrema H, Tremaroli V, Bakker GJ, Attaye I, Pinto-Sietsma SJ, van Raalte DH, Snijder MB, Nicolaou M, Peters R, Zwinderman AH, Bäckhed F, Nieuwdorp M. Depicting the composition of gut microbiota in a population with varied ethnic origins but shared geography. *Nat Med* 2018; **24**: 1526-1531 [PMID: 30150717 DOI: 10.1038/s41591-018-0160-1]

111 **Gupta VK**, Paul S, Dutta C. Geography, Ethnicity or Subsistence-Specific Variations in Human Microbiome Composition and Diversity. *Front Microbiol* 2017; **8**: 1162 [PMID: 28690602 DOI: 10.3389/fmicb.2017.01162]

112 **Hester CM**, Jala VR, Langille MG, Umar S, Greiner KA, Haribabu B. Fecal microbes, short chain fatty acids, and colorectal cancer across racial/ethnic groups. *World J Gastroenterol* 2015; **21**: 2759-2769 [PMID: 25759547 DOI: 10.3748/wjg.v21.i9.2759]

113 **Ou J**, Carbonero F, Zoetendal EG, DeLany JP, Wang M, Newton K, Gaskins HR, O'Keefe SJ. Diet, microbiota, and microbial metabolites in colon cancer risk in rural Africans and African Americans. *Am J Clin Nutr* 2013; **98**: 111-120 [PMID: 23719549 DOI: 10.3945/ajcn.112.056689]

114 **Jung SY**, Papp JC, Sobel EM, Pellegrini M, Yu H, Zhang ZF. Pro-inflammatory cytokine polymorphisms in ONECUT2 and HNF4A and primary colorectal carcinoma: a post genome-wide gene-lifestyle interaction study. *Am J Cancer Res* 2020; **10**: 2955-2976 [PMID: 33042629]

115 **Chiuve SE**, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, Stampfer MJ, Willett WC. Alternative dietary indices both strongly predict risk of chronic disease. *J Nutr* 2012; **142**: 1009-1018 [PMID: 22513989 DOI: 10.3945/jn.111.157222]

116 **Wang DD**, Leung CW, Li Y, Ding EL, Chiuve SE, Hu FB, Willett WC. Trends in dietary quality among adults in the United States, 1999 through 2010. *JAMA Intern Med* 2014; **174**: 1587-1595 [PMID: 25179639 DOI: 10.1001/jamainternmed.2014.3422]

117 **Lu SSM**, Mohammed Z, Häggström C, Myte R, Lindquist E, Gylfe Å, Van Guelpen B, Harlid S. Antibiotics Use and Subsequent Risk of Colorectal Cancer: A Swedish Nationwide Population-Based Study. *J Natl Cancer Inst* 2022; **114**: 38-46 [PMID: 34467395 DOI: 10.1093/jnci/djab125]

118 **Tsong WH**, Koh WP, Yuan JM, Wang R, Sun CL, Yu MC. Cigarettes and alcohol in relation to colorectal cancer: the Singapore Chinese Health Study. *Br J Cancer* 2007; **96**: 821-827 [PMID: 17311023 DOI: 10.1038/sj.bjc.6603623]

119 **Ali Khan U**, Fallah M, Sundquist K, Sundquist J, Brenner H, Kharazmi E. Risk of colorectal cancer in patients with diabetes mellitus: A Swedish nationwide cohort study. *PLoS Med* 2020; **17**: e1003431 [PMID: 33186354 DOI: 10.1371/journal.pmed.1003431]

120 **Rebersek M**. Gut microbiome and its role in colorectal cancer. *BMC Cancer* 2021; **21**: 1325 [PMID: 34895176 DOI: 10.1186/s12885-021-09054-2]

121 **Scepanovic P**, Hodel F, Mondot S, Partula V, Byrd A, Hammer C, Alanio C, Bergstedt J, Patin E, Touvier M, Lantz O, Albert ML, Duffy D, Quintana-Murci L, Fellay J; Milieu Intérieur Consortium. A comprehensive assessment of demographic, environmental, and host genetic associations with gut microbiome diversity in healthy individuals. *Microbiome* 2019; **7**: 130 [PMID: 31519223 DOI: 10.1186/s40168-019-0747-x]

122 **Blekhman R**, Goodrich JK, Huang K, Sun Q, Bukowski R, Bell JT, Spector TD, Keinan A, Ley RE, Gevers D, Clark AG. Host genetic variation impacts microbiome composition across human body sites. *Genome Biol* 2015; **16**: 191 [PMID: 26374288 DOI: 10.1186/s13059-015-0759-1]

123 **Goodrich JK**, Davenport ER, Beaumont M, Jackson MA, Knight R, Ober C, Spector TD, Bell JT, Clark AG, Ley RE.

Genetic Determinants of the Gut Microbiome in UK Twins. *Cell Host Microbe* 2016; **19**: 731-743 [PMID: 27173935 DOI: 10.1016/j.chom.2016.04.017]

124 **Goodrich JK**, Waters JL, Poole AC, Sutter JL, Koren O, Blekhman R, Beaumont M, Van Treuren W, Knight R, Bell JT, Spector TD, Clark AG, Ley RE. Human genetics shape the gut microbiome. *Cell* 2014; **159**: 789-799 [PMID: 25417156 DOI: 10.1016/j.cell.2014.09.053]

125 **Ashktorab H**, Azimi H, Varma S, Lee EL, Laiyemo AO, Nickerson ML, Brim H. Driver genes exome sequencing reveals distinct variants in African Americans with colorectal neoplasia. *Oncotarget* 2019; **10**: 2607-2624 [PMID: 31080553 DOI: 10.18632/oncotarget.26721]

126 **Brim H**, Yooseph S, Lee E, Sherif ZA, Abbas M, Laiyemo AO, Varma S, Torralba M, Dowd SE, Nelson KE, Pathmasiri W, Sumner S, de Vos W, Liang Q, Yu J, Zoetendal E, Ashktorab H. A Microbiomic Analysis in African Americans with Colonic Lesions Reveals Streptococcus sp.VT162 as a Marker of Neoplastic Transformation. *Genes (Basel)* 2017; **8** [PMID: 29120399 DOI: 10.3390/genes8110314]

127 **Ogino S**, Nowak JA, Hamada T, Milner DA Jr, Nishihara R. Insights into Pathogenic Interactions Among Environment, Host, and Tumor at the Crossroads of Molecular Pathology and Epidemiology. *Annu Rev Pathol* 2019; **14**: 83-103 [PMID: 30125150 DOI: 10.1146/annurev-pathmechdis-012418-012818]

128 **Nishi A**, Milner DA Jr, Giovannucci EL, Nishihara R, Tan AS, Kawachi I, Ogino S. Integration of molecular pathology, epidemiology and social science for global precision medicine. *Expert Rev Mol Diagn* 2016; **16**: 11-23 [PMID: 26636627 DOI: 10.1586/14737159.2016.1115346]

129 **Turpin W**, Espin-Garcia O, Xu W, Silverberg MS, Kevans D, Smith MI, Guttman DS, Griffiths A, Panaccione R, Otley A, Xu L, Shestopaloff K, Moreno-Hagelsieb G; GEM Project Research Consortium, Paterson AD, Croitoru K. Association of host genome with intestinal microbial composition in a large healthy cohort. *Nat Genet* 2016; **48**: 1413-1417 [PMID: 27694960 DOI: 10.1038/ng.3693]

130 **DeStefano Shields CE**, White JR, Chung L, Wenzel A, Hicks JL, Tam AJ, Chan JL, Dejea CM, Fan H, Michel J, Maiuri AR, Sriramkumar S, Podicheti R, Rusch DB, Wang H, De Marzo AM, Besharati S, Anders RA, Baylin SB, O'Hagan HM, Housseau F, Sears CL. Bacterial-Driven Inflammation and Mutant *BRAF* Expression Combine to Promote Murine Colon Tumorigenesis That Is Sensitive to Immune Checkpoint Therapy. *Cancer Discov* 2021; **11**: 1792-1807 [PMID: 33632774 DOI: 10.1158/2159-8290.CD-20-0770]

131 **Davis MB**. Genomics and Cancer Disparities: The Justice and Power of Inclusion. *Cancer Discov* 2021; **11**: 805-809 [PMID: 33811116 DOI: 10.1158/2159-8290.CD-21-0225]

132 **Sherman RM**, Forman J, Antonescu V, Puiu D, Daya M, Rafaels N, Boorgula MP, Chavan S, Vergara C, Ortega VE, Levin AM, Eng C, Yazdanbakhsh M, Wilson JG, Marrugo J, Lange LA, Williams LK, Watson H, Ware LB, Olopade CO, Olopade O, Oliveira RR, Ober C, Nicolae DL, Meyers DA, Mayorga A, Knight-Madden J, Hartert T, Hansel NN, Foreman MG, Ford JG, Faruque MU, Dunston GM, Caraballo L, Burchard EG, Bleecker ER, Araujo MI, Herrera-Paz EF, Campbell M, Foster C, Taub MA, Beaty TH, Ruczinski I, Mathias RA, Barnes KC, Salzberg SL. Assembly of a pan-genome from deep sequencing of 910 humans of African descent. *Nat Genet* 2019; **51**: 30-35 [PMID: 30455414 DOI: 10.1038/s41588-018-0273-y]

133 **Peterson RE**, Edwards AC, Bacanu SA, Dick DM, Kendler KS, Webb BT. The utility of empirically assigning ancestry groups in cross-population genetic studies of addiction. *Am J Addict* 2017; **26**: 494-501 [PMID: 28714599 DOI: 10.1111/ajad.12586]

134 **Adedokun B**, Du Z, Gao G, Ahearn TU, Lunetta KL, Zirpoli G, Figueroa J, John EM, Bernstein L, Zheng W, Hu JJ, Ziegler RG, Nyante S, Bandera EV, Ingles SA, Press MF, Deming-Halverson SL, Rodriguez-Gil JL, Yao S, Ogundiran TO, Ojengbede O, Blot W, Troester MA, Nathanson KL, Hennis A, Nemesure B, Ambs S, Fiorica PN, Sucheston-Campbell LE, Bensen JT, Kushi LH, Torres-Mejia G, Hu D, Fejerman L, Bolla MK, Dennis J, Dunning AM, Easton DF, Michailidou K, Pharoah PDP, Wang Q, Sandler DP, Taylor JA, O'Brien KM, Kitahara CM, Falusi AG, Babalola C, Yarney J, Awuah B, Addai-Wiafe B; GBHS Study Team, Chanock SJ, Olshan AF, Ambrosone CB, Conti DV, Ziv E, Olopade OI, Garcia-Closas M, Palmer JR, Haiman CA, Huo D. Cross-ancestry GWAS meta-analysis identifies six breast cancer loci in African and European ancestry women. *Nat Commun* 2021; **12**: 4198 [PMID: 34234117 DOI: 10.1038/s41467-021-24327-x]

135 **Schumacher FR**, Schmit SL, Jiao S, Edlund CK, Wang H, Zhang B, Hsu L, Huang SC, Fischer CP, Harju JF, Idos GE, Lejbkowicz F, Manion FJ, McDonnell K, McNeil CE, Melas M, Rennert HS, Shi W, Thomas DC, Van Den Berg DJ, Hutter CM, Aragaki AK, Butterbach K, Caan BJ, Carlson CS, Chanock SJ, Curtis KR, Fuchs CS, Gala M, Giovannucci EL, Gogarten SM, Hayes RB, Henderson B, Hunter DJ, Jackson RD, Kolonel LN, Kooperberg C, Küry S, LaCroix A, Laurie CC, Laurie CA, Lemire M, Levine D, Ma J, Makar KW, Qu C, Taverna D, Ulrich CM, Wu K, Kono S, West DW, Berndt SI, Bezieau S, Brenner H, Campbell PT, Chan AT, Chang-Claude J, Coetzee GA, Conti DV, Duggan D, Figueiredo JC, Fortini BK, Gallinger SJ, Gauderman WJ, Giles G, Green R, Haile R, Harrison TA, Hoffmeister M, Hopper JL, Hudson TJ, Jacobs E, Iwasaki M, Jee SH, Jenkins M, Jia WH, Joshi A, Li L, Lindor NM, Matsuo K, Moreno V, Mukherjee B, Newcomb PA, Potter JD, Raskin L, Rennert G, Rosse S, Severi G, Schoen RE, Seminara D, Shu XO, Slattery ML, Tsugane S, White E, Xiang YB, Zanke BW, Zheng W, Le Marchand L, Casey G, Gruber SB, Peters U. Genome-wide association study of colorectal cancer identifies six new susceptibility loci. *Nat Commun* 2015; **6**: 7138 [PMID: 26151821 DOI: 10.1038/ncomms8138]

136 **Tsilidis KK**, Helzlsouer KJ, Smith MW, Grinberg V, Hoffman-Bolton J, Clipp SL, Visvanathan K, Platz EA. Association of common polymorphisms in IL10, and in other genes related to inflammatory response and obesity with colorectal cancer. *Cancer Causes Control* 2009; **20**: 1739-1751 [PMID: 19760027 DOI: 10.1007/s10552-009-9427-7]

137 **Li D**, Achkar JP, Haritunians T, Jacobs JP, Hui KY, D'Amato M, Brand S, Radford-Smith G, Halfvarson J, Niess JH, Kugathasan S, Büning C, Schumm LP, Klei L, Ananthakrishnan A, Aumais G, Baidoo L, Dubinsky M, Fiocchi C, Glas J, Milgrom R, Proctor DD, Regueiro M, Simms LA, Stempak JM, Targan SR, Törkvist L, Sharma Y, Devlin B, Borneman J, Hakonarson H, Xavier RJ, Daly M, Brant SR, Rioux JD, Silverberg MS, Cho JH, Braun J, McGovern DP, Duerr RH. A Pleiotropic Missense Variant in SLC39A8 Is Associated With Crohn's Disease and Human Gut Microbiome Composition. *Gastroenterology* 2016; **151**: 724-732 [PMID: 27492617 DOI: 10.1053/j.gastro.2016.06.051]

138 **Rühlemann MC**, Hermes BM, Bang C, Doms S, Moitinho-Silva L, Thingholm LB, Frost F, Degenhardt F, Wittig M, Kässens J, Weiss FU, Peters A, Neuhaus K, Völker U, Völzke H, Homuth G, Weiss S, Grallert H, Laudes M, Lieb W, Haller D, Lerch MM, Baines JF, Franke A. Genome-wide association study in 8,956 German individuals identifies influence of ABO histo-blood groups on gut microbiome. *Nat Genet* 2021; **53**: 147-155 [PMID: 33462482 DOI: 10.1038/s41588-020-00747-1]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2022 Baishideng Publishing Group Inc. All rights reserved.