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The interplay of pineal hormones and socioeconomic status leading to colorectal cancer disparity

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ABSTRACT

Colorectal cancer (CRC) is the third leading cause of cancer-related deaths in the United States. Despite increased screening options and state-of-art treatments offered in clinics, racial differences remain in CRC. African Americans (AAs) are disproportionately affected by the disease; the incidence and mortality are higher in AAs than Caucasian Americans (CAs). At the time of diagnosis, AAs more often present with advanced stages and aggressive CRCs, primarily accounting for the racial differences in therapeutic outcomes and mortality. The early incidence of CRC in AAs could be attributed to race-specific gene polymorphisms and lifestyle choices associated with socioeconomic status (SES). Altered melatonin-serotonin signaling, besides the established CRC risk factors (age, diet, obesity, alcoholism, and tobacco use), steered by SES, glucocorticoid, and Vitamin D status in AAs could also account for the early incidence in this racial group. This review focuses on how the lifestyle factors, diet, allelic variants, and altered expression of specific genes could lead to atypical serotonin and melatonin signaling by modulating the synthesis, secretion, and signaling of these pineal hormones in AAs and predisposing them to develop more aggressive CRC earlier than CAs. Crosstalk between gut microbiota and pineal hormones and its impact on CRC pathobiology is addressed from a race-specific perspective. Lastly, the status of melatonin-focused CRC treatments, the need to better understand the perturbed melatonin signaling, and the potential of pineal hormone-directed therapeutic interventions to reduce CRC-associated disparity are discussed.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the United States, regardless of gender [87]. The American Cancer Society estimates that, in 2021, there will be about 149,500 new colorectal cancer cases and 52,980 deaths in the United States. The lifetime risk of developing CRC is 1 in 23 (4.3%) for men and 1 in 25 (4.0%) for women. Theoverall death rate from CRC continues to drop due to early diagnosis and state-of-art interventions enabled by continued research studying the disease pathogenesis.We have shown the significance of optimum acetaldehyde dehydrogenase expression in maintaining gut epithelial integrity [15] and association of CCR6-CCL20 chemokine axis in CRC pathogenesis [44]. However, the incidence and mortality rates for African Americans (AAs) have not decreased to the same extent relative to non-Hispanic Caucasian Americans (CAs) [2,4,41,87]. The racial discrepancy in mortality rates reflects differential CRC incidence and patient survival. The five-year relative survival is lower for AAs than CAs irrespective of disease stage (i.e., localized, regional metastasis, distant metastasis, and all stages combined) [31,87]. Racial differences in relative survival may be related to barriers to CRC screening; however, the gap persists even after normalizing the socioeconomic status (SES) and differences in access to treatment [19,64,68]. Notably, the effect that low SES-induced chronic stress has on the pathobiology of CRC and the racial disparity is not explored adequately. Hence, the purpose of this review is to evaluate the association of the earlier onset, higher incidence, and poor outcomes of CRC

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in AA patients with SES driven chronic stress and chronic stress-induced changes in biochemical signaling, specifically that of pineal hormones.

Association of modifiable and non-modifiable risk factors with CRC disparity

Modifiable risk factors, such as environmental factors, obesity, physical activity, nutrition/diet, smoking, and alcohol consumption, are well defined [39,86,94] and manageable [42]. A consistent body of evidence indicates that geographical location, overweight, and obesity are positively associated with the lifetime risk of developing CRC [51, 94]. In the United States, AAs have higher obesity prevalence rates than other racial groups. Dietary habits independently influence the risk of CRC, in addition to contributing to obesity [92]. Avoiding high fat and red meat consumption reduces CRC risk [43,50]. Animal fat increases the conversion of bile salts to potential carcinogens by the gut microbiome [50]. Studies published by our group suggest that natural products like emodin and cinnamtannin B1 reduce CRC progression [13,84] while glutamine supplementation improves epithelial integrity of the gut [16]. Besides the dietary ingredients, high-temperature food preparation methods also increase CRC risk by generating carcinogenic heterocyclic amines and polycyclic aromatic hydrocarbons [82,88]. Further, physical activity reduces CRC risk by increasing metabolic activity, oxygen uptake, and gut motility while reducing body weight [7, 18,94]. Long-term exercise reduces CRC risk also by reducing insulin resistance [52]. In this regard, AAs who often belong to low socioeconomic status (SES), a multidimensional concept measured at the individual level (education, income, and occupation); the household level (poverty, family income, and wealth); and neighborhood level (i.e., community structural characteristics, neighborhood, and crime), [48, 93] are forced to make poor lifestyle and food choices (i.e., processed food and high fat intake), which results in high BMI, increasing their risk of CRC. In addition, individuals with low SES exhibit abnormally high p53 [90], which contributes to an immunosuppressive environment conducive to cancer immune evasion and tumor tolerance- two critical factors in the development and progression of CRC and amplifying racial disparity.

Non-modifiable factors such as genetic background, history of inflammatory bowel disease (IBD) and adenomatous polyps, and age are associated with a higher risk of CRC. Family history increases CRC risk by 20%, while ~5–10% of CRCs are hereditary [38]. Interestingly, AAs and CAs do not show any differences in the CRC risk factor, IBD [1,63]. Adenomatous polyps, the pre-cancerous lesions contributing to about 95% of sporadic CRCs [39], take 5–10 years to develop tumors[18,27]. Hence, early removal of adenomatous polyps reduces the risk of developing CRC. However, this intervention is not readily available for AAs with low SES due to lack of awareness and poor access to care.

Moreover, although aging increases the risk of CRC irrespective of ethnicity [87], CRC presents at an earlier age in AAs compared to CAs. Considering these factors, AAs are generally at a higher risk of developing CRC at an earlier age than their CA counterparts. Moreover, AAs with a history of other malignancies are more prone to develop CRC. Hence, for this ethnic population, lack of timely screening, poor access to care, and poor food choice due to low SES contribute to the observed disparity in incidence, prognosis, and mortality. It is, therefore, imperative to identify race-specific risk factors and biomarkers to improve the therapeutic outcome in AAs.

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and melatonin in African Americans and their effects on CRC risk

Poor SES is associated with increased stress that is evident from variations in diurnal rhythms of cortisol [17]. AAs have a more blunted diurnal cortisol slope than CAs as assayed using salivary samples [30], whereas hair cortisol levels are higher in AAs than CAs [96]. Besides, irregular sleep schedule, which is often found in AAs, is associated with significantly higher levels of salivary cortisol in AAs compared to CAs, in addition to smoking [99]. These deviations reflect dysregulation of the HPA axis [47,83] in AAs. Regulation of the HPA axis and the pineal gland is closely related [91] and interestingly, glucocorticoids and melatonin have contrasting effects. Glucocorticoids negatively regulate melatonin synthesis by the pineal gland [73], and extra-pineal melatonin produced after food intake affects cortisol rhythms [10]. This is noteworthy because many of the CRC risk factors could be related to melatonin's atypical or anomalous status [10,11]. Like CRC risk, melatonin production varies by race, gender, and age [45,74,81]. This hormone acts as a free radical scavenger, regulates food digestion, gut motility, and bowel movement through specific receptor signaling [10]. In addition to this, melatonin affects obesity risk by controlling food intake [11] and regulating mucosal immunity [62]; both factors associate with CRC and are frequently compromised in AAs [46].

Remarkably, several investigators have reported differences in melatonin levels in people of different ancestries. One report asserts that the highest melatonin levels are found in AAs, and within the racial groups, levels are highest among young AAs (ages 30–50) and older CAs (ages 60–90) [45]. Another study found that AAs have lower melatonin levels relative to CAs [40]. The difference could be attributed to the fact that melatonin levels are affected by the circadian clock [37] and the time of sample collection was different in both studies. Nevertheless, a variance of melatonin levels by race is apparent and may lead to a disturbed sleep-wake cycle for AAs, predisposing them to develop CRC. This possibility is supported by studies demonstrating a higher risk for rectal cancer in night shift workers due to changed melatonin rhythms [77] and the fact that a higher percentage of AAs are night shift workers. Nonetheless, these findings warrant studies of melatonin profiles to test its potential as a race-specific biomarker to better predict CRC risk in AAs.

Impaired serotonin signaling in African Americans and CRC risk

Melatonin disturbances in the body reflect a more complex molecular issue since the metabolism and signaling of melatonin are tightly coordinated with serotonin (5-hydroxytryptamine, 5HT) signaling [11]. Both melatonin and serotonin are brain-derived and locally generated in the gut. Enterochromaffin cells lining the gut are the primary producers of serotonin. Tryptophan hydroxylase, coded by *TPH1,* catalyzes serotonin synthesis from dietary tryptophan. A small amount of serotonin is also produced by the *TPH2*-coded enzyme of enteric neurons. Serotonin regulates gut motility, secretion, and sensation via serotonin receptors (5-HTRs). Of the 5-HTR family, five components (5-HTR1–4 and 5-HTR7) are expressed in the gut. The receptor-mediated signaling is controlled mainly by the serotonin transporter (SERT) facilitated serotonin reuptake and its consequent degradation by monoamine oxidase A [67].

Intriguingly, there is a high frequency of race-specific polymorphism in genes involved in serotonin synthesis, reuptake, and signaling. Specifically, there are polymorphisms in genes (Table 1) coding for tryptophan hydroxylases (*TPH1* and *2*) and those coding for enzymes converting serotonin to melatonin, namely acetyltransferases (*NAT1* and *2*), coding for N-acetyltransferases 1 and 2, and *ASMT*, coding for acetyl serotonin O-methyltransferase. Notably, a variance in *NAT2* is associated with prostate cancer susceptibility for AAs [35]. However, the only evidence for its clinical significance in CRC comes from the human protein atlas database, which indicates NAT2 as a favorable marker for CRC. A higher percentage of African descendants exhibit SLC6A4 (L)-allele (serotonin transporter coding gene) relative to those of European ancestry [24,75]. The L-allele is associated with elevated transcription of the serotonin transporter, meaning that reduced extracellular serotonin levels will be available for signaling to surrounding cells in these individuals [55]. AAs also carry mutations in serotonin receptor 1F (HTR1F) [12,29]. At present, not much is known about this G-protein-coupled receptor, other than its association with migraines

Table 1
Polymorphisms associated with serotonin and melatonin signaling and their predicted effects.

Gene	Product	Polymorphism	Effect
SLC6A4	Serotonin transporter	L (long) and S (short) allele	L allele is associated with elevated transcription of the gene and reduced serotonin signaling.
HTR1F	Serotonin receptor		Associated with migraines.
NAT2	N-acetyl transferase 2		Associated with prostate cancer susceptibility of AAs.
TPH1	Tryptophan hydroxylase (Gut)	A218C	A allele is associated with borderline personality disorder due to serotonergic dysfunction [51].
TPH2	Tryptophan hydroxylase (Enteric neurons)	rs4290270; rs4570625; rs41317118; rs11178998; rs7305115; rs17110747; rs10748185; rs18438099; rs11316791; rs1386493; rs1386494	rs4290270 (A/T allele) could be associated with major depressive disorder [52].

[36]. In-depth studies will help determine if polymorphism(s) in these genes correlate with CRC pathogenesis.

High cortisol and vitamin D deficiency in African Americans mount melatonin-serotonin signaling anomalies

As found in AAs, excess cortisol negatively regulates vitamin D receptor expression and vitamin D synthesis [28,89]. Consequently, AAs suffer chronic vitamin D deficiency more frequently than CAs [32,33,61]. Plasma vitamin D levels relate to CRC risk [21,26,95], and deficiencies may contribute to high CRC-related mortality [22,28]. One of the pleiotropic effects of vitamin D is its influence on sleep quality and duration [8,66] by its action on serotonin-melatonin signaling. A heterodimeric complex of vitamin D bound receptor and retinoid X receptor regulates serotonin and melatonin synthesis via its effect on the vitamin D responsive element (VDRE) on *TPH1* and *TPH2* genes [71,79]. Low vitamin D leads to elevated *TPH1* expression [79] and gut serotonin production, resulting in inflammatory conditions [54,56]. Thus, glucocorticoids could affect melatonin synthesis and circadian rhythm by regulating vitamin D (Fig. 1).

Based on the current body of knowledge, it is difficult to determine which of these defects- high glucocorticoid levels, vitamin D deficiency, and deregulated serotonin-melatonin signaling, is the primary causative factor leading to elevated CRC risk in AAs. It is also possible that vitamin D deficiency, SLC6A4 (L) allele expression or *NAT* variants present in AAs are merely compensatory alterations. Furthermore, which of these variations is more significant in regulating extracellular serotonin levels and melatonin synthesis is also unclear. A detailed understanding of HPA-pineal regulation on CRC pathogenesis is required to answer these questions.

Crosstalk between the diet-influenced gut microbiome and the serotonin-melatonin axis affecting CRC risk in African Americans

Gut flora responsive to dietary intake, cortisol, and melatonin, can vary CRC risk by a constant dialog with the intestinal epithelia. A fiber-rich diet reduces CRC risk by increasing the butyrate and other short-chain (SCFAs, such as propionate and acetate) fatty acids-producing commensal bacteria that are protective against carcinogenesis while the economical food choices made due to poor SES have high-fat, low-fiber content which reduce the beneficial microbes by promoting gut dysbiosis. The beneficial effects of SCFA-producing microbes could be attributed to the repression of *IDO-1 (indole dioxygenase-1)* and induction of *AANAT* (*aralkylamine N-acetyltransferase*) and *HIOMT* (*hydroxyindole-O-methyltransferase*) in the intestinal epithelial cells by butyrate [3,65] (Fig. 1). IDO-1 catalyzes the step that commits the bulk of

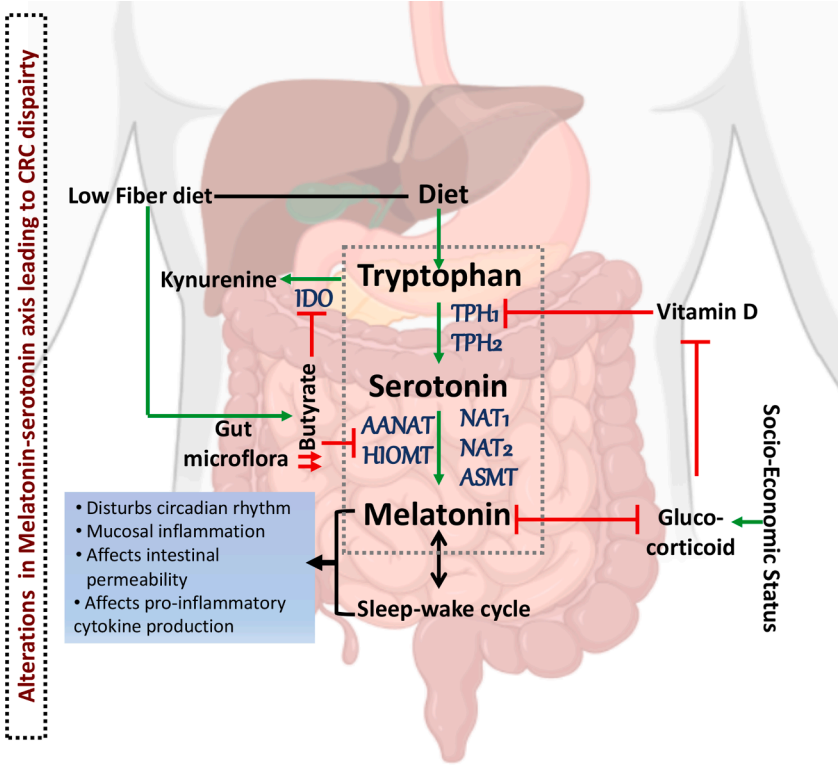

Fig. 1. Factors affecting the melatonin-serotonin axis and CRC risk. Increased socioeconomic stress leads to an increase in glucocorticoids, which have a negative impact on melatonin and vitamin D. Vitamin D downregulates expression of tryptophan hydroxylase 1, the gene product of which generates serotonin. A diet rich in fat reduces butyrate-producing species of bacteria in the gut. Low butyrate levels remove the inhibitory effect on indole dioxygenase and acetyl and methyl transferases, thereby affecting melatonin production in the gut. African Americans (AAs) have high levels of glucocorticoids due to lower SES and vitamin D deficiency. They also tend to have a high-fat, low-fiber diet. Further, AAs express allelic variants of genes encoding the serotonin receptor and reuptake proteins, and enzymes converting serotonin to melatonin. These factors affect the conversion of dietary tryptophan to serotonin, changing melatonin production. Changes in melatonin production affect the sleep-wake cycle, and together these two altered factors modulate circadian rhythm, intestinal permeability, cytokine production, and mucosal immunity. The dotted gray box indicates the serotonin-melatonin metabolism that is prone to be affected in AAs to increase their CRC risk.

tryptophan to the kynurenine pathway, and aralkylamine N-acetyltransferase and acetyl serotonin O-methyltransferase, the respective gene products of *AANAT* and *HIOMT*, convert serotonin to melatonin. Therefore, butyrate directly influences tryptophan metabolism and diverts the flux towards melatonin synthesis. However, differences in intestinal flora caused only due to the dietary choices have been associated with higher CRC incidence and outcomes in AAs [76]. The gut microbiome of AAs is low in butyrate-producing microbes; instead, it is dominated by potentially pathogenic *Escherichia* and *Acinetobacter* species. However, as stated earlier, this difference is due to a high-fat and low-fiber diet [76] and is not associated with racial ethnicity *per se* [100].

Gut microbes also generate 5-HT and indole derivatives from tryptophan [9]. The crosstalk is bidirectional since melatonin affects the microbiome as well [80]. More research with data stratification based on age, physical activity, and diet is required to determine if there are any racial disparities in the microbiome and the gut epithelial tryptophan-serotonin-melatonin axis.

Prospective race-specific CRC biomarkers associated with serotonin-melatonin signaling

In AAs, genes encoding the serotonin receptor (5-hydroxytryptamine receptor 1F, HTR1F) are specifically mutated [12,29]. HTR1F is the transducer of intracellular serotonin signaling [36], which could be used as a potential race-specific biomarker considering the above discussed findings implying disturbed melatonin-serotonin signaling axis in AAs. However, further research is needed to establish a more specific function of HTR1F in CRC, particularly in AAs. Whole-exome sequencing of CRC tissues from AAs and CAs shows fifteen preferentially mutated genes in AAs [29]. Mutations in these genes accounted for 41% of all AA CRCs but only 15% of CA CRCs. In addition to HTR1F, mutations in *epha6* (ephrin type-A receptor 6) and *flcn* (folliculin) were detected exclusively in AA CRCs. Mutations in *flcn* (a tumor suppressor gene) are also associated with Birt-Hogg-Dubé syndrome, kidney cancer, and lung complications [12,29,72]. Mutation frequencies of *htr1f* and *flcn* are low, and the association with AAs is not statistically significant ($P = 0.086$ for each gene). However, lack of statistically significant association could be attributed to the small sample size (AA = 103 & CA = 129) and lack of ancestry genotyping. More research is necessary to define and validate FLCN and HTR1F as prognostic tools for AA CRCs. Further, studies focusing on factors regulating serotonin and melatonin signaling, as discussed above, should be undertaken, as these could be potential biomarkers for predicting CRC risk for AAs. It is also likely that some of these factors could cumulatively work as CRC predictors.

Clinical relevance of the melatonin-serotonin axis in CRC outcome

Investigating differences in melatonin and serotonin among different races may be clinically significant given the above background. Recently, melatonin has gained considerable attention in the field of chemotherapeutic intervention [49] due to its onco-static effects [20,25,69]. Melatonin imposes its anti-CRC effects by targeting the processes that support the hallmarks of cancer [85]. It reestablishes the balance between cellular apoptosis and survival by downregulating survival factors [53] and by inducing cell cycle arrest and apoptosis [34]. It also reduces the metastatic potential of cancer cells by impeding the epithelial to mesenchymal transition [97] and by inhibiting migration [98]. Further, the combination of melatonin and 5-fluorouracil (5-FU) is more effective than 5-FU alone in controlling CRC progression in murine model [23,78]. Colon cancer growth also reduces after the administration of melatonin in combination with irinotecan metabolite and curcumin analog. Combining melatonin with somatostatin hampers colon cancer growth more efficiently as well. The combination treatments worked by reducing cellular superoxide/hydrogen peroxide ratio and cellular proliferation/apoptotic index ratio, respectively [5,70]. Thus, melatonin clearly shows anti-cancer effects *in vitro* and *in vivo* experimental models of CRC. However, clinical data supporting its therapeutic potential in cancer is less promising. Melatonin treatment in combination with interleukin-2 shows a partial response in CRC patients [59]. It improves the performance status of cancer patients who are non-responsive to standard therapies [60], like those with metastatic CRCs resistant to 5-FU [6]. In similar other studies, the efficacy enhancing effect of melatonin when administered in combination with irinotecan (CPT11) as a second line of treatment to metastatic CRC patients are also studied [14,57,58]. Melatonin improves the quality of life of patients receiving radio/chemotherapy irrespective of stages [25]. Thus, though melatonin treatment is beneficial, the results are not as favorable as projected based on the *in vitro* and preclinical studies. Race-specific differences in the melatonin-serotonin signaling axis and inadequate participation of the AA population in clinical trials may be leading to such ambiguous clinical output. Hence, studying the race-specific impact of serotonin-melatonin targeted CRC therapy might give more assuring results and discover new therapeutic targets opening novel avenues for designing racially tailored treatments for CRC.

Conclusion

The racial gap in CRC incidence, mortality, and therapeutic outcome could be attributed to a combination of late-stage diagnosis due to early incidence, increased aggressiveness of the disease, and poor SES-induced poor access to care in the AAs compared to CAs. The influence of the genetic predisposition of AAs and their SES on the interplay of the neuronal system and pineal hormone signaling and, in turn, its effect on CRC biology and contribution to disease aggressiveness is a crucial aspect that needs urgent consideration. Namely, the changes in pineal hormone profile support CRC promoting cellular phenotypes while creating a tolerogenic immune environment resulting in inadequate therapeutic response to standard care in AA CRC patients. Therefore, targeting the pineal hormonal changes, addressing social and economic factors of individual patients, and following race-specific screening protocols may improve the therapeutic outcome and overall survival in AAs with CRC and promise health equity.

CRediT authorship contribution statement

Talaijha Haynes: Writing – original draft. **Gabriela Oprea-Ilies:** Writing – review & editing. **Upender Manne:** Writing – review & editing. **Rajesh Singh:** Writing – review & editing. **Shailesh Singh:** Writing – review & editing. **Hina Mir:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest.

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