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Role and Controversies in the Management of Colorectal Cancer

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Abstract: Colorectal cancer (CRC) is the third most prevalent malignancy globally, with marked disparities in incidence and management between high-income countries (HICs) and low- and middle-income countries (LMICs). Incidence rates in LMICs are rising due to lifestyle factors and limited healthcare access. Key risk factors include high-fat diets and obesity. While high-income countries (HICs) benefit from advancements in treatment, such innovations remain largely inaccessible in low- and middle-income countries (LMICs), further complicated by challenges such as late-stage presentations and inadequate health literacy. Nevertheless, HICs continue to encounter issues related to the accuracy of these treatment procedures. This review highlights the need for integrated strategies, combining dietary interventions, innovative treatments, and public health initiatives, in order to improve CRC outcomes worldwide. Colorectal cancer (CRC) exhibits significant disparities in incidence and management globally, influenced by racial, ethnic, and socioeconomic factors. Key modifiable risk factors include obesity, physical inactivity, and diet, while non-modifiable factors encompass genetic predispositions and age. Enhanced screening, access to innovative treatments, and public health initiatives are essential to address these disparities, particularly for underserved populations. A multidisciplinary approach and tailored interventions are crucial for improving CRC outcomes worldwide.

Keywords: *Colorectal Cancer (CRC), Risk Factors, Incidence Rates, Healthcare Access, Screening.*

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I. INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy worldwide, with 152,810 cases reported in 2024 with a 5 year relative survival of 65.0%, making it the second leading cause of cancer-related deaths in men and women combined [1,2]. The global burden of CRC highlights significant disparities in incidence, prognosis, and management between high-income countries (HICs) and low- and middle-income countries (LMICs). Data for CRC mortality follows the pattern of the incidence rates, with individuals of African descent showing the highest mortality among racial/ethnic groups due to lifestyle differences and tumor biology [3]. This disparity underscores the complex interplay of genetic, dietary, and systemic healthcare factors influencing CRC outcomes, particularly for individuals between the age of 20-49 years [4].

II. RISING COLORECTAL CANCER BURDEN IN HIGH-INCOME COUNTRIES: THE ROLE OF AGING POPULATIONS AND WESTERNISED LIFESTYLES

While it is stated that LMICs have a potential of developing CRC due to genetic factors and lifestyle changes, high-income countries (HICs) are experiencing a rising colorectal cancer (CRC) burden due to various interconnected factors. Risk factors include the aging populations, resulting from increased life expectancy, are a significant driver, as age is a major risk factor for CRC. Additionally, westernized lifestyles contribute heavily to this trend, with diets high in processed and red meats, low fiber intake, increased alcohol consumption, obesity, and sedentary behavior becoming common [4,5]. Dietary shifts toward ultra-processed, energy-dense foods further contribute to CRC risk by reducing the intake of protective nutrients found in fruits, vegetables, and whole grains. This indicates that while CRC incidence among older adults has stabilized or decreased due to screening, a concerning rise in cases among individuals aged 20–49 has emerged, linked to poor diets, obesity, physical inactivity, and environmental or genetic factors [4,5]. These lifestyle

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factors often offset the benefits of advanced healthcare systems and preventive measures.

III. DISPARITIES IN COLORECTAL CANCER DETECTION AND TREATMENT: IMPACT OF SCREENING. SURGICAL INNOVATIONS, AND RESOURCE LIMITATIONS

Improved screening programs in HICs have led to higher detection rate (five-year survival rates exceeding 60% [1]), including early and asymptomatic cases, which may inflate incidence statistics compared to low- and middle-income countries (LMICs), where such programs are less accessible. Despite the survival rate, there is a greater set of data highlighting the incidence of CRC in HICs, due to the availability of screening and tests. Despite significant advancements in CRC management, several contentious areas remain. Surgical innovations like Total Mesorectal Excision (TME) and laparoscopic techniques (laparoscopic colon resection) have improved outcomes [6]. Particularly for laparoscopic colectomy, multiple studies have demonstrated that the incidence of port-site metastasis is low, of around 1.1% , yet their adoption is limited in most developing countries due to resource constraints [6,7,8]. Minimally invasive laparoscopic surgery offers benefits like reduced pain and quicker recovery without compromising oncological outcomes. The role of adjuvant therapies, such as chemotherapy (ACT) for high-risk stage II colon cancer (T4 or poorly differentiated tumours) and radiotherapy for rectal cancer, continues to be debated [9].

Innovative treatments, including neoadjuvant chemotherapy for liver metastases and procedures like the colonic J-pouch, have enhanced quality of life by downgrading tumours and facilitating hepatic resection, but remain inaccessible in resource-limited settings [10]. This is predominantly due to scarcity of surgeons, delays in diagnosis and treatment until tumour has progressed to a high grade, limited surgical capacity of underserved hospitals, poor health literacy, and misconceptions surrounding surgery [11]. Moreover, resection for liver metastases is the best treatment for eligible patients, with neoadjuvant chemotherapy expanding resectability in previously inoperable cases [12]. Considering this context, the functional outcomes and overall quality of life following radical resection of the rectum continue to be less than optimal. The 'watch-and-wait' (WW) strategy presents a non-invasive therapeutic alternative aimed at preserving organ function and minimizing surgical complications. Under this approach, patients diagnosed with locally advanced rectal cancer who exhibit a favorable clinical response after neoadjuvant therapy are monitored through active surveillance instead of proceeding with surgical intervention for rectal cancer. Despite proven safe and effective, further studies need to be conducted to validate this approach [13]. Surgical practice controversies, such as the effectiveness of mechanical bowel preparation to reduce anastomotic leakage and the importance of optimal resection margins, further complicate management regarding uncertainty of best practices and managing patient risk [14].

IV. THE ROLE OF LIFESTYLE, ENVIRONMENT, AND HEALTHCARE DISPARITIES

The obesity epidemic exacerbates the issue, as excess body fat promotes chronic inflammation, insulin resistance, and hormonal changes that drive cancer development. Sedentary lifestyles, driven by office-based jobs and modern conveniences, also increase CRC risk by slowing digestion and extending the colon's exposure to carcinogens. Additionally, industrialization, pollution, and widespread antibiotic use may alter the gut microbiome, with dysbiosis (imbalance in gut bacteria) emerging as a potential contributor to CRC. These factors underscore the complex interplay of aging, lifestyle, diet, and environmental influences driving the CRC burden in high-income countries. Challenges are compounded by late-stage presentations, inadequate access to healthcare, and resource constraints, necessitating cost-effective, evidence-based strategies to address these disparities. Expanding screening programs such as a three yearly stool or colonoscopy test, can enhance public awareness of modifiable risk factors, and establish centralized healthcare frameworks [15]. Initiatives like "Choosing Wisely" (CW approach) can guide resource-limited settings in prioritizing high-value interventions, in order to prevent unnecessary medical tests, treatments and procedures [16]. While CRC research and management have advanced considerably, addressing global disparities remains critical. A comprehensive approach integrating dietary adjustments, innovative therapies, public health initiatives, and tailored guidelines for regional healthcare contexts is essential.

This review aims to highlight the progress, challenges, and opportunities in CRC prevention and treatment, emphasizing the importance of targeted interventions to reduce the global burden of CRC. Over the last two decades, the management of rectal cancer has progressed considerably due to advancements in staging technologies and therapeutic concepts, specifically in HICs. This has evolved into a multidisciplinary approach that emphasizes collaboration between oncologists and colorectal surgeons [17]. This article critically analyzes key controversial aspects of colorectal cancer management, acknowledging progress while highlighting ongoing uncertainties in treatment strategies in both HICs and LMICs, as their targeted approaches vary.

V. MODIFIABLE AND NON MODIFIABLE RISK FACTORS

The management of colorectal cancer (CRC) encompasses diverse strategies marked by evolving roles and ongoing controversies. These can be divided into modifiable and non-modifiable risk factors These disparities are attributed to lifestyle differences, tumor biology, and healthcare access issues, such as being uninsured and lower screening rates.

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Table 1 Comprehensive Overview of Non-Modifiable and Modifiable Risk Factors for Colorectal Cancer

Section	Subsection	Content
Non modifiable Risk Factors	**Disparities in Racial/Ethnic Populations**	
	Epidemiology of CRC Disparities in Racial/Ethnic Populations	- Black Americans experience the highest CRC incidence (41.9 per 100,000) and mortality (16.8 per 100,000) rates in the U.S. - Younger median age of diagnosis for Black Americans (63 for men). - Lower survival rates for Black Americans (61%) compared to White Americans (67%). - Black individuals are more likely to receive colonoscopies from physicians with lower polyp detection rates, increasing interval CRC risk (7.1% for Black persons vs. 5.8% for White persons).
	Root Causes for CRC Risk Disparity in Racial/Ethnic	- Differences in healthcare access and quality, rather than biological or lifestyle factors,
	Populations	are primary contributors. - Socioeconomic inequities (education, income) reduce access to healthy food, healthcare, and CRC screening. - Screening utilization is lower among Black Americans, leading to late diagnosis and treatment delays.
	Biological and Genetic Contributions to CRC Risk in Racial/Ethnic Populations	- 65% of CRC risk is attributed to environmental factors, 35% to genetics. - Higher prevalence of advanced adenomas and right-sided CRC in some groups. - Common genetic mutations include TP53, LRP1B, TCF7L2, and FBXW7. - Lower rates of MSI-H CRC among Europeans (5-24%), African Americans (12-24%), and Egyptians (37%), affecting treatment and outcomes.
	Screening Utilization Contributions to CRC Risk in Racial/Ethnic Populations and Mitigation Strategies	- Lower screening rates among underserved populations contribute to CRC disparities. - Barriers include distrust in healthcare, socioeconomic challenges, and lack of follow-up care after abnormal screenings.
	Disparities in Sex	- Males have 1.5 times higher CRC risk than females. - Females are more prone to right-sided colon cancer, which is more aggressive. - Research favors male models for CRC studies, leading to underrepresentation of female-specific factors.
	Disparities in Age	- Gender differences in CRC risk have narrowed among older adults in recent decades. - Younger patients (<50 years) experience shorter progression-free survival (PFS)
		and overall survival (OS). - Genomic analysis of younger patients reveals distinct mutations and amplifications. - Early-onset mCRC patients face unique symptoms and worse survival outcomes.
	Disparities in Hereditary Mutations	Hereditary CRCs account for 7-10% of cases, including Lynch syndrome, FAP, and hamartomatous syndromes. - Lynch syndrome: 2-4% of cases, dominant inheritance, high lifetime CRC risk (50% by age 70). - FAP: Nearly 100% risk of CRC by age 40 with thousands of precancerous polyps. - Hamartomatous syndromes (e.g., Peutz-Jeghers) follow a different progression pattern and are rare.
Modifiable Risk Factors	**Obesity and Physical Inactivity**	- Regular physical activity reduces CRC risk by 25%, while inactivity increases it by 50%. - Obesity disrupts gut microflora, causes inflammation, and promotes carcinogenesis. - Obese men have a 50% higher risk of colon cancer and 20% higher risk of rectal cancer; women have 20% and 10% increased risks, respectively. - A 3% CRC risk increase occurs for every 5 kg of weight gained. - Rising obesity rates in developed countries correlate with increasing CRC incidence.

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	Diet	- Diet influences CRC risk by affecting the microbiome. - Red and processed meats increase CRC risk (RR of 1.22 for high consumers). - Protective factors include calcium, fiber, vitamin D, and fruits/vegetables.
		- Fiber promotes faster stool transit, reducing exposure to carcinogens. - Cooking methods (e.g., smoking, high-temperature cooking) can increase carcinogen exposure.
	Smoking	- Smoking increases CRC risk by 18%, particularly for rectal cancer. - Smoking causes common molecular abnormalities (e.g., microsatellite instability, CpG methylation, BRAF mutation). - Former smokers (HR = 1.12) and current smokers (HR = 1.29) have worse CRC prognosis. - Quitting smoking improves overall and CRC-specific survival.
	Alcohol	- Moderate drinking (2-3 drinks/day) increases CRC risk by 20%, while heavy drinking (4+ drinks/day) increases it by 40%. - Binge drinking and genetic variations in alcohol metabolism further exacerbate risk. - Men are more susceptible due to differences in alcohol metabolism.
	Medications	- NSAIDs (e.g., aspirin) reduce CRC risk through cyclooxygenase-2 inhibition, but long-term use poses risks (e.g., gastrointestinal bleeding, heart attacks). - Low-dose aspirin is recommended for high-risk individuals over 50. - Combinations of NSAIDs and statins show promise in reducing CRC risk, but clinical trials are needed. - Hormone use (e.g., postmenopausal hormone therapy) has mixed evidence regarding CRC risk reduction.

This table summarizes the key factors contributing to colorectal cancer (CRC) risk, divided into non-modifiable (e.g., genetic predispositions, age, sex, and racial/ethnic disparities) and modifiable factors (e.g., lifestyle choices, diet, and medication use). It highlights epidemiological data, root causes, and actionable insights, offering a detailed understanding of how various factors influence CRC incidence, progression, and outcomes. The information provides a foundation for targeted prevention, early detection, and personalized management strategies.

➢ *Non Modifiable Risk Factors:*

- *Disparities in Racial/Ethnic Populations:*

✓ *Epidemiology of CRC Disparities in Racial/Ethnic Populations:*

Colorectal cancer (CRC) incidence and mortality rates exhibit significant disparities among racial and ethnic groups in the U.S., with Black Americans experiencing the highest incidence (41.9 per 100,000) and mortality (16.8 per 100,000) rates. Despite a general decline in overall CRC incidence since the 1980s due to enhanced screening efforts, rates among individuals under 50 are increasing in these individuals living in HICs. Black Americans tend to present with CRC at younger ages, with a median age of 63 for men, and often have a higher proportion of advanced disease at diagnosis. Their survival rates are consistently lower (61% overall) compared to White Americans (67%), especially in advanced stages of the disease [3,18].

Additionally, in a follow-up study, spanning 235,146 person-years, described 2,735 cases of interval CRC were identified in the United States, predominantly affecting the rectum and distal colon. A higher proportion of Black individuals (52.8%) compared to White individuals (46.2%) received colonoscopies from physicians with a lower polyp detection rate (PDR), which was significantly associated with an increased risk of interval CRC. By the end of the follow-up, the probability of interval CRC was 7.1% in black persons and 5.8% in white persons [19].

✓ *Root Causes for CRC Risk Disparity in Racial/Ethnic Populations:*

Several interconnected factors that contribute to CRC risk disparities include differences in healthcare access and quality, rather than inherent biological differences or lifestyle factors. Socioeconomic inequities, such as lower education and income levels, limit access to health care and healthy food options, leading to unhealthy lifestyle choices (e.g., poor diet, smoking, and lack of exercise). These factors create an environment conducive to CRC development. Additionally, the utilization of CRC screening is lower among Black Americans, resulting in later diagnoses and treatment delays. Those with lower socioeconomic status, exacerbate the disparities [3,20].

✓ *Biological and Genetic Contributions to CRC Risk in Racial/Ethnic Populations:*

Approximately 65% of CRC risk is attributed to environmental factors, while 35% is genetic. There is a higher prevalence of advanced adenomas and right-sided CRCs, which are associated with poorer outcomes. Patients under the age of 50 show to have mutations in genes such as TP53, LRP1B, TCF7L2, and FBXW7 [21]. Genetic predisposition, including familial syndromes and unique somatic mutations, also plays a role. Studies indicate lower rates of microsatellite instability-high (MSI-H) CRCs among Europeans (5-24%), African Americans (12-24%), and Egyptians (37%), which may affect treatment responses and survival outcomes [3,22]. High MSI-H CRC's are caused by mutations in somatic DNA mismatch repair genes, such as hMLH1, hMSH2, hMSH6, and hPMS2*Screening Utilization Contributions to CRC Risk in Racial/Ethnic Populations and Mitigation Strategies:*

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Screening rates for CRC are lower among underserved populations, contributing to incidence and mortality disparities. The screening process for colorectal cancer (CRC) involves multiple steps: risk assessment, screening initiation, regular rescreening, follow-up for abnormal results, and treatment. Its effectiveness depends on completing these steps, but failures, especially in underserved populations, are common [23]. Barriers to screening include distrust in the healthcare system, socioeconomic factors, and lack of follow-up care after abnormal screening results.

➢ *Disparities in Sex:*

Males have a 1.5 times higher risk of developing colorectal cancer (CRC) than females across all ages and nations. Women tend to be more susceptible to right-sided colon cancer, which is generally more aggressive than left-sided colon cancer. Additionally, the 5-year survival rates for females over 70 are lower than those for males [3]. Male cell lines vastly outnumber female ones in research repositories, leading to biased, single-sex analyses. Many studies do not report the sex of cell lines, and even when they do, the original sex identity may change during cell culture. Additionally, the hormonal environment of cultured cells is often not matched with their sex, and factors like the estrogenic effects of culture media and labware are rarely considered [24]. This shows that research favours male models over female models for CRC management.

➢ *Disparities in Age:*

However, in recent decades, the gender difference in CRC risk among older adults in the US has diminished, aligning more closely with that of younger adults (<50). According to [et.al], they utilized data from three clinical trials and an external validation cohort, the research analyzed 1,223 patients, revealing that younger patients (<50 years) experienced significantly shorter progression-free survival (PFS) and overall survival (OS) compared to those aged 50-65. The younger cohort also showed a higher incidence of specific adverse events, such as nausea/vomiting and severe abdominal pain, but lower rates of fatigue-related issues [25]. Additionally, this group exhibited earlier onset of several symptoms and shorter durations for some, and certain severe conditions were linked to poorer survival outcomes. Genomic analysis highlighted unique mutations and amplifications prevalent in the younger cohort, suggesting a distinct genomic profile. The findings indicate that early onset mCRC patients face worse survival and specific adverse events, which could inform personalised treatment strategies and management of chemotherapy side effects [3,25].

➢ *Disparities in Hereditary Mutations:*

Hereditary colorectal cancers (CRCs) account for 7-10% of cases, including syndromes like hereditary non-polyposis colorectal cancer (HNPCC, or Lynch syndrome), familial adenomatous polyposis (FAP), and hamartomatous polyposis syndromes (e.g., Peutz-Jeghers syndrome). Approximately 30% of CRC patients have a family history, indicating potential unidentified germ-line mutations. Those with a first-degree relative with CRC have a 2-4 times higher risk [3]. Lynch syndrome, the most common hereditary CRC syndrome, accounts for 2-4% of cases and has a dominant inheritance pattern, with a 20% chance of developing CRC by age 50 and a 50% chance by age 70. Awareness of Lynch syndrome is low, with less than 1% of affected individuals diagnosed before cancer develops, often relying on family history for identification [3].

FAP is the second most frequent hereditary syndrome, presenting with thousands of pre-cancerous polyps by ages 10-12, leading to nearly a 100% risk of CRC by age 40. Attenuated FAP involves fewer than 100 polyps but still carries a CRC risk. MUTYH-associated polyposis (MAP) is less clearly defined. Hamartomatous syndromes, such as PJS, juvenile polyposis syndrome (JPS), and PTEN hamartoma tumor syndrome (PHTS), are rare and follow a different progression, starting in the lamina propria rather than the epithelium [3].

➢ *Modifiable risk factors:*

- *Obesity and Physical Inactivity:*

Regular physical activity can reduce colorectal cancer (CRC) risk by 25%, while sedentary lifestyles can increase risk by up to 50%. Inactivity often leads to obesity, which disrupts gut microflora and causes inflammation, promoting carcinogenesis. Obesity is linked to elevated cancer risk beyond the digestive system, as adipose tissue releases tumor-promoting cytokines and free radicals. Obese men have a 50% higher risk of colon cancer and 20% higher risk of rectal cancer, while women have respective risks of 20% and 10%. The cumulative risks from obesity and inactivity are significant, with a meta-analysis indicating a 3% CRC risk increase for every 5 kg weight gain. In developed countries, rising obesity correlates with increasing CRC incidence; in the US, obesity rates rose from 15% in 1979 to 39.8% in 2016. In Europe, about 11% of CRCs are linked to obesity, which also complicates cancer management and screening. The role of bariatric surgery in reducing rectal cancer risk remains uncertain [26].

- *Diet:*

Diet significantly influences colorectal cancer (CRC) risk, independent of obesity, by affecting the colon's microbiome, where bacteria outnumber human cells. A diverse microflora is essential for health, and certain foods can impact bacterial populations and intestinal inflammation. Red and processed meats are associated with increased CRC risk, with a relative risk (RR) of 1.22 for high consumers. A meta-analysis found that red meat consumption has an RR of 1.12, while processed meat has an RR of 1.15. Cooking methods like high-temperature cooking and smoking contribute to carcinogenesis. In contrast, calcium, fiber, vitamin D, and fruits and vegetables have protective effects against CRC. Folate may inhibit carcinogenesis but can promote existing tumor growth, leading health agencies to recommend it primarily for pregnant women or those with specific metabolic disorders. Fiber, particularly from fruits, vegetables, and whole grains, is protective by promoting faster stool transit, reducing exposure to potential carcinogens [3,27].

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- *Smoking:*

Cigarette smoking and rural residence (independent of specialist density) were most strongly associated with GI cancer–related mortality. In 2009, the IARC confirmed that smoking tobacco causes colorectal cancer (CRC), identifying it as the leading preventable cause of cancer deaths, mainly due to its link to lung cancer. Regular smoking increases CRC risk by 18%, particularly for rectal cancer, and is associated with common molecular abnormalities such as high microsatellite instability, CpG methylation, and BRAF mutation, likely due to mutagens in tobacco smoke [28]. A meta-analysis of 14 cohort studies indicated that both former (HR = 1.12) and current smokers (HR = 1.29) have worse CRC prognoses compared to non-smokers, while quitting smoking is linked to better overall and CRC-specific survival [29].

- *Alcohol:*

Moderate drinkers (2-3 drinks/day) have a 20% increased risk, while heavy drinkers (4 or more drinks/day or >50g/day) face a 40% increase or a relative risk (RR) of 1.52 [28]. This association is stronger in men due to differences in alcohol metabolism and reporting as genetic variations in alcohol metabolism, particularly in Asian populations, have been associated with CRC risk [30]. Binge drinking may also increase CRC risk due to metabolic effects.

- *Medications:*

There is increasing evidence from various studies indicating that non-steroidal anti-inflammatory drugs (NSAIDs) can play a beneficial role in colorectal cancer (CRC) chemoprevention by reducing the risk of colorectal polyps, primarily through cyclooxygenase-2 inhibition [31]. The long-term use of NSAIDs, such as aspirin, sulindac, and celecoxib, is associated with a decreased risk of colorectal cancer in at-risk patients and less aggressive tumors in affected individuals, although the exact benefits are not fully quantified [31]. Low-dose aspirin is advised for those over 50 at higher risk for cardiovascular disease or CRC. However, despite their protective effects, NSAIDs pose risks of gastrointestinal bleeding and heart attacks, leading to limited recommendations for their use in the general population. Additionally, sulindac has shown mixed results in preventing colorectal adenomas. Combinations of NSAIDs and statins have demonstrated significant reductions in CRC risk in studies, but clinical trials in humans are lacking. The protective effects of postmenopausal hormone use and oral contraceptives on CRC risk remain controversial, with recent studies failing to provide supportive evidence [32].

VI. COMPREHENSIVE REVIEW ON DEMOGRAPHIC, LIFESTYLE AND GENETIC FACTORS

The management of colorectal cancer (CRC) is intricately linked to understanding the disparities in risk factors and outcomes among various demographic groups. Despite overall declines in CRC incidence due to improved screening, significant racial, ethnic, sex, age, and hereditary disparities remain. Racial and ethnic disparities are particularly pronounced, with African Americans experiencing the highest rates of CRC incidence and mortality. This is compounded by factors such as limited access to quality healthcare and socioeconomic inequities, which hinder effective screening and timely treatment. Interventions aimed at overcoming these barriers encompassing patient outreach, provider education, and healthcare legislation to address financial obstacles [33]. Recent studies have concentrated on identifying factors that influence the intention to undergo colorectal cancer screening [33]. Furthermore, studies indicate that individuals of African descent are more likely to receive colonoscopies from physicians with lower polyp detection rates, increasing their risk of interval CRC. A higher polyp rate is associated with higher patient outcomes. This demographic group also has lower follow up colonoscopies for abnormal stool based tests in comparison to Caucasians [34].

Sex-based differences also play a crucial role in CRC outcomes. Males have a higher overall risk of developing CRC, while females are more susceptible to right-sided colon cancer, which is often more aggressive. The ability for men to develop CRC at a more prevalent rate is due to variations in sex steroid hormone and gut microbiome, whilst the aggressive nature of women may be due to the toxicity of medications provided such as fluoropyrimidines and immunotherapies [35,36]. The research community's bias towards male models further complicates effective management for females, indicating a need for more balanced research approaches that consider sex-specific differences in CRC. This can include identifying gaps in knowledge regarding female specific CRC characteristics, conducting gender inclusive studies (equal representation), and creating animal and cellular models which represent the female physiology. Age disparities highlight the growing concern of early-onset CRC, with younger patients (<50 years) facing worse progression-free and overall survival rates compared to their older counterparts. The distinct genomic profiles observed in younger patients suggest that personalized treatment strategies could enhance management outcomes for this group, as the demographic can develop unique mutations. This is because the younger population tend to have poorly differentiated mucinous or signet ring histology with perineural or lymphovascular invasion at distal colon or rectum on the left side; in opposed to older adults who have tumours mainly in the proximal colon on the right hand side. The diagnosis in younger patients is sporadic and idiopathic in nature, usually found as a result of symptoms and not due to screening processes [37,38]. Hereditary factors also contribute significantly to CRC risk, with conditions like Lynch syndrome and familial adenomatous polyposis (FAP) accounting for a notable portion of cases in younger populations. The low awareness and diagnosis rates of these hereditary syndromes before cancer development emphasize the need for increased awareness of hereditary syndromes, importance of early detection, and increasing access to genetic counseling to mitigate risks effectively.

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- *Bariatric Surgery and Its Effect on Colorectal Cancer Risk:*

Management also involves understanding the influence of modifiable risk factors, which are crucial for developing effective prevention strategies. Obesity and physical inactivity significantly increase CRC risk, as sedentary lifestyles promote obesity, disrupt gut microflora, and lead to inflammation. Chronic inflammation and abnormal lipid metabolism can lead to tumour growth [39]. Other factors are insulin resistance and decreased testosterone levels in men which are developed when one is obese, leading to an increased risk of CRC [40]. Meta-analyses were conducted comparing the association of adiposity, measured by body mass index and waist circumference, with colorectal cancer (CRC) [41,42]. Interventions promoting physical activity and healthy weight management are essential in reducing obesity rates and potentially lowering the risk of colorectal cancer.. While bariatric surgery may potentially reduce rectal cancer risk, its role remains uncertain. Studies have shown that Roux-en-Y gastric bypass (RYGB) may lead to hyperproliferation and increased inflammation in the rectal mucosa, potentially increasing CRC risk due to gut microbiota changes and high bile acid exposure. Laparoscopic sleeve gastrectomy seems to have a less pronounced impact, but more research is needed to confirm whether increased CRC risk is specific to RYGB or applies to other bariatric procedures as well [43]. Diet also plays a pivotal role in CRC risk. High consumption of red and processed meats increases risk, likely due to carcinogenic compounds/ chemicals such as N-nitroso-compound formation containing heterocyclic aromatic amines and polycyclic aromatic hydrocarbons formed during high-temperature cooking [44]. Conversely, diets rich in calcium, fiber, vitamin D, and fruits and vegetables have protective effects. These foods contribute to a diverse and healthy colon microbiome, reducing inflammation and exposure to carcinogens. Despite folate's (B vitamin) potential to inhibit carcinogenesis, its role is complex, as it may also promote tumor growth as high doses of medication and late intervention may actually promote cancer progression [45]. Smoking is another critical modifiable factor, with tobacco use significantly increasing CRC risk and associated with molecular abnormalities. A prospective study [46] of older women found that cigarette smoking was linked to colorectal cancer subtypes characterized by MSI-high, CIMP-positive, and BRAF mutation–positive statuses, suggesting that epigenetic modifications may play a role in smoking-related colorectal cancer development. Quitting smoking improves CRC prognosis, underscoring the importance of smoking cessation programs.

- *Chemoprevention and Medical Interventions:*

Similarly, alcohol consumption, particularly in heavy drinkers and binge drinkers, is linked to increased CRC risk, with genetic variations in alcohol metabolism further influencing this risk. When alcohol is metabolized, it produces acetaldehyde, acetate, and other byproducts that can lead to DNA damage, inflammation, and immune disruption [47]. Genetic differences in enzymes that metabolize alcohol can influence acetaldehyde production; for instance, the ALDH2*2 allele is linked to elevated acetaldehyde levels and a higher colorectal cancer risk [47,48]. Additionally, alcohol consumption can interact with factors like folate levels, further increasing the risk of colorectal cancer [48]. Medications, particularly non-steroidal anti-inflammatory drugs (NSAIDs), show promise in CRC chemoprevention by reducing polyp formation. However, their use is limited by potential side effects, such as gastrointestinal bleeding and cardiovascular risks.This is as aspirin/NSAIDs inhibits cyclooxygenase and phospholipase activity, as well reduce the production of protective prostaglandins in the stomach lining, which can increase the risk of ulcers and bleeding. Similarly, inhibiting phospholipase can disrupt cell membrane integrity and mucus production, contributing to gastrointestinal issues [42], therefore, further studies are needed to balance their benefits against potential side effects. There is a notable negative correlation between the use of hormone therapy (HT) and the overall risk of colorectal cancer (CRC), which may affect tumors arising from both the adenoma-carcinoma pathway and other pathways, including those in the distal colon and rectum [49]. Nevertheless, the impact of postmenopausal hormone therapy (PHT) and oral contraceptives on CRC risk is still debated, as recent research has produced inconclusive results.

- *Tailored Approaches:*

To bridge these gaps, a multifaceted approach is needed, which should concentrate on improving screening rates and healthcare accessibility for underserved communities, increasing awareness of hereditary cancer syndromes, and ensuring that research represents a wide range of populations. Tailored interventions that consider the unique biological, socioeconomic, and genetic factors affecting different groups are essential for lowering CRC incidence and mortality and improving overall management outcomes. By implementing these targeted approaches, we can more effectively mitigate the impact of CRC across various demographics and strengthen the quality of care for all individuals.

VII. CONCLUSION

In conclusion, the management of colorectal cancer (CRC) is fraught with complexities, particularly concerning the disparities in incidence and treatment outcomes across diverse populations. This review underscores the critical need for integrated strategies that encompass not only innovative treatment options for CRC but also a comprehensive understanding of the underlying risk factors, both modifiable and non-modifiable, that influence CRC progression and survival. Addressing the systemic barriers faced by underserved populations is paramount for improving screening rates and access to quality care. Furthermore, the ongoing controversies surrounding surgical techniques, adjuvant therapies, and the role of genetics in treatment decisions underscore the necessity for personalized approaches tailored to individual patient profiles. As we move forward, a multidisciplinary effort that combines advancements in medical technology, enhanced public health initiatives, and increased awareness of lifestyle factors will be essential to effectively mitigate the global burden of colorectal cancer and improve outcomes for all individuals affected by this disease.

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