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Review

Colorectal Cancer in Pakistan: genetic, molecular, and epidemiological perspectives

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Abstract

Colorectal cancer (CRC) stands as a major health concern globally, with a notable impact in Pakistan. The epidemiology of CRC in this region reveals a higher prevalence in men and an increasing incidence in younger age groups. Risk factors contributing to CRC encompass a blend of lifestyle choices and genetic predispositions. The genetic and molecular pathways which are crucial to understanding of CRC pathogenesis include the CpG Island Methylator Phenotype (CIMP), Chromosomal Instability (CIN), and Microsatellite Instability (MSI). The challenge of late-stage diagnosis due to limited screening is a critical factor affecting survival rates in Pakistan. Compared to higher incidence rates in developed countries, the situation in Pakistan underscores the need for region-specific research and healthcare strategies. The review provides an in-depth analysis of CRC's epidemiology, risk factors, and molecular mechanisms in Pakistan, highlighting the urgent need for enhanced research, prevention, diagnosis, and treatment methods in the region.

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Introduction: Colorectal cancer (CRC) is a critical health concern, characterized by the uncontrolled growth of cells in the colon or rectum. Globally, CRC has emerged as one of the most common forms of cancer, with its incidence rising particularly in areas experiencing rapid economic development 1,2. This trend has prompted increased attention from the medical and scientific communities.

Recent epidemiological data reveals a significant upsurge in both the incidence and mortality rates of CRC. This increase is more pronounced in certain demographic groups, with a disparity in the rates between men and women [3]. A substantial portion of CRC cases can be linked to lifestyle choices. Factors such as dietary habits, physical inactivity, obesity, alcohol consumption, and tobacco use have been identified as major contributors to the risk of developing CRC [4]. These modifiable risk factors underscore the potential for preventive strategies in reducing the burden of CRC. Alongside lifestyle factors, genetics play a crucial role in the susceptibility to CRC. Research has highlighted the mutation of specific genes, such as APC, KRAS, and p53, as significant contributors to the development of CRC [5-7]. These mutations can lead to various forms of genetic instability, which are central to the progression of the disease[8].

The progression of CRC typically starts with benign adenomatous polyps in the colon or rectum [9]. Over time, these can transform into malignant forms, a process influenced by various genetic and environmental factors. Recent studies have specifically focused on the role of oncogenic mutations, such as those in the KRAS gene, in influencing the immune response to CRC [10,11]. This line of research holds promise for developing targeted therapies and improving patient outcomes. The geographical distribution of CRC incidence is varied [12]. High-incidence regions like the United States exhibit different characteristics of the disease compared to lower-incidence areas such as Pakistan [13]. This variation suggests that environmental and lifestyle factors, along with genetic predispositions, play a significant role in the epidemiology of CRC. Understanding these regional differences is crucial for developing effective public health strategies and tailored medical interventions.

In light of these global and regional trends, this article aims to delve deeper into the specific context of CRC in Pakistan. It will focus on the genetic, molecular, and epidemiological aspects of the disease in the Pakistani population. Our aim is to provide a comprehensive overview to the readers that not only enhances their understanding of CRC in this particular region but also contributes to the broader global discourse on managing and researching this increasingly prevalent form of cancer.

Risk Factors Associated with Colorectal Cancer (CRC)

Colorectal cancer (CRC) is a leading cause of cancer-related deaths, ranking third globally [14]. Its prevalence is notably higher in more industrialized, first-world countries [1]. Understanding the risk factors associated with CRC is crucial for effective prevention and management strategies. These risk factors are generally categorized into two types: modifiable and non-modifiable.

Modifiable risk factors are significant contributors to CRC incidence, accounting for approximately 60-65% of cases [1]. These factors largely relate to lifestyle choices and environmental exposures. Conversely, non-modifiable risk factors, contributing to around 30-35% of CRC cases, include elements beyond individual control, such as genetic predispositions and certain inherent demographic characteristics [15]. Non-modifiable risk factors for CRC primarily involve genetic components. A notable aspect is the heightened risk associated with a family history of CRC, particularly in first-degree relatives [16,17]. This suggests a strong genetic linkage in the disease's development. On the modifiable front, several lifestyle factors have been identified as influencing CRC risk. Obesity and a sedentary lifestyle are prominent contributors [18]. Higher levels of lipids and fats in the body, often linked to dietary choices, also increase CRC risk [19]. Alcohol consumption and hypertension are additional factors that elevate the risk of developing CRC [20]. Medical conditions like ulcerative colitis are also associated with an increased likelihood of CRC [21].

Gender and age play a significant role in CRC risk and outcomes. Studies have shown that men are more likely to develop cancer in the proximal colon compared to women [22]. In older age groups, men exhibit a higher vulnerability to CRC and generally have lower survival rates compared to their male counterparts of the same age group [23]. Diet is a crucial modifiable risk factor for CRC. The consumption of processed foods, red meats, and diets high in cholesterol has been linked to an increased risk of CRC [24]. These dietary elements contribute to the overall risk profile and are areas where intervention and education can potentially reduce the incidence of CRC. CRC risk is influenced by a complex interplay of genetic, lifestyle, and demographic factors. Recognizing and addressing these risk factors, particularly the modifiable ones, is essential for reducing the global burden of this disease. This understanding also underscores the importance of tailored public health strategies and individual lifestyle modifications in mitigating the risk of colorectal cancer.

Genetics of Colorectal Cancer (CRC): The role of genetics in colorectal cancer (CRC) is pivotal for understanding its development and progression [25]. CRC's genetic landscape is intricate, characterized by mutations across various genes that cumulatively influence the disease's trajectory. Colorectal cancer can be categorized into three primary types: sporadic, hereditary, and familial, based on genetic mutations. Sporadic CRC, accounting for about 70% of cases, typically arises from random genetic mutations. Hereditary CRC, making up about 5% of cases, is directly inherited through familial genes. The remaining 25% of cases, familial CRC, are not directly inherited but occur more frequently within certain families, likely due to a combination of genetic and environmental factors [26].

Central to the genetics of CRC are mutations in key oncogenes and tumor suppressor genes, notably APC, KRAS, and p53 [27]. These mutations are instrumental in the disease's development. The APC gene plays a crucial role in controlling cell growth via the Wnt signaling pathway [28]. Mutations in the APC gene can lead to uncontrolled cell proliferation, a cornerstone in the development of CRC. Familial adenomatous polyposis (FAP), a hereditary form of colon cancer, is directly linked to germline mutations in the APC gene [29]. In sporadic CRC cases, somatic mutations in the APC gene often serve as the initial genetic alteration.

The p53 gene encodes a protein that regulates the cell cycle and plays a role in DNA repair and apoptosis [30]. Mutations in p53 are associated with advanced stages of CRC and poorer prognoses, particularly in rectal tumors [31]. The ras gene family is another critical component in CRC genetics. K-ras mutations are commonly found in colon cancer and are involved in cell signaling pathways that regulate cell growth and differentiation. Mutations in K-ras can lead to continuous stimulation of cell growth, contributing to the malignancy [32].

Another crucial aspect of CRC genetics involves DNA mismatch repair genes such as hMLH1, hMSH2, hMSH3, hPMS1, hPMS2, and hMSH6 [33]. These genes play a vital role in correcting errors during DNA replication. Mutations in these genes can lead to microsatellite instability, a hallmark of hereditary non-polyposis colorectal cancer (HNPCC) [34]. The development of CRC typically follows a multi-step process, historically described by the "Vogelstein model" which initially posited a sequence of genetic events involving APC, KRAS, and p53 mutations [35,36]. However, recent research suggests a revised sequence, possibly starting with APC mutations, followed by p53 and then KRAS alterations [37]. This evolving understanding reflects the dynamic nature of CRC research and underscores the complexity of its genetic underpinnings. The genetics of CRC involves a diverse array of genes and pathways, each contributing to the disease's development and progression. This complexity necessitates a nuanced approach to CRC research and treatment, considering the individual genetic makeup of each patient.

Pathogenesis of Colorectal Cancer (CRC): The pathogenesis of colorectal cancer (CRC) is characterized by genetic instability, a defining hallmark of the disease. This instability manifests through several molecular pathways: Chromosomal Instability (CIN), Microsatellite Instability (MSI), and the CpG Island Methylator Phenotype (CIMP) [38]. Additionally, a subset of CRCs, which do not exhibit CIN or MSI, are categorized as Genome Stable (GS) CRCs. In GS CRCs, DNA repair genes and tumor suppressor genes are typically disrupted by CIMP [39]. Interestingly, a significant proportion of MSI CRCs and a smaller fraction of CIN CRCs also show GS features. CRC can exhibit characteristics of different pathways, and the nature and extent of this overlap is an area of ongoing research.

Chromosome Instability Pathway (CINP): The CIN pathway is the most prevalent in CRC, accounting for approximately 80-85% of cases [40]. CIN leads to alterations in chromosome structure and number, resulting in aneuploidy and loss of heterozygosity (LOH). The causes of CIN include telomere dysfunction, defects in DNA repair mechanisms, and problems with chromosomal segregation. These issues affect crucial genes such as APC, KRAS, p53, and others, essential for proper cellular function and regulation [41,42].

Microsatellite Instability Pathway (MSIP): Microsatellites are the short repeating DNA sequences that are prone to mutations due to their high occurrence in the genome [43]. Mutations in these sequences, particularly in coding and non-coding regions, can lead to frameshift mutations in oncogenes and tumor suppressor genes, contributing to tumor development [44]. The DNA mismatch repair (MMR) system is responsible for correcting errors during DNA replication. Deficiencies in MMR genes can lead to MSI, an alternative pathway in CRC pathogenesis [37]. Germline mutations in MMR genes result in hereditary non-polyposis colorectal cancer (HNPCC) or Lynch Syndrome, while somatic mutations or hypermethylation can lead to sporadic CRC [45].

CpG Island Methylator Phenotype (CIMP): In addition to genetic instability, epigenetic changes significantly contribute to CRC development [46]. These changes, which affect gene expression without altering the nucleotide sequence, can be triggered by environmental factors or methylation of gene promoter regions. DNA methylation, often occurring at CpG islands, leads to gene silencing [47]. Hypermethylation of tumor suppressor genes like APC, MLH1, MGMT, and others represents an alternative pathway in CRC, known as CIMP [48]. The identification of CIMP involves assessing methylation in specific markers, including CACNA1G, IGF2, NEUROG1, RUNX3, and SOCS1, with methylation in at least three of these markers indicative of CIMP [49].

Epidemiology of Colorectal Cancer (CRC) in Pakistan: In Pakistan, a country with a population of approximately 220 million, colorectal cancer (CRC) poses a significant health challenge. Despite limitations in national-level cancer registry data, various studies have attempted to quantify the incidence and prevalence of CRC. Reports indicate that CRC is the leading cause of cancer-related deaths in Pakistan, as highlighted by the Shaukat Khanum Memorial Cancer Hospital and Research Centre 50. However, the scarcity of comprehensive data complicates the full understanding of CRC's impact [51]. This study anticipates an increase in CRC incidence among the younger population (ages 20-49) by 2030. The survival rates for CRC in Pakistan vary significantly by stage. The chances of survival are approximately 72% at stage 1, decreasing to 57% at stage 2, 50% at stage 3, and only 30% at stage 4. Late diagnosis, often at stage 4, is a critical issue due to inadequate screening [52]. CRC incidence in Pakistan is higher in men compared to women. A study conducted at Civil Hospital Karachi found that 56% of male patients, typically aged 42 to 43 years, and 43.47% of female patients, with an average age of over 40 years, were affected by CRC. This study also revealed that CRC is more likely (52%) in individuals aged 40 years or below, and 47% in those over 40 years [53]. A 2008 study at Shaukat Khanum Memorial Hospital reported a higher prevalence of CRC in men than women, with a male-to-female ratio of 1.9:1. The study also noted a mortality rate of about 27.7%. CRC tends to be more common in younger individuals, with a predicted increase in cases due to late diagnosis and treatment. The study emphasizes the need for proper screening to reduce the mortality rate [52]. An age-based analysis from another study indicated that less than 5% of CRC cases occurred in individuals aged 15-19 years, over 50% in those aged 50 years or older, and 30% or less in individuals aged 60 years and above. The ratio of colon cancer was approximately equal between men and women, while rectal cancer was more prevalent in men than women, with a ratio of 2:1 54. The data underscores the necessity of improved screening and early diagnosis to

enhance survival rates and effectively manage CRC in the Pakistani context.

Conclusion: Colorectal cancer (CRC), as one of the most prevalent and researched cancers globally, presents ongoing challenges due to the complexity of its molecular subtypes and the associated genetic and epigenetic changes. This review has sought to encapsulate the current understanding of CRC carcinogenesis, particularly in Pakistan, highlighting known risk factors, molecular pathways, and the significant gaps in understanding, especially in early-onset sporadic malignancies. The urgent need for further research, particularly in the identification of early biomarkers, stands out as a critical factor for advancing prevention, diagnosis, and personalized treatment strategies. Given the rising incidence of CRC in younger populations in Pakistan and the varying epidemiological trends compared to developed countries, targeted research and tailored healthcare interventions are essential for bridging these knowledge gaps and enhancing patient outcomes in the fight against CRC.

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AI Assistance in Manuscript Language Enhancement

The authors employed Artificial Intelligence (AI) tools for language enhancement, due to English not being their first language. This usage was limited to linguistic improvements. The authors affirm that they have meticulously verified the content for accuracy post AI-assistance.

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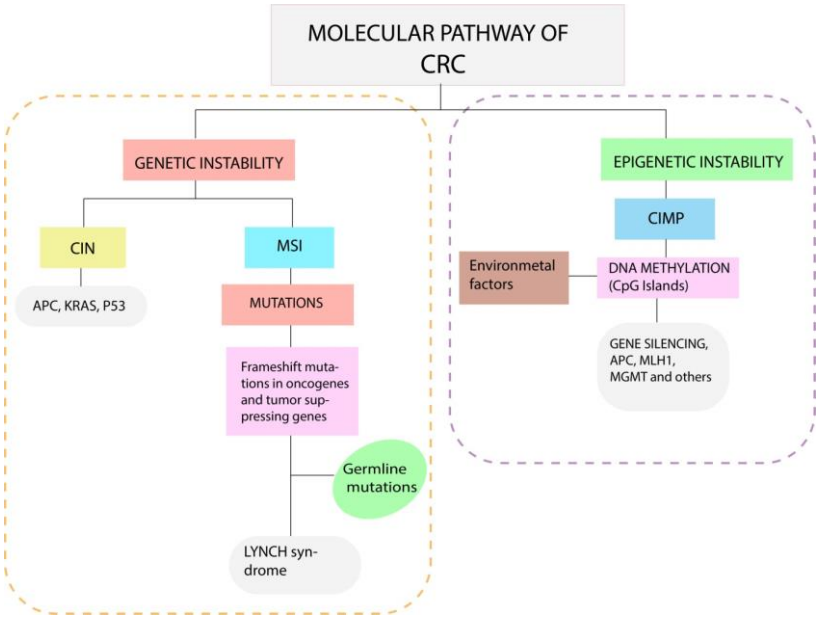

Figure 1: Pathways of Colorectal Cancer (CRC) Progression. This illustration delineates the primary mechanisms contributing to CRC development, namely genetic and epigenetic instabilities. Genetic instability is subdivided into two key pathways: Chromosomal Instability (CIN) and Microsatellite Instability (MSI). The CIN pathway is characterized by mutations in genes essential for cell regulation, including APC, KRAS, and P53. The MSI pathway involves frameshift mutations affecting genes crucial for DNA mismatch repair. On the other hand, epigenetic instability is marked by environmental influences leading to DNA methylation in CpG Islands. This process results in the suppression of critical genes like APC, MLH1, MGMT, and others that are vital in controlling cellular activities.