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The Cancer Control Challenge:
Better Understanding It to Better Face It

GENOMIC PROFILE OF COLORECTAL TUMORS IN YOUNG ADULTS: A RETROSPECTIVE STUDY IN THE AMAZON REGION

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Introduction: Early-onset colorectal cancer (EOCRC) has shown a global increase over recent decades, affecting individuals under the age of 50. Although there is evidence that EOCRC presents distinct molecular characteristics compared to late-onset colorectal cancer, data regarding populations from the Brazilian Amazon remain scarce. **Objectives:** This study aims to characterize the genetic and epigenetic profile of early-onset colorectal cancer in young adults from the Amazon region, exploring somatic mutations, polymorphisms, molecular signatures, as well as the influence of genomic ancestry on tumor susceptibility. **Methods:** This is a retrospective study involving young adults (<50 years) diagnosed with colorectal cancer in the Amazon region. Genotyping was performed using real-time PCR and next-generation sequencing (NGS). Single nucleotide polymorphisms (SNPs) in carcinogenesis-related genes and genomic ancestry were analyzed using 61 ancestry-informative markers (AIMs) and adjusted statistical analyses. **Results:** Genomic analyses revealed a complex and heterogeneous molecular profile in colorectal tumors of young adults from the Amazon. Recurrent mutations were identified in the *PIK3CA*, *TP53*, and *KRAS* genes, in addition to alterations in *AXIN2*, *RNF43*, and *ARID1A*, which are involved in epigenetic regulation and DNA repair. These findings suggest that carcinogenesis in young individuals may involve alternative pathways beyond the classical ones, such as activation of non-canonical Wnt signaling, genomic instability, and chromatin remodeler alterations. Furthermore, the rs1128503 polymorphism in the *ABCB1* gene was associated with a lower risk of colorectal cancer, indicating a possible protective genetic role. Another relevant aspect was the influence of genomic ancestry. A high frequency of mutations in genes such as *CDKN1A*, *MAP3K1*, *AURKA*, *EPCAM*, and *KDM5A* was also observed, particularly in samples without a family history or known hereditary syndromes, reinforcing the hypothesis of a sporadic EOCRC subset with distinct molecular signatures. Additionally, tumors located in the right colon—more prevalent among young patients—exhibited increased rates of microsatellite instability (MSI), high tumor mutational burden (TMB), and mutations in DNA repair genes such as *MSH2*, *POLE*, and *BRCA1*, highlighting their potential as therapeutic targets, particularly in immunotherapy strategies. At the epigenetic level, EOCRC tumors were shown to rapidly accumulate methylation alterations, notably LINE-1 hypomethylation and the presence of 234 differentially methylated regions compared to late-onset tumors. Epigenetic markers were also detectable in peripheral blood leukocytes, suggesting that systemic changes may precede or accompany tumor development and offer new

avenues for non-invasive screening. In this context, the presence of European, African, and Amerindian genetic components was found to alter the frequency of risk-associated variants, revealing a unique landscape of genetic susceptibility in this population. Such genetic admixture, still underrepresented in major international genomic consortia, may affect the functional interpretation of variants and influence clinical decisions regarding targeted therapies. **Conclusion:** Colorectal cancer in young adults from the Amazon region reveals a distinct genetic profile. The influence of ancestry and molecular heterogeneity underscores the need for personalized diagnostic strategies and the inclusion of admixed populations in genomic studies and precision medicine policies.

Keywords: Oncology; Genomic Ancestry; Somatic and Epigenetic Mutations.