Shedding Light on the Surge: Investigating the Etiology of Young Onset Colorectal Cancer

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Abstract

Background: The incidence of Young Onset Colorectal Cancer (YOCRC), defined as diagnosed <50 years of age, has been steadily increasing since the mid-1990s, posing significant clinical and public health challenges. Despite the growing recognition of this problem, the cause of this increased incidence of YOCRC remains unknown, and even more fundamentally, our understanding of the etiologic mechanisms and molecular drivers of tumorigenesis in YOCRC is limited. Somatic profiling of cancer genomes and transcriptomes can provide a historical record of the mutational processes, both endogenous and exogenous, that were active in tumor initiation and progression, providing a characteristic "signature" for each cancer.

Methods: We propose a comprehensive tumor-focused approach utilizing a large, well-characterized cohort of YOCRC cases from the Ontario Familial Colorectal Cancer Registry (OFCCR) as part of MOHCCN. Somatic mutation analysis, whole transcriptomics, and deep learning-derived histologic profiling will be employed to elucidate molecular and histologic signatures of YOCRC. Known environmental and lifestyle risk factors will be correlated with identified signatures to explore etiologic mechanisms.

Research plan: The overall objective of the proposed research is to identify etiologic mechanisms contributing to YOCRC. In Aim 1, we will identify molecular and histologic signatures present in YOCRCs through multi-omics analysis integrating somatic mutations, whole transcriptomics and pathologist-supervised digital H&E profiling. Aim 2 will correlate unknown molecular and histologic signatures from Aim 1 with known etiologic (environmental and lifestyle) risk factors from our heavily curated, epidemiologically informed cohort, providing insights into novel YOCRC signatures. Aim 3 seeks to identify temporal signatures by comparing YOCRC cases diagnosed over a 10-year period, shedding light on evolving molecular and histologic characteristics.

Innovation and anticipated results: This study will contribute to a deeper understanding of YOCRC by unraveling temporal signatures and elucidating underlying etiologic mechanisms. The findings may inform early screening strategies and personalized interventions for individuals at higher risk of YOCRC.

Plain language summary

Colorectal cancer (CRC) is becoming more common among young adults under 50 years old around the world. This increase has been happening since the 1990s, affecting people born in the 1960s and later. In the USA alone, the number of young adults getting CRC has gone up from 8.6 to 13.1 cases per 100,000 people between 1992 and 2016, representing a 1% annual increase.

This rise in CRC among young adults is a big problem for doctors and public health experts because it's now the second most common cancer and the third leading cause of cancer deaths. Young people with CRC often have different symptoms and are frequently found at a later stage, which can make it harder to treat. We are unsure why more young adults are getting CRC, but we think it might be because of changes in lifestyle and environment. Things like not being active enough, being overweight, having diabetes, or using certain antibiotics might also play a part. But it's probably not just one thing causing this increase.

To address these gaps, we propose a comprehensive study using advanced sequencing technologies and machine learning techniques to find the molecular signatures of young onset CRC. We plan to take advantage of the Ontario Familial Colorectal Cancer Registry (OFCCR), a rich cohort with detailed personal and family health information and banked cancer specimens from Ontario residents who are diagnosed with colorectal cancer spanning over 2 decades. We plan to combine the DNA, RNA, and histology (how these cells look under the microscope) with each patient's history to identify known and new risk factors. By comparing our results with data from other studies, we hope to learn more about what is causing young people to get CRC. The goal is to be able to learn ways to prevent CRC among young adults and identify who should get early screening.