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Obesity and Gastrointestinal Cancer: A Life Course Perspective

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Gastrointestinal (GI) cancers account for about 27% of new cancer cases and 37% of cancer deaths globally,[1] with colorectal cancer (CRC) as the most common type in the United States.[2] Obesity (defined as body mass index [BMI] ≥30, where BMI is calculated as weight in kilograms divided by height in meters squared) has tripled in prevalence in the past several decades and is an established risk factor for multiple GI cancers, including esophageal adenocarcinoma, gastric cardia, liver, gallbladder, pancreatic, and colorectal cancer.[3] However, most epidemiologic studies examined BMI at one time point, missing the opportunity to delineate the contribution of adiposity throughout the life course. In this issue, Loomans-Kropp et al[4] explored the associations between BMI at early adulthood (aged 20 years), middle adulthood (aged 50 years), and later adulthood (aged ≥55 years), as well as BMI changes (from early or middle adulthood to later adulthood) with risk of CRC and non-CRC GI cancers (including esophageal, gastric, liver, and pancreatic cancer), using data from 135 161 participants aged 55 to 74 years at enrollment from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (1993-2014). In the baseline questionnaire, participants self-reported weight and height at 20 years of age, 50 years of age, and current weight and height. During up to 21 years of follow-up, 2803 incident CRC cases and 2285 non-CRC GI cancer cases occurred. Overall, overweight (BMI, 25.0-29.9) and obesity (BMI, ≥30) at each studied life stage was associated with subsequent risk of CRC and non-CRC GI cancers. Furthermore, maintaining overweight or obese BMI or increasing BMI to overweight or obese in later adulthood was also associated with increased CRC and non-CRC GI cancer risk.

The findings by Loomans-Kropp et al[4] provide relatively consistent messaging that overweight or obesity from early to later adulthood as well as BMI increases throughout adulthood were associated with increased risk of GI cancers, especially CRC. Such important findings highlight the unmet need to identify the critical time window linking adiposity and GI cancer. In addition to adulthood BMI trajectory and weight changes, there is a growing interest and unmet need in understanding the role of childhood and maternal adiposity in subsequent GI cancer risk, due to the rising incidence of several GI cancers (colorectal, gallbladder, pancreatic, and gastric noncardia cancer) in adults aged younger than 50 or 55 years[5] and the long induction period of carcinogenesis. However, to date, studies are limited with mixed findings and limited samples size, in part due to the lack of large-scale cohorts and clinical data with extended follow-up and repeated weight and/or BMI measurements across lifespan. Equally important, the associations between obesity throughout the life course with GI cancer risk among people from minoritized racial and ethnic groups have not been well studied.

Despite increasing recognition of health consequences associated with obesity beginning early in life, effective interventions are thus far limited. Lifestyle changes that include diet, physical activity, and behavior therapy remain the mainstay. Although newer antiobesity medications (eg, glucagon-like peptide-1 receptor antagonist) and diabetes medications (eg, sodium-glucose cotransporter-2 inhibitors) are more effective in inducing rapid weight loss, their long-term effect on cancer risk requires further evaluation. To date, bariatric surgery is the most effective strategy to achieve substantial initial and sustained weight loss among individuals with morbid obesity. Recent studies have also demonstrated the potential for bariatric surgery to reduce the risk of certain obesity-related cancers, with consistent benefits observed for breast cancer and emerging data in liver, colorectal, and esophageal cancer.[6] However, further research is warranted to determine which

specific bariatric surgery procedures are most effective for reducing risk of each type of obesity-related cancer and whether these benefits are mediated primarily through weight loss or additional surgery-specific mechanisms.

The development of effective, precision-based cancer prevention strategies in patients with overweight or obesity requires better understanding of the causative mechanisms linking obesity to cancer. Although alterations in insulin signaling, such as hyperinsulinemia and insulin resistance, and inflammation mediated by adipose tissue and gut microbiota have been increasingly recognized as crucial factors,[7] many questions remain unaddressed. To delineate the effect of age of weight gain and/or loss and cumulative exposures to adiposity on GI cancer and obesity-related cancers, we need transformative epidemiologic and mechanistic studies, involving comprehensive, longitudinal characterization of obesity throughout the lifespan complemented with deeper molecular profiling of malignant tumors, precursors, as well as normal tissues and biospecimens. It is also worth noting that the predictive value of obesity of a particular type of cancer is low. Therefore, precision-based risk stratification strategies that incorporate additional risk factors and/or biomarkers are essential before implementing targeted cancer prevention strategies among individuals with overweight or obesity.

Finally, as we continue to investigate precision-based interventions to intercept the link between obesity and cancer, it is imperative to reiterate the importance of maintaining a healthy weight and lifestyle from an early age and incorporate it widely into cancer prevention strategies at all levels with immediate implementation.

ARTICLE INFORMATION

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