Editorial

Could "Eating Behavior" be a novel lifestyle factor that modulates risk of gastrointestinal cancers?

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Lifestyle factors are important risk modulators of chronic diseases such as gastrointestinal (GI) cancer. The role of diet, specifically, has been studied for decades, and our knowledge on its impact continues to grow. For instance, it is well established that consumption of diets high in red and preserved meat and low in fruits and vegetables increases the risk of developing a variety of digestive system cancers. However, while different types of diets have been widely investigated in epidemiological studies regarding the risk of GI cancers, the effects of timing and patterns of eating have not yet been thoroughly explored.

Zhang *et al.* recently published a study (1) in *The American Journal of Clinical Nutrition* exploring the potential association between unrestrained eating behavior and the development of digestive system cancers. They analyzed data from the Nurses' Health Study, a large prospective cohort study with bi- and quadrennial questionnaire responses from US female nurses regarding medical history, diet, physical activity, and more. "Unrestrained eating behavior" was defined if subjects stated that they either ate anything at any time or did not pay a great deal of attention to changes in their figure. Outcomes included a variety of digestive system cancers. Patients were followed until report of any cancer diagnosis, follow-up completion or loss, or death.

The authors found that those who endorsed unrestrained eating behavior had a significantly increased risk of overall digestive system cancer. Upon further analysis by individual types of GI tract cancers, unrestrained eating led to an elevated risk of several types of upper GI cancers as well as colorectal cancer, a disease closely linked to lifestyle and diet (2,3). The results did not significantly change after adjusting for relevant variables, such as meal frequency, socioeconomic status, and history of depression.

Although the findings were not based on a systematic questionnaire to capture meal timing pattern, there are several strengths to the study that still make the findings of this paper robust. The prospective design and high follow-up rates of the questionnaires help minimize recall bias. The database provided the authors a very large sample size of tens of thousands of participants to analyze as well as extensive patient information that allowed them to control for a wide range of potentially confounding variables. Furthermore, to investigate reverse causation, they performed latency analysis, which did not significantly alter most of the results.

The discoveries of this study supplement growing evidence of the impact of time and pattern of eating on disease pathogenesis (4-8). How is food timing linked to clinical outcomes including GI carcinogenesis? One such explanation involves dyssynchrony between central and peripheral circadian rhythms. While the light/dark cycle regulates the central circadian clock, the timing of meals contributes to the regulation of circadian rhythms in peripheral tissues, particularly the GI tract. Recently, we showed that eating close to or during physiologic rest time disrupts circadian rhythms in mice by causing central-peripheral dyssynchrony. This circadian dyssynchrony, when

combined with another risk factor for colorectal cancer (i.e., alcohol), predisposed the polyp-prone animals to increased intestinal inflammation and colorectal tumor formation (9). These results are consistent with the established role of the circadian clock in regulating several pathways, including those involved in metabolic and immune function as well as carcinogenesis (7,10,11).

Mechanistically, circadian dyssynchrony impinges on the host pathways at least in part via alterations in the GI microbiome, also known as dysbiosis. Dysbiosis is characterized by disruption of the normal gut flora including increased relative abundance of pro-inflammatory tumor-associated bacteria, such as those from the Turcibacteraceae family, and a decreased abundance of protective bacteria such as those that contribute to the gut barrier function via production of short-chain fatty acids (SCFAs) including butyrate. Butyrate is an SCFA with known anti-tumor properties, and reduced butyrate production has been associated with intestinal barrier dysfunction, systemic inflammation, and alterations in metabolism (5,9). The link between dysbiosis and circadian dyssynchrony in the setting of eating pattern is particularly noteworthy, as it opens up opportunities for intervention. For example, we have shown that use of prebiotics that increase the levels of SCFA-producing bacteria and SCFA metabolites could ameliorate the burden of polyps in mouse models of colorectal cancer and partially offset the effects of abnormal food timing combined with alcohol (9,12).

In summary, the study by Zhang *et al.* emphasizes the role of eating behaviors, an unexplored lifestyle factor on the risk of digestive system cancers, including colorectal cancer. This study adds to an evolving body of work exploring the impact of disordered dietary habits on the formation of GI cancers and possesses important clinical implications. These findings suggest that, in addition to other well-established risk factors such as family history, obesity, and alcohol use, irregular or abnormal timing of meals deserves consideration as a potentially significant component when attempting to identify patients at high risk for developing GI cancers. To establish the link between eating behavioral phenotypes and several disease pathologies, we need to design screening tools and questionnaires to capture food timing and circadian phenotyping accurately and quickly at population base levels. Our group has contributed to this domain by developing and using screener food timing tools that are validated against standard food and circadian questionnaires (4,13). Eating time and behavior as a novel risk factor for GI cancers can bring prospects of implementing circadian-directed interventions, such as limiting food intake to daylight hours, to help optimize circadian homeostasis and prevent cancer formation. Future well-designed longitudinal cohort studies are needed to establish the role of eating behavior and its possible interaction with other known lifestyle associated risk factors on developing chronic diseases including GI cancers.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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