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The influence of dietary sugar intake on colorectal cancer

Yi Jing

Southwest Medical University, 646099 No. 319, Section 3, Zhongshan Road, Luzhou City, Sichuan Province, China

844224110@qq.com

Abstract. Research Question: This study aims to investigate the consequences of daily sugar intake on human health, particularly focusing on its role in the development of colorectal cancer. The research question explores the intricate mechanisms linking elevated sugar consumption to colorectal cancer and aims to understand the diverse dietary regimens' influence on this association. **Methods:** A comprehensive analysis was conducted to examine the impact of persistent, elevated sugar consumption on the integrity of the intestinal tract and its correlation with colorectal cancer. Various dietary regimens, characterized by different sugar types and quantities, were studied to understand their role in exacerbating the likelihood of developing colorectal cancer. Detailed investigations were carried out to unravel the underlying mechanisms, including insulin resistance, systemic cellular inflammatory responses, and the shift in colonic biological milieu. Inflammatory mediators and specific pro-inflammatory cytokines were analysed in different tissue compartments to comprehend the complex interplay leading to compromised intestinal barrier integrity and increased susceptibility to colorectal cancer. **Conclusion:** Our study reveals compelling evidence linking high-sugar diets to the development of colorectal cancer. Elevated sugar consumption disrupts the integrity of the intestinal tract, primarily through insulin resistance and systemic cellular inflammatory responses. This disruption leads to an upsurge in inflammatory mediators and specific pro-inflammatory cytokines within various tissue compartments. Consequently, the compromised intestinal barrier loses its ability to prevent the infiltration of pathogenic microorganisms, significantly elevating the risk of colorectal cancer. The diverse range of dietary regimens further complicates this association, highlighting the need for comprehensive research in understanding the intricate role of dietary factors in colorectal cancer.

Keywords: Sugar, Inflammation, Insulin Resistance, Colorectal Cancer

1. Introduction

Cancer stands as a formidable adversary, maintaining its position as the leading cause of global mortality [1, 2]. Within this expansive realm of malignancy, colorectal cancer stands out with its commendable early postoperative survival rate and the potential for prevention [3, 4]. While the initial postoperative phase boasts a remarkable 90% survival rate, once the disease progresses to its middle and late stages, the grim statistics tell a different story, with recurrence and mortality rates soaring beyond 50%. Thus, the importance of vigilant attention and proactive measures in addressing colorectal cancer cannot be overstated. Over the past six decades, Norway has witnessed a notable surge in the incidence of colorectal cancer. Among Norwegian women, the incidence rate has surged from a modest 9.9 cases per

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100,000 in the years 1955-1959 to a concerning 52.5 cases per 100,000 during the period spanning 2011-2015. This alarming increase finds a significant correlation with the prevalence of high lactose diets among the Norwegian population [5, 6]. Notably, factors such as diet-induced obesity, which is exacerbated by these high-lactose dietary practices, have been identified as significant contributors to the onset of colorectal cancer [7]. High sugar diets present another facet of dietary influence, as they have been linked to the development of insulin resistance, consequently leading to elevated levels of insulin and insulin-like growth factors. These hormonal shifts potentially serve as catalysts in the development of colorectal cancer [8]. The energetic demands of cancer cells, necessitating a substantial supply of energy, intertwine intimately with our daily sugar intake. In the context of populations with high-sugar diets, the escalation in the number of colorectal cancer cases and incidence rates has prompted a growing body of research indicating that dietary sugar plays a direct role in amplifying the occurrence of colorectal tumors. A pivotal report from the Nurses' Health Study in the United States, conducted over the span of three decades (1984-2014), shed light on this matter. Among the 2,733 confirmed colorectal cancer patients who participated, a disheartening 901 individuals succumbed to colorectal cancer. In this cohort, a discernible and statistically significant positive correlation emerged between dietary sugar intake and both colorectal cancer mortality and incidence. This finding underscores the importance of understanding the intricate interplay between dietary factors, especially sugar consumption, and the development of colorectal cancer [9, 10].

2. Classification of Sugars

In the realm of dietary sugars, a fundamental classification emerges, encompassing three primary categories: monosaccharides, disaccharides, and polysaccharides. These categories offer critical insights into how these sugars interact with the human body, particularly with regard to their digestion and absorption.

Glucose, a monosaccharide, holds a unique status in the world of dietary sugars. It stands as a sugar that the human body can promptly and directly absorb, making it readily available for cellular energy production [11]. In contrast, disaccharides such as sucrose and lactose present a more intricate journey within the digestive system, requiring enzymatic breakdown before their constituent monosaccharides, fructose, and glucose, can be effectively absorbed and utilized.

Sucrose, a prominent disaccharide, constitutes a combination of fructose and glucose. Importantly, the digestion, absorption, and metabolic pathways for these two sugar components diverge notably from one another. This divergence in metabolic fates introduces a layer of complexity when considering the physiological responses to various dietary sugars [12].

Given the diverse dietary practices across populations, it is crucial to recognize that distinct types of sugars are consumed in varying proportions. These dietary variations in sugar types have the potential to exert differing effects on the human body, which necessitates in-depth investigation. To comprehensively grasp the implications of these variations, further research is indispensable in elucidating how different sugar types may contribute to the complex interplay between diet and colorectal cancer. By investigating the intricate relationship between sugar classification and colorectal cancer risk, we can unravel essential insights that may inform preventive strategies and dietary recommendations [13].

2.1. Total Sugar Intake

The intricate relationship between total sugar intake and cancer risk has been a subject of extensive investigation. A notable contribution to this field comes from a meta-analysis conducted by Debras and colleagues, which analyzed data from the NutriNet-Santé cohort spanning the years 2009 to 2019. Their research scrutinized the association between total sugar intake, various categories of added sugar, and dietary sources of sugar with the risk of cancer. This comprehensive analysis unearthed compelling findings. It revealed that moderate elevations in total sugar intake were indeed linked to an overall escalation in cancer risk. However, the magnitude of this risk varied based on whether the increased sugar intake was derived from total sugar or added sugar alone. Specifically, heightened total sugar

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intake, as opposed to an exclusive focus on added sugar, was found to be modestly associated with an elevated overall risk of cancer (Hazard Ratio (HR) for Q4 compared to Q1: 1.17; 95% Confidence Interval (CI): 1.00, 1.37). This nuance underscores the importance of distinguishing between the sources of sugar when evaluating their impact on cancer risk [14].

The impact of sugar intake, particularly concerning its association with colorectal cancer, is of significant interest. Colorectal cancer incidence varies notably among populations characterized by high sugar consumption in their daily diets, and this variability is often shaped by ethnic factors. Epidemiological research consistently underscores that increased consumption of whole-grain foods, fruits, vegetables, and dairy products is frequently linked to a reduced risk of developing colorectal cancer. Conversely, high consumption of other fruits and added sugars among African Americans has been strongly correlated with a substantial increase in their susceptibility to colorectal cancer.

Conversely, the dietary patterns of white Americans, characterized by the inclusion of vegetables, fish, poultry, fruit, and whole-grain dairy products, demonstrate a significant reduction in the risk of developing colorectal cancer. It is evident that dietary disparities influenced by cultural and geographical factors are pivotal in shaping the profiles of colorectal cancer risk among different populations.

Moreover, the influence of sugar intake on colorectal cancer risk is not confined to a singular population, as exemplified by a study in Japan. In this research, a cohort of participants comprising 42,405 men and 48,600 women, aged between 45 and 74 years, was followed over a substantial period. Data gathered through a prospective study initiated by the Japan Public Health Center from 1995 to 1999 unveiled intriguing insights. For women, a notable positive correlation emerged between total sugar intake and the risk of colorectal cancer (Risk Ratio (RR) 1.75 [95% CI: 1.07–2.87] for Q1 vs. Q5; p for linear trend = 0.03). However, in the case of men, no statistically significant trend was observed. This gender-specific divergence raises the possibility that even in middle-aged Japanese adults, an underlying increase in colorectal cancer risk associated with higher total sugar intake cannot be categorically dismissed.

In summary, the intricate relationship between sugar consumption and colorectal cancer risk is multifaceted and influenced by numerous factors, encompassing the source of sugar, dietary patterns, and even gender disparities. These complexities underscore the necessity for additional research to refine our comprehension of the intricate interplay between sugar intake and the development of colorectal cancer. Such insights can ultimately pave the way for more precise recommendations pertaining to cancer prevention and dietary strategies [15].

2.2. Impact of Monosaccharides

Recent investigations into the landscape of early-onset colorectal cancer have unveiled an unsettling trend intimately tied to the dietary consumption of sugar, particularly focusing on the role of monosaccharides. These studies have delved into the nuanced connection between the ingestion of these simple sugars in early dietary habits and the subsequent development of colorectal cancer.

Within the domain of prospective clinical trials, a significant revelation emerged when examining patients with stage III colon cancer. The findings underscored that an elevated intake of monosaccharides was undeniably linked to a heightened risk of cancer recurrence and mortality. This insight suggests that the repercussions of sugar consumption extend beyond the realm of cancer development, reaching into the vital arena of cancer management, where aspects such as recurrence and survival assume paramount significance.

Expanding on these insights, a prospective cohort study targeting individuals with colon cancer brought forth compelling evidence. It elucidated the detrimental effects of consuming two or more servings of sugar-sweetened beverages on a daily basis. This level of consumption was associated with a substantial 75% increase in the risk of cancer recurrence and a pronounced escalation in the risk of mortality when compared to those who maintained a more conservative sugar-sweetened beverage intake (95% Confidence Interval: 1.04–2.68). This observation underscores the pivotal role of monosaccharides, particularly when delivered in the form of sugar-sweetened beverages, in influencing

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the trajectory of colorectal cancer. This influence is discernible in terms of both disease recurrence and patient survival.

In the context of early-onset colorectal cancer, these findings paint a vivid picture of the substantial impact of monosaccharide intake on disease outcomes. This places the spotlight firmly on the need for a comprehensive understanding of the role of sugar, especially in its simplest form, in colorectal cancer etiology and progression. Further research and in-depth exploration of these connections are imperative to guide interventions that can effectively mitigate the risks and consequences associated with the consumption of monosaccharides in the context of colorectal cancer [16].

2.3. Impact of Disaccharides

The intricate relationship between sugar intake and its influence on colorectal cancer risk delves further into the specific role of disaccharides, uncovering pronounced associations with sucrose, non-fruit-derived sugars, and added sugars. Among the array of disaccharides, lactose, composed of glucose and galactose, stands out alongside lactulose (comprising fructose and galactose) and lactitol (galactosyl-sorbitol), each potentially yielding similar effects within the lower small intestine. Underpinning the link between disaccharides and colorectal cancer risk are potential biological mechanisms that bear investigation. Notably, higher intake of disaccharides has been correlated with increased insulin secretion and heightened inflammatory responses. These physiological responses are considered integral in the path toward the development of colorectal cancer. An additional dimension to this narrative is the pertinence of circulating fasting insulin levels. Research reveals that elevated levels of fasting insulin are instrumental in elevating the risk of colorectal cancer, with a notable emphasis on its impact on male colorectal cancer risk concerning the rise in glycated hemoglobin concentration [7].

These discoveries serve as a catalyst for exploring potential preventative strategies in the context of colorectal cancer. Recent research suggests that interventions, whether they be pharmaceutical or lifestyle-oriented, directed at lowering circulating insulin levels, may hold promise in the prevention of colorectal tumors. This emphasizes the potential utility of insulin as a modifiable factor in reducing the risk of colorectal cancer. The influence of disaccharides extends far beyond the cellular level and reaches into the intricate ecosystem of the colorectal microbiota.

Alterations within this microbial community have been observed in response to disaccharide consumption, while the overall equilibrium between aerobic and anaerobic bacteria remains largely unaffected [17, 18]. Notably, in germ-free rats, the effects induced by lactulose are absent, signifying the pivotal role of the microbiota in mediating the connection between disaccharides and colorectal cancer risk. The therapeutic potential of this microbial influence has also been explored, with the administration of encapsulated lactobacillus strains to individuals with hepatic encephalopathy demonstrating therapeutic effects. This further substantiates the intricate interplay between disaccharides, the microbiota, and specific disease outcomes.

Within this framework, it becomes increasingly evident that disaccharides hold significant relevance in the etiology and progression of colorectal cancer. Nevertheless, the intricacies of this relationship underscore the imperative for comprehensive research to unveil the mechanisms underpinning the role of disaccharides in colorectal cancer. In summary, a concise overview of a prospective cohort research indicates that the consumption of sugar-sweetened carbonated beverages does not yield a statistically significant increase in the risk of colorectal cancer (95% Confidence Interval: 0.66–1.32). This highlights the critical need for further investigation and a more profound comprehension of the mechanisms through which disaccharides exert their influence on colorectal cancer [19].

3. Results

3.1. Insulin Resistance in CRC

The implications of sugar-induced insulin resistance in the context of colorectal cancer are multifaceted, as underscored by the research conducted by Hamid Farahani in Norway. This study delved into the plasma levels of insulin and resistance, providing critical insights into their role in colorectal cancer

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(CRC). Notably, the Homeostatic Model Assessment of insulin resistance revealed a substantial disparity between CRC cases and the control group, with values significantly higher in CRC cases (1.8 ± 0.4) compared to the control group (1.4 ± 0.3), emphasizing the relevance of insulin resistance in the disease's pathophysiology ($P < 0.001$). Furthermore, when scrutinizing CRC cases by tumor location, the findings became even more compelling. Higher levels of resistance and insulin were observed in colorectal cancer cases, with HOMA-IR significantly surpassing that of the control group (resistance: 5.9 ± 1.2 vs. 5.4 ± 1.3, $P = 0.043$; insulin: 5.9 ± 1.2 vs. 5.4 ± 1.3, $P = 0.039$; HOMA-IR: 1.9 ± 0.4 vs. 1.3 ± 0.3, $P < 0.001$). This nuanced stratification further elucidated the role of insulin resistance in different anatomical contexts within the colorectal region, underscoring its significance in CRC pathogenesis. An intriguing facet of this study was the observed positive correlation between insulin resistance and insulin levels, a relationship found in both the control group ($r = 0.737$, $P < 0.001$) and colorectal cancer cases ($r = 0.881$, $P < 0.001$). These correlations suggest the intricate interplay between insulin and resistance and their shared influence in colorectal cancer [20].

The epidemiological context of colorectal cancer reveals notable trends, particularly evident in the case of Finland, where the incidence of colorectal cancer has more than doubled since the 1950s. This increase has led to a significant rise in cases, with dietary and modifiable factors contributing to as much as 90% of these instances [21]. Of particular interest is the role of high insulin levels, which have been associated with the activation of insulin-like growth factor 1 (IGF-1) receptors, thereby enhancing the potential for carcinogenesis by inhibiting apoptosis [22]. Laura A. Colangelo's extensive research extended this investigation, utilizing data derived from a survey encompassing 191,126 men and 20,433 women, excluding diabetic patients. Among this cohort, there were 433 recorded cases of colorectal cancer-related deaths among men and 149 cases among women.

The examination of risk factors linked to insulin resistance syndrome yielded a relative risk (RR) that presented compelling evidence. Men with at least three of the four risk factors - being in the PLG gender-specific highest quartile, having elevated systolic blood pressure, a high body mass index, or an increased resting heart rate - exhibited a noteworthy RR of 1.67 (95% Confidence Intervals (CI): 1.04-2.70) compared to those not in the upper quartile for these factors. In the case of women, the RR was 1.29 (95% CI: 0.70-2.37). Importantly, this association held consistent for both men and women, with a RR of 1.50 (95% CI: 1.03-2.19). These findings underline the existence of a moderate connection between PLG and insulin resistance syndrome and colorectal cancer mortality, offering substantial support for the insulin hypothesis.

In conclusion, the complex interplay between insulin resistance, sugar-induced factors, and colorectal cancer unveils a multifaceted landscape. The significance of these findings prompts further exploration to understand the intricate mechanisms underpinning the role of insulin resistance in colorectal cancer etiology and progression [23].

3.2. The Impact of Inflammation on CRC

The intricate relationship between inflammation and colorectal cancer (CRC) unfolds as a pivotal determinant in both disease onset and survival [24]. The interconnectedness of local and systemic inflammatory responses emerges as an influential and independent predictor of colorectal cancer and its ultimate prognosis. Diet plays a pivotal role in shaping this intricate relationship. Different diets have the power to significantly alter the composition of the gut microbiome. Notably, excessive consumption of sucrose appears to exert a more profound impact on metabolic changes, while fructose takes center stage in inducing intestinal barrier dysfunction and inciting subclinical inflammation. Interestingly, the absorption of sucrose serves to enhance the bioavailability of fructose, leading to metabolic outcomes like obesity and potentially sugar addiction. The increasing intake of various sugar types contributes to the development of chronic inflammation within the intestinal environment [25].

In a comprehensive report by Sergei I. Grivennikov, the multifaceted roles of immune cells, cytokines, and other immune mediators come to the fore, illustrating their involvement in nearly all stages of colorectal tumor development, spanning tumorigenesis, promotion, progression, and even metastasis [26]. For an extended period, a high sugar intake has been identified as carrying a notable risk for

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inflammatory bowel disease, marking a critical connection between dietary sugars and intestinal inflammation [27].

Excessive sugar consumption exerts a deleterious impact by disrupting metabolic processes, giving rise to an increase in inflammatory mediators and specific pro-inflammatory cytokines across various tissues. This disruption sets the stage for the emergence of low-grade chronic inflammation. In parallel, elevated fructose intake exacerbates this scenario, as it heightens intestinal permeability, facilitating the release of inflammatory factors into the liver. This, in turn, triggers elevated levels of liver and systemic inflammation [28, 29].

A crucial consequence of high sugar intake is the reduction in microbial diversity within the gut microbiome. This dietary effect leads to a depletion of short-chain fatty acids (SCFAs) within the intestinal lumen. SCFAs play a pivotal role in shaping the recruitment of regulatory T cells and influencing the antimicrobial activity of macrophages, both of which contribute to the overall functionality of the mucosal immune system [30].

Central to this intricate cascade of events is the integrity of the intestinal barrier. When the intestinal barrier becomes compromised, its ability to ward off the invasion of pathogenic microorganisms is compromised. This breach paves the way for the translocation of substances like lipopolysaccharides (LPS) originating from Escherichia coli. These LPS and analogous molecules activate specific receptors, such as Toll-like receptor 4 (TLR4), thereby triggering downstream Nuclear factor-kappa B signaling pathways. The outcome is the induction of heightened levels of inflammatory factors, including IL-1β, TNF-α, and IL-6, accompanied by an increase in neutrophil infiltration. These collective events contribute to the potentiation of colorectal cancer, with more severe manifestations stemming from this chain of inflammatory events [31].

In summary, the intricate interplay between sugar consumption, inflammation, and colorectal cancer is an area of paramount importance. These multifaceted connections demand in-depth research and investigation to illuminate the underlying mechanisms. Understanding this interplay is vital in the context of developing preventive strategies and interventions that can effectively curb the impact of sugar-induced inflammation on colorectal cancer [32].

3.3. The Impact of BMI on CRC

Amidst global epidemics of obesity and cardiovascular diseases, the issue of high dietary sugar intake emerges as a prominent concern, further compounding the perils of excessive sugar consumption. This concern is underscored by the fact that, according to the 2005 U.S. Dietary Guidelines, the consumption of added sugars significantly surpasses recommended limits for discretionary calorie intake, irrespective of energy requirements. A stark illustration of this is seen in the period between 2001 and 2004, when the average daily intake of added sugars in the United States reached a staggering 22.2 teaspoons per day, equating to 355 additional calories daily. This marked increase is part of a more substantial trend that unfolded from 1970 to 2005, during which the average annual availability of sugars and added sugars surged by 19%, contributing an extra 76 calories to the daily energy intake of the average American [33].

Amidst these shifts in dietary patterns, the association between Body Mass Index (BMI) and sugar-induced obesity takes on significant importance, given its profound implications for the risk of colorectal cancer development. An extensive study conducted by the Department of Surgery at Erlangen University Hospital meticulously examined the survival rates of 612 patients diagnosed and treated for colorectal cancer between 2003 and 2010. The findings are quite revealing, as they indicate that patients classified as having obesity class II or higher (BMI ≥ 35 kg/m2, n = 25) and those falling into the underweight category (BMI < 18.5 kg/m2, n = 5) experienced reduced overall survival (hazard ratio (HR) = 1.6; 95% confidence interval (CI) 0.9–2.7) and a higher incidence of distant metastases (HR = 1.7; 95% CI 0.9–3.3) in contrast to patients with normal body weight (BMI ranging from 18.5 to < 25 kg/m2, n = 209), those classified as overweight (BMI ranging from 25 to < 30 kg/m2, n = 257), or individuals in obesity class I (BMI ranging from 30 to < 35 kg/m2, n = 102).

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Notably, it's essential to emphasize that both underweight and overweight conditions were linked to decreased overall survival and elevated rates of distant metastasis among individuals diagnosed with colorectal cancer [34].

Moreover, gender disparities have a significant effect on the intricate relationship between Body Mass Index (BMI) and colorectal cancer. Data indicates that obese men exhibit a heightened risk of developing colorectal cancer in comparison to men with normal body weight. However, this association is less pronounced in women, with no significant correlation observed in obese women. This gender-specific variation in risk factors underscores the complexity of the interactions between BMI and colorectal cancer among different gender cohorts [35].

Epidemiological evidence consistently points to obesity being linked to a 30% to 70% increase in the risk of colorectal cancer in men, although this association is less uniform in women. Similar trends can be observed concerning colorectal adenomas, albeit with a less pronounced risk profile. It's worth noting that visceral fat, or abdominal obesity, appears to be of more significant concern than subcutaneous fat obesity. A mere 1 kg/m2 increase in BMI is associated with additional risk (hazard ratio 1.03). This manifestation underscores the importance of considering not only overall BMI but also the distribution of adipose tissue.

Importantly, it should be acknowledged that obesity may have consequences that extend beyond colorectal cancer risk. Indeed, obesity might be correlated with unfavorable cancer outcomes, as evidenced by higher rates of primary cancer recurrence and increased mortality. The intricate interplay of dietary sugar intake, BMI, and colorectal cancer risk underscores the necessity for comprehensive research endeavors to elucidate the underlying mechanisms. These insights are pivotal for the development of precisely targeted interventions and preventive strategies aimed at mitigating the multifaceted impacts of sugar-induced obesity on colorectal cancer.

4. Conclusion

In conclusion, this review reveals a discernible correlation between sugar consumption and the risk of colorectal cancer (CRC). Among various sugar types, sucrose, non-fruit-derived sugars, and added sugars stand out as having a more pronounced impact on CRC. It is worth noting that the current body of evidence linking sugar intake to CRC primarily relies on findings from case-control studies. The extent to which different populations in diverse geographic regions are influenced by dietary sugar intake exhibits variation. High-sugar diets appear to have a comparatively smaller impact on Japanese individuals, while they exert a more substantial effect on African Americans, closely linked to their dietary patterns.

This paper takes into consideration the influence of multiple factors such as obesity, high salt intake, sleep patterns, among others, in an effort to establish a connection between CRC and dietary sugar habits. The primary aim is to underscore the robust positive association between excessive sugar-rich diets and the occurrence of CRC. However, it is important to acknowledge that this association demonstrates subtle variations across different regions and among diverse ethnic groups due to variations in dietary cultures. In CRC cases attributed to high-sugar diets, factors like insulin resistance and systemic inflammatory responses are likely to play pivotal roles. Nevertheless, further experimental data is essential to conclusively establish the relationship between daily sugar intake in humans and CRC.

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