Exploring the nexus between obesity, metabolic syndrome, and colorectal cancer

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The increasing global prevalence of obesity and metabolic syndrome (MetS) is strongly associated with the incidence of colorectal cancer (CRC). Obesity and MetS detrimentally impact the treatment outcomes of CRC and share similar mechanisms that contribute to the development of CRC. Increased insulin resistance in patients with obesity is linked to CRC, and altered levels of sex hormones and adipokines affect cell growth and inflammation. Obesity and MetS also alter the gut microbiome. Bile acids, which are crucial for lipid metabolism, are elevated in patients with obesity. Moreover, specific bile acids are associated with colonic damage, inflammation, and the development of CRC. Obesity and MetS increase the risk of postoperative complications and affect the response to chemotherapy. The promotion of weight loss and the resolution of MetS can reduce the occurrence of CRC and increase treatment efficacy. Therefore, it is imperative to implement appropriate management strategies to address obesity and MetS with the aim of improving the prognosis and reducing the incidence of CRC. Moreover, additional research should be conducted to determine the optimal timing for tailored CRC screening in patients with obesity or MetS. In this review, we explore the impact of obesity and MetS on the development of CRC and examine potential strategies to mitigate CRC risk in individuals with obesity and MetS.

Keywords: Colorectal neoplasms; Metabolic syndrome; Obesity

Introduction

Colorectal cancer (CRC) ranked third among the most frequently diagnosed malignancy and second among the leading cause of cancer-related deaths globally in 2022 [1]. Approximately 60% to 65% of patients with CRC do not have a familial history of CRC or inherited genetic mutations that increase the risk of CRC. In these patients, CRC may be due to acquired somatic genetic and epigenetic abnormalities or is associated with modifiable risk factors, such as obesity, a Westernized diet, physical activity, alcohol consumption, and smoking. These modifiable risk factors contribute to sporadic CRC [2].

Globally, the prevalence of obesity increased four-fold among men and doubled among women between 1975 and 2016. During this period, the absolute number of adults with obesity soared nearly 7-fold, from 100 to 671 million [3]. The overall age-adjusted prevalence of obesity in the United States in 2014 was 37.7%, affecting 35.0% of men and 40.4% of women [4]. There was a noticeable linear increase in obesity prevalence among women over the previous decade, while the trend in men did not exhibit the
same pattern. Notably, obesity is three times more prevalent in the United States (37.7%) than in Europe (12.8%) [4]. The number of individuals with obesity in Korea also increased by 101.6% from 2017 to 2021 [5]. Obesity is defined by a body mass index (BMI) ≥30 kg/m², while overweight is defined by a BMI ≥25 kg/m². An increased waist circumference is defined as ≥90 cm for obese men and ≥80 cm for obese women. According to the guidelines provided by the World Health Organization, overweight is defined as having a BMI between 23–25 kg/m², and obesity is defined as having a BMI ≥25 kg/m² for patients of Asian-Pacific descent.

Comparable to the trend observed in obesity, the prevalence of metabolic syndrome (MetS) is also increasing. In the United States, the prevalence of MetS was notably high, reaching 32.8% for men and 36.6% for women among adults aged 20 years or older in 2012 [6]. In Korea, since the initiation of the Korea National Health and Nutrition Examination Survey, there has been an increase in MetS rates from 22.4% and 27.9% in men and women, respectively, in 1998. Subsequently, it rapidly rose from 29.0% in 2007 to 32.9% [7]. Other studies indicate a slight increase among men, from 27.9% in 2008 to 30.8% in 2013, while women displayed a stable trend, maintaining a rate of 26.4% from 2008 to 2013 [8].

Obesity is associated with MetS, which includes diabetes or glucose intolerance, hypertension (HTN), obesity, and dyslipidemia. It is also associated with irritable bowel syndrome, gastroesophageal reflux disease, and celiac disease [9-11]. Thirteen types of cancer, including CRC, have been associated with obesity or MetS [12]. Approximately two-thirds of individuals with MetS are considered obese; however, not all individuals with obesity experience poor health [11,13,14]. Furthermore, MetS and insulin resistance are closely related [15]. Insulin resistance has been hypothesized to play a role in the incidence of CRC via various pathways that contribute to the understanding of the intricate relationship between metabolic disorders and an increased risk of colon cancer.

This review discusses the effects of obesity and MetS on the development of CRC and explores strategies for reducing the risk of CRC in patients with obesity and MetS.

Epidemiological evidence substantiating an association between obesity, MetS, and CRC

Several studies and meta-analyses have reported data supporting the increased incidence of CRC in individuals with obesity. In a previous meta-analysis, as the BMI increased, the risk of CRC also increased, demonstrating a progressive trend with X values of 1.14 (95% confidence interval [CI], 1.06–1.23) for patients with a BMI <23.0 kg/m², 1.19 (95% CI, 1.13–1.25) for patients with a BMI of 23.0–24.9 kg/m², 1.24 (95% CI, 1.15–1.35) for patients with a BMI of 25.0–27.4 kg/m², and 1.41 (95% CI, 1.30–1.53) for patients with a BMI of 27.5–29.9 kg/m² [16]. Another meta-analysis reported a correlation between weight gain and an increased risk of CRC (relative risk [RR], 1.02 per 5 kg increase in weight; RR, 1.06 per 5 kg/m² increase in BMI; RR, 1.02 per 10 cm increase in waist circumference) [17].

While the parameters for defining obesity vary, recent research suggests that waist circumference is a superior predictive marker of advanced colorectal neoplasia compared to BMI [18]. This is because waist circumference more accurately reflects visceral obesity, which is considered the most carcinogenic type of obesity. In a sex-specific analysis, increased waist circumference was associated with an increased RR of CRC. Men and women with a larger waist circumference exhibited 1.477 times and 1.442 times higher RR, respectively, than that of patients with a smaller waist circumference [12,19].

Moreover, a population-based study examining the correlation between CRC and changes in obesity levels demonstrated that patients maintaining obesity exhibit a higher incidence of CRC than those transitioning from being obese to non-obese [20]. This suggests the continuous contribution of obesity to the development of CRC and emphasizes the lasting impact of obesity rather than the obesity status at the time of measurement.

MetS includes a cluster of clinical MetS that occur together, such as diabetes, glucose intolerance, HTN, obesity, and dyslipidemia. A lack of physical activity, persistent stress, an unbalanced diet, and lipodystrophy can increase the likelihood of developing MetS [21]. Epidemiological investigations have revealed a positive correlation between MetS, the components of MetS, and the risk of cancer including CRC [22,23]. Similar to obesity, MetS is correlated with the
onset of CRC (RR, 1.34; 95% CI, 1.24–1.44). The cumulative incidence of CRC increases with the diagnosis of conditions that meet the diagnostic criteria for MetS [24,25]. The risk of early-onset CRC (EOCRC) may vary depending on the presence or absence of MetS. In a prospective cohort including over 85,000 women, the risk of EOCR was increased with a multivariate RR of 1.93 (95% CI, 1.15–3.25) in women with obesity. Furthermore, a BMI >23 kg/m² at the age of 18 years independently increased the risk of EOCR (modified RR, 1.63; 95% CI 1.01–2.61) [26]. A case-control study reported that individuals with MetS had approximately 31% increased risk of EOCR compared to that of those without MetS. In a study conducted among women who received prenatal care in Oakland, California, between 1959 and 1966, involving a total of 18,751 live births from 14,507 mothers, it was found that maternal obesity (with BMI of ≥30 kg/m²) was associated with a 2.51-fold increase in the risk of CRC in offspring. Additionally, babies born with a weight exceeding 4,000 g showed a 1.95-fold increased risk of CRC [27].

The mechanisms through which obesity and contribution of MetS to CRC development

The mechanisms associated with obesity are likely similar to those of MetS. A positive correlation between obesity and MetS has been reported, linked to an increased incidence of CRC. Several mechanisms are involved in this process.

Adipose tissue includes insulin, insulin-like growth factor (IGF), adipokines, and several inflammatory cytokines including tumor necrosis factor-α, C-C motif chemokine ligand 2, and plasminogen activator inhibitor. These factors influence the secretion of various interleukins. An increased expression of leptin receptors in patients with CRC is associated with increased insulin resistance in patients with obesity [28,29]. Furthermore, alterations in sex hormone and adipokine levels can affect cell growth, inflammation, and other processes associated with cancer development [29,30]. Leptin acts on the hypothalamus to suppress appetite, promote energy consumption, and regulate eating behavior. Patients with obesity have higher serum leptin levels than do patients without obesity due to leptin resistance. Soluble leptin receptor (sOB-R) is a potential marker of leptin resistance and is deficient in patients with obesity. One study reported an inverse relationship between serum sOB-R levels and the risk of CRC [31]. Adiponectin, a hormone that regulates insulin sensitivity, is reduced in patients with obesity. In addition, adiponectin is involved in cell growth, survival, and protein synthesis. Several studies have reported an increased risk of CRC with decreased serum adiponectin levels [32,33].

Bile acids play a vital role in lipid metabolism and are involved in intestinal fat absorption. Total bile acid secretion is positively correlated with BMI in patients with obesity. While the total bile acid levels are slightly increased in patients with obesity, the levels of conjugated bile acids and deoxycholic acid (DCA), a secondary bile acid, are significantly increased in the plasma and liver of these patients. DCA is associated with cytotoxicity, damages colonic epithelial cells, stimulates inflammatory responses, induces the production of reactive oxygen species, promotes genomic instability, and contributes to the development of CRC through resistance to apoptosis [34,35]. Obesity and MetS induce changes in the gut microbiome, influencing these mechanisms. Insulin resistance is a pivotal mechanism in this context as it leads to hyperinsulinemia, subsequently activating the phosphoinositide 3-kinase/protein kinase B/mammalian target of the rapamycin signaling pathway in patients with CRC. This leads to increased IGF-1 levels and modified peroxisome proliferator-activated receptorγ (PPARγ) and nuclear factor kappa B (NF-κB) signaling, contributing to the development of CRC [36-38].

Correlation between obesity, MetS, treatment modalities, and CRC prognosis

Previous studies have reported that obesity affects the diagnosis and treatment of CRC. The precision of CRC staging can be compromised by the quantity of visceral adipose tissue. In a study involving 216 patients with CRC, computed tomography revealed mis-staging in 39% of cases [39]. Factors independent of each other associated with an increased probability of mis-staging encompassed reduced visceral adipose tissue (less than 122 cm², p<0.001) and a tumor located proximally (p=0.004). For individuals classified as obese, the accuracy of radiological evaluations for cancer staging might be compromised. Given the critical importance of accurate diagnosis in determining treatment
strategies, this can potentially impact the initial treatment plan for CRC in patients with obesity.

An increased incidence of postoperative complications, such as an increased conversion rate after initial laparoscopy, prolonged operative time, and postoperative morbidity, has been reported in patients with obesity undergoing colorectal surgery [40,41]. In a recent meta-analysis, BMI was identified as a contributing factor for anatomical leakage during CRC surgery [42]. In addition, the incidence of infection was higher in patients with obesity. According to a meta-analysis, patients with a BMI ≥30 kg/m² had more than twice the risk of surgical site infection compared to those with a BMI <30 kg/m² (odds ratio [OR], 2.13; 95% CI, 1.66–2.72; p<0.001). In addition, Asian patients with a BMI >25 kg/m² faced a 63% higher likelihood of surgical site infection compared to those with a BMI <25 kg/m² (OR, 1.63; 95% CI, 1.29–2.06; p<0.001) [43]. Similar findings have been reported in studies investigating the relationship between MetS and the adverse events following colon surgery. According to a prior meta-analysis, individuals with MetS exhibited a higher likelihood of experiencing severe complications compared to those without MetS (RR, 1.62; 95% CI, 1.01–2.59). Although not statistically significant, trends indicating an elevated risk for various complications were observed, including mortality (RR, 1.19; 95% CI, 1.00–1.43), and any complication (RR, 1.35; 95% CI, 0.91–2.00), anastomotic leakage (RR, 1.67; 95% CI, 0.47–5.93). Furthermore, preoperative hyperglycemia was linked to an increased risk of surgical site infection (RR, 1.35; 95% CI, 1.01–1.81) [44].

In addition to surgery, another treatment option for CRC is chemotherapy. Previous studies have reported that patients with obesity respond poorly to chemotherapy compared with patients with normal weight. First-line chemotherapy combined with bevacizumab resulted in a longer progression-free survival and more favorable 2-year survival rates in patients without obesity than in those with obesity [45]. Nevertheless, individuals categorized in the group with low visceral fat area displayed a median overall survival that was shorter compared to those in the high visceral fat area group. Additionally, a low visceral fat area was recognized as an independent predictive factor associated with enhanced overall survival [46]. The effects of obesity on chemotherapy outcomes remain controversial due to various factors that influence the assessment of chemotherapy effectiveness. Therefore, well-designed, prospective randomized studies are necessary.

A recent meta-analysis including 45 studies and 607,266 patients with stages I–IV CRC reported an increased incidence of CRC (OR, 1.27; 95% CI, 1.11–1.45) and overall mortality rate (OR, 1.20; 95% CI, 1.06–1.36) among individuals with obesity compared with that of those with normal weight [47]. This finding indicates a distinct role of obesity in determining the prognosis of patients.

MetS is associated with an unfavorable prognosis in patients with CRC. According to a recent meta-analysis, MetS has been linked to elevated all-cause mortality and mortality specifically related to CRC among CRC patients. Diabetes, considered as one component of MetS, has been individually associated with heightened overall mortality in CRC patients, alongside obesity. Moreover, an escalation in the number of metabolic risk factors correlates with an increased risk of mortality related to CRC [48]. It is widely acknowledged that obesity and MetS not only contribute to the onset of CRC but also exert an influence on the overall survival rate and play a crucial role in shaping the prognosis of patients with the disease.

Strategies to mitigate CRC risk

Obesity and MetS are clearly correlated with CRC. This can be used to develop strategies to prevent the development of CRC and improve patient prognosis. Some studies have explored the impact of weight loss on the risk of CRC. In a multicenter prospective cohort study, a decrease in BMI through weight loss was associated with a reduced risk of CRC (hazard ratio, 0.69; 95% CI, 0.52–0.92) [49]. In another study, post-menopausal women who intentionally lost weight showed a notable reduction in CRC risk, with a hazard ratio of 0.79 (95% CI, 0.63–0.99) [50].

This effect is also observed in patients who undergo bariatric surgery. In recent research, two studies investigated the incidence and mortality of CRC following bariatric surgery. Combining data from the seven largest studies involving 1.2 million patients with obesity, these meta-analyses revealed a substantial decrease in CRC risk among individuals who underwent bariatric surgery (RR, 0.73; 95% CI, 0.58–0.90 and RR, 0.64; 95% CI, 0.42–0.98) [51,52]. However, there are conflicting results, indicating the need for additional research to better CRC understand the effectiveness of bariatric surgery in preventing CRC [53].
A population-based study indicated that patients with resolved MetS exhibited a reduced incidence of CRC [54]. Nevertheless, no prospective study has specifically investigated the impact of changes in MetS status on CRC occurrence. Despite this, there is ample evidence supporting the idea that weight loss or the resolution of MetS contributes to a reduction in CRC incidence.

The risk of developing CRC tends to increase with age; however, it is noteworthy that approximately 10% of newly diagnosed cases are found in individuals younger than 50 years, a category termed EOCRC. The decline in CRC rates is believed to be attributed, in part, to an increased proportion of the population undergoing screening colonoscopies, leading to the removal of benign precancerous lesions. In contrast, there has been a noticeable increase in the incidence rate of CRC among individuals under the age of 50, known as EOCRC. Between 1988 and 2015, there was a 63% increase in the age-adjusted incidence of EOCRC in the United States, rising from 7.9 to 12.9 cases per 100,000 people [55]. Alongside the United States, multiple countries, including Australia, Canada, Brazil, Japan, China, and the United Kingdom, have exhibited elevated rates of EOCRC in recent decades [56]. Comparable outcomes were noted in a comprehensive systematic review that encompassed all studies examining trends in EOCRC incidence at the population level [57]. Recently, there has been a substantial rise in EOCRC cases in South Korea, leading to a change in the age distribution of diagnosed CRC [5,58]. In light of these circumstances, the US Preventive Services Task Force has lowered the screening age for CRC from 50 to 45 years [59]. The incidence of EOCRC is increasing, and obesity and MetS play a significant role in this increase. In a recent meta-analysis, it was noted that individuals with obesity exhibited an increased likelihood of EOCRC (RR, 1.54; 95% CI, 1.01–2.35), while those with hyperlipidemia, characterized by elevated levels of fat such as cholesterol and triglycerides in the blood, also showed a heightened risk (RR, 1.62; 95% CI, 1.22–2.13) [58].

Early CRC screening for individuals with obesity is a relevant consideration, although the optimal starting age remains uncertain. One study suggested that the most notable increase in CRC incidence among individuals with obesity in the last two decades occurred in the aged 25–29 years group [60]. Another study strongly recommended implementing routine CRC screening for those aged 40–49 years who are morbid obesity or belong to the average risk MetS population [61]. This recommendation is based on findings indicating a colorectal neoplasia rate of 35.6% in individuals aged ≥50 years and 22.1% in those aged 40–49 years (p=0.053). Additionally, advanced colorectal neoplasia rates were not significantly different between these age groups (8.4% in 40–49 years group, 9.6% in 50–65 years group; p=0.792). In another study, an analysis of individuals in whom colonic adenoma, a precursor lesion of CRC, was detected before the age of 50 years revealed a close association with obesity and MetS [62]. Till date, there have not been any recommendations regarding the optimal timing for personalized.

The current evidence pointing towards an increased occurrence of EOCRC or young-onset colorectal adenoma in individuals with obesity and MetS sets the groundwork for potential early CRC screening for this demographic in the future. These circumstances may also prompt the creation of tailored CRC screening tests. Consequently, there is a requirement for research into personalized CRC screening, taking into account factors like obesity and MetS. Furthermore, it is crucial to develop guidelines based on such data.

Conclusion

Recent studies have substantiated the close association between increased rates of obesity and MetS and an increased incidence of CRC. The metabolic state of patients with obesity or MetS increases the adverse effects of surgery and may affect the response to anticancer treatments. This also affects the prognosis of patients with CRC. Therefore, it is imperative to implement appropriate management strategies to address obesity and MetS, aiming to enhance the prognosis and reduce the incidence of CRC. Moreover, the optimal timing for tailored CRC screening in patients with obesity or MetS should be determined through additional research.

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