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The risk of colonic adenomas and colonic cancer in obesity

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Abstract

Increasing body fatness has been associated with an increased burden from colorectal cancer. An increased susceptibility spanning the entire continuum from precancerous adenomatous polyps to the development of colorectal cancer, poor outcome with treatment, and reduced survival when compared to those with normal body weight has been described. It is unknown which age period and which degree and duration of excess weight are associated with increased colorectal cancer risk. It is uncertain whether weight loss can reverse this risk. If it can, how long will the new lower or normal weight be maintained to effect enduring risk reduction? Furthermore, it is controversial whether the increased burden of colorectal cancer warrants earlier and/or more frequent screening for obese persons. This article reviews the relationship between obesity and colorectal neoplasia, explores the postulated mechanism of carcinogenesis, discusses interventions to reduce the burden of disease, and suggests future directions of research.

Keywords

Colorectal cancer; obesity; body mass index; adenomatous polyps; colonic neoplasm

A. Epidemiology of obesity and colorectal cancer

Obesity has been increasing at an alarming rate throughout the world (1–9). The prevalence of obesity is higher in developed countries (1–4). In developing countries, the prevalence of obesity is lower, but continues to rise as people adopt Western lifestyles (5–9). In the United States, approximately 35% of adults aged 20 years or older are obese (1). The epidemiology of obesity appears to align with the incidence of colorectal cancer (CRC). CRC is a very common cancer affecting 1.36 million persons worldwide (10). It is the third most common cancer in men with an estimated 746,000 cases annually and second most common cancer in women with an estimated 614,000 cases annually. CRC exhibits wide geographical variation

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with the highest rates in the developed countries such as the United States, Australia/New Zealand, and Europe, lower rates in Asia and the lowest rates in Western Africa (10). CRC is the third leading cause of cancer related death among both sexes in the United States (11).

Although, the ideal measurement of the degree of body fatness that correlates well with colorectal cancer risk is uncertain, the body mass index (BMI) which is defined as the weight in kilograms divided by the square of height in meters is the most widely studied metric. People with BMI less than 18.5 kg/m^2 are considered underweight, 18.5 to 25 kg/m^2 are normal, 25 to 30 kg/m^2 are overweight and 30 kg/m^2 and over are obese. Of note, some studies (especially in regions of the world with less prevalence of obesity) combine overweight and obese as ≥ 25 kg/m^2 in their analyses. Other measurements of obesity include the waist to hip ratio (WHR), waist circumference, visceral adipose tissue (VAT) and body surface area (BSA). All these measurements are based on anthropometric parameters of weight, height and waist circumference and have been used frequently to evaluate the association of obesity with colorectal neoplasia except BSA. BSA is sometimes considered to be a better indicator of metabolic mass than body weight because it may be less affected by abnormal adipose mass and it is used clinically to dose chemotherapeutic agents (12).

In many parts of the world, (particularly in the Western Hemisphere), there has been increasing efforts to increase CRC screening either as programmatic or opportunistic endeavors (13–16) and reduction in colorectal cancer burden has been reported (17). However, there is a growing concern that the gains of CRC screening may be offset by the growing obesity epidemic.

B. Pathophysiological link of obesity to colorectal neoplasia

Several postulations have been made regarding the underlying pathophysiological mechanisms of neoplasia risk with increasing fat mass. These have generally involved mechanisms related to insulin and insulin-like growth factor (IGF-I) signaling pathways, adipokines secretion, chronic low grade inflammation, metabolic syndrome and recently, gut microbiota (18–24). The role of micronutrients in the association between obesity and colorectal neoplasia is uncertain.

As fat mass increases, an individual will typically develop an increase in insulin secretion in order to maintain the body's metabolic functions. Therefore, obese subjects develop hyperinsulinemia that is independent of the development of diabetes mellitus (25). Insulin is an anabolic hormone with its direct effect on adipose tissue, muscle and liver. Studies that have explored the association between insulin and CRC have predominantly suggested increased risk of 20% to two-fold (26–29) but no association was found in a nested case-control study from Sweden (30). Similarly, increased association has been reported with IGF-I due to its promotion of proliferation and reduction in apoptosis and may be related to initiation rather than progression of the disease (31, 32).

Adipokines are hormones, cytokines and peptides produced by adipose tissue. Several studies have investigated the relationship between some of these factors and colorectal neoplasia, but the results have been inconsistent (33–45). In general, adiponectin level was

inversely associated with the risk of colorectal neoplasia (33–35), leptin with elevated risk (36–38), resistin and visfatin with increased risk of colorectal neoplasia (39–42) while other studies did not report such associations (43–45).

Metabolic syndrome comprises of hypertension, visceral (central) obesity, hypertriglyceridemia, low high density lipoprotein, or diabetes and has been associated with elevated risk of colorectal neoplasia with stronger association reported among men (46, 47). Finally, chronic subclinical inflammation and recently, gut microbiota, have been implicated in the development of obesity and in the development of colorectal neoplasia (48, 49)

C. Obesity and adenoma

Several studies have evaluated the association between the prevalence of colorectal adenoma and obesity and have generally reported an increased risk in both sexes with slightly stronger association among men (50–54). The increased risk has been noted among ethnically diverse population (53) and among obese but metabolically healthy individuals (54). Most studies evaluated this association using BMI. Other observational studies have examined this relationship using waist-hip circumference ratio (WHR) and in a meta-analysis of these studies, a similar association has been reported (55). The degree of visceral obesity using Computerized Tomography (CT) scan have also been studied and investigators have reported increased risk of adenoma (56, 57), but a small study with 54 case subjects and 50 controls in Turkey did not find an association (58). In summary, evidence suggests an increasing risk of adenoma with increasing obesity regardless of which common metric of obesity was used.

Other studies have evaluated the risk of adenoma recurrence following polypectomy (59–64). In the adenoma pooling project of eight completed studies with patient level data, Martinez et al. (59) reported an increased risk of adenoma recurrence (OR = 1.23; 95%CI: 1.08–1.41), but a non-statistically significant increased risk of advanced adenoma recurrence (OR = 1.13; 95%CI: 0.93–1.38) over a median follow-up of 47.2 months. Similarly, Jacobs et al. (60) reported an increased risk of adenoma recurrence over 3.1 years of follow-up among men (OR = 1.36; 95%CI: 1.01–1.83) without any association among women (OR = 0.90; 95%CI: 0.60–1.33). This was comparable to the report by Kitahara et al. (61) using data from the Prostate, Lung, Colorectal and Ovarian (PLCO) screening Trial. The authors found a borderline increased risk of adenoma recurrence among men (OR, 1.50; 95% CI, 0.98 to 2.30) but not among women. In another analysis of data pooled from seven studies, the authors reported an increased risk of adenoma recurrence in association with obesity among men (OR = 1.36; 95%CI: 1.17–1.58), but not among women (OR = 1.10; 95%CI: 0.89–1.37) (62). However, this increased risk was confined to the proximal colon ($P_{trend}<0.001$), but not distal colon ($P_{trend} = 0.85$). The increased risk in men was consistent, whether BMI, waist circumference or WHR was used as the measurement of obesity (63). Similarly, among participants in the Polyp Prevention Trial (PPT), obesity was associated with an increased risk of adenoma recurrence (RR = 1.19; 95%CI: 1.01–1.39) and advanced adenoma recurrence (RR = 1.62; 95%CI: 1.01–2.57) within 4 years of follow-up and the association was only seen among men (64).

An important question that often arises is whether weight loss can reduce the risk of adenoma recurrence among obese persons. Although clinicians often recommend weight loss and maintenance of healthy weight as an intervention to reduce the risk of colorectal adenoma and adenoma recurrence to their patients, there is little evidence for this recommendation. Few studies have evaluated the relationship between colorectal adenoma and weight change. In the multicenter multiethnic Insulin Resistance Atherosclerosis Study cohort, Sedjo et al. (65) reported that participants who gained weight (more than 4 pounds i.e. 1.81 Kg) over 5 years (OR = 2.30; 95%CI: 1.25–4.22) and over 10 years (OR = 2.12; 95%CI: 1.25–3.62) were more likely to have prevalent adenoma at colonoscopy performed at a mean age of 64 years. However, few participants lost weight over the study period and the data on weight loss was not presented. Among Japanese men, Kono et al. (66) reported an increased prevalence of adenoma among those who gained 6 Kg (13.2 pounds) up to 10 years prior to their colonoscopy. The authors suggested that weight gain in mid-life leading to abdominal obesity increases the risk of colon adenoma, but weight loss was not discussed in this study. In a retrospective study of average risk Japanese, Yamaji et al. (67) reported that weight loss of 5% or more over 1 year was associated with reduction in adenoma recurrence (OR = 0.47; 95% CI: 0.26 – 0.83). However, there was no increased risk of recurrence among subjects who gained 5% or more of their body weight over the same period. Conversely, there was no association between weight loss or gain of 5 pounds or more (2.27 Kg) over 4 years of follow-up among men and women participants in the Polyp Prevention Trial (64). In summary, obesity in adulthood is associated with an increased risk of adenoma prevalence and recurrence. However, it is unknown what duration of obesity increases the risk and it is uncertain whether short-term weight loss can reduce this risk. Nonetheless, maintenance of a normal weight has health benefits beyond cancer prevention and should be encouraged.

D. Obesity and colorectal cancer

Several studies have reported an increased risk of colorectal cancer with obesity (68–75). An increased progression from adenoma to cancer may be a contributing factor. Almendingen et al. (76) reported that obesity as determined by increasing triceps skin fold thickness, percentage total body fat as measured with Futrex 5000 or BMI was associated with growth of adenoma that were left in situ for 3 years. The increased risk of colon cancer is somewhat consistent across studies regardless of the measure of obesity used. It is noteworthy that in Asia where lower cut off points are sometimes used (e.g. overweight = BMI 24.0 – 27.9 kg/m^2 and obese = BMI ≥28.0 kg/m^2), an increased burden of colon cancer was still noted in both overweight and obese categories (77). Studies have suggested that the risk is stronger among men (71, 72), the risk is mainly related to colonic cancer and less to rectal cancer, and obesity may be associated with advanced stages (stage 3 or stage 4 diseases) at presentation (73). Prediagnosis BMI and not postdiagnosis BMI was associated with an increased mortality among the Cancer Prevention Study-II Nutrition Cohort (78) but among participants in the Women's Health Initiative study, neither prediagnosis nor postdiagnosis BMI was associated with CRC mortality (79). Rather, those reporting prediagnosis recreational physical activity levels of ≥18 metabolic equivalent task (MET) - hours per week (MET-h/week) had significantly lower colorectal cancer-specific mortality (hazard

ratio (HR) = 0.68; 95%CI: 0.41–1.13) and all-cause mortality (HR = 0.63; 95 % CI: 0.42–0.96). Similar inverse relationship was noted for postdiagnosis recreational physical activity.

Surgery is the most definitive treatment modality for CRC with a potential for cure. However, obesity has been associated with poor surgical outcomes (80–82). Longer operating times, more blood loss, wound complications such as wound dehiscence and poor wound healing and anastomotic leakage have been reported from both laparoscopic and open procedures.

Obesity was associated with poorer outcome after CRC diagnosis among participants with stage II and stage III disease enrolled in the National Surgical Adjuvant Breast and Bowel Project randomized trials and in the Adjuvant Colon Cancer Endpoints (ACCENT) database (83, 84). These findings may be related to challenges in determining the appropriate dose of chemotherapy to administer to obese patients as clinicians struggle to achieve the same maximum dose-intensity in the obese by balancing the risk of underdosing with the risk of toxicity. Recent guidelines encourage the use of full weight–based calculation of BSA to determine optimal doses rather than using a reduced weight metric or dose capping (12). However, other strategies such as titrating an individual patient's dose to a maximum tolerated exposure (MTE) by means of therapeutic drug monitoring have been proposed (85).

Although it is intuitive to encourage adult obese persons to lose weight as a strategy to reduce their risk of CRC, it is uncertain if such risk reduction is possible and how long the new weight has to be maintained for the risk reduction to be accomplished. Steins Bisschop et al. (86) reported that adulthood BMI and moderate weight gain was associated with an increased risk of colon cancer, but weight loss had no effect on colon or rectal cancer. Furthermore, Meyerhardt et al. (87) reported that neither BMI nor weight change (loss or gain) during the time period between chemotherapy and 6 months after completion of therapy was significantly associated with an increased risk of cancer recurrence or death in patients with stage III colon cancer among patients in Cancer and Leukemia Group B 89803.

In summary, it is unknown if there is a critical age at which obesity confers increased susceptibility to colorectal carcinogenesis, but it appears that obesity in adulthood increases the risk and short-term weight loss may not be sufficient to reverse this susceptibility. Recreational physical activities may reduce this risk to an unknown degree. Therefore, maintenance of normal weight at adulthood is important and should be encouraged for all.

Future directions

As the incidence of obesity continues to increase, there are some aspects of the association between obesity and colon cancer that warrant further investigation.

Measurement of obesity—Although it is fairly well established that obesity is associated with an increased burden from colorectal cancer, it is controversial what measurement of obesity correlates best with the risk. Most studies used BMI, waist circumference or WHR in their evaluations. Another modality of measuring body fat mass is the use of Bioelectrical Impedance Analysis (BIA) from electronic scales. This is readily available and relatively

inexpensive, but it is unknown how well this modality of measurement correlates with important estimate of visceral fat distribution. Although Frantz et al. (88) did not find an association between the percent body fat measured by BIA and prevalence of adenoma, more studies on this technology is warranted. Also, obesity is widely considered to be a metabolic disease. BSA is often regarded as a better indicator of metabolic mass and it is already being used clinically to determine the dosage of chemotherapeutic agents (12). Future studies should evaluate this metric in the burden of colorectal cancer.

The role of colon cancer screening—Obesity is recognized as a risk factor for CRC, but there is no CRC screening guideline that recommends earlier or more frequent evaluations for obese persons (89). The increased risk of colorectal neoplasia associated with obesity is probably not related to lower screening rates (90) or inferior quality of screening as measured by inadequate bowel preparation or incomplete examinations from screening endoscopy (91–93). Studies evaluating whether CRC screening will eliminate the increased risk of CRC associated with obesity are needed.

The role of weight loss—Maintenance of normal weight is good for overall well-being. However, there is a lack of robust evidence that weight loss in adult obese patients substantially reduces the risk of colon cancer. It is possible that the weight loss achieved in these studies were too small for any meaningful metabolic changes or the duration of the new weights were too short for a natural physiologic recalibration of risk to be effected. Furthermore, majority of these studies did not evaluate whether the weight loss achieved by the subjects normalize their BMI. In recent times, bariatric surgery has provided an opportunity for substantial and enduring weight loss for obese patients. Although initial studies demonstrated mortality reduction, in part due to less occurrence of cancer in general (94, 95), no significant reduction in colon cancer specific risk was demonstrated among bariatric surgery patients (96, 97). This may be due to a relatively short duration of follow-up. Nonetheless, this population represents a very important group to study in assessing the effect of weight loss in adulthood on colon cancer burden. Therefore, further studies among this population are warranted.

Summary

Obesity is an established risk factor for colorectal adenoma and cancer and portends a poor outcome. This may be related to multiple metabolic derangements associated with increasing body fatness, late stage diagnosis of cancer, and the challenges of achieving optimal surgical and chemotherapeutic interventions. It is essential to develop a good metric for determining and measuring obesity as fat distribution and percentage body fat that is associated with higher burden of colon cancer. It is important to evaluate when and what degree of obesity is associated with increased colon cancer risk. We should promote colon cancer screening and encourage enduring weight loss.

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Practice Points

- Obesity continues to increase in developed and developing countries of the world
- Obesity increases the risk of colorectal cancer and worsens survival from the disease
- The risk of adenoma, adenoma recurrence and colon cancer is slightly higher among men
- Rising obesity may undermine the reduction in colorectal cancer burden achieved with increasing colon cancer screening
- Maintenance of healthy weight should be encouraged for all patients

Research agenda

- Is obesity better measured with BMI or WHR or waist circumference and do we need a better metric to measure obesity?
- Will weight loss reverse the risk of colon cancer and how long will the new weight need to be maintained for the risk reduction to be achieved?
- Should colorectal cancer screening guidelines be modified for the obese?