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**Body mass index and colon cancer screening: The road ahead**

Tandon K *et al*. Body mass index and colon cancer screening

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**Abstract**

Screening for colorectal cancer (CRC) has been associated with a decreased incidence and mortality from CRC. However, patient adherence to screening is less than desirable and resources are limited even in developed countries. Better identification of individuals at a higher risk could result in improved screening efforts. Over the past few years, formulas have been developed to predict the likelihood of developing advanced colonic neoplasia in susceptible individuals but have yet to be utilized in mass screening practices. These models use a number of clinical factors that have been associated with colonic neoplasia including the body mass index (BMI). Advances in our understanding of the mechanisms by which obesity contributes to colonic neoplasia as well as clinical studies on this subject have proven the association between BMI and colonic neoplasia. However, there are still controversies on this subject as some studies have arrived at different conclusions on the influence of BMI by gender. Future studies should aim at resolving these discrepancies in order to improve the efficiency of screening strategies.

**Key words:** Body mass index; Colorectal cancer; Adenomas; Colon cancer screening; Adipokines; Obesity

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**Core tip:** Colorectal cancer has been associated with various risk factors like gender, race, smoking, obesity, diet, but these have not been utilized to refine our screening practices. The available evidence, the suggested role of inflammatory markers and the practical ease of use suggests that incorporation of body mass index accounting for gender and age differences can be used to supplement risk calculators for predicting the occurrence of colorectal adenomas and hence fine tune our screening practices.

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**Introduction**

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide, with over 1.2 million new cancer cases and 608700 estimated deaths in 2008[1]. In the United States, it was estimated that in 2013, nearly 51000 deaths were due to CRC[2]. Different techniques are used to screen for colon cancer including colonoscopy, flexible sigmoidoscopy, fecal occult blood testing, virtual colonoscopy and double contrast barium enema. Despite the benefits of screening methods, the numbers just mentioned indicate that there is still room for improvement. Despite the association of readily identified data such as gender, race, smoking, with variable risks for colon cancer[3-6] , these factors have not been incorporated into mass screening programs to stratify patients according to their risk for CRC. Other risk factors such as non-steroidal anti-inflammatory drugs, calcium, folate, excessive alcohol use, dietary fiber, have been also shown to influence the incidence of adenomas and CRC but their association is not consistent and its clinical application difficult as these factors are subject to recall bias that may prove unreliable[7,8] .

Body mass index (BMI) is a measure of relative weight based on an individual's mass and height. Obesity, a term used to denote patients with BMI > 30 has been linked to several medical problems including CRC[3] with each 2 kg/m2 increase in BMI accounting for a 7% higher risk[9].In addition, two recent met-analyses, have identified patients with high BMI to be at higher risk for colorectal adenomas[10,11]. Therefore, BMI as a measure of obesity can be a valuable and easy to use tool for optimizing screening methods.

**Pathogenesis**

The mechanisms by which obesity is linked to increased risk of colon polyps and colorectal cancer are still being investigated with most of the available evidence being on colorectal cancer[12]. However, there is growing evidence on associations between BMI, waist circumference with number, type and location of adenomatous colon polyps.

Compared to lean adipose tissue, obese (or visceral) adipose tissue has more prominent immunologic and endocrinologic properties through secretion of different inflammatory markers that regulate the systemic inflammation and also contribute to the process of carcinogenesis. Increase in visceral adipose tissue is accompanied by a rise of pro-inflammatory adipokines [including leptin, interleukin (IL)-6 and tumor necrosis factor (TNF)-α] and a decrease in anti-inflammatory adipokines (mainly adiponectin)[13]. Elevated inflammatory factors are believed to enhance polyp formation and carcinogenesis through creation of an inflammatory microenvironment, which leads to genetic mutations and activation of tissue proliferation rather than apoptosis[14]. (Table 1)

One of the main inflammatory adipokines is leptin. Higher levels of leptin are observed in obese patients and those with increased waist circumference, and actually leptin levels correlated with higher risk of tubular adenoma and presence of 3 or more polyps[14,15]. Leptin receptors are expressed on multiple cells including normal epithelial and epithelial derived tumor cells. Experimental treatment of such cells with leptin resulted in not only cell proliferation but also angiogenesis and production of other cytokines like IL-6[16]. A study on obese mice that are genetically deficient in leptin receptors showed significant inhibition of colorectal tumor cell growth[17]. These observations may indicate a crucial role of leptin among other adipokines in colorectal neoplasm development.

Another inflammatory mediator that has been investigated is interferon gamma-inducible protein-10 (IP-10, also known as C-X-C motif chemokine 10) which is secreted by a number of cells including mature human adipocytes, and functions as chemo-attractant to enhance local inflammation and tissue damage of pathogen and abnormal (including malignant) cells[18]. As with leptin, high levels are associated with presence of 3 or more polyps and higher risk of tubular adenoma[14]. Additionally, high serum concentrations of IP-10 are associated with poorer prognosis for CRC patients[19].

Controversial evidence exists as regard to IL-6 and TNF-α. There is a significant association with higher IL-6 and colorectal adenoma in some studies, mostly in Japanese population[20], and significantly higher levels were seen in colorectal cancer patients especially those with more advanced stages[21]. However other studies failed to prove this association[22,23].Similarly, higher level of TNF-α was significantly associated with presence of tubular adenoma and advanced adenomas[14,24], however, other studies showed no significant correlation[25].

On the other hand, high serum adiponectin was inversely associated with lower BMI and waist circumference[14]. This high level was significantly associated with lower risk of both colorectal adenoma and malignancies[26].

**Literature review on BMI and adenomas**

Several studies have linked BMI and obesity to risk of developing colorectal adenoma and cancer. A large prospective study has shown evidence for increased risk of incident adenoma (OR = 1.32) and colorectal cancer (OR = 1.48) as well as a borderline increased risk of recurrent adenoma (OR = 1.50; 95%CI: 0.98-2.30) in men with a BMI > 30[27]. Moreover, a cross-sectional study controlling for age, gender, exercise and smoking showed BMI > 30 to increase the risk of advanced neoplasia (OR = 3.83; 95%CI: 1.94-7.55][28]

The literature on this subject is not without controversy. Two recent meta-analysis found an association of BMI with presence of colorectal adenomas. However, they arrived at different conclusions on its relationship with gender. Okabayashi concluded that subjects with a BMI of ≥ 25 had a significantly higher prevalence of colorectal adenomas but this association was found only in females[10]. On the contrary, Ben noted that a 5 unit increase in BMI was correlated with an increased risk of colon adenomas in both men and women[11]. The studies had distinct methodologies leading to inclusion of different manuscripts but it raises the question of whether the effects of BMI on colorectal neoplasia are the same for both genders. Indeed, estrogen and progesterone in pre-menopausal women may play a role in attenuating the effects of obesity on colon adenoma formation[29,30]. Short-term exogenous estrogen and progestin have been shown to delay the presentation of colorectal neoplasia in women although; once colorectal cancer developed it was more advanced in patients on estrogen and progestin as compared to placebo[31].

Another study reporting gender differences included 4122 participants revealing an association between metabolic syndrome and colorectal adenoma only in men (OR = 1.44, 95%CI: 1.16-1.80)[29].

The predilection of colorectal cancer to certain colon sub-sites (proximal *vs* distal) in obese individuals appears to be minimal. A study looking at the site of occurrence of colorectal cancer in obese individuals revealed a positive correlation between BMI and cancer for all colorectal sub-sites[32].The literature on the influence of BMI with proximal colonic polyps is limited. A study of just over 1300 patients noted that proximal adenomas were positively associated with higher BMI[33].

In patients who are overweight (25-29.9 kg/m2), as physical activity increases the odds of having a colorectal adenoma are decreased but this does not extend to obese individuals[34]. In addition weight loss has not been found to reduce adenoma recurrence[35].

The link between BMI and colorectal adenomas may also have a genetic association, as studies reveal that polymorphisms in the fat-mass and obesity-associated (*FTO*) gene could be related to development of colorectal adenoma. This was shown in African Americans where FTO polymorphisms were associated with BMI and risk of colorectal adenoma[36].

**Other indirect measures of obesity**

The use of other indirect measures of obesity has been traditionally limited to waist circumference and waist/hip ratio. Studies have also shown that waist circumference[37] and waist/hip ratio[38] are significant factors influencing the occurrence of adenomas. Although feasible to record, these measurements could prove embarrassing for some patients and are not part of the routine medical evaluation. Researchers have recently tried to develop a new index using the waist circumference to height index ratio. However, the literature on this index as it pertains to colorectal neoplasia is limited[39].

The measurement of visceral adipose tissue (VAT) by using computed tomography (CT) scan has been identified as a risk factor for colorectal adenoma[33]. Significant association of VAT area with colorectal adenoma in both men and women has been seen. This technique also demonstrated the association of visceral fat tissue with adenoma number and size[40]. More recently, the use of CT scan to measure VAT has also been combined with measures of atherosclerosis like pulse wave velocity and ankle brachial index to formulate adenoma detection risk[41]. However, the use of CT scan for determining VAT is impractical and would be limited to those patients undergoing CT for other reasons.

In another effort to measure the amount of body fat, an electronic device using bioelectrical impedance analysis (BIA) has been utilized. Body fat percentage was calculated by BIA using a proprietary scale. Although BIA was found to be a quick and convenient measure of adiposity, it has not been predictive of adenoma risk perhaps because it does not measure the distribution of body fat but only the amount of body fat[42]. Also the universal availability of such devices is questionable at this point.

**Future Directions**

In the past few decades, obesity has emerged as a global epidemic. In a 2003–2004 cross-sectional survey, 66.2% of United States adults 20–74 years old were either overweight or obese[28]. Although controlling the obesity epidemic would be the best strategy to neutralize its association with colonic neoplasia this is unlikely to occur in the near future. Despite recent advances in the mechanisms linking obesity with colonic neoplasia, there is still controversy on the individual impact of the implicated inflammatory mediators and developing effective medical therapies remains a challenge. Therefore, for the foreseeable future, utilizing markers of obesity to tailor screening practices for CRC seems the most realistic goal in this field.

Some studies have shown markers of obesity such as CAT scan evaluating visceral adiposity or even the waist to hip ratio to correlate with colonic neoplasia but no marker is as simple as BMI and this has significant clinical implications as complicated measures are unlikely to be applied in mass screening. In addition, the influence of BMI on colonic neoplasia formation has been reported in multiple studies across the globe and seems to be uniform across nations.

Despite the association of BMI with colorectal neoplasia, it has not proven to be a strong enough factor to alter CRC screening if used alone. In an effort to improve screening practices for CRC, risk calculator models have been developed utilizing clinical and demographic factors shown to influence colorectal neoplasia such as sex, age, smoking, family history of CRC, alcohol use and most of these models also include BMI. However, even these models have only moderate discriminatory power and this is felt to be insufficient for implementation of mass screening[43]. Combining these models with fecal immunochemical testing has resulted in improved discriminatory power[44].

Notwithstanding the extensive literature on the influence of BMI on colon adenomas, controversies remain that could potentially improve CRC risk calculator models if clarified. As previously mentioned, two recent meta-analysis on the influence of BMI on adenomas had different methods for study selection and arrived at different conclusions on the relationship of BMI with gender. One meta-analysis found a positive correlation only in females[10], whereas the other noted increased BMI with a higher risk of colon adenomas in both men and women[11]. Besides the previously discussed effects of female hormones, another possible explanation for this discrepancy lies on differences in BMI measurements in men and women as most studies have used the same BMI cutoff values for both genders[45]. Another controversial area is the association of BMI with advanced adenomas. One of these meta-analyses found an association between advanced adenomas and increasing BMI whereas the other did not. This could be explained by inclusion of studies with patients in different age groups as some have reported that the influence of BMI on adenoma and advanced adenoma formation may not be uniform across all age groups[46].

Although colonoscopy remains the preferred screening method for CRC prevention in the United States and many countries, it is a limited resource and improvements could be done to better identify patients at higher risk for colonic neoplasia. Although risk calculator models have yet to reach the desired precision, refinement of risk factors such as BMI could result in enhanced accuracy. How each country would use risk calculator models to target patients for colonoscopy or other screening methods would depend on their resources.

As age remains the most powerful clinical risk factor for predicting advanced colonic neoplasia, future studies on the influence of BMI on colon polyps should focus on populations at borderline age groups to consider earlier or later CRC screening than the customary age of 50. Therefore, study populations should focus on individuals around the ages of 40-65 analyzed separately for gender and age group. Although evaluating for the presence of non-advanced adenomas may be worthwhile, the primary objective of studies aimed at refining screening practices should be on large polyps and advanced neoplasia.

**Conclusion**

BMI has been identified as a risk factor for colorectal adenoma, advanced adenoma and colorectal cancer. Its use after adjusting for age and gender, along with other risk factors for colon cancer can help refine CRC screening practices.

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**Table 1 Effect of different adipokines on colorectal polyps and colorectal cancer**

|  |  |  |  |
| --- | --- | --- | --- |
| **Type of marker** | **Level of marker in obesity** | **Effect on risk of colon adenoma** | **Risk of colorectal cancer** |
| Leptin | Increase | Increase | ---- |
| IL-6 | Increase | Increase/none  | ---- |
| TNF-α | Increase |  May Increase (only in tubular adenoma) | --- |
| Adiponectin | Decrease  | Decrease/none | Decrease  |
| IP-10 or CXCL10 | Increase | Increase | Increase (Poor prognosis of CRC) |

IL-6: Interleukin 6; TNF-α: Tumor necrosis factor-α; IP-10: Interferon-γ Inducible protein-10; CXCL10: C-X-C motif chemokine 10; CRC: colorectal cancer.