# Factors that Increase Risk of Colon Polyps

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## ABSTRACT

Adenomatous polyps are common and factors that increase risk include race, gender, smoking, and obesity. This author summarizes the evidence supporting increased risk with these factors and describes how epidemiological data may be used to tailor screening programs.

**KEYWORDS:** Polyps, risk factors, epidemiology

**Objectives:** Upon completion of this article, the reader should be familiar with factors that increase the risk of colon polyps.

Colorectal cancer is the second most common cause of cancer death in the United States.[1] Adenomatous polyps are known precursors of colorectal cancer. The importance of identification and removal of polyps for the prevention of colorectal cancer is clear. In the National Polyp Study, colonoscopic surveillance was associated with a 76 to 90% reduction in the cancer incidence compared with reference populations.[2] The U.S. Preventive Services Task Force recommends colon cancer screening for all persons at average risk who are older than 50 years with any of the following tests: fecal occult blood test (FOBT) annually, flexible sigmoidoscopy every 5 years, double-contrast barium enema (DCBE) every 5 years, flexible sigmoidoscopy every 5 years plus FOBT annually, or colonoscopy every 10 years.[3] These recommendations are for individuals with average risk without consideration of other risk factors such as race, gender, smoking, or obesity. Those with increased risk may warrant adjustment of surveillance recommendations to identify lesions early, before malignant transformation occurs. In addition, some of the recommendations for screening are based on the assumption that the majority of colorectal neoplasms occur in the distal colon, within reach of the sigmoidoscope. There are several factors, including race, which can lead to a different distribution of neoplasms within the colon making evaluation of the proximal colon even more prudent for high-risk groups. Furthermore, education regarding the importance of surveillance and access to colon cancer screening may vary among both racial groups and genders. There may not be one best screening algorithm, but optimal strategies will need to be defined for different population subgroups. The current capacity of those performing screening colonoscopy is exceeded by demand. Screening recommendations depend on data from epidemiologic studies; thus, incorporating specific risk factors may help triage patients for colorectal screening.

## RACE INFLUENCES RISK

Data on screening and site distribution of colorectal adenomas in different ethnic groups are limited. Overall, ~145,000 Americans were diagnosed with colorectal cancer and 56,000 died from colorectal cancer in 2006. Despite standard screening recommendations and effective interventions for colorectal cancer prevention, colon cancer is associated with significant

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Polyps and Polyposis Coli; Guest Editor, Janice F. Rafferty, M.D.

Clin Colon Rectal Surg 2008;21:247–255. 
DOI 10.1055/s-0028-1089939. ISSN 1531-0043.

differences in mortality among ethnic groups.[4] Some studies have also shown differences in cancer prevention services among ethnic groups,[5,6] whereas others have not.[7]

In a large study of nearly 600,000 Medicare beneficiaries, only 18.3% of the eligible population had undergone a screening colon test during the 2-year study. Non-white persons were half as likely to be screened for colorectal cancer than were white persons (relative risk [RR] = 0.52; 95% confidence interval [CI] = 0.50 to 0.53).[8] Similarly, in a 2001 telephone survey, African Americans were half as likely to ever have had any colon cancer screening tests (odds ratio [OR] = 0.48, 95% CI = 0.33 to 0.70).[9]

When looking at Hispanics versus non-Hispanics, Polack et al noted that fewer Hispanic individuals older than 49 years were up to date with their screening tests than were their non-Hispanic counterparts (41.9% versus 55.2%, respectively). After adjusting for differences in education, income, and insurance status, Hispanic individuals remained significantly less likely than non-Hispanics to have colorectal cancer testing.[10] These findings are consistent with other studies that show lower cancer screening rates within minority groups.[11]

Among Asian Americans, colorectal cancer (CRC) is the second most commonly diagnosed cancer, and it is the third highest cause of cancer-related mortality. In a population-based telephone survey of 1771 Asian Americans age 50 years and older, colorectal cancer screening of any kind was low in all populations.[12] Non-Latino whites had the highest rate of screening at 75%. The Asian American rates were 58% for any screening (not just colorectal). Koreans had the lowest rate of any screening (49%). Japanese had rates of screening that were similar to non-Latino white rates. Overall, Asian Americans were less likely to undergo screening if they were older, male, less educated, recent immigrants, poor, or uninsured. With this in mind, screening programs may need to focus on education in culturally sensitive ways.

Along with racial variations in screening, there are racial differences in the location of neoplasms within the colon. This may have implications for the colorectal screening modality recommended for different racial groups. Thornton and colleagues demonstrated that African Americans were less likely overall to have polyps [adjusted OR = 0.77; 95% CI = 0.70 to 0.84], but the odds of having proximal polyps was higher for African Americans (OR = 1.30; 95% CI = 1.11 to 1.52) compared with whites. Interestingly, African Americans were significantly more likely to have malignant tumors (OR = 1.78; 95% CI = 1.14 to 2.77) and four times more likely to have proximal tumors than whites (OR = 4.37; 95% CI = 1.16 to 16.42).[13] This is consistent with other reports that African Americans are more likely to have proximal lesions.[14,15] In another study of asymptomatic individuals screened with a sigmoidoscopy that had distal lesions and went on to have a full colonoscopy, synchronous proximal neoplastic lesions were found in 67% of Hispanics, 64% of whites, 59% of African Americans, and only 26% of Asian Americans.[16] Similarly, African American individuals have a greater frequency of synchronous polyps and have a higher incidence of recurrent polyps.[17]

In regards to cancer, a study by Shavers showed the odds of a diagnosis of cancer proximal to the sigmoid colon and proximal to the splenic flexure was significantly higher for African Americans, but lower for Hispanics and Asian Americans/Pacific Islanders compared with non-Hispanic whites.[18] There is substantial data that African Americans have a high incidence of colorectal cancers as well as higher cancer-related mortality.[19] In addition, Theuer et al found that significantly more African Americans with cancer were under the age of 50 years (10.6% of cancers) compared with whites (5.5%).[20] These findings suggest that the total colonic surveillance to adequately screen for large-bowel neoplasia is essential in African American individuals and screening may need to start at age 45 years.[19]

In general, Hispanics have a relatively lower rate of cancer relative to whites.[18,20] Hispanics and whites have been found to have a similar site distribution of colorectal adenomas and similar adenoma histologies. Screening modalities excluding the area proximal to the splenic flexure would miss greater than 30% of the polyps in both populations.[21] Some have even suggested delaying onset of screening in Hispanics to age 55.[22]

In Asia, the risk of having advanced colonic lesions is increased by 1.05-fold for every single-year increase in age. In addition, there is > 4-fold increase in prevalence of advanced colonic neoplasm in patients > 70 years compared with those < 50 years.[23] A similar age-related increase in prevalence of colorectal neoplasm has been observed in Western studies.[24] The prevalence of colorectal neoplasms appears to be higher in Japanese and Korean populations than in other Asian populations.[23] Soon et al[25] found lower rates of adenoma in Chinese American patients in Seattle compared with whites.

Within the United States, there may be differences in family history among different racial groups. One study found hereditary nonpolyposis colorectal cancer and familial adenomatous polyposis in 17% and 9% of whites, respectively, and 6% and 0% of African Americans, respectively.[26] Unknown paternal history was found in 6.5% of whites and 18.9% of African Americans (23% men, 11% women). It was concluded that African Americans and men had significantly decreased rates of paternal history cancer knowledge. Unknown family history may also add to the risk of colonic neoplasia among African Americans.

Some studies show that African Americans may have more advanced neoplasms at the time of diagnosis,[13,27] but this has also been refuted.[24] In a large population screening study, Lieberman and colleagues found that increased age, male gender, and African American race were associated with increased risk of large polyps.[27] In another study of Veterans Affairs (VA) patients, however, Lieberman et al found no increase incidence of advanced lesions when whites were compared with African Americans or Hispanics.[24]

In summary, screening for colorectal cancer is comparatively low among minority groups. Recognition of African Americans as a higher-risk group highlights the need for increased education about the need for screening; this should extend to patients, primary healthcare providers, as well as gastroenterologists and surgeons, The higher incidence of proximal lesions in African Americans makes sigmoidoscopy less effective. Although the data suggests differences based on race, there is insufficient evidence that customizations of screening based on race will alter outcome. It has been suggested that screening recommendations based on individual risk may improve education and compliance, rather than screening based on an arbitrary age (22 years). Further data are needed.

## GENDER

In general, studies indicate that men are more likely to have colonic neoplasms and twice as likely to have advanced lesions.[23,27,28] The incidence of colon cancer is higher in men as well with an odds ratio of 1.32 for proximal lesions and 1.68 for distal lesions).[15] Men also tend to have lesions at an earlier age. There appears to be a time delay for women with a low absolute risk of advanced neoplasia in women of ~2.9% in their 50s compared with 4.7% risk in men in the same decade.[29] Based on this relatively lower risk in the sixth decade some authors suggest deferring screening in women until a later age.[22]

In population studies regarding colorectal cancer screening, only 37% were up to date. In a population based study from California assessing colorectal screening, men were more likely to be screened than women. In addition, women were more likely than men to say that their physician did not inform them the test was needed and that CRC tests were painful or embarrassing.[11] Similarly, older women were less likely to be tested (62.6% for women versus 56.7% for men $>75$ years). When compared with white women, African American women were less likely to be up to date with CRC screening (OR = 0.79, 95% CI = 0.65 to 0.95).[6]

The use of sigmoidoscopy may not be adequate screening for women. One study demonstrated that if flexible sigmoidoscopy alone had been used for screening in average risk women, 50 to 80 years old, advanced neoplasia would be identified in 1.7% and missed in 3.2%. Therefore, only 33% would have their lesions identified on sigmoidoscopy as compared with 66% of lesions in matched men from the VA cooperative study 380. This may affect differences in detected incidence of colonic neoplasms between men and women.[24,29]

## SMOKING

Carcinogens from cigarette smoke are absorbed into the blood stream and are known to cause malignancies in organs not in direct contact with smoke. Epidemiologic studies of tobacco smoking have consistently shown an association with colonic polyps. In a recent review, Giovannucci[30] reported that 21 of 22 studies found that long term, heavy cigarette smokers have a 2- to 3-fold increased risk of colorectal adenoma.

Tobacco use has been examined in a variety of ways, including cigarettes per day, duration of smoking, past smoking history, and total cigarette pack-years. Studies of the intensity of smoking seems to indicate that one to two packs a day to accumulate 20 to 40 pack-years of smoking is associated with a 2- to 3-fold increased risk for colorectal adenomatous polyps as compared with nonsmokers.[31] This association has been observed consistently among past smokers as well.

The duration of smoking has also been found to be influential. In a study by Nagata, they found an elevated risk in those who smoked for greater than 30 years (RR = 1.60; 95% CI = 1.02 to 2.62), but not less (RR = 1.1; 95% CI = 0.69 to 1.84).[32] Others have shown a similar increased risk of adenomas among those who have smoked for $>25$ to 40 years.[33–35] Monnet found that compared with men who had never smoked, the estimated relative risk of adenoma increased with the pack-year smoking number, the average number of cigarettes per day, and the total years smoked. The estimated overall relative risk was 2.2 (95% CI = 1.1 to 4.3).[31]

Giovannucci also showed in a cohort of 118,334 women a significant increased relative risk of large adenoma by pack-years of smoking before the age of 30 years. Those with greater than 16 pack-years prior to age 30 years had a relative risk of 1.9 (CI = 1.1 to 2.99). This trend was statistically significant even when controlling for family history of colorectal cancer, body mass index (BMI), dietary fiber, folate, and alcohol. Overall, total pack-years of smoking by age 30 years was modestly related to risk of colon cancer (RR = 1.3; 95% CI = 0.97 to 1.76) and associated with a significant for rectal cancer (RR = 2.06; 95% CI = 1.24 to 1.61). There is speculation that initiation of smoking prior to the age of 30 years, although accounting for only 20% of the total lifetime smoking, may account for the elevated risk of colon cancer with a long induction period of at least 35 years.

There has also been shown to be an increase in size (> 1 cm)[35] and number of polyps (> 1) in those who smoke.[33] Reid et al showed a significant increase in prevalence of multiple versus single adenomas in those who smoked for more than 35 years or more than 10 pack-years.[36] In contrast, a study by Longnecker did not find and increase in large adenomas in those who had smoked in the distant past relative to nonsmokers (RR = 0.88; 95% CI = 0.23 to 3.42).[37]

Two studies have looked at the association of time since quitting with the risk of adenomas. One used a 2-year period and the other a 10-year period. Both found that those who quit within the specified period had a higher risk than those who quit prior to that period, but both groups still had a higher incidence of adenomas compared with those who never smoked.[31,38] These findings were not statistically significant, but indicate the increased risk persists even after smoking cessation.

There have been few studies that address smoking and the risk of recurrent adenomas. Jacobson et al showed an increased risk of recurrent adenomas in men with more than 13 pack-years compared with those who had never smoked (OR = 2.4; 95% CI = 1.3 to 4.4). Similar results were seen in women with more than 30 pack-years compared with their counterparts who had never smoked (OR = 2.8; 95% CI = 1.2 to 6.5).[39] In a prospective endoscopic screening examination of 200 men and 200 women, aged 50 to 59 years, Hoff et al showed a 2.5-fold greater risk of new polyps among active smokers compared with male ex-smokers on a 2-year follow-up examination with a trend toward significance. However, no significant difference was found when comparing smokers with those who never smoked.[40] Of note, smokers are significantly less likely to undergo recommended cancer screening (33% of smokers versus 46% of nonsmokers).[41]

In a meta-analysis of 42 independent observational studies, Botteri et al reported the pooled risk estimates for adenomatous polyps of current, former, and ever smokers in comparison with never smokers as 2.14 (95% CI = 1.86 to 2.46), 1.47 (95% CI = 1.29 to 1.67), and 1.82 (95% CI = 1.65 to 2.00), respectively.[42] They also demonstrated a significant association between smoking and advanced lesions and a higher relative risk in studies that screened with a full colonoscopy. This meta-analysis further supports the notion that smoking significantly increases the risk of colon polyps.

In summary, there is a consistent association between smoking and risk of adenomatous polyps in the colon. There is also an association with increased size, number, advanced size, and histology, as well as recurrence of polyps. The relationship of smoking to cancer is somewhat less clear. It has been hypothesized that the carcinogens in smoke may act to initiate adenomas that may have an induction period of more than 35 years. Many of the earlier studies might have had insufficient follow-up time to demonstrate a significant increased incidence of cancer.

## OBESITY

Although obesity has been on the rise since the 1980s, it was not until 1997 that the World Health Organization accepted it as a major health problem. James reported that in 2007, more than 1.5 billion people worldwide were overweight, with a BMI > 25. An additional 523 million people were considered to be obese, with a BMI > 30. That same year, more that 30% of people in the United States were considered obese.[43] With the rising incidence of obesity over the past several decades, there has been increasing evidence that obesity is not only related to cardiovascular and metabolic diseases, but there are also associations with gastrointestinal diseases including esophageal cancers, pancreatic cancer, as well as colon polyps and cancer.[44] In parallel to the geographic distribution of obesity around the world, colorectal cancer incidence is highest in affluent industrialized countries such as the United States, Australia, and Western Europe.[45]

Most studies show an association of higher BMI and increased incidence of colorectal neoplasia. Neugut et al was the first to describe an increased risk of adenomas with increasing BMI in women (OR = 2.1, 95%; CI = 1.1 to 4.0; for highest versus lowest quartile, linear trend, $p = 0.02$). A nonsignificant trend was observed for men, but overall the men enrolled had a lower BMI.[46]

Several years later in a large cross-sectional study, Bayerdorffer found a significant association between men with high-risk adenomas and increased BMI (OR for the top quintile versus the lowest quintile, 3.21; 95% CI = 1.15 to 8.98). High-risk adenomas were defined as polyps > 1 cm, or containing high-grade dysplasia, villous tissue, or adenocarcinoma. It was concluded that the risk of developing high-risk adenomas is significantly increased in men who are overweight.[47] Further studies confirmed a 2- to 3-fold increased incidence of colorectal neoplasms in overweight individuals in studies from Germany, Japan, and the United States.[48–50]

Recently, Anderson et al reported on the impact of BMI on the risk of advanced colorectal neoplasia in a cross-sectional study of 2493 asymptomatic white patients undergoing screening colonoscopy. Advanced colorectal neoplasia was defined as polyps > 1 cm, or containing high-grade dysplasia, villous tissue, or adenocarcinoma.[51] In this study, age, diet, exercise, and other lifestyle factors where taken into account. Thinner patients were more likely to consume fruits and vegetables, exercise, or drink alcohol than their heavier counterparts. Increased age and smoking were significantly associated with increased risk of colorectal neoplasia and

were evaluated in a multivariate analysis. In women, there was a significant relationship between increasing BMI and colorectal neoplasia with an OR of 4.26 (95% CI = 2.0 to 9.11) for those with a BMI $\geq$ to 40 compared with women with a BMI $< 25$. Again, there was a trend toward significance for men. Men who had gained at least 40 pounds since age 21 years also had an elevated risk for colon neoplasm (age-adjusted RR = 1.91; 95% CI = 1.15 to 3.16).

Interestingly, not only does the incidence of adenomas increase with increased body fat, there is evidence that adenoma growth rate is also associated with increasing indices of body fat. In a group of patients with subcentimeter polyps observed in situ for 3 years, those who had growth on repeat colonoscopy had significantly higher BMI and triceps skinfold thickness.[52] This study indicates that obese patient may need more frequent surveillance.

In addition, there is evidence that adenomas are not only more frequent in obese patients, but also more advanced. In large cross-sectional study, Betes et al found a 2-fold increase in advanced adenomas in patients with a BMI $> 30$. Overall, patients with any adenoma had significantly higher mean BMI (27.4 versus 26.9 kg/m$^2$). Those with advanced lesions had an even higher BMI than those with nonadvanced adenomas.[28] In contrast, in a study out of Norway, Larsen et al identified BMI as an important factor in predicting low-risk adenomas, but not advanced adenomas. However, this was a mixed group of patients who only had flexible sigmoidoscopy, which may inevitably miss patients with proximal lesions and misclassify some individuals.[53] The association of obesity and adenoma appears to be on a continuum with BMI adding increased risk in terms of incidence, growth rate, recurrence, and advanced pathology. These factors are all likely to result in an increased risk of cancer.[54]

## GENDER AND BODY SIZE

A positive association between BMI and risk of colon adenoma has been found in most studies with variable reports with regards to gender and the association between body size and increased risk of colon polyps. The cause of this sex discrepancy is unclear. It may be related to differences in the indices used (BMI versus waist to hip ratio), differences in the location of lesions in men and women and the screening test used, and other confounding variables like smoking, alcohol, or menopausal status.

There is data to suggest that abdominal or visceral adiposity is a risk factor independent of BMI. One population based study by Moore et al, examined waist circumference, and showed a stronger association with BMI and colorectal cancer in men than in women.[55] They propose there are sex differences in the mechanism of development of polyps and progression to colorectal cancer. Similarly, in a study of 47,723 male health professionals 40 to 75 years of age, Giovannucci showed an increase in colon neoplasms in men with a BMI of greater 27 compared with those with a BMI of $< 22$ (RR = 1.62; 95% CI = 1.03 to 2.55). Waist-to-hip ratio has also been found to be a strong risk factor for large distal colon adenomas, but not small adenomas. Waist-to-hip ratio remained a significant risk factor for large adenoma even after controlling for physical activity and body mass (multivariate relative risk 2.86; 95% CI = 1.28 to 6.41, $P$ for trend = 0.04).[56] Although trends are relatively consistent, the optimal way to assess the association of obesity and colorectal adenomas is neither uniformly reported nor clearly defined.

Another variable in the relationship between colorectal neoplasms, obesity, and gender may be influenced by location of lesion and the screening modality used. The location of colon neoplasms may be different in men and women. As previously mentioned, sigmoidoscopy may identify only 33% of lesions in women as compared with 66% of lesions in matched men. This may affect differences in detected incidence and therefore the relationship to other risk factors if studies are using sigmoidoscopy only instead of complete colonoscopy.[24,29] Another concerning factor highlighted by Rosen et al in a survey study with 53,000 patients showed that morbidly obese women were significantly less likely than normal weight women to be screened with fecal occult blood or endoscopy (adjusted rate difference = -5.6%; 95% CI = -2.6 to -8.50).[41]

In addition to variability in the literature about the screening modality, there are also differences in accounting for potential risk factors such as smoking and exercise. In a colonoscopic screening study of 1744 men and women, there was an increased prevalence of polyps with increased age up to 69 years. There was also a 1.5-fold increased rate of polyps in men at each age group up to 69 years compared with age-matched women. The association with polyps and BMI was only significant for men younger than 40 and women between 40 and 50. There were some flaws in this study in that there was a significant difference in proportion of smokers and alcohol drinkers between the men and women (42% versus 1.5%, 13.6% versus 2.4%, respectively), which may confound the analysis.[57] This study further draws attention to the complex interactions of risk factors including gender, diet, smoking, and activity level.

Hormonal status and age have also been proposed to have a role in the association between obesity colorectal neoplasms. Female patients within these studies may be stratified by age, but this may not accurately reflect hormone status thereby making it hard to draw clear conclusions. In a recent study, there was a 4-fold increased incidence of colorectal neoplasia in women with a BMI $\geq 40$. This impact was even more pronounced in

women with a BMI > 40 of whom 33.3% had colorectal neoplasia compared with 10.7% of women > 55 years of age with BMI < 25. The relationship is less clear for women with BMI between 30 and 40 in that the OR is 1.3, but statistically not significant at any age.[51] The hormonal status of these patients was not defined. Kim et al showed that among premenopausal women with a BMI > 25 there is 3- to 5-fold increased risk of colonic adenoma. This positive association in premenopausal obese women was striking with both small (OR = 3.79; 95% CI = 1.33 to 10.82) and large adenomas (OR = 5.89; 95% CI = 1.51 to 22.03), after age adjustment. In contrast, the prevalence was similar between both obese and nonobese postmenopausal women (20 to 30%).[57] Similarly, Terry and colleagues, reported a 2-fold increase in colon neoplasm in those with a BMI of ≥ 30 in premenopausal, but not postmenopausal women compared with matched women with BMI < 25.[58] Hormone replacement therapy may also confound the issue as their use has been associated with risk reduction in older women.[59]

The influence of activity level has been studied and consistently shows an inverse relationship with the incidence of colorectal neoplasia. Men in the highest quintile of physical activity had approximately half the incidence of colon cancer seen in men in the lowest quintile. These findings suggest that physical inactivity and obesity influence the promotion or growth of adenomas.[56] In a study nested within a randomized double blinded placebo-controlled chemoprevention trial, Wallace et al did not find an association between BMI and incidence of recurrent adenomas in either men or women, but did find that men who were active had a significantly lower relative risk for advanced polyps than those who were less active( RR = .35; 95% CI = 0.17 to .72).[60] Others have also found no relationship between obesity and adenomas when controlling for level of activity and dietary fiber intake.[61] Many of the studies looking strictly at BMI or other anthropomorphic measurements fail to factor in activity level and other dietary issues, again making it difficult to assign all of the increased risk directly to obesity.

It is clear that there are other factors associated with obesity that may contribute to increased risk of polyps including diabetes, lower fiber intake, lower folate, vitamin D, vitamin E, and calcium intake, and higher animal fat intake. In general, activity level of obese patients tends to be lower.[56] In the Nurses' Health Study, frequent consumption of fruit was inversely related to the risk of being diagnosed with polyps, whereas little association was found for vegetable consumption. Women who reported consuming five or more servings of fruit a day had an OR of 0.60 (95% CI = 0.44 to 0.81) for developing colorectal adenomas compared with women who consumed only one or fewer servings of fruit per day, after adjustment for relevant covariates ($P$ of trend = 0.001).[62] There is a broad body of literature regarding dietary factors and chemoprevention that is reviewed by Dr. Robb in this issue.

In summary, BMI has been associated with colorectal adenoma in many epidemiological studies.[54,56,60] There is an increased incidence of adenomas which tend to be more advanced, as well as an increased adenoma growth rate. There may be several unmeasured factors within this association including genetic predisposition, dietary and exercise habits that may lend to this increased risk. The mechanism of this association has yet to be fully elucidated, but there are several hypotheses regarding the mechanism by which increasing adiposity may increase the risk of colorectal neoplasia.

## ENERGY BALANCE, METABOLIC CHANGES, AND CHRONIC INFLAMMATION

Obesity has been measured by several anthropomorphic indexes, including waist to hip ratio, waist circumference, as well as BMI. These are surrogate markers for an overall energy intake in excess of energy expenditure. This disturbance of energy balance can lead to various energy perturbations that may be involved in colorectal carcinogenesis. Biological mechanisms involved in the association of obesity and colorectal adenoma include insulin resistance. In this setting, there are several metabolic abnormalities including elevated triglycerides, glucose levels, and blood pressure – a physiologic constellation called "metabolic syndrome." Excess glucose and fatty acids may lead to alterations in cell signaling, oxidative stress, and metabolic disregulation.[54] In addition, high insulin levels, commonly seen in obese individuals, have been associated with colorectal neoplasia,[63] and insulin-like growth factor has also been implicated.[64] It has been observed that individuals with type II diabetes have a 3-fold increase in colon cancer compared with nondiabetics. Metabolic syndrome is also associated with an increased risk of colorectal adenoma (OR = 1.51; 95% CI = 1.18 to 1.93).[65] Elevated serum insulin levels are significantly associated with colonic adenomas (OR = 1.8; 95% CI = 1.2 to 2.5; $p = 0.002$).[66] Serum levels of insulin, IGF, and IGF-1/IGFBP- ratio are also significantly higher in individuals with advanced adenomas compared with those without adenomas.[67] High levels of insulin may have mitogenic effects within colonocytes and act as colon tumor promoter.[54,68,69]

It is also known that insulin-like growth factor I (IGF-I) plays an important role in proliferation, growth, differentiation and inhibiting apoptosis of both epithelial and carcinoma cells. Patients with colon adenomatous polyps have higher serum IGF-I concentrations compared with the control group. Patients with adenomas with dysplasia also have higher concentrations of C-peptide.[70]

The role of insulin in colon neoplasia may be related to insulin directly affecting colon cells. It has been shown that insulin stimulates proliferation via mitogen-activated protein kinase (MAPK) and reduces apoptosis via phosphatidylinositol 3-kinase in cancer cell lines and promotes colorectal tumor growth in animal models.[54] Because colonocytes are not classical insulin-targeted tissue, they may lack specific mechanisms of regulation of the mitogenic effects of insulin.

An additional relationship between insulin resistance and colonic neoplasia may be through energy excess. Excess energy, in the form of glucose and triglycerides may induce specific changes in cell signaling. This excess energy may also increase reactive oxygen species within the colonocytes leading to lipid oxidation, depletion of antioxidants and an overall milieu of oxidative stress leading to further disregulation.[71]

Insulin effect may also act through insulin-like growth factor (IGF) and its effects on cellular growth patterns. Once colonocytes bind IGF, apoptosis is inhibited and the cell cycle progresses which can lead to clonal expansion of epithelial cells with abnormal growth. In addition, excess IGF inhibits hepatic sex hormone binding globulin thereby increasing circulating estrogen and testosterone. The gender differences in relation to obesity and colonic neoplasia may be related, in part, to alterations in sex hormone levels.

A final explanation for the relationship between obesity and colon polyps is obesity inducing a state of chronic inflammation. High circulating levels of glucose and lipids create an oxidative environment.[72] Under conditions of increased adiposity, adipose tissue has been shown to have increased macrophages and increased production of various proinflammatory peptides such as leptin, resistin, adipsin, IL-6, and TNF-$\alpha$. This chronic inflammation is even further supported by the fact that there are increased levels of C-reactive protein (CRP) in patients with higher BMI. This chronic inflammation may act in conjunction with the insulin resistance mechanisms.[73]

Consistent with the data regarding obesity and increased risk of polyps, there is data to support the association of obesity and colon cancer. A recent review cited eight case controlled studies that linked BMI and colon cancer, which demonstrated a RR $>1$ for both those that are overweight (BMI 25 to 30) and those that are obese (BMI $>30$). Similar results were shown in 10 prospective cohort studies reporting the association of obesity with colorectal cancer with a relative risk ranging from 1.2 to 3.4.[54]

## CONCLUSION

Adenomatous polyps are common, occurring in up to 25% of the population older than 50 years of age in the United States. There are several factors that increase risk, including race, gender, smoking, and obesity. African Americans have a 1.2- to 2-fold increased risk while Hispanic and Chinese Americans may be at lower risk compared with whites. In addition, the participation in screening programs is lower for minority groups. Similarly, gender may impart increased risk as men have higher rates of polyps than women, but women in general are less likely to be screened. With this epidemiological data, tailoring screening programs to include higher risk patients at younger ages, while delaying screening, as well as the inherent risk of complications, for those less likely to benefit may in the long run reduce the risk of colorectal cancer in a cost-effective manner.

Other risk factors that may be modifiable include smoking and obesity, both of which significantly increase risk of colorectal neoplasia. Smoking increases the risk by 1.2 to 2-fold, and obesity increases the risk 2- to 3-fold. Although there are many potential confounding lifestyle factors including diet and exercise that make studying these associations challenging, the trend toward increased risk is clear. With this knowledge, screening of patients with these risk factors including obesity and smoking should be encouraged.

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