

# Risk factors for colorectal cancer

## Abstract

In this review, modifiable and non-modifiable risk factors that contribute to development of colorectal cancer are discussed, exploring the role of genetics and heritable colon cancer syndromes along with medical comorbidities that influence risk. Socioeconomic factors that contribute to colorectal cancer risk are explored along with various health-related behavioral patterns such as obesity, smoking, and diet. Recent data suggesting changes in the incidence of colorectal cancer in the last decade is also reviewed. The rationale for a long-term population-based exploration of these issues is laid out to identify areas in which intervention can promote healthy behaviors, avoid disease, and optimize treatments.

**Keywords:** colorectal cancer, risk factors, genetics, inflammatory bowel disease, diet, obesity, socioeconomic status, young-onset

Volume 2 Issue 2 - 2015

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**Received:** February 20, 2015 | **Published:** April 10, 2015

**Abbreviations:** CRC, colorectal cancer; FAP, familial adenomatous polyposis; CI, confidence interval; ASR, age-specific rate; IBD, inflammatory bowel disease; RR, relative risk; OR, odds ratio; SIR, standard incidence ratio; SES, socioeconomic status; BMI, body mass index; APC, annual percentage change; SEER, surveillance epidemiology and end results

## Introduction

Colon and rectal cancer is a disease that affects people of all ages and races with an annual incidence in the United States of approximately 135,000 and an annual mortality of 51,000.<sup>1</sup> The rectum, including those tumors arising within the terminal 12cm of the gastrointestinal tract, encompasses a disproportionately large volume of malignancy—nearly a third of all colorectal cancers—for reasons that are poorly understood. The primary treatment for non-metastatic colon cancers remains surgical excision; however, rectal cancer is much more challenging to treat as the rectum lies within the bony confines of the pelvis and is closely associated with a number of vital pelvic organs, making surgical removal challenging and facilitating the need for Neoadjuvant treatments. While treatment strategies may differ, it is thought that colon and rectal cancer share the same etiologic and risk factors, thus they are included together within the larger cohort of colorectal cancer (CRC).

The most common form of CRC is adenocarcinoma, which is derived from the glandular mucosal cells that line the gastrointestinal tract and arises from adenomatous polyps. Central to the adenoma-carcinoma sequence, a cell in the mucosa develops mutations that lead to increased cellular division and development of a polypoid lesions.<sup>2</sup> As more mutations accumulate, the cells become dysplastic and develop the ability to invade and grow into deeper layers of the bowel wall, thus transforming into malignant adenocarcinoma. Adenocarcinoma of the colon and rectum is unique because of its well understood premalignant disease process, which has a long preclinical phase allowing for intervention before malignant invasive disease develops. Colonoscopy has been shown in multiple studies to decrease the incidence of colorectal cancer and improve survival.<sup>2-4</sup> It is associated with some risks, such as bowel perforation and bleeding and requires sedation; therefore, it is not an ideal screening tool for every person in a population. Understanding the epidemiology of rectal cancer and how it is changing in our current society can allow

us to better target screening interventions and improve detection and treatment.

The aim of this review is to discuss the current literature on modifiable and non-modifiable risk factors for colon and rectal cancer and to explore changes in the incidence of colorectal cancer in recent years. To achieve this aim, the PubMed database was searched for keywords including “rectal cancer” and “epidemiology,” resulting in 10,722 studies. The search was further refined using keywords of “family history,” “diet,” “risk factors,” “inflammatory bowel disease,” “socioeconomic status,” “young,” “race,” “minorities,” “nationality,” “meat,” “aspirin,” “metformin,” “cholecystectomy,” “radiation,” “obesity,” and “physical activity.” Further studies for review were gleaned from the reference section of initial articles. When multiple articles addressing a topic with similar findings were identified, the most robust, newest, or novel study was selected for inclusion.

## Risk factors for colorectal cancer

Colorectal cancer is a disease that strikes patients in all countries and regions of the world. In a global assessment of cancer incidence in 2012, the latest year which there are statistics, CRC was the third most common cancer overall and the fifth in terms of mortality. The data also support that CRC incidence is higher in more developed regions and almost 55% of CRC cases occur here, with Australia/New Zealand having the highest rate (Age-specific rate (ASR) for men=44.8 per 100,000) and Western Africa the lowest (ASR for men=4.5 per 100,000). Furthermore, there appears to be a slight male predominance with ASR amongst men of 21 per 100,000 compared to an ASR of 14 per 100,000 for women.<sup>5</sup> This translates into a 67% increase in cumulative risk for men, the etiology of which is unclear.

Family history, usually defined as first-degree relatives with colon or rectal cancer, is a classic risk factor and is present in 25% of patients presenting with colorectal cancer.<sup>6</sup> Several dominantly inherited syndromes, familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (also known as Lynch Syndrome), have defined germ line genetic mutations that contribute to an increased risk among family members, but account for less than five percent of all cancers, and there are an endless possibility of other here-to-date unknown mutations that likely contribute. In a large meta-analysis evaluating 8091 cases in 16 studies exploring risk factors for colorectal cancer, the risk for developing CRC was

reported as nearly double in patients with a family member who had a history of CRC (RR=1.80, 95% Confidence Interval (CI) 1.33-1.92).<sup>7</sup>

One of the shortcomings of the literature is the heterogeneous definition of “significant family history;” it can vary from including any colon polyp to only invasive cancer in any family member or only first-degree relatives. Church<sup>8</sup> developed a scoring system and validated this in a prospectively maintained cohort of over 900 colonoscopy patients, classifying patients into low or high-risk groups based upon the total score. The authors found that the mean adenoma rate, a known precursor to CRC, increased with increasing risk assessment in sync with the increasing CRC rate seen in these groups (1% controls, 1.6% low risk, and 3.6% incidence of CRC for high risk).<sup>8</sup> Interestingly, family history has also been associated with improved survival after treatment for CRC. In one Swedish study, patients with one first-degree relative with CRC were 75% less likely to succumb to their disease.<sup>9</sup> This is somewhat counter-intuitive to what is expected, as patients with a positive family history should be more prone to developing polyps and metachronous cancers. The understanding of family history or heritable unclassified genetic changes and their contribution of CRC etiology, epidemiology, and outcomes are still poor, despite recent genetic advances.

Inflammatory bowel disease (IBD), either ulcerative colitis or Crohn’s disease, carries an increased risk of CRC, which is thought to arise from the chronic mucosal inflammation, increased cell turnover, and increased rate of sporadic mutations. In a meta-analysis of 13 studies including nearly 45,000 patients with IBD, the risk of CRC was found to be nearly three times higher than among controls without IBD (RR=2.93, 95%CI 1.79-4.81).<sup>7</sup> In a retrospective Finnish study, where detailed medical databases are maintained due to a national health system, patients with ulcerative colitis were found to be at over twice the risk of developing rectal cancer (SIR=1.76, 95%CI=1.35-2.25) and the risk was highest for younger patients.<sup>10</sup> These results are corroborated by a number of both prospective and retrospective studies in multiple settings and countries.<sup>11-14</sup> Additionally, colonoscopy in patients with IBD has also been shown to reduce CRC risk (OR=0.56, 95%CI 0.39-0.80) and all-cause mortality (OR=0.34, 95% CI=0.12-0.95), suggesting that CRC in this patient population is derived from adenomas similar to the general population.<sup>15</sup>

Very recently, the association of IBD and CRC is being called into question after several large population-based studies did not show an increased risk of CRC among IBD patients.<sup>16,17</sup> Several concerns are raised by the incongruent findings. First, previous literature demonstrating an increased risk was obtained in an era of poor medical control of IBD. The newer biologic agents frequently used to treat inflammatory bowel disease are significantly more effective at controlling the mucosal inflammation, thus reducing the inciting events thought to precipitate CRC in this setting. Secondly, much of the data was acquired from tertiary referral centers whom disproportionately care for patients with severe disease, leading to an inherent referral and sampling bias as the study population reported initially may not reflect the overall true general population of IBD patients. Lastly, IBD patients begin surveillance for CRC at an earlier age and at more frequent intervals than the general population. This may have led to a detection bias in early studies – we are more likely to see something if we are looking for it. IBD is an important consideration when evaluating a patient’s risk factors for rectal cancer, but the true effect is not entirely clear.

The role that race and socioeconomic status (SES) plays in both cancer incidence and mortality is very far from clear and heavily inter-related. The incidence of CRC in the United States in 2013 was 65 per 100,000 for African-American men, while only 53 per 100,000 for Caucasian men, a trend that is also found in women and in mortality data where African-American men have a CRC mortality rate 50% higher than Caucasian men (30 vs. 20 per 100,000). There is some thought that the higher incidence may be a reflection of higher rates of high-risk comorbidities, such as obesity and smoking, as well as consumption of a high-risk diet. In support of this, the authors note that in South Africa, where white patients consume a low-fiber high-meat Western-type diet, the rate of CRC is considerably higher in the white population than the native black population (40 vs. <5 per 100,000).<sup>18</sup> It is incredibly difficult to discern if underlying differences in tumor biology contribute to the higher incidence and mortality rates among black persons in the United States, or if access to care, decreased rates of screening, and utilization of treatment differences are playing significant roles.<sup>18,19</sup>

The risk of CRC is higher among patients in the lowest SES levels, who tend to be older, females, minorities, and tend to have more comorbidities.<sup>20,21</sup> The reasons behind such findings are uncertain and contributing factors can be classified into three groups that help formulate possible hypotheses: tumor, health care, and patient characteristics. How tumor characteristics might be influenced by differences in SES was explored in an excellent review of inequalities in cancer survival by Woods et al.<sup>22</sup> The authors explored the role of cancer stage at diagnosis and found there is little evidence that delays in diagnosis by either patients or providers, which may result in increased stage at presentation, contributes to the disparities in CRC incidence.<sup>22</sup> Health care factors can play a significant role in a patient’s likelihood to be screened for CRC; patients with low incomes are less likely to have received screening, even in health systems where such services are part of government-sponsored preventive care, such as in Germany and the United Kingdom.<sup>22-24</sup> Precisely how these factors influence another to result in disparities in outcomes for different SES levels is still an ongoing area of research.

Patient factors in SES and health risk behavior is yet another area in which the literature is unclear. In a large study from Canada, Goy et al.<sup>25</sup> explored the contribution of health risk behaviors, specifically obesity, smoking, and diet, to the SES association with increased rates of CRC. The authors identified cases from the Ontario Cancer Registry, along with age- and gender-matched controls from the larger population, and collected detailed information regarding potential risky behaviors such as obesity, smoking, coffee and tea consumption, vitamin use, and intake of fiber. The role of these potentially influential behaviors, each thought to have some association with CRC, was determined to contribute <5% to the total increased CRC risk associated with low SES (colon: OR=2.83, 95%CI 2.05-3.93; rectum: OR=2.42, 95%CI=1.78-3.29); however, the authors were unable to account for the level of physical activity, another cofactor and potential confounding variable.<sup>25</sup> In a contrary report, Doubeni et al.<sup>26</sup> also explored the role of behavioral risk factors and obesity in contributing to SES differences in CRC from a National Institutes of Health-AARP Diet and Health Study cohort. This study, which followed participants from a number of U.S. states, collected information on dietary patterns, level of physical activity, smoking, and body mass index (BMI) and ascertained cancer incidence by correlation with each state’s tumor registry data. The authors concluded that behavioral risk factors and BMI explained 44% (95%CI=35.1-57.9%) of the CRC

disparity when evaluated by education and 36% (95%CI=28.0-51.2%) when evaluated by residence location.<sup>26</sup> Complicating matters further, another report demonstrated that in patients with schizophrenia and bipolar disorder, mental health diseases that are disproportionately over-represented in the lowest SES levels, the risk of colon cancer is nearly three times that of the general population (OR=2.90, 95%CI=1.85-4.57).<sup>27</sup> Clearly, these behavioral factors are highly inter-related and interact in a complex way not well approximated by the current modeling systems available.

Obesity is another patient characteristic that is strongly associated with risk of colon and rectal cancers, but it is unique in that it is potentially modifiable. Johnson et al.<sup>7</sup> performed a meta-analysis including 23 studies evaluating BMI and CRC risk finding that for every 8kg/m<sup>2</sup> increase in BMI, the risk of cancer increased by 10%. Even obesity during childhood or adolescence can increase the risk, though the data is less clear due to the significant potential for recall bias.<sup>28,29</sup> Subjects with metabolic syndrome, which includes obesity, diabetes, and pulmonary disease, are at a higher risk for advanced neoplasms found during colonoscopy.<sup>30</sup> In a case-control study of 126 asymptomatic men recruited at colonoscopy, the risk of adenoma directly correlated with BMI and elevated circulating adipokines, suggesting that these obesity-related hormones may influence the development of polyps.<sup>31</sup> In addition to the abundance of clinical data correlating obesity and CRC, there is genetic data linking the two diseases; an international study evaluating the correlation of genetic polymorphisms in obesity-related genes with the incidence of CRC found that two genes had polymorphisms significantly associated with risk of CRC.<sup>32</sup> What remains unclear is if there is any benefit in weight loss to reduce the risk. To date, no longitudinal evaluation of the CRC risk in patients after bariatric surgery has been performed. A surrogate marker for weight loss, physical activity, has been correlated with a reduced risk of CRC, but a study of postmenopausal women who had at least one previous episode of intentional weight loss did not reach a significant decrease in colorectal cancer incidence.<sup>7,33</sup> To evaluate this in a novel way, Sainsbury et al.<sup>34</sup> obtained rectal biopsies from patients after undergoing bariatric surgery and found an elevation in mucosal biomarkers of CRC and evidence of a hyper-proliferative state in the mucosa, findings more characteristic of pro-carcinogenic changes. Future research exploring the potential risk reduction after weight loss and bariatric surgery is certainly warranted, given the high incidence of obesity and the potential impact to the larger population.

Tobacco use has been associated with a number of malignancies, from lung, esophageal and endometrial, and it is also associated with colorectal cancers. In a large case-control study of patients undergoing colonoscopy, those who reported 30 or more cigarettes per day had nearly twice the risk of developing polyps and this was elevated even further for those who had genetic changes making them poor metabolizers of tobacco carcinogens.<sup>35</sup> When looked at in a meta-analysis including 15 studies and nearly 10,000 patients, the risk of CRC increased with increasing duration of tobacco use, topping out at a 26% increased risk for those with a 30 pack-year history.<sup>7</sup> A criticism of these studies is the strong recall bias and the inaccuracies of self-reporting, especially for stigmatized behaviors. Cross et al.<sup>36</sup> evaluated the levels of active tobacco metabolites and self-reported tobacco use, correlating both with CRC risk. The presence of active tobacco metabolites was more strongly associated with risk of CRC than self-reported smoking behaviors (OR 2.68 versus 1.90).<sup>36</sup> The carcinogenic effects of tobacco are thought to occur through CpG island methylation polymorphisms, a known pathway leading to

CRC, as increased CpG methylation is seen in smokers with colorectal cancers.<sup>37</sup> The direct carcinogenic and mutagenic effects of tobacco use are more subtle in colorectal cancers than in other tobacco-associated cancer, but are none-the-less significant.

Dietary factors have long been thought related to the risk of developing colorectal cancer. Meat consumption in particular, both processed and red meat, has been implicated in a multitude of studies with an increased risk estimated at 15-50%.<sup>7,38,39</sup> There are several possible physiologic pathways in which meat consumption can increase cancer risk: heme molecules can produce carcinogens as well as act as DNA mutagens themselves, cooking meat produces carcinogenic compounds, and ingestion of meat can raise bile acids which act on the intestinal mucosa.<sup>38</sup> The consumption of fruits and vegetables is also negatively correlated with the incidence of CRC in a dose dependent manner.<sup>7</sup> Fiber intake has also been associated with a reduced incidence of risk for CRC. In one study examining the food diaries of participants enrolled in a UK cohort study, those with the highest intake of fiber had a 44% decreased risk of CRC compared to those in the lowest fiber intake group.<sup>40</sup> The literature in dietary factors is difficult to interpret as nearly all the information is based upon self-reporting and the confounding nature of covariates (eating vegetables, exercising, and having a normal weight are all part of a "healthy lifestyle") is hard to decipher outside of a controlled experimental laboratory.

Two additional patient-factors also need to be explored as they relate to an increased risk of colorectal cancer; that is previous history of cholecystectomy and ionizing radiation exposure. Cholecystectomy is thought to increase CRC risk by increasing bile salt exposure to the GI mucosa, particularly the proximal colon that may increase the rate of adenoma formation or the rate of transformation to invasive carcinoma. Several large meta-analyses have reported an association, though more recent studies have not demonstrated this effect.<sup>41-43</sup> To explore this association, a large cohort population study of patients undergoing colonoscopy were evaluated for lifestyle and dietary conditions that might be associated with adenoma formation. The authors found 151 of 1,437 patients had cholecystectomy previously and after controlling for confounders such as age, race, and BMI, there was no effect of cholecystectomy on the risk of colorectal adenoma formation.<sup>44</sup> The risk of CRC after ionizing radiation exposure is much less controversial. The greatest evidence comes from Japanese survivors of atomic bomb survivors. In a long-term study of survivors where estimations of radiation exposure can be calculated, the risk of CRC in a person who received more than 2Gray(Gy) of radiation was three times that of those receiving <0.05Gy (Relative Risk 3.11 vs. 1.06, respectively). A similar association of radiation exposure and increased risk of CRC is also seen in childhood cancer survivors. Nottage et al.<sup>45</sup> noted that in long-term follow-up of their patients who underwent radiation from 1960 to 2009, there was a significant association with incidence of CRC. They found that childhood cancer survivors with documented colon radiation exposure had a 11-fold higher risk of secondary CRC compared to the general population, and for every 10-Gy increase in radiation exposure, patients had a 70% increased risk of a secondary CRC. While the increased risk with radiation appears valid and substantial, the risk of CRC after cholecystectomy remains uncertain, however is certainly less than the pain and ongoing risk of complications of untreated gallstone disease.

Much attention has been brought on the possibility of chemoprevention for adenoma development, thus decreasing the risk

of malignancy. Aspirin and other non steroidal anti-inflammatory medications have been explored in several studies, but the data has not been strongly convincing. In one meta-analysis, the reduction on CRC mortality was 44% with aspirin, but this evaluation excluded two large studies using every-other-day aspirin dosing and when these studies were added, the significance was lost.<sup>46</sup> One of the problems with aspirin is the increased risk of bleeding; the reported risk of harm from aspirin use is near 60%, mostly negating any beneficial effects of tumor prevention.<sup>47</sup> Another promising agent is metformin, an oral medication used to treat hyperglycemia in type II diabetes. It's hypothesized that metformin may act by both inhibiting hepatic glucose production and improving peripheral insulin sensitivity, thus reducing hyperinsulinemia, which is known to be carcinogenic.<sup>48</sup> In a systematic review of studies evaluating CRC in diabetic patients, those taking metformin were found to have an 11% reduction in CRC risk, whereas use of other anti diabetic medications was not associated with changes in CRC risk.<sup>49</sup> In another Danish study with significantly longer follow-up, the authors performed a case-control analysis of patients with type II diabetes taking metformin who were retrospectively evaluated for incidence of CRC. They found an association between long-term metformin use and a decreased risk of CRC (OR=0.83, 05%CI=0.49-0.90) that was also dose-and duration-dependent.<sup>50</sup> To date, the literature exploring metformin for chemoprevention is retrospective and observational and includes significant selection bias in who is prescribed the medication along with significant confounding issues. However, the initial results are encouraging and further randomized trials are should be done.

### Changing incidence of colorectal cancer

The incidence of colorectal cancer in the United States is in the midst of changes in recent years. In general, the incidence among persons over 50years of age is decreasing as we have improved upon screening methods and access over the last several decades, as well as risk factor modifications and lifestyle changes.<sup>51</sup> A disturbing new trend has emerged, however. The incidence among young patients, specifically those persons under the age of 40years, has significantly increased in recent years. In a recent publication, You et al.<sup>52</sup> reported the results of an exploratory study in the National Cancer Database, which includes approximately 70% of all new cancers, identifying patients with new CRC.<sup>52</sup> They found that the incidence decreased by 2.5% annually for patients over age 50, while the incidence of CRC in patients under age 50 increased by 2.1% per year since 2001, with the sharpest increase in young patients with rectal cancer (Annual Percentage Change (APC)=3.9%). Furthermore, rectal cancer was more prevalent among minorities (29% versus 17%,  $p<0.001$ ) and those who were not insured or only insured by Medicaid (16% versus 4%,  $p<0.001$ ). When specific age groups were evaluated, the most significant increase in CRC incidence is seen in those ages 20-34years old-even younger than initially thought.<sup>51</sup> If the trend continues, by 2030 there will be a 165% increase in the incidence of rectal cancers for persons under the age of 50-a shocking value by any account.

Not only is the rate of CRC in young person's increasing, but these do not appear to be the same "flavor" of cancer, either. O'Connell et al.<sup>52,53</sup> reported in an extensive review that CRC patients under 40years of age were more likely to have advanced tumors (57-66% versus 32-49% in Dukes' Stage C or D) and poor pathological markers (12-21% versus 10-15% tumors with mucinous features).<sup>52,53</sup> Despite

this, the five-year overall survival for young patients was not different, likely reflecting the increased physiologic reserve of young patients to tolerate aggressive treatments.

### Discussion

The reasons for this changing incidence in the last 15years is not entirely clear. Several hereditary CRC syndromes are associated with young-onset CRC, however, this reflects only a minority of all CRC in patients under age 50. There is some initial research to suggest that young-onset CRC may be characterized by unique mutations when compared to older-onset, but these are still heterogeneous changes and not clearly described or associated with age of onset.<sup>54</sup> What is more suspect, is the increased incidence of other risk factors in the population as a whole. In this review, we have explored how a number of modifiable and non-modifiable risk factors are associated with the incidence of colorectal cancer. It is entirely possible that changes in the incidence of these risk factors have changed the baseline population risk for persons in certain age groups, perhaps leading to a future shift in the mean age of colorectal cancer onset. For example, the rate of obesity in children and young adults is higher than ever before, a plight that is well documented both in the United States and in other countries around the world.<sup>55</sup> These same persons are eating more processed foods and foods that are low in fiber and fresh fruits and vegetables, potentially leading to both poor nutrition and obesity.<sup>56</sup> Lastly, physical activity is becoming less rigorous and young people are participating more and more in hobbies that promote a sedentary lifestyle, such as video-gaming, which may contribute to obesity.<sup>57</sup> It seems quite possible that these changes in such modifiable risk factors as diet, activity, and obesity in a key young age group could be leading to a major shift in the demographics of colorectal cancer in the future.

### Conclusion

As is made clear in this review, the understanding of what causes and contributes to an increased risk for colorectal cancer is woefully incomplete. We do not understand fully how genetics and family history, inflammation, obesity, diet and activity, and socioeconomic status interact to influence the development of adenomatous polyps and colorectal cancer. What we do know, is there is no single inciting event for the vast majority of patients and a multitude of various factors contribute in a complex and inter-related way. One of the limitations of studying a process such as this is the long-term follow-up of patients and study participants. In the United States, there is no single institution that leads a "National Colorectal Cancer Database" that includes important data not only for evaluating how the incidence changes and exploring possible causes, but also for looking at outcomes after treatment and trends in survival. Several large, national databases attempt to compile oncology data-the Surveillance, Epidemiology, and End Results (SEER) database and the National Cancer Database of the American College of Surgeons are two commonly used ones - however, they lack detail specific for colorectal cancer regarding exposures, treatments, comorbidities, and surgical outcomes as well as longitudinal data in individual patients that would make them useful for such analysis. Furthermore, they do not contain a tissue bank or repository, and correlating pathologic or genetic details with outcomes or inciting exposures is impossible.

A longitudinal cohort study or database of colorectal cancer patients should include information directed at a number of

questions that currently need to be addressed: How do the changing characteristics of our population influence the face of colorectal cancer? Is exposure in a wide population contributing to changes in CRC incidence? How are we doing at treating this disease and what are the outcomes? Is there any benefit in chemoprevention for high-risk patients? In addition, a longitudinal database would allow us to collect information on loco-regional trends in colorectal cancer that can help improve outcomes for the patients in our own communities. This level of detail and information is sorely needed to continue the investigation into the changing face of colorectal cancer in the modern age.

## Acknowledgements

I would like to thank Dr. Jane Kotchen, of the Department of Epidemiology at the Medical College of Wisconsin, for her assistance and feedback in developing this article.

## Conflict of interest

The author declares no conflict of interest.

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