Chapter 16

Acquired Risk Factors for Colorectal Cancer

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Abstract

The risk of developing colorectal cancer (CRC) is influenced by several acquired risk factors, including environmental exposures and comorbid medical conditions that are partially genetic in nature. These risk factors are based on data almost exclusively derived from observational studies. Because of the possibility of bias due to confounding, these acquired risk factors should not be automatically assumed to be causative, and in fact some may not be truly independent risk factors. Acquired risk factors include the following categories: 1) dietary factors, 2) lifestyle factors, 3) side-effects of medical interventions, and 4) comorbid medical conditions.

Dietary factors that potentially increase the risk of CRC include low fruit, vegetable, or fiber intake, high red meat or saturated fat consumption, and exposure to caffeine or alcohol. Of these factors, the significance of low fruit, vegetable, and fiber intake has been called into question because of contradictory results from large observational studies and negative results from randomized trials. The association of high red meat or saturated fat consumption with increased CRC risk is supported by the preponderance of observational data. Lifestyle factors include lack of exercise and smoking. These risk factors are supported by observational data of moderate quality.

Medical interventions that may increase the risk of CRC include pelvic irradiation, cholecystectomy, and ureterocolic anastomosis after major surgery of the urinary and intestinal tracts. Aside from cholecystectomy, these risk factors are supported by observational data from small studies only, therefore their validity is not well established.

Finally, comorbid medical conditions that are associated with increased risk of CRC include Barrett's esophagus, human immunodeficiency virus infection, acromegaly, and inflammatory bowel disease. The association between inflammatory bowel disease and CRC is well established and it forms the basis for widely adopted colonoscopic surveillance recommendations from national medical organizations. The other factors are supported by limited observational data only and are still controversial.

Key words: Colorectal cancer, adenoma, risk factors, fiber, inflammatory bowel disease, surveillance.

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1. Introduction

The risk of developing colorectal cancer (CRC) is influenced by both environmental and genetic factors. This chapter reviews acquired risk factors, including environmental exposures and comorbid medical conditions that are associated with CRC. Genetic factors such as family history or genetic cancer syndromes (e.g., familial adenomatous polyposis) will not be discussed; however, we will cover some medical conditions associated with an increased the risk for CRC that may be partially genetic in nature (e.g., diabetes and inflammatory bowel disease [IBD]). Acquired risk factors are divided into the following categories: 1) dietary factors, 2) lifestyle factors, 3) side-effects of medical interventions, and 4) comorbid medical conditions.

2. Dietary Factors

2.1. Fruit, Vegetable, and Fiber Intake

Several epidemiologic studies have shown an association between a diet low in fruits and vegetables and increased risk of CRC *(1, 2)*. It is hypothesized that the fiber, antioxidant vitamin, folic acid, micronutrient, or phytochemical (flavone) content in vegetables and fruits may exert a protective effect. The relative risk of CRC is approximately 0.5 when we compare groups with the highest vegetable and fruit intake to those with the lowest *(2)*. Furthermore, some observational studies have noted an inverse relationship between dietary fiber consumption and risk of colorectal adenomas and/or CRC *(3–6)*.

On the other hand, some studies have not shown this association. In an analysis that combined data from the Nurses Health Study (88,764 female subjects) and the Health Professionals Follow-up Study (47,325 male subjects), there was no significant association between the intake of fruits or vegetables and the incidence of CRC *(7)*. Another study looking at data only from the Nurses Health Study also found no relationship between fiber intake and the risk of CRC or colorectal adenoma *(8)*. Moreover, two large randomized controlled studies in the USA concluded that fiber supplementation had no significant protective effect against the development of metachronous adenomas in patients who had undergone colonoscopic polypectomy *(9, 10)*. More recently, the Women's Health Initiative Trial also found no protective effect of a low fat, high fiber and high fruit and vegetable content diet against CRC development *(11)*. Formal meta-analyses have corroborated these findings. For example, a Cochrane systematic review of five studies concluded that increased dietary

fiber did not appear to reduce the incidence or recurrence of colorectal adenoma over a 4-year period *(12)*. Similarly, a meta-analysis of 13 prospective cohort studies found that dietary fiber intake was not an independent risk factor for CRC *(13)*. The reasons for the discrepancies among the available studies are unclear. At present, the degree of protection from the consumption of vegetables, fruits, or dietary fiber remains unsettled.

2.2. Red Meat and Saturated Fat Intake

Some studies have suggested that a diet high in red meat, animal fat, or cholesterol content may be associated with CRC development, especially in the left colon *(14–19)*. In one study, subjects in the highest quartile of cholesterol consumption had a significantly higher risk of CRC compared with subjects in the lowest quartile (relative risk of 3.26), even after adjusting for other variables such as fruit and vegetable intake *(15)*. Most studies have not shown a similarly increased risk for poultry meat. However, it should be noted that there are also some studies that have failed to find a significant relationship between red meat intake and CRC *(20)*. Although the data are not completely consistent, the bulk of the available evidence supports the view that red meat consumption is associated with an increased risk of CRC, as shown by a systematic review *(21)*.

2.3. Alcohol

An association between heavy alcohol consumption and increased risk of CRC has been reported in several observational studies *(22, 23)* as well as meta-analyses *(24)*. As with most epidemiologic associations, there were contradicting data as well *(25, 26)*. A pooled analysis of eight cohort studies estimated that the CRC risk was increased slightly (relative risk of 1.41) in those whose alcohol consumption exceeded 45 g/day *(27)*. The risk was increased to a lesser degree in those with alcohol consumption between 30 to 45 g/day. This phenomenon may be the result of decreased folate absorption and intake in alcoholic patients *(28, 29)*.

2.4. Caffeine

The relationship between caffeine consumption and CRC is unresolved. Although a link between low rates of coffee consumption and an elevated risk of CRC was reported in a meta-analysis of 12 case–control studies *(30)*, data from the Nurses Health Study and the Health Professionals Follow-up Study did not support this *(7)*.

3. Lifestyle Factors

3.1. Physical Activity

Observational data suggest that inadequate regular physical activity is associated with increased risk of CRC, an effect that may interact with high energy intake, obesity, and the metabolic syndrome *(31–33)*.

In one study, sedentary workers had a significantly increased risk of CRC compared with those engaged in light or heavy physical activity *(34)*. The mechanism for the apparent protective effect of physical activity is not known.

3.2. Cigarette Smoking

Smoking has been associated with increased CRC incidence and mortality in some studies *(35–37)*.

4. Previous Medical Interventions

4.1. Pelvic Irradiation

Previous exposure to pelvic radiation may be associated with a higher risk of CRC after a 5- to 10-year lag period *(38)*. A history of radiation therapy for prostate cancer correlated with an increased risk of rectal cancer in a large retrospective study *(39)*. The magnitude of risk was similar to that observed in patients with a family history of colorectal neoplasia, suggesting that tighter surveillance may be appropriate. However, whether such increased screening would improve CRC outcomes and prognosis is unclear.

4.2. Cholecystectomy

A relationship between cholecystectomy and right-sided colon cancer has been described in some reports. Patients who had undergone cholecystectomy demonstrated a slightly increased risk of right-sided colon cancer (with a standardized incidence ratio of 1.16) but not left-sided cancer *(40)*. However, discordant data have also been published *(41, 42)*. Although publication bias needs to be kept in mind, the results of meta-analyses have in general supported this association with proximal colon cancers *(43, 44)*.

4.3. Ureterocolic Anastomosis

A few studies have reported an apparently increased risk of colorectal neoplasia near ureterocolic anastomoses after major surgery of the urinary or intestinal tract *(45, 46)*. The presumed mechanism is exposure of colonic mucosa to carcinogenic substances from the urinary system.

5. Concurrent Medical Conditions

5.1. Barrett's Esophagus

An association between CRC and Barrett's esophagus has been proposed *(47–49)*, but conflicting data are also available *(50–55)*. Pooling of data in formal meta-analysis has supported the increased risk of CRC in patients with Barrett's esophagus *(56)*.

This apparent association may be due to bias and confounding because patients with Barrett's esophagus and CRC share many risk factors.

5.2. Human Immunodeficiency Virus Infection

Some studies have shown an increase in the incidence of colorectal neoplasia in patients infected with the human immunodeficiency virus *(57)*. This is thought to be a result of increased susceptibility to carcinogenesis due to chronic immunosuppression.

5.3. Diabetes Mellitus

Diabetes mellitus may be associated with an elevated risk of CRC *(33, 58–60)*. A meta-analysis of 15 studies found a significantly increased risk of CRC in diabetic patients compared with nondiabetic control subjects (relative risk of 1.30) *(61)*. One possible explanation linking diabetes to CRC is hyperinsulinemia because insulin and insulin-like growth factor are important growth factors for colonic mucosal cells and stimulate colonic neoplastic cells *(62)*. A relationship between serum levels of C-peptide, an indicator of insulin production, and CRC risk was reported from the Physicians' Health Study *(63)*. Chronic insulin therapy may also increase the risk of CRC in diabetic individuals. A case–control study estimated that the age- and sex-adjusted risk of CRC associated with more than 1 year of insulin use was 2.1 *(64)*.

5.4. Acromegaly

There is some evidence that colorectal adenomas occur with increased frequency in acromegalic patients *(65, 66)*. A prospective controlled study found that adenomatous polyps occurred in 22% of male acromegalic patients compared with 8% of control subjects *(65)*. Patients with acromegaly were more likely to have multiple and proximal adenomas. Reduced expression of the peroxisome proliferator-activated receptor gene has been implicated in such patients.

5.5. Inflammatory Bowel Disease

Patients with chronic IBD involving the colon are at significantly increased risk for CRC *(67, 68)*, and special colonoscopic surveillance measures are recommended for such individuals *(69–71)*.

In ulcerative colitis (UC), the risk of CRC depends on the duration and extent of disease. The risk is highest in those with extensive colitis or "pancolitis," with a standardized incidence ratio of 2.4 according to a population-based study in the USA *(72)*. Compared with age-matched controls, the risk begins to increase 8–10 years following the onset of UC symptoms *(73)*. Overall, the approximate cumulative incidence of CRC is 5–10% after 20 years, 12–20% after 30 years, and 30% after 35 years of UC *(67, 73)*. However, in a Danish study, the risk of CRC in patients with long-standing UC was not different from that of the general population, a finding that may be a reflection of the more aggressive surgical approach in Europe toward patients poorly responsive to medical treatment *(74)*. It is believed that

the risk of CRC increases after 15–20 years (approximately 10 years later than in pancolitis) in patients with left-sided colitis distal to the splenic flexure *(75)*. However, some studies on patients with left-sided colitis have described rates of CRC similar to those seen in patients with pancolitis *(76)*. Most authorities agree that patients with limited ulcerative proctitis are not at increased risk for CRC, and therefore do not require special surveillance *(77)*.

Several factors may influence the risk of CRC in IBD patients. For example, the risk is increased in those with early onset of disease (prior to age 15 years). One study reported that "backwash ileitis" was an independent risk factor for CRC *(78)*, but subsequent studies have not confirmed this association *(79, 80)*. The severity of inflammation may also be an important marker of CRC risk, as suggested by case–control studies *(79)*. A meta-analysis concluded that there is an increased risk of CRC in patients with UC complicated by primary sclerosing cholangitis (PSC), when compared with UC patients without PSC *(81)*. In patients with PSC and UC, the colon cancer was more likely to occur in the proximal colon, suggesting a possible carcinogenic role of bile acids.

Earlier reports found no increased risk of CRC in patients with Crohn's disease (CD), but these did not adjust for disease duration and extent. More recent studies have reported that the risk of CRC in long-standing CD involving the colon is probably comparable to that of UC *(68, 82–84)*. In a population-based study from Sweden, the relative risk of CRC was 5.6 in CD patients with disease restricted to the colon *(68)*. Increased risk of CRC in CD patients has been reported in other studies *(85, 86)*. CRC in CD develops over a similar time frame as in UC *(87, 88)*. The median duration of disease prior to the diagnosis of CRC was comparable for CD and UC (15 and 18 years, respectively); however, the median age at diagnosis of CRC was somewhat older in CD (55 years) than in UC (43 years).

The mean age of onset for IBD-associated CRC is lower than that for sporadic CRC (45 versus 60 years). Unlike CRC associated with CD, which is evenly distributed between the right and left colon, CRC associated with UC is more common in the rectum and sigmoid colon *(87)*. Synchronous tumors are much more common in patients with IBD than in those with sporadic CRC. Furthermore, poorly differentiated, anaplastic, and mucinous carcinomas are more common in IBD-associated CRC. Despite this, there are conflicting data as to whether patients with IBD-associated CRC have a worse prognosis compared with patients with sporadic CRC *(89, 90)*. Interestingly, some studies suggest that the prognosis for IBD-associated CRC is similar to (or better than) that for sporadic CRC when matched for stage *(91, 92)*.

Although no large randomized controlled trials have proven that intensive colonoscopic surveillance reduces mortality, surveillance is widely practiced and recommended by guidelines from

various societies *(69–71)*. For UC, it is generally recommended that colonoscopic surveillance should begin after 8 years in patients with pancolitis, and after 15 years in patients with colitis involving the left colon. Colonoscopy should be repeated every 1 to 2 years. Two to four random colonic biopsy specimens every 10 cm should be taken with additional samples of suspicious areas. Patients with PSC (including those who have undergone orthotopic liver transplant) may need more frequent colonoscopy. For CD involving substantial areas of the colon, the UC surveillance strategy discussed above also applies, according to most guidelines.

It is generally accepted that CRC in IBD is preceded by dysplastic changes. Thus, dysplasia may be a marker for coexisting and subsequent malignancy. This hypothesis serves as the rationale for colonoscopic surveillance. There is agreement that the finding of high-grade dysplasia warrants prompt colectomy because of the high risk of synchronous CRC. The approach to low-grade dysplasia seen in random colonic biopsies is more controversial, although some institutions currently also recommend colectomy for patients with definite low-grade dysplasia confirmed by at least two expert pathologists *(93)*. This is justified by the high rate of progression from low-grade to high-grade dysplasia or CRC, estimated to be 53% at 5 years *(94)*. However, other studies have not shown such a high rate of progression *(95–97)*. IBD patients who have dysplasia associated with a lesion or mass (DALM) are also at high risk for CRC and may benefit from prophylactic colectomy *(98, 99)*. Whereas non-adenoma-like DALMs are an indication for colectomy, sporadic adenomas may be removed endoscopically with close follow-up. As mentioned above, there have been no randomized trials showing a direct mortality benefit from surveillance. However, there is evidence from retrospective studies that cancers tend to be detected at earlier stages during surveillance and that IBD patients diagnosed with CRC after they developed symptoms had worse prognosis than those detected during surveillance *(100, 101)*. Also, a case–control study found that the incidence of CRC was reduced by surveillance colonoscopy *(102)*.

6. Conclusions

In summary, numerous acquired risk factors for CRC have been reported in the medical literature. These risk factors are based on data almost exclusively derived from prospective, retrospective, or cross-sectional observational studies, large case series or retrospective case–control studies. Because of the possibility of bias and confounding in such studies, these risk factors should not be automatically assumed to be causative, and in fact some may not

be truly independent risk factors. This review serves to highlight the need for additional high-quality studies, preferably prospective, interventional, and randomized (if feasible), in order to further investigate the importance of each of these risk factors.

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