Colorectal Adenocarcinoma and Inflammatory Bowel Disease: An Update and Review

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Abstract

Inflammatory bowel disease and its two prototypic illnesses: Crohn's disease and ulcerative colitis have long been thought to confer an increased risk of colorectal cancer, although the magnitude of this effect has been difficult to elucidate. The driving factors behind this relationship include genetics, microbial disturbances, alongside molecular and inflammatory misregulation. The epidemiologic understanding of the inflammatory bowel disease-colorectal cancer relationship has evolved over the last decade. This review will focus on the epidemiology of colorectal cancer in inflammatory bowel disease, and detail the elements driving disease development. Patient risk factors, many that increase the intensity or duration of inflammation, will be detailed. Finally, a practical approach to the tools that clinicians have at their disposal in preventing this disease, including the effect of different medications and timing of colonoscopy will be presented.

Introduction

Inflammatory bowel disease (IBD) encompasses two illnesses - Crohn's disease (CD) and ulcerative colitis (UC) - that are characterized by chronic intestinal inflammation. The disease progression of IBD is heterogeneous, as is the response of individual patients to different treatments. Typically IBD and the resultant inflammation cause a combination of abdominal pain, diarrhea, intestinal bleeding, weight loss, malabsorption and nutritional deficiencies. The onset of IBD is greatest in early adulthood, with peak incidence among those aged 18 to 35 [1]. Diagnosis at this stage of life has a significant impact on employment and psychosocial functioning of the affected. Up to 25% of cases of IBD are diagnosed during childhood [2]. There are approximately 1.4 million Americans living with IBD, with a prevalence of 201 and 238 per 100,000 for CD and UC respectively [3]. Medical costs for each IBD patient in the United States is estimated to be over $18 000 per year [4].

There is a concern in patients with IBD that their disease can predispose them to an increased risk of neoplasia of the bowel. This increased risk was first noted by Crohn and Rosberg in 1925 [5] and further explored in the 1930s in patients undergoing an at-the-time popular procedure for IBD, bypass of the diseased segment. Those who had a section of diseased small bowel left in situ seemed to develop carcinoma at an abnormally high rate [6]. The increase in risk was thought to be secondary to long-standing chronic inflammation [7]. This literature review, constructed after a review of PubMed and Medline databases using the search terms 'Crohn's Disease', 'Ulcerative Colits', 'inflammatory bowel disease' and 'colorectal cancer' will provide a narrative overview of the epidemiology of cancer in IBD, the molecular basis of these changes, how different IBD phenotypes affect cancer, and how the tools modern clinicians use to treat IBD affect the progression of this disease.

Epidemiology

CRC is a major cause of mortality throughout the world [8], is the third most common cancer worldwide and is the fourth most common cause of death among cancers [9]. In IBD the outcomes may be worse than in the general population, with a 2 fold increase in mortality associated with IBD-associated CRC compared to sporadic cancers [10]. Although an increased CRC risk associated with IBD has been suspected, the exact effect, and its magnitude, has been difficult to determine. This difficulty stems from a number of factors, one of which is the scope of patient recruitment. Tertiary referral based studies likely overestimate the risk by including mainly subjects with severe disease, and population-based studies, are likely to underestimate the risk by including patients with mild disease. Another factor that limits the generalizability of epidemiological results is the geographic gradient in CRC and IBD-associated CRC [11]. Studies from both European and Asian centres have shown differences in IBD-associated CRC within each respective region [12-15]. Regardless of these issues, there are important lessons to be learned from the data.

First, UC seems to be associated with a greater risk of IBD-associated CRC than CD, and in fact, the role of CD in the development of CRC is equivocal. Initial studies involving UC-associated CRC were hospital based, and neglected the general IBD population [16]. A widely-cited 2001 meta-analysis of these studies indicated that incidence in UC patients was 3/1000 person-years disease duration (PYD) [16]. In this analysis, there was a 2% probability of suffering from a CRC in UC patients after 10 years of disease, 8% by 20 years and 18% by 30 years. However, care of UC patients has changed a great deal in the intervening years, and along with changes in the methodology of patient recruitment, this has led to a change in reported prevalence. From 1979 to 1988 the relative risk of CRC in UC was noted to be 1.34 with that decreasing to 0.57 between 1999 and 2008 [17], and similarly incidence rates have decreased from 4.29/1000 PYD in the 1950s to 1.09/1000 in the first part of the 2000s [18]. Moreover, incidence rates in the first, second, and third decades of disease have decreased to 1.01/1000, 3.75/1000 and 5.85/1000 PYD respectively [18].

Though the link between CRC development and UC seems to

be weakening, the association between CD and CRC has never been especially strong. This may be due to the heterogeneity of disease phenotype, and specifically the degree of colonic involvement. That is, in those CD subjects with extensive colitis, there appears to be somewhat of an increased risk, while those with disease limited to the small bowel appear to be at a baseline risk [19-21]. When all phenotypes of Crohn's disease are included, some studies place the relative risk of CRC between 2 and 3 [22-24], whereas others do not demonstrate any increased risk [17,25,26].

The development of CRC and the impact of IBD

There are a variety of epithelial-derived neoplastic growths that occur in the colon, ranging from benign tumors to invasive cancers. Over 90% of CRC are carcinomas, and 95% of those cancers are adenocarcinomas [27]. It is hypothesized that adenocarcinomas arise from adenomas, which arise from normal epithelium [28]. A large body of work has focused on the molecular and genetic basis of CRC, with genomic instability, the mutational inactivation of tumor-suppressor genes, and the activation of oncogene pathways taking center stage [29]. A number of pathways have garnered special interest, and seem to play a prominent role in IBD-associated CRC.

One such pathway involves an important class of molecules, toll-like receptors (TLRs). TLRs recognize molecules unique to microbes, and constitute the primary strategy for self versus non-self-discrimination. TLR-4 variants are associated with Crohn's disease [30] and with the adaptor protein- myeloid differentiation factor 88 (MYD88), a common signal transduction molecule for many TLRs-. MYD88-knockout mice were shown to be highly susceptible to the development adenocarcinoma of the colon in some experiments [31] but decrease intestinal tumorgenesis in other models [32,33]. The role of TLR and carcinogenesis is complex, and future work may focus on downstream molecules (i.e. MYD88) to pinpoint their effect.

Cytokines encompass a wide-body of signaling proteins and include a number of pro-inflammatory markers, such as tumor necrosis factor-α (TNF-α), interleukin-6 and interleukin-21. TNFA is highly expressed in the colon of IBD patients [34], anti-TNF antibodies are commonly used in the treatment of IBD. Blocking downstream TNFA products in a mouse-model has demonstrated a reduction in tumor formation [35]. Interleukin-6 is also associated with IBD and IBD-associated CRC [36]. Interleukin-21 has a broad set of target cells, including T cells, B cells, natural killer cells and dendritic cells [37]. In interlukin-21 knockout mice tumorgenesis has shown to be decreased, along with a decrease in colitis [38]. The inflammatory effects of these three cytokines likely play a role in IBD-associated CRC, though other mechanisms of tumorigenesis are a possibility.

A number of transcription factors have been implicated in IBD-associated CRC [39], the two most well understood being NF-κB, and STAT3. NF-κB, which is hyperactive in IBD, regulates a number of cytokines, and has been seen to regulate proliferation, and survival in tumor cells [40]. By blocking its effect in the intestinal epithelial cells of a mouse model, a dramatic decrease in tumor incidence was noted, despite an increase in inflammation [41]. This suggests that an increase in inflammation may stimulate tumorigenesis but cells first must possess the ability to proliferate in these environments for abnormal cells to take hold. STAT [3], which is activated downstream in a pathway initiated by interleukin-6, is present in the inflammatory environment of tumor cells [42]. It regulates antiapoptotic proteins, and proto-oncogenes [43]. STAT3 expression is greater in UC patients with CRC [44]. Taken together, these molecular changes provide a framework for which IBD-associated CRC can take hold.

Microbes

The human intestine provides a diverse ecosystem which supports a multitude of microorganisms. It has been estimated that the average human's gut contains approximately 10^{14} microorganisms [45]. The majority of these species cannot yet be cultured [45]. There are only a few dominant phyla found in the gut. These include Firmicutes, Bacteroides, Actinobacteria, Proteobacteria, and Fusobacteria. Although these types dominate, there are over 1500 genera and thousands of different species present [45]. IBD patients exhibit a "dysbiosis" in their gut microbiota but whether these changes are causative or associative remains to be shown [46,47]. A number of difference have been described in the literature, with studies having found changes in the number of microbes present, alterations in community composition, increased adherence to mucosa, invasiveness or virulence of select species, and alterations in functional and metabolic characteristics [46,47]. Germ-free mice, those with no intestinal bacteria, are less likely to develop oncogenetic mutations or tumor formation [48,49].

A number of individual bacterial species have been indicated in the development of IBD-associated CRC. Helicobacter species leads to cancer development in a mouse-model of colitis, while eradication protected the gut from tumor formation [50]. Adherent-invasive Escherichia coli is also associated with invasive carcinoma in the same mouse model [51]. *B. fragilis* triggers colitis but also seems to contribute to oncogenic signaling via disruption of E-cadherin signaling [52,53]. The question of whether this microbe causes CRC or simply thrives in a niche created by the development of CRC remains to be seen.

Risk Factors

A number of factors are thought to be associated with an increased risk of IBD-associated CRC. The majority of these can be thought of as those that increase the intensity or duration of inflammation. Classicaly, disease duration has been implicated, and the landmark meta-analysis by Eaden demonstrated appreciable risk occurring at approximately 10 years after disease onset [16]. This wisdom has been called into question recently, as two large studies did not show any trend of increased incidence with increased disease duration [54,55].

An increase in inflammation extension seems to increase the risk of CRC. Regarding UC, proctitis has a low relative risk (1.7) while pan-colitis demonstrates a much high relative risk (5.6) [55]. As previously stated CD subjects with colitis appear to incur an increased risk of CRC compared to those with disease limited to the terminal ileum [19-21]. These observations are consistent with the cancer field effect theory, where when a large number of cells are exposed to a potentially carcinogenic insult, in this case inflammation, there is a higher likelihood in developing carcinogenic alterations. There is also evidence that inflammation intensity increase the risk of CRC. C-reactive protein and erythrocyte sedimentation rate are markers of inflammation, and can be taken as surrogate for disease activity [56]. IBD patients with an increase in either of these markers have been shown to be more likely to develop CRC [56]. Histologic inflammation has been shown to be associated with IBD-associated CRC [57,58]. In terms of disease flares and increased CRC risk evidence is mixed. Some studies demonstrated an association between increased hospitalizations and increased frequency of IBD exacerbations and increased risk of CRC [59,60]. On the other hand, other studies have shown that exacerbations have not increased CRC risk [61].

Factors outside of extent and intensity of inflammation may also

affect CRC risk. There is equivocal evidence regarding age at diagnosis of IBD, and CRC risk. Initially early diagnosis was associated with increased risk [16,19], while other work has demonstrated the opposite effect, with those who are elderly at diagnosis at higher risk [62,63]. Male gender also increase the risk Primary sclerosing cholangitis confers a 4-fold increase in risk of CRC development in UC patients [17,64-66], with the increased risk persisting following liver transplantation [67,68].

Familial clustering in cases of inflammatory bowel disease and Crohn's disease is well recognized. A concordance study focusing on twins in northern Europe was the first large scale study to demonstrate a genetic component 1. A familial predisposition has also been noted in patients with CRC. IBD patients may have up to a 2.5 times risk of developing CRC if they have a family history of CRC, and up to a 9 times higher risk if a first-degree relative has been diagnosed with a CRC before 50 years of age [69].

Prevention of CRC

While the understanding of the initiating events of IBD-associated CRC will be important in preventing this disease in the future, there are currently a number of clinical treatment options which can alter the disease's course. Of course, total proctocolectomy totally removes the risk of CRC, but less extreme options are often preferable, especially in CD where complete removal of colonic tissue would not eliminate the CD.

5- aminosalicylic acid (5-ASA) compounds are used to interfere with a number of metabolic and genomic pathways, some of which are implicated in CRC [70]. Some evidence for a beneficial effect comes from a 2005 meta-analysis, which demonstrated a decrease in CRC in those using 5-ASA [71]. There appears to be a dose-response relationship for chemoprevention, with a greater benefit being shown when subjects used 1.2g per day compared to those using less, though lower doses still exhibited a protective effect [61,72]. A meta-analysis of the data revealed inconsistent results though, largely dependent on the referral base of each study [73]. 5-ASA is a treatment that is recommended in some cases of UC, while expert opinion cautions against its use in CD [74,75].

Ursodoxycholic acid was first used in UC patients, to treat effects of contaminant primary sclerosing cholangitis, and a relationship with decreased CRC was noted [76]. Follow-up studies have demonstrated mixed results [77-79], with some studies even noting an increase CRC risk in when high-doses of ursodoxycholic acid were employed [80].

Immunomodulators are another popular class of drug in IBD [81]. This class of medications mainly refers to azathioprine and methotrexate. Both of these drugs are considered anti-inflammatory. Methotrexate and its breakdown products act to inhibit enzymes in the metabolic pathway for creation of folic acid. At high doses, methotrexate is responsible for inhibition of DNA, RNA and protein synthesis, but at lower doses it likely decreases other folate dependent enzymes that prompt and propagate inflammation. Azathioprine is a purine analogue. It inhibits DNA synthesis, by acting as a prodrug for mercaptopurine. It has a strong effect on immune cells, and can leave the patient at risk of bone marrow suppression [81]. Recent evidence, in the form of a large prospective epidemiologic study suggested that thiopurines are protective against CRC in IBD [82]. Despite other recent literature has supporting this decrease [83,84], the risk profile associated with these drugs leave them an unlikely candidate to be recommended as therapy as a preventative method alone.

The newest drug classes used in IBD have been termed 'biologics'. These are anti-tumor necrosis factor (TNF) drugs, the two most prominent examples being infliximab and adalimumab [81]. Infliximab is a chimeric monoclonal artifical antibody developed in mice and engineered for humans. Adalimumab is a human monoclonal antibody. Both of these agents have been shown to be very potent in inducing and maintaining remission of CD, but due to their relatively recent discovery, long term efficacy and side effects have not been well described [81]. They can induce and maintain IBD remission, and that reduction in long standing inflammation may decrease CRC risk. A direct effect has been suggested, where mice with a pre-disposition to colonic neoplasia are delivered an TNF-α antagonist, tumor number and size decreased [85].

Initial studies on folate supplementation in the IBD population demonstrated a greater than 60% decrease in the incidence of colonic neoplasia [86], though this study failed to achieve statistical significance. Vitamin D deficiency has been associated with an increased risk of CRC [87], and supplementation should be considered in IBD.

Statins may promote apoptosis of colon cancer cells [88], and a subset analysis of a population-based study demonstrated a 94% CRC risk reduction in IBD patients taking statins [89].

Another tool that clinicians have is screening colonoscopy, with the caveat that screening has not been shown to improve survival in patients with extensive colitis [90]. The goal of most surveillance programs is early detection and mortality reduction from IBD-associated CRC. Recent advance in chromoendoscopy have shown improved dysplasia detection rates, and should prove to be an effective tool against IBD-associated CRC [91-95]. Guidelines agree that dysplasia screening should take place through colonoscopy beginning 8 to 10 years after diagnosis (excluding isolated proctitis who should be screened as the general population) [96-98]. The picture becomes less clear following the initial colonoscopy as patients must be risk stratified at this point. Low-risk patients are those with quiescent disease or left-sided colitis alone, and should be screened every five years. Intermediate-risk includes those with mild inflammation, post-inflammatory polyps or a family history of CRC in a first degree relative over [50]. These patients require screening every three years. The high-risk group, who should be screened yearly, includes those with moderate or severe disease activity, primary scleroscing cholangitis, colonic stricture in the previous 5 years, previous dysplasia in the last 5 years and a family history of CRC in a first degree relative under [50,98].

Conclusion

The relationship between IBD and the inflammation that it causes, the CRC that arise in this environment is a complicated one. Currently, the clinician can use the available tools to first, control inflammation, and second, actively screen and risk stratify those with IBD, in an attempt to optimize the care of this condition. The important question of the interaction between risk factors at the genetic and molecular level will continue to be explored in the hope that a greater understanding of IBD-associated CRC will lead to more targeted preventative therapies, and better management of this disease process.

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