Gastrointestinal & Digestive System

Jones et al., J Gastroint Dig Syst 2014, 4:1
http://dx.doi.org/10.4172/2161-069X.1000164

Review Article Open Access

The Risk of Colon Cancer in Inflammatory Bowel Disease

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Abstract

Inflammatory Bowel Disease (IBD) involves chronic inflammation in the patient's digestive track, leading to the development of ulcerative colitis and Crohn's disease. IBD is painful and debilitating disease that develops into life threatening risk in the long run, particularly colorectal carcinoma (CRC). As per the studies, there are 18% of chances for the IBD to develop into colorectal carcinoma after 30 years. Although IBD is contributing to only 1% of overall Colorectal Cancer cases, the mortality rate is pretty high among the colorectal cancer developed due to IBD. The present article prescribes guidelines for screening and surveillance that minimizes the risks of CRC.

Keywords: Inflammatory Bowel Disease (IBD); Colitis and crohn's disease; Colorectal cancer (CRC), Screening and surveillance

Introduction

Inflammatory Bowel Disease (IBD), in the form of Ulcerative Colitis or Crohn's Disease, is considered a high risk condition for the development of colorectal carcinoma (CRC). Previous studies, based predominantly upon patients with Ulcerative Colitis, have demonstrated an 18% chance of developing CRC after 30 years of disease [1,2]. Although IBD accounts for less than 1% of colorectal cancers diagnosed, IBD associated CRC has been shown to carry a higher mortality rate compared to CRC arising in average risk populations [3].

Although surveillance has never been shown to have a positive effect on mortality, guidelines on screening and surveillance have been established for this specific population. These current guidelines based upon expert opinion focus on the detection of dysplasia and identification of patients who will benefit from closer, more frequent endoscopic screening and surveillance. The risk for development of CRC is not uniform for all IBD patients and different patient characteristics and disease manifestations need to be taken into account. This article will review specific risk factors as they relate to CRC development in the IBD population and the current screening/therapeutic guidelines for these patients.

Colon Cancer Risk in IBD

Overall risk

Much of the data related to the epidemiology of CRC in IBD is older and largely related to UC. In addition, difficulties arise when comparing studies looking at different patient populations in terms of severity, disease location, disease extent and the time-period in question. Many early cohort studies focused on referral populations which likely had more extensive, severe disease at presentation compared to more recently published population studies. There has been wide variability in reported risk of CRC in IBD patients, ranging from almost no risk compared to general population to an incidence 60% higher than the general public, with a reported 18% cumulative chance of CRC after 30 years [1,4-6]. An early meta-analysis by Eaden et al. [2] reported an overall risk of 2% at 10 years and up to 18% at 30 years. Other studies have shown a downtrend in the overall apparent risk of developing CRC in UC patients, although one large 30-year surveillance study from the United Kingdom showed only a slightly lower rate of 15% at 30 years [5].

More recent population studies have yielded conflicting results. A recent large Danish cohort study of 47,374 patients found that there has been a general change in the relative risk for CRC development over the past 30 years [6,7]. Their data demonstrated a downward trend in the risk for CRC development in IBD patients and they postulated that these findings were likely due to the increased use of immune modulators and the newer biologic agents such as in fliximab. The relative risk (RR) of CRC was found only to be 1.07 [95% CI, 0.95-1.21]. However, the RR score was markedly increased in certain populations including patients diagnosed at age <19 years [RR of 43.8, 95% CI, 27.2-70.7] as well as those diagnosed prior to the year 1988 [RR of 1.34; 95% CI, 1.13-1.58]. As mentioned earlier, CRC risk has been much more extensively studied in UC patients compared to CD patients. Many of the recommendations for screening and surveillance are based upon UC that has been extrapolated to CD. There has been, however, one study in which the incidence of CRC has been compared in a head to head fashion between UC and CD [8]. This study demonstrated similarities in risk, age at diagnosis and overall survivability when the location, extent and duration of disease were taken into account.

Risk related to extent of disease progression

IBD involvement of the colon can, by its very nature, be localized or extensive. UC typically exhibits confluent involvement of the colon ranging from only the rectum (proctitis) to the entire colon (pancolitis). Left sided disease generally refers to disease distal to the hepatic flexure.

Crohn's colitis usually affects segments of the colon but can present as pancolitis as well. Extent of disease is usually determined endoscopically and to a lesser degree by histology [9]. Isolated proctitis carries no significant increase in CRC risk above the general population and left sided UC carries a risk intermediate to that of pan-colitis [10]. In a Swedish-cohort study [1], the RR of CRC was dependent on the extent of disease as follows: 14.8 [95%CI, 11.4-18.9] for pan-colitis, 2.8 (95%CI, 1.6-4.4) for left-sided colitis, and 1.7 (95%CI, 0.8-3.2) for proctitis. Although left-sided colitis is more favorable than pancolitis after 10-20 years, it seems to have a similar risk compared to pancolitis by the fourth decade of disease [11-13]. Crohn's colitis of at least 1/3 colon involvement assumes the same risks as listed above of pancolitis [14,15].

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Received December 12, 2013; **Accepted** December 30, 2013; **Published** January 08, 2014

Citation: Jones R, Scobey M, Cheng J (2014) The Risk of Colon Cancer in Inflammatory Bowel Disease. J Gastroint Dig Syst 4: 164. doi: 10.4172/2161-069X.1000164

Risk Related to the Presence of Both IBD and Primary Sclerosing Cholangitis (PSC).

PSC and IBD are two diseases that have a strong association with one another. The prevalence of IBD has been reported as high as 60-80% in PSC patients [DDS #5]. The clinical importance of this association was highlighted by a meta-analysis by Soetikino et al. [16], who reported an almost 5-fold increase in the risk of colorectal dysplasia compared to patients with UC alone. The odds ratio (OR) for dysplasia was 4.79 (95%CI, 3.58-6.41) for dysplasia and for CRC itself was 4.09 (95%CI, 2.89-5.76). This study has been further supported by study from Sweden as well [17].

The reason for this increased risk is not fully understood. A study by Sokol et al. [18] showed that PSC-UC patients are given more 5-ASA treatment, suggesting more inflammation, which is possibly responsible for the PSC-UC association. Due to this high risk of CRC and dysplasia in PSC-UC patients, current recommendations are to begin screening all PSC patients for colorectal inflammation at the time of PSC diagnosis and to continue yearly surveillance in PSC patients with concurrent colitis. This recommendation continues even after liver transplantation for PSC after alarming results were reported in this population as well [17].

Risk related to other factors

Additional risk factors for CRC development in IBD include disease duration, earlier age of onset, family history of sporadic CRC, and persistent inflammation of the colon. Based on the meta-analysis performed by Eaden et al. [2], the risk of CRC becomes a significant concern after 10 years of disease. Disease onset should be defined as the beginning of symptoms rather than the time of actual IBD diagnosis as this will significantly decrease the amount of CRC's found at time of screening colonoscopy [19,20]. Both Eaden's meta-analysis [2] and the bulk of older studies [1,5,6] showed a relationship to disease duration. Nevertheless, disease duration is still the major factor for screening and surveillance recommendations, In regard to age of onset, the data concerning risk is conflicting. Studies by Rutter et al. [5] showed no correlation with an early age of diagnosis and more rapid progression to CRC. A retrospective study by Karvellas et al. [21], however, showed that patients diagnosed with UC prior to 40 years of age developed CRC more quickly than those diagnosed over the age of 40 years [OR 11.5; 95%CI, 2.41-20.16]. Because of the conflicting data, current screening recommendations do not factor in the age at diagnosis. A family history of sporadic colorectal cancer has been reported to be twice as likely in IBD patients with CRC compared to IBD patients without CRC. A study by Askling et al. [22] found that a positive family history of CRC translated in to a RR of 2.5 [95% CI, 1.4-4.4] for the development of CRC in patients with IBD. That RR increased to 9.2 if that relative was a first-degree relative. Relatives of patients with IBD have not been shown, however, to have an increased risk of CRC. Currently, family history is not formally noted in screening and surveillance guidelines, but may influence stratification and discussion about CRC risk in individual IBD patients.

IBD is characterized by underlying inflammation, so it would be presumed that the degree of inflammation would further increase the CRC risk in IBD. Rutter et al. [4] found that both macroscopic and microscopic changes were associated with increased risk for neoplasia, with OR of 2.5 and 5.1 respectively. The presence of histologic disease may also continue even when disease appears quiescent endoscopically [5,23,24]. In a study from Mayo Clinic, post-inflammatory polyps were shown to be associated with the development of IBD associated CRC. Another study by Rutter, further amplified this with a reported OR of 2.14 for CRC in patients with post-inflammatory polyps. Although they are not thought to possess malignant potential themselves, post-inflammatory polyps as markers of ongoing histologic inflammation appear to increase the risk of CRC [25].

Screening and surveillance recommendations

Although the degree of risk of CRC in IBD may be debated, multiple societies (AGA, ASGE etc.) currently endorse screening and surveillance programs for IBD patients. In order for a screening and surveillance strategy to be effective, patients must be made aware of the risk. The goal of IBD screening and surveillance programs is to identify the presence of dysplasia prior to the development of CRC. It should be noted; however, that colorectal dysplasia in IBD is thought to be progress along an accelerated timeline compared to that seen in sporadic CRC [26]. It is the presence of dysplasia that increases the risk of CRC and has direct implications in the patient's health. A meta-analysis of over 1225 patients found that 42% of patients with high-grade dysplasia and 19% of patients with low-grade dysplasia actually had a concurrent CRC that was not noted on their colonoscopy exam [27]. Low grade dysplasia is also concerning as noted by one review that showed 34% of patients with low grade dysplasia at initial exam, progressing to CRC at later follow-up exams [28].

Due to these concerns over dysplasia and eventual CRC development, current guidelines generally recommend initiation of screening colonoscopy 8-10 years after onset of pan-colitis and suggest considering initiating surveillance at 15 years after onset of left-sided colitis [9]. No surveillance recommendations are made for proctitis. Surveillance should begin immediately upon diagnosis of PSC in an IBD patient.

Current screening and surveillance guidelines recommend random colon biopsies every 10cm in 4 quadrants. The goal of these biopsies is to detect flat lesions that are not obvious endoscopically. These recommendations stem from a study by Rubin et al. [29], showing that 33 biopsies were needed to detect dysplasia with 90% probability, and 64 biopsies were needed to increase the probability to 95%. This is in addition to additional biopsy and endoscopic removal of any raised or abnormal appearing polyps or lesions.

Per recent AGA guidelines, the endoscopic treatment of raised lesions depends on the features of the lesion. Raised lesions containing dysplasia that are not deemed to be endoscopically resectable typically should be referred for colectomy. Endoscopic management of more polypoid lesions depends on location of the mass. If contained outside active colitis, the lesion should be removed endoscopically and surveillance continued. However, if contained within an area of active colitis, the lesion should be removed and the surrounding tissue margin biopsied to assess presence of any associated flat dysplasia. The presence of associated flat dysplasia warrants referral for colectomy. A completely removed lesion with no apparent flat lesions associated, may proceed with increased surveillance. However, any further development of dysplasia should prompt colectomy [9].

The best method for detecting these dysplastic lesions is evolving. Current U.S. societies do not advocate for or against more advanced imaging or targeting techniques to help identify dysplastic lesions. The British Gastroenterology Society [30] advocates the use of chromo endoscopy, a technique that involves spraying either Indigo carmine or methylene blue onto the colonic mucosa to help identify abnormalities in the tissue. This has been shown in multiple studies to be more effective for dysplasia detection. In a prospective study of 700 patients by Hurlstone et al. [31], chromo endoscopy identified 69 dysplastic lesions compared to only 24 that were found with conventional white

light endoscopy and random biopsies ($p<0.001$). Similar results have been reported by Kiesslich [32] with the use of methylene blue.

Conclusion

IBD carries an increased risk for the development of colorectal cancer. Additional risk factors to consider include disease duration, the presence of PSC, the age at onset, the extent of affected colon and a positive family history of CRC. Per guideline recommendations, patients with IBD involving the colon should be considered for CRC screening and surveillance after 8 years of disease with modifications based upon the presence or absence of other risk factors which may help to tailor individual approaches to CRC risk

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