Chronic Inflammatory Bowel Disease Risk Factors related to Colorectal Cancer

Healthcare

Kewords: bowel disease, inflammation, patients, dysplasia, cytokines, cancer, smoking, chemoprevention, etc.

Mereme Tusha

Preclinical and Clinical Department, Faculty of Nursing University of "Aleksander Xhuvani" - Elbasan, Albania.

Abstract

Patients with inflammatory bowel disease have an increasing risk for colorectal cancer which is believed to begin from no dysplasia progressing to indefinite dysplasia, low-grade dysplasia, high-grade dysplasia and finally to invasive adenocarcinoma, although colorectal cancer can arise without proceeding through each of these steps. As regards to the risk factors predisposing to colorectal cancer in the setting of inflammatory bowel disease, it seems that the risk increases with longer duration and greater anatomic extent of colitis, the degree of inflammation, and the presence of primary sclerosing cholangitis and family history of colorectal cancer. Concerning the mechanisms of carcinogenesis, it is now well established that the molecular alterations responsible for sporadic colorectal cancer,namely chromosomal instability, microsatellite instability and hypermethylation, also play a role in colitis-associated colon carcinogenesis. Chemoprevention strategies include the management of medicaments such as aminosalicylates, ursodeoxycholic acid, and possibly folic acid, the exact role of which remains to be further elucitated.

Introduction

Inflammatory bowel disease (IBD) carries an increased risk of developing colorectal cancer (CRC) and depending on study design, length of follow-up, case definitions, environmental diversity, treatment strategies the study and country, the risk of developing CRC in patients with UC fluctuates between 0.9 to 8.8-fold and between 0.8 and 23-fold in patients with pancolitis. IBD-related CRC is estimated to be responsible for less than 2% of all CRC appearing annually [1].

Eaden *et al.* accumulate the results of 116 studies including 55,000 patients with UC [2]. In this cohort of patients, 1,700 CRC were diagnosed and the probability of developing CRC 10 years after diagnosis was 2% , reaching the level of 8% after 20 years and 18% after 30 years. In general, the risk of CRC begins to increase 8 or 10 years after the establishment of diagnosis [1]. According to a study in Denmark, Winther et al[3] followed 1160 patients with UC over 22 290 person-years (1962-1987) and found 13 cases of IBD-CRC, giving an annual crude incidence of 0.06% and cumulative risk of 2.1% at 30 years.

They found no statistically significant increase for CRC between IBD and non-IBD populations, but it is related with high colectomy rate. According to a recent analysis the risk of CRC has decreased in patients with UC, despite the low frequency of colectomies. The annual incidence rate of CRC in UC ranges from approximately 0.06% to 0.16% with a relative risk of 1.0-2.75. due to the widespread use of maintenance therapy with 5-ASA compounds and surveillance colonoscopy [4].

In another population-based study, it was found that the risk for CRC among patients with IBD was associated with the anatomic location of the diseased bowel and that the risk of rectal cancer was increased 2-fold in UC but not in Crohn's colitis [5].

Patients who have only had small intestinal CD without colonic involvement are not considered to be at high risk for CRC. The risk of developing adenocarcinoma in the small intestine of patients with small bowel CD is increased, being approximately 10-12-fold greater than for the general population[5]. However, patients with longstanding Crohn's colitis have similar risk of developing CRC with UC patients and was shown to be 2.9% at 10 years of disease duration, 5.6% at 20 years and 8.3% at 30 years [6].

The risk of colorectal dysplasia and neoplasia in these patients is influenced by environmental, genetic and individual factors. It increases with age and this hazard is further compounded by specific disease characteristics including disease duration, area of colonic involvement, and degree of inflammation.

The role of inflammation as a risk factor is supported by the fact that CRC risk increases with longer duration of colitis, greater extent of colitis, the concomitant presence of other inflammatory manifestations such as primary sclerosing cholangitis, and the fact that certain drugs used to treat inflammation may prevent the development of CRC [7].

It has been recently shown that cytokines (Interleukin-6 and -23) and growth factors released during inflammation may influence the carcinogenesis process [8].

Inflammatory cytokines stimulate a signaling cascade that results in the activation of IKK (inhibitor of NF-κB kinase), which then phosphorylates IκB and than it is ubiquitinated and degraded, thereby liberating NF-κB. Free NF-κB translocates to the nucleus where it then induces the transcription of target genes. NF-κB activation upregulates the expression of many proinflammatory mediators including adhesion molecules and cytokines (e.g., TNF-a and IL-6) that play a critical role in IBD and have been implicated in tumor development and progression in both humans and animal models [9].

NF-κB has been proposed to be a main molecular link between inflammation and carcinogenesis. Moreover, NF-κB activation by proinflammatory stimuli can, in turn, directly promote cell survival by inducing the production of proteins such as Bcl-2 and Bcl-XL that inhibit apoptosis. It also can induce the production of factors that have been shown to drive tumor invasion and metastasis including chemokines, matrix metalloproteinases, and serine proteases.

Persistent activation of the nuclear factor-κB and cyclooxygenase-2/prostaglandin pathways, release of proinflammatory mediators such as tumor necrosis factor-a and interleukin-6, and enhanced local levels of reactive oxygen and nitrogen species, which induce carcinogenesis in the following ways:

1) enhancing levels of reactive oxygen and nitrogen species that have mutagenic affects on DNA, thus contributing to tumor initiation;

2) activating prosurvival and antiapoptotic pathways in epithelial cells, thereby contributing to tumor promotion; and

3) creating an environment that supports sustained growth, angiogenesis, migration, and invasion of tumor cells, thus supporting tumor progression and metastasis [8].

According to recent study Toll-like receptor4 (TLR4) signalling is essential for colon carcinogenesis in chronic colitis and its activation appears to promote the development of colitis-CRC by enhancement of Cox-2 expression and increased EGFR signalling [3]. TNF-a is known to

upregulate the production of cyclooxygenase-2 (COX-2) which influence on tumor cell growth and angiogenesis.

Moreover, inhibition of TNF-a reduced enterocyte levels of nuclear b-catenin, that have been implicated in tumorigenesis [9]. iNOS expression is increased during inflammation and catalyzes the production of nitric oxide (NO). NO, and reactive species derived from NO such as peroxynitrite, can induce DNA damage and posttranslational modification of DNA repair enzymes, apoptotic effectors, and the p53 protein [9].

Moreover, the presence of p53 mutations was associated with increased inducible nitric oxide synthase (iNOS) activity in these tissues. The tumor suppressor protein p53 plays a key role in preventing clonal expansion of mutated cells by initiating apoptosis or cell cycle arrest in cells with DNA damage and its alterations is suggested to be an important early event in colitis-associated tumorigenesis. Indeed, alterations to the p53 gene occur in 47%– 85% of colitis-associated cancers.

Recent study shows that other factors may contribute to CRC development which include family history of CRC, smoking, the presence of pseudopolyps and primary sclerosing cholangitis.

A family history of CRC increases the risk of CRC by at least two-fold as compared to patients with UC without positive family history for CRC [10].

Primary sclerosing cholangitis (PSC) appearing on the ground of UC increases the risk of CRC by 4.8-fold compared with patients with UC without PSC and should be enrolled in colonoscopic surveillance program regardless of UC duration [11].

There are contradictory results about the younger age at UC onset as a risk factor, a meta-analysis suggested that the overall annual incidence rate of 0.6% to pediatric patients was only numerically higher than that calculated for adults (0.3%) [2] while other authors suggest that younger age at UC onset is an independent risk factor [2].

Smoking reduces the risk of CRC in UC by 50% but increases the risk of CRC in CD 4-fold, due to the opposite effect smoking has on inflammation in each disease [9].

Pseudopolyps increase the risk of CRC in UC by 2.5-fold as a marker of severe inflammation , or because they may obscure the sensitivity of surveillance colonoscopy [12].

Sporadic CRC originate from mucosal polyps but colitis-associated CRC may present as flat or raised lesions. Chromosomal instability is the reason for most p53 and APC dysfunction. In sporadic CRC an early event in the adenoma-carcinoma pathway is APC dysfunction, whereas p53 mutations are at later stages of disease.

In colitis-associated CRC, p53 chromosomal abnormalities are observed in earlier stages while APC defects are less frequent and seen later in disease course [9,13].

This may explain the flat morphology of dysplasia observed in IBD-associated CRC, as APC mutations are considered the reason for polyp formation.

Dysplasia

Dysplasia is determined as neoplasia of the epithelium localized to the basement membrane, without invasion into the lamina propria and can be classified as raised or flat based on its endoscopic appearance [14].

Elevated lesions that are endoscopically visible, but not amenable to endoscopic resection are often referred to as DALMs (dysplasia associated lesion or mass) referred to the high rate of malignancy associated with these lesions [14].

ALM (adenoma-like lesion or mass) describe the finding of a polypoid lesion resembling a sporadic adenoma that is found in an area of the colon not involved by chronic colitis. Despite the endoscopic appearance of a lesion as raised or flat, pathologists use a standardized classification system introduced by Riddell and colleagues in 1983 divides dysplasia into categories, including indefinite dysplasia, low grade dysplasia (LGD), high grade dysplasia (HGD) and cancer [14].

Low-grade tubuloglandular adenocarcinomas usually arise directly from low-grade or even indefinite dysplasia. They may progress in turn to more aggressive types of cancer, thus bypassing high-grade dysplasia. According to a study at the Mount Sinai Hospital, who study the prognosis of patients with biopsy description as negative for dysplasia, IND, and flat LGD, showed a 5-year progression rates to HGD or CRC of 1.1%, 9% and 45%, respectively [15].

Recently Ullman at al, study 56 patients with biopsies reported indefinite for dysplasia and showed a 9.0% 5-year progression rate to HGD or CRC [16]. Regarding the CCFA consensus guideline the patients with biopsies indefinite for dysplasia should be followed with annual surveillance examinations. Patients with no evidence of dysplasia are consider low-risk for CRC, and should have repeat surveillance endoscopy within 1 to 3 years. More recent studies have shown that patients with low-grade dysplasia have a lower risk of colorectal cancer than previously were thought (2–10% during a 10-year follow-up) [16], so is recommend close colonoscopic surveillance of these patients rather than total colectomy.

Five and 10-year progression rates of LGD to HGD and colorectal cancer. Other experts suggest that the presence of multifocal low-grade dysplasia should be managed with a total colectomy but when a single focus of low-grade dysplasia is found than it should be discussed with the patient. If he refuse surgery, then is recommended a second colonoscopy within 3 months and no later than 6 months from the reported of the low-grade dysplasia [16].

DALMs are associated with increased incidence of CRC and colectomy is generally recommended following diagnosis [17]. Several studies have observed a low risk of developing CRC after complete endoscopic resection of an adenoma-like DALM (mean follow-up period of forty-nine to eighty-two months), when the biopsies from around the lesion and elsewhere in the colon show no flat dysplasia [17].

An incomplete resection is associated with a significant risk of developing CRC, then colectomy is recommended. In practice, once the diagnosis of high grade dysplasia is confirmed by a second expert GI pathologist, colectomy is indicated.

Conclusion

Inflammatory bowel disease clearly predisposes to CRC development although the risk differs in different parts of the world. Cancer follows the sequence of no dysplasia, indefinite dysplasia, low-grade dysplasia, high-grade dysplasia and carcinoma.

Low-grade dysplasia can progress to CRC without the intermediate stage of high-grade dysplasia. Similar to sporadic CRC, colitis-associated CRC is a consequence of sequential episodes of somatic genetic mutation and clonal expansion. In IBD, neoplastic lesions arise within areas of the mucosa that have been involved with colonic inflammation. A balance between cell proliferation and apoptosis may partly explain this epidemiological feature.

Knowledge of the mechanisms of carcinogenesis could identify patients at high risk for development of CRC. In the near future, some chemopreventive agents could play a role in reducing the incidence of CRC in IBD patients. The future looks promising with respect to new developments in the management of cancer risk in IBD.

References

1. Danila Guagnozzi and Alfredo J Lucendo Colorectal cancer surveillance in patients with inflammatory bowel disease: What is new? World J Gastrointest Endosc. 2012 April 16; 4(4): 108-116.

2. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001; 48:526-535

3. Judith E Baars The Risk of Inflammatory Bowel Disease-related Colorectal Carcinoma European Gastroenterology & Hepatology Review, 2012;8(2):86–9

4. Jessica K Dyson and Matthew D Rutter. Colorectal cancer in inflammatory bowel disease: What is the real magnitude of the risk?World J Gastroenterol. 2012 August 7; 18(29): 3839-3848

5. Kiran RP., Khoury W., Church JM., Lavery IC., Fazio VW & Remzi FH. Colorectal cancer complicating inflammatory bowel disease: similarities and differences between Crohn's disease and ulcerative colitis based on three decades of experience. Ann Surg, 252, Aug 2010, 330-5.

6. Shih DQ, Targan SR (2009) Insights into IBD Pathogenesis. Curr Gastroenterol Rep 11: 473-480.

7. Velayos FS, Terdiman JP, Walsh JM. Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: a systematic review and metaanalysis of observational studies. Am J Gastroenterol. 2005;100: 1345–1353.

8. Emilie Viennois[1], Fengyuan Chen[1], Didier Merlin[1] NF-κB pathway in colitis-associated cancersTransl Gastrointest Cancer 2012;2(1). Doi**:**10.3978/j.issn.2224-4778.

9. Judith E Baars and C Janneke van der Woude Colorectal Carcinoma Complicating Inflammatory Bowel Disease Department of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands Annals of Gastroenterology & Hepatology AGH 2011; 000:(000).

10. Askling J, Dickman PW, Karlen P, Brostrom O, Lapidus A, et al. (2001) Family history as a risk factor for colorectal cancer in inflammatory bowel disease. Gastroenterology 120: 1356-1362.
11.Torres J, de Chambrun GP, Itzkowitz S, Sachar DB, Colombel JF. Review article: colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease. Aliment Pharmacol Ther 2011;34:497-508.
12. Xie J and Itzkowitz SH: Cancer in inflammatory bowel disease World J Gastroenterol 14: 378-389, 2008
13. Feagins LA, Souza RF, Spechler SJ. Carcinogenesis in IBD: potential targets for the prevention of colorectal cancer. Nat Rev Gastroenterol Hepatol 2009; 6: 297-305
14. Thomas Ullman, MD,* Robert Odze, MD,† and Francis A. Farraye, Diagnosis and Management of Dysplasia in Patients with Ulcerative Colitis and Crohn's Disease of the Colon Inflamm Bowel Dis 2009;15:630–638.
15. Ullman T, Croog V, Harpaz N, et al. Progression to colorectal neoplasia in ulcerative colitis: effect of mesalamine. Clin Gastroenterol Hepatol. 2008; 6(11):1225–1230.
16. Itzkowitz SH, Present DH.: Consensus conference: Colorectal cancer screening and surveillance in inflammatory bowel disease. Inflamm Bowel Dis 11(3):314–321, 2005.
17. Danila Guagnozzi, Alfredo J LucendoColorectal cancer surveillance in patients with inflammatory bowel disease: What ¡s new? D World J Gastrointest Endosc 2012 April 16; 4(4): 108-116