Review

Colorectal Cancer in Patients With Inflammatory Bowel Disease: The Need for a Real Surveillance Program

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Abstract

The association between inflammatory bowel disease (IBD) and colorectal cancer (CRC) has been widely shown. This association is responsible for 10% to 15% of deaths in patients with IBD, even if according to some studies, the risk of developing CRC seems to be decreased. An adequate surveillance of patients identified as at-risk patients, might improve the management of IBD-CRC risk. In this article we review the literature data related to IBD-CRC, analyze potential risk factors such as severity of inflammation, duration, and extent of IBD, age at diagnosis, sex, family history of sporadic CRC, and coexistent primary sclerosing cholangitis, and update epidemiology on the basis of new studies. Confirmed risk factors for IBD-CRC are severity, extent, and duration of colitis, the presence of coexistent primary sclerosing cholangitis, and a family history of CRC. Current evidence-based guidelines recommend surveillance colonoscopy for patients with colitis 8 to 10 years after diagnosis, further surveillance is decided on the basis of patient risk factors. The classic white light endoscopy, with random biopsies, is now considered unsatisfactory. The evolution of technology has led to the development of new techniques that promise to increase the effectiveness of the monitoring programs. Chromoendoscopy has already proved highly effective and several guidelines suggest its use with a target biopsy. Confocal endomicroscopy and autofluorescence imaging are currently being tested and for this reason they have not yet been considered as useful in surveillance programs.

Clinical Colorectal Cancer, Vol. 15, No. 3, 204-12
Keywords: Colorectal cancer, Crohn's disease, Endoscopy, Inflammatory bowel disease, Surveillance, Ulcerative colitis

Introduction

The association between inflammatory bowel disease (IBD) and colorectal cancer (CRC) has been recognized for nearly a century and it is known to be promoted by a process of cancerogenesis linked to chronic inflammation, in combination with a genetic predisposition.[1-7] In 1925 Crohn and Rosenberg were the first to clarify the relation between ulcerative colitis (UC) and CRC and in 1928 Bargen described 20 cases of CRC in patients with UC.[8] The magnitude of the risk of CRC in IBD is still the focus of heated debate. Recent studies show a progressive reduction in the risk of CRC in IBD over the past 2 decades. Surveillance programs and new treatment strategies, particularly a top-down strategy with early surgery and biological drugs, might be the reason for the decrease in the rate of CRC in IBD.[9-11] In this study risk factors for CRC in patients with IBD and its prevention were evaluated, with particular reference to endoscopic surveillance.

Aim and Methods

The aim of this clinical narrative review was to evaluate the epidemiological aspects of the association between CRC and IBD and to determine the real risk factors for the development of CRC. The intent is to identify an effective surveillance program to reduce the risk of CRC in IBD patients. A literature search was conducted using MedLine, Embase, Ovid Journals, and Science Direct. All published studies on IBD and risk of developing CRC were identified using the following key words: "Colorectal cancer and inflammatory bowel disease," "Colorectal cancer in IBD patients and

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Submitted: Oct 8, 2015; Revised: Dec 31, 2015; Accepted: Feb 3, 2016; Epub: Feb 13, 2016

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1533-0028/$ - see frontmatter
http://dx.doi.org/10.1016/j.clcc.2016.02.002

risk factors," "Crohn's disease and colorectal cancer," and "Ulcerative colitis and colorectal cancer." Full articles and abstracts, only in English and Italian language, were included. Studies such as case reports, letters, and commentaries were excluded from the analysis if appropriate data could not be extracted. Studies in pediatric populations were excluded.

Results and Discussion

Epidemiology

The incidence of CRC in patients with IBD is a much debated topic. If compared with the general population the risk of CRC in IBD patients is now undoubted. In fact this risk is documented as the cause of death in up to 15% of IBD patients.[1,12-15] Most studies refer to the incidence of CRC in patients with UC. According to a recent meta-analysis by Jess et al, UC increases this risk by approximately 2.4-fold and approximately 1.6% of patients with UC developed CRC during 14 years of follow-up.[16] Another recent meta-analysis by Castaño-Milla et al, who compared 81 studies on the basis of reference centers and population, reported an incidence rate of CRC in patients with UC of 1.58/1000 patients per year (95% confidence interval [CI], 1.39-1.76).[17] Eaden et al had already shown, in their meta-analysis of 116 studies involving 54,478 IBD patients with 1698 CRCs diagnosed, an overall CRC rate of 3.7% in all UC patients with increasing cumulative probabilities of 2% by 10 years, 8% by 20 years, and 18% by 30 years.[18]

As for Crohn's disease (CD), in 2007 Von Roon et al reported a relative risk (RR) of colon cancer of 2.59 in CD patients compared with the general population.[19] Laukoetter et al, in a meta-analysis including 20 studies on the basis of population and reference centers, reported an incidence rate of CRC in patients with CD of 0.5/1000 patients per year (95% CI, 0.3/1000-0.6/1000).[20] Similarly, in another recent study, 5.6% of CD patients developed CRC or dysplasia during 30 years of follow-up.[21] Lutgens et al, in a recent meta-analysis of studies regarding CD and UC, reported an overall incidence of CRC in patients with IBD of 1.7/1000 patients per year (95% CI, 1.2-2.2) in population-based studies and 6.9/1000 patients per year (95% CI, 4.1-9.7) in studies on the basis of reference centers.[22] Patients with IBD develop CRC at a younger age and have a slight increase in mortality at 5 years, compared with the general population.[23] Overall, according to a study involving 47,374 patients with IBD over a 30-year period, it seems that there is a reduction in the risk of development of CRC in IBD.[24] This result might be because of improved therapies for patients with IBD and to the advent of surveillance colonoscopy programs.[3]

Risk Factors

The main risk factors for the development of CRC in IBD patients are: long disease duration, extent of disease, young age at diagnosis, coexistence of primary sclerosing cholangitis (PSC), severity of inflammation, and family history of CRC.[5,6,22,25,26] Patients with IBD show a risk of developing CRC that is proportional to duration and extent of disease. The higher risk in this kind of patient is due to persistent colonic inflammation. The knowledge and quantification of such risk is fundamental to set an appropriate monitoring program.[3,25,26]

Compared with UC, CRC in CD has not been as well studied.[27] Although the relationship between UC and CRC has been appreciated for many years, the association between CD and CRC has gained increasing recognition recently.[28]

Duration of Disease

An increased risk of IBD-CRC is linked to a longer duration of colitis. Eaden et al reported a CRC risk in patients with left-sided UC disease or pancolitis of 0.3% per year or of 3 cases per 1000 patients per year. For the first decade of disease incidence rate was estimated at 2 cases per 1000 patients per year (95% CI, 1/1000-2/1000), for the second decade 7 cases per 1000 patients per year (95% CI, 4/1000-12/1000), and 12 cases per 1000 patients per year (95% CI, 7/1000-19/1000) for the third decade. The long-term cumulative incidence resulted in being 1.6% at 10 years, 8.3% at 20 years, and 18.4% at 30 years of disease.[18] Later published studies, however, showed lower cumulative incidence rates. In particular Lakatos et al reported a long-term cumulative risk of CRC of 0.6% at 10 years, 5.4% at 20 years, and 7.5% at 30 years.[29] Rutter et al reported a cumulative incidence of CRC of 2.5% at 20 years, 7.6% at 30 years, and 10.8% at 40 years.[30] Finally, a recent meta-analysis by Castaño-Milla et al reported an incidence rate of CRC in patients with UC of 0.91/1000 patients per year (95% CI, 0.61-1.2) in the first decade of disease, of 4.07/1000 patients per year (95% CI, 2.58-5.56) with regard to the second decade of disease, and 4.55/1000 patients per year (95% CI, 2.64-6.46) for the third decade.[17] Regarding CD, Canavan et al reported a cumulative incidence of CRC of 2.9% at 10 years, 5.6% at 20 years, and 8.3% at 30 years of disease.[7] Lutgens et al reported a risk of CRC in IBD patients amounting to 1%, 2%, and 5%, respectively after 10, 20, and $>$ 20 years of disease.[22]

Two studies reported the RR of developing CRC stratified according to the duration of CD from initial diagnosis. In 1268 patients who were followed for fewer than 10 years, the RR was reported to be 2.34 (95% CI, 1.07-5.12). For patients who were followed for $>$ 10 years, no statistically significant difference in RR could be shown (RR, 1.71; 95% CI, 0.59-4.94; $P = .32$), although there was a nonsignificant upward trend in patients who were followed for $>$ 20 years (RR, 3.2; 95% CI, 0.4-11.4; $P =$ not significant).[19,31,32] Also, Freeman noticed that a long history of CD could be a risk factor for the development of CRC. Over a period of 20 years, he studied 877 patients (385 men, 492 women) with CD. A total of 6 patients (approximately 0.68%) developed CRC. The mean estimated duration from the time of diagnosis of CD to the time of diagnosis of CRC was $>$ 20 years.[33] Choi et al studied 6217 patients with either CD or UC. Eighty (28 CD and 52 UC) of these patients had CRC. With regard to CD, the median duration of disease to the time of the diagnosis of CRC was 15 years; in fact cancer was diagnosed only in seven of 28 (25%) patients with CD within the first 8 years of disease.[27]

Extension of the Inflammatory Process

The greater the disease extent, the greater the risk of CRC. Patients with proctitis and proctosigmoiditis are at the lowest risk, left-sided colitis carries moderate risk, and patients with pancolitis are at the highest risk of CRC.[3]

In this regard, Ekbom et al reported a lower risk of developing CRC in patients with less extended disease; in particular for patients with UC characterized only by proctitis the standardized incidence