Best Practice & Research Clinical Gastroenterology 32-33 (2018) 103–109

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

journal homepage: https://ees.elsevier.com/ybega/default.asp

Colorectal cancer prevention in patients with ulcerative colitis

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ARTICLE INFO

Article history:
Received 17 April 2018
Accepted 10 May 2018

Keywords:
Ulcerative colitis
Colorectal cancer
Dysplasia
Prevention
Colonoscopy
5-ASA
Thiopurines

ABSTRACT

Ulcerative colitis is characterized by chronic inflammation, which may lead to the accumulation of high levels of pro-inflammatory cytokines within the colonic mucosa, and thus to dysplastic lesions and cancer. Although the trend is decreasing, ulcerative colitis patients still have a 2.4 fold higher risk of colorectal cancer compared to the general population. The key task is to control colonic inflammation, and a rapid step-up approach while closely monitoring intestinal inflammation are recommented. Surveillance colonoscopy program demonstrated its efficacy for reducing the incidence of colorectal cancer in ulcerative colitis. The impact of medication on the reduction of colorectal cancer risk was hardly investigated and it remains unclear whether they have intrinsic anti-neoplastic properties or only downregulate inflammatory pathways. Several studies showed a decreased risk of colorectal cancer in ulcerative colitis patients treated with 5-aminosalicylic acid and chemoprevention with mesalamine compounds is currently recommended. The current level of evidence is too low for thiopurines and anti-TNFα agents. Large, prospective cohort studies are ongoing and are likely to bring new findings about the impact of drugs on colorectal cancer risk in the current era of biologics.

1. Introduction

The increased risk of colorectal cancer (CRC) among inflammatory bowel disease (IBD) patients is an old preoccupation, described first almost a century ago for ulcerative colitis (UC) [1]. In 2001, Eaden et al. reported the first systematic review assessing the risk of CRC in UC, showing a cumulative risk of 2% at 10 years, 8% at 20 years and 18% at 30 years [2]. However, a most recent meta-analysis of population-based cohort studies found much lower cumulative colorectal risk rates in UC patients, with estimations less than 1% at 10 years and from 1.1 to 5.3% at 20 years [3]. A Danish study even suggested the absence of an increased risk of CRC in UC [4]. In a nationwide cohort of 47,374 IBD patients followed over a 30-year period, the overall risk of CRC among patients with UC was comparable with that of the general population, with a relative risk (RR) of 1.07 (95% confidence interval [CI], 0.95–1.21) [4]. In IBD-related CRC, chronic inflammation is assumed to play a key-role, with oxidative stress–induced DNA damage resulting in the activation of procarcinogenic genes and silencing of tumor-suppressor pathways [5]. In UC progressors, there is a preneoplastic field of inflammation, telomere shortening, and senescence promoting tumor progression [6]. Over the past few years, the concept of 'deep remission' emerged as a major therapeutic goal, in which the simple control of symptoms does not appear sufficient and should be associated with mucosal healing [7]. This paradigm shift may explain the decrease of CRC risk, especially because the severity of microscopic inflammation over time was found to be an independent risk factor for developing advanced colorectal neoplasia among patients with long-standing UC [8,9]. The increased proportion of patients with mucosal healing is probably related with intensive immunosuppressive strategies based on prescription of biotherapies alone or combined with thiopurines or 5-aminosalicylic acid (5-ASA). However, 5-ASA [10] and thiopurines

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https://doi.org/10.1016/j.bpg.2018.05.010
1521-6918/

[11] also have a potential chemoprotective effect, supported by their intrinsic anti-neoplastic properties.

In this review, we highlight the epidemiology and risk factors of CRC development in UC, expose the central role of colonic inflammation in CRC development, and focus on the different strategies in the prevention and timely detection of CRC in UC patients.

2. Epidemiology

IBD patients are considered as 'high-risk' patients for CRC, but this excess risk has long been overestimated in case of UC, at the origin of disproportionate anxiety in both patients and physicians. Fifteen years ago, we believed that one UC patient out of five would develop a colorectal cancer 30 years after initial diagnosis [2]. It was based on a meta-analysis conducted on 116 studies and 54 478 UC patients, but high CRC rates were likely to be related to a heterogeneity bias because different study designs were pooled: referral center and private hospital studies, surgical and histological series, population-based studies, surveillance programs. In a most recent meta-analysis, the authors only included 8 population-based studies and showed that the cumulative risk of CRC in UC patients varied from 1.1 to 5.3% at 20 years [3]. This rate was 3% in an Australian cohort study including 504 patients [12]. Another Danish team did not find an increased risk of CRC among UC patients in two separate nationwide cohort studies (RR, 1.07; 95% CI, 0.95–1.21 [4] and standardized incidence ratio [SIR], 1.12; 95% CI, 0.97–1.28 [13]). However, patients diagnosed with UC in childhood or adolescence, those with long duration of disease, and those with concomitant primary sclerosing cholangitis (PSC) were still at increased risk [4,13]. In the largest and longest-running colonoscopic surveillance program for CRC in patients with long-standing UC, incidence rates of advanced CRC and interval CRC have steadily decreased over past four decades (Pearson's correlation, −0.99; $p = 0.01$ for both trends) [14].

To conclude, UC is still associated with an increased risk of CRC, estimated to be 2.4-fold higher compared with the general population [3], but this trend is decreasing. This may reflect the implementation of surveillance strategies, the introduction of drugs that control inflammation more effectively, or the changing approach to maintenance therapy or colectomy.

3. Risk factors

The 2017 ECCO consensus reported several risk factors for developing CRC in case of UC (Table 1) [15]. As described previously, longer disease duration is associated with a greater risk of CRC [3]. Mean disease duration in the meta-analysis of Jess et al. at the time of diagnosis was 14 years [4]. In the CESAME cohort study, the SIR of CRC was 7.0 (95% CI, 4.4–10.5; $p < 0.001$), for patients with long-standing extensive colitis [16]. In an updated meta-analysis of population-based cohort studies published in 2013, an IBD diagnosis before age 30 was associated with higher risk of CRC (SIR, 7.2; 95% CI, 2.9–17.8) [17]. The most consistent risk factor reported for CRC is PSC, with an increased absolute risk of up to 31% [18–22]. As known in sporadic cancer, a family history of CRC is an independent risk factor for CRC in UC, with an odds ratio (OR) of 2.33 (95% CI, 1.06–5.14; $p = 0.03$) [23]. The exact role of post-inflammatory polyps in CRC pathophysiology is not well-known, but they may be markers of previous inflammatory severity, and have also been found to be a strong risk factor [24]. Finally, chronic colonic mucosal inflammation seems to be the primer of multifocal precancerous and cancerous lesions. In a cohort study conducted in 418 UC patients undergoing regular endoscopic surveillance for dysplasia, histologic inflammation score was an independent factor for developing advanced colorectal neoplasia (HR, 3.8; 95% CI, 1.7–8.6) [9]. In another case-control study, inflammation was scored on a new 6-point histologic inflammatory activity (HIA) scale in 4449 biopsy fragments from 141 UC patients [25]. HIA was associated with colorectal neoplasia in multivariate analysis (OR, 3.68; $p = .001$).

Table 1
Risk factors for colorectal cancer in ulcerative colitis patients.

Risk factor	Reference
Disease duration	[3]
Young age at diagnosis	[17]
Extensive colitis	[16]
Primary sclerosing cholangitis	[18–22]
Family history of colorectal cancer	[23]
Chronic colonic mucosal inflammation	[9,25]
Post-inflammatory polyps	[24]

4. Colonic inflammation: a key player in colorectal cancer development

Compared with sporadic CRC, colitis-associated cancer (CAC) exhibits its own genetic pathway, with the confounding interference of the gut microbiota.

As described above, the pathogenic role of longstanding inflammation is supported by the increased risk of CAC along with the duration and the severity of the disease. Chronic inflammation results in high levels of pro-inflammatory cytokines within the colonic mucosa (e.g. tumor necrosis factor-alpha [TNF-α], interleukin-6 [IL- 6], interleukin-10 [IL-10], interferon-gamma [IFN-γ]) [26], leading to the activation of several transcription factors involved in cancer development. At a molecular level, IL-6 promotes tumor growth and inhibits apoptosis by activating the JAK/STAT signaling pathway [27]. Cyclooxygenase 2 (COX-2) overexpression occurs early in CAC, mainly due to pro-inflammatory cytokines IL-1 and TNF-α, leading to cell proliferation, angiogenesis, and apoptosis [28]. Pro-inflammatory cytokines are also able to enhance the production of reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI) which create DNA damages in an oxidative stress-dependent manner [29].

There is a growing body of evidence that the commensal microbiota has an impact on carcinogenesis and tumor progression. Dysbiosis is highly implied in cancer-associated inflammation, by activating survival genes within neoplastic cells and inflammation-promoting genes in the tumor microenvironment [30]. In the ApcMin/+ mouse model of intestinal tumorigenesis, *Fusobacterium nucleatum* generates a pro-inflammatory microenvironment by recruiting tumor infiltrating myeloid cells, leading to CRC progression [31]. In humans, some bacterial species seem to be frequently associated with CRC: *Streptococcus gallolyticus*, *Enterococcus faecalis*, enterotoxigenic *B. fragilis* (ETBF), *Escherichia coli*, and *F. nucleatum* [32–37]. In a meta-analysis published in 2011, patients with *S. gallolyticus* infection had a strongly increased risk of having CRC (pooled OR, 7.26; 95% CI, 3.94–13.36) compared with *S. bovis* biotype II-infected patients [32]. Pro-carcinogenic effect of *S. gallolyticus* may be mediated by its pilus protein and enhanced inflammatory signals including COX-2 [33]. *F. nucleatum* provided the strongest evidence about the role of microbes in colon carcinogenesis [34–36]. Carcinogenic properties of *F. nucleatum* could be due to a bacterial cell surface adhesion component (FadA) which activates the β-catenin/Wnt pathway [37]. Microbiota seems to contribute to carcinogenesis, involving pro-inflammatory and immunosuppressive signals, but it maintains a complex relationship with cancer, through multiple interactions with the diet, bile acids and the immune system.