Chapter 2
Incidence and Risk Factors

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Abstract Epidemiological data indicate that inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is the third highest risk condition for the development of colorectal cancer (CRC), namely, colitis-associated cancer (CAC). CD is also associated with an increased risk of small-bowel adenocarcinoma, in response to chronic inflammation of the small intestine. In studies published in the 1990s, the risk for CAC in IBD was approximately 7 % at 20 years after diagnosis. In recent studies, the overall incidence of CAC in IBD is lower, less than 5 % at 20 years. However, several factors, such as the longer duration of colitis, extensive or severer colitis, and coexistent primary sclerosing cholangitis, have continued to be important in the development of CRC in patients with IBD. Despite clinical and experimental investigations, the molecular mechanisms by which chronic inflammation promotes cancer progression are still unknown.

Keywords Chronic inflammation • Duration of colitis • Extensive colitis • Primary sclerosing cholangitis

2.1 Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is an idiopathic inflammatory disorder of the gastrointestinal tract that consists of two major forms: ulcerative colitis (UC) and Crohn's disease (CD) [1]. UC extends proximally from the anal verge and involves the entire colon or a part of it. The inflammation in UC is limited to the mucosal layer. By contrast, CD can affect any part of the gastrointestinal tract but typically involves the distal part of the small intestine (ileum) and the colon. The affected segments frequently show a discontinuous pattern. The inflammation is transmural and extends to all layers of the intestine.

IBD is characterized by episodes of remission and exacerbation. Despite various effective treatments, some patients experience frequent flares of inflammation or

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develop treatment-resistant disease with chronic inflammation. IBD is associated with various intestinal and extraintestinal complications, with one of the most serious being the development of colorectal cancer (CRC) [2]. IBD patients are at a higher risk of CRC than the general population [3], although the pathogenesis of CRC in IBD is unknown.

2.2 Inflammation and Cancer

Chronic inflammation increases the risk of carcinogenesis in various organs [4], and the link between inflammation and cancer development is well recognized. The molecular biology, immune pathobiology, and genetics of IBD-associated CRC are the focuses of intense research [5].

A link between inflammation and cancer was determined approximately 150 years ago, when, in 1863, Rudolf Virchow discovered the presence of leukocytes in neoplastic tissues. He hypothesized that the "lymphoreticular infiltrate" reflected the origin of cancer at sites of chronic inflammation [6].

Epidemiological data also indicate that inflammation plays an important role in the initiation, promotion, and progression of many types of cancer [7]. Distinct host immune cells, cytokines, and chemical mediators participate in all steps of inflammation-related carcinogenesis: tumor initiation, promotion, progression, and metastasis [8]. Among the chronic inflammatory diseases linked to colorectal carcinogenesis, IBD is perhaps the most widely recognized.

2.3 Sporadic and Hereditary Colorectal Cancer

As the third most common malignancy, CRC is a major cause of cancer-related death worldwide [9, 10]. Sporadic CRC, the most common type of CRC, is thought to develop from benign adenomas. Fearon and Vogelstein characterized the development of sporadic CRC in their model of the adenoma→carcinoma sequence, in which genetic abnormalities accumulate in a stepwise manner and ultimately lead to the development of malignancy [11].

Hereditary CRC accounts for 5–10 % of all CRC cases [9, 10] and consists of two major types: familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome. FAP is an autosomal-dominant inherited disorder resulting from germ-line mutations in the adenomatous polyposis coli (APC) gene [12]. In patients with FAP, numerous adenomatous polyps develop, mainly in the colon and rectum. Although they are benign, they are at extremely high risk of becoming malignant. HNPCC, or Lynch syndrome, is also an autosomal-dominant inherited syndrome. It results from defective mismatch repair proteins that show high microsatellite instability [13]. Patients with HNPCC have a tendency to develop CRC and are at increased

risk of other cancers, such as endometrial, ovarian, gastric, small intestinal, hepatobiliary, pancreatic, upper urinary, prostate, brain, and skin cancers.

2.4 Colitis-Associated Cancer

IBD-associated CRC, or colitis-associated cancer (CAC), is a form of CRC arising in patients with IBD [14]. Chronic inflammation of the large bowel such as that which occurs in IBD is associated with the subsequent development of CRC [15], as the repeated flare-ups of inflammation characteristic of IBD often lead to oncogenic insults to colonic epithelial cells.

In 1925, Crohn and Rosenberg reported a case of rectal carcinoma complicating UC and postulated that the lesion developed as a late manifestation of UC [16]. In 1948, Warren and Sommers reported a case of adenocarcinoma of the ascending colon in a patient with CD complicating regional enteritis [17]. Much later, in 2005, CD was also shown to be associated with an increased risk of small-bowel adenocarcinoma, due to chronic inflammation of the small intestine [18].

IBD is the third highest risk condition for the development of CRC, after FAP and HNPCC. Unlike sporadic and hereditary CRC, CAC usually derives from a focal or multifocal dysplastic mucosa in areas of chronic inflammation via an inflammation→dysplasia→carcinoma sequence [2]. CAC accounts for 1–2 % of all cases of CRC and for 10–15 % of all deaths among IBD patients. It is thus one of the most important causes of mortality in IBD patients [1, 2].

2.5 Clinical Features of CAC

The clinical features of CAC are distinct from those of sporadic CRC and are reviewed below.

2.5.1 Age at Diagnosis

The mean age of CAC development in IBD patients is lower than that of sporadic CRC in the general population.

Several studies have examined the age of CAC development in patients with UC. In the meta-analysis by Eaden et al. [19], the mean age at UC-CAC diagnosis was 43.2 years. Lakatos et al. [20] reported a median age of 51 years at the time of UC-CAC diagnosis, which, in Hungary, is almost 15 years younger than that of sporadic CRC development in the general population. In the study of Watanabe et al. [21], the mean age at UC-CAC diagnosis was 56.8 years, younger than the

62.5 years of patients in the Japanese general population who are newly diagnosed with sporadic CRC.

2.6 Pathological Features of CAC

CAC frequently progresses from flat or nonpolypoid dysplasia to invasive adenocarcinoma. The tumors show aggressive growth and early metastasis [22].

In patients with UC, the rectum and the sigmoid colon are the most common sites of CAC. Compared with the general population, CAC arising in UC patients shows a more proximal distribution in the colon. Watanabe et al. [21] showed that UC-CAC tended to be of a higher histologic grade, such as mucinous or signet ring cell type, and had a greater frequency of developing as multiple synchronous CRCs.

In CD patients, CAC is evenly distributed between the different colonic segments [22].

2.7 Prognosis of CAC

The prognosis for patients with sporadic CRC and CAC is very similar, with 5-year survival rates of 50–60 % [21, 22].

In the study of Watanabe et al. [21], the 5-year overall survival rates of patients with UC-CAC and sporadic CRC were 64.2 % and 68.7 % ($P = 0.585$), respectively. According to Delaunoit et al. [23], 5-year survival rates were 54 % in patients with UC-CAC and 53 % in those with sporadic CRC ($P = 0.94$). However, patients with stage III UC-CAC were shown to have a significantly lower 5-year overall survival rate than those with sporadic CRC (43.3 % vs 57.4 %, $P = 0.032$), whereas the differences for stages I, II, and IV were not significant. Watanabe et al. [21] similarly concluded that the prognosis of patients with advanced-stage UC-CAC is poorer than that of patients with sporadic CRC.

2.8 Molecular Mechanisms of CAC Development

The premalignant lesion→carcinoma sequence of both sporadic CRC and CAC suggests the involvement of multiple gene alterations as the mechanism leading to carcinogenesis [24]. However, CAC differs from sporadic CRC with respect to tumor biology and the pathways leading to malignancy.

Sporadic CRC develops from a premalignant adenoma(s) through mutations in genes such as APC, KRAS (Kirsten rat sarcoma viral oncogene homolog), p53, and DCC (deleted in colorectal carcinoma netrin 1 receptor) [25]. In CAC,

tumorigenesis is via a transition from low- to high-grade dysplasia, although multiple gene alterations are likewise involved [26]. However, there are significant differences in the timing and frequency of the gene alterations leading to sporadic CRC vs CAC.

2.8.1 APC

In sporadic CRC, mutations in the tumor suppressor gene APC have been identified as one of the earliest genetic alterations in the pathogenesis of CRC. APC gene mutations are also found in CAC but generally as much later genetic events.

In the series of Aust et al. [27], one (3 %) out of 30 UC-CAC patients had an APC mutation compared with 11 (26 %) of the 42 patients with sporadic CRC. Similarly, in the study of Tarmin et al. [28], two (6 %) of their 33 patients with UC-associated dysplasia and CAC had a total of three truncating APC mutations compared with 17 (74 %) of the 23 patients with sporadic CRC. The results of these two studies suggest that the loss of APC function is a common initiating event in sporadic CRC but not in CAC.

2.8.2 p53

In sporadic CRC, p53 late-developing mutations are characteristic of morphologically aggressive lesions. Loss of p53 function occurs in approximately 85 % of CAC and is an important step in CAC progression. Mutations in p53 are found not only in dysplastic or malignant cells but also in chronically inflamed nondysplastic mucosa, suggesting that they are an early genetic event in the pathogenesis of CAC [29].

2.8.3 KRAS

KRAS mutations are another early genetic event in the pathogenesis of CAC [30].

2.9 Incidence of CRC in IBD

Table 2.1 summarizes the incidence of CAC in patients with IBD, and Table 2.2 the incidence of CAC and small-bowel cancer in those with CD.

In studies published in the 1980s to 1990s, the risk for CRC in UC was around 7 % 20 years after UC diagnosis [31] and around 14 % at 25 years [32, 33]. In the

Table 2.1 Incidence of colitis-associated cancer in inflammatory bowel disease (IBD)

Author	Year of publication	Type of study	IBD patients	No. of CAC patients	Incidence or risk ratios
Eaden et al. [19]	2001	Meta-analysis	UC	1,698	10 years, 1.6; 20 years, 8.3; 30 years, 18.4 %
Jess et al. [36]	2012	Meta-analysis	UC	229	10 years, <1 %; 15 years, 0.2–2.0 %; 20 years, 1.1–5.3 %
Lutgens et al. [37]	2013	Meta-analysis	UC and CD	NA	10 years, 1 %; 20 years, 2 %; >20 years, 5 %
Ekbom et al. [45]	1990	Population based	UC	91	5.7 (1958–1984)
Winther et al. [34]	2004	Population-based cohort	UC	124	10 years, 0.4 %; 20 years, 1.1 %; 30 years, 2.1 %
Rutter et al. [35]	2006	Prospective	UC	30	20 years, 2.5 %; 30 years, 7.6 %; 40 years, 10.8 %
Lakatos et al. [20]	2006	Population based	UC	13	10 years, 0.6 %; 20 years, 5.4 %; 30 years, 7.5 %
Söderlund et al. [41]	2009	Population based	UC and CD	188	10 years, 1 %; 20 years, 1.5 %; 30 years, 2.7 %
Jess et al. [42]	2012	Nationwide survey	UC and CD	UC: 268, CD: 70	1.34 (1979–1988), 0.57 (1999–2008)
Manninen et al. [43]	2013	Population based	UC and CD	21	1.83 in IBD, 1.99 in UC, 1.82 in CD

CAC, colitis-associated cancer; UC, ulcerative colitis; CD, Crohn's disease; NA, not available

Table 2.2 Incidence of colitis-associated cancer in Crohn's disease (CD)

Author	Year of publication	Type of study	IBD patients	Risk of CAC	Risk of small-bowel cancer
Jess et al. [18]	2005	Meta-analysis	CD	0.9–2.2	3.4–66.7
Canavan et al. [38]	2006	Meta-analysis	CD	2.5	33.2
von Roon et al. [39]	2007	Meta-analysis	CD	2.4	28.4
Laukoetter et al. [40]	2011	Meta-analysis	CD	0.5 person-years	0.3 person-years
Lovasz et al. [44]	2013	Population-based cohort	CD	7.73	NA

IBD, inflammatory bowel disease; NA, not available

early 2000s, the probability of developing CRC in UC was 1.6 % at 10 years, 8.3 % at 20 years, and 18.4 % at 30 years [19]. According to more recent data, the cumulative incidences of CRC in UC are approximately 1.0 % at 10 years, 2.0–5.0 % at 20 years, and 5.0–7.5 % at 30 years [20, 34, 35]. The decreased incidence

of CAC in IBD may be because of the improved therapeutic management of colitis, with higher rates of mucosal healing, but definitive clinical and experimental evidence supporting these observations is lacking.

Because chronic inflammation of the large bowel is an important factor in the development of CRC, anti-inflammatory agents have been considered as chemopreventive agents.

2.9.1 Meta-analysis of the Incidence of CRC in UC

The reported incidence varies widely between studies, which reflects the different periods of data collection, different methodologies, and data originating from studies in different countries. The results of the three meta-analyses published in the English-language literature are summarized briefly below.

Eaden et al. [19] accumulated the results of 116 studies comprising 54,478 patients with UC. In this cohort, there were 1,698 cases of CRC. The probability of developing CRC 10 years after UC diagnosis was 1.6 %, rising to 8.3 % after 20 years and 18.4 % after 30 years. The overall prevalence of CAC in UC in that series was 3.7 %, increasing to 5.4 % in patients with pancolitis. The data pointed to an association between the extent of colitis and the increased risk of CAC.

Jess et al. [36] carried out a meta-analysis of eight studies on the basis of strict inclusion and exclusion criteria. During 14 years of follow-up, 1.6 % of the patients in their study were diagnosed with UC-CAC. The pooled standardized incidence ratio (SIR) was 2.4 (range, 1.05–3.1). The cumulative incidences of CRC development were $<$1.0 % at 10 years, 0.4–2 % at 15 years, and 1.1–5.3 % at 20 years of follow-up. The sex-specific risk ratio was 1.9 in females and 2.6 in males. The age-specific risk ratio was 8.6 in patients 0–39 years of age, 2.1 in those 40–60 years of age, and 1.7 in those 60 years of age and older. Patients with extensive colitis and pancolitis (beyond proctosigmoiditis) had a 4.8-fold higher risk of UC-CAC.

Lutgens et al. [37] reported that the pooled SIR of CRC in IBD patients was 1.7 (range, 1.2–2.2). The cumulative risk of CRC was 1 %, 2 %, and 5 % after 10, 20, and $>$20 years of disease duration, respectively. The authors concluded that the risk of CRC in IBD patients is significantly higher in patients with longer disease duration, extensive disease, and IBD diagnosed at a young age.

2.9.2 Meta-analysis of the Incidence of CRC in CD

In an earlier meta-analysis, Jess et al. [18] evaluated six population-based studies in which the incidence of intestinal malignancies in CD patients was examined. The overall pooled risk estimates (SIRs) for CRCs in CD ranged from 0.9 to 2.2. The SIR for small-bowel cancer ranged from 3.4 to 66.7. The overall pooled estimate for

intestinal malignancies in CD was 27.1. These results showed that CD patients have an overall higher risk of CRC and small-bowel cancer.

Canavan et al. [38] accumulated the results of 13 studies comprising 11,840 patients with CD to examine the incidence of intestinal malignancies in that group. The overall relative risk (RR) of CRC in CD was 2.5 (range, 1.3–4.7). The risk of CRC in CD was shown to be significantly higher than in the general population but not significantly different from that in UC. The cumulative RR for CRC development in CD was 2.9 % at 10 years after CD diagnosis, 5.6 % at 20 years, and 8.3 % at 30 years. However, the authors also found that the overall RR for small-bowel cancer in CD was 33.2 (range, 15.9–60.9). Thus, the risk of small-bowel cancer is much higher in CD patients than in the general population.

Von Roon et al. [39] accumulated the results of 34 studies with a total of 60,122 patients with CD. Compared with the baseline general population, the RRs of CRC and small-bowel cancer were 2.4 (95 % confidence interval, 1.6–4.4) and 28.4 (95 % confidence interval, 14.5–55.7), respectively.

Laukoetter et al. [40] analyzed the results of 20 studies comprising 40,547 patients with CD. The incidence of CD-associated cancer (CDAC) was 0.8/1,000 person-years, meaning that during a 1-year observation period, 0.8 CD patients out of 1,000 developed CDAC. The incidence of CRC and small-bowel carcinoma in CD was 0.5/1,000 and 0.5/1,000 person-years, respectively. The mean age at CRC diagnosis in CD patients was 51.5 years, which is 20 years earlier than in the general population. The mean duration between CD diagnosis and CDAC was 18.3 years.

2.9.3 Incidence of CRC in IBD in a Population-Based Cohort Study

S-derlund et al. [41] assessed cancer occurrence and cancer-related mortality in 7,607 Swedish IBD patients in a population-based cohort study. CRC was detected in 188 IBD patients during 198,227 person-years of follow-up. Compared with the general population, the incidence of CRC in IBD corresponded to an overall twofold higher risk (SIR, 2.3). The overall cumulative incidence of CRC in IBD at 10, 20, and 30 years after IBD diagnosis was 1 %, 1.5 %, and 2.7 %, respectively.

Jess et al. [42] studied CRC risk in a nationwide cohort of 47,374 Danish patients with IBD over a 30-year period. Over the course of the follow-up evaluation, 268 patients with UC (0.5 %) and 70 patients with CD (0.1 %) developed CRC. The overall RR of CRC in UC patients was comparable to that of the general population (RR = 1.1), whereas the RR of CRC in CD patients was slightly lower (0.9) but did not change significantly over time. In UC patients, the overall RR for CRCs decreased from 1.34 between 1979 and 1988 to 0.57 between 1999 and 2008.

Manninen et al. [43] studied the risk of CRC in a nationwide cohort of 1,915 Finnish patients with IBD (1,254 with UC, 550 with CD, and 111 with

inflammatory bowel unclassified). CRC was found in 21 patients. The SIR was 1.83 for IBD, 1.99 for UC, and 1.92 for CD.

Lovasz et al. [44] examined the CRC risk in 640 CD patients with colonic involvement and stenosing disease in a population-based cohort from Hungary. CRC was diagnosed in six CD patients during a follow-up of 7,759 person-years. The mean overall CRC incidence rate was 7.73 per 10,000 patient-years.

2.9.4 Incidence of CRC in UC in a Population-Based Cohort Study

Ekbom et al. [45] examined a population-based cohort of 3,117 patients with UC. In 91 patients with UC, there were 92 cases of CRC (2.9 %). Compared with the general population, the RR for CRC was 1.7 for patients with proctitis, 2.8 for those with left-sided colitis, and 14.8 for those with pancolitis. Less extensive colitis at diagnosis was associated with a lower risk of CRC development.

Winther et al. [34] evaluated a population-based cohort of 1,160 patients with UC in Copenhagen County. After a follow-up of up to 36 years, there were 124 malignancies (10.7 %). The cumulative probability of CRC was 0.4 % by 10 years, 1.1 % by 20 years, and 2.1 % by 30 years of disease. The authors concluded that neither the overall cancer risk nor the risk of CAC was increased after a median of 19 years of follow-up. In their analysis of surgical intervention, the overall cumulative probability of colectomy was 21.3 % after 10 years, 27.9 % after 20 years, 29.9 % after 30 years, and 31.1 % after 35 years. This is in contrast to a rate of 9.1–16.4 % in the cohort reported by Eaden et al. [19]. An active surgical approach after medical treatment failure may explain the low rate of CRC development in the former study.

Rutter et al. [35] examined 600 patients who underwent 2,627 colonoscopic surveillance procedures over a 30-year period, during which 74 patients (12.3 %) developed neoplasia, including 30 cases of CRC (5 %). The cumulative incidence of CRC by colitis duration was 2.5 % at 20 years, 7.6 % at 30 years, and 10.8 % at 40 years. During the surveillance program, 89 patients (14.8 % of the study population) underwent colonic surgery.

Lakatos et al. [20] evaluated the relevant epidemiological and clinical data of 723 UC patients in a Hungarian population-based cohort study. CRC was detected in 13 patients (8,564-person-year duration). The cumulative risk of developing CRC after a 10-year duration of colitis was 0.6 %, which increased to 5.4 % at 20 years and 7.5 % at 30 years.

2.10 Risk Factors for CAC

The increased risk of CAC in IBD patients is thought to be due to genetic and acquired factors (Table 2.3), including the duration, extent, and severity of colitis, the presence of post-inflammatory polyps (pseudopolyps), young age at onset of colitis, sex, family history of sporadic CRC, coexistence of primary sclerosing cholangitis and/or colonic strictures, and the presence of colonic dysplasia. Of these, the most important and well-recognized risk factors for CAC are the duration and extent of colitis.

2.10.1 Duration of Colitis

The importance of colitis duration as a risk factor for the development of CRC in IBD patients is supported by several studies, including the above-cited studies of Eaden et al. [19] (Sect. 2.9.1), Lakatos et al. [20] (Sect. 2.9.4), and Rutter et al. [35] (Sect. 2.9.4). In the study of Lakatos et al. [20], a longer duration of colitis (10 years) was identified as a risk factor for developing CRC, according to a logistic regression model (odds ratio, 8.3; $P = 0.04$). Nieminen et al. [46] examined 183 IBD patients with dysplasia or CRC and 368 matched control patients in a case-control study. They concluded that an increasing degree of inflammation and disease duration cumulatively increased the risk of dysplasia in IBD.

Table 2.3 Risk factors for colitis-associated cancer

Risk factor	Relevant references
Duration of colitis	Eaden et al. [19]; Lakatos et al. [20]; Rutter et al. [35]; Nieminen et al. [46]
Extent of colitis	Ekbom et al. [45]; Eaden et al. [19]; Lakatos et al. [20]; Söderlund et al. [41]; Jess et al. [36]
Severity of colitis	Rutter et al. [47]; Gupta et al. [48]
Post-inflammatory polyps	Rutter et al. [47]; Velayos et al. [49]; Baars et al. [50]
Young age at onset of colitis	Ekbom et al. [45]; Eaden et al. [19]; Jess et al. [36]
Sex	Jess et al. [42]; Ekbom et al. [45]
Family history of sporadic colorectal cancer	Askling et al. [51]; Velayos et al. [49]
Primary sclerosing cholangitis	Broomé et al. [56]; Soetikno et al. [57] Lakatos et al. [20]; Loftus et al. [58]; Nuako et al. [59]
Colonic stricture	Rutter et al. [47]
Colonic dysplasia	Lakatos et al. [20]

2.10.2 Extent of Colitis

Current evidence suggests that the risk of CAC begins to increase after 8–10 years of extensive colitis, defined as left-sided colitis extending from the anal verge to the splenic flexure, and pancolitis (beyond the splenic flexure). By contrast, several studies have shown that there is little or no increased risk of CRC in patients with proctitis or proctosigmoiditis. Chronic colonic inflammation presumably leads to dysplasia and thus eventually to cancer.

The relationship between the extent of colitis and CRC was cited in the abovementioned study of Ekbom et al. [45] (Sect. 2.9.4). In the study of Eaden et al. [19], among UC patients with pancolitis, the cumulative incidence of CRC was 2.1 % at 10 years, 8.5 % at 20 years, and 17.8 % at 30 years disease duration. These data are very similar to the cumulative incidence of CRC in all UC patients, indicating that the development of CRC in UC is associated with pancolitis.

In their univariate analysis, Lakatos et al. [20] showed that patients with pancolitis had a higher risk of CRC than those with left-sided colitis (odds ratio, 5.3; $P = 0.001$). Pancolitis was also identified as a risk factor for CRC development in their logistic regression model (odds ratio, 1.8; $P = 0.04$).

In the above-cited study of Söderlund et al. [41] (Sect. 2.9.3), compared with the general population, the RR of CRC was 2.7 for all UC patients and 5.6 for those with pancolitis. Compared with patients with UC proctitis (RR = 1), the RR of incident CRC was 1.2 for patients with left-sided colitis and 2.0 for those with pancolitis. These data suggest that the greater the extent of colitis, the greater the risk of CRC.

In their meta-analysis (see Sect. 2.9.1), Jess et al. [36] demonstrated that patients with extensive colitis and pancolitis had a 4.8 times higher risk of UC-CAC.

2.10.3 Severity of Colitis

Several reports have demonstrated a significant correlation between the severity of colitis and the risk of CAC, in which chronic inflammation is believed to initiate and promote carcinogenesis in various organs.

Rutter et al. [47] studied 68 patients with CRC and 136 control patients who were matched with respect to sex, extent of colitis, age at diagnosis, duration of colitis, and year of index surveillance colonoscopy. In a multivariate analysis, the authors demonstrated that the histologic severity of colitis was an independent risk factor for the development of CRC (odds ratio, 4.7; $P < 0.001$). A multivariate analysis also showed that a macroscopically normal colonoscopy examination was an independent factor for a lower risk of CRC development (odds ratio, 0.38; $P = 0.003$).

Gupta et al. [48] examined 418 patients with no initial dysplasia who underwent regular endoscopic surveillance. Among them, 15 (3.6 %) progressed to advanced

neoplasia (high-grade dysplasia or colorectal cancer). The authors found a significant relationship between histologic inflammation over time and progression to advanced neoplasia. According to a multivariate analysis, the microscopically determined severity of inflammation was an independent risk factor for developing advanced colorectal neoplasia.

2.10.4 Post-inflammatory Polyps (Pseudopolyps)

Post-inflammatory polyps (colonic pseudopolyps) are irregular islands of colonic mucosa that form by colonic inflammation and regeneration. They are not premalignant lesions and in themselves have no malignant potential. Rather, the presence of post-inflammatory polyps is thought to be a historical marker of previous severe inflammation. As such, they are a known risk factor for CAC.

In the above-cited study of Rutter et al. [47] (Sect. 2.10.3), patients with post-inflammatory polyps had a higher risk of CRC, according to both a univariate (odds ratio, 2.1; $P = 0.006$) and a multivariate (odds ratio, 2.3; $P = 0.005$) analysis.

In a case-control study, Velayos et al. [49] evaluated 188 UC patients with CRC and 188 matched control patients. Based on a univariate analysis, there was a significant association between a prior diagnosis of pseudopolyps and CRC (odds ratio, 2.0; $P < 0.05$), even after adjusting for surveillance colonoscopy and anti-inflammatory therapy (odds ratio, 2.5; $P < 0.05$). These results suggested that a history of post-inflammatory pseudopolyps is a predictive factor for CRC in UC patients.

However, Baars et al. [50] studied the characteristics of IBD-related CRC in a nationwide IBD cohort, in which 251cases of IBD-related CRC were diagnosed (UC, $n = 171$; CD, $n = 77$; unclassified colitis, $n = 3$). The median time from IBD diagnosis to CRC diagnosis was 12 years. Type of IBD, sex of the patient, concomitant PSC, pseudopolyps, extent of inflammation, and medication use were not related to early CRCs that developed within 8 years after the diagnosis of IBD.

2.10.5 Young Age at Onset of Colitis

Young age at colitis onset is recognized as a risk factor for the development of CAC. Ekbom et al. [45] found that the RR of CRC decreased for each increase in age at diagnosis (under 15 years, 15–29 years, 30–39 years, 40–49 years, 50–59 years, and ≥60 years). For patients with extensive disease after 35 years of colitis, the cumulative risk for CRC was 40 % for those diagnosed under the age of 15 years and 25 % for those diagnosed at 15–39 years of age.

Eaden et al. [19] analyzed the incidence of CRC in children diagnosed with UC (average age at UC onset, 10 years). Within this group, the cumulative risk of CRC

was 5.5 % at 10 years, 10.8 % at 20 years, and 15.7 % at 30 years. These rates are higher than the corresponding rates for adults (3 %, 5.9 %, and 8.7 %, respectively).

In the above-cited meta-analysis of Jess et al. [36] (Sect. 2.9.1), the age-specific risk ratio was 8.6, 2.1, and 1.7 in patients 0–39, 40–60, and ≥60 years of age, respectively. Thus, young age at UC diagnosis increased the risk of CRC in UC patients.

2.10.6 Sex

The association between sex and the risk of CRC in IBD has been reported. Jess et al. [36] reported a sex-specific risk ratio of 1.9 in females and 2.6 in males. Ekbom et al. [45] showed a similar risk for IBD-CRC in males and females. Among patients with UC, the RR was 5.6 and 5.9, respectively. In those with CD, the RR was 2.8 and 2.1, respectively.

2.10.7 Family History of Sporadic CRC

Askling et al. [51] assessed the significance of a family history of CRC on the risk of CRC in a population-based cohort study of 19,876 patients with UC or CD. A family history of CRC was associated with a more than twofold risk of CRC (adjusted RR = 2.5). Patients with a first-degree relative diagnosed with CRC before age 50 years also had a higher risk (RR = 9.2).

In the abovementioned case-control study of Velayos et al. [49] (Sect. 2.10.4), a family history of CRC was an independent risk factor for IBD-CRC in patients with UC (odds ratio, 3.7).

2.10.8 Coexistent Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a chronic cholestatic hepatobiliary disease characterized by inflammation and fibrosis of the intrahepatic and extrahepatic biliary tract [52]. PSC causes multiple intrahepatic and extrahepatic biliary strictures, resulting in cholestasis, liver cirrhosis, portal hypertension, and liver failure. Its etiology is thus far unknown, but autoimmunity is thought to be the main cause.

The incidence of IBD in patients with PSC is 25–30 %. However, the association between PSC and CD is relatively rare, such that 85–90 % of the patients with PSC and IBD are those with UC [53].

The association between PSC and CD was first reported by Atkinson and Carroll [54], in 1964, and between PSC and UC by Smith and Loe [55], in 1965. Since then, many studies have identified PSC as a risk factor for the development of CRC in

patients with UC. In the study by Broomé et al. [56], five (28 %) of the 17 UC patients who developed dysplasia or carcinoma had PSC. Soetikno et al. [57] performed a meta-analysis of 11 studies comprising 16,844 patients with UC. Overall, 21 % of the patients with both UC and PSC developed colorectal neoplasms, compared with 4 % of the UC patients without PSC. Among patients with PSC, the RR of developing dysplasia or cancer was 4.8. In both a univariate analysis and a logistic regression model, Lakatos et al. [20] showed that patients with PSC had a higher risk of CRCs (odds ratio, 27.1 and 9.5, respectively). However, these results of an association between PSC and an increased risk of CRC in UC have been contradicted by others [58,59].

2.10.9 Colonic Strictures

In their case-control study of 68 patients with UC and colorectal neoplasia and 136 matched control patients, Rutter et al. [47] found that colonic strictures increased the risk of colorectal neoplasia in UC (odds ratio, 4.62).

2.10.10 Colonic Dysplasia

As noted above, the premalignant histological changes in UC develop from dysplasia rather than adenoma. Adenocarcinoma of the colon develops from a dysplastic precursor lesion. In their univariate analysis and in a logistic regression model, Lakatos et al. [20] showed that patients with dysplasia had a higher risk of CRC (odds ratio, 19.3; $P = 0.0001$ and odds ratio 4.72; $P = 0.05$, respectively).

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