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REVIEW OPEN ACCESS

Risk Factors for Colorectal Cancer in Patients with Inflammatory Bowel Disease and Management During Cancer Treatment: A Systematic Review

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Abstract

Introduction: Inflammatory bowel disease (IBD) is a group of conditions involving inflammation of the gastrointestinal tract. Patients with IBD are at an increased risk of developing colorectal cancer (CRC). Current evidence regarding risk factors for CRC in IBD patients and guidelines for IBD treatment upon cancer diagnosis is inconclusive. A systematic review was conducted to evaluate evidence on risk factors resulting in an increased incidence of CRC among IBD patients and modifications made to IBD management during cancer treatment.

Methods: The PubMed database was searched from inception to 2019 with an English-language restriction, and two independent reviewers screened the articles for inclusion according to established criteria.

Results: Eight studies (five literature reviews and three retrospective cohort studies) were included. Of the eight articles, six reported several risk factors for CRC in IBD patients such as duration of IBD, extent of IBD, co-existing primary sclerosing cholangitis, family history of CRC, age at IBD onset, vitamin D deficiency, and gender. The other two articles discussed IBD management during cancer treatment in the form of suspending immunosuppressive medications and administering those of an anti-inflammatory nature.

Discussion: An individualized, case-by-case approach for IBD patients diagnosed with cancer was recommended. No standardized course of treatment was found.

Conclusion: Despite the limitations of this review, numerous potential risk factors for CRC in IBD patients were identified. However, a lack of definitive evidence pertaining to modifications made to IBD management during cancer treatment suggests that additional research is needed to draw material conclusions.

Keywords: colorectal cancer; inflammatory bowel disease; ulcerative colitis; Crohn's disease; primary sclerosing cholangitis

Introduction

Inflammatory bowel disease (IBD) comprises two main chronic inflammatory disorders of the gastrointestinal tract: Crohn's disease (CD) and ulcerative colitis (UC) [1]. CD can occur anywhere from the mouth to the anus, while UC is limited to the colon and rectum [2,3]. IBD is estimated to affect up to ten million people worldwide with North America and Northern Europe reporting the greatest incidence [4,5]. Patients with IBD commonly experience diarrhea, abdominal pain, nausea, vomiting, rectal bleeding, and weight loss [6]. IBD is a risk factor for colorectal cancer (CRC) due to the presence of chronic inflammation [7]. CRC encompasses a group of cancers of the colon and rectum, and typically presents with weight loss, rectal bleeding, constipation, and/or diarrhea [8,9]. Worldwide, approximately one million new cases of CRC are diagnosed annually with up to one million deaths reported [10,11].

Past studies that assessed risk factors associated with the development of CRC in IBD patients are inconclusive as a result of differences in study design [12]. These include varying follow-up time intervals, prior medications or bowel resections, patient population sizes, and misclassification of patient data relating to any of these aforementioned factors [13]. A retrospective study assessing CRC in UC patients reported an increased risk in patients older than 40 years of age [14]. However, this study included a small patient population of 31 CRC patients, the majority of whom were male [14]. In contrast, a meta-analysis of 116 studies evaluating the risk of CRC in UC patients indicated a higher incidence of CRC among children with UC compared to adults, though fewer studies pertaining to children were analyzed compared to the adult population [15]. Similarly, a cohort study evaluating 1,655 CD patients found that there was a greater risk of CRC in those under 30 years of age compared to older adults [16]. Conversely, a meta-analysis of 20 studies assessing the risk of intestinal cancer in CD reported a higher incidence of CRC in older adults with a mean age of 50.5 years [17].

Current guidelines pertaining to the modification of IBD management during cancer treatment are nonuniform. Some

suggest employing a two-year drug holiday where the use of immunosuppressants and biologics such as anti-tumour necrosis factor medications (anti-TNFs) is suspended to minimize the risk of additional cancer development. However, continued use of immunosuppressive medications during cancer treatment may be required in cases of highly active IBD if cancer outcomes are not negatively affected [18].

Given the increasing incidence of IBD worldwide and the additional challenges presented upon CRC diagnosis, a closer examination of this subject is justified [19]. Thus, this systematic review analyzes risk factors that result in an increased incidence of CRC among IBD patients and modifications made to IBD management during cancer treatment.

Methods

This systematic review was conducted as a requirement for an academic course. An electronic search was performed using PubMed from inception to the date of the search (October 17, 2019) with an English-language restriction. Search terms included 'colorectal cancer', 'inflammatory bowel disease', 'risk factors', 'management', and 'incidence'. Since the first search did not yield results relating to the second goal of this systematic review, a second search was conducted with the same date range as the first search. The second search included terms such as 'chemotherapy', 'radiation', 'treatment', 'management', 'colorectal cancer', 'inflammatory bowel disease', and 'incidence'.

The following inclusion criteria were employed for the first search: (a) patients with clinically diagnosed IBD and CRC; and (b) examination of one or more epidemiological risk factors for CRC in IBD patients. For the second search, the inclusion criteria were as follows: (a) patients with clinically diagnosed IBD and cancer; and (b) discussion of the modification of IBD management during cancer treatment. It is noteworthy that articles solely investigating surveillance for CRC were excluded as this is a preventative measure rather than treatment. Moreover, neither search included a year restriction to ensure that all potentially relevant studies could be analyzed.

Two reviewers (BJR and VD) independently screened the title, abstract, and full text of the resulting articles for inclusion using an Excel spreadsheet. Any discrepancies in the article screening were resolved by consensus.

Upon selecting the final studies from the first search, one of the reviewers (BJR) extracted the following variables from the full-text articles: sample size, patient characteristics (gender measure, race/ethnicity, age, and prior treatment), time period of study, location of study, results of study, and risk factors noted for CRC in IBD patients. For the second search, similar variables were extracted from the final full-text articles: sample size, patient characteristics (gender measure, race/ethnicity, age, and prior treatment), time period of study, location of study, results of study, and modifications made to IBD management during cancer treatment. The variables for both searches were recorded on an Excel spreadsheet.

Results

A total of 45 studies were identified through two PubMed literature searches. The first PubMed search pertained to risk factors for CRC in IBD patients, and the second related to the modification of IBD management during cancer treatment. Of these, 10 articles were retrieved for full-text screening based on the inclusion criteria previously presented. After screening, two articles were excluded. Figures 1 and 2 describe the flow diagrams for the selection of studies from the first and second searches, respectively.

Characteristics of the included studies from the first search are depicted in Table 1. The most common risk factors identified were duration of IBD (noted in three studies), extent of IBD (two studies), co-existing primary sclerosing cholangitis (PSC) (three studies), family history of CRC (three studies), and age at IBD onset (two studies). Four of the studies (66.7%) were located in the United States, one (16.7%) was located in Sweden, and one (16.7%) was located in the European Union. In total, these studies assessed at least 231,804 patients.

With respect to duration of IBD, Söderlund et al. reported an elevated risk of CRC in both male and female IBD patients at 10 (0.5% and 0.7%, respectively), 20 (2.0% and 1.2%), and 40 years (8.3% and 3.5%) following IBD diagnosis [20]. Lashner et al. reported a significant correlation between UC duration and CRC development ($p < 0.05$) [21]. Sebastian et al. referenced a study that reported an increased risk of CRC 10 years following UC diagnosis [22]. However, two additional studies reported a lower risk or no risk of CRC with longer IBD duration [22].

In addition, Sebastian et al. reported an elevated risk of CRC in extensive UC compared to left-sided UC [22]. CD patients were found to have a similar risk of CRC compared to UC patients with analogous disease duration and extent [22]. Lashner et al. indicated a greater risk of CRC in UC patients with more extensive disease [21].

Furthermore, PSC is a chronic disease of the liver that may result in transplantation [23]. Approximately 80% of PSC patients are also diagnosed with IBD, mainly UC [23]. Safaeian et al. reported that patients with PSC and IBD had an increased risk of CRC following liver transplantation (incidence rate ratio (IRR) 5.32, 95% confidence interval (CI) 3.73-7.58) [23]. Moreover, patients with PSC and UC had a greater CRC risk than those with UC alone [23]. Sebastian et al. reported a risk of CRC four times greater in patients with PSC and UC than in patients with UC only [22]. CRC risk was also elevated in patients with PSC and extensive colitis [22]. However, studies evaluating the risk of CRC in patients with CD and PSC were ambiguous with one indicating an elevated risk (odds ratio (OR) 6.78, 95% CI 1.65-27.9) and another demonstrating no heightened risk (OR 1.64, 95% CI 0.14-18.7) [22]. Söderlund et al. reported

an estimated prevalence of PSC with IBD in 10% of male patients and 5% of female patients and indicated that the risk of CRC was four times greater in these patients [20].

Additionally, Janakiram et al. and Sebastian et al. reported an increased risk of CRC in IBD patients with a family history of CRC [22,24]. Lashner et al. indicated a large but insignificant risk of CRC in UC patients when CRC was present in a first-degree relative (OR 9.97, 95% CI 0.87-114.06) [21].

Moreover, Sebastian et al. reported an increased risk of CRC in patients with a young age at IBD onset [22]. However, other studies have indicated that CRC risk may be elevated in older patients diagnosed with IBD [22]. Lashner et al. reported a greater but insignificant risk of CRC in patients with an older age at UC onset (OR 1.07 years, 95% CI 0.96-1.20) [21].

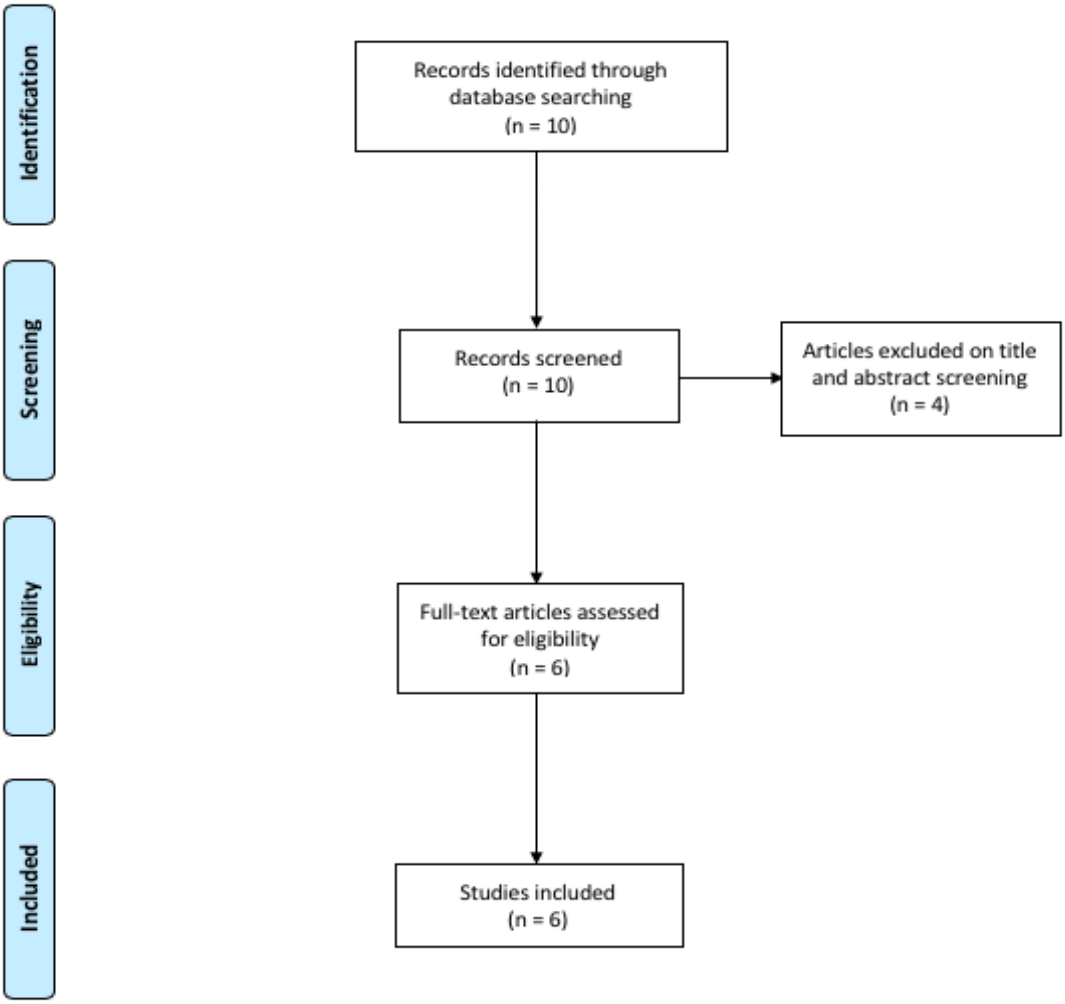

Figure 1. Flow Diagram for the First Search - This flow diagram illustrates the selection of studies from the first search pertaining to risk factors for CRC in IBD patients. A total of 10 articles were identified; six were included after title and abstract screening. This figure was created using Microsoft Word based on a PRISMA 2009 flow diagram template [31].

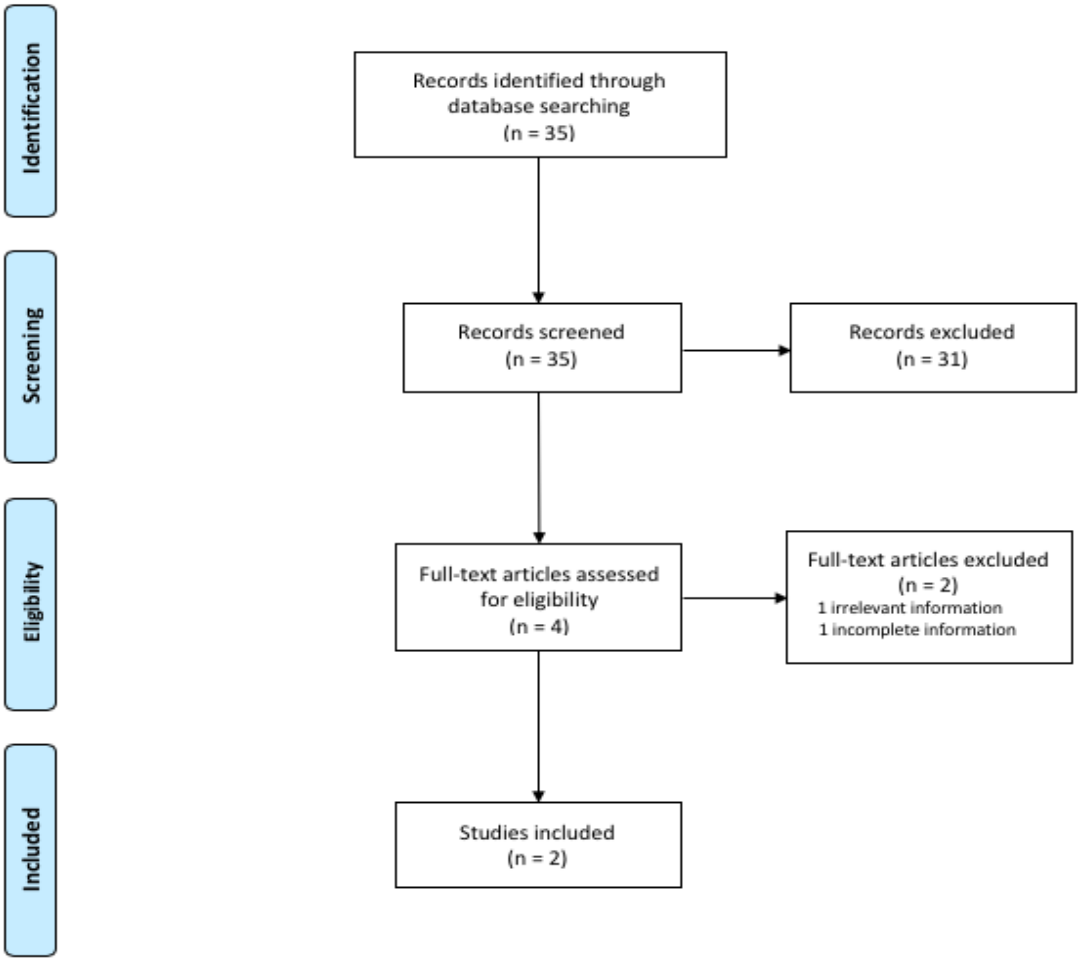

Figure 2. Flow Diagram for the Second Search - This flow diagram illustrates the selection of studies from the second search relating to the modification of IBD management during cancer treatment. A total of 35 articles were identified; two were included after title and abstract screening. This figure was created using Microsoft Word based on a PRISMA 2009 flow diagram template [31].

Five studies also reported other risk factors. Meeker et al. reported an inverse relationship between CRC development and vitamin D levels in IBD patients, and Janakiram et al. indicated a potential increase in CRC risk resulting from high-fat diets [24,25]. Northern latitudes (0.9% prevalence compared to 0.25% for southern latitudes, $p = 0.17$) and persistent colonic inflammation were reported to be risk factors for CRC in IBD patients by Sebastian et al. [22]. This article also referenced a study by Söderlund et al. which reported a 60% greater CRC risk among males compared to females (relative risk 1.6, 95% CI 1.2-2.2) [20,22]. Both Söderlund et al. and Lashner et al. (OR 1.14, 95% CI 0.94-1.38) indicated an elevated risk of CRC in IBD patients with a history of cigarette smoking [20,21]. Söderlund et al. also reported a slight increase in CRC risk in IBD patients with prior mesalamine treatment, and Lashner et al. reported folate deficiency (OR 0.38, 95% CI 0.12-1.20 for folate supplementation) and sulfa allergy to be additional risk factors ($p < 0.05$) [20,21].

Characteristics of the included studies from the second search are depicted in Table 2. Both studies (100%) were located in the United States.

Modifications made to IBD management during cancer treatment included the suspension of immunosuppressive medications, the administration of 5-aminosalicylic acid (5-ASA) and non-systemic steroids, and the suspension of thiopurines, calcineurin inhibitors, and anti-TNFs during CRC treatment.

Table 1. Summary of Study Characteristics for the First Search: Location of Study, Design, Types of IBD, Sample Size, Gender, Prior Treatment, and Risk Factors

References	Location of study	Design	Types of IBD	Sample size	Gender (female; male)	Prior treatment	Risk factors noted
[20]	Sweden	Cohort; retrospective	CD; UC	7,607 IBD patients	3,671; 3,936	Not provided	Male sex; IBD duration; IBD with PSC; smoking; mesalamine treatment
[21]	United States	Cohort; retrospective	UC	99 pancolitis patients	39; 60	Sulfasalazine; prednisone	Folate deficiency; IBD duration; extensive IBD; older age at IBD onset; sulfa allergy; family history of CRC; smoking
[22]	European Union	Literature review	CD; UC	Various	Various	5-ASA; ursodeoxycholic acid; azathioprine; folic acid; statins	Northern latitudes; IBD duration; extensive IBD; young age at IBD onset; family history of CRC; IBD with PSC; persistent colonic inflammation; male sex
[23]	United States	Cohort; retrospective	UC	224,098 solid organ transplant patients	87,035; 137,063	Cyclosporine-azathioprine	IBD with PSC
[24]	United States	Literature review	CD; UC	Various	Not provided	Non-steroidal anti-inflammatory drugs; 5-aminosalicylic acid (5-ASA); mesalamine	Family history of CRC; High-fat diet
[25]	United States	Literature review	CD; UC	Various	Not provided	Not provided	Vitamin D deficiency

Table 2. Summary of Study Characteristics for the Second Search: Location of Study, Design, Types of IBD, Types of Cancer, Sample Size, Gender, Prior Treatment, and Modifications made to IBD Treatment

References	Location of study	Design	Types of IBD	Types of cancer	Sample size	Gender (female; male)	Prior treatment	Modifications made to IBD treatment
[26]	United States	Literature review	CD; UC	Extra-intestinal cancer	Various	Not provided	Various	Suspension of immunosuppressive medications
[27]	United States	Literature review	CD; UC	Colorectal cancer	Not provided	Not provided	Not provided	Administration of 5-ASA medications and non-systemic steroids; Suspension of thiopurines, calcineurin inhibitors, and anti-TNFs during CRC treatment

The 2016 review by Axelrad et al. reported that immunosuppressive treatment for IBD is usually suspended following cancer diagnosis and can continue throughout cancer treatment and remission [26]. In addition, the 2019 review by Keller et al. reported that 5-ASA medications and non-systemic steroids are recommended to manage IBD during CRC treatment and indicated that IBD treatment in the form of thiopurines, calcineurin inhibitors, and anti-TNFs should be suspended during CRC treatment [27].

Discussion

In this systematic review, the literature was assessed to examine risk factors for CRC in IBD patients and modifications made to IBD management during cancer treatment. The risk factors that were identified included duration of IBD, extent of IBD, co-existing PSC, family history of CRC, age at IBD onset, vitamin D deficiency, high-fat diets, northern latitudes, persistent colonic inflammation, male sex, smoking, mesalamine treatment, folate deficiency, and sulfa allergy. Only the most common risk factors will be discussed: duration of IBD, extent of IBD, co-existing PSC, family history of CRC, and age at IBD onset. Modifications made to IBD management during cancer treatment included the suspension of immunosuppressive medications, administration of 5-ASA medications and non-systemic steroids, and suspension of thiopurines, calcineurin inhibitors, and anti-TNFs during CRC treatment.

Three articles in this systematic review discussed duration of IBD as a risk factor for CRC with no overall consensus [20,21,22]. Söderlund et al. reported an elevated CRC risk in both male and female IBD patients at 10, 20, and 40 years after IBD diagnosis [20]. Similar results were reported by Lashner et al., who indicated a significant correlation between UC duration and CRC development despite examining a small sample size of 99 UC patients, predominantly white males, with long UC duration of over seven years [21]. Furthermore, Sebastian et al. examined three studies which presented contradictory findings on duration of IBD as a risk factor for CRC [22].

In addition, both Sebastian et al. and Lashner et al. reported a higher risk of CRC in patients with more extensive IBD, especially those with UC. Although the latter had a small sample size, the former referenced four separate studies in which both CD and UC patients had a comparable risk of CRC. This strongly suggests a correlation between greater extent of IBD and CRC risk [21,22].

Furthermore, three articles assessed co-existing PSC as a risk factor for CRC in IBD patients and indicated that UC patients with PSC had an elevated risk of CRC. However, the risk of CRC in CD patients with PSC was unclear [20,22,23]. For instance, two studies referenced by Sebastian et al. were contradictory on this matter, with one reporting an increase in CRC risk and the other reporting no increase in risk [22]. Hence, additional studies examining CRC risk in CD patients with PSC are warranted to draw more definitive conclusions.

Moreover, three articles reported an elevated risk of CRC in IBD patients with a family history of CRC [21,22,24]. However, family history of CRC is a potential independent risk factor for CRC, suggesting that IBD may not be directly responsible for CRC development in these patients [28].

Additionally, the two articles relating to age at IBD onset as a risk factor for CRC were inconclusive [21,22]. Lashner et al. reported an elevated risk of CRC in patients with an older age at UC onset [21]. However, Sebastian et al. referenced studies that suggested an increased risk of CRC in patients with either a younger or older age at IBD

onset [22]. Therefore, additional studies are needed to further investigate this potential risk factor.

Other studies have also suggested that longer duration of IBD, greater extent of IBD, co-existing PSC, and family history of CRC are among the primary risk factors for CRC in IBD patients [29,30]. However, this review was only able to corroborate co-existing PSC in UC patients and greater extent of IBD as risk factors with the others being inconclusive. Moreover, these studies indicate that post-inflammatory polyps and intestinal strictures–which did not arise from this review–have historically been considered to be major risk factors for CRC in IBD patients but have recently been called into question in light of new evidence [29,30]. Despite this ambiguity, European, Australian, and American guidelines state that family history of CRC, post-inflammatory polyps, and intestinal strictures are associated with high or intermediate CRC risk in IBD patients and warrant surveillance of the colon every one to three years [29]. Thus, these guidelines may require an update to reflect the most recent developments in CRC and IBD research.

Regarding IBD management during cancer treatment, Axelrad et al. and Keller et al. proposed the suspension of immunosuppressive medications, the administration of 5-ASA medications and non-systemic steroids, and the suspension of thiopurines, calcineurin inhibitors, and anti-TNFs during CRC treatment. However, no consensus was found [26,27]. Currently, an individualized patient-care approach to IBD management is taken during cancer treatment by gastroenterologists and oncologists [27]. Therefore, more studies, particularly with large sample sizes, are required to formulate universal guidelines.

Several limitations were present in this review. The scope of the search strategy was limited to English-language articles only which may have excluded relevant publications in other languages. Additional search terms could also have been used in the search strategy such as ‘neoplasia’, ‘malignancy’, ‘colonic’, ‘epidemiology’, and ‘colitis-associated cancer’, and the second search could have been expanded to include other gastrointestinal and IBD-related cancers, not solely CRC. However, this review had strengths such as rigorous methods, an extensive search strategy, and a team of two reviewers to mitigate bias.

Conclusions

This systematic review explored risk factors that result in an increased incidence of CRC among IBD patients and modifications made to IBD management during cancer treatment. These are important considerations for the quality of life of IBD patients with cancer and for those who may develop cancer in the future, health care providers who are directly involved in caring for these patients, and researchers who work to discern the relationship between IBD and cancer to develop new preventative treatment options. The risk factors identified were duration of IBD, extent of IBD, co-existing PSC, family history of CRC, age at IBD onset, vitamin D deficiency, high-fat diets, northern latitudes, persistent colonic inflammation, male sex, smoking, mesalamine treatment, folate deficiency, and sulfa allergy [20-25]. However, greater extent of IBD and co-existing PSC were the only risk factors strongly associated with the development of CRC in IBD patients–the latter being most notable in UC patients–while the others were inconclusive. This highlights the need for further study of the risk factors for CRC in IBD patients in order to yield more definitive conclusions. With respect to the modification of IBD management during cancer treatment, the suspension of immunosuppressive medications, administration of 5-ASA medications and non-systemic steroids, and suspension of thiopurines, calcineurin inhibitors, and anti-TNFs during CRC treatment were found [26,27]. Despite these potential treatment options, an individualized approach for these patients was recommended due to a lack of established guidelines [27]. Additional studies with large sample sizes would be beneficial to better understand the risk of CRC in IBD patients and develop guidelines for IBD management following cancer diagnosis.

List of Abbreviations Used

5-ASA: 5-aminosalicylic acid
anti-TNFs: anti-tumour necrosis factor medications
CD: Crohn’s disease
CI: confidence interval
CRC: colorectal cancer
IBD: inflammatory bowel disease
IRR: incidence rate ratio
OR: odds ratio
PSC: primary sclerosing cholangitis
UC: ulcerative colitis

Conflicts of Interest

The author declares that they have no conflicts of interest.

Ethics Approval and/or Participant Consent

No ethics approval or participant consent was required to perform this systematic review.

Authors' Contributions

BJR: made contributions to the design of the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.

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