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Ulcerative colitis and its correlation with the incidence of colorectal cancer

Felix Ongko[1], Erwin Kurniawan Santosa[2], Edward Then[3], Lucky Anthonny Setiawan[4], Vivian Ongriana[5]

[1,2,3,4]Faculty of Medicine, Tarumanagara University
[5]Faculty of Medicine, Atma Jaya University

ARTICLE INFO

Article history:
Received Mar 2, 2023
Revised Apr 20, 2023
Accepted Apr 26, 2023

Keywords:
Cancer
Colorectal cancer
Ulcerative colitis,

ABSTRACT

The purpose of this research to further reviewed the pathogenesis, risk factors, screening, and preventive interventions for colorectal cancer associated with ulcerative colitis. The research method used descriptive qualitative through the Literature Review (LR) approach. The data source used a secondary source. Data analysis technique selects literature based on title, year, and indexed articles, then reviews articles that match the subject matter. A literature search was performed using databases, such as PubMed, Cochrane Library, and Science Direct. Colitis-associated neoplasia is thought to result from chronic inflammation, which induces changes in epithelial proliferation, survival, and migration through the effects of various chemokines and cytokines. The risk factors are in three main categories: disease-related, patient-related, and pathology-related. The most reliable screening test is colonoscopy, parallel with a structured endoscopic surveillance program that includes ongoing medical management for disease control. There are several chemopreventive options for the early prevention of colorectal cancer in cases of ulcerative colitis. In general, long-standing chronic inflammation in the intestinal mucosa increases the risk of colorectal cancer due to genetic and molecular alterations. Identifying high-risk groups and colonoscopic surveillance programs have been considered useful early detection measures.

Corresponding Author:
Felix Ongko
Faculty of Medicine, Tarumanagara University
Universitas Tarumanagara
Letjen S. Parman 1, Tomang, Grogol petamburan, Jakarta, Indonesia
Email: felix.ongko12@gmail.com

INTRODUCTION

Ulcerative colitis is a form of chronic inflammatory bowel disease (IBD) mediated by immune activity. This condition is often associated with inflammation of the rectal area, but can extend in a proximal direction so that it involves additional areas of the colon characterized by relapse and musselsi (Rubin *et al.*, 2019). The severity of a ulcerative colitis can vary according to the severity of the disease, among which include bloody diarrhea, rectal bleeding, tenesmus, urgency and incontinence of alvi (Magro *et al.*, 2017). The exact etiology for this disorder cannot yet be defined, but it involves a complex interaction between immune dysregulation, microbiota dysbiosis, and environmental triggers in individuals with an underlying genetic predisposition (Shah &

Itzkowitz, 2022). Family history with IBD also increases the risk of developing ulcerative colitis (Magro *et al.,* 2017).

Besides having a role in the severity of the disease, the above factors also contribute to one of the most feared chronic inflammatory complications in the colon, namely colorectal cancer. It is one of the most common cancers worldwide and one of the leading causes of death from cancer (Siegel *et al.,* 2012). According to the population-based data, patients with ulcerative colitis have a two to three times higher risk of developing colorectal cancer than the common population (Li *et al.,* 2022). A meta-analysis of 31.287 patients with ulcerative colitis from 44 studies conducted in Asian countries reported a combined prevalence of colorectal cancer that assembled with ulcerative colitis of 0,85%, with a cumulative risk of 0,02%, 4,8%, and 13,9% at durations of 10, 20, and 30 years (Bopanna *et al.,* 2017).

The chronic inflammatory process encourages neoplastic development and produces dysplastic precursor lesions that may arise in some areas of the colon through the process of cancer formation. Some unique molecular differences are found in the pathogenesis of colularity-associated colorectal cancer (CAC), but their role in the formation patterns of inflammatory-related cancers remains to be explained further (Shah & Itzkowitz, 2022;Li *et al.,* 2022 ; Lopez *et al.,* 2018). Ulcerative colitis related to colorectal cancer has given rise to a series of clinical problems reflected in a worse prognosis and higher mortality compared to sporadic colorectal cancer. According to studies, about half of colorectal cancer cases can be prevented or managed through risk modification and screening (Fisher *et al.,* 2021). However, the condition of ulcerative colitis and its subsequent development into colitis-associated neo-plasia (CAN) give a unique challenges related to the supervision and management of dysplasia (Reznicek *et al.,* 2021). The type of unconventional dysplasia has been known, but its natural history has not been well defined. As an allegation, the cumulative inflammatory load over time is considered as an important risk factor for ulcerative colitis-related colorectal cancer.

This study aims to provide the latest reference regarding pathogenesis, risk factors, screening, as well as preventive interventions for colorectal cancer related to ulcerative colitis; where the authors expect that this review can provide a better understanding of ulcerative colitis and its correlation to the incidence of colorectal cancer to foster awareness of the optimal screening, early detection, and prevention that enables this conditions is more quickly predicted and managed in the future.

RESEARCH METHOD

The research method used descriptive qualitative through the Literature Review (LR) approach. The data source used a secondary source. Data analysis technique selects literature based on title, year, and indexed articles, then reviews articles that match the subject matter. The samples used in this literature study are related to scientific publications published within the last 10 (ten) years. Literature searches were conducted using databases, such as PubMed, Cochrane Library, and Science Direct with the keywords of "ulcerative colitis" and "colorectal cancer". The inclusion criteria in this study are the studies that address the correlation between ulcerative colitis and colorectal cancer, as well as effective interventions to prevent colorectal cancer in patients with ulcerative colitis. Studies that do not address populations and corresponding samples are excluded. The literature that meets the inclusion criteria is systematically analyzed to examine the correlation between ulcerative colitis and colorectal cancer. Last, the results of the analysis are presented in the form of appropriate articles, tables and diagrams to facilitate understanding of pathogenesis, risk factors, screening, early detection, and preventive interventions from colorectal cancer associated with ulcerative colitis.

RESULTS AND DISCUSSIONS

Sporadic colorectal cancer develops from one or two foci of dysplasia or adenoma. Colitis-associated neoplasia is believed to develop from multiple dysplastic foci, where the chronically inflamed mucosa produces local molecular and histological changes (Dulai *et al.,* 2016). Dysplasia is an abnormal or irregular growth of cells and signals a precancerous lesion of the mucosa. Dysplasia is sub-divided into low-grade dysplasia (LGD) and high-grade dysplasia (or HGD). Low-grade dysplasia (LGD) is characterized only by cytological changes, such as the atypical nucleus and carries a relatively low risk for malignant transformations. In contrast, high-level dysplasia (HGD) exhibits cytological and architectural changes, such as loss of polarity or the formation of cribiform glands, and it has a higher risk of developing into malignancy. Biopsy results can be indefinitive for dysplasia if acute inflammation in the tissues is present since the picture can mask or mimic dysplastic changes (Robles *et al.,* 2016). Chronic inflammation that occurs in this case does not form discrete lesions as in sporadic dysplasia polyps (e.g. adenoma), but it can manifest as large swaths of mucosal inflammation prone to neoplastic transformation in the process of field cancerization or cancerization in a particular field (Shah & Itzkowitz, 2022). In a study involving ulcerative colitis patients with recurrent colonoscopy monitoring, genome instability represented by aneuploidy cell populations remained in the same colonic segment, but there is a spread over time until it occupied a wider mucosal area (C. H. R. Choi *et al.,* 2017).

Colitis-associated neoplasia is thought to be the result of chronic inflammation which induces changes in epithelial proliferation, survival, and migration through the effects of various chemokines and cytokines (Dulai *et al.,* 2016). On the background of inflammation, innate immune system cells are activated and release various reactive oxygen species (SOR) and reactive nitrogen species (RON), among which are superoxide, hydroxyl radicals, hydrogen peroxide, singlet oxygen, nitric oxide, nitrogen dioxide, and peroxynitrite (Pereira *et al.,* 2015). These reactive species are produced in significant quantities, so it can result in DNA damage, such as single and double-stranded terminations, nucleobase oxidation, nucleotide modification (Waldner & Neurath, 2015). This DNA damage can alter the encoding sequence and regulation of ethical genes, such as p53, APC, and DPC4. Frick, *et al.* in their study stated that there was an increase in markers of DNA double-strand damage that progressively increased in inflammatory progressivity sequences that developed into dysplasia into carcinoma (Frick *et al.,* 2018). Factors were produced by the host's immune response, with the contribution of the gut microbiome and its products, contribute to inflammatory, and carcinogenic processes. The net result is a sequence of events that cause genetic (e.g. mutational) and epigenetic (e.g. methylation) changes, followed by the expansion of somatic epithelial cell clones, with influences emanating from the surrounding stromal and immune cells.

Exome sequencing analysis conducted by The Cancer Genome Atlas aims to compare the mutational profiles of colitis-related and sporadic colorectal cancers suggested the significant results. Although both show similar frequencies of acquired genetic abnormalities, such as chromosomal instability and microsatellite instability, there are important differences in the timing and frequency of sequencing anomalies. Generally, p53 mutations tend to appear frequently and earlier in CAN whereas APC mutations appear later and K-RAS mutations rarely appear. On the other words, APC and K-RAS mutations occur frequently and at the beginning of CRC sporadically, whereas p53 mutations develop later in the course of carcinogenesis (Robles *et al.,* 2016).

Furthermore, through the participation of the gut microbiota, several pathways including NF-κB, IL-6/STAT3, interleukin-23 (IL-23)/ß type 17 (Th17), cyclooxygenase-2 (COX-2)/Prostaglandin E2 (PGE2), and Wnt/β-catenin were activated for the initiation and development of ulcerative colitis-associated colorectal cancer (Luo & Zhang, 2017; Takehiro *et al.,* 2020). Prolonged infiltration of inflammatory cells results in the production of pro-inflammatory cytokines (IL-1, IL-6, TNF-α) and chemokines, which activate nucleus transcription factors (NF-kB and STAT3) to retain inflammation and increase carcinogenesis through the loss of the tumor

suppressor gene p53 and the activation of NF-kB and STAT3. The loss of p53 promotes uncontrolled cell growth and inhibits apoptosis while adding cytokine-mediated DNA damage. Active transcription factors stimulate the production of cytokines and reactive oxygen species (SORs) and increase the expression of proto-oncogen MYC. This feedback loop of inflammation, DNA damage, and cell growth ultimately leads to remodeling the extracellular matrix and metastases (Dulai *et al.,* 2016;(Rennoll, 2015; Saraggi *et al.,* 2017). Last but not least, disbiosis of genotoxic microorganisms has been shown to have implications as a risk factor for carcinogenesis through decreased production of anti-inflammatory cytokines, such as IL-10 (Reznicek *et al.,* 2021).

The pathogenesis of colitis-associated neoplasia involves a complex system of interactions between environmental factors, microbiota gut, and genetics. This system dysregulation causes chronic inflammation, which induces cellular and architectural changes over time and eventually develops into malignancy.

In order to improve the prognosis of colorectal cancer cases about ulcerative colitis, knowledge about the risk factors of this condition is necessary to categorize patients who require intensive observation. Some of the risk factors discussed in this review are divided into three main categories: a) disease-related risks; b) patient-related risks; and c) pathology-related risks (Li *et al.,* 2022).

One of the main risks of developing colorectal cancer from ulcerative colitis is related to the extent and duration of the disease, where a larger area and longer duration increase the risk of colorectal cancer. Extensive ulcerative colitis commonly defined as inflammation extending to the proximal flexura lienalis is correlated with a 2–3-fold higher risk of developing neoplasia (Wijnands *et al.,* 2021). Another important risk factor was verified by a Cohort study involving 504 ulcerative colitis patients with the cumulative incidence of colitis-related colorectal cancer outcomes that varies depending on the duration of the disease, i.e. 1% at a duration of 10 years, 3% at a duration of 20 years, and 7 % at a duration of 30 years. In other words, it can be concluded that the longer the duration, the greater risk of developing malignancy (Bopanna *et al.,* 2017;Choi *et al.,* 2015; Selinger *et al.,* 2014). A population-based meta analysis also reported similar results, in which the cumulative risk of colitis-related colorectal cancer was 2.6% and 6.6%, respectively at the duration of the disease in 10-20 years and >20 years, with a cumulative incidence of 21% after 20 years of extensive disease (Lutgens *et al.,* 2013). Its theory may be related to the chronic inflammatory stimulation that can result in the release of inflammatory cytokines, immune dysfunction, and epigenetic changes (Scarpa *et al.,* 2014). In addition, changes in the anatomical structure of the colon, including the formation of strictures and post-inflammatory polyposis (PIP) also has a role in this increased risk. This may be due to more severe histological inflammation of the strictures and PIP. Thus, it is associated with the inflammatory load, referred to as a structural marker of the cumulative inflammatory load. However, if this structural factor is found independently without being accompanied by other factors, then the condition does not meet the indications for observation colonoscopy (Axelrad *et al.,* 2022; Jong *et al.,* 2020).

In terms of patient-related factors, the age of initial diagnosis about ulcerative colitis in each individual is one variable that is quite influential, regardless of the risk of sporadic colorectal cancer that is not related to ulcerative colitis in the older age group (Wijnands *et al.,* 2021). Increased risk occurs in age groups with a younger onset of ulcerative colitis, where this group is more likely to reflect the duration of the disease and cumulative inflammation over time, and by an accelerated process of carcinogenesis in young colitis ulcerative onset (Hata *et al.,* 2019;Lutgens *et al.,* 2013). Moreover, (Jess *et al.,* 2014) has analyzed the relative risk of patients categorized by age, namely a relative risk of 43,8 in the group of respondents diagnosed in childhood (0-19 years) and 2,65 in the group of respondents diagnosed in childhood (0-19 years) and 2,65 in the respondents groups diagnosed in young adulthood (20-39 years). The study shows that young age at the onset of ulcerative colitis has been reported as an independent risk factor for the development of colorectal cancer (Jess *et al.,* 2012). By the age, gender also becomes a risk factor that cannot be

ruled out. Several previous studies have stated that the risk of colitis-related colorectal cancer in men is higher than in women (Wijnands *et al.,* 2021;J. kyu Choi *et al.,* 2016). In a meta-analysis of eleven Cohort studies using multi-variable analysis, men showed a 1,50-1,58-fold times increased risk of developing malignancy from colitis than women (Wijnands *et al.,* 2021). This gender difference can be explained by the protective effect of estrogen on the development of colorectal cancer. Estrogen has been shown to intervene directly in the activity of core *kB* factors and the production of interleukin-6. Therefore, it is offering a protective effect on cancer in female mammals. Similarly, the study using experimental animal of rats with colorectal cancer associated with colitis, MyD-88 deficiency has an increased resistance to cancer progression in men (Söderlund et al., 2010). Although many analyses support a similar family history as a convincing risk factor in healthy individuals, only few is known about its role in the development of ulcerative colitis. A Cohort study with 9505 respondents reported that a history of colitis-related colorectal cancer in the family was associated with an almost eightfold increase in the risk of developing this malignancy (de Campos Silva *et al.,* 2020; Samadder *et al.*, 2019). Smoking is an environmental factor that is thought to be involved in the pathogenesis of colorectal cancer related to colitis. However, some studies reveal that the results obtained are inconsistent (Wijnands *et al.,* 2021). Other risk factors, such as obesity, physical activity, history of red meat consumption, and other dietary factors are thought to be relevant but have not been specifically analyzed in populations with ulcerative colitis.

Histological inflammation in the process of pathogenesis of ulcerative colitis is a major risk factor for colorectal cancer. Colitis-related colorectal cancer develops through the inflammation-dysplasia-carcinoma pathway. So, dysplasia at both high levels (HGD) and low levels (LGD) is an important risk factor in the development of neoplasia (Fumery *et al.,* 2017). Provided the undoubted role of intestinal inflammation in the development of cancer, the severity of inflammation has a great impact on the occurrence of neoplasia among patients with ulcerative colitis. Cumulative inflammation burden (CIB) is a new formula for describing persistent inflammation defined as: each histological inflammatory activity multiplied by the observation interval in a few years and significantly associated with colitis-related evolution (C. H. R. Choi et al., 2019). Therefore, CIB can be considered as an index for predicting the development of neoplasia in ulcerative colitis patients. This has been reconfirmed by Yvellez, *et al.* in his studies that the results provided are consistent with previous studies (Yvellez *et al.,* 2021).

In order to facilitate effective clinical management and better predict which patients are more likely to develop carcinoma, it is important to apply follow-up observations on the dysplasia and colorectal cancer related to ulcerative (Bye *et al.*, 2018). Unlike colorectal cancer in common which provides a wide range of screening test options, there are no specific non-invasive biomarkers to detect neoplasia in colitis patients, although some stool-based tests may be considered (Azuara *et al.,* 2013; Kisiel & Ahlquist, 2013). The most reliable examination is a colonoscopy, in parallel with a structured endoscopic surveillance program that includes ongoing medical management for disease control (Shah & Itzkowitz, 2022). Screening for neoplasia is performed in several series, where the first performed colonoscopy is referred to "screening colonoscopy" and the next examination is called as "surveillance". Re-evaluation to understand the degree of histological inflammation and structural abnormalities aims to stratify risks is also possible (Axelrad *et al.,* 2022). Wherever it is possible, screening and supervision examinations must be carried out on patients in remission conditions in compliance with standard colonoscopy quality matrices. Therefore, endoscopy must be performed by an expert experienced in similar cases (Magro *et al.,* 2017; Rubin *et al.,* 2019).

Most guidelines recommend the implementation of the first colonoscopy screening in the range of 8-10 years after the onset of the first symptoms of colitis. In addition, the specific interval for subsequent screening is based on the results of risk stratification: high risk, medium-risk, and low-risk determined by the clinical characteristics of the disease (Axelrad & Shah, 2020; Magro *et*

al., 2017). Every year, regular monitoring is recommended for high-risk patients. The conditions that can be categorized as the high risk are those with extensive colitis with severe active inflammation, a familiar history of colorectal cancer, especially at the age of <50 year, a history of dysplasia in the last five years. A Cohort study examined the familial history of colorectal cancer in colitis patients which showed that the respondents with first-degree relatives diagnosed with colorectal cancer had a relatively high risk of developing similar diseases (Magro *et al.,* 2017; Murthy *et al.,* 2021). As for patient with medium risk, it is recommended to carry out colonoscopy supervision once every 2-3 years. According to the studies, Ulcerative colitis patients with first-degree relatives diagnosed with colorectal cancer with >50 years have a lower risk but consistently increased. In term of inflammatory aspects, European Crohn's and Colitis Organisation (ECCO) guidelines classify moderate active endoscopic/histological inflammation as an intermediate risk factor. In contrast, the published guidelines from the American Gastroenterological Association (AGA) and the British Society of Gastroenterology (BSG) categorized them as the high risk factors. This may be due to different target respondents to some of these guidelines. On the other hand, patients with low risk factors including left-sided colitis and/or without active inflammation are advised to have screening once every five years (Lamb *et al.,* 2019). The AGA guidelines state continuous remission of the disease since the last colonoscopy, and two consecutive examinations with no dysplasia or a history of minimal colitis classified as a low risk factor.

Based on the hypothesis, most cases of colorectal cancer in patients with ulcerative colitis arise as a result of chronic inflammation. Continuous control of inflammation may be the best way to prevent this condition. However, although histological inflammation is not ongoing, there is still a risk of colitis-related neoplasia. Therefore, research continues to be conducted to find chemoprevention agents that are effective in preventing or stopping carcinogenesis.

The ECCO's latest guidelines recommend the use of mesalamine compounds in patients with widespread ulcerative colitis as a form of chemoprevention based on available evidence, including several case-control, Cohort, and meta-analyses that support reducing the risk of colorectal cancer events in patients with ulcerative colitis (Magro *et al.,* 2017). Recent meta-analyses report that the use of 5-aminosalicylates (5-ASA) may be associated with a reduction in the risk of colorectal cancer by up to 49% when compared to non-use (pooled multivariable OR 0,51; 95% CI 0,39-0,66) (Wijnands *et al.,* 2021). However, the accuracy of dosage, the timing of initiation, the formulation and route of administration, and the minimum duration required to achieve benefits still need to be clarified. Results from at least two large Cohort studies suggest that 5-ASA has limited usefulness in reducing development after dysplasia develops. So, the use of 5-ASA should preferably begin early in the inflammatory-associated stage of carcinogenesis and be continued for a long time to achieve benefits. Another chemopreventive agent of thiopurine has conflicting data, including conclusions from meta-analyses (Gong *et al.,* 2013;Jess *et al.,* 2014;Wijnands *et al.,* 2021) In a retrospective study involving 831 patients with ulcerative colitis, it was found that colitis patients who had long been treated with thiopurine had a lower risk of developing colorectal neoplasms than the patients who had never been treated with tiopurin (Gordillo *et al.,* 2015). A meta-analysis of 76.999 patients also showed that thiopurine therapy had a fairly significant protective effect (Lu *et al.,* 2018). However, there is an increased risk of malignancies, such as nonmelanoma skin cancer, lymphoma, and urinary tract tumors in the use of thioppurine caused by immunosuppression, DNA structure digestion, DNA replication and repair disorders, as well as mutagenicity (Pasternak *et al.,* 2013). Therefore, there are still doubts about the use of thiopurine in reducing the risk of developing colitis-related neoplasia. The ECCO guidelines also state that the evidence currently available is insufficient to recommend the use of thiophinine as a chemoprevention (Kucharzik *et al.,* 2021).

CONCLUSION

In general, long-lasting chronic inflammation in the intestinal mucosa increases the risk of colorectal cancer due to genetic and molecular changes. Identifying of high-risk groups and colonoscopy surveillance programs have been considered useful in early detection measures. Although an understanding of the molecular mechanisms, management, and prevention of colorectal cancer has made significant progress, there are still some areas that need further research, such as monitoring more adjusted to individual risk profiles, development of non-invasive biomarkers to avoid colonoscopy procedures that are not needed, a better understanding of the mechanisms that can help reduce tumor formation through action on new targets, and prospective trials of other chemoprevention agents that can be used for early prevention. The future research more research on the involvement of ulcerative colitis, surveillance strategies, and prevention of colitis-related colorectal cancer is needed.

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