**Name of Journal: *World Journal of Gastrointestinal Oncology***

**ESPS Manuscript NO: 18981**

**Manuscript Type: Topic Highlight**

**2016 Inflammatory Bowel Disease: Global view**

**Status of colitis-associated cancer in ulcerative colitis**

Kinugasa T *et al*. The status of CAC in UC

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**Author contributions:** Kinugasa T contributed to concept and design; both authors contributed to this paper.

**Conflict-of-interest** **statement:** Authors declare no conflict of interests for this article.

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**Received:** April 28, 2015

**Peer-review started:** May 5, 2015

**First decision:** July 1, 2015

**Revised:** January 24, 2016

**Accepted:** February 16, 2016

**Article in press:**

**Published online:**

**Abstract**

Surgical therapy for ulcerative colitis (UC) depends on the medical therapy administered for the patient’s condition. UC is a benign disease. However, it has been reported that the rare cases of cancer in UC patients are increasing, and such cases have a worse prognosis. Recently, surgical therapy has greatly changed, there has been quite an increase in the number of UC patients with high-grade dysplasia and/or cancer. These lesions are known as colitis-associated cancer (CAC). The relationship between inflammation and tumorigenesis is well-established, and in the last decade, a great deal of supporting evidence has been obtained from genetic, pharmacological, and epidemiological studies. Inflammatory bowel disease, especially UC, is an important risk factor for the development of colon cancer. We should determine the risk factors for UC patients with cancer based on a large body of data, and we should attempt to prevent the increase in the number of such patients using these newly identified risk factors in the near future. Actively introducing the surgical treatment in addition to medical treatment should be considered. Several physicians should analyze UC from their unique perspectives in order to establish new clinically relevant diagnostic and treatment methods in the future. This article discusses CAC, including its etiology, mechanism, diagnosis, and treatment in UC patients.

**Key words:** Inflammatory bowel disease; Ulcerative colitis; Colitis-associated cancer; Colorectal cancer surveillance; Surgical therapy

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**Core tip:** Inflammatory bowel disease, especially ulcerative colitis, is an important risk factor for development of colon cancer. There has been quite increased in the number of patients who had high-grade dysplasia and/or cancer. The relationship between inflammation and tumorigenesis is well-established and in the last decade has received a great deal of supporting evidence from genetic, pharmacological, and epidemiological data. To avoid such a problem, there is a need for appropriate diagnosis and treatment. It should be considered that actively introduce the surgical treatment in addition to medical treatment.

Kinugasa T, Akagi Y. Status of colitis-associated cancer in ulcerative colitis. *World J Gastrointest Oncol* 2016; In press

**INTRODUCTION**

Ulcerative colitis (UC) is of unknown cause inflammatory bowel disease (IBD) associated with inflammation of the large intestine mucosa. UC number of the patients that have been recorded in Japan in 2014 at 166110 people, this number is increasing every year. As a recent problem, in patients with UC, it has been reported that it is easy to develop colorectal cancer (CRC). The longer the period of UC, the higher is the risk of developing UC-associated CRC. The mechanism of IBD-related colon cancer is different from sporadic CRC. The former is an inflammation–dysplasia–carcinoma sequence[[1](#_ENREF_1)] and the latter is from the adenoma–carcinoma sequence in sporadic CRC (Figure 1).

Therefore the UC patient becomes the indication of the operation when the pathological findings are demonstrated high-grade or multifocal low-grade dysplasia in colonic mucosal which means that the entire mucosal lining of the colon exposed to chronic inflammation is at increased risk of cancer[[1](#_ENREF_1),[2](#_ENREF_2)].

***IBD***

Crohn’s disease (CD) and UC, which include IBD, is a chronic, relapsing inflammatory condition of the gastrointestinal tract. IBD has a clear pathological and clinical characteristic. Though many studies were performed about this cause of IBD for the past several decades, the cause is not yet clear. The only consensus was obtained about IBD which was deregulated the mucosal immune response in the host. Some various components, which including environmental intestinal epithelial cells, and microbial factors, genetic susceptibility, and components of the innate and adaptive immune system, are implicated in the pathogenesis of IBD,

***Mechanism of colitis-associated cancer in UC patients***

The connection between inflammation and tumorigenesis is well established, and in the last decade, a great deal of supporting evidence has been obtained through genetic, pharmacological, and epidemiological studies. IBD is an important risk factor for the development of colon cancer.

As a result has high mortality, it is difficult to treat colitis-associated cancer (CAC), which is the CRC subtype that is associated with IBD[[3](#_ENREF_3)]. When the patients with IBD are the higher the probability within 30 years disease duration, and > 50% of these patients will die from CAC[[4](#_ENREF_4)]. Some of the essential stages of cancer development, including the formation of aberrant crypt foci, polyps, adenomas, and carcinomas, are similar in noninflammatory CRC and CAC. However, several different pathogenic sequences CAC, has been reported including a well-defined inflammation and damage dysplasia cancer that occurs without the formation of the gland. Nevertheless, both of in the CRC and CAC had changed same genetic and signaling pathways which involving Wnt, β-catenin, K-ras, p53, and transforming growth factor (TGF)-β. However, the difference activation timing between CRC and CAC were reported about p53, adenomatous polyposis coli (APC) and K-ras[[4](#_ENREF_4),[5](#_ENREF_5)]. A > 2-fold higher risk for colon cancer development with a family history of CRC have than without in IBD patients, suggesting an overlap in the mechanisms driving CRC and CAC[[6](#_ENREF_6)]. Kinugasa *et al*[[7](#_ENREF_7)] also showed that high-grade dysplasia (HGD) and CAC in patients with UC results in an increase in β-catenin transcriptional activity that may contribute to increased claudin (CL)-1 expression. According to above things, the expression of CL-1 was increased in CAC and dysplasia than normal mucosa is likely to be involved in neoplastic progression in UC patients. Thus, I propose that there is a possibility that increased CL-1 expression may contribute to carcinogenesis in UC. CL-1 is a tight junction specific protein that was first described by Furuse *et al*[[8](#_ENREF_8)] in 1998. The signaling pathways, including TGF-β/SMAD and β-cateni[[9](#_ENREF_9),[10](#_ENREF_10)] were interacted with the CL protein that is separate from their effects on the barrier function. We reported that CL-1 is regulated by β-catenin/TCF/lymphocyte-enhancer factor signaling[[11](#_ENREF_11),[12](#_ENREF_12)] suggests that the expression of CL-1 is concerned in β-catenin activation (Figure 2).

These mechanisms are the basis for the current discussion about CAC as well as for new approaches to prevention and therapy.

***Is the frequency of colorectal cancer in UC patients higher than in the normal population?***

Patients with IBD are at an increased risk of developing colorectal advanced neoplasia, including colorectal HGD and CRC[[13-16](#_ENREF_13)]. Chronic intestinal inflammation is considered to be a promoter of carcinogenesis[[17](#_ENREF_17)]. The two major drivers of the excess risk of CRC in IBD are disease extension[[18](#_ENREF_18)] and duration[[13](#_ENREF_13)]. Concomitant primary sclerosing cholangitis[[19](#_ENREF_19)], family history of CRC[[6](#_ENREF_6)], and active intestinal inflammation[[20-23](#_ENREF_20)] are the other established risk factors.

The risk of CRC in patients with IBD was recognized as far back as 1925 for UC and 1948 for CD[[24](#_ENREF_24)]. There were many reports of risk for colon cancer development about UC patients mainly, and which ratio was indicated from 16% to 43%[[25-28](#_ENREF_25)]. In 2001 Eaden *et al*[[13](#_ENREF_13)] estimated CRC risk as 2% at 10 years, 8% at 20 years and 18% at 30 years using a widely cited meta-analysis of 116 studies with age stratified data. Interestingly, recent studies we could get two different conclusions about IBD with CRC. Jess *et al*[[29](#_ENREF_29)] suggested that the risk of CAC is almost same between UC patients and the general population in a population-based study from Denmark. In contrast, the risk of CRC is 60% higher with IBD than without IBD matched cohorts of people from California, and the risk remained the same throughout the study period of 14.5 years by Herrinton *et al*[[15](#_ENREF_15)]. There are few reports from Asia on CRC in UC which reports that the presure ranges from 0.87% to 1.8% in the general population, and it can be as high as 13.5% in patients with extensive type of UC. Thus, the risk of CRC is increased in IBD, though there is variation due to various factors, such as hospital- or population-based data, referral center bias, and small numbers of patients.

IBD is a lifelong diseases that primarily affects young patients. Sustained mucosal healing is becoming the standard objective of the long-term treatment of IBD[[30](#_ENREF_30)]. This objective can be achieved currently by maintenance treatment with immunosuppressants, including thiopurines, methotrexate, and anti-tumor necrosis factor (TNF)[[31](#_ENREF_31),[32](#_ENREF_32)]. Unfortunately, there is no major trend towards the spontaneous extinction of IBD activity with time[[33](#_ENREF_33),[34](#_ENREF_34)], and disease activity often recurs after the withdrawal of immunosuppressants[[35](#_ENREF_35),[36](#_ENREF_36)]. Similarly, another report showed that there is an unclear risk of colonic HGD and CRC among patients with IBD treated with immunosuppressants. Beaugerie *et al*[[37](#_ENREF_37)] analyzed data on CRC development among patients with IBD and found that patients with IBD and long-standing extensive colitis are at increased of CRC, although the risk is lower among patients receiving thiopurine therapy. Patients without long-standing extensive colitis have a risk for CRC similar to that of the general population, but they can develop IBD-related lesions within 10 years after their diagnosis of IBD. Table 1 compares CAC with CRC.

**DOSE THE SURVEILLANCE STRATEGY NEED TO TAKE INTO ACCOUNT THIS DECREASING RISK OF CAC IN UC PATIENTS?**

We have to debate about the surveillance techniques for CAC and high grade dysplasia whether adequate or not under currently way[[38](#_ENREF_38)]. Presently, surveillance of using colonoscopy for UC patients is recommended every 2 years over 8 years after the onset of UC diagnosis. However, sometimes it is very hard to determinate the CRC findings under the UC mucosa, and do not match between the biopsy results and excisional tissue results in pathological diagnosis, this is that colonoscopy is often burdensome for the patient with UC patients[[39-41](#_ENREF_39)]. Surprisingly, 20% to 50% of UC patients with CRC were diagnosed with only dysplasia in preoperative pathological diagnosis. This indicates that it is difficult surveillance for UC patients using colonoscopy.

Furthermore, endoscopic findings of IBD-related cancers have been found to easily overlook by colonoscopy because it is not a mass-like lesions to compared with sporadic CRC. As a result, it is very difficult to appropriate for diagnosis of adenocarcinoma for UC patients using biopsied tissue taken from the lesion. Meanwhile, we could find unexpectedly in a specimen resected for medically refractive IBD without previous diagnosis of dysplasia or adenocarcinoma[[42](#_ENREF_42),[43](#_ENREF_43)].

It is clear that colonoscopic surveillance in the present form is neither ideal nor practical. We should reconsider the guidelines about the colonoscopy surveillance based on the other new reliable date and method. The ideal frequency of surveillance is not clear. Further studies are necessary to optimize the frequency of surveillance, including cost-effectiveness, and to make guidelines considering emerging methods and technologies.

Despite the proven usefulness of colonoscopy surveillance protocols and increased risk of CRC with UC, we could not determinant a useful in clinical diagnosing such as genetic or serological marker. After analyzing the association of the whole genome, the single nucleotide polymorphism (SNP) 300 or more and the genetic loci 160 or more were found to be associated with IBD[[44](#_ENREF_44)]. There was another genetic instability report[[45](#_ENREF_45)] that sought to identify IBD-associated SNPs that are potential markers for CAC by comparing groups of UC patients with and without neoplasia matched for sex, disease duration and age at diagnosis. Their conclusion was that none of the 314 studied IBD-associated SNPs were strongly associated with UC-neoplasia which may be the result of genetic mutations in molecular pathways other than those that predispose to inflammation.

On the other hand, there was a unique report that applied the tree models by considering the response variable as the CAC or UC group and the explanatory variable as the criteria studied by univariate analysis[[46](#_ENREF_46)].

We proposed the useful method which analysis is a tree model permits the automatic execution of the process of determining the factors, setting the threshold value and by differentiating the patients successively into two groups during the process automatically. Therefore, it might be another possibility to help identify the indication and timing for surgery in UC patients, because the ideal surveillance methods have not yet been established.

***Treatment for CAC including surgery***

The overall prevalence of CRC in patients with UC has been estimated as 3.7% in a meta-analysis[[13](#_ENREF_13)]. Chronic UC for > 10 years and pancolitis are known risk factors for CAC[[47](#_ENREF_47)]. On the other hand, sporadic adenoma and adenocarcinoma can arise coincidentally in patients with UC. From the perspective of clinical considerations, accurate pathological diagnosis is very important for distinguishing between different pathological entities, given their different therapeutic consequences such as sporadic adenocarcinoma and CAC.

Anal function and quality of life differ substantially between total proctocolectomy with ileal pouch anal anastomosis (IPAA) and low anterior resection (LAR). A key point is that further proctocolectomy and IPAA may be suitable for sporadic cancers in the lower rectum. In patients with UC, irrespective of the degree of colitis, LAR should not be selected for sporadic cancer in the lower rectum except in older patients, based on considerations of quality of life and risk of further colitis. In elderly patients with poor anal function, surgical procedures should obviously be considered based on overall considerations including prognosis of the cancer, degree of inflammation with colitis, and potential requirements for further treatment. In view of the risk of recurrent colitis and cancer, partial resection might be less advantageous than proctocolectomy. Proctocolectomy with IPAA may be safe for advanced CRC regardless of the origin as colitic or sporadic cancer, because of the difficulty of differentiation, ready invasive behavior against an inflamed background and worsened potential for further progressive colitis in younger patients. Decisions on surgical procedures should be made based on full consideration of background factors including age, degree of colitis and cancer prognosis.

There was an interesting report on the risk of ileoanal pouch neoplasia in patients with IBD[[48](#_ENREF_48)]. Although restorative proctocolectomy with IPAA substantially reduces the risk of CRC in patients with IBD, subsequent pouch neoplasia can develop. The purpose of their study was to determine the cumulative incidence of pouch neoplasia in patients with IBD and to identify risk factors for developing pouch neoplasia. The incidence and prevalence of pouch neoplasia in patients with IBD are probably low. According to the latest review, only 42 pouch adenocarcinomas have been described in the literature[[49](#_ENREF_49)]. A previous study reported a cumulative incidence of pouch neoplasia of 1.9% after 15 years and 5.1% after 25 years[[50](#_ENREF_50)]. However, these data were collected in a single tertiary pouch referral center and may not be representative of the general IBD population with IPAA. Furthermore, the relatively low incidence makes it difficult to assess risk factors for the development of pouch neoplasia. The result of the study indicated that the incidence of pouch neoplasia in patients with IBD without a history of colorectal neoplasia is relatively low. Prior dysplasia or colon cancer is associated with an approximately 4- and 25-fold increase in risk, respectively, of developing pouch neoplasia.

**CONCLUSION**

UC is a benign disease. However, according to the recent reports that the rate of CAC is increasing in UC patients, and such cases have a worse prognosis. As such, there is a need for appropriate diagnosis and treatment. Actively introducing the surgical treatment in addition to medical treatment should be considered. Several physicians should analyze UC from their unique perspectives in order to establish new clinically relevant diagnostic and treatment methods in the future. We should determine the risk factors for UC patients with cancer based on a large body of data, and we should attempt to prevent the increase in the number of such patients using these newly identified risk factors in the near future.

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**P-Reviewer:** Nakajima N **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Table 1 A comparison colitis-associated cancer and sporadic colorectal cancer**

|  |
| --- |
| CAC: Up to 20% of UC patients develop CAC within 30 yr of disease onset |
| CAC: High overall mortality rate |
| NSAID use reduces the risk of CRC, suggesting a potential role for anticytokine therapy |
| CRC: Classic adenoma to carcinoma sequence |
| CAC: Chronic inflammation, injury, dysplasia, and CRC |
| The common genetic and signaling pathways are different between |
| CRC and CAC including β-catenin, p53, k-ras, B-raf |
| Both CRC and CAC are associated with transcription factors, such as |
| NF-kB and/or STAT3 which mediate the immune response |
| and oncogenesis |
| Both CRC and CAC depend on the quality and quantity of |
| intestinal microflora |

CRC: Colorectal cancer; CAC: Colitis-associated cancer; UC: Ulcerative colitis; NSAID: Nonsteroidal anti-inflammatory drug; NF-kB: Nuclear factor-kB; STAT3: Signal transducer and active of transcription 3.

Figure 1

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normal

ACF

adenoma

carcinoma

APC

-catenin

K-Ras

COX-2

p53

TGFR

Spontaneous　colon cancer

TNF

IL-17

IL-23

IL-6

NF-kB

Stat3

-catenin

APC

K-Ras

COX-2

p53

TGFR

Colitis-associated　cancer

Claudin-1

Claudin-1

**Figure 1 Mechanisms of colorectal cancer and colitis-associated cancer development.** APC: Adenomatous polyposis coli; TGF-β: Transforming growth factor-beta; NF-kB: Nuclear factor-kB; TNF: Tumor necrosis factor; IL: Interleukin.



**Figure 2 Hematoxylin-eosin (left) and immunostaining of CL-1 (middle) and β-catenin (right) in ulcerative colitis mucosa (upper) and ulcerative colitis-associated colorectal cancer tissue (bottom) of a patient with ulcerative colitis-associated colorectal cancer.**