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## Primary sclerosing cholangitis as an independent risk factor for colorectal cancer in the context of inflammatory bowel disease: A review of the literature

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### Abstract

To examine and evaluate recent evidence regarding the epidemiology, pathogenesis and management of colorectal cancer (CRC) development in inflammatory bowel disease (IBD)-primary sclerosing cholangitis (PSC) patients. Using the PubMed database, a literature search was conducted for relevant articles in English from the past 10 years. Relevant studies investigating PSC as a risk factor for CRC in IBD in the context of incidence and prevalence, pathogenesis, prevention and prognosis were included in this review. Recent evidence increasingly points to PSC as a significant risk factor in the development of CRC in patients with concomitant IBD. PSC may be an important risk factor for CRC in different populations worldwide. The mechanism for this increase in risk is still unclear. The efficacy of UDCA as a chemopreventive agent remains controversial. Liver transplantation does not halt the development of CRC, although there is not enough evidence to suggest that it is associated with increased

incidence of CRC. While routine colonoscopic surveillance should be performed in patients with concurrent PSC and IBD, more high-level evidence is required to support the benefits of the procedure. While many new developments have taken place in the last decade, the pathogenesis and optimal management of CRC development in IBD-PSC patients remain unclear.

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**Key words:** Primary sclerosing cholangitis; Ulcerative colitis; Crohn's; Inflammatory bowel disease; Colorectal cancer; Liver transplantation; Ursodeoxycholic acid

**Core tip:** The widely accepted risk factors for malignant transformation in inflammatory bowel disease (IBD) are disease duration and extent of inflammation. Since first proposed in 1992, one increasingly recognised independent risk factor for colorectal cancer development in IBD patients is concomitant primary sclerosing cholangitis.

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### INTRODUCTION

Inflammatory bowel disease (IBD) is a widely accepted risk factor for colorectal cancer (CRC). The development of CRC complicating IBD only occurs in 1%-2% of CRC cases and has been reported to account for up to a third of mortality in ulcerative colitis (UC) patients<sup>[1]</sup>.

**Table 1 Summary of studies investigating colorectal cancer as a risk factor in patients with concurrent primary sclerosing cholangitis and inflammatory bowel disease**

Ref.	Location	IBD-PSC patients (n)	Colorectal neoplasms (n)	Matched controls?	Study type	Is IBD-PSC a risk for CRC?
[24]	The Netherlands	IBD (126)	CRC (16)	No	Retrospective	Yes
[9]	Belgium	IBD (107)	CRC (10)	No	Retrospective	Yes
[12]	Sweden	IBD (152)	CRC/Dys (3)	No	Retrospective	No
[31]	Germany	IBD (120)	CRC (7)	No	Prospective	Only with dominant stenosis
[28]	Argentina	UC (39)	CRC (7)	Yes	Prospective	Yes
[30]	United States	UC (50)	N/S	Yes	Retrospective	No
[32]	Sweden	CD (28)	CRC/Dys (9)	Yes	Retrospective	Yes
[33]	United Kingdom	CD (35)	Dys (1)	No	Retrospective	No

UC: Ulcerative colitis; CD: Crohn's disease; Dys: Dysplasia; N/S: Not specified; CRC: Colorectal cancer; PSC: Primary sclerosing cholangitis; IBD: Inflammatory bowel disease.

Established risk factors for malignant transformation in IBD include disease duration and extent<sup>[2-4]</sup>, family history of CRC<sup>[5,6]</sup>, and concomitant primary sclerosing cholangitis (PSC).

PSC is a chronic syndrome of unknown aetiology. PSC is characterised by destruction and stenoses of intrahepatic and extrahepatic biliary ducts by inflammation and fibrosis, leading to cholestasis. As the disease progresses, portal tract fibrosis and biliary cirrhosis may develop, which may ultimately lead to death from hepatic cirrhosis and failure<sup>[7]</sup>. Besides CRC, PSC has been associated with other malignant conditions, including cholangiocarcinoma<sup>[8,9]</sup>, pancreatic carcinoma<sup>[10]</sup>, gallbladder cancer<sup>[11]</sup>, hepatobiliary cancer<sup>[12]</sup>, and hepatocellular carcinoma<sup>[10,13]</sup>.

The incidence of PSC may be increasing, possibly due to earlier recognition and increasing index of suspicion<sup>[14]</sup>. The mean age of PSC diagnosis is 40 years, and the median survival time from diagnosis to death or liver transplantation is approximately 12 years<sup>[15]</sup>. PSC has a slightly male predominance<sup>[16]</sup>. Currently, the only definitive long-term treatment of PSC is liver transplantation<sup>[7]</sup>.

The association of PSC with UC is stronger than with Crohn's disease (CD). The prevalence of concurrent PSC in UC patients is up to 8%, compared to only 1% to 3% for CD<sup>[17,18]</sup>. Evidence suggests that this figure varies according to the extensiveness of disease; the prevalence of PSC is approximately 5.5% in patients with pancolitis, but only 1% in those with distal colitis<sup>[18,19]</sup>. Overall the prevalence of PSC is approximately 10% in CD and 80% in UC<sup>[19,20]</sup>. Broomé *et al.*<sup>[21,22]</sup> first proposed the association of PSC and CRC in UC patients in 1992 with a cumulative risk of 50% at 25 years of developing CRC in UC = PSC patients.

The suggestion that PSC is an independent risk factor for CRC in IBD patients is one that has widely debated. Currently, no explanation of how PSC increases the risk of CRC in IBD patients has been agreed upon. Numerous literature reviews, including a meta-analysis conducted in 2002<sup>[23]</sup>, have evaluated earlier research concerning this topic. This review aims to evaluate research within the last decade and examine recent evidence concerning epidemiology, pathogenic mechanisms

and management strategies of CRC development in IBD-PSC patients.

## RESEARCH

A literature search was conducted using the PubMed database for relevant articles from January 2002 until January 2014. The keywords used were: primary sclerosing cholangitis, colorectal, cancer, neoplasia, carcinoma, inflammatory bowel disease, Crohn's disease and ulcerative colitis. Relevant studies investigating PSC as a risk factor for CRC in IBD in the context of incidence and prevalence, pathogenesis, prevention and management, and prognosis were included in this review. Articles not written in English, review articles and published abstracts were not included.

## EVALUATION OF EVIDENCE

Since the initial proposal in 1992 by Broomé *et al.*<sup>[21]</sup>, recent research continue to support concurrent PSC as a key risk factor in the development of CRC in IBD. The studies evaluated in this section are summarised in Table 1. Many studies now recognise PSC as just an important risk factor for CRC development as previously established risk factors such as duration and extent of IBD.

Early studies of PSC patients were characterised by small cohorts, small statistical power and disparate measurable outcomes. The increasing awareness of the link between PSC and CRC has allowed larger and better designed studies to be conducted. A retrospective Dutch study in 2009 investigated 211 PSC patients. Of that cohort, 60% had concurrent IBD. The risk of CRC development was 14% at 10 years and 31% at 20 years in PSC patients with concurrent IBD, compared with a steady risk of 2.3% in patients without concurrent IBD ( $P < 0.01$ )<sup>[24]</sup>. The study also found that the majority of CRCs were located in the right colon, proximal to the splenic flexure, a result that has been confirmed by numerous other studies<sup>[25,26]</sup>. The same group went on to confirm this finding in a subsequent study, where the majority (67%) of IBD-PSC patients that developed CRC had tumours in the right-sided colon ( $P < 0.01$ ) in contrast to patients with IBD alone. Based on this finding, a differ-

**Table 2** Summary of studies investigating the efficacy of ursodeoxycholic acid a chemopreventive agent in primary sclerosing cholangitis patients with concurrent inflammatory bowel disease

Ref.	Location	UDCA (n)	CRN incidence UDCA (n)	No UDCA (n)	CRN incidence no UDCA (n)	Study type	Is UDCA chemopreventive?
[36]	United States	29	3	23	8	RCT	Yes
[37]	United States	28	3	92	13	Retrospective	No
[38]	Sweden	37	13	40	15	RCT	No
[39]	United States	25	9	31	3	RCT	No-high dose UDCA
[40]	Germany	120	7	N/A	N/A	Prospective	No-short term; yes-long term

CRN: Colorectal neoplasm (dysplasia and cancer); RCT: Randomised controlled trial; N/A: Not applicable; UDCA: Ursodeoxycholic acid; PSC: Primary sclerosing cholangitis; IBD: Inflammatory bowel disease.

ence in pathogenesis of CRC may occur in patients with PSC and concurrent IBD, compared to patients with IBD alone<sup>[27]</sup>.

Other studies have also evaluated the cumulative risk of CRC development in the long-term. Fevery *et al*<sup>[9]</sup> studied 200 PSC patients in a long-term, single-centre study in Belgium, where 60% of the cohort had concomitant IBD. The cumulative incidence for the diagnosis of CRC after IBD diagnosis was found to be 2% in 5 years, 7% in 10 years and 15% in 20 years. Additionally, the median age of CRC diagnosis was 49.5 years, leading the authors to conclude malignancy to be the major cause of early mortality in patients with PSC.

Terg *et al*<sup>[28]</sup> prospectively recruited a Latin American PSC cohort from 1333 patients with UC. The prevalence of PSC was 2.9% and the cumulative risk of CRC after 10 and 20 years in these patients was 11% and 18% respectively, compared to 2% and 7% in UC without PSC ( $P < 0.01$ ). Hence, it was confirmed that patients with UC and PSC indeed have a higher risk of CRC. An Asia-Pacific Consensus Group consisting of representatives from a host of countries, including India, China, Philippines and Australia published a paper in 2010 outlining various findings in UC patients in these countries. There was consensus on the statement that PSC associated with UC is less prevalent in the Asia-Pacific region compared to Western nations, though the level of evidence on this finding was classified as fairly weak. There was also some consensus on the statement that PSC in the setting of UC significantly increased the risk of development of CRC<sup>[29]</sup>.

Some studies have not confirmed PSC as an independent risk factor of CRC in IBD. A 2006 case-control study investigating predictive and protective risk factors associated with CRC in UC patients did not find PSC to be significant<sup>[30]</sup>. A Swedish population-based cohort of 199 PSC patients revealed that while the disease was associated with a four-fold increase in mortality compared with the general population (SMR = 4.20, 95%CI: 3.01-5.69), the researchers unexpectedly could not confirm that PSC or PSC with concurrent IBD was associated with a higher incidence of CRC and colorectal dysplasia compared with the general population<sup>[12]</sup>. This cohort of patients was diagnosed from 1992 to 2005, which is relatively recent compared with other large-scale studies of PSC patients with cases recruited from

the 1980s<sup>[24]</sup>. This led the researchers to postulate that the lowered incidence of CRC in this cohort was a result of better management of IBD in recent years<sup>[12]</sup>.

Studies have also disease subtypes in the prediction of CRC. A prospective study of 171 PSC patients being treated with ursodeoxycholic acid (UDCA) found that IBD coexisting with dominant ISC bile duct stenosis had an increased CRC incidence, whereas IBD without dominant stenosis had no effect on the incidence of carcinoma ( $P < 0.05$ ). The authors did not speculate whether this observation was a result of the interaction between dominant stenosis and IBD, or whether it was to do with UDCA treatment<sup>[31]</sup>.

While the risk of CRC is established for UC-PSC patients, studies have also evaluated their association with CD. The overall risk of CRC development in CD-PSC is not as strong as UC-PSC. Lindström *et al*<sup>[32]</sup> studied the development of CRC in 28 patients with both PSC and CD, compared to controls with CD only. They found PSC to be a risk factor for development of CRC and dysplasia in CD (OR = 6.78, 95%CI: 1.65-27.9), but the study was limited by its small cohort and retrospective design. Another retrospective review of 166 PSC-IBD patients did not find an increased risk of CRC or dysplasia in CD<sup>[33]</sup>.

## PREVENTION OF CRC

The cause of the increased risk of CRC in PSC is largely unknown. Studies have evaluated whether the risk of CRC can be reduced. Strategies such as colonoscopic surveillance, UDCA and liver transplantation have been investigated as potential methods of preventing the development of CRC.

### UDCA

The chemopreventative effects of UDCA against CRC in IBD-PSC patients remain controversial. UDCA is a synthetic, hydrophilic bile acid that purportedly prevents the carcinogenic effects of secondary bile acids in the colon<sup>[34,35]</sup>. A summary of recent data concerning the efficacy of UDCA is presented in Table 2.

A randomised, placebo-controlled trial evaluated the effect of UDCA on CRC and colorectal dysplasia in patients with concurrent UC and PSC<sup>[36]</sup>. Colorectal neoplasia developed in 10% of the patients assigned to the

UDCA group compared to 35% of the patients assigned to the placebo group (RR = 0.26, 95%CI: 0.06-0.92). Wolf *et al.*<sup>[37]</sup>, however, reported that the incidence of CRC and colorectal dysplasia was not significantly different between patients treated with UDCA and patients that were not, but the UDCA patients did report a lower mortality rate ( $P < 0.05$ ).

A long-term, randomised placebo-controlled trial of IBD-PSC patients prescribed UDCA *vs* placebo followed-up patients for more than 10 years yielded no difference in the CRC rate between the UDCA (13%) and placebo (16%) groups. There also was no significant difference in cancer-free survival between the two groups<sup>[38]</sup>. Another long-term, randomised placebo-controlled trial assessed the effects of high dose UDCA (28 to 30 mg/kg per day) on the development of colorectal dysplasia and CRC in UC-PSC patients. The study found that UDCA had an adverse effect on neoplasia development where high dose UDCA significantly increased development of colorectal dysplasia and CRC compared to control (HR = 4.44, 95%CI: 1.30-20.1)<sup>[39]</sup>.

Some studies have attempted to reconcile these conflicting findings. In a prospective cohort study conducted by Rudolph *et al.*<sup>[40]</sup>, the trend of colorectal carcinoma development in patients treated with UDCA was observed to increase up to 6 years after the start of treatment, plateaued between 6 to 9 years, and after treatment for more than 9 years (up to at least 12 years) no further colorectal carcinomas developed. This finding, together with others, suggests that the effects of UDCA in UC-PSC patients may not be straightforwardly beneficial or non-beneficial, and that longer term, placebo-controlled trials are needed to provide evidence for or against UDCA as a chemopreventative agent. Lower doses of UDCA have been used to avoid possible adverse events.

A recent meta-analysis reporting 177 cases of CRC in 763 patients with PSC-IBD failed to demonstrate significant protective association between UDCA use and CRC with OR = 0.81, 95%CI: 0.41-1.61. However, a significant chemopreventive effect was found on the risk of advanced neoplasia defined as CRC and/ or high-grade dysplasia (OR = 0.35, 95%CI: 0.17-0.73). Low-dose UDCA (8-15 mg/kg per day) did significantly reduce CRC (OR = 0.19, 95%CI: 0.08-0.49)<sup>[41]</sup>. Another meta-analysis of a similar dataset showed similar results<sup>[42]</sup>.

### Liver transplantation

Currently, liver transplantation remains the only effective treatment of PSC with end-stage liver disease. It follows that liver transplantation in PSC may offer prevention against CRC development by improving PSC status, however, the evidence is largely contrary.

A study from the United Kingdom identified 152 patients with PSC following liver transplantation. Of these patients, 5.3% developed CRC, of which all of them had concurrent IBD with an intact colon. The cumulative risk of CRC development in IBD-PSC patients was calculated to be 14% at 5 years and 17% at

10 years. The risk of developing CRC in PSC patients without IBD was 0% at 10 years<sup>[43]</sup>. Another study from the Cleveland Clinic found that coexistent IBD and PSC had a colorectal neoplasia incidence rate of 34% following liver transplantation, very similar to the incidence in matched IBD-PSC controls without liver transplantation (30%). However, the rate of colorectal neoplasia in IBD-PSC patients following liver transplantation was higher than if liver transplantation was performed for non-PSC indications (34% and 0%, respectively;  $P < 0.05$ )<sup>[44]</sup>.

In a large-scale study, Dvorchik *et al.*<sup>[45]</sup> identified 192 patients with both PSC and IBD, and found no increase in the risk of CRC in these patients ( $P < 0.001$ ). van de Vrie *et al.*<sup>[46]</sup> conducted a retrospective study of patients having had liver transplantation for PSC, and concluded that transplantation was not adversely affected by IBD, nor was the course of IBD different after liver transplantation. High incidence rates of CRC remain following liver transplantation for PSC according to a recently published meta-analysis. The incidence rates of CRC were 5.8 per 1000 person-years but increased to 13.5 per 1000 person-years in those with an intact colon at the time of transplantation. A long duration of IBD and extensive colitis were confirmed as risk factors for CRC but specific transplant-related factors that may increase CRC risk were not identified<sup>[47]</sup>. Overall, the evidence suggests that liver transplantation does not offer protection against CRC in PSC patients with concomitant IBD, and that post-liver transplantation patients are just as likely to develop CRC as non-transplanted patients. However, there is a lack of evidence to suggest that liver transplantation is an added risk factor for CRC development in IBD-PSC patients.

### Surveillance

With increasing evidence conferring the increased risk of CRC in IBD-PSC patients, the importance of colonoscopic surveillance after the diagnosis of PSC in IBD patients has been stressed. The general consensus is that routine surveillance colonoscopy and random biopsies should be performed one to two years post PSC diagnosis in IBD patients<sup>[48-51]</sup>.

Despite these recommended guidelines, research show that scheduled colonoscopy is rarely performed in UC-PSC patients. A Canadian study followed up IBD-PSC patients for five years, and found that only 36% of the expected annual surveillance colonoscopies were conducted. 33% of patients did not undergo a single colonoscopy, and 11% of patients developed colorectal dysplasia or CRC during the follow-up period<sup>[52]</sup>. Another study of 771 patients with an  $\geq 8$  years history of UC found the prevalence of annual surveillance amongst UC-PSC patients to be 38.5%, higher than that of the total study population (24.6%)<sup>[53]</sup>. A recent study from the Mayo Clinic showed that the rate of colorectal neoplasm (dysplasia and carcinoma) discovery within two years of diagnosis of coexisting IBD and PSC (21.5 per 100 patients) was similar to rate of discovery within eight to ten years (20.4

per 100 patients)<sup>[54]</sup>. This finding supports current guidelines for annual colonoscopic surveillance for IBD-PSC patients, starting from when concurrent PSC and IBD are diagnosed.

Rationale is lacking for the benefit of annual surveillance in IBD-PSC patients in the form of grade A supporting evidence, and current guidelines have been mainly based on expert opinion and retrospective studies. Little research has been done in the form of controlled trials to compare the rate of CRC diagnosis and prognosis between patients that undergo routine colonoscopy and those that do not. Data are unavailable that surveillance offers any prevention against CRC development or reduction in CRC mortality.

## MECHANISMS OF PATHOGENESIS

Currently, the pathogenic mechanisms for the increased risk of CRC in UC-PSC patients remain unknown. One hypothesis suggests bile acids as the key culprit. PSC and other cholestatic conditions typically exhibit impaired hepatic excretion of bile acids, which may result in colonic build-up of secondary bile acids<sup>[55]</sup>. Bile acids have long been suspected as a carcinogen in human gastrointestinal cancers. Studies in animal models have shown secondary bile acids to cause DNA damage and promote cell mutation<sup>[56]</sup>. The observed increase in prevalence of CRC in the right proximal colon, where secondary bile acid concentrations are the highest suggests the role of bile acid in carcinogenesis<sup>[25-27]</sup>. The strongest evidence for this hypothesis comes from the beneficial role of UDCA. Ursodeoxycholic acid modifies the bile acid pool to reduce levels of the secondary bile acid deoxycholic acid, thereby purportedly reducing the carcinogenic potential of bile acid<sup>[57]</sup>. However, the preventative role of UDCA remains controversial, and similarly the role of bile acids in the development of CRC is also still up for debate.

Long-standing inflammation is a recognised risk factor in CRC development in IBD patients<sup>[4]</sup>. Studies have shown that coexisting IBD in PSC patients often exhibit milder clinical courses. Patients often require less use of steroids, immunomodulators and surgery, and have reduced disease activity or even asymptomatic disease<sup>[22,58]</sup>. Primary sclerosing cholangitis may be associated with a milder subclinical IBD for many years before diagnosis<sup>[4,19]</sup> and hence have had longer disease duration than apparent, increasing their risk of CRC development and requiring surveillance to commence immediately upon diagnosis of PSC<sup>[4]</sup>.

## CONCLUSION

Recent evidence increasingly points to PSC as a significant risk factor in the development of CRC in patients with concomitant IBD. Data suggest that the risk of CRC development can reach up to 30% at 20 years after diagnosis of concurrent IBD and PSC. PSC may be an important risk factor for CRC in different populations

worldwide. The mechanism for this increase in risk is still unclear. Various methods to prevent CRC development have been extensively investigated. The efficacy of UDCA remains controversial, and more longer term randomised placebo-controlled trials are needed. Liver transplantation does not halt the development of CRC, although there is not enough evidence to suggest that it is associated with increased incidence of CRC. Patients with concurrent PSC and IBD should be educated about the risk of CRC, and while routine colonoscopic surveillance should be performed, more high-level evidence is required to support the benefits of the procedure.

While many new developments have taken place in the last decade, the pathogenesis and optimal management of CRC development in IBD-PSC patients remain unclear. Further research in these directions will lead to better insight into the relationship between IBD, PSC and CRC.

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