

Update on inflammatory bowel disease in patients with primary sclerosing cholangitis

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Abstract

Patients with primary sclerosing cholangitis (PSC) complicated by inflammatory bowel disease (IBD) represent a distinct subset of patients with unique characteristics, which have serious clinical implications. The aim of this literature review was to shed light to the obscure clinical and molecular aspects of the two diseases combined utilizing current data available and putting issues of diagnosis and treatment into perspective. The prevalence of IBD, mainly ulcerative colitis in PSC patients is estimated to be 21%-80%, dependent on screening programs and nationality. PSC-associated colitis is likely to be extensive, characterized by rectal sparing, backwash ileitis, and generally mild symptoms. It is also more likely to progress to colorectal malignancy, making it imperative for clinicians to maintain a high level of suspicion when tackling PSC patients. There is no optimal surveillance strategy but current guidelines advocate that colonoscopy is necessary at the time of PSC diagnosis with annual endoscopic follow-up. Random biopsies have been criticized and a shift towards targeted biopsies using chromoendoscopy, laser endomicroscopy and narrow-band imaging has been noted. Techniques directed towards genetic mutations instead of histological abnormalities hold promise for easier,

more accurate diagnosis of dysplastic lesions. Chemo-preventive measures against colorectal cancer have been sought in these patients. Ursodeoxycholic acid seemed promising at first but subsequent studies yielded conflicting results showing anticarcinogenic effects in low doses (8-15 mg/kg per day) and carcinogenic properties in high doses (15-30 mg/kg per day).

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Key words: Primary sclerosing cholangitis; Inflammatory bowel disease; Ulcerative colitis; Crohn's disease

Core tip: Combination of primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD) has recently arisen as a challenging research field. Recent data highlight the specific clinical and genetic traits that differentiate PSC-IBD from the two diseases individually. We reviewed the literature on colorectal neoplastic susceptibility in this subset of patients and the underlying pathogenetic mechanisms. We also emphasize the technological advances that have provided novel diagnostic tools for more accurate detection of dysplastic lesions. Finally, we present current guidelines on follow-up as well as all evidence available as to whether ursodeoxycholic acid should be used prophylactically against colorectal cancer.

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic progressive disease characterized by inflammation and fibrosis of

medium size and large ducts in the intrahepatic and extrahepatic biliary tree^[1,2]. This disorder results in multifocal intrahepatic and extrahepatic biliary strictures, leading to cholestasis, liver cirrhosis, portal hypertension, and ultimately, premature death from liver failure. It was first reported in the German literature in 1867 by Hoffman, but was described in more detail in the 1920s by two French surgeons, Delbet and Lafourcade. The term sclerosing cholangitis was first used in 1954 by Castleman and later by Schwartz and Dale in their review article^[3]. Its etiology remains largely unknown, although it is strongly believed that autoimmunity is the main culprit. The differential diagnosis of PSC includes congenital diseases (*e.g.*, Caroli disease and choledochal cysts) and secondary cholangiopathy, as observed in patients with collagen vascular diseases (*e.g.*, systemic lupus erythematosus, rheumatoid arthritis, and systemic sclerosis) and in those with infiltrative diseases (*e.g.*, mediastinal fibrosis, Riedel thyroiditis, eosinophilic cholangitis, and histiocytosis X). Parasitic, fungal, viral or bacterial infections or recurrent cholangitis itself, especially in patients who are immunocompromised, can cause multifocal liver abscesses that lead to a PSC-like appearance of the bile duct. This disease is associated with many cancers including cholangiocarcinoma, gallbladder cancer, hepatocellular carcinoma and colorectal cancer (CRC), thus establishing a link between chronic inflammation and carcinogenesis.

THE PSC-INFLAMMATORY BOWEL DISEASE INTERPLAY

The overwhelming majority of PSC cases have underlying inflammatory bowel disease (IBD). IBD is defined as a chronic condition characterized by immune-mediated inflammation of the gastrointestinal system. The prevalence ranges from 21% to 80%, with the higher rates seen in settings where screening programs are more intense and rectal and sigmoid biopsies are routinely obtained. A geographical variation also exists, with northern European and American societies exhibiting higher rates of PSC-IBD than southern regions and Asia. About 85%-90% of patients with PSC and IBD are comprised of ulcerative colitis (UC) patients and the remainder involves patients with Crohn's colitis or Crohn's ileocolitis^[4]. The association of PSC and Crohn's disease (CD) was first described by Atkinson and Carroll in 1964^[5]. A year later, Smith and Loe described an association between PSC and UC^[6]. Conversely, it has been estimated that PSC occurs in about 5% of UC patients and 3% of CD patients^[7].

IBD may be diagnosed at any time during the course of PSC. Until recently, the diagnosis of IBD more frequently preceded that of PSC, even by several years^[8-11]. Nowadays, there has been a shift in the timing of diagnosis of IBD and PSC. PSC is most commonly diagnosed first, or at least there is a concomitant diagnosis of the two diseases. It is intriguing that *de novo* IBD may present after liver transplantation for PSC^[12], and PSC may present several years after proctocolectomy for IBD. The

altered trend in diagnostic timing can be attributed to two factors. First, the advent of noninvasive imaging techniques such as magnetic resonance cholangiography has enabled early diagnosis of pathological liver biochemistry. Second, the increasing awareness among physicians of the PSC-IBD association has led to early routine endoscopic screening in patients diagnosed with PSC, even in the absence of symptomatic colitis. A study comparing the interval from PSC to IBD diagnosis in 1993-1997 and 2003-2007 showed a decrease from 9 to 7 mo respectively^[13].

The genetic factors for PSC development are still poorly understood. There is an obvious geographic clustering with high prevalence in northern countries compared to Southern Europe and Asia. It has been shown that first-degree relatives of PSC patients have a disease prevalence of 0.7%, representing a nearly 100-fold increased risk of developing PSC compared to that in the general population^[14]. In siblings the prevalence even reaches 1.5%^[15]. Taken together, these epidemiologic data and heritability studies have revealed a strong genetic background for PSC. Genome-wide association studies have shed some light on the subcellular maze of PSC and its overlap with IBD. Human leucocyte antigen (HLA) and non-HLA haplotypes have been identified. The HLA-A1 allele^[16], HLA-C7^[17], major histocompatibility complex class I chain-related A (MICA)*002 and 008/5.1 alleles^[18,19], as well as the tumor necrosis factor (TNF) α promoter -308 A allele^[20] were identified as risk loci for PSC susceptibility. Data from five different European countries (United Kingdom, Italy, Norway, Spain and Sweden) demonstrate that PSC is positively associated with three different HLA class II haplotypes: DRB1*03, DQA1*0501, DQB1*02 (which confers the highest relative risk for PSC development); DRB1*15, DQA1*0102, DQB1*0602; and the DRB1*13, DQA1*0103, DQB1*0603^[21]. However, non-HLA associations have also been confirmed. Of note, MMEL1 and TNFRS14 on chromosome 1p36 encoding a membrane metallo-endopeptidase-like protein of unknown function and a receptor for cytokines and membrane-bound ligands, respectively, have been identified as risk loci for PSC^[22]. The risk of PSC has also been associated with the *FUT2* gene encoding fucosyltransferase^[22], which is an enzyme that regulates expression of the ABO blood group antigens on the surface of epithelial cells. To date, there is scarcity of molecular evidence regarding the shared susceptibility loci between PSC and IBD. A Scandinavian study comparing PSC with UC patients showed distinct HLA associations^[23]. No significant differences were noted between PSC patients with concurrent UC and PSC patients without IBD. This study provides genetic evidence that UC in PSC patients follows a distinct course and demonstrates phenotypic uniqueness compared with UC in isolation. More recently, *REL*, *IL-2* and *CARD9* have been identified as genetic links between the two diseases^[24].

Taking into consideration its associations with HLA haplotypes, autoimmune diseases and the presence of IBD in the majority of PSC patients, immunopathoge-

Table 1 Characteristics of inflammatory bowel disease associated with primary sclerosing cholangitis

Extensive colitis (with right-sided predominance)
Rectal sparing
Backwash ileitis
Mild or quiescent course
Increased risk of colorectal cancer
Increased risk of pouchitis in patients undergoing proctocolectomy with ileal pouch anal anastomosis
Increased risk of peristomal varices in patients undergoing proctocolectomy with ileostomy

netic mechanisms have been sought in PSC pathogenesis. In this regard, two theories have been proposed: the leaky gut hypothesis and the gut lymphocyte homing hypothesis. According to the leaky gut hypothesis, bacteria or bacterial products enter the portal-venous system due to the increased intestinal permeability resulting from inflammation, and translocate to the liver. Bacteria trigger the release of cytokines by Kupffer cells and macrophages in the liver and lead to periductal fibrosis^[8]. The gut lymphocyte homing hypothesis supports the notion that T lymphocytes primed in the inflamed gut may persist as long-lived memory cells, undergo enterohepatic circulation, and trigger portal inflammation in PSC *via* aberrantly expressed adhesion molecules in the liver and gut^[25].

IBD IN PSC: A UNIQUE PHENOTYPIC EXPRESSION

There are many clinical and endoscopic features that differentiate patients with IBD and concomitant PSC and those with IBD in isolation (Table 1). Loftus *et al*^[10] compared 71 patients with PSC who had IBD with a matched group of 142 patients with UC. Among the PSC patients, 86% had UC, 7% had CD, and 7% had indeterminate colitis. The PSC patients more frequently had pancolitis (87% *vs* 54%), rectal sparing (52% *vs* 6%), and backwash ileitis (51% *vs* 7%) than the control group. It is now commonly believed that the colitis associated with PSC is frequently extensive and characterized by rectal sparing and backwash ileitis^[26,27]. These special traits impede the definitive classification of IBD. For instance, the presence of rectal sparing or ileitis may be misinterpreted for CD or indeterminate colitis, rather than UC. In addition, PSC-associated colitis runs a milder, quiescent course, sometimes with absent clinical manifestations, thus delaying diagnosis^[28]. Another intriguing trait in PSC-IBD patients is the higher rate of colorectal neoplasia, which tends to be proximal, is diagnosed at a later stage and has a worse prognosis. The colorectal neoplastic potential in these patients will be discussed later.

Of note, PSC patients who have an ileal pouch anal anastomosis (IPAA) after colectomy have an increased risk of pouchitis compared to patients with UC without PSC^[29,30]. The underlying mechanism for this complica-

tion remains obscure. There is also one report suggesting that patients with PSC and IPAA run an increased risk of development of dysplasia in the ileal pouch mucosa compared with UC patients without PSC, and that these patients consequently should be under intensive surveillance^[31]. However, more studies are required to substantiate these claims. Interestingly, it has been suggested that PSC-IBD patients undergoing proctocolectomy with ileostomy develop peristomal varices more frequently than IBD patients without evidence of hepatobiliary disease^[32]. Bleeding from these often is recurrent and is challenging to treat. This complication can be controlled with a portosystemic shunt or transjugular intrahepatic portosystemic shunt, but liver transplantation may be considered.

PSC in patients with IBD does not seem to run a different course when compared to patients without IBD. Nevertheless, one study has demonstrated that PSC in patients with concomitant IBD has a predilection for men, is more likely to manifest itself for the first time with abnormal liver biochemistry, and has intrahepatic and extrahepatic biliary tree strictures^[33]. Proctocolectomy, as a surgical treatment for UC, has no effect on liver function tests, histology or survival of patients with PSC^[34].

COLORECTAL NEOPLASTIC POTENTIAL IN PSC-IBD PATIENTS

The increased occurrence of CRC in IBD patients has been well documented since 1925, when it was first described by Crohn and Rosenberg^[35]. The cancer risk involves both UC and CD^[36-39], and has been linked with prolonged duration and extent of disease, associated PSC and active inflammation^[40,41]. Data on the relative risk of CRC in IBD are not in agreement in different studies. The cumulative risk varies from 1.4% after 18 years^[42] to 34% after 25 years from onset of disease^[43]. Some studies even advocate that the risk is not increased at all^[44].

Recent investigations have unveiled another relationship, that of PSC-IBD patients and CRC. The concept that PSC is associated with an increased risk of colorectal neoplasia in patients with UC was proposed by Broomé *et al*^[45] in 1992. In a study of 17 patients with UC who were found to have dysplasia, carcinoma, and/or DNA aneuploidy, 28% had coexistent PSC. This led to the hypothesis that PSC is an independent risk factor for the development of colorectal neoplasia in patients with existing UC. There has been a wealth of studies since then reporting the connection of PSC-IBD and CRC, particularly highlighting the compounding neoplastic risk when the two disorders coexist as opposed to patients with IBD alone^[46-53] (Table 2). Soetikno *et al*^[54] performed a meta-analysis of 11 studies and described an odds ratio (OR) of 4.79 (95%CI: 2.89-5.76) when comparing patients with UC and PSC to UC patients without PSC. However, two studies (both from the Mayo Clinic but using different groups of patients) have yielded contradictory results rejecting the hy-

Table 2 Summary of studies evaluating primary sclerosing cholangitis as a risk factor for colorectal neoplasia in chronic ulcerative colitis

Ref.	UC case group (No)	Centre	End point (No)	Matched controls	Colectomy rate	Is PSC a risk factor?
Broomé <i>et al</i> ^[45]	Dys (17)	Hudding, Sweden	PSC (5)	Yes	0%	Yes
D'Haens <i>et al</i> ^[46]	Dys (29)	Chicago, United States	Cholestasis/PSC (10)	Yes	0%	Yes
Broomé <i>et al</i> ^[47]	PSC (40)	Hudding, Sweden	CRC/Dys (15)	Yes	30%	Yes
Brentnall <i>et al</i> ^[48]	PSC (20)	Seattle, United States	Dys (9)	No	0%	Yes
Leidenius <i>et al</i> ^[49]	PSC (45)	Helsinki, Finland	CRC/Dys (13)	Yes	29%	Yes
Marchesa <i>et al</i> ^[50]	PSC (27)	Cleveland, United States	CRC (4)/Dys (14)	Yes	All postop	Yes
Shetty <i>et al</i> ^[51]	PSC (132)	Cleveland, United States	CRC (17)/Dys (16)	No	0%	Yes
Loftus <i>et al</i> ^[52]	PSC (143)	Mayo Clinic, United States	CRC (8)	No	37%	No
Nuako <i>et al</i> ^[53]	CRC (171)	Mayo Clinic, United States	PSC (30)	Yes	14%	No

CRC: Colorectal cancer; CRN: Colorectal neoplasia; Dys: Dysplasia; PSC: Primary sclerosing cholangitis.

pothesis that there is an increased risk for CRC in PSC-IBD patients^[52,53]. In general, the increased neoplastic potential in PSC-IBD patients could be ascribed to late diagnosis due to the subclinical course of colitis and the conservative treatment of mild flare-ups as opposed to colectomy, thereby increasing the duration and extent of colitis.

CRCs associated with PSC display a number of characteristics. They appear to have a more proximal localization with up to 76% right-sided distribution. A full colonoscopy is therefore mandatory for surveillance purposes. CRCs in this subset of patients are diagnosed at a more advanced stage and tend to be fatal. In a recent study, PSC patients with IBD and CRC were found to be younger at onset of IBD than patients who had IBD and CRC without PSC (19 *vs* 29 years; $P = 0.04$). The time interval from onset of colitis until diagnosis of CRC was, however, similar in the two groups (17 *vs* 20 years; $P = 0.02$)^[55].

PATHOGENETIC MECHANISMS OF CRC IN PSC

The mechanisms underlying the pathogenesis of CRC in IBD patients have been rigorously investigated and many differences in comparison with sporadic CRC have been addressed^[56,57]. Even though IBD-CRC usually follows a dysplasia-cancer pattern, as in sporadic cancer, molecular and genetic events seem to occur in an unconventional sequence. Alterations to the *p53* tumor suppressor gene occur earlier in colitis-related CRC^[58], whereas adenomatous polyposis coli (*APC*) gene alteration is usually a later event^[59]. The reverse applies to sporadic CRC. It is also noteworthy that *p53* mutations can be present in nondysplastic mucosa in IBD-CRC, but only in dysplastic areas in sporadic cancer^[60]. Another noteworthy difference is that low-grade dysplasia is often in flat lesions in CRC-IBD, which are difficult to detect endoscopically, whereas such dysplasia occurs within raised polyps in sporadic cancer. The role of microsatellite instability, hypermethylation, chromosomal instability, interleukin (IL)-23/IL-17 signaling and E-cadherin (*CDH1*) has been addressed in studies but is not yet fully understood^[61-64]. Polymorphisms of the mismatch repair genes *MLH1* and *MSH2*

have been incriminated for the pathogenesis of IBD and related malignancy^[65,66].

The direct impact of PSC on colorectal carcinogenesis has not yet been delineated. Another theory highlights the significance of the cholestasis-associated secondary bile salt pool in the colon^[67]. Bile acids such as deoxycholic acid and lithocholic acid (LCA) are thought to contribute to tumorigenesis through disruption of the balance between colorectal crypt cell proliferation, differentiation and apoptosis^[68-71]. Mucosa in carcinoma displayed an increased frequency of bile acid receptors compared with normal tissue^[72]. A higher fecal bile acid concentration was found in patients with UC who developed neoplasia compared with those without UC^[73]. Folate deficiency has also been implicated in the pathogenesis of CRC in IBD patients. Folate deficiency arises from sulfasalazine use to treat UC, which is a competitive inhibitor of folate absorption. Folate supplementation was associated with a 62% reduction in the incidence of neoplasia in patients with pancolonic UC compared with placebo^[74]. This theory, however, contradicts epidemiological reports according to which maintenance therapy in UC reduces risk of carcinogenesis^[75].

SURVEILLANCE RECOMMENDATIONS

Periodic surveillance colonoscopy is the milestone of cancer prevention in IBD^[76,77]. PSC in combination with IBD further enhances the risk for CRC as described above and necessitates increased alertness. That along with the fact that IBD in PSC patients usually follows an asymptomatic, subclinical course raises the need for routine colonoscopy at the time of PSC diagnosis, which should be repeated on an annual basis^[78]. However, a recent study by Imam *et al*^[79] showed a low risk of colonic neoplasia in young patients with a combined diagnosis of PSC and IBD, with an estimated prevalence of 1.3% and an incidence of 0.4% per year. This finding raises the question whether annual surveillance is unnecessary in this selected group of patients.

Three categories of dysplasia have been identified according to the IBD Dysplasia Morphology Study Group^[80]: (1) negative for dysplasia; (2) indefinite for dysplasia; and (3) positive for dysplasia, which is further subdivided into low-grade dysplasia (LGD) and high-grade

dysplasia (HGD). Each of these categories necessitates a different approach. A finding of indefinite dysplasia dictates a repeat colonoscopy in 3-6 mo. The management of LGD is debatable with no clear evidence of optimal approach. St Mark's Hospital^[81] demonstrated a 54% cumulative probability of LGD progressing to HGD or CRC. Mayo Clinic reported a 33% 5-year progression^[82], while other studies described an even lower rate^[83,84]. Thus, in the case of LGD different options should be discussed with patients and informed consent for conservative or operative management should be obtained. Patients with multifocal flat LGD in one screening or unifocal LGD in more than one screening should prompt prophylactic total proctocolectomy. HGD, however, needs unquestionable referral for total proctocolectomy due to the increased risk of concurrent or subsequent malignancy^[85].

There has been increased skepticism in the medical community about the random biopsies used for surveillance purposes. New methods enable targeted biopsies to be obtained from identifiable lesions. Chromoendoscopy, confocal laser endomicroscopy and narrow-band imaging (NBI) are new promising techniques that are likely to replace old-fashioned random biopsies that have proven their inadequacy in many studies^[86,87]. Chromoendoscopy uses the application of indigo carmine or methylene blue to stain dysplastic areas on the colonic mucosa. Hurlstone *et al*^[88] examined 700 patients in a prospective case-control trial and diagnosed 69 dysplastic lesions with chromoendoscopy and only 24 with random biopsies ($P < 0.001$)^[88]. Confocal laser endomicroscopy enables the histological visualization of the mucosa in real time. It is easily inferred that this technique requires specialized training for histological interpretation. A randomized controlled trial was conducted by Kiesslich *et al*^[89] showing an increase of 4.75 times in yield of neoplasia when using endomicroscopy ($P = 0.005$). NBI uses optical fibers to enable a clear visualization of vessels, pit pattern and soft tissue structures. A study showed that NBI cannot be recommended as a chromoendoscopy substitute because it detected fewer lesions than chromoendoscopy in chronic colitis, although most were not dysplastic^[90].

Newer techniques that target genetic alterations rather than histological abnormalities have been proposed to increase detection efficacy. Deletions and point mutations of tumor-suppressor genes such as *p53*, *Rb*, *APC*, *mcv* and the Sialosyl-Tn antigen have been found in dysplastic lesions and could be a useful tool for early diagnosis^[91,92]. DNA evaluation by flow cytometry could reveal aneuploidy and predict suspicious areas likely to progress to CRC. The main drawback is that aneuploidy is not always a prerequisite for cancer occurrence and its presence does not always lead to malignancy.

CHEMOPREVENTION

Many studies have investigated the potential protective effects of different drug agents against malignancy in patients with UC. Pinczowski *et al*^[93] was the first to report

that CRC risk is diminished by therapy with 5-aminosalicylic acid (5-ASA) in 1994. Ever since, studies have failed to demonstrate a clear relationship between 5-ASA therapy and CRC, rendering its potential protective effect presumptive rather than definitive. Azathioprine and mercaptopurine have not been shown to have a beneficial effect with regards to CRC in IBD^[85]. Likewise, research has yielded inconclusive results regarding the use of corticosteroids, nonsteroidal anti-inflammatory drugs or folates for chemopreventive purposes.

Ursodeoxycholic acid (UDCA) is a drug commonly used in PSC patients due to its safe profile and favorable effects on the biochemical parameters of the disease. *In vitro* and animal studies have revealed a chemoprophylactic effect of UDCA. UDCA appears to arrest proliferation of colon cancer cell lines *in vitro*^[94]. CRC induced by N-methylnitrosourea^[95] and azoxymethane^[96,97] in rats appeared to respond to UDCA therapy with a decrease in size. UDCA also decreased fecal concentrations of deoxycholic acid in animals, suggesting a potential protective effect through control of bile acid concentration in colon^[98]. Several molecular mechanisms have been proposed to explain the chemoprophylactic effect of UDCA, including downregulation of cyclo-oxygenase-2 expression^[97], prevention of carcinogen-induced changes in protein kinase C isoforms^[99], suppression of epidermal growth factor receptor^[100], cell cycle modulation by inhibiting the expression of cyclin D1 and promoting that of E-cadherin^[101], and stabilization of mitochondrial membranes against damaging free radicals^[102]. These results triggered a number of investigations in humans in order to shed light on the real effect of UDCA. Two studies have confirmed the protective effect of the drug. Tung *et al*^[103] conducted a retrospective review of 59 patients showing a reduced OR of 0.18 (95%CI: 0.05-0.61) of colonic dysplasia after ursodiol use. Pardi *et al*^[104] also performed a randomized placebo controlled study evaluating the effect of UDCA in the subgroup of UC patients with concomitant PSC. Patients who received a low dose of UDCA (13-15 mg/kg per day) showed a relative risk of 0.26 for developing CRC or dysplasia. Wolf *et al*^[105] showed in a retrospective study of 120 patients that there was no reduction of CRC or dysplasia in the UDCA group. A hallmark study by Eaton *et al*^[106] has recently reversed the long-standing conviction that UDCA has a place in CRC prevention in PSC-IBD patients. Using high doses of UDCA (28-30 mg/kg per day), they showed an increased risk of CRC in the UDCA group. The majority of patients developed colorectal neoplasia after > 2 years of use. This association remained significant after adjusting for smoking history and UC duration. High-dose UDCA also resulted in an increased risk of liver transplantation and/or death^[107]. The discrepancy between different studies can be attributed to their inherent limitations and their failure to adjust for confounding factors such as age at onset of colitis, extent of colitis, family history of CRC, cigarette smoking, use of other drugs such as 5-ASA and folate, and use of the same criteria for dysplasia classification.

There has been speculation with regard to mechanisms underlying the toxic and carcinogenic UDCA properties. The most prevalent theory implicates the alteration of colonic bile acid milieu when high doses are used. An increase in serum UDCA and LCA levels in the treatment group has been reported^[108]. That combined with results from *in vitro* studies stating that bile acids stimulate cell invasion in a dose-dependent fashion and reduce apoptosis could possibly provide a plausible explanation of the differing effects when low and high UDCA doses are used^[109-111]. It is therefore prudent to recommend UDCA chemoprevention only to a high-risk subset of patients, including those with a personal or family history of CRC, and those with long-standing extensive colitis. This rationale has been incorporated to recent European guidelines^[112].

In conclusion, PSC-IBD patients represent an important public health concern. Significant steps have been made towards the elucidation of the pathogenetic mechanisms underlying this complex disease. HLA and non-HLA susceptibility genes have been thoroughly studied and proven their association with PSC-IBD. Further investigations are warranted to reveal PSC- and IBD-specific genes and clarify their real impact on the disease. Genome-wide association studies could be invaluable in this direction but are severely undermined by the rarity of the disease and therefore the limited number of PSC patients that can be recruited. In terms of diagnosis, biomarkers currently in use are liver function tests and histology. A couple of new methods have been introduced to facilitate the evaluation of PSC patients. Fibroscan and a breath test assessing the elasticity and metabolic capacity of the liver respectively have paved the way for rapid, non-invasive diagnosis. Their diagnostic accuracy in PSC, however, remains under scrutiny.

CRC is a well-established risk for PSC-IBD patients. Aggressive colonoscopic surveillance is therefore imperative, even in those who have undergone liver transplantation^[113]. In an attempt to relieve the socioeconomic and medical burden that PSC-IBD poses, many studies have explored potential pharmaceutical agents that may retard disease progression and protect against colorectal neoplasia. Antibiotics, immunomodulators, UDCA and antifibrotic agents have attracted the attention of researchers but their full potential has not yet been unraveled. Recent meta-analyses have demonstrated that UDCA in low to medium doses seems to have a chemoprophylactic effect, whereas high doses are carcinogenic^[114,115]. Further investigations are required to test the efficacy of existing drug agents and promote the development of new ones. Understanding and harnessing molecular events seems a pivotal step towards this direction.

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