Inflammatory Bowel Disease in Primary Sclerosing Cholangitis: Clinical Characteristics in Liver Transplanted and Non-Transplanted Patients

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Abbreviations

AIH	autoimmune hepatitis
5-ASA	5-aminosalicylic acid
ATG	antithymocyte globulin
CCL25	chemokine ligand 25
CCR9	chemokine receptor 9
CD	Crohn's disease
CI	confidence interval
CMV	cytomegalovirus
CsA	ciclosporine A
DALM	dysplasia-associated lesion or mass
ECCO	European Crohn's and Colitis Organisation
ERC	endoscopic retrograde cholangiography
GWAS	genome-wide association studies
HGD	high-grade dysplasia
HR	hazard ratio
IAC	IgG4 associated cholangitis
IBD	inflammatory bowel disease
IPAA	ileal pouch-anal anastomosis
IRA	ileorectal anastomosis
LGD	low-grade dysplasia
Ltx	liver transplantation
MAdCAM-1	mucosal addressin cellular adhesion molecule 1
Mdr2	multidrug resistance protein 2
MMF	mycophenolate mofetil
MRC	magnetic resonance cholangiography

OKT3	muromonab-CD3
OR	odds ratio
pANCA	perinuclear anti-neutrophil cytoplasmic antibody
PBC	primary biliary cirrhosis
PFIC3	progressive familial intrahepatic cholestasis type 3
PSC	primary sclerosing cholangitis
PXR	pregnane X receptor
rLGD	recurrent low-grade dysplasia
RR	relative risk
SCCAI	Simple Clinical Colitis Activity Index
SXR	steroid and xenobiotic receptor
UC	ulcerative colitis
UDCA	ursodeoxycholic acid

List of publications

Paper I

Jørgensen KK, Grzyb K, Lundin KEA, Clausen OPF, Aamodt G, Schrumpf E, Vatn MH, Boberg KM. Inflammatory Bowel Disease in Patients with Primary Sclerosing Cholangitis: Clinical Characterization in Liver Transplanted and Nontransplanted Patients. Inflamm Bowel Dis 2012;3:536-545

Paper II

Jørgensen KK, Lindström L, Cvancarova M, Castedal M, Friman S, Schrumpf E, Foss A, Isoniemi H, Nordin A, Holte K, Rasmussen A, Bergquist A, Vatn MH, Boberg KM. Colorectal Neoplasia in Patients with Primary Sclerosing Cholangitis undergoing Liver Transplantation: a Nordic Multicenter Study. Scand J Gastroenterol 2012;47:1021-1029

Paper III

Jørgensen KK, Lindström L, Cvancarova M, Karlsen TH, Castedal M, Friman S, Schrumpf E, Foss A, Isoniemi H , Nordin A, Holte K, Rasmussen A, Bergquist A, Vatn MH, Boberg KM. Immunosuppression after liver transplantation for primary sclerosing cholangitis influences activity of inflammatory bowel disease. Clin Gastroenterol Hepatol 2013;11:517-523.

1. Introduction

1.1 Background

Although primary sclerosing cholangitis (PSC) is a fairly rare disease, it affects relatively young people and often implicates serious complications that have an impact on patient morbidity and mortality. Earlier studies of inflammatory bowel disease (IBD) in PSC have depicted that the characteristics of IBD in PSC differ from IBD unrelated to hepatobiliary disease regarding several aspects. However, previous studies display diverging results, probably due to differences in patient selection, size of the cohorts, study design and statistical methods used. To answer the unsolved questions regarding PSC-IBD, further studies are warranted. The high prevalence of PSC in the Nordic countries and the close collaboration between the Nordic liver transplant units through the Nordic Liver Transplant Registry have given our centre, as the only third-line PSC referral centre in Norway, an excellent opportunity to study various disease aspects of PSC and concomitant IBD in large patient cohorts.

This thesis discusses various aspects of IBD in patients with PSC. The aims have been to describe the clinical features of IBD in PSC, with special emphasis on IBD disease activity and development of colorectal neoplasia, in both liver transplanted and non-transplanted patients.

Firstly, an overview of PSC and IBD is given, including the characteristics of IBD in PSC, regarding in particular disease activity and development of colorectal neoplasia. Then, after accounting for the aims and the material and methods of the studies, a short summary of the results is given. The last part of the thesis aims at discussing the main results of the papers in a general context regarding both current knowledge and desirable future studies in the field of IBD in PSC.

1.2 Primary sclerosing cholangitis

PSC is a chronic, cholestatic liver disease of largely unknown aetiology, characterized by inflammation and fibrosis of the biliary tree. Although the course is variable, it is frequently progressive, leading to end stage liver disease after a median of 10-15 years.[1,2] The diagnosis is based on elevated cholestatic serum markers and characteristic cholangiographic findings on endoscopic retrograde cholangiography (ERC) or magnetic resonance cholangiography (MRC), consisting of multifocal strictures and dilatations of the intrahepatic and/or extrahepatic bile ducts.[3] The median age at PSC diagnosis is 30-40 years, and approximately 2/3 of patients are male.[1,2] The most common symptoms of PSC include abdominal pain, jaundice, pruritus, fatigue, fever, weight loss and eventually, symptoms of chronic cholestasis and portal hypertension.[4] A majority of PSC patients have concomitant IBD, but a variety of other immune-mediated diseases, such as sarcoidosis, thyroid disease and diabetes mellitus type I are also overrepresented.[5,6] There is also an increased risk of malignancy, especially in the biliary tree (cholangiocarcinoma), the liver (hepato-cellular carcinoma), the large intestine (colorectal carcinoma) and the pancreas.[7-10]

1.2.1 Epidemiology of PSC

The reported incidence and prevalence rates of PSC vary widely, and incidence rates of 0-1.31 and prevalence rates 0-16.2 per 100.000 inhabitants have been described (table 1).[11-20] Higher rates are reported among Northern European descendants than in Southern Europe and Asia, and the rates seem to be increasing.[21] In Norway, the mean yearly incidence and the prevalence of PSC have been calculated to be 1.3 and 8.5 per 100.000 inhabitants, respectively.[14]

1.2.2 Pathogenesis of PSC

The pathogenetic mechanisms leading to inflammation and fibrosis with development of multiple strictures and dilatations of both intrahepatic and extrahepatic bile ducts in PSC are essentially unknown. At the stage when the diagnostic cholangiographic changes become evident, it is difficult to determine if observations represent primary disease mechanisms or secondary processes. A number of hypotheses on the

pathogenesis have been put forward, and several lines of research are currently pursued.[22-24] The results of genetic studies in PSC must also be taken into account, since disease associated genes may give clues to pathogenetic pathways.

Genetic susceptibility to PSC

There is evidence of a genetic predisposition to PSC involving multiple genes, including both HLA- and non-HLA genes.[25,26] Variants of these genes may contribute to the disease in combination with environmental factors and seem to mainly influence immunological processes. The importance of genetic factors in the etiology of PSC has been underscored by the finding in a large Swedish study that first-degree relatives of PSC patients carry an increased risk of PSC.[27] Siblings of PSC patients had a risk of developing PSC that was 9-39 times higher than that of the general population (relative sibling risk). Of note, siblings of PSC patients had an increased risk of developing ulcerative colitis (UC) (odds ratio (OR) 8.4, 95% confidence interval (CI) 4.1-17.3), which may indicate the presence of shared genetic susceptibility factors for PSC and UC. The strongest genetic associations in PSC have been detected in the HLA complex on chromosome 6.[28,29] Most likely, both HLA class I and HLA class II genes are involved, but it has so far been difficult to define these associations precisely. By genome-wide association studies (GWAS) of a large number of PSC patients, several non-HLA susceptibility loci have also been identified.[30,31] Some of these overlap with associations found in prototypical autoimmune diseases (*IL2RA, IL2/IL21, MMEL1* and *REL*) and some with associations known from studies of IBD (3p21, 2q35, *CARD9* and *FUT2*).[25] The largest genetic study of PSC patients until now, including 3 789 PSC cases and 25 079 controls, has revealed another 9 novel risk loci for PSC.[32]

The "leaky gut" hypothesis

A hypothesis that directly links development of bile duct damage with the presence of an inflamed bowel would be attractive in PSC. The "leaky gut" hypothesis suggests that bacteria or bacterial components enter the portal venous system via an increased intestinal permeability caused by ongoing inflammation. Bacteria that in this way are translocated to the portal tracts in the liver, may subsequently stimulate the release of cytokines/chemokines and activate innate immune responses that lead

to cholangitis.[23,24] This hypothesis has been supported by experiments in animal models. On the other hand, evidence of increased portal vein bacteremia in PSC-IBD patients is lacking. Antimicrobial treatment in PSC has not appeared to be effective in reducing disease progression,[24] however, an improvement in serum alkaline phosphatase levels, the revised Mayo Risk Score and liver histology under treatment with metronidazole in combination with ursodeoxycholic acid (UDCA) has been noted.[33] It can not be excluded that an infectious trigger is involved in PSC pathogenesis.[23]

The "gut lymphocyte homing" hypothesis

This hypothesis also takes the interrelationship between PSC and IBD into account and could additionally explain that the course of PSC apparently runs independently of the IBD.[34] It is proposed that memory T-lymphocytes generated in the inflamed gut persist in the enterohepatic circulation. Aberrant expression of the mucosal addressin cellular adhesion molecule 1 (MAdCAM-1) ligand on portal vein- and sinusoidal endothelium demonstrated in PSC livers, could recruit these lymphocytes by binding to their integrin α4/β7 receptor. In PSC there is also an aberrant expression in the liver of the chemokine ligand 25 (CCL25), which binds the chemokine receptor 9 (CCR9) on memory T-lymphocytes and may support the recruitment of mucosal lymphocytes to the liver.[35] Since MAdCAM-1 staining in portal veins has also been observed in other liver diseases, MAdCAM-1 expression might rather be secondary to chronic inflammation.

The "autoimmune" hypothesis

Several observations support the contention that autoimmune factors are involved in PSC pathogenesis. The strong HLA association is a typical trait of autoimmune disorders. A variety of autoantibodies have been detected,[36] although none of these are PSC specific. Interestingly, the most frequent antibody in PSC (in up to 94% of cases) is a particular type of perinuclear anti-neutrophil cytoplasmic antibody (pANCA). pANCA is also frequently observed in UC and autoimmune hepatitis (AIH), suggesting common pathogenetic mechanisms. The concomitant diagnosis of other autoimmune disorders and the presence of features of AIH in some PSC patients also support a pathogenetic role for immunological factors.

The "toxic bile" hypothesis

Bile acids may exert toxic effects, and several lines of evidence suggest that detrimental effects of bile acids also play a role in the development and progression of PSC. Mice that lack the phospholipid transporter multidrug resistance protein 2 (mdr2) (abcb4 -/- mice) spontaneously develop severe PSC-like biliary fibrosis, initiated by bile leakage into the portal tracts.[37] This protein corresponds to MDR3 (ABCB4) in humans. Mutations in the *ABCB4* gene in humans give rise to progressive familial intrahepatic cholestasis type 3 (PFIC3). Cholestatic liver disease has been observed in adults with certain *ABCB4* mutations.[38] Although *ABCB4* mutations have not been associated with risk of PSC, particular *ABCB4* variants may contribute to a more severe disease course in both PSC and primary biliary cirrhosis (PBC).[23,39] Likewise, genetic variants of the steroid and xenobiotic receptor (SXR, also designated pregnane X receptor, PXR), a nuclear receptor involved in bile acid detoxification, are associated with a more aggressive disease course in PSC.[40] The improvement of biochemical parameters of cholestasis by treatment with the bile acid UDCA also supports the concept of bile acid toxicity.

The pathogenetic hypotheses are not mutually exclusive and at least some components of each of them may play a role at one or more stages of the disease progression in PSC.

1.2.3 Clinical variants of PSC

Small duct PSC

The term small duct PSC designates a group of patients who present with a cholestatic biochemical profile along with clinical and histological features compatible with PSC, but who prove to have a normal cholangiogram.[41] The definition of small duct PSC has varied in reports from different centers.[18,42-45] Some reports have restricted a diagnosis of small duct PSC to patients with concomitant IBD, whereas IBD has been present in only a proportion (50-88%) of cases in other studies. In a population-based study from Canada including both adults and children, the diagnosis of large duct PSC occurred five times more frequently than small duct PSC, with annual incidence rates of 0.75/100.000 and 0.15/100.000, respectively.[18]

In other reports, small duct PSC has been estimated to represent approximately 6–11% of PSC patients.[44,45] Small duct PSC appears to have a more favourable course than large duct PSC, with fewer patients progressing to end-stage liver disease and without a definite increased risk of cholangiocarcinoma. In a follow-up study of 83 small duct PSC patients from three previous studies,[43-45] 19 (22.9%) patients progressed to large duct PSC in a median of 7.4 years.[46] Only one patient developed cholangiocarcinoma, but this was after progression to large duct PSC. In comparison, cholangiocarcinoma was diagnosed in 19/157 (12%) in a matched group of patients with large duct PSC. Small duct PSC patients had a significantly longer liver transplantation-free survival compared with large duct cases. The differential diagnosis between small duct PSC and intrahepatic classic PSC, both progressing to liver cirrhosis, is a particular challenge. Treatment with UDCA (13–15 mg/kg/day) did not delay disease progression in a study including 30 treated and 7 untreated small duct PSC patients.[47] Small duct PSC is considered a distinct clinical entity, different from large duct PSC,[48] but it is also possible that the two conditions represent different aspects of the same disease spectrum.

PSC-AIH "overlap" conditions

It is a common clinical experience that some patients with PSC present with clinical, biochemical, serological and histological characteristics of both a cholestatic liver disease and AIH. These patients have cholangiographic findings qualifying for a diagnosis of PSC, but may concomitantly have relatively high serum aminotransferase activities, elevated immunoglobulin levels, positive autoantibody titres and histological interface hepatitis. This variant condition is often designated a PSC-AIH "overlap syndrome".[49-51] Internationally standardized criteria to define the PSC-AIH "overlap" condition and the corresponding PBC-AIH "overlap", are lacking. In most reports, PSC-AIH "overlap" has been defined according to the original or revised International Autoimmune Hepatitis Group scoring system that originally were constructed for the diagnosis of AIH and not intended for defining "overlap" groups.[52,53] In the largest among the series of PSC patients in which the frequency of PSC-AIH "overlap" has been studied, 7 – 14% of PSC patients scored for features of AIH.[51]

In some patients considered PSC-AIH "overlap", the initial diagnosis has been AIH, often preceding the diagnosis of PSC by several years.[54,55] It is relevant to suspect a diagnosis of PSC in AIH patients who have relatively marked cholestatic liver tests, histological evidence of bile duct injury or unsatisfactory response to immunosuppressive therapy, in particular if they also have IBD. Sequential development of features of AIH in patients with established PSC has been noted.[54] Cases of overlapping AIH and small duct PSC have also been reported.[56]

There are several reports on the treatment of PSC-AIH "overlap" patients with corticosteroids with or without azathioprine, but no randomized, controlled clinical trials of therapy have been carried out. Both the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) recognize that the subgroup of PSC-AIH "overlap" patients may benefit from corticosteroids or other immunosuppressives, although the therapy is not evidence-based.[57,58] It is important that treatment is individualized and adjusted according to the response, with attention to side effects.[51]

IgG4-associated cholangitis

The condition termed "IgG4-associated cholangitis" (IAC) is a biliary disease that presents with cholangiographic features similar to those of PSC.[59,60] It is included in this context, since some IAC patients most likely have been classified as PSC. IAC is characterized by histological findings of dense lymphoplasmacytic infiltrates, fibrosis (often storiform in character) and obliterative phlebitis. The diagnosis requires an elevated $IgG4^{+}$/IgG cell ratio by immunohistochemical staining of bile duct biopsies.[61] IAC is also associated with elevated serum IgG4 levels, but levels may be normal at presentation and rather rise during follow-up.[59] In a study including 53 cases of AIC, the sensitivity of serum IgG4 was 74%.[62] Elevated levels of serum IgG4 were present in 9% among 127 PSC patients,[63] however, no classical IAC could be identified in a study of 41 explanted PSC livers.[64] In similarity with PSC, there is a male predominance in IAC. Age at presentation varies, but IAC patients generally are older at diagnosis that patients with classic PSC. In contrast to PSC, concomitant IBD is uncommon in IAC.[62] The cholangiographical findings in IAC typically include distal bile duct stenosis, but proximal extrahepatic and intrahepatic bile ducts may also be

affected.[62] IAC is frequently associated with pancreatic involvement with a diffuse enlargement or a pancreatic mass (autoimmune pancreatitis).[59] IAC may also be associated with other fibrosing conditions. IAC is characterized by responsiveness to corticosteroid treatment that may result in resolution of symptoms and biochemical signs of cholestasis, reduction of serum IgG4 levels, as well as improvement or resolution of biliary strictures.[57,59,60] It is therefore important to be aware of this condition. Algorithms for the diagnosis and management of suspected IAC have been proposed.[57,62]

1.2.4 Therapy of PSC

Medical therapy

There are several difficulties related to the development of effective medical therapy in PSC. Since the aetiology and pathogenesis remain essentially unknown, the design of targeted, causal therapeutic approaches is hampered.[58,65-67] The apparent heterogeneity of the disease, the unpredictable disease course in the single patient, the overall slow disease progression and the relative scarcity of patients, are all factors that have contributed to make it difficult to perform sufficiently powered randomized, placebo-controlled clinical trials. There is currently no medical therapy that has been shown to definitely halt the disease progression in PSC.

Immunosuppressives and other agents. Several categories of drugs have been evaluated, including corticosteroids and other immunosuppressive agents (azathioprine, tacrolimus, ciclosporine A (CsA), methotrexate, mycophenolate mofetil (MMF)), TNF-α-antagonists (pentoxiphylline, etanercept, infliximab), antifibrotics (penicillamine, colchicine, pirfenidone), antibiotics (minocycline) and a group of miscellaneous compounds (cladribine, nicotine, probiotics).[67] None of these have proven to be effective in classical PSC, and several are associated with side effects. An exception applies to the subgroup of PSC patients who present with features of AIH who may benefit from immunosuppressive therapy.

Bile acids. The hydrophilic, dihydroxy bile acid, UDCA, is the drug that has been most extensively tested in PSC. Small pilot trials of UDCA showed improvement in biochemical parameters of cholestasis and liver histology using dosages of 10–15 mg/kg/day.[68,69] A larger, double-blind placebo-controlled trial in the US including 105 patients and UDCA at a dosage of 13-15 mg/kg/day for 2 years, confirmed improvement in biochemistry, but did not find improvement of symptoms, histology or disease progression.[70] In a Scandinavian randomized placebo-controlled study including 219 patients and UDCA dosage of 17-23 mg/kg/day for 5 years, there was a trend toward improved survival in the UDCA treated group, however, this did not reach statistical significance.[71] A more recent randomized double-blind controlled trial carried out in the US, including 150 PSC patients and a high dosage of 28-30 mg/kg/day of UDCA, was terminated because of an increased risk in the UDCA group for reaching the primary endpoints (death or liver transplantation (Ltx)).[72] There was a higher risk of serious adverse events in the UDCA treated patients, despite overall biochemical improvement. The mechanism for the unexpected detrimental effect of UDCA is not evident. A potential beneficial effect of UDCA on the risk of cholangiocarcinoma has been suggested, but no significant effect on this risk has been demonstrated in double-blind placebo-controlled trials.[71,72] Based on the sum of current evidence, international guidelines do not recommend a routine prescription of UDCA in PSC.[57,58] 24-*nor*UDCA, in which the side chain is reduced by one carbon atom, has been effective in an animal model of PSC.[73] Clinical studies of this compound are now in progress.

Symptoms and complications of PSC (*e.g.* pruritus, bacterial cholangitis, metabolic bone disease, complications of liver cirrhosis and portal hypertension) should be treated according to guidelines.[57,58]

Endoscopic therapy

Approximately 50% of PSC patients develop localized, high-grade strictures, so called “dominant” strictures during follow-up. These may cause symptoms of cholestasis and have a potential effect on prognosis. In an observational study, survival free of Ltx was significantly reduced in patients with a dominant stenosis (n=91) compared with those without (n=74) ($p = 0.038$).[74] Endoscopic therapy is

commonly used to treat such strictures, but no randomized, controlled trials have evaluated the efficacy or optimal method.[75] In any case, cholangiocarcinoma must be excluded, as far as possible. Both the EASL and the AASLD[57,58] guidelines recommend that dominant strictures with significant cholestasis should be treated with biliary dilatation, with or without stenting. A stent should be placed in cases where dilatation is unsatisfactory. Prophylactic antibiotics during such procedures is recommended. There are, however, still some unresolved issues: Which is the best endoscopic approach? What is the optimal duration of stent placement? What is the optimal frequency of procedures? What are long-term results? A multicenter, prospective, randomized intervention trial to compare the efficacy of single session balloon dilatation and short-term stenting is now ongoing in the International PSC Study Group (http://www.ipscsg.org/).

Liver transplantation

Ltx is the only curative therapy for PSC. In the Nordic countries, PSC is a major cause of Ltx, constituting approximately 17% of all indications.[76] Results of Ltx are favourable with 5-year survival rates close to 85%.[67] Selection for and timing of Ltx is difficult due to the variable disease course and the frequent and unpredictable occurrence of hepatobiliary malignancies. Primarily, the indication for Ltx is liver failure with complications, similar to those for end-stage liver disease of other causes.[58,67,77,78] PSC patients with liver cirrhosis are also at risk of developing hepatocellular carcinoma that may indicate transplantation in line with indications for other causes of this malignancy.[58] PSC patients with recurrent, severe bacterial cholangitis, intractable pruritus or severely impaired quality of life due to fatigue, should also be considered for transplantation.

The presence of cholangiocarcinoma is usually considered a contraindication to Ltx due to poor results.[78] In a previous study from the Nordic Liver Transplant Group, 17 liver transplanted PSC patients proved to have cholangiocarcinoma, and for this group of patients the 5-year survival was 35%.[79] This result may be improved by including patients with limited stage hilar tumors in a specific, extensive protocol comprising radiochemotherapy.[58,80] PSC patients with biliary brush cytology

dysplasia may benefit from Ltx,[81] and guidelines recommend that patients with evidence of cholangiocyte dysplasia are considered for Ltx.[57]

1.3 Inflammatory bowel disease

IBD is characterized by a chronic, relapsing inflammation in the gastrointestinal tract. It can be divided into UC and Crohn's disease (CD) based on clinical, endoscopic, histologic and radiological criteria.[82] In approximately 10% of cases an overlapping pattern exists; these are categorised as IBD unclassified.[83] UC is characterised by a uniform, diffuse mucosal inflammation, with a variable distribution from involvement limited to the rectum (proctitis) to total affection of the large intestine (total colitis). CD may occur in all parts of the gastrointestinal tract and involves the entire bowel wall. At endoscopy, the picture is dominated by rectal sparing, apthous ulcers, skip lesions (areas of inflammation alternating with normal mucosa), cobblestone pattern and longitudinal irregular ulcers.

The most frequent symptom of UC is visible blood in the stools (>90%) with associated symptoms such as decrease in stool consistency, diarrhoea, abdominal pain, malaise, fever and weight-loss, depending on the severity and extension of the disease.[84] The prognosis of UC is reported to be usually good during the first decade of disease with a low rate of colectomy (9.8%) and remission in most patients (55%).[85] The disease is often (21-47%) associated with extra-intestinal manifestations, most commonly with affection of the eyes, joints, skin, liver and bile ducts.[86] Whereas manifestations involving the skin, eyes and joints often parallel the disease activity in the gut, the hepatobiliary manifestations do not appear to correspond to the IBD activity.[87]

1.3.1 Epidemiology of IBD

The incidence and prevalence of UC and CD are increasing and linked to westernised environment and lifestyle.[88] The highest occurrence of IBD is reported in Northern Europe and North America. In a recent systematic review by Molodecky et

al., the annual incidence of UC and CD was found to be, respectively, 24.3 and 12.7 per 100.000 person years in Europe, 19.2 and 20.2 in North America and 6.3 and 5.0 in Asia and the Middle East (table 2).[88] The highest reported prevalence values for UC and CD were found to be, respectively, 505 and 322 per 100.000 person years in Europe and 249 and 319 in North America (table 3).[88]

1.3.2 Pathogenesis of IBD

IBD is precipitated by a complex interaction of environmental, genetic and immunoregulatory factors. Regardless of the underlying genetic predisposition, a growing body of data implicates a dysfunctional mucosal immune response to commensal bacteria in the pathogenesis of IBD, especially in CD. Possible triggers include a chronic inflammatory response precipitated by infection with a particular pathogen or virus or a defective mucosal barrier. The characteristic inflammatory response begins with an infiltration of neutrophils and macrophages, which then release chemokines and cytokines. These in turn exacerbate the dysfunctional immune response and activate either TH1 or TH2 cells in the gut mucosa, respectively associated with CD and, less conclusively, with UC. Elucidation of immunological and genetic factors indicate multiple points at which the inflammatory cascade may be interrupted, yielding the possibility of precise, targeted therapies for IBD.[89]

1.3.3 Colorectal dysplasia and cancer in IBD

IBD patients with colonic inflammation have an increased risk of colorectal cancer.[90] The magnitude of the risk, however, varies considerably in the literature and is a constant topic of debate.[91,92] Some studies use data from tertiary referral centres or population-based studies, while others are based on small case series or individual case reports. The patients at greatest risk for the development of colorectal cancer are those with disease in the colon extending to the hepatic flexure or even more proximally (pancolitis). An overview of the factors associated with colorectal cancer in IBD is presented in figure 1.[93] Approximately 8 to 10 years after the onset of symptoms, the risk of cancer begins to increase when compared to age-matched

controls.[94-96] The approximate cumulative incidence of cancer is 5-10% after 20 years and 12-20% after 30 years of disease.[94,96-98] In contrast, when colitis is limited to the left colon, most studies have found that the risk of developing colorectal cancer increases first after 15 to 20 years.[99] Ulcerative proctitis likely does not place patients at greater risk for colorectal cancer.[100] In a meta-analysis from 2001, comprising 116 studies, Eaden et al. estimated the risk for cancer in patients with UC to be approximately 2% after 10 years, 8% after 20 years and 18% after 30 years of disease.[90]

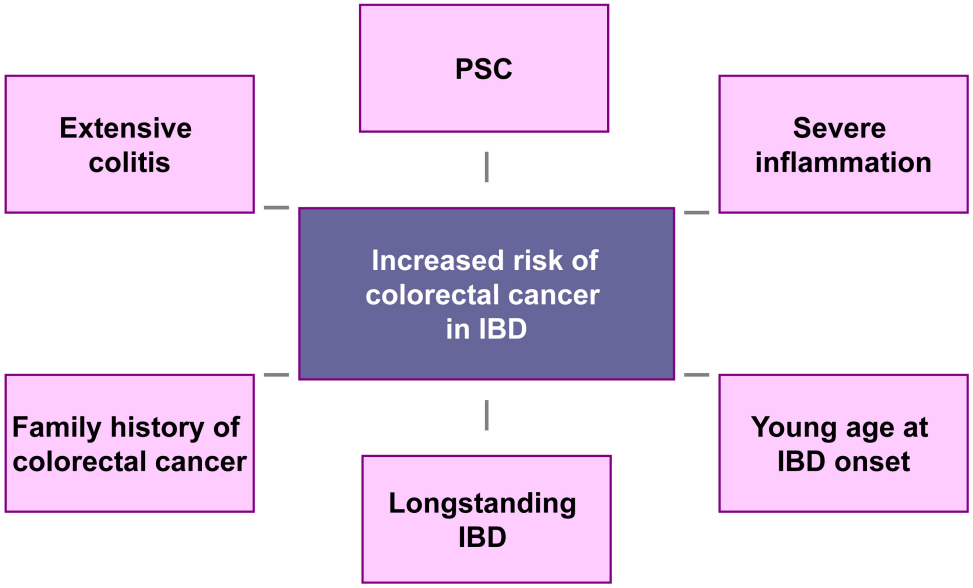

Figure 1. Risk factors for development of colorectal cancer in IBD

Like in other cancers, IBD-associated colorectal carcinogenesis is believed to follow a multistep process from inflamed, regenerative epithelium, to hyperplastic epithelium, to flat dysplasia and finally to invasive adenocarcinoma.[101,102] The interaction of macrophages and neutrophils with the colonic epithelial cell plays a pivotal role in IBD-induced carcinogenesis. The interplay between reactive oxygen/nitrogen species overproduction, key arachidonic acid metabolites and cytokines/growth factors and activated inflammation-associated signal transduction pathways, along with immune system dysfunction, may contribute to the multistep

progression of IBD-associated carcinogenesis.[103,104] Molecular alterations in IBD-associated colon cancer, similar to sporadic colorectal cancer, include accumulation of gene mutations in tumor suppressor genes, oncogenes and DNA repair genes, as well as genomic instabilities such as aneuploidy, chromosome instability and microsatellite instability. Although similarities exist in the molecular pathogenesis of IBD-associated and sporadic colorectal cancer, there are also many differences, as illustrated by figure 2. The timing and frequency of the molecular genetic alterations are unique and are believed to result from different etiologic factors and cellular microenvironments.

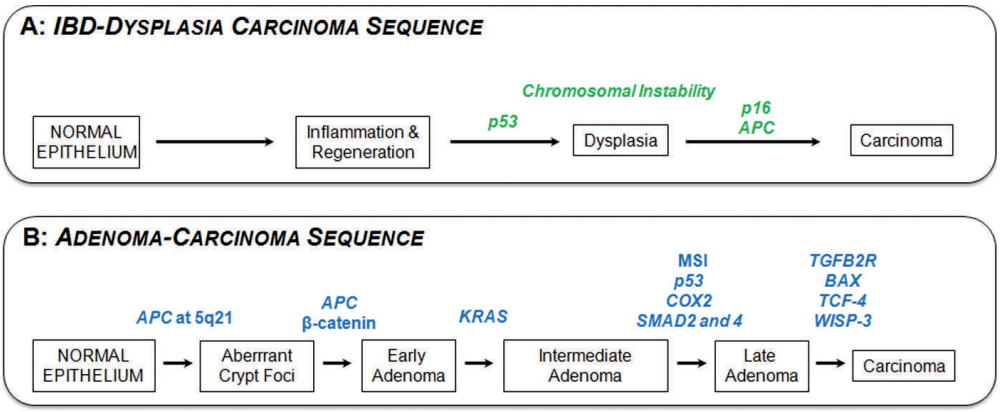

Figure 2. Carcinoma sequence pathway. (A) The IBD-associated carcinoma pathway with earliest identified molecular changes in p53, followed by chromosomal instability and finally β-catenin/WNT signaling. (B) The adenoma-carcinoma sequence with a stepwise progression of mutational activation of oncogenes and inactivation of tumor suppressor genes, resulting in cancer. (Matkowskyj et al., Acta Pathol Lab Med 2013, with permission)[101]

1.3.4 Medical therapy of IBD

Conventional medical therapies for UC and CD include aminosalicylates, corticosteroids, thiopurines, methotrexate and biologic compounds such as anti-tumour necrosis factor agents, in addition to combinations with certain antibiotics. Although conventional drugs are the mainstay of current therapy in IBD, timely surgery must be considered. Algorithms for guidance of therapy have been suggested to provide optimal management of patients.[105] The treatment algorithm for mild-to-moderately active UC is displayed in figure 3.

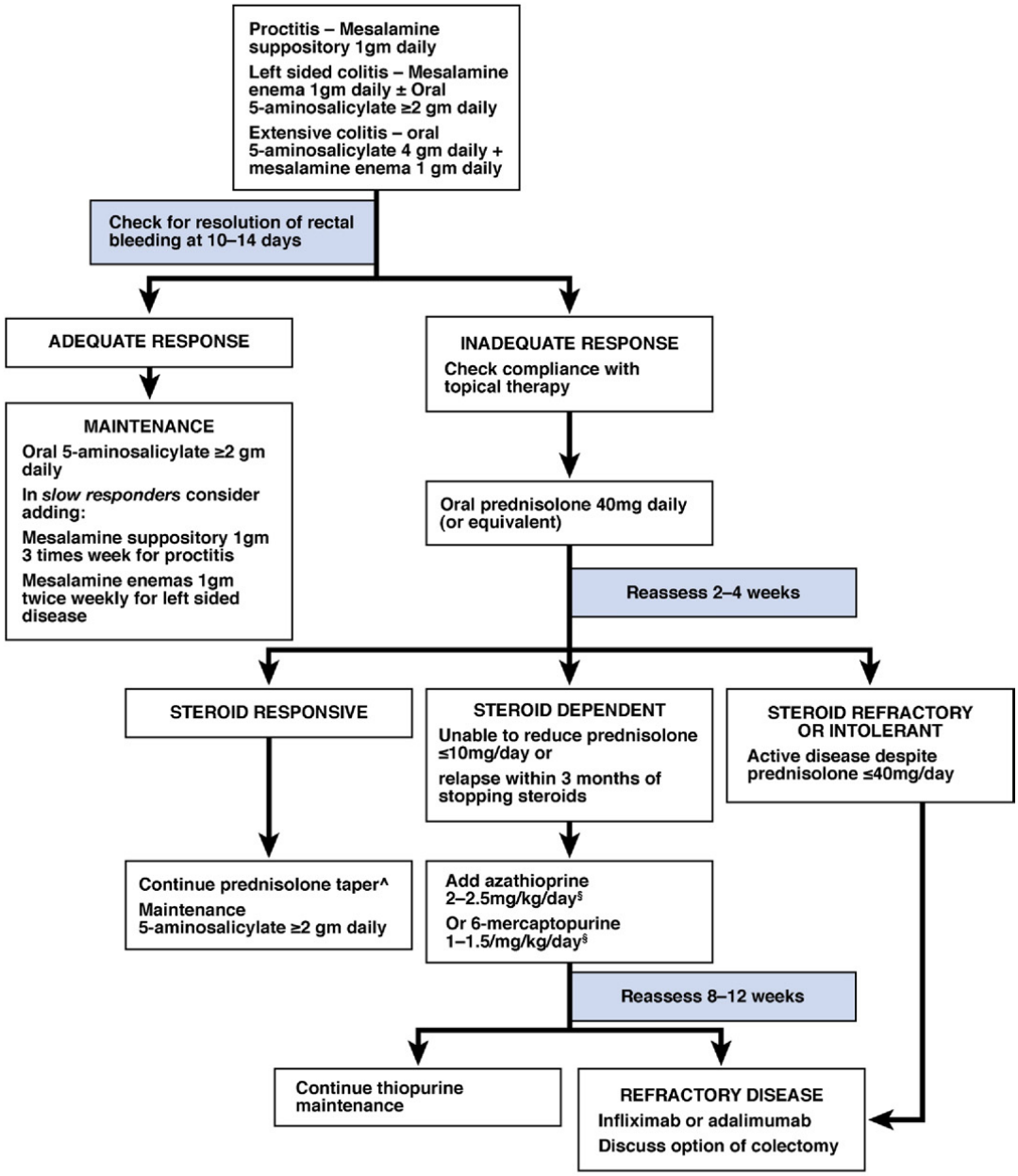

Figure 3. Management algorithm for mild-to-moderatly active UC. (Burger and Travis, Gastroenterology, 2011, with permission)[105]

1.4 Characteristics of PSC-IBD

1.4.1 General characteristics of PSC-IBD

PSC is strongly associated with IBD, with a prevalence of IBD in PSC as high as 60-80% in patients of Northern European descent whereas the prevalence has been found to be considerable lower (20-25%) in Asian studies (table 4).[1-3,11,12,15,16,18-20,106-125] UC accounts for the majority of cases (around 80%). Approximately 10% of cases are diagnosed with CD and 10% are classified as indeterminate colitis. Conversely, the reported prevalence of PSC is in the range 2-7.5% in UC patients and 1.4-3.4% in patients with CD (table 5). [86,116,126-136] IBD can develop both before and after diagnosis of PSC and also after Ltx (*de novo* IBD). The bowel disease is, however, most commonly diagnosed several years before PSC.[137] Previous studies have suggested that IBD in PSC differs phenotypically from IBD unrelated to hepatobiliary disease regarding several aspects. PSC-IBD patients appear to have an increased incidence of pancolitis, rectal sparing and ileal involvement compared to IBD patients without hepatobiliary disease.[138] In a case-control study, Loftus et al. found that 87% of the 71 PSC patients included had pancolitis compared to 54% in the control group consisting of 142 UC patients.[138] The frequencies of rectal sparing and terminal ileitis were 52% and 51%, respectively, in the PSC patients compared to 6% and 7%, respectively, among the controls.[138] IBD in PSC also seems to have a milder course.[139] In addition, PSC-UC patients with an ileal pouch-anal anastomosis (IPAA) seem to be more prone to develop chronic pouchitis than UC patients without PSC (60% vs. 15%).[140]

Some of the genetic associations detected in PSC overlap with known associations in IBD, but there are also distinct differences that comprise both HLA- and non-HLA genes (figure 3).[32,141] Among the 16 established PSC associated loci (counting several associations within the HLA region as one locus), only 8 also display significant association in IBD. Among the 163 currently known IBD associated loci, only 8 are significantly associated to PSC.

A majority of the performed clinical studies regarding IBD in PSC have important limitations with a limited number of patients included and a retrospective design. A larger, prospective study with a thorough assessment of the clinical features of IBD in PSC could therefore bring new insight in this field.

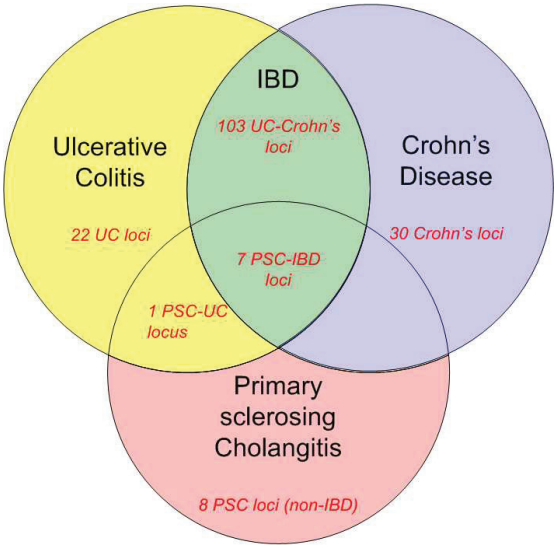

Figure 4. Venn diagram illustrating 163 IBD- and 16 PSC susceptibility loci and the overlap between them. Multiple associations within the HLA region are counted as one locus, both for PSC, ulcerative colitis and Crohn`s disease.

1.4.2 Colorectal neoplasia in PSC-IBD

Several studies have shown that PSC-IBD patients have a higher risk of colorectal malignancies than IBD patients without hepatobiliary disease,[7,9,142-151] although these findings have not been universally agreed upon.[10,152,153] In an early study, Broomé et al. matched 40 PSC-UC cases with 80 UC controls, where both groups were under endoscopic surveillance. The cumulative risk for colorectal neoplasia at 10, 20 and 25 years after diagnosis of IBD was 9, 31 and 50%, respectively, in the PSC-UC group, compared to 2, 5 and 10%, respectively, in the control group.[142] When Loftus et al. at the Mayo Clinic compared a group of 178 PSC-UC patients with the general population, a tenfold increase in risk of colorectal cancer (relative risk (RR) 10.3, CI

2.1-30) was displayed.[152] However, no significantly elevated risk was found when compared to a population-based Swedish UC control group.[152] Conversely, a metaanalysis from 2002 showed a fourfold increase in the risk of colorectal neoplasia in PSC-UC (OR 4.8, CI 3.6-6.4) when comparing 16.280 UC patients with 564 PSC-UC patients.[7]

PSC patients with CD are also found to have an increased risk of colorectal neoplasia. In a recent study, Lindström et al. showed that a study group of 28 PSC-CD patients were more likely to develop colorectal neoplasia than a matched control group of 46 CD patients (OR 6.8, CI 1.65-27.9).[154] On the contrary, Braden et al. did not find that the presence of PSC increased the risk of colorectal neoplasia in a group of patients with colonic CD.[155]

Earlier studies have displayed some clinical characteristics regarding colorectal neoplasia that diverge between PSC-IBD and IBD patients. PSC patients tend to be younger at onset of IBD and at diagnosis of colorectal cancer.[150,156] Yet, the time span between onset of IBD and colorectal cancer seems to be similar.[145,156,157] The distribution of malignancy in the colon tends to be right-sided in PSC-IBD whereas it is shown to be more widespread in IBD.[143,144,148,150,157] In one study from the Netherlands, IBD patients with colorectal cancer with and without PSC were compared and right-sided tumors were found to be more prevalent in the PSC group (67% vs. 36%). Additionally, tumors in patients with PSC were also found to be more advanced.[157]

The diverging clinical characteristics between IBD patients with and without PSC may suggest a different colorectal carcinogenesis in PSC-IBD and IBD patients. The possible mechanisms behind this difference in cancer risk are, however, unclear. It has been speculated if PSC simply acts as a surrogate marker for a subclinical, long-standing colonic inflammation.[139,158] Interestingly, one study has recently shown an association between development of colorectal cancer (in addition to cholangiocarcinoma and gall bladder cancer) and a dominant bile duct stenosis in PSC patients with concomitant IBD.[74] One hypothesis is that the tendency of right-

sided colonic neoplasia in PSC-IBD could be due to alterations in the composition and concentration of the bile salt pool in PSC patients that leads to a high concentration of toxic secondary bile acids in the colon.[143,159] In both animal and human studies, exposure of cells of the gastrointestinal tract to high levels of bile acids has been shown to be an important risk factor for cancer.[160] This theory has been supported by earlier studies of UDCA, indicating preventive effects on the development of colorectal cancers in PSC.[161,162] On the other hand, the fact that PSC patients without IBD do not seem to have an increased risk of colorectal neoplasia suggests that other mechanisms (*i.e.* genetic factors) might play a role in the colorectal carcinogenesis.[8]

1.5 Chemoprevention in PSC-IBD

Although 5-aminosalicylic acid (5-ASA) and thiopurine analogues have been considered as potential chemopreventive agents against dysplasia and cancer in IBD, no agents have been shown to have indisputable chemopreventive activity in IBD. Steroids, folic acid and UDCA have been considered promising in a few population based, as well as in retrospective and in case control studies.[163]

1.5.1 5-ASA

In addition to reduce inflammation, 5-ASA has been shown to decrease epithelial cell turnover and promote apoptosis in laboratory research. A metaanalysis including 9 studies showed a protective association between the use of 5-ASA and colorectal neoplasia (OR 0.51).[164] However, several of the studies included in this analysis lack statistical power since they have been predominantly observational, have included a small number of patients and have not taken into account important information regarding for example extent and duration of UC and use of concomitant medication. Later published, more robust studies have not shown the same degree of protective association of 5-ASA as previously described. The European Crohn's and Colitis Organisation (ECCO) recommends however in their guidelines that all UC patients should be considered for chemopreventive treatment with 5-ASA.[165]

1.5.2 UDCA

A few retrospective studies have shown a potential chemopreventive effect of UDCA on colorectal neoplasia in PSC patients with IBD. In a study including 59 PSC patients with UC undergoing colonoscopic surveillance, patients receiving UDCA experienced a significantly reduced prevalence of colonic dysplasia, but the rate of dysplasia in the control group of this study was exceptionally high.[162] In a follow-up of 52 PSC patients with concomitant UC who participated in a placebo-controlled trial, UDCA (13-15 mg/kg/day) was also associated with a significantly reduced risk of developing colorectal dysplasia or cancer.[161] Other the other hand, there are also studies that do not support a chemopreventive effect of UDCA on colorectal cancer. In a study comparing 28 PSC-UC patients receiving UDCA with 92 untreated patients, the cumulative incidence of dysplasia or cancer was not significantly different between cases and controls.[159] In a retrospective analysis of the study of high-dose UDCA (28-30 mg/kg/day) mentioned above,[72] the risk of colorectal neoplasia was even higher in the UDCA- than in the placebo group (hazard ratio (HR) 4.4, 95% CI 1.30-20.10, p = 0.02).[166] Guidelines diverge in their recommendation regarding the use of UDCA as a chemoprophylactic agent. ECCO recommends the use of UDCA in PSC-IBD, the European guidelines suggest that UDCA should be considered in patients with a strong family history of colorectal cancer, previous colorectal neoplasia or longstanding extensive colitis, whereas the AASLD actually recommends against the use of UDCA .[57,58,165]

1.6 Neoplasia surveillance in IBD and PSC-IBD

Surveillance colonoscopy with multiple biopsies is recommended for all IBD patients at risk of developing colorectal neoplasia. The intensity of the program should, however, be dependent on the estimated risk in each individual patient. Nevertheless, it has not been proven in prospective studies that such a precaution increases survival.[165,167] According to guidelines, a screening colonoscopy to reassess disease extent is recommended 8-10 years after onset of IBD.[165] Four random biopsies every 10 cm of the colon should be performed and extra biopsies should be taken from abnormal areas. Chromoendoscopy with targeted biopsies of visible lesions has proven to be superior of random biopsies for detection of

neoplastic lesions.[168] In high-risk patients (*i.e* extensive colitis) surveillance should start after the screening colonoscopy. In patients with moderate risk (*i.e*. left-sided or distal inflammation) the surveillance should start at a later stage, whereas patients without increased risk (proctitis) do not require further surveillance.[165] If high-grade dysplasia (HGD) or adenocarcinoma is detected, a proctocolectomy should be performed. The further approach after the finding of low-grade dysplasia (LGD) regarding surgical treatment or more intensified surveillance should be individually tailored. In PSC, guidelines recommend full colonoscopy with biopsies at time of diagnosis, independently of IBD symptoms.[58,165] After diagnosis of IBD, surveillance colonoscopy is recommended at 1-year to 2-year intervals.[58,165] Some experts recommend a repeated colonoscopy after 4 years in PSC patients with a normal initial endoscopy, even if IBD symptoms are lacking.[169]

1.7 PSC-IBD after liver transplantation

1.7.1 Effect of Ltx on the clinical and endoscopic course of IBD

One might anticipate that the clinical course of pre-existing IBD in PSC should improve after Ltx, given that some of the immunosuppressive drugs administered after Ltx are proven to be effective treatment of refractory IBD. Previous studies have, however, demonstrated conflicting results (table 6a).[170-188] Some studies have depicted a mainly unchanged or improved course of IBD in PSC after Ltx,[172,175,183] whereas others have found disease deterioration in a majority of patients.[173,178,182,187] In the largest study up to now, Dvorchik et al. showed an increased rate of colectomy due to active disease after Ltx compared to that before Ltx (HR 3.1, $p = 0.001$).[178] In contrast, van de Vrie et al. showed no alteration of IBD after Ltx.[175] Maclean et al. displayed highly variable IBD activity post Ltx with one third of patients experiencing an improved course, on third an unchanged course and one third a worsened course.[179] The reasons behind the reported variable activity of IBD post Ltx are not clear. Some previous studies have shown that factors like younger age at IBD diagnosis, smoking at time of Ltx, use of tacrolimus and cytomegalovirus (CMV) infection post Ltx are associated with active inflammation post Ltx.[173,177,180,188] Conversely, a combined HLA-DR and DQ disparity between donor and recipient, use

of 5-ASA, use of steroids and use of azathioprine alone or in combination with CsA and steroids have been shown to have a protective effect. [171,173,176,187] In cases of active IBD post Ltx, the course tends to be aggressive and induction and maintenance of remission can be very challenging.[173,176,182]

IBD can also occur *de novo* after Ltx (table 6b),[170,173,175-177,182,187,188] and the annual incidence after solid organ transplantation has been shown to increase tenfold compared to the expected incidence in the general population.[189] In PSC, the development of *de novo* IBD could, to some extent, be related to the expected incidence of naturally occurring IBD. *De novo* IBD tends to develop later in the course post Ltx compared to relapse of pre-existing IBD. In a study by Haagsma et al. the median time from Ltx to *de novo* IBD and to relapse of IBD was 3.9 years and 1 year ($p = 0.045$), respectively.[173] The cumulative risk of *de novo* IBD 1, 3, 5 and 10 years post Ltx was 0, 4, 11 and 14%, respectively, and the risk of exacerbation of IBD was 20, 28, 39 and 39%, respectively.[173] Promoting factors for development of *de novo* IBD have been shown to be CMV infection, CMV mismatch between donor and recipient and use of tacrolimus.[173,176,177] Use of azathioprine has shown protective effects.[173] *De novo* IBD seems to respond better to medical therapy than relapsing IBD post Ltx.[176,190]

1.7.2 Effect of Ltx on colonic neoplasia

There has been a concern that Ltx could increase the risk of colorectal neoplasia due to the immunosuppressive treatment given.[137,191] In contrast, it has also been speculated if Ltx could act as a protecting factor because of correction of cholestasis as a consequence of a normal functioning liver. Earlier studies have reported conflicting results regarding this issue (table 7).[174,175,178,181,182,185,186,191-195] In a study by Loftus et al. the risk of colorectal carcinoma post Ltx was found to be increased fourfold, although not significantly so, compared to a historical cohort of non-transplanted PSC-IBD patients.[193] In contrast, a recent study from Cleveland, Ohio, displayed a similar rate of colorectal cancer when comparing liver transplanted and non-transplanted PSC-IBD patients.[195] However, a higher rate of colorectal cancer was found post Ltx when comparing PSC and non-PSC patients,[195] confirming the

results of a former study.[194] In a study by Dvorchik et al., Ltx was not found to have any influence on the incidence of colorectal cancer in a cohort of 192 PSC-IBD cases.[178] Earlier studies have found colorectal dysplasia, duration of IBD > 10 years and pancolitis to be risk factors for development of colorectal cancer post Ltx.[194] Additionally, one study has shown CMV infection post Ltx to be a risk factor for colorectal dysplasia and cancer.[195]

Due to small sample sizes, possible referral biases and discrepancy in study design and statistical methods used in earlier studies, the impact of Ltx on both the activity of IBD and the risk of colorectal malignancies in PSC-IBD post-transplant remains unsettled and calls for further studies.

2. Aims

The aims of the present thesis were to study the characteristics of IBD in PSC, in particular the clinical disease activity and the development of colorectal neoplasia, both in liver transplanted and non-transplanted patients. The specific aims were:

1. To describe the clinical, endoscopic and histopathologic features of IBD in a large, nationally centralised cohort of PSC patients.

2. To assess the overall risk of colorectal neoplasia in PSC patients undergoing Ltx and to compare this risk before and after the transplantation. We also aimed to identify risk factors for the development of colorectal neoplasia post Ltx, in a longitudinal follow-up of a large Nordic PSC-IBD cohort undergoing Ltx.

3. To describe the natural history of IBD in liver transplanted PSC patients by comparing the clinical course of IBD before and after Ltx and to identify factors associated with altered activity of IBD post Ltx, in a longitudinal follow-up of a large Nordic PSC-IBD cohort undergoing Ltx.

3. Material and methods

3.1 Patient selection and design

Paper I depicts the characteristics of IBD in a prospective, cross-sectional study in a nationally based cohort of PSC patients (n=184) admitted to the Medical Department, Oslo University Hospital, Rikshospitalet, between September 2005 and September 2008. Of these, 164 patients were consecutively included, whereas 20 liver transplanted patients were called upon since they were not scheduled for follow-up in the study period. The cause of referral was primarily related to the patients` liver disease, the majority being referred for either confirmation of diagnosis, management of PSC, or follow-up after Ltx. The patients underwent a clinical evaluation including ileocolonoscopy with assessment of segmental histopathology at inclusion. One investigator (KKJ) assessed the clinical data from the patient records, interviewed the patients and carried out the majority of the endoscopic examinations. The histopathologic evaluation was performed blindly according to a standardised protocol by an experienced pathologist (KG). Additionally, biopsies from 24 randomly selected study patients were evaluated independently by another, experienced pathologist (OPFC).

In papers II and III the Nordic Liver Transplant Registry was used to identify all PSC patients (n=461) undergoing Ltx from November 1984 through December 2006 in Denmark (Copenhagen), Finland (Helsinki), Norway (Oslo) and Sweden (Gothenburg, Stockholm).[76] With a retrospective, longitudinal study design, the characteristics of IBD regarding disease activity and development of colorectal neoplasia were described. Twenty-two patients were excluded due to lack of histopathologic confirmation of PSC in the explanted liver or loss to follow-up. All 439 included patients were regularly followed up at the transplant centres. The medical records of the patients were reviewed by one experienced physician at each transplant centre. The patients were included at time of diagnosis of IBD and they were followed through Ltx until last clinical follow-up. Colorectal neoplasia and parameters regarding activity of IBD were recorded and the findings before and after Ltx were compared.

3.2 Diagnostic criteria

PSC was diagnosed according to accepted criteria, with typical findings of bile duct irregularities on cholangiography.[3] In patients with normal cholangiography, small duct PSC was diagnosed based on the histopathologic findings in liver biopsies.[46] The diagnosis of IBD was based on conventional clinical, endoscopic and histopathologic criteria.[3,196-198]

3.3 Statistical analysis

Data were described with proportions for categorical variables and median with range for continuous variables. Crude associations between categorical variables were assessed with Chi-square test or the Fisher's exact test, when appropriate. Comparisons between groups with respect to continuous variables were performed using Mann-Whitney test. For comparison of dependent observations McNemars test was used. Crude patient survival after Ltx and cumulative risk of *de novo* IBD free survival were calculated using the Kaplan-Meier method and survival times were compared with the log-rank test. In paper I, Cohen's kappa was used to investigate the reliability between the pathologists. A linear-by-linear trend test was used to see if there was a systematic change of segmental active inflammation from the caecum to the rectum. In papers II and III the possible effect of medication and other factors on the development of colorectal neoplasia and the course of IBD post Ltx were studied using a Cox proportional hazards model. Firstly, we fitted univariate models and secondly, we performed multivariate analyses. Since there was a potential difference in the detection rate of both activity of IBD and neoplasia given the selected centres, we stratified all analyses by centres.

In paper II the cumulative risks of colorectal neoplasia in PSC-IBD patients both overall and before and after Ltx were estimated using competing risk regression analyses.[199,200] The diagnosis of neoplasia was defined as the main event of interest and death and colectomy for other reasons than neoplasia were the competing events.[199] For comparison purposes, a Cox model was used to calculate the cumulative hazard of neoplasia before and after Ltx. To investigate the effect of IBD

duration on the risk of neoplasia after Ltx, a competing risk regression model was fitted with neoplasia being the main event and death and colectomy for other reasons than neoplasia the competing events.

In paper III the different outcomes in IBD activity post Ltx were presented as percentages with 95% CI. CI was constructed using the normal distribution approximation. The severity of IBD activity pre- and post Ltx in each patient and the relapse rate before and after Ltx were compared using Wilcoxon signed ranks test for paired data. The cumulative risks of colectomy due to refractory IBD before and after Ltx were estimated using competing risk regression analysis where colectomy for refractory IBD defined the main event of interest and colectomy due to other reasons and death were the competing events.[199,200]

Due to the small number of CD patients included, a comparison between the IBD subgroups (CD and UC) with regard to risk of colorectal neoplasia[154,155] and disease activity[201,202] was not performed.

P-values ≤ 0.05 were considered statistically significant. All statistical analyses were performed with SPSS version 18 and Stata version 11.

3.4 Ethics

In paper I the study was approved by the Regional Committee for Research Ethics in South Eastern Norway and the patients gave their informed consent. In paper II and III the studies were approved by the ethical committees in the respective countries.

4. Summary of the results

Paper I

In the included PSC cohort, 155 (84%) of 184 patients had IBD; 134 were initially diagnosed as UC, 15 as CD and six as IBD unclassified. In the liver transplanted group, colectomy had been performed in 15/60 (25%) patients (10 refractory disease, 3 neoplasia, 1 both, 1 other). In the non-transplanted group, 24/95 (25%) patients had undergone colectomy (15 refractory disease, 6 neoplasia, 3 both). The patients with an intact colon and complete tissue samples (n=110) were further investigated. The median time since diagnosis of IBD was 11 (0-50) years. Forty-two (38%) patients had undergone Ltx with a median follow-up post Ltx of 3 (0-19) years. A majority (65%) of patients had a long-term clinical remission. Inflammatory findings were more frequent by histology than by endoscopy (89% vs. 47%, $p<0.001$). Histopathological signs of inflammation involved the right colon in 86% of patients and were purely right-sided in 23%. The general inflammatory activity was low, but higher in the right compared to the left colon ($p<0.001$). Terminal ileitis was present in 20% (17/87) of patients and rectal sparing in 65% (70/107). The liver transplanted patients had lower clinical ($p=0.035$) and histological ($p=0.013$) IBD activity than the non-transplanted group. In conclusion, our findings support the hypothesis that PSC-IBD may represent a distinct entity of colitis.

Paper II

Among the 439 PSC patients included, 353 (80%) had IBD at the time of Ltx and 15 (3%) patients developed *de novo* IBD post Ltx. The median duration of IBD was 15 (0-50) years at the time of Ltx and follow-up after Ltx was 5 (0-20) years. IBD was diagnosed before, simultaneously with and after PSC in 243 (66%), 43 (12%) and 82 (22%) of patients, respectively. Ninety-one (25%) PSC-IBD patients developed colorectal neoplasia with a cumulative risk of neoplasia of 6.4% and 17%, 10 and 20 years after diagnosis of IBD, respectively. The cumulative risk of colorectal neoplasia was higher after than before Ltx (HR 1.9, 95% CI 1.3-2.9, $p=0.002$). A multivariate analysis demonstrated aminosalicylates and UDCA to be significantly associated with an increased risk of colorectal neoplasia post Ltx (HR 2.6, 95%CI 1.0-6.6, $p=0.041$ and 4.0, 95% CI 1.4-11.4, $p=0.011$, respectively). Neither duration nor activity of IBD was significant risk factors. Likewise, treated rejections and CMV infections did not

significantly contribute to an increased risk of colorectal neoplasia. The results underscore the importance of regular surveillance colonoscopies in PSC-IBD patients, also after Ltx. The novel association of aminosalicylates and UDCA to colorectal neoplasia in liver transplanted patients warrants further studies.

Paper III

The 218 among the 353 PSC-IBD patients who had an intact colon and had undergone pre- and post Ltx colonoscopies, were further characterized. Macroscopic colonic inflammation was more frequent after than before Ltx (153 vs. 124 patients, $p<0.001$). The degree of inflammation after Ltx was improved in 37 (17%), unchanged in 93 (43%) and worsened in 88 (40%) patients ($p<0.001$). The relapse rate after Ltx was higher than that before ($p<0.001$). The overall clinical IBD activity was also increased after Ltx ($p<0.001$). In addition, the cumulative risk of colectomy due to active disease after Ltx was increased compared to the corresponding risk before Ltx, although not reaching statistical significance (HR 1.4, 95% CI 0.4-1.2, $p=0.22$). Young age at diagnosis of IBD and dual treatment with tacrolimus and MMF were significant risk factors for worsened IBD activity post Ltx (HR 1.8, 95% CI 1.1-2.9, $p=0.011$ and HR 3.9, 95% CI 1.9-7.9, $p=0.001$, respectively), whereas combination treatment with CsA and azathioprine showed a protective effect (HR 0.4, 95% CI 0.2-0.9, $p=0.043$). Neither use of aminosalicylates, steroid- and antithymocyte globulin (ATG)/ muromonab-CD3 (OKT3) treated rejections nor treated CMV infections were significant risk factors. In conclusion, IBD activity in PSC-IBD patients increases after Ltx and appears to be related to the immunosuppressive regimen. CsA and azathioprine should be considered an alternative maintenance treatment in liver transplanted PSC patients.

5. Discussion

This thesis describes the clinical characteristics of IBD in PSC, both in a national cohort (study I) and in a Nordic cohort of liver transplanted patients (studies II and III). In study I, we found that the majority of patients had a long term clinical remission of IBD. The histopathological signs of inflammation involved the right colon in the majority of cases and although the general inflammatory activity was low, it was higher in the right compared to the left colon. The overall IBD activity was lower in liver transplanted than in non-transplanted patients. In study II, we estimated the overall risk of colorectal neoplasia to be 6.4% and 17% at 10 and 20 years, respectively, after diagnosis of IBD. The risk was significantly higher after compared to before Ltx, also when taking duration of IBD into account. Aminosalicylates and UDCA were significantly associated with an increased risk of colorectal neoplasia post Ltx. Study III showed an increased inflammatory activity after compared to before Ltx regarding macroscopic colonic inflammation, relapse rate and overall clinical IBD activity. There was also a trend towards a higher risk of colectomy due to active IBD post- as compared with pre Ltx. Young age at diagnosis of IBD and dual treatment with tacrolimus and MMF were significant risk factors for increased IBD activity post Ltx, whereas combination treatment with CsA and azathioprine showed a protective effect.

Our studies comprise the highest number of PSC patients included up to now in this field of research, both regarding the characterization of PSC-IBD and the comparison of IBD activity and risk of colorectal neoplasia before and after Ltx. The results of the studies provide novel knowledge about IBD in PSC and raise new questions that call for future studies.

5.1 Methodological considerations

5.1.1 Patient selection

In paper I, we included all PSC patients admitted to the Medical Department, Oslo University Hospital, Rikshospitalet, during a three year period. This study might be

regarded as population based since our centre has access to PSC patients from all over the country, being both the single transplant centre and the only third line PSC referral centre in Norway. However, we most likely do not see all of the patients with limited, uncomplicated PSC. In addition, the majority of patients are referred to us because of liver related- and not IBD related reasons. Even if a clear correlation between the severity of PSC and IBD is highly questionable,[202-206] these factors might contribute to a referral bias. If taking into account the reported prevalence of PSC in Norway,[14] our cohort constitutes almost half of the estimated number of present Norwegian PSC patients.

In papers II and III, the Nordic Liver Transplant Registry was used to identify the liver transplanted PSC patients. This registry has been continuously updated since the first Ltx was performed in 1983 and it contains a complete survey of the Nordic liver transplanted patients. In these studies, the patient inclusion was almost complete, only 5% of patients were excluded (due to a lack of histopathologic confirmation of PSC in the explanted liver or loss to follow-up). All included patients had been regularly followed up and the clinical data were carefully recorded by experienced physicians at each transplant centre. Due to the high number of patients in the registry, the high inclusion rate and the completeness of data, we regard this cohort as highly representative of transplanted PSC patients.

5.1.2 Design

Paper I contains the first prospectively performed study with a systematic assessment of clinical, endoscopic and histopathologic characteristics of IBD in PSC. With the cross sectional design and the high number of patients included, we consider our results a valuable contribution to the existing literature on the characteristics of IBD in PSC. The most important limitation of the study is, however, the lack of a control group. The ideal control group would have been a population-based UC cohort without hepatobiliary disease, matched for gender, age and disease duration and ongoing medication accounted for. Unfortunately, we were not able to include such patients in our study. As described above, the PSC patients are referred to our centre mainly due to the hepatobiliary disorder and not because of IBD issues.

The IBD cohort followed at our institution was regarded as unsuitable as a control group because of a high grade of selection due to our status as a third line referral center for patients with complicated IBD. Establishing a prospective population based control group at another institution was considered difficult because of a presumably long inclusion period and a time consuming and resource demanding study inclusion. Nevertheless, we regard the results of study I as valuable because it, with the cross sectional design, describes PSC-IBD patients as they present in clinical practice. Moreover, it is possible, to some extent, to compare these patients with published population based cohorts of IBD patients without hepatobiliary disease.[85]

The approximately 3000 biopsies taken (four biopsies from each of the six colonic segments and four from the terminal ileum on each occasion) were assessed by one experienced pathologist (KG). Twenty-four (22%) of the 110 patients in the cohort were picked randomly and approximately 700 tissue samples were evaluated blindly by another experienced pathologist (OPFC). Based on former common practice, one fourth of the cohort was regarded as an adequate number for assessing interrater agreement. The percentage of agreement was calculated to evaluate the reliability of the interpretation of the histopathological evaluations. The detailed accordance regarding inflammatory changes in each recorded segment is displayed in table 8. The overall interrater agreement between the two pathologists was 70%, which is considered as good according to commonly used definitions.[207] The agreement was highest in chronic active inflammation (90%) and lowest in goblet cell depletion (59%). Likewise, the accordance was highest in evaluating the terminal ileum (97%) and lowest in the cecum (38%). The reason for this variability is not quite clear. It can not be excluded that other factors besides direct interrater variations, like technical qualitites, changed rating conditions and day to day variation might be responsible for these differences.

Papers II and III have a multicenter, retrospective, longitudinal, observational design. Due to the increased risk of colorectal neoplasia, all Nordic PSC patients undergo repeated colonoscopies and we assessed what we consider the most relevant colonoscopies relative to Ltx and the disease course post Ltx. We cannot rule out that inter- and/or intra-observer variability regarding the macro- and microscopic

evaluation of colonic inflammation and neoplasia might have influenced our results to some extent. This, together with the retrospective design, represents the most important weaknesses of the study. The strength of the study is the high and almost complete number of patients included. In addition, all patient data were recorded by only one investigator at each transplant centre. A prospective approach would have been the ideal design for investigating the aims of the study. A prospective study would, however, have been very challenging to conduct due to the low prevalence of liver transplanted PSC-IBD patients.

In paper II, we included LGD as a neoplastic category in our analysis, in spite of well-known reliability problems, such as sampling errors at endoscopy, inter-pathologist variation and the validity and specificity of dysplasia as a marker of neoplasia.[93] We regard, however, LGD as an important entity because it represents the earliest recognizable histologic precursor of colorectal cancer known at present.[208] Since colorectal cancer in PSC-IBD after all is a rare condition, the inclusion of LGD increased the number of events and made it feasible to utilize advanced statistical methodology to analyse the risk of neoplasia in the material.

The assessment of increased risk of colorectal neoplasia after Ltx due to either duration of IBD or to other factors related to Ltx, represents a major methodological challenge in our study. However, both the competing risk analysis and the hazard ratio plot in study II displayed that IBD duration could not alone explain the increasing risk of colorectal neoplasia post Ltx. An exact estimation of the influence of disease duration versus Ltx on the risk of neoplasia was, however, not feasible in our study model. To analyse this further, a control group consisting of non-transplanted PSC-IBD patients matched for IBD duration and age should have been included in the study. Such a patient cohort would, however, be very challenging to establish due to the low prevalence of PSC-IBD.

5.1.3 Statistics

Competing risk regression analysis

In study II, the most suitable statistical method for estimating the risk of colorectal neoplasia was found to be competing risk regression analysis because of the high frequency of informative censoring in the study sample. During the study, the patients were censored due to colectomy for non-neoplastic reasons or death, both events making it impossible to develop the event (neoplasia) at a later stage of the IBD disease. In contrast, if we used cause-specific Kaplan-Meier survival analysis, we would obtain a higher estimate of the cumulative incidence of the event of interest because all other events would be considered as censored. A major assumption of the Kaplan-Meier method is non-informative censoring which was not fulfilled in our sample. Our statistical method generated risk estimates generally lower than those previously reported, which is to be expected since cause-specific Kaplan-Meier estimates are always biased when informative censoring is present and by that tends to overestimate the risk.

Uni- and multivariate analysis

To test the possible effect of medication and other explanatory variables on the development of colorectal neoplasia (study II) and change in IBD activity (study III) post Ltx, we used a Cox proportional hazards model fitted firstly with one and then with several covariates. Since the number of possible variables to be tested is dependent on the sample size, we could only test a limited number of variables in our study and we chose the ones regarded most clinically relevant. We cannot exclude, however, that other untested or not recorded variables could possibly have an impact on the event.

5.2 Characteristics of IBD in PSC

In study I, our results were in accordance with the earlier findings of Loftus et al. regarding the distribution of colitis and the frequency of rectal sparing.[138] We could not, however, confirm the high frequency of terminal ileitis in our study. Our finding of a 20% frequency of backwash ileitis is markedly lower than previously reported

results. The discrepant findings may be partly explained by the varying criteria of classification regarding endoscopic and histologic features, a difference in ongoing medication and sample size of the studies. Loftus et al also found a significantly higher prevalence of terminal ileitis in PSC-IBD compared to the UC control group (51% vs. 7%).[138] On the contrary, Joo et al. did not report any difference in the presence of backwash ileitis in 40 PSC-UC patients compared to 40 UC controls (36 vs. 27%).[209] The significance of terminal ileitis regarding symoms, severity of disease and prognosis in PSC-IBD is highly unclear.

We also showed a relatively quiescent course of IBD in a majority of patients based on endoscopic data, calprotectin levels and the patient's own opinion as assessed by the Simple Clinical Colitis Activity Index (SCCAI). This result is in consistency with the outcome of earlier, retrospective studies.[139,144,210] In a Swedish case-control study for example, the PSC-IBD patients used less systemic steroids and were less hospitalized compared with the UC control group during 20 years of follow-up.[139] Sokol et al. found that PSC-IBD patients required less immune-suppressors, less intestinal resections and had a lower cumulative colectomy rate than IBD patients without liver disease.[144] In study I, the liver transplanted patients had a lower clinical and histological IBD activity compared to the non-transplanted group. The overall mean SCCAI score was, however, low (0.23) and in accordance with a slightly elevated median calprotectin level at 59 mg/kg (normal value <50). In accordance with the clinical and histological results, the calprotectin level was lower in the liver transplanted compared to the non-transplanted group, 46 (1-1945) vs. 61 (1-2844) mg/kg, but this difference was not significant (p=0.328). The lack of significance might be due to the overall low calprotecin level in both groups. Yet, to our knowledge, a study of the correlation between the activity of inflammation and the level of calprotectin in PSC-IBD has not been performed.

Our novel finding of a higher degree of microscopic inflammation in the right compared to the left colon were in 2009, during preparation of our study results, verified in a retrospective study by Joo et al. who investigated the pathological findings of UC with and without PSC.[209] In this study, the PSC-UC patients showed a higher degree of inflammatory activity in the cecum and a lower degree of activity in

the rectum compared with UC patients.[209] Additionally, this study reported an overall lower grade of inflammation in PSC-IBD and neither the frequency of rectal sparing nor terminal ileitis were significantly higher in the study group compared to controls.[209] Interestingly, two recent studies from Korea and Japan have displayed a similar disease pattern in PSC-IBD regarding pancolitis, right-sided predominance of inflammation, disease course and risk of colorectal neoplasia as shown in our and other Western studies.[211,212]

In both the national and the Nordic cohorts of PSC patients, the diagnosis of IBD preceded that of PSC in the majority of cases (93/155 (60%) and 243/368 (66%), respectively). This is in accordance with previous findings.[139,209] Due to the potential subclinical course of both PSC and IBD, the exact onset of the diseases is, however, difficult to ascertain. A recently published study by Sinakos et al. displays a shift in the timing of diagnosis of the two diseases, in that PSC in the recent years more often is diagnosed first, probably due to an increased use of MRC.[213]

In the national PSC cohort, 15 of 184 (8%) patients were initially diagnosed with CD and in the majority of patients, CD was diagnosed before PSC. The diagnosis of CD was in most cases established due to the colonic distribution of inflammatory findings. Very few patients had definite CD histopathology and none had small bowel affection, fistulas or strictures. These findings are in accordance with previous studies.[106,131,138,154,201] In five of the 15 (33%) CD patients, there was a shift of diagnosis from CD to UC during the disease course. Hence, there seems to be a tendency to overdiagnose CD in PSC, probably due to the distribution pattern of the colonic inflammation, increased ileal affection and difficulties in the interpretation of subgroups of IBD in low grade colitis.

At inclusion in study I, the study colonoscopy revealed significant neoplasia in four patients with IBD; two had a dysplasia-associated lesion or mass (DALM), one an adenocarcinoma and one a tubular adenoma. At diagnosis of neoplasia, the mean age was 54 years and the mean duration of IBD 17.4 was years. All lesions were localized proximally to the splenic flexure. At endoscopy, three out of the four patients

lacked active macroscopic colonic inflammation, whereas all patients had inflammatory changes by histology (data not shown in the article). None of the patients had undergone Ltx. These findings are in accordance with known risk factors for development of neoplasia in IBD, both regarding age, duration of IBD and presence of microscopic inflammation.[93,214]

The results of this thesis further underscore the previous findings that IBD in PSC differs from IBD without liver disease regarding distribution and activity of colonic inflammation, severity of IBD symptoms and risk and distribution of colonic neoplasia. These phenotypic characteristics indicate that IBD in PSC might represent a distinct entity of colitis. Additionally, genetic studies have shown that HLA associations differ between PSC and UC patients whereas no significant differences are found between PSC patients with and without IBD.[215] This supports the possibility that IBD in PSC may also differ from UC at a molecular level.

5.3 Risk of colorectal neoplasia in PSC-IBD

Several studies have shown that PSC patients with IBD have a higher risk of colorectal dysplasia and cancer than IBD patients without hepatobiliary disease,[7,9,142-144] but the reported magnitude of the risk varies considerably. Broomé et al. estimated the 20 year cumulative risk of colorectal neoplasia in PSC-IBD to be 31%,[142] whereas the corresponding risk in our study was only 17%. In a more recent study, Claessen et al. found the risk of colorectal cancer in PSC-IBD after 10 and 20 years to be 14% and 31%, respectively.[9] Our lower risk estimates could be due to our use of competing risk analysis, as earlier accounted for (page 42), instead of the more widely used Kaplan-Meier survival analysis. Differences in study design and patient selection might also have influenced these results.

We found a significantly higher risk of colorectal neoplasia after, as compared to before Ltx, also when taking duration of IBD into account. A high risk of colorectal neoplasia post Ltx in PSC patients has also been shown in earlier studies. Both Vera et al. and Hanouneh et al. found a higher risk of neoplasia after Ltx in PSC patients

compared to non-PSC patients.[194,195] Loftus et al. displayed a fourfold, although not significant, increase in the risk of colorectal cancer, comparing liver transplanted PSC patients with a historical cohort of non-transplanted PSC patients.[193] However, these studies are not directly comparable to our, since we estimated the risk of neoplasia in the same patients, before and after Ltx. On the contrary, in a study by Dvorchik et al. with a design similar to ours, PSC-IBD patients who underwent Ltx were followed and no difference in the risk of colorectal cancer before and after Ltx was shown.[178] This study estimated the hazard rates by using Cox regression analysis and not competing risk as we did. Furthermore, it encompassed a considerably lower number of endpoints (n=19) than our study, as it reported no other neoplasias than colorectal cancer. These factors might explain the diverging outcomes.

We consider our risk estimates of colorectal neoplasia after Ltx as conservative due to the use of competing risk regression analysis. They are also conservative in the sense that we chose to censor patients who received an ileo-rectal anastomosis due to active IBD, despite their continued risk of rectal neoplasia.

Competing risk analysis was regarded as the most suitable statistical method because of the high frequency of informative censoring in the study sample.[199,200] For comparison purposes, a Cox regression analysis was additionally performed, since this statistical method has been widely used in earlier studies.[194,195] The HR for colectomy due to any type of neoplasia using competing risk and Cox regression analysis was 1.9 ($p=0.002$) and 4.2 ($p<0.001$), respectively. For DALM, HGD and carcinoma combined, the HR using competing risk and Cox regression was 1.55 ($p=0.121$) and 3.1 ($p=0.001$), respectively. These results further underscore that our risk estimates are more conservative than those of earlier studies. Yet, we regard the competing risk analysis as the most appropriate method in this setting.

The mechanism behind the high risk of colorectal neoplasia in both transplanted and non-transplanted PSC-IBD patients is unclear. It has been hypothesized that alterations in the bile acids due to liver disease might have a carcinogenic effect on the proximal colon by an increased exposure of primary bile acids to intestinal

bacteria with a high rate of conversion of primary to carcinogenic secondary bile acids.[143,160] This might explain both our and previous findings, although not universal,[216] of a tendency to right-sided neoplasia in PSC-IBD.[143,150,157] The predominantly right-sided inflammation, as demonstrated in paper I and in several other studies, [209,217,218] might also act as a factor predisposing for neoplasia in this region. The high risk might also be due to longstanding inflammation, as the histological signs of IBD in PSC can precede symptoms with many years,[158] or it might be due to factors related to PSC itself. After Ltx, we cannot exclude the possibility that other untested or not recorded factors related to PSC or IBD, the transplantation procedure, or the course after Ltx could have an impact on the development of neoplasia. Likewise, the immunosuppressive regimen might play a role in the development of colonic neoplasia as displayed in earlier studies,[219,220] even though we found no significant association between these factors in our study.

5.4 Chemoprevention in PSC-IBD

Both 5-ASA and UDCA have been promoted as colorectal chemopreventive agents in IBD.[161,162,164,165] In study III we found, rather surprisingly, that the use of these compounds in the liver transplanted PSC-IBD patients was associated with the development of colorectal neoplasia. A similar result, although not significant, was shown in a recent study; Hanouneh et al. included 43 liver transplanted PSC-IBD patients and demonstrated an association between 5-ASA and UDCA and post Ltx colonic neoplasia with HR of 3.3 and 2.7, respectively.[195]

5.4.1 5-ASA

In addition to its role as a therapeutic agent for mild to moderate UC, both preclinical and clinical studies have reported antineoplastic properties of 5-ASA,[164,221-223] although the results have been conflicting.[224,225] As earlier accounted for, a majority of the previous clinical studies have been observational with disparate methodologies and it has been frequently questioned whether the reported results are robust enough to answer the question of chemoprophylactic properties of 5-ASA. In a recent metaanalysis, including only non-referral populations and by that avoiding a referral

bias, Nguyen et al. did not find a protective effect of 5-ASA on colorectal cancer in IBD with a pooled, adjusted OR of 0.95 (95% CI 0.66-1.38).[226] To our knowledge, no chemopreventive benefit of 5-ASA in PSC-IBD has been shown, neither in non-transplanted nor in transplanted patients. In an earlier study, Sokol et al. compared PSC-IBD with IBD patients and found, despite lower colonic inflammation and a higher use of 5-ASA, a higher risk of colorectal cancer in the PSC-IBD patients.[144] Likewise, in a Swedish study, Lindberg et al. found no significant effect of sulfasalazine on the rate of colorectal neoplasia in PSC-UC patients.[150] In our study, a possible explanation for the result could be that the use of 5-ASA represents a surrogate marker for high inflammatory activity. However, when comparing patients with and without use of 5-ASA (data not shown in the article), we did not find any difference in the frequency of macro- and microscopic inflammation, neither at the pre Ltx nor the post Ltx colonoscopy. It can be speculated that our results reflect carcinogenic differences between IBD patients with and without PSC, resulting in a lack of colonic chemoprotective effect of 5-ASA in PSC-IBD.

5.4.2 UDCA

Our result, indicating that UDCA is associated with colorectal neoplasia in PSC-IBD patients post Ltx, is in conflict with two earlier studies that showed a protective effect of UDCA towards colorectal neoplasia. [161,162] However, several new studies support our finding.[159,166,227,228] Lindström et al. recently found no difference in colorectal neoplasia-free survival between 48 UDCA-treated and 50 placebo-treated Nordic PSC-IBD patients with a total follow-up time of 760 years.[227] In a study from the US, Eaton et al. reported an even higher risk of colorectal neoplasia in PSC-UC patients receiving UDCA at high doses compared to placebo-treated patients.[166] Finally, in a recent metaanalysis including four studies and 281 patients, the use of UDCA did not appear to decrease the risk of adenomas or colonic cancer in PSC-IBD.[228]

Since neither UDCA nor 5-ASA seem to reliably reduce the elevated risk of colorectal neoplasia in PSC-IBD patients, we cannot recommend the use of these compounds for chemopreventive purposes post Ltx.

5.5 Surveillance of IBD in PSC

It is well established that the cumulative risk of colorectal neoplasia in IBD increases with time.[90] According to guidelines, all PSC patients should undergo a screening colonoscopy at diagnosis due to the high frequency of subclinical colitis in PSC,[58,158] which is in accordance with the results of study I. Once IBD is confirmed, surveillance colonoscopy should be performed at 1- to 2-year intervals.[57,58] This recommendation is in line with the findings of a recent study in which Thackeray et al. found that the risk of colonic neoplasia in PSC-IBD is similar for the periods 0-2 years and 8-10 years after IBD diagnosis.[216] Our finding of an even higher risk of colorectal neoplasia after Ltx, further underscores the importance of repeated surveillance colonoscopies in PSC-IBD, also after Ltx.

5.6 *De novo* IBD

The frequency and time of onset of *de novo* IBD post Ltx in our study is in consistency with earlier studies.[173,176,188] Our findings of a decreased *de novo* IBD-free survival in the group of patients receiving tacrolimus versus those who did not ($p<0.001$) and an increased *de novo* IBD free survival in the group receiving CsA versus those who did not ($p<0.001$) (data not shown in article), are also in accordance with previous results.[173] Similarly, when performing a univariate Cox regression analysis, tacrolimus was associated with *de novo* IBD (HR 22, $p=0.005$), whereas CsA showed a protective effect (HR 0.5, $p=0.005$) (data not presented in article). Even if our study encompasses a limited number (n=11) of patients with *de novo* IBD, it represents, as far as we know, the largest cohort reported up to now. Due to the low prevalence of PSC, advanced statistics is very challenging to perform and our results should be interpreted with caution. However, the fact that 10 out of 11 patients who developed *de novo* IBD received tacrolimus may suggest a role for this compound in the pathogenesis of IBD post Ltx.

5.7 Activity of IBD after liver transplantation

Study III depicts an increased activity of IBD after Ltx, regarding colonic inflammation, number of relapses and overall IBD activity. Several earlier studies, with a variety of endpoints, study designs and statistical methods, have presented conflicting results related to this topic. Some have shown a mainly deteriorated IBD after Ltx,[173,178,182,186,187,229] whereas others reveal an unchanged or improved IBD course post Ltx.[172,175,183,184,203] In a recent study, based on the recordings of UC flares in 77 PSC patients, Navaneethan et al. concluded that UC remains quiescent after Ltx.[203] On the contrary, in a newly published study from Hungary, Gelley et al. demonstrated a significant increase in Mayo Disease Activity Index after Ltx in a cohort of 44 PSC-UC patients.[229] We consider our study results an important contribution to this field of research, due to the multicenter design, the large sample size, as well as the evaluation of IBD activity using multiple modalities. However, liver transplanted patients constitute a challenging subset of patients to follow up, given their medical complexity and immunocompromised status. Symptoms and clinical signs consistent with active IBD could possibly have other causes, such as side effects of medications (*e.g.* tacrolimus, MMF-colitis)[230] and colonic infections (*e.g.* CMV and clostridium difficile colitis).[231] In our study, these factors were excluded as far as possible by careful assessment of the patient records by experienced physicians at each transplant centre.

Our finding of an increased IBD relapse rate after Ltx compared to before was based on six different predefined relapse criteria. In 80% of the recordings pre Ltx and in 90% of those post Ltx, the identification of each relapse was based on the presence of two or more of the criteria. In 60% of cases, the recordings of IBD relapse post Ltx included an endoscopy (data not shown in article), which further strengthens the results.

At the colonoscopies included in the study, both the macroscopic and microscopic findings pre- and post Ltx were recorded. We cannot exclude that the inclusion of microscopic data in our analysis could be useful, but we chose to use only the endoscopic recordings since these data were more complete than the reported

histology and because this modality traditionally has been regarded as the main tool to assess IBD activity. The multicenter design might represent a weakness of the study because of possible interobserver variability between the endoscopists performing the colonoscopies.

The tendency towards an increased risk of colectomy due to active disease post Ltx is in consistency with the earlier results of Dvorchik et al. who used a study design similar to ours.[178] The reason why our result, as opposed to that of Dvorchik, did not reach significant value, might be the disparate statistical methods used, as we estimated the risk in a competing risk regression analysis whereas Dvorchik used the Cox regression analysis. Finally, we cannot exclude the possibility that other untested or not recorded factors related to PSC or IBD, the transplantation procedure or the course after Ltx, might have an impact on the level of IBD activity.

In paper I, we concluded that the disease course was milder in the liver transplanted compared to the non-transplanted group. This might seem contradictory to the findings of increased inflammatory activity after Ltx in study III. The reason behind this could be the disparate study designs and patient selection. In paper I we compared the activity of IBD in two groups; the liver transplanted and the non-transplanted patients. In this analysis, the patients who had undergone colectomy had been excluded due to the study design. Adversely, in paper III, when comparing the activity of IBD in each patient before and after Ltx, colectomy due to active disease post Ltx was taken into account.

It might seem contradictory that dual treatment with tacrolimus and MMF was found to be associated with worsening of IBD post Ltx, since tacrolimus, and to some extent also MMF, are effective treatment options for IBD.[232,233] Nevertheless, our study confirms the results by Verdonk et al. and Haagsma et al. that depict that the use of tacrolimus plays a role both in active IBD post Ltx and in the development of *de novo* IBD.[173,176] The reason behind these observations is not known. One theory is that the immune system reaches a new balance as a consequence of organ transplantation and that tacrolimus at some level interferes with the pathogenesis of IBD and

enhances colonic inflammation.[205] It is also difficult to determine to what extent MMF plays a role in the worsening of IBD post Ltx. The dose-related gastrointestinal toxicity linked to damage of enterocytes has over the last years become a well-known side effect of MMF and studies show that the histologic features of MMF-colitis in certain cases can mimic IBD colitis.[230] Furthermore, we cannot exclude that the observation could be related to unidentified factors related to time, since a majority of patients used CsA before and a majority used tacrolimus after year 2000. However, neither patient follow-up, nor the endoscopic or histopathologic assessment and interpretation of the findings in IBD, have changed noteworthy during the study period. Likewise, there was not a significant difference in the number of patients that underwent Ltx due to end-stage liver disease before and after 2000 (p=0.061, data not shown in the article). Finally, we cannot exclude that a tendency to use higher dosage of the immunosuppressive compounds in earlier days might have affected the result.

Both CsA and tacrolimus are calcineurine inhibitors and effective immunosupressants.[234]Although previous studies indicate some disparities regarding effects and side effects between CsA and tacrolimus,[234] there is, to our knowledge, a lack of randomised studies demonstrating superiority for one compound over the other regarding *i.e.* rejection treatment or neurotoxicity. Based on the results of study III, we therefore recommend considering a shift from present standard maintenance treatment of tacrolimus and MMF to CsA and azathioprine in PSC patients undergoing Ltx, although an overall assessment of pros and cons must first be carried out.

6. Conclusions and future studies

Study I is the first prospective study that clinically characterises IBD in the largest cohort of PSC patients up to now. It confirms previous findings of a high frequency of pancolitis, rectal sparing and a relatively quiescent course of IBD in PSC. Moreover, it displays the novel findings of a higher frequency of colonic inflammation by histology than by endoscopy and an isolated right-sided colitis in nearly 25% of cases. Additionally, with its cross-sectional design, a lower clinical and histologic IBD activity was found in the liver transplanted patients compared to the non-transplanted group. These phenotypic characteristics of IBD in PSC further support the hypothesis that PSC-IBD may represent a distinct entity of colitis. Newly developed methodology now enables characterisation of IBD in PSC also at a genetic, epigenetic and microbiotic level and this should be the aim of further studies.

The findings of an increased risk of colorectal neoplasia and a higher IBD activity after compared to before Ltx, in a study of the hitherto largest cohort of PSC patients undergoing Ltx, confirms the results of some earlier, smaller studies. The increased risk of neoplasia post Ltx further supports the importance of repeated surveillance colonoscopies in PSC-IBD, also after Ltx. Our novel finding of an association between the use of UDCA and aminosalicylates and colorectal neoplasia post Ltx needs further verification. At present, we cannot recommend the use of these compounds for chemopreventive purposes post Ltx. Even though several theories exist, the cause behind the increased risk of colorectal neoplasia in PSC-IBD is still unknown. Future studies should focus on molecular mechanisms and other factors that contribute to the development of colorectal neoplasia in PSC-IBD.

The finding that IBD activity post Ltx seems to be influenced by the immunosuppressive regimen given, warrants further studies. The aim of these studies should be to optimise and individually tailor the immunosuppressive therapy given after Ltx in PSC patients.

7. Appendix

Table 1. Summary of studies reporting incidence and prevalence of PSC

Reference	Geographical region	Study Period	Population	No. of PSC patients	Incidence, per 100 000/year (95% CI)	Prevalence, per 100 000 (95% CI)
Escorsell et al.[16]	Spain	1984-1988	19,230,000	43	0.07	0.22
Boberg et al.[14]	Oslo, Norway	1986-1995	130,000	17	1.31 (0.81- 2.10)	8.5 (2.8-14.2)
Berdal et al.[13]	Akershus, Norway	1985-1994	180,000	12	0.7	5.6
Hurlburt et al.[17]	Alaska, US	1984-2000	100,312	0	0	0
Ang et al.[11]	Singapore	1989-1998	750,000	10	NR	1.3
Bambha et al.[12]	Olmsted County, Minnesota, US	1976-2000	NR	22	0.90 (0.56-1.36)	13.6 (7.1-20.1)
Kingham et al.[19]	South Wales, UK	1984-2003	251,000	46	0.91	12.7
Kaplan et al.[18]	Alberta, Canada	2000-2005	1,112,521	49	0.92	n.a.
Card et al.[15]	UK	1987-2002	2,027,909	223	0.41 (0.34-0.48)	3.85 (3.04- 4.80)
Lindkvist et al.[20]	Västra Götaland, Sweden	1992-2005	1,492,000	199	1.22	16.2

NR, not reported

Table 2. Summary of studies reporting incidence of UC and/or CD (Molodecky et al., Gastroenterology 2012, with permission)[88]

Appendix 2. Summary of Studies Reporting Incidence of UC and/or CD, Stratified by Geographic Region

Lead author	Year	Country	Region	Study period	CD incidence rate (10^5)	UC incidence rate (10^5)	Annual average percent change	
							CD	UC
North America								
Lowe AM[1]	2009	Canada	Quebec	1998–2000	20.2			
Bernstein CN[2]	1999	Canada	Manitoba	1984–1995	14.6	14.3		
Blanchard JF[3]	2001	Canada	Manitoba	1987–1996	15.6	15.6		
Green C[4]	2006	Canada	Manitoba	1990–2001	14.83	13.45	−0.2	−2.0
Pinchbeck BR[5]	1988	Canada	Alberta	1966–1981	6.56	3.31	9.2[a]	10.7[a]
Bernstein CN[6]	2006	Canada	Canada	1998–2000	13.4	11.8		
			British Columbia		8.8	9.9		
			Alberta		16.5	11.0		
			Saskatchewan		13.5	10.4		
			Manitoba		15.4	15.4		
			Nova Scotia		20.2	19.2		
Loftus CG[7]	2007	United States	Olmsted County, Minnesota	1940–2000	6.3[a]	8.1[b]	2.1[a]	2.4[a]
				1990–2000	7.9 (6.3, 9.5)	8.8 (7.2, 10.5)		
Gollop JH[8]	1988	United States	Olmsted County, Minnesota	1943–1982	4.0		4.7[a]	
Loftus EV[9]	2000	United States	Olmsted County, Minnesota	1940–1993		7.6	3.1[a]	2.2
Loftus EV[10]	1998	United States	Olmsted County, Minnesota	1940–1993	5.8 (5.0, 6.5)			
Sedlack RE[11]	1980	United States	Olmsted County, Minnesota	1935–1975	4.2		5.1[a]	
Sedlack RE[12]	1972	United States	Olmsted County, Minnesota	1935–1964	2.1	3.4	−2.1	2.8
Calkins BM[13]	1984	United States	Baltimore	1977–1979	2.8	1.83		
Garland CF[13c]	1984	United States	Baltimore	1973	3.01	3.16		
Monk M[14]	1968	United States	Baltimore	1960–1963	3.32	7.05		
Kurata JH[15]	1992	United States	Fontana and Sunset, California	1982–1988	3.6			
Herrinton LJ[16]	2008	United States	Northern California	1996–2002	6.3 (5.6, 7.0)	12.0 (11.0, 13.0)		
Garland CF[17]	1981	United States	Total	1973	2.38 (1.4, 3.36)	3.52 (2.32, 4.72)		
			Portland, Maine		4.87 (−0.45, 10.2)	6.50 (0.012, 7.70)		
			Bridgeport		4.07 (0.80, 7.34)	0.64 (−0.61, 1.89)		
			Ithaca, New York		1.23 (−1.18, 2.46)	0		
			York, Pennsylvania		0	3.63 (−1.58, 8.84)		
			Lansing, Michigan		4.29 (0.51, 8.07)	2.25 (−0.34, 4.84)		
			Topeka, Kansas		1.89 (−0.74, 4.52)	4.97 (0.99, 8.95)		
			Winona, Minnesota		2.70 (−2.57, 7.97)	8.09 (−3.87, 20.0)		
			Clarksville, Tennessee		4.84 (−4.65, 14.33)	0		
			Maryville, Tennessee		0	14.3 (−5.52, 34.1)		
			Eunice, Louisiana		0	0		
			Albuquerque, New Mexico		0.82 (−0.32, 1.96)	3.09 (0.58, 5.60)		
			Boulder, Colorado		0.67 (−0.64, 1.98)	6.38 (−1.05, 13.81)		
			Banning, California		0	4.19 (−4.0, 12.38)		
			Eureka, California		0	4.76 (−4.57, 14.09)		
			Medford, Oregon		3.76 (−3.59, 5.07)	3.72 (−3.57, 11.01)		
Nunes GC[18]	1983	United States	Spokane	1971–1981	7.3			
Stowe SP[19]	1990	United States	Rochester, New York	1920–1989	2.33	1.55	4.6[a]	5.0[a]
Stonnington CM[20]	1987	United States	Rochester, Minnesota	1960–1979		15.0		
Spencer RJ[21]	1974	United States	Rochester, Minnesota	1935–1964		11.6		
Ognubi[22]	1998	United States	Georgia	1986–1995	8.8			
Appleyard CB[23]	2004	Puerto Rico	Southwestern	1996–2000	1.18	2.50		
Edwards CN[24]	2008	Barbados	Nationwide	1980–2004	0.7 (0.51, 0.95)	1.85 (1.53, 2.22)	1.4	1.1
South America								
Victoria CR[25]	2009	Brazil	São Paulo	1986–2005	1.48	3.96		
Souza MHLP[26]	2002	Brazil	Ribeirao Preto, Sao Paulo	1980–1999	2.55	2.43	4.0	0.2
Linares de la Cal JA[27]	1999	Panama	District of Colon	1987–1993	0	1.2		
		Argentina	Partido General Pueyrredon	1987–1993	0.06	2.17		
Asia and the Middle East								
Lok KH[28]	2007	China	Hong Kong	1991–1906	0.19		4.9[a]	−0.1
Leong RWL[29]	2004	China	Hong Kong	1986–2001	0.6	0.87	10.8[a]	6.3[a]
Lok KH[30]	2008	China	Hong Kong	1997–2006		0.59		
Lai CL[31]	1985	China	Hong Kong	1966–1980		0.11		3.8
Chow ÐKL[32]	2009	China	Hong Kong	2006		2.1 (1.1, 3.7)		
Zheng JJ[33]	2005	China	Nationwide	1950–2002	0.28			
Zheng[34]	2010	China	Nationwide	1950–2007	0.85			
Niv Y[35]	1990	Israel	Upper Galilee	1967–1986		2.33		
Fireman Z[36]	1989	Israel	Tel Aviv Jafo	1970–1980	1.55		14.3[a]	
Grossman A[37]	1989	Israel	Tel Aviv Jafo	1970–1980		3.86		4.7[a]
Gilat T[38]	1974	Israel	Tel Aviv Jafo	1961–1970		3.66		1.2
Rozen P[39]	1979	Israel	Tel Aviv Jafo	1970–1976	1.28			
Odes HS[40]	1994	Israel	Southern Israel	1968–1992	4.2			
Odes HS[41]	1987	Israel	Southern Israel	1961–1985		2.98 (2.42, 3.54)		
Shapira M[42]	1998	Israel	Kinneret Subdistrict	1965–1994		3.5		5.5
Shapira M[43]	1994	Israel	Kinneret Subdistrict	1960–1990	1.96		5.8[a]	
Odes HS[44]	1987	Israel	Beer Sheva	1961–1985		2.87 (2.31, 3.42)		7.5[a]
Krawiec J[45]	1984	Israel	Beer Sheva	1961–1980	1.1		9.7	
Jacobsohn WZ[46]	1986	Israel	Jerusalem	1973–1978		6.3		

Appendix 2. Continued

Lead author	Year	Country	Region	Study period	CD incidence rate (10^5)	UC incidence rate (10^5)	Annual average percent change	
							CD	UC
Niv Y[47]	1999	Israel	Kibbutz residents	1987–1997	5.0			
Niv Y[48]	2000	Israel	Kibbutz residents	1987–1997		5.04		
Odes HS[49]	1989	Israel	Beer Sheva	1979–1987	2.1	5.4		
Sood A[50]	2003	India	Punjab	1999–2000		6.02 (1.2, 17.6)		
Abdul-Baki H[51]	2007	Lebanon	Nationwide	2000–2004	1.4	4.1		
Utsunomiya T[52]	1983	Japan	Nationwide	1955–1980		0.16		9.1[a]
Morita N[53]	1995	Japan	Nationwide	1991	0.51	1.95		
Yoshida Y[54]	1990	Japan	Nationwide	1965–1979	0.40	0.28		
Kitahora T[55]	1995	Japan	Nationwide	1960–1985		0.28		10.0[a]
Yao T[56]	2000	Japan	Nationwide	1986–1998	0.9		7.2[a]	
Yang SK[57]	2000	South Korea	Songpa-Kangdong, Seoul	1986–1997		0.68		18.1[a]
Yang SK[58]	2008	South Korea	Songpa-Kangdong, Seoul	1986–2005	0.53 (0.44, 0.62)	1.51 (1.34, 1.67)	21.4[a]	14.4[a]
Al-Ghamdi AS[59]	2004	Saudi Arabia	Riyadh	1983–2002	0.94			
Lee SK[60]	1974	Singapore	Nationwide (Chinese)	1965–1970	0.04			
Fung WP[61]	1971	Singapore	Nationwide (Chinese and Indians)	1956–1970		0.11		
Niriella MA[62]	2010	Sri Lanka	Colombo and Gampaha	2007–2008	0.09 [0.002–0.18]	0.69 [0.44–0.94]		
Wei S-C[63]	2009	Taiwan	Nationwide	1988–2008	2			
Tozun N[64]	2009	Turkey	Nationwide	2000–2003	2.2	4.4		
Tezel A[65]	2003	Turkey	Trakya	1998–2001		0.77		
Radhakrishnan S[66]	1997	Oman	Nationwide	1987–1994		1.35		
Al-Shamali M[67]	2003	Kuwait	Nationwide	1985–1999		2.8 (1.7, 4.1)		0.3
Al-Nakib[68]	1984	Kuwait	Nationwide	1977–1982	0.45	2.27		
Europe[d]								
Shivananda S[69]	1996	Europe		1991–1993	5.0	9.8		
		Iceland	Reykjavik		8.2	24.3		
		Norway	Oslo		6.9	15.6		
		Denmark	Copenhagen		6.6	10		
		Ireland	Dublin		5.9	14.8		
		United Kingdom	Leicester (nonimmigrants)		3.2	9.2		
		United Kingdom	Leicester (immigrants)		4.7	15.1		
		The Netherlands	Maastricht		7.7	13.1		
		Germany	Essen		3.5	4.3		
		France	Amiens		8.1	5.6		
		Italy	Milan-Varese		3.2	10		
		Italy	Crema-Cremona		2.7	7.5		
		Italy	Reggio Emilia		4	7.5		
		Italy	Florence		2.7	8.1		
		Italy	Palermo, Sicily		5.8	8.5		
		Spain	Vigo		4.8	7		
		Spain	Sabadell		4.9	9		
		Portugal	Braga		3.7	5.5		
		Portugal	Almada		2.3	1.7		
		Greece	Northwest Greece (Ioannina)		1	8.5		
		Greece	Heraklion, Crete		3.9	16.6		
		Israel	Beer Sheva		4.3	8.5		
Northern Europe								
Bonnevie O[70]	1968	Denmark	Copenhagen and Gentofte	1961–1967		7.3		
Langholz E[71]	1991	Denmark	Copenhagen	1962–1987		8.1		1.4
Munkholm P[72,73]	1992	Denmark	Copenhagen	1979–1987	4.1		10.2[a]	
Vind I[74]	2006	Denmark	Copenhagen	2003–2005	8.6 (7.5, 9.8)	13.4 (11.9, 14.9)		
Binder V[75]	1982	Denmark	Copenhagen	1962–1978	1.9	8.1	12.3[a]	1.1
Jacobsen BA[76]	2006	Denmark	North Jutland	1978–2002	6.73	12.16	4.9[a]	4.0[a]
Fonager K[77]	1997	Denmark	Nationwide	1981–1992	4.6	13.2	3.4[a]	−2.1[a]
Berner J[78]	1986	Faroe Islands	Nationwide	1964–1983	1.94	7.8		9.5[a]
Roin F[79]	1989	Faroe Islands	Nationwide	1981–1988	3.6	20.3		
Salupere R[80]	2001	Estonia	Tartu County	1993–1998	1.4	1.7		
Linden G[81]	1971	Finland	Nationwide	1967		4.8		
Moller C[82]	1971	Finland	Nationwide	1956–1967		0.93		4.4[a]
Halme L[83]	1989	Finland	Helsinki	1975–1985	2.3		11.4[a]	
Manninen P[84]	2010	Finland	Tampere	1986–1999	7.2	16.5		
Björnsson S[85]	2000	Iceland	Nationwide	1990–1994	5.5	16.5		
Björnsson S[86]	1998	Iceland	Nationwide	1980–1989	3.1	11.7		
Bjornsson S[87]	1983	Iceland	Nationwide	1950–1979		4.97		4.9[a]
Bjornsson S[88]	1989	Iceland	Nationwide	1950–1979	0.6	5.0	4.5[a]	5.0[a]
Romberg-Camps MJL[89]	2008	The Netherlands	South Limburg	1991–2003	6.21	7.72	−1.8	−5.1[a]
Russel MG[90]	1998	The Netherlands	South Limburg	1991–1994	6.9 (5.9, 7.9)	10 (8.7, 11.2)		
Shivananda S[91]	1987	The Netherlands	Leiden	1979–1983	3.9			
Shivananda S[92]	1987	The Netherlands	Leiden	1979–1983		6.8		
Haug K[93]	1989	Norway	Western Norway	1984–1985	5.3			
Haug K[94]	1988	Norway	Western Norway	1984–1985		14.8		
Kildebo S[95]	1989	Norway	Total Northern region	1983–1986	5.8			
			Nordland		3.9			
			Troms		5.4			

Appendix 2. Continued

Lead author	Year	Country	Region	Study period	CD incidence rate (10^5)	UC incidence rate (10^5)	Annual average percent change	
							CD	UC
			Finnmark		6.7			
Kildebo S[96]	1990	Norway	Total Northern region	1983–1986		13.2		
			Nordland			13.5		
			Troms			12.1		
			Finnmark			11.6		
Myren J[97]	1971	Norway	Nationwide	1964–1969	1.05	3.29		
Moum B[98]	1996	Norway	Southeast	1990–1993		13.6		
Moum B[99]	1996	Norway	Southeast	1990–1993	5.8			
Bengtson MB[100]	2009	Norway	Southeast (Oslo)	1990–1993	6	12.8		
Moum B[101]	1995	Norway	Southeast	1990	5.1	10.6		
Brahme F[102]	1975	Sweden	Malmo	1958–1973	4.8		6.4[a]	
Stewenius J[103]	1994	Sweden	Malmo	1958–1982		6.3		4.7[a]
Ekbom A[104]	1991	Sweden	Uppsala Health Care Region	1965–1983	6.1	10.4	−0.5	3.1[a]
Bergman L[105]	1975	Sweden	Uppsala and Västmanland	1968–1973	5.0			
Norlen BJ[106]	1970	Sweden	Uppsala and Västmanland	1956–1967	2.5		11.6[a]	
Lapidus A[107]	1997	Sweden	Stockholm	1955–1989	3.7		3.8[a]	
Nordenvall B[108]	1985	Sweden	Stockholm	1955–1979		1.7		4.4[a]
Lapidus A[109]	2006	Sweden	Stockholm	1990–2001	8.3		2.1	
Nyhlin H[110]	1986	Sweden	Umea	1974–1981	4.97			
			Northern Sweden	1974–1981	4.45			
Lindberg E[111]	1991	Sweden	Örebro Medical Center Hospital catchment area	1963–1987	6.1		1.7[a]	
Tysk C[112]	1992	Sweden	Orebro	1963–1987		13.1		5.5[a]
Ronnblom A[113]	2010	Sweden	Uppsala	1945		2.0		
				2005–2007		17.5		
Keighley A[114]	1976	United Kingdom	Nottingham	1958–1973	2.33			
Smith IS[115]	1975	United Kingdom	Clydesdale, Scotland	1961–1970	3.12			
Kyle J[116]	1971	United Kingdom	Aberdeen	1955–1968	1.98			
Yapp TR[117]	2000	United Kingdom	Cardiff	1930–1995	3.29[b]			
				1991–1995	5.6 (4.4,6.8)			
Thomas GA[118]	1995	United Kingdom	Cardiff	1931–1990	3.24[b]		5.2[a]	
				1986–1990	5.9 (4.7, 7.3)			
Srivastava ED[119]	1992	United Kingdom	Cardiff	1968–1987		6.3		
Mayberry J[120]	1979	United Kingdom	Cardiff	1934–1977	1.73		8.1[a]	
Gunesh S[121]	2008	United Kingdom	Cardiff	1931–2005	3.79 (3.01, 4.86)		3.9[a]	
Rubin GP[122]	2000	United Kingdom	North Tees	1990–1994	8.3 (3.4, 13.2)	13.9 (7.5, 20.3)		
Devlin HB[123]	1980	United Kingdom	Stockton on Tees	1971–1977	5.3	10.4		
Tsironi E[124]	2004	United Kingdom	Tower Hamlets (Bangledashis)	1981–1989	8.2	2.4		
				1997–2001	7.3	2.3		
Probert CS[125]	1992	United Kingdom	Tower Hamlets	1972–1989	3.86			
Jayanthi V[126]	1992	United Kingdom	Tower Hamlets	1972–1989		4.03		
Probert CS[127]	1992	United Kingdom	Leicestershire	1972–1989		6.77		
Jayanthi V[128]	1992	United Kingdom	Leicestershire	1972–1989	3.7			
Morris T[129]	1984	United Kingdom	Cardiff	1968–1977		7.2		−0.7
Carr I[130]	1999	United Kingdom	Leicester City	1991–1994		9.1		
Farrokhyar F[131]	2001	United Kingdom	Wolverhampton, Salisbury, and Swindon	1978–1986	4.98	9.20		
Fellows IW[132]	1990	United Kingdom	Derby	1951–1985	3.01		8.4[a]	
Fellows IW[133]	1988	United Kingdom	Derby	1976–1985	6.91		0.9	
García Rodríguez LA[134]	2005	United Kingdom	Nationwide	1995–1997	8.0	2.0		
Kyle J[135]	1980	United Kingdom	Aberdeen	1955–1975	2.94		4.7	
Evans JG[136]	1965	United Kingdom	Oxford	1951–1960		6.5 (6.0, 7.0)		9.7[a]
De Dombal FT[137]	1971	United Kingdom	Leeds	1963–1968	3.50			
Lee FI[138]	1994	United Kingdom	Northwest England	1971–1990	5.8 (5.2, 6.3)		3.2	
Lee FI[139]	1985	United Kingdom	Blackpool	1968–1980	4.0		20.3[a]	
Miller DS[140]	1974	United Kingdom	Nottingham	1958–1971	1.99		12.7[a]	
Tresadern JC[141]	1973	United Kingdom	Gloucester	1966–1970	1.5			
Thompson NP[142]	1998	United Kingdom	England and Wales	1991–1992	10.6			
Brown JS[143]	1988	United Kingdom	Northern Ireland	1966–1981	1.82			
Kyle J[144]	1992	United Kingdom	Northeastern and Northern Isles, Scotland	1955–1988	5.54		6.7[a]	
Kyle J[145]	1965	United Kingdom	Northeast Scotland	1955–1963	1.3			
Rose[146]	1988	United Kingdom	Wales - Cardiff	1981–1985	8.3 (7–10.1)			
Humphreys WG[147]	1990	United Kingdom	Northern Ireland	1966–1981	1.83			
Seagroatt V[148]	2003	United Kingdom	Southern England	1979–1998	5.9	6.1		
Mediterranean/Southern Europe								
Pavlovic-Calic N[149]	2008	Bosnia and Herzegovina	Tuzla	1995–2006	2.3		24.0[a]	
Salkic NN[150]	2010	Bosnia and Herzegovina	Tuzla	1995–2006		3.43 [2.97–3.89]		14.7[a]
Jojic N[151]	2000	Serbia	Zvezdara, Belgrade	1988–1998	1.84	1.31		
Jovanovic Z[152]	1999	Croatia	Rijeka and Istra	1973–1994	1.52		11.4[a]	

Appendix 2. Continued

Lead author	Year	Country	Region	Study period	CD incidence rate (10^5)	UC incidence rate (10^5)	Annual average percent change	
							CD	UC
Sincic BM[153]	2006	Croatia	Primorsko-goranska County	2000–2004	6.5 (5.3, 7.8)	4.6 (3.5, 5.7)		
Vucelic B[154]	1991	Croatia	Zagreb	1980–1989		1.5 (0.8, 2.2)		−2.8
Vucelic B[155]	1991	Croatia	Zagreb	1980–1989	0.7 (0.2, 1.2)		3.7	
Saro Gismera C[156]	2003	Spain	Liege, Asturias	1954–1997	2.08 (0.76, 3.39)	2.84 (1.30, 4.37)		
Saro Gismera C[157]	2000	Spain	Gijon, Asturias	1954–1997	2.33 (0.34, 4.32)	3.14 (0.83, 5.45)		
Martinez G[158]	1983	Spain	Asturias	1965–1980	0.49		9.4[a]	
Sebastian Domingo JJ[159]	1989	Spain	Madrid	1983–1988	1.3	2.37		
Pajares Garcia JM[160]	1987	Spain	Madrid	1976–1983	0.51			
Mate-Jimenez J[161]	1994	Spain	Madrid	1981–1988	1.61	3.16		
Garrido A[162]	2004	Spain	Huelva	1996–2003	6.6	5.2		
Lopez-Serrano[163]	2009	Spain	Madrid	1998–2005	7.3	7.1		
Ruiz V[164]	1989	Spain	Galicia	1976–1982	0.82			
Ruiz Ochoa V[165]	1984	Spain	Galicia	1976–1983	0.8			
Rivera Irigoin R[166]	2007	Spain	Costa del Sol	2000–2001		7.26		
Sola Lamoglia R[167]	1992	Spain	Cataluna (Barcelona and Gerona)	1978–1987	0.4	0.6		
Martinez Sabater A[168]	2005	Spain	La Safor (Valencia)	1994–2003		7.8		
Arin Letamendia A[169]	1999	Spain	Pamplona	1983–1993	2.47 (1.51,3.43)	3.71 (2.25, 5.25)		
Brullet E[170]	1998	Spain	Total	1991–1993	5.5	8.0 (6.3, 9.7)		
			Sabadell		5.2 (2.2, 8)	9.8 (5.8, 13.7)		
			Vigo		5.0 (2.7, 7.2)	7.7 (4.7, 10.6)		
			Mallorca		5.8 (3.4, 8.3)	7.8 (5, 10.7)		
			Motril		6.5 (1, 12)	4.3 (0, 8.8)		
Brullet E[171]	1991	Spain	Sabadell	1985–1989		5.26		
Alonso P[172]	1992	Spain	Soria	1981–1990	1.3	3.2		
Monferrer Guardiola R[173]	1999	Spain	Castellon	1992–1996	1.9	6.8		
Martinez-Salmeron JF[174]	1993	Spain	Granada	1979–1988	0.9	2.0	6.1[a]	13.5[a]
Hinojosa J[175]	1990	Spain	Sagunto	1983–1989	3.1	4.0		
Yanguela JM[176]	1991	Spain		1975–1990	0.7	2.5		
Garcia-Cano Lizcano J[177]	1994	Spain	Cuenca	1986–1993	1.3	3.4		
Cella Lanau J[178]	1995	Spain	Aragon	1975–1992	1.7	2	16.0[a]	12.8[a]
Lopez Miguel C[179]	1999	Spain	Aragon	1992–1995	2.86	4.42		
Pozzati L[180]	2002	Spain	Merida	1996–2000	2.15	5.08		
Rodrigo L[181]	2004	Spain	Oviedo	2000–2002	7.5 (3.8, 11.2)	9.1 (5.0, 13.1)		
Arin Letamendia A[182]	2008	Spain	Navarra	2001–2003	5.85 (3.99, 8.14)	9.57 (7.27, 12.57)		
Manousos ON[183]	1996	Greece	Heraklion	1990–1994	3.0			
Manousos ON[184]	1996	Greece	Heraklion	1990–1994		8.9 (7.2, 10.4)		
Ladas SD[185]	2005	Greece	Trikala	1990–1994		10.2		
Tsianos EV[186]	1994	Greece	Northwest Greece (Ioannina)	1982–1991	0.3 (0.1, 0.8)	4 (3, 5)		16.0[a]
Tsianos EV[187]	2003	Greece	Northwest Greece	1982–1997	0.5 (0.4, 0.7)	6.6 (5.3, 6.9)		
Tsianos EV[188]	2005	Greece	Northwest Greece	1981–1997	0.5 (0.4, 0.7)	4.5 (3.9, 4.8)		
Economou M[189]	2007	Greece	Northwest Greece (Ioannina)	1983–2005	2.7 [1.7–4.1]	0.9 [0.1–1.7]	1.2[a]	8.0[a]
Trallori G[190]	1991	Italy	Florence	1978–1987	1.5	4.0	9.0[a]	14.6[a]
Trallori G[191]	1996	Italy	Florence	1978–1992	2.8	7.7	4.7[a]	7.5[a]
Lanfranchi GA[192]	1976	Italy	Bologna	1972–1973	1.85	0.75		
Tragnone A[193]	1993	Italy	Bologna	1986–1989	2.7	5.0		
Cottone M[194,195]	1991	Italy	Sicily	1987–1989	2.7			
Cottone M[196]	2006	Italy	Casteltermini (Sicily)	1979–2002	12.7	5.8	4.0[a]	2.6[a]
Ranzi T[197]	1996	Italy	Lombardia	1990–1993	3.4	7.0		
Tragnone A[198]	1996	Italy	Total	1989–1992	2.28 (1.98, 2.58)	5.17 (4.71, 5.62)		
			Padova		2.37 (1.61, 3.31)	3.79 (2.85, 4.72)		
			Modena		2.44 (1.45, 3.43)	3.44 (2.27, 4.61)		
			Bologna		2.49 (1.69, 3.30)	4.47 (3.42, 5.51)		
			Forli		2.85 (1.80, 3.90)	5.90 (4.39, 7.42)		
			Firenze		1.86 (1.15, 2.57)	6.08 (4.82, 7.35)		
			L'Aquila		2.45 (1.39, 3.52)	7.17 (5.32, 9.02)		
			Avellino		2.30 (1.27, 3.33)	5.14 (3.59, 6.69)		
			Messina		1.91 (1.07, 2.75)	7.11 (5.49, 8.74)		
Dal Pont E[199]	2010	Italy	Northeast (Belluno)	1997–2008	3.4	7.8	3.4	−2.5
Cachia E[200]	2008	Malta	Nationwide	1993–2005	1.29	7.88	4.0	2.7
Western Europe								
Latour P[201]	1998	Belgium	Liege	1993–1996	4.5	3.6		
Latour P[202]	1996	Belgium	Liege	1993–1994	5.5	3.5		
Van Gossum A[203]	1996	Belgium	Brussels	1992–1993	3.7	3.0		
Piront P[204]	2002	Belgium	Liege	1993–1996 (<60 years)	4.8	3.4		

Appendix 2. Continued

Lead author	Year	Country	Region	Study period	CD incidence rate (10^5)	UC incidence rate (10^5)	Annual average percent change	
							CD	UC
				1993–1996 (>60 years)	3.45	4.5		
Colombel JF[205]	1990	France	Nord-Pas de Calais region	1988	6.3	4.6		
Flamenbaum M[206]	1997	France	Puy-de-Dome county	1993–1994	5.7	1.9		
Gower-Rousseau C[207]	1994	France	Northern France	1988–1990	4.9	3.2		
Molinie F[208]	2004	France	Northern France	1988–1999	5.8 (5.6, 6.0)	4.0 (3.8, 4.1)	2.1[a]	−2.2[a]
Abakar-Mahamat A[209]	2007	France	Corsica	2002–2003	4.05	9.5		
Nerich V[210]	2006	France	Metropolitan France	2000–2002	8.2	7.2		
Pagenault M[211]	1997	France	Brittany	1994–1995	2.8	2.9		
Edouard A[212]	2005	France	Guadeloupe and Martinique	1997–1999	1.85	2.23		
Colombel JF[213]	1989	France	Nord-Pas-de-Calais	1988	4.23	2.96		
Loffler A[214]	1993	Germany	Cologne	1985–1986	5.1			
Goebell H[215]	1994	Germany	Total	1980–1984	4.0			
			Essen		3.5			
			Mülheim		5.9			
			Duisburg		3.8			
			Oberhausen		4.2			
Daiss W[216]	1989	Germany	Tübingen	1970–1984	3.12	1.32	8.1[a]	7.2[a]
Dirks E[217]	1994	Germany	Ruhr area, Western Germany	1980–1984		2.9		
Timmer A[218]	1999	Germany	Ruhr area, Western Germany	1980–1984		2.4 (1.8, 3.0)		
				1991–1995		3.0 (2.4, 3.7)		
Timmer A[219]	1999	Germany	Ruhr area, Western Germany	1980–1984	4.9 (4.2, 5.6)			
				1991–1995	5.2 (4.4, 6.1)			
Brandes JW[220]	1983	Germany	Marburg/Lahn, Western Germany	1964–1975	3.0			
				1962–1973		5.08		
Ott C[221]	2008	Germany	Oberpfalz	2004–2006	6.6 (5.6,7.7)	3.9		
Fahrlander H[222]	1971	Switzerland	Basle	1960–1969	1.6			
Eastern Europe								
Bitter J[223]	1980	Czech	North Bohemia	1978		1.3		
Lakatos L[224]	2004	Hungary	Veszprem Province	1977–2001	2.23 (0.5, 3.96)	5.89 (2.15, 9.63)	11.1[a]	8.9[a]
Lakatos L[225]	2009	Hungary	Western	2002–2006	8.87			
Prikazska M[226]	1996	Slovakia	Nationwide	1994	6.75			
Chojecki Z[227]	1964	Poland	First Medical Clinic, Warsaw Medical Academy	1951–1960	0.66			
Gheorghe L[228]	1997	Romania	Bucharest	1990–1997	0.42			
Gheorghe C[229]	2004	Romania	National	2002–2003	0.50	0.97		
			Northeast		0.39	0.76		
			Southeast		0.50	0.82		
			South		0.38	0.76		
			Southwest		0.44	1.05		
			West		0.58	1.10		
			Northwest		0.42	1.13		
			Centre		0.55	0.86		
			Bucharest		0.88	1.49		
Africa								
Wright JP[230]	1983	South Africa	Cape Town	1970–1979	1.14		23.3[a]	
Wright JP[231]	1983	South Africa	Cape Town	1970–1979		1.96		4.6[a]
Wright JP[232]	1986	South Africa	Cape Town	1980–1984	1.79	2.63		
Novis[233]	1975	South Africa	Cape Town	1970–1974	0.5			
Rajput HI[234]	1992	South Africa	Durban (Indian population)	1983–1987		2.7		
Australia and New Zealand								
Anseline PF[235]	1995	Australia	Hunter Valley	1967–1988	1.38			
Wilson J[236]	2010	Australia	Geelong, Victoria	2007–2008	29.3 (23.5–36.7)	17.4 (13.0–23.2)		
Eason RJ[237]	1982	New Zealand	Auckland (Caucasian)	1969–1978	1.75	5.5		
Schlup M[238]	1986	New Zealand	Dunedin	1972–1981	2.4			
Gearry RB[239]	2006	New Zealand	Canterbury	2004–2005	16.5	7.6		

NOTE. Annual average percent change in incidence for IBD studies that reported incidence rates for periods spanning at least 10 years. 95% Confidence Intervals are in the parentheses.

[a]Statistically significant (ie, $P < .05$) for time-trend analysis.

[b]Study incorporates previous data and provides update.

[c]Reference from Calkins.[13]

[d]Study contains data from many regions within Europe and can therefore not be stratified further.

Table 3. Summary of studies reporting prevalence of UC and/or CD (Molodecky et al., Gastroenterology 2012, with permission)[88]

Appendix 3. Summary of Studies Reporting Prevalence of UC and/or CD, Stratified by Geographic Region

Lead author	Year	Country	Region	Study period	CD prevalence (10^5)	UC prevalence (10^5)
North America						
Lowe AM[1]	2009	Canada	Quebec	1993–2002	189.7	
Bernstein CN[2]	1999	Canada	Manitoba	1994	198.5	169.7
Green C[3]	2006	Canada	Manitoba	1990–2001	222.2	197.9
Pinchbeck BR[4]	1988	Canada	Alberta	1981	44.4	37.5
Bernstein CN[5]	2006	Canada	Canada	1998–2000	279.2	193.7
			British Columbia	1998–2000	233.7	162.1
			Alberta	1998–2000	160.7	185
			Saskatchewan	1998–2000	263.8	234.3
			Manitoba	1998–2000	271.4	248.6
			Nova Scotia	1998–2000	318.5	247.9
Loftus CG[6]	2007	United States	Olmsted County, Minnesota	2001	213.9	213.9
Gollop JH[7]	1988	United States	Olmsted County, Minnesota	1980	90.5	
Loftus EV[8]	2000	United States	Olmsted County, Minnesota	1991		229
Loftus EV[9]	1998	United States	Olmsted County, Minnesota	1991	132.7	
Sedlack RE[10]	1980	United States	Olmsted County, Minnesota	1975	105.7	
Sedlack RE[11]	1972	United States	Olmsted County, Minnesota	1965	28	117
Stonnington CM[12]	1987	United States	Rochester, Minnesota	1979		225.2
Kurata JH[13]	1992	United States	Fontana and Sunset, California	1984–1988	25.9	
Herrinton LJ[14]	2008	United States	Northern California	2002	96.3	155.8
Herrinton LJ[15]	2007	United States	Nationwide	1999–2001	129	191
Kappelman MD[16]	2007	United States	Nationwide	2003–2004	201 (197–204)	238 (234–241)
Appleyard CB[17]	2004	Puerto Rico	Southwestern	1996–2000	41.4	12.5
Edwards CN[18]	2008	Barbados	Nationwide	2004	16.7	44.3
South America						
Sobrero JM[19]	2009	Argentina	Nationwide	2009	15.0 (9.8–22.7)	76.1 (63.2–91.6)
Asia and Middle East						
Lok KH[20]	2007	China	Hong Kong	1991–2006	1.5	
Lok KH[21]	2008	China	Hong Kong	2006		7.0
Sung JJ[22]	1994	China	Hong Kong	1992	1.25	
Chow DKL[23]	2009	China	Hong Kong	1985–2006		26.5 (22.6–30.9)
Zheng JJ[24]	2005	China	Nationwide	1950–2002	1.38	
Zheng[25]	2010	China	Nationwide	1950–2007	1.13	
Niv Y[26]	1990	Israel	Upper Galilee	1986		44.58
Fireman Z[27]	1989	Israel	Tel Aviv Jafo	1970–1980	13.28	
Grossman A[28]	1989	Israel	Tel Aviv Jafo	1980		55.16
Gilat T[29]	1974	Israel	Tel Aviv Jafo	1970		37.4
Rozen P[30]	1979	Israel	Tel Aviv Jafo	1976	12.31	
Odes HS[31]	1994	Israel	Southern Israel	1992	50.6	
Shapira M[32]	1994	Israel	Kinneret Subdistrict	1960–1990	20.24	
Odes HS[33]	1987	Israel	Beer Sheva	1985		70.6
Krawiec J[34]	1984	Israel	Beer Sheva	1980	14.0	
Niv Y[35]	1999	Israel	Kibbutz residents	1987–1997	45.3	
Niv Y[36]	2000	Israel	Kibbutz residents	1987–1997		144.1
Odes HS[37]	1989	Israel	Beer Sheva	1987	30 (23–38)	89 (77–103)
Niv Y[38]	1991	Israel	Kibbutz	1987		121.08
Odes HS[39]	1991	Israel	Southern Israeli (Arab population)	1990	3.2	9.8
Birkenfeld S[40]	2009	Israel	Kibbutz	1987–2007		168.3
Zvidi I[41]	2009	Israel	Kibbutz	1987–2007	67.9	
Sood A[42]	2003	India	Punjab	2000		44.3
Abdul-Baki H[43]	2007	Lebanon	Nationwide	2000–2004	53.1	106.2
Morita N[44]	1995	Japan	Nationwide	1991	5.85	18.12
Yao T[45]	2000	Japan	Nationwide	1986–1998		7.6
Higashi A[46]	1988	Japan	Nationwide	1985	1.86	7.85
Asakura K[47]	2009	Japan	Nationwide	2003–2005	18.6	57.3
Yoshida Y[48]	1990	Japan	Nationwide	1975	0.88	5.5
Yang SK[49]	2000	South Korea	Songpa-Kangdong, Seoul	1997		7.57 (5.95–9.19)
Yang SK[50]	2008	Korea	Songpa-Kangdong District, Seoul	2005	11.24	30.87
Tan Y-M[51]	2005	Malaysia	Kuala Lumpur	1985–1998		9.11
Lee YM[52]	2000	Singapore	Nationwide	1985–1996	3.6	6

Appendix 3. Continued

Lead author	Year	Country	Region	Study period	CD prevalence (10^5)	UC prevalence (10^5)
Tan CC[53]	1992	Singapore	Nationwide	1981–1990	1.3	8.6
Law N-M[54]	1998	Singapore	Nationwide - Chinese Singaporeans	1986–1993	15.1	
Niriella MA[55]	2010	Sri Lanka	Colombo and Gampaha	2007–2008	1.2 (1.0–1.4)	5.3 (5.0–5.6)
Tezel A[56]	2003	Turkey	Trakya	2002		4.9
Al-Shamali M[57]	2003	Kuwait	Nationwide	1985–1999		41.7
Northern Europe						
Bonnevie O[58]	1968	Denmark	Copenhagen and Gentofte	1967		44.1
Langholz E[59]	1991	Denmark	Copenhagen	1987		161.2
Munkholm P[60,61]	1992	Denmark	Copenhagen	1987	54	
Jacobsen BA[62]	2006	Denmark	North Jutland	2002	151	294
Binder V[63]	1982	Denmark	Copenhagen	1978	34	117
Berner J[64]	1986	Faroe Islands	Nationwide	1983	31.8	157.3
Manninen P[65]	2010	Finland	Tampere	1986–1999	82	205
Bjornsson S[66]	1983	Iceland	Nationwide	1950–1979		52.6
Bjornsson S[67]	1989	Iceland	Nationwide	1950–1979	6	72
Shivananda S[68]	1987	The Netherlands	Leiden	1979–1983	48	
Shivananda S[69]	1987	The Netherlands	Leiden	1979–1983	48	58.4
Haug K[70]	1988	Norway	Western Norway (Sogn and Fjordane, Hordaland, and Rogaland)	1984–1985		92
Bengtson MB[71]	2009	Norway	Southeast (Oslo)	1990–1993	262 (196–328)	505 (420–599)
Brahme F[72]	1975	Sweden	Malmo	1965–1973	48.1	
				1968		89
Bergman L[73]	1975	Sweden	Uppsala and Västmanland	1967–1973	38.5	
Norlen BJ[74]	1970	Sweden	Uppsala and Västmanland	1967	27	
Lapidus A[75]	2006	Sweden	Stockholm	2001	213	
Lindberg E[76]	1991	Sweden	Immediate catchment area of Örebro Medical Center Hospital	1987	146	
Lindgren A[77]	1996	Sweden	Goteborg	1990	94 (84–104)	
Tysk C[78]	1992	Sweden	Orebro	1987		198
Keighley A[79]	1976	United Kingdom	Nottingham	1971	34.99	
Evans JG[80]	1965	United Kingdom	Oxford	1960	9	65.7
Rubin GP[81]	2000	United Kingdom	North Tees	1994	144.8	243.4
Fellows IW[82]	1990	United Kingdom	Derby	1985	85	
Fellows IW[83]	1988	United Kingdom	Derby (West Indians)	1986	60.6	
De Dombal FT[84]	1971	United Kingdom	Leeds	1968	25	
Lee FI[85]	1985	United Kingdom	Blackpool	1980	47	
Miller DS[86]	1974	United Kingdom	Nottingham	1958–1971	26.5	
Kyle J[87]	1992	United Kingdom	Northeastern and Northern Isles, Scotland	1988	147	
Mayberry JF[88]	1980	United Kingdom	Wales Nationwide	1967–1976	40.2	
Penny WJ[89]	1985	United Kingdom	Britain and Ireland (Mormons)	1981	79	389
Montgomery SM[90]	1998	United Kingdom	England Nationwide 26 year olds	1996	21.4 (12.3–30.6)	12.2 (5.3–19.2)
Stone MA[91]	2003	United Kingdom	Central England (Trent)	2002	130 (107–157)	243 (211–278)
Probert CSJ[92]	1993	United Kingdom	England - Leicestershire	1990	European 75.8 South Asian 33.2 Hindu 31.9 Sikh 30.8 Muslim 53.8	European 90.8 South Asian 136.0 Hindu 151.5 Sikh 138.4 Muslim 107.6
Mediterranean/Southern Europe						
Pavlovic-Calic N[93]	2008	Bosnia and Herzegovina	Tuzla	2006	28.2	
Salkic NN[94]	2010	Bosnia and Herzegovina	Tuzla	2006		43.1 (37.3–48.8)
Vucelic B[95]	1991	Croatia	Zagreb	1989	8.3	
Jovanovic Z[96]	1999	Croatia	Rijeka and Istra	1973–1994	11.5	

Appendix 3. Continued

Lead author	Year	Country	Region	Study period	CD prevalence (10^5)	UC prevalence (10^5)
Azevado LF[97]	2010	Portugal	Nationwide	2003–2007	58	57
Saro Gismera C[98]	2003	Spain	Province of Liege, Asturias	1997	87.45	109.96
Saro Gismera C[99]	2000	Spain	Gijon, Asturias	1997	116.47	121.79
Mate-Jimenez J[100]	1994	Spain	Madrid	1988	19.8	43.4
Ruiz Ochoa V[101]	1984	Spain	Galicia	1982	5.2	
Brullet E[102]	1991	Spain	Sabadell	1985–1989		3.95
Alonso P[103]	1992	Spain	Soria	1990	13	32
Martinez-Salmeron JF[104]	1993	Spain	Granada	1979–1988	9	21
Hinojosa J[105]	1990	Spain	Sagunto	1983–1989	21.4	28.87
Pajares Garcia JM[106]	1987	Spain	Madrid	1976–1983	3.5	
Trallori G[107]	1996	Italy	Florence	1992	40	121
Cottone M[108]	2006	Italy	Casteltermini (Sicily)	1979–2002	322 (290–383)	142 (117–167)
Dal Pont E[109]	2010	Italy	Northeast (Belluno)	2008	45	93
Western Europe						
Tsianos EV[110]	2005	Greece	(Ioannina, Arta, Preveza, Thesprotia, Corfu and Lefkas) Northwest Greece	1981–1997	0.6	4.9
Loffler A[111]	1993	Germany	Cologne	1986	30.67	
Goebell H[112]	1994	Germany	Total	1984	36	
Daiss W[113]	1989	Germany	Tübingen	1984	54.6	24.8
Dirks E[114]	1994	Germany	Ruhr area, Western Germany	1984		27.3
Brandes JW[115]	1983	Germany	Marburg/Lahn, Western Germany	1975	30.5	
				1973		48.8
Juillerat P[116]	2008	Switzerland	Vaud	2003–2004	100.7 (98.2–103.4)	105.0 (102.3–107.7)
Bitter J[117]	1980	Czech	North Bohemia	1968–1978		17.6
Eastern Europe						
Lakatos L[118]	2004	Hungary	Veszprem Province	1991–2001	35	101
Prikazska M[119]	1996	Slovakia	Nationwide	1994	6.75	
Chojecki Z[120]	1964	Poland	First Medical Clinic, Warsaw Medical Academy	1951–1960	66	
Gheorghe C[121]	2004	Romania	National	2002–2003	1.51	2.42
Australia and New Zealand						
Anseline PF[122]	1995	Australia	Hunter Valley	1988	34	
Gearry RB[123]	2006	New Zealand	Canterbury	2004	155.2	145

Note: 95% Confidence Intervals are in the parentheses.

Table 4. Summary of studies reporting prevalence of IBD in PSC

Reference	Geographical region	Study period	No. of PSC patients	Ulcerative colitis, no (%)[β]	Crohn`s disease, no (%)[β]	Indeter-minate colitis, n (%)[β]	Total prevalence of IBD (%)
Chapman et al.[3]	London, UK	NR	29	21 (72)	0	-	21 (72)
Wiesner et al.[125]	Minnesota, US	1970-1977	50	24 (48)	3 (6)	-	27 (54)
Sivak et al.[120]	Cleveland, Ohio, US	1974-1978	13	10 (77)	1 (8)	0	11 (85)
Aadland et al.[106]	Oslo, Norway	1975-1984	45	37 (82)	6 (13)	2 (4)	45 (100)
Helzberg et al.[110]	Connecticut, US	1956 - 1985	53	31 (58)	2 (4)	-	33 (62)
Stockbrügger et al.[121]	Gothenburg, Sweden	1975-1984	46	36 (78)	2 (4)	5 (11)	43 (93)
Wiesner et al.[1]	Minnesota, US	1970-1984	174	«Most commonly UC»	-	-	124 (71)
Rabinovitz et al.[118]	Pennsylvania, US	1985-1987	66	39 (59)	8 (12)	-	47 (71)
Martin et al.[113]	Boston, US	1950-1989	178	70 (39)	15 (8)	3 (2)	88 (50)
Farrant et al.[107]	London, UK	1972-1989	126	83 (66)	2 (2)	-	85 (67)
Schrumpf et al.[119]	Oslo, Norway	1975-1989	77	58 (75)	11 (14)	7 (9)	76 (98)
Escorsell et al.[16]	Spain	1984-1988	43	19 (44)	1 (2)	-	20 (47)
Wilschanski et al.[124]*	Canada	1986-1994	32	14 (44)	3 (9)	-	17 (53)
Lemmer et al.[112]	Cape Town, South Africa	1981-1991	36	20 (56)	2 (6)	4 (11)	26 (72)
Broomé et al.[2]	Sweden	NR	305	220 (72)	20 (7)	9 (3)	249 (82)
Kochhar et al.[111]	Chandigarh, India	1984-1994	18	9 (50)	0	0	9 (50)
Okada et al.[114]	Japan	NR	155	29 (19)	2 (1)	4 (3)[#]	35 (23)
Okolicsanyi et al.[115]	Italy	1973-1993	117	42 (36)	12 (10)	9 (8)	63 (54)
Takikawa et al.[122]	Japan	1975-1995	192	38 (20)	2 (1)	-	40 (21)
Faubion Jr. et al.[108]*	Minnesota, US	1975-1999	52	32/36 (89)[§]	4/36 (11)[§]	-	43 (83)
Parlak et al.[116]	Turkey	1993-2000	18	9 (50)	4 (22)	-	13 (72)
Ang et al.[11]	Singapore	1989-1998	10	-	2 (20)	-	2 (20)
Ponsioen et al.[117]	The Netherlands	1970-1999	174	83 (48)	28 (16)	3 (2)	114 (66)
Bambha et al.[12]	Olmsted Co., Minnesota, US	1976-2000	22	12 (55)	3 (14)	1 (5)	16 (73)

Feldstein et al.[109]*	Minnesota, US	1980-1999	52	30 (58)	8 (15)	4 (8)	42 (81)
Kingham et al.[19]	South Wales, UK	1984-2003	53	30 (57)	3 (6)	-	33 (62)
Tischendorf et al.[123]	Hannover, Germany	1978-2004	273	141 (52)	29 (11)	2 (1)	172 (63)
Kaplan et al.[18]	Alberta, Canada	2000-2005	49	14 (29)	19 (39)	-	33 (67)
Card et al.[15]	UK	1987-2002	223	67 (30)	13 (6)	28 (13)	108 (48)
Lindkvist et al.[20]	Västra Göta-land, Sweden	1992 - 2005	199	129 (65)	17 (9)	5 (3)	152 (76)

[β]of all study patients, *pediatric study, [#]designated “Other type of colitis” in the publication, [§]with sufficient diagnostic evaluation, NR, not reported

Table 5. Summary of studies reporting prevalence of PSC in IBD

Reference	Geographical region	Study period	No. of IBD patients	No. (%) of PSC patients
Schrumpf et al.[129]	Oslo, Norway	1974-1978	336 (UC)	14 (4.2)*
Shepherd et al.[132]	Oxford, UK	NR	681 (UC)	17 (2.5)
Lupinetti et al.[134]	Baltimore, Maryland, US	1966-1977	202	2 (1.0)
Tobias et al.[135]	South Africa	1975-1981	250 (UC) 164 (CD)	8 (3.2) 2 (1.2)
Monsén et al.[127]	Stockholm, Sweden	1955-1979	1274 (UC)	13 (1.0) [β]
Olsson et al.[128]	Sweden	1988	1500 (UC)	55 (3.7)
Wewer et al.[130]	Herlev, Denmark	NR	396 (UC) 125 (CD)	3 (0.8) 0
Broomé et al.[133]	Stockholm, Sweden	1955-1979	1274 (UC)	29 (2.3)
Rasmussen et al.[136]	Aalborg, Denmark	1976-1987	305 (UC)	11 (3.6)
Rasmussen et al.[131]	Aalborg, Denmark	1976-1991	262 (CD)	9 (3.4)
Bernstein et al.[86]	Manitoba, Canada	1984 -1996	4454 (IBD)	UC: males 3%, females 1% CD: males 0.4%, females 0.3%
Parlak et al.[116]	Turkey	1993-2000	386 (UC) 110 (CD)	9 (2.3) 4 (3.6)
Mendes et al.[126]	Rochester, Minnesota, US	2000-2001	544	25 (4.6)

*later follow-up: 25 (7.5%)[235]36, [β]including 11 patients with pericholangitis, UC, ulcerative colitis; CD, Crohn`s disease; NR, not reported

Table 6a. Summary of studies reporting IBD activity after liver transplantation in PSC patients

Reference	Study period	No. of PSC-IBD patients[#]	Median follow-up post Ltx, yrs	Course of IBD post Ltx, promoting and protecting factors for increased IBD activity post Ltx
Gavaler et al.[172]	1982-1985	23	1.9[β]	14 better, 9 unchanged, 0 worse
Shaked et al.[174]	1985-1990	24	2.5[β]	4 better, 12 unchanged, 8 worse
Stephens et al.[184]	1985-1991	27	NR	18 better, 4 unchanged, 5 worse
Knechtle et al.[185]	1986-1994	21	NR	7/21 (33%) active IBD
Miki et al.[180]	1982-1992	26	NR	9/26 (35%) active IBD Promoting: Younger age at IBD diagnosis
Narumi et al.[181]	1988-1993	24	3	6/19 (32%) progressive IBD
Papatheodoridis et al.[182]	1989-1996	16	3.2	0 better, 8 unchanged, 8 worse
Befeler et al.[170]	1985-1996	23	3.1[β]	11 better, 12 unchanged, 0 worse
Saldeen et al.[183]	NR	17	4[β]	10 better, 6 unchanged, 1 worse
Dvorchik et al.[178]	1981-1997	206	5.9[β]	Increased colectomy rate due to active IBD
Maclean et al.[179]	1985-2000	44	6.1[β]	14 better, 16 unchanged, 14 worse
Van de Vrie et al.[175]	1987-2000	17	5	2 better, 12 unchanged, 3 worse
Haagsma et al.[173]	1979-2001	25*	7.2	9/25 (36%) active IBD Promoting: pre Ltx IBD, use of TL Protecting: use of Azt, use of CsA/Azt/CS
Ho et al.[186]	1992-2003	26	4.4	Higher CS requirement rate post Ltx Higher IBD relapse rate post Ltx
Verdonk et al.[177]	1987-2002	31*	NR	12/31 (39%) active IBD Promoting: CMV infection
Verdonk et al.[176]	1994-2004	49*	6.1	32/49 (65%) active IBD Promoting: IBD symptoms at time of Ltx, short interval of IBD before Ltx, use of TL Protecting: use of 5-ASA
Cholongitas et al.[171]	1989-2004	33	2.8	0 improved, 16 unchanged, 17 worse Protecting: combined HLA-DR and -DQ disparity between donor and recipient
Moncrief et al.[187]	1989-2006	49	5.7	3 better, 33 unchanged, 13 worse[$] Protecting: longer use of CS
Joshi et al.[188]	1990-2009	74	6.6[β]	33/74 (45%) flare (active IBD) Promoting: smoking at time of Ltx

[#]with intact colon at time of Ltx, [β]mean, *PSC and autoimmune hepatitis patients, [$]5 *de novo* IBD included, NR, not reported; TL, tacrolimus; Azt, azathioprine; CsA, Ciclosporine A: CS, corticosteroids

Table 6b. Summary of studies reporting *de novo* IBD in PSC

Reference	Study period	Median follow-up post Ltx, yrs	Prevalence, n (%)	Time Ltx – *de novo* IBD, median, yrs	Cumulative incidence, promoting and protecting factors for *de novo* IBD post Ltx
Papatheo-doridis et al.[182]	1989-1996	3.2	3/12 (25)	2[β]	NR
Befeler et al.[170]72	1985-1996	3.1[¥]	1/6 (17)	NR	NR
Haagsma et al.[173]	1979-2001	7.2	6/53 (11)*	3.9	Cum. ins. at 1, 3, 5, 10 yrs: 0, 4, 11, 14% Promoting: use of TL Protecting: use of Azt, use of CsA/Azt/CS 5/6 *de novo* patients used TL
Van de Vrie et al.[175]	1987-2000	5	1/11 (9)	0.8	NR
Verdonk et al.[177]	1987-2002	6.4	6/53 (11)*	NR	Promoting: CMV infection 6/6 *de novo* patients experienced CMV infection
Verdonk et al.[176]	1994-2004	6.1	8/42 (19)*	5.2	Cum. ins. at 1, 3, 5, 10 yrs: 0, 5, 10, 30% Promoting: CMV mismatch, use of TL (NS) Protecting: Azt (NS)
Moncrief et al.[187]	1989-2006	5.7	5/17 (29)	4.8	NR
Joshi et al.[188]	1990-2009	6.6	6/36 (17)	2.4[β]	Cum. incidence at 1, 5, 10 yrs: 7, 22, 29% 6/6 *de novo* patients used TL

*PSC and autoimmune hepatitis patients, [β]mean, NR, not reported; NS, not significant; TL, tacrolimus; Azt, azathioprine; CsA, Ciclosporine A

Table 7. Summary of studies reporting colorectal neoplasia in PSC-IBD after liver transplantation

Reference	No. of PSC-IBD patients[#]	Median follow-up post Ltx, yrs	Prevalence of, cumulative risks and risk factors for colorectal neoplasia post Ltx
Higashi et al.[191]	36	3.8	2 (2 CRC)
Shaked et al.[174]	29	2.5[β]	0
Bleaday et al.[192]	27	3.3[β]	3 (2 CRC, 1 villous adenoma with severe dysplasia)
Knechtle et al.[185]	21	NR	3 CRC
Narumi et al.[181]	22	3.1	4 (3 CRC (2 recurrent), 1 CR dysplasia)
Loftus et al.[193]	57	4.2	3 CRC. Cum. risk for CR dysplasia 5, 8 yrs post Ltx: 15, 21% Increased risk of CRC post Ltx but NS compared to non-transplanted PSC-IBD patients (RR 4.4) No risk factors found for CR neoplasia in univariate analysis
Papatheodoridis et al.[182]	18	3.2	0
Dvorchik et al.[178]	169	5.91[β]	7 CRC Not increased risk of CRC post Ltx compared to pre Ltx
Van de Vrie et al.[175]	17	5.2	4 (2 CRC, 2 CR dysplasia)
Vera et al.[194]	83	NR	8 CRC. Cum. risk for CRC 5, 10 yrs post Ltx: 14, 17% Increased incidence of CRC in PSC vs. non PSC patients post Ltx (5.3% vs.0.6%, p<0.001) Risk factors for CRC: CR dysplasia post Ltx, IBD >10 years, pancolitis
Ho et al.[186]	26	4.4	3 (1 CRC, 2 CR dysplasia)
Hanouneh et al[195]	43	4.6	11 CR dysplasia Similar rate of CRN in PSC patients with and without Ltx (34% vs.30%, p=0.24) Higher rate of CRN in PSC vs. non PSC patients post Ltx (34% vs. 0%, p=0.018) Risk factor for CRN: CMV infection post Ltx

[#]with intact colon at time of Ltx, [β] mean, NR, not reported; NS, not significant; Ltx, liver transplantation; CR, colorectal; CRC, colorectal cancer; CRN, colorectal neoplasia; RR, relative risk

Table 8. Interrater agreement in interpretation of histological findings in terminal ileum and colon (%)

Feature	Term. ileum	Cecum	Asc. colon	Transv. colon	Desc. colon	Sigmoid colon	Rectum	Interrater agreement
Presence of inflammatory changes	100	41	67	68	86	50	65	**75**
Chronic active inflammation	100	37	67	86	55	60	87	**90**
Atrophy	100	23	80	82	48	68	87	**91**
Crypt distortion	95	45	65	68	91	43	65	**72**
Goblet cell depletion	90	41	74	50	95	57	48	**59**
Interrater agreement	**97**	**38**	**70**	**71**	**75**	**55**	**70**	**70**

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9. Errata

Page 17, third paragraph, line 8: “AIC” should be replaced with “IAC”

Article II, first page, affiliation no.8: “Section for Transplantation Surgery, Department of Transplantation Medicine, Division of Cancer, Surgery and Transplantation, Oslo University Hospital, Oslo, Norway” should be replaced with: “Transplantation and Liver Surgery Clinic, Helsinki University Hospital, Helsinki, Finland”

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