Prevalence and long-term outcome of sub-clinical primary sclerosing cholangitis in patients with ulcerative colitis

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Abstract

Background: Primary sclerosing cholangitis (PSC) is closely associated with inflammatory bowel disease, particularly ulcerative colitis (UC), with an increased risk of biliary and colorectal malignancy. We sought to clarify the prevalence, characteristics and long-term outcome of sub-clinical PSC diagnosed by magnetic resonance cholangiogram (MRC) in patients with UC and normal liver biochemistry, with or without colorectal dysplasia (CRD).

Methods: In this prospective case-control study, 70 patients with UC and normal liver function (51 extensive UC, 19 CRD), 28 healthy volunteers (negative controls) and 28 patients with PSC and cholestasis (positive controls) underwent MRC and blood evaluation. MRC scans were interpreted blindly by two radiologists who graded individually, the scans as definitive for PSC, possible PSC or normal. Clinical outcome was assessed by blood monitoring, abdominal imaging and endoscopic surveillance.

Results: 7/51 (14%) with extensive UC and 4/19 (21%) with CRD had biliary abnormalities on MRC consistent with PSC. 7/11 (64%) with sub-clinical PSC had isolated intrahepatic duct involvement. Sub-clinical PSC was associated with advanced age (P = .04), non-smoking (P = .03), pANCA (P = .04), quiescent colitis (P = .02), absence of azathioprine (P = .04) and high-grade CRD (P = .03). Inter-observer (kappa = 0.88) and intra-observer (kappa = 0.96) agreement for MRC interpretation was high. No negative controls were assessed as definite PSC, 4/28 were considered on blinding as possible PSC. During follow-up of sub-clinical PSC (median 10.1(3.1-11.9) years), four patients developed abnormal liver biochemistry, two had radiological progression of PSC and seven developed malignancy, including two biliary and one colorectal carcinoma.

Abbreviations: ALM, adenomatous lesion or mass; ALP, Alkaline phosphatase; ALT, Alanine transferase; AMA, antimitochondrial antibodies; ANA, antineutrophil antibody; ANCA, antineutrophil cytoplasmic antibody; ASUC, acute severe ulcerative colitis; CRC, Colorectal cancer; CRD, Colorectal dysplasia; CT, computerised tomography; DALT, dysplasia-associated lesion or mass; EHD, extrahepatic duct; ERC, endoscopic retrograde cholangiogram; GGT, gamma-glutamyl transferase; HGD, high-grade dysplasia; HLA, human leucocyte antigen; HPB, hepatopancreatobiliary; IBD, inflammatory bowel disease; IgG, Immunoglobulin G; IHD, intrahepatic duct; K, Kappa statistic; LGD, low-grade dysplasia; MRCP, magnetic resonance cholangiopancreatogram; NIHR, National Institute Heath Research; PSC, primary sclerosing cholangitis; SMA, antismooth muscle antibody; UC, ulcerative colitis; UDCA, ursodeoxycholic acid.

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Primary sclerosing cholangitis (PSC) is a progressive liver disease characterised by inflammation and fibrosis leading to multi-focal biliary strictures and cirrhosis. The clinical presentation of PSC is variable; 50% of patients are asymptomatic at presentation and identified while investigating cholestatic liver biochemistry. An elevated alkaline phosphatase (ALP) is the most frequent abnormality, although this can be normal in approximately 8.5% of cases, and may fluctuate during the course of disease. The diagnosis of large-duct PSC is established on the basis of a cholangiogram. Magnetic resonance cholangiography (MRC) is now considered the gold standard in diagnosis, as it is non-invasive, uses non-ionising radiation and can delineate distal bile duct anatomy in the presence of proximal obstruction. A position paper from the international PSC study group (IPSCG) confirms the importance of MR imaging in the assessment of PSC. In a meta-analysis of 456 subjects (185 with PSC and cholestasis), MRC was reported to have a high sensitivity (86%) and specificity (94%) for detecting PSC.

PSC is strongly associated with inflammatory bowel disease (IBD), with a reported association in Northern Europe and America of 60-80%. Ulcerative colitis (UC) accounts for most cases and often precedes the development of PSC, although it may be diagnosed at any time during the course of the liver disease. Traditionally, PSC is considered to be present in 0.8% to 5.6% of patients with UC, more frequently in those with extensive (5.5%) rather than distal (0.5%) colitis. A recent Norwegian study of 322 IBD patients screened with MRC found 8% had diagnostic features of PSC. Only 2.2% had been previously known to have PSC.

The colitis associated with PSC has characteristic features: pancolitis with co-existent ileitis ("back-wash ileitis"), more severe inflammation in the proximal colon, non-inflamed rectum ("rectal sparing"), and a quiescent or prolonged sub-clinical course, compared to UC without PSC. Genome-wide association and susceptibility studies suggest that PSC-UC is a unique disorder, genetically distinct from classical UC.

Patients with PSC-UC are at a greater risk of developing colorectal carcinoma (CRC) and CRD than those with UC alone; a meta-analysis of 11 studies concluded that the risk was increased by approximately four-fold. In view of this high risk of colorectal malignancy, and in contrast to classical UC without PSC, current guidelines recommend annual surveillance colonoscopy in patients with PSC-UC, starting from the time that PSC is diagnosed. Patients with PSC are also at an increased risk of cholangiocarcinoma and gallbladder carcinoma, and annual surveillance by abdominal ultrasound is recommended to detect gallbladder polyps, which may be premalignant.

Given the distinct phenotype and increased risk of malignancy in patients with PSC-UC compared to UC alone, we sought to determine whether sub-clinical PSC (defined as radiological PSC in the presence of normal liver biochemistry) could be detected by MRC in patients with UC and no clinical or biochemical evidence of liver disease. We aimed to investigate the prevalence and clinical course of PSC in two cohorts: patients with extensive UC and normal liver biochemistry, and patients with UC complicated by CRD and normal liver biochemistry. We hypothesised that those patients with UC-CRD may have a higher prevalence of sub-clinical PSC than those with UC alone. We followed these cohorts with blood tests, imaging and endoscopic surveillance as per current guidelines, to establish whether there was progression of disease and/or development of complications.
2.1.2 | CRD cohort

Patients with UC and histologically confirmed CRD/CRC identified at colorectal surveillance endoscopy were recruited from the IBD clinic at the John Radcliffe Hospital in Oxford from 2007 to 2010. The diagnosis of CRD/CRC was identified from the histopathology database searched from 1990 to 2010.

2.1.3 | Controls

Positive controls were recruited from the hepatology outpatient clinic with an established diagnosis of PSC, confirmed on MRC (n = 28/28) and liver biopsy (n = 20/28). Normal healthy controls were recruited via an open invitation to healthy individuals advertised through the John Radcliffe Hospital information boards between 2005 and 2008.

2.2 | Inclusion and exclusion criteria for cases

2.2.1 | Extensive UC cohort

Inclusion criteria were those over 18 years of age, with an endoscopic and histological diagnosis of UC confirmed on two separate colonoscopies and biopsy specimens, normal liver function tests, and no known evidence of biliary disease. Exclusion criteria were those patients with histology suggestive of indeterminate colitis or Crohn’s disease, no documented extent of colitis, left sided colitis (distal or proctitis), abnormal liver biochemistry at any time prior to the study (excluding isolated elevations of bilirubin), previous imaging or endoscopic evidence suggestive of biliary abnormalities, or contraindications to MRC (pacemaker, metallic implants, severe claustrophobia etc).

2.2.2 | CRD cohort

Inclusion criteria were as for the extensive UC cohort, with the addition of histological evidence of CRD or CRC within a segment of colitis. Exclusion criteria were as for the extensive UC cohort with the additional exclusion of those with histologically indefinite CRD or sporadic adenomas arising proximal to the upper limit of colitis.

2.3 | Definitions for this study

The extent of colitis was defined as the maximum documented extent histologically at any time during the course of the disease. Liver biochemistry was defined as normal if the serum alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and alanine transferase (ALT) values were below the upper limit of normal for our institution at the time of recruitment and on all previous hospital records. An isolated mildly elevated bilirubin (up to two times the upper limit of normal) was accepted after assessment by a consultant hepatologist (RWC) as attributable to Gilbert’s syndrome. The presence of CRD or CRC was identified at colonoscopy and confirmed histologically. CRD was classified at the time of this study, as either flat or associated with a raised lesion or mass (dysplasia-associated lesion or mass (DALM) or adenoma-like mass (ALM)), and confirmed histologically as arising within an area of documented colitis. In accordance with current SCENIC classification, these would be classified as endoscopically invisible dysplasia, endoscopically resectable non-polypoid and polypoid lesions. Two separate gastrointestinal pathologists blinded to clinical details (BW and DD) reviewed the colonic biopsies and re-defined the degree of dysplasia using the WHO classification: (a) low-grade CRD (none, mild or moderate); or (b) high-grade CRD (severe dysplasia, carcinoma in situ or intramural carcinoma).

2.4 | Enrolment of patients and controls to the extensive UC and CRD cohorts

Enrolment to both cohorts of this study for cases and controls is outlined in the flowcharts in Figure S1A and B.

2.4.1 | Extensive UC cohort

Sixty-two patients identified from the IBD clinic with documented extensive UC and normal liver function tests opted into this study. Eleven of these were excluded; five because of limited extent or incorrect classification of colitis on review, five because of claustrophobia or other contraindication to MRC and one because of abnormal liver biochemistry at recruitment itself. Fifty-one patients participated, who all underwent an MRC and blood tests at recruitment. Forty-eight patients were followed up in IBD clinic in Oxford and three patients were follow-up at other UK institutions, contacted by telephone to establish clinical outcome. Routine follow-up included annual review with repeat blood tests, with abdominal imaging and endoscopic surveillance as clinically indicated according to national guidelines. Demographics, clinical details, laboratory data, endoscopy and histology reports were reviewed retrospectively.

Twenty-eight healthy volunteers (negative controls) were matched for age and gender, and underwent an MRC under the same conditions as the cases. Twenty-eight patients with PSC (positive controls) were matched for age and gender, and their MRC scans and blood tests at the time of diagnosis were retrospectively reviewed.

2.4.2 | CRD cohort

Forty-eight patients were identified from the histopathology database with UC and histological evidence of CRD. Twenty-eight
patients who attended the IBD clinic with UC and prior CRD/CRC opted into this study. Eight were excluded; three because of the presence of sporadic adenomas, two because of incorrect classification of colitis, two because of contraindications to MRC and one because of distance living away from the hospital. Nineteen patients participated, who all had an MRC and blood tests at recruitment. At the analysis stage, two patients were excluded from this study because consensus histological opinion defined “indefinite” rather than low-grade dysplasia. Thus, 17 patients received follow-up in IBD clinic (virtually and/or in person); 15 in Oxford and 2 elsewhere who were contacted, as per the extensive UC cohort patients, to establish clinical outcome. MRC scans from 24 positive and negative controls (age and gender matched) were blinded and re-analysed for the CRD cohort.

2.5 | Ethics and consent

Ethical approval was granted from the Oxfordshire Research Ethics Committee (Extensive UC cohort: 05/Q1606/151 and CRD cohort: 09/H0607/4). Written informed consent was obtained from each patient and control for this study. A letter was sent to the patient/control with a copy to their GP informing them of the results of their study bloods and MRC scan. Results that required further discussions were followed up by the research team and contact made. Further assessment was determined by clinical need. For extensive UC patients this was routine in outpatients with liver tests performed on an annual basis and colonoscopy as per disease duration and severity.

2.6 | Magnetic resonance scans and protocol

Magnetic resonance cholangiograms (MRC) for cases and negative controls were obtained between 2005 and 2010, within 3 months of recruitment into this study. MRC followed a standard protocol with the same 1.5T GE Signa Echospeed MR scanner for each, acquiring axial and coronal T2-weighted gradient echo and thick and thin slice heavily T2-weighted gradient echo MRC sequences. All positive controls had MRC sequences within a 10-year period of the cases and negative controls, although the MR scanners used varied for this group.

2.7 | Evaluation of MRC scans for biliary changes consistent with PSC

Each MRC was evaluated for evidence of intrahepatic duct or extrahepatic duct irregularity, beading, strictures, associated biliary dilatation, diverticula or webs, an increased angle of ductal confluence and/or “disconnected” peripheral ducts. The certainty of the radiologist’s interpretation was scored through a three-level classification of “definite,” “possible” or “absent” biliary abnormalities consistent with PSC, according to Gestalt theory. The final diagnosis made was based on separate expert opinions of two Hepatobiliary Radiologists, and where there was disagreement consensus was reached.

A classification of “definite” was made when clear irregularity, beading and strictures of the ducts were visible. A classification of “possible” was made when the ducts (usually intrahepatic) were irregular, with a degree of uncertainty as to whether this was a true finding, caused by blood vessels impinging on the ducts, or artefact caused by technical factors. “Absent” biliary abnormalities was defined by the absence of biliary irregularity, strictures and/or dilatation. The radiological diagnosis of cirrhosis was made by assessing regional changes in hepatic morphology.

2.8 | Blinded interpretation of MRC scans

MRC scans were individually interpreted by a gastrointestinal radiologist in the study team within 24 hours of conducting the scan and an individual report prepared for each scan. Subsequently (within 12 months of the first scan being performed), all MRC scans (cases and controls) were anonymised, randomised and pooled. Two gastrointestinal radiologists interpreted anonymised pooled MRC images (cases and controls) independently, at interactive workstations and findings were recorded on standardised sheets. Both were blinded to the clinical profiles and any previous imaging, to avoid possible bias. All scans included in this study were deemed of adequate quality to identify evidence of intra- or extrahepatic duct abnormalities.

2.9 | Intra- and Inter-observer variation

Methods for MRC pooling and reporting are detailed in Figure S2. All MRC images of the cases and controls were pooled (total 107 MRCP scans for extensive UC and 67 MRCP scans for CRD cohorts) and reported on two separate occasions (total 214 independent reads for the extensive UC cohort) by two consultant gastrointestinal radiologists with a special interest in hepatobiliary disease (HB with 10 years’ and MB with 9 years’ consultant experience at the time of reporting). In the event of intra- and inter-observer disagreement, definitive decisions were taken by consensus between the two radiologists. The overall quality of MRCs was considered high, with only one study repeated because of poor quality.

2.10 | Blood tests

Serum liver tests (specifically bilirubin, ALP, ALT, GGT and albumin) were performed at the time of recruitment and within 4 weeks of the MRC scan. Immunological studies and HLA testing were performed between 3 months and 12 months after recruitment. Immunological markers included immunoglobulin G (IgG)
and IgG4 subclass, antineutrophil antibody (ANA), antineutrophil cytoplasmic antibody (ANCA) and antimitochondrial antibodies (AMA) and antineutrophil cytoplasmic antibody (ANCA). Immunotyping for human leucocyte antigen (HLA) was performed. Compatible HLA haplotypes favourable of PSC were considered to include B8-DRB1*0301-DQB1*0201, DRB1*1301-DRB3*0101-DQB1*0603 and DRB1*1501-DRB5*0101-DQB1*0602.20

2.11 | Statistical analysis

Cases were divided into two groups according to the presence or absence of MRC abnormalities consistent with PSC (sub-clinical PSC). The clinical, laboratory and histological characteristics of the groups were compared using Pearson's Chi-squared test or Fisher's exact test, where appropriate for categorical variables, and the Wilcoxon rank test for continuous variables. Non-parametric variables in independent and multiple comparisons were compared with the Mann-Whitney test and Kruskal-Wallis test respectively. Variables associated with MRC abnormalities were included in a regression logistic analysis, with correction for multiple comparisons. To assess the degree of intra-observer and inter-observer agreement between radiologists, a kappa statistic was calculated (two raters, categorical data) to take account of amount of agreement that can occur by chance. The equation used to calculate kappa is $\kappa = \frac{Pr(a) - Pr(e)}{1 - Pr(e)}$, where $Pr(a)$ is the relative observed agreement among the
raters and $P(r)$ is the hypothetical probability of the raters indicating a chance agreement, interpreted according to the guidelines by Landis and Koch.\textsuperscript{21} Statistical analysis was performed using Graphpad Prism v6 and SPSS v25. Continuous variables are expressed as the median (range), categorical variables as percentages (%) and $P$ values $<.05$ were considered statistically significant.

3 | RESULTS

3.1 | Patient demographics and clinical features

Demographics and clinical features of UC patients in the extensive UC and CRD cohorts are outlined in Table 1, and features specific to UC patients with CRD are shown in Table S1. Positive and negative controls were well matched to cases (age $P = .90$; gender $P = .19$). Overall, most patients were male, had extensive UC and were taking 5-ASA prior to MRC evaluation. Patients in the extensive UC cohort were younger (49 vs 71 years, $P < .0001$) with a shorter duration of UC at the time of recruitment (median 10 vs 36 years; $P < .0001$) compared with those in the CRD cohort. The colectomy rate was lower in patients with extensive UC compared to CRD (10% vs 53%, $P = .0005$), and the surgical indication for the extensive UC cohort was active disease. In the CRD cohort, dysplasia was the sole indication for surgery. Elevated total IgG and IgG4 subclass levels were detected more frequently (IgG 10% vs 41%; $P = .007$ and 0% vs 24%; $P = .003$) in those with CRD compared with extensive UC, although the absolute values were not raised overall (IgG $P = .80$; IgG4 $P = .79$).

3.2 | Prevalence of Sub-clinical PSC

MRC interpretation is shown in Table 2. In the extensive UC cohort, 9/51 (18%) patients, 28 (100%) positive controls with PSC and none (0%) of 28 negative healthy controls had biliary abnormalities consistent with a diagnosis of PSC on initial radiological evaluation ($P < .0001$, cases vs negative controls $P = .02$). In the CRD cohort, 4/19 (21%) patients with UC and CRD, 24 (100%) positive controls and none (0%) of 28 negative controls had biliary abnormalities consistent with PSC on initial radiological evaluation ($P < .0001$, cases vs negative controls $P = .02$).

3.3 | Prevalence of Sub-clinical PSC after pooling and blinding of MRC scans

MRC interpretation after pooling of randomised and blinded scans is shown in Table 2. In the extensive UC cohort, 7/51 (14%) patients (cases) and 28 (100%) of positive controls with PSC had biliary abnormalities consistent with a diagnosis of PSC ($P < .0001$). Surprisingly, after randomisation and blinding, 4/28 (14%) negative healthy controls were reported to have biliary abnormalities consistent with a diagnosis of PSC (cases vs negative controls $P = 1.0$).

### Table 2

|                     | Cases | Positive controls | Negative controls | $P$ value |
|---------------------|-------|-------------------|-------------------|-----------|
|                     | Total | C vs PC | C vs NC | NC vs PC |
| A. MRC scans interpreted at initial evaluation |       |         |         |         |
| Extensive UC Cohort |       |         |         |         |
| Number of patients  | 51    | 28      | 28      | $<0.0001$ |
| Consistent with PSC | 9 (18)| 28 (100)| 0       | $<0.0001$ |
| CRD Cohort          |       |         |         |         |
| Number of Patients  | 19    | 24      | 24      | $<0.0001$ |
| Consistent with PSC | 4 (24)| 24 (100)| 0       | $<0.0001$ |
| B. MRC scans interpreted after being randomised, blinded and pooled |       |         |         |         |
| Extensive UC cohort |       |         |         |         |
| Number of patients  | 51    | 28      | 28      | $<0.0001$ |
| Consensus numbers   | 7 (14)| 28 (100)| 4 (14)  | $<0.0001$ |
| Definite and possible | (3 D; 4 P) | (26 D; 2 P) | (4 P) | $<0.0001$ |
| CRD cohort          |       |         |         |         |
| Number of patients  | 19    | 24      | 24      | $<0.0001$ |
| Consensus numbers   | 4 (24)| 24 (100)| 0       | $<0.0001$ |
| Definite and possible | (2 D; 2 P) | (24 D) |         | $<0.0001$ |

Note: Definitions in Methods.

Abbreviations: C, Cases; D, definite PSC; NC, negative control; P, possible PSC; PC, positive control.
whom were reported to have normal scans at initial evaluation. After consensual assessment by both radiologists, of the seven cases with sub-clinical PSC, three (6%) were defined as “definite” and four as “possible” PSC. Of the 28 positive controls, 26 (93%) patients were defined as “definite” and the remaining 2 (7%) as “possible” PSC. The four negative controls with biliary abnormalities were all defined as having features of “possible” PSC.

In the CRD cohort, 4/19 (21%) patients with UC and CRD, 24 (100%) positive controls and none (0%) of 24 negative controls had biliary abnormalities consistent with a diagnosis of PSC (P < 0.0001). After consensual assessment by both radiologists, of the four cases in the CRD cohort with sub-clinical PSC, 2/19 (12%) had “definite” and 2/19 had “possible” PSC. Of the 24 positive controls, all 24 (100%) had “definite” PSC. Radiological features of definite and possible PSC on MRC scans are described for each cohort in Table S2.

### 3.4 MRC Inter- and Intra-Observer variation

MRC observer variation after pooling of blinded scans is detailed in Table S3. Inter-observer agreement between radiologists for all scans (cases and controls) was good in the extensive UC (kappa = 0.88) and very good in the CRD (kappa = 0.97) cohorts. Final outcomes were reported differently on each occasion by radiologist ‘A’ and ‘B’ a total of nine times (A 3/51 patients; 2/28 positive controls; 4/28 negative controls and B 4/51 patients; 2/28 positive controls; 3/28 negative controls). Intra-observer agreement by radiologists for MRC interpretation was defined as almost perfect (kappa = 0.96). Overall, 100% of positive PSC controls and 98% of negative healthy controls were identified correctly.

### 3.5 MRC features in those with Sub-clinical PSC

MRC evidence of biliary abnormalities consistent with PSC for the two cohorts is shown in the flowchart in Figure 1A and B. Representative MRC images of ‘definite’ and ‘possible’ PSC are shown in Figure 2A and B.

In the extensive UC cohort, of the 7/51 (14%) patients with UC and normal LFTs and 28/28 (100%) consistent with PSC, 28/28 (100%) had both intrahepatic duct (IHD) and extrahepatic duct (EHD) involvement and 3/7 (43%) patients had both intrahepatic duct (IHD) and extrahepatic duct (EHD) involvement and 3/28 (11%) had IHD involvement alone. Of the 28 negative controls, 4/28 (14%) had IHD irregularities alone. In the CRD cohort, of the 4/19 (24%) patients with sub-clinical PSC, 7/17 (29.2%) had IHD+IHD involvement and 17/28 (100%) had IHD+IHD involvement alone.
all 4 (100%) had IHD involvement. Of the 24 positive controls, all 24 (100%) had definite PSC; 17/24 (71%) had both IHD and EHD involvement and 7 (29%) had IHD involvement alone. In the 24 negative controls, none had biliary abnormalities.

MRC bile duct abnormalities identified on blinded reporting of cases and controls are shown in Table S4. In the extensive UC cohort, 3 of 51 (5.9%) patients were defined as ‘definite’ PSC (representative Figure 2A) with MRC findings including IHD irregularity with beading (3/3), increased angle of ductal confluence (3/3), disconnected peripheral ducts (3/3), CD irregularities and strictures with webs (2/3), 4/51 (8%) patients had ‘possible’ PSC (representative Figure 2B), with MRC findings including IHD irregularity with beading (4/4) and a CD stricture (1/4). In the CRD cohort, 2 of 19 (11%) patients were defined as ‘definite’ PSC, with MRC findings of IHD irregularity and beading (2/2), with increased angle of ductal confluence (2/2) and disconnected peripheral ducts (2/2), 2/19 (11%) had ‘possible’ PSC, with MRC findings of IHD irregularities in multiple segments (2/2).

3.6 | Variables associated with Sub-clinical PSC

Demographics and characteristics of UC patients with sub-clinical PSC are shown in Table S5. Variables associated sub-clinical PSC in the two cohorts are shown in Tables 3 and 4 respectively. In the extensive UC cohort, all seven patients with sub-clinical PSC had extensive colitis by definition, which was quiescent or mildly active in terms of clinical course. The presence of sub-clinical PSC was associated with older age at the time of MRC (P = .04), a negative smoking history (P = .03), the presence of pANCA ≥1:40 titre (P = .04), the absence of acute severe colitis necessitating hospital admission (P = .04) and the absence of azathioprine therapy (P = .04) (Table 3).

In the CRD cohort, all four patients with sub-clinical PSC had extensive colitis, quiescent or mildly active disease, a negative smoking history and the absence of other extra-intestinal manifestations of disease. The presence of high-grade dysplasia (HGD) rather than low-grade dysplasia (LGD) was more frequent in those with sub-clinical PSC (P = .03) (Table 4).

3.7 | Variables in clinical and sub-clinical PSC

Comparison of baseline clinical features in all patients with sub-clinical PSC and established clinical PSC (positive controls) are detailed in Table S6. Positive controls with clinical PSC were diagnosed by MRC at an earlier age (46 vs 70 vs 71 years P = .003) and had a shorter duration of UC (10 vs 25 vs 40 years; P = .006) compared with sub-clinical PSC in the extensive UC and CRD cohorts respectively. While serum IgG levels were higher in positive controls with clinical PSC (18.0 vs 12.0 vs 9.1g/l; P = .025) than in both cohorts with sub-clinical PSC, serum IgG4 subclass levels were similar (P = .53); elevated levels of serum IgG4 have been associated with a more severe clinical phenotype in PSC patients.

3.8 | Outcomes in sub-clinical PSC

Patients with UC were followed up in the IBD clinic and underwent colonoscopic surveillance; the frequency was determined by activity and duration of disease, risk factors and development of complications, in accordance with national guidelines. Most patients diagnosed with sub-clinical PSC underwent annual outpatient clinic follow-up (9/11; 82%). Clinical outcomes of the sub-clinical PSC groups and definitions of these are shown in Table 5. During a median follow-up of 10.1 (range 3.1-11.9) years, 4/11 (36%) patients developed persistently abnormal liver biochemistry, 1 (9%) developed cirrhosis, 2/11 (18%) had radiological evidence of progression of PSC, and 2 (18%) patients died. 7/11 (64%) patients developed...
malignancy: two hepatobiliary, two pancreatic, one anorectal, one breast and one prostate cancer.

4/11 (36%) patients developed persistently abnormal liver biochemistry during a median follow-up of 4.6 years (140 months), and were investigated by standard liver screen and abdominal imaging. One patient developed obstructive jaundice and had evidence of metastatic malignancy with a gallbladder mass and liver involvement on MRC and CT imaging after 7.2 years of follow-up; histology confirmed bile duct/gallbladder adenocarcinoma. One patient had evidence of a fatty liver on ultrasound, elevated liver stiffness on fibroscan (11.3 kPa), with no progression of biliary changes on MRC. The remaining 2/11 patients had normal ultrasound findings, liver stiffness < 5kPa on fibroscan, and no progression of biliary abnormalities on repeat MRC. Two (18%) patients had evidence of progression of biliary disease on repeat MRC; one with increased intraductal bile dilatation and new common duct dilatation, and the second with both intra- and extrahepatic bile dilatation, as well as an irregular liver contour consistent with cirrhosis. There were no clinical episodes of liver decompensation and no liver transplants. Colorectal polyps were identified in 4/8 patients; three had adenomatous polyps in the right colon and two had hyperplastic polyps. An anorectal cuff adenocarcinoma was diagnosed in one patient, after 5.1 years of follow-up and 17 years after their original ileoanal pouch formation for CRD. 2/11 patients died; death was attributed to biliary malignancy and cardiovascular disease.

In the cohort of patients with sub-clinical PSC-UC, only those assessed as definite PSC had the outcomes of progression of MRC changes (n = 2), development of cirrhosis (n = 1) and anorectal adenocarcinoma (n = 1). However, both those assessed as possible PSC and definite PSC developed abnormal liver biochemistry (possible PSC n = 2 with raised ALT or ALP/GGT/ALP; definite PSC n = 2 with raised ALP/ALT) and hepatobiliary malignancy (possible PSC n = 1 with gallbladder/biliary carcinoma; definite PSC n = 1 with ampullary carcinoma).

3.9 Comparison of outcomes in cases and control groups

Clinical outcome during long-term follow-up of all cases and controls is shown in Table S7. Cirrhosis (P = .03) and hepatobiliary carcinoma (P = .03) developed more frequently in the sub-clinical PSC group compared with those patients without biliary abnormalities on MRC. Progression of PSC on subsequent imaging (P = .03), liver-related decompensation (P = .04) and liver transplantation (P = .04) was more common in the clinical PSC controls than the sub-clinical PSC group. In contrast, non-GI malignancy was more common in the sub-clinical PSC group compared with clinical PSC positive controls (P = .04), but not compared with the patients with UC and a normal MRC (P = .09). Surprisingly, there was no difference in colorectal adenomatous polyp (P = .16) or colorectal cancer (P = .25) detection across the four groups, with one colorectal carcinoma detected in each of the sub-clinical and clinical PSC groups. Mortality was highest in the positive clinical PSC control group (29%), compared with UC patients with sub-clinical PSC (18%), UC patients with a normal MRC (10%), and healthy volunteers (none) over a similar follow-up period (P = .15).
| TABLE 4  Baseline variables associated with sub-clinical PSC in the CRD cohort |
|---------------------------------|----------------|----------------|
|                                  | Abnormal MRCP | Normal MRCP    |
| Number of patients (% of total)  | 4 (24)         | 13 (77)        |
| Gender, male (%)                 | 3 (75)         | 9 (69)         |
| Age at time of MRC, median (range) years | 71 (60-80)    | 71 (52-87)    |
| Age at diagnosis of UC, median (range) years | 35 (19-42)    | 36 (21-60)    |
| Duration of UC at time of MRC, median (range) years | 40 (35-42)    | 34 (5-51)     |
| Extensive UC                     | 4 (100)        | 11 (85)        |
| Extra-intestinal manifestations (%) | 1 (25)         | 3 (23)        |
| Ever Smoker (%)                  | 0              | 7 (54)        |
| Quiescent or mildly active UC (%) | 4 (100)        | 9 (69)        |
| Admission for ASUC (%)           | 2 (50)         | 5 (38)        |

**Serology**

|                                  | Abnormal MRCP | Normal MRCP |
|---------------------------------|---------------|-------------|
| ANA positive (%)                | 1 (25)        | 0           |
| pANCA positive (%)              | 1 (25)        | 2 (15)      |
| IgG, median (range) G/L         | 9.09 (8.24-14) | 11.7 (7.07-15.2) |
| IgG elevated > 13g/L ULN (%)    | 1 (25)        | 6 (46)      |
| IgG4, median (range) G/L        | 0.30 (0.09-1.77) | 0.45 (0-3.1) |
| IgG4 > 1.4g/L ULN (%)           | 1 (25)        | 2 (15)      |
| HLA consistent with PSC (%)     | 2 (50)        | 2 (15)      |

**Treatment**

|                                  | Abnormal MRCP | Normal MRCP |
|---------------------------------|---------------|-------------|
| 5-ASA (%)                       | 7 (100)       | 12 (92)     |
| Immunosuppressive (%)           | 1 (25)        | 7 (54)      |
| Azathioprine (%)                | 0             | 2 (15)      |
| Methotrexate (%)                | 0             | 0           |
| Biological agents (%)           | 0             | 0           |
| Colectomy (%)                   | 3 (75)        | 6 (46)      |
| Active disease (%)              | 0             | 0           |
| CRD/CRC (%)                     | 3/3           | 6/6         |

**CRD or CRC**

|                                  | Abnormal MRCP | Normal MRCP |
|---------------------------------|---------------|-------------|
| High-grade CRD (%)              | 4 (100)       | 4 (31)      |
| Low-grade CRD (%)               | 0             | 9 (70)      |
| Adenocarcinoma (%)              | 2 (50)        | 1 (8)       |

**Polypoid lesions**

|                                  | Abnormal MRCP | Normal MRCP |
|---------------------------------|---------------|-------------|
| DALM (%)                        | 2 (50)        | 5 (39)      |
| ALM (%)                         | 3 (75)        | 5 (39)      |

**Non-polypoid lesions**

|                                  | Abnormal MRCP | Normal MRCP |
|---------------------------------|---------------|-------------|
| Flat CRD (%)                    | 0             | 4 (31)      |
| Site of CRC or CRD              | 1 (25)        | 2 (15)      |
| Right colon (%)                 | 3 (75)        | 11 (85)     |

**Activity of colitis at time of CRD**

|                                  | Abnormal MRCP | Normal MRCP |
|---------------------------------|---------------|-------------|
| Quiescent or mild activity (%)  | 4 (100)       | 9 (69)      |
| Moderate activity (%)           | 0             | 4 (31)      |
| FH CRC < 50 years old           | 1 (25)        | 1 (8)       |
| Surgery for CRC or CRD          | 3 (75)        | 6 (46)      |

Abbreviations: ALM, adenomatous lesion or mass; DALM, dysplasia-associated lesion or mass; FH, family history. Significance level: * p<0.05.
In this prospective study, the prevalence of sub-clinical PSC on MRC was two- to three-fold higher (14%) in those with extensive UC and normal liver biochemistry, and three- to four-fold higher (24%) in those with UC and prior CRD/CRC, compared with the reported prevalence in those with UC and cholestatic liver biochemistry (0.8%-5.6%). A study from Norway reported an 8% prevalence of sub-clinical PSC in a population-based IBD cohort 20 years after original diagnosis (screening 322 IBD patients with MRC). Overall, 8% had radiological features of PSC, of whom 2% had known PSC and 6% (17/322) were newly identified based on MRC images alone. Although the relatively low prevalence of clinical PSC in the Norwegian cohort may amplify those identified with sub-clinical disease, this three-fold elevated risk was mirrored in our prospective study. In contrast to our study limited to
UC patients with extensive colonic involvement, the Norwegian study, which was uncontrolled, included UC patients with left sided disease and Crohn's colitis, both known to be associated with a lower risk of PSC.10 This was confirmed by their finding of a significantly higher prevalence in the extensive colitis group. This probably explains the higher prevalence found in our study. However, it should be stated that if only the definite PSC cases are included then the prevalence rates in our study are similar to the Norwegian findings. A French study evaluating the use of MRC in a mixed IBD population included a small cohort of 30 patients with normal liver biochemistry, reporting 1 patient (3%) to have an abnormal scan.25

In the Norwegian sub-clinical PSC cohort, the patients were older and there were more females compared with classical cohorts, and this was also the case in our cohort.10 However, the overall female predominance in their study may be accounted for by the proportion of patients with Crohn's disease (11 of 26 with sub-clinical disease) compared with the usual clear predominance of UC in patients with PSC. PSC-CD is known to be associated with a unique phenotype.26 In contrast to the Norwegian study, we reported a milder disease course in those with sub-clinical PSC, with fewer admissions for acute severe colitis and a negative association with azathioprine therapy.26 The latter may be because of these patients having less active UC or a protective effect of azathioprine itself. A similar protective effect was not seen with methotrexate or biological agents, although numbers of patients are too small to be certain.

We demonstrated other features in the sub-clinical PSC group consistent with classical large-duct PSC including extensive colitis, the presence of pANCA and a negative smoking history. Although a range of non-specific autoantibodies can be detected in PSC, atypical pANCA has the strongest association, reported in 88% of the presence of pANCA and a negative smoking history. Although consistent with classical large-duct PSC including extensive colitis, methotrexate or biological agents, although numbers of these patients having less active UC or a protective effect of limited to peripheral IHD.

MRC is established as a suitable screening tool for the diagnosis of PSC and is superior to endoscopic cholangiography in terms of proximal duct visualisation and rate of stricture detection.4,31 In a meta-analysis of 456 subjects, MRC had a high sensitivity (86%) and specificity (94%) for detection of PSC, with high positive (15.3) and low negative (0.15) predictive ratios.6 Of note, this analysis excluded series with healthy negative control subjects and those without cholestatic liver function. In other studies, false positives have been reported in patients with hepatic fibrosis or cirrhosis and false negatives in those with disease limited to peripheral IHD.32 Furthermore, negative control groups reported in the literature are usually those patients with other HPB diseases (not true negative controls), which may be appropriate for endoscopic cholangiography, but not for MRC which can detect other pathology, such as cirrhosis or metastatic disease. It should be noted that the Norwegian study of sub-clinical PSC did not contain either a normal or disease control group.10

Technical factors can limit the ability to detect subtle ductal changes (eg movement because of poor breath holding) and normal structures can give the impression of ductal irregularity (eg vessels crossing the ducts). This means there will always be a group of patients in whom the presence of ductal irregularity is possible, but uncertain. In this study, we wished to detect early changes of PSC, so wanted high sensitivity. Consequently possible cases were included as positives for the analysis. This is at the expense of specificity, with false positives in the negative control group, who were deemed as ‘possible’ rather than ‘definite’ PSC, unlike those reported in other prospective series of MRC evaluation. It is noteworthy that two previous studies of MRC in UC reporting on the presence of sub-clinical PSC did not contain healthy normal controls.10,25 We believe that the inclusion of normal controls adds to the strength of our study. It is clear from our clinical experience and confirmed in this study that artefacts from normal anatomical variants can sometimes mimic PSC particularly if the technical quality of the scan is suboptimal.

The radiological diagnosis of sub-clinical PSC was considered definite in 5/11 cases and none of the negative controls. All those with biliary abnormalities on MRC had IHD irregularity, which suggests that in asymptomatic patients with UC and normal liver function, IHD irregularity is the first manifestation of PSC.

The accuracy of MRC in the diagnosis of PSC may be influenced by radiological experience and disease spectrum.33 In this study, we used a three-tier definition of definite, possible or absent PSC to define biliary abnormalities consistent with PSC, as used previously,34 with a higher yield to detect more subtle biliary abnormalities when compared to alternative definitions based on duct strictureing.32 Our inter-observer and intra-observer variations were small. Inter-observer agreement for intrahepatic bile duct abnormalities was better than for extrahepatic duct disease, mirroring a study by Vitellas et al15 The optimal protocol for MRC has only recently been defined,3 with differences in instrument manufacture or magnetic field strengths accounting for variability between studies. In this study, the same MRC scanner was used for all cases and negative controls, although some of the positive controls were imaged at an earlier date. The overall quality of MRCs was high, with only 1 of 174 MRC scans needing to be repeated.34

Patients with classical PSC-UC are at a four-fold greater risk of developing CRD or CRC than those with UC alone.35,36 Because of the increased CRC risk, patients with PSC-UC are enrolled in surveillance programs with annual colonoscopy and biopsies from the time of diagnosis of PSC.11 Importantly, we detected a three- to four-fold increased frequency of sub-clinical PSC in patients with UC and a prior history of CRD/CRC compared to that described for classical PSC. Furthermore, all these patients had been diagnosed
with colorectal adenocarcinoma or HGD lesions, not LGD lesions, three of whom required colectomy and one who developed a new adenocarcinoma in the cuff 17 years after pouch surgery for CRD. This finding is supported by evidence that PSC-IBD cancers are more aggressive than IBD cancers at diagnosis.\(^{37}\) Interestingly, elevated serum IgG4 levels were found more frequently in the group with HGD or CRC. IgG4 has been described as an immune mediator in the context of malignancy,\(^{38}\) and an abundance of mucosal IgG4 in UC has been associated with more severe disease activity and the presence of PSC.\(^{39}\) Early identification of sub-clinical PSC, with an increased frequency of colorectal surveillance, may have had an impact on CRD detection and management. The role of UDCA in chemoprevention of CRC remains debated.\(^{40,41}\)

The main limitations of this study are (a) its small sample size, (b) the spatial resolution of MRC scans performed between 2007 and 2010, with inherent challenges of interpreting subtle changes of small bile ducts, (c) a lack of liver histology to confirm evidence of PSC, although European and US guidelines do not recommend routine liver biopsy for diagnosis of large-duct PSC; histology useful to stage fibrosis, for evidence of autoimmune hepatitis overlap, and for differentiation from IgG4-related sclerosing cholangitis. The main strengths of our study are (a) its prospective nature, minimising selection bias, (b) the presence of a matched positive and negative control group, (c) the long-term follow-up period, to assess the impact of sub-clinical PSC.

Our study suggests that MRC in all patients with extensive UC, regardless of liver biochemistry, could be an option in order to identify patients with sub-clinical PSC. This may modify surveillance strategies for both colonic and hepatobiliary malignancy, with the prospect of earlier recognition of premalignant lesions. This study also supports the role of MRC in patients with UC found to have CRD, regardless of liver biochemistry. What remains to be addressed is the timing of MRC evaluation, both in terms of the prevalence of PSC at the time of UC diagnosis and whether earlier detection of sub-clinical PSC could improve overall management.

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REFERENCES

1. Karlsten TH, Felseraas T, Thorburn D, Vesterhus M. Primary sclerosing cholangitis - a comprehensive review. J Hepatol. 2017;67:1298-1323. https://doi.org/10.1016/j.jhep.2017.07.022
2. Broomé U, Olsson R, Löff L, et al. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. Gut. 1996;38:610-615.
3. Chapman RW, Cotton M, Selby WS, Shepherd HA, Sherlock S, Jewell DP. Serum autoantibodies, ulcerative colitis and primary sclerosing cholangitis. Gut. 1986;27:86-91. https://doi.org/10.1136/gut.27.1.86
4. Vitellas KM, El-Dieb A, Vaswani KK, et al. MR cholangiopancreatography in patients with primary sclerosing cholangitis: interobserver variability and comparison with endoscopic retrograde cholangiopancreatography. Am J Roentgenol. 2002;179:399-407. https://doi.org/10.2214/ajr.179.2.1790399
5. Schramm C, Eaton J, Ringe KI, Venkatesh S, Yamamura J. MRI working group of the IPSCSG. Recommendations on the use of magnetic resonance imaging in PSC: A position statement from the International PSC Study Group. Hepatology. 2017;66:1675-1688. https://doi.org/10.1002/hep.29293
6. Dave M, Elmunzer BJ, Dvamena BA, Higgins PDR. Primary sclerosing cholangitis: meta-analysis of diagnostic performance of MR cholangiopancreatography. Radiology. 2010;256:387-396. https://doi.org/10.1148/radiol.10091953
7. Tischendorf JWW, Hecker H, Krüger M, Manns MP, Meier PN. Characterization, outcome, and prognosis in 273 patients with primary sclerosing cholangitis: a single center study. Am J Gastroenterol. 2007;102:107-114. https://doi.org/10.1111/j.1572-0241.2006.00872.x
8. Berstad A, Aabakken L, Smith H, Aasen S, Boverg K, Schrum E. Diagnostic accuracy of magnetic resonance and endoscopic retrograde cholangiography in primary sclerosing cholangitis. Clin Gastroenterol Hepatol. 2006;4:514-520. https://doi.org/10.1016/j.cgh.2005.10.007
9. DysonJK BU, Beuers U, Jones DEJ, Lohse AW, Hudson M. Primary sclerosing cholangitis. Lancet. 2018;391:2547-2559.
10. Lunder AK, Hov JR, Borthne A, et al. Prevalence of sclerosing cholangitis, detected by magnetic resonance cholangiography, in patients with long-term inflammatory bowel disease. Gastroenterology. 2016;151:660-669.e4. https://doi.org/10.1053/j.gastro.2016.06.021
11. Ellingham D, Jostins L, Spain SL, et al. Analysis of five chronic inflammatory diseases identifies 27 new associations and highlights disease-specific patterns at shared loci. Nat Genet. 2016;48:510-518. https://doi.org/10.1038/ng.3528
12. Ji S-G, Juran BD, Mucha S, et al. Genome-wide association study identifies the genetic relationship with inflammatory bowel disease. Nat Genet. 2017;49:269-273. https://doi.org/10.1038/ng.3745
13. Escorsell A, Parés A, Rodés J, Solís-Herruzo JA, Miras M, de la Morena E. Epidemiology of primary sclerosing cholangitis in Spain. Spanish Association for the Study of the Liver. J Hepatol. 1994;21:787-791.
14. Beuers U, Boergen KM, Chapman RW. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol. 2009;51:237-267. https://doi.org/10.1016/j.jhep.2009.04.009
15. Weismüller TJ, Trivedi PJ, Bergquist A, et al. Patient age, sex, and inflammatory bowel disease phenotype associate with course of primary sclerosing cholangitis. Gastroenterology. 2017;152:1975-1984. e8. https://doi.org/10.1053/j.gastro.2017.02.038

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16. Laine L, Kaltenbach T, Barkun A, et al. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. *Gastrointest Endosc.* 2015;81:489-501.e26. https://doi.org/10.1016/j.gie.2014.12.009

17. Riddell RH, Goldman H, Ransohoff DF, et al. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. *Hum Pathol.* 1983;14:931-968.

18. Koontz NA, Gunderman RB. Gestalt theory: implications for radiology education. *Am J Roentgenol.* 2008;190:1156-1160. https://doi.org/10.2214/AJR.07.3268

19. Hagen PJ, Hartmann UC, Hoekstra OS, Stokkel MPM, Teule GJJ, Prins MH. How to use a gestalt interpretation for ventilation-perfusion lung scintigraphy. *J Nucl Med.* 2002;43:1317-1323.

20. Karlsen TH, Franke A, Melum E, et al. Genome-wide association analysis in primary sclerosing cholangitis. *Gastroenterology.* 2010;138:1102-1111. https://doi.org/10.1053/j.gastro.2009.11.046

21. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics.* 1977;33:159-174.

22. Mendes FD, Jorgensen R, Keach J, et al. Elevated serum IgG4 concentration in patients with primary sclerosing cholangitis. *Am J Gastroenterol.* 2006;101:2070-2075. https://doi.org/10.1111/j.1572-0241.2006.00772.x

23. Cairns SR, Scholefield JH, Steele RJ, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). *Gut.* 2010;59:666-689. https://doi.org/10.1136/gut.2009.179804

24. Grigoriadis A, Morschbach F, Voulgarakis N, Said K, Bergquist A. Inter-reader agreement of interpretation of radiological course of bile duct changes between serial follow up magnetic resonance imaging/3D magnetic resonance cholangiopancreatography of patients with primary sclerosing cholangitis. *Scand J Gastroenterol.* 2020;55:228-235. https://doi.org/10.1080/00365521.2020.1720281

25. Belle A, Laurent V, Pouillon L, et al. Systematic screening for primary sclerosing cholangitis with magnetic resonance cholangiography in inflammatory bowel disease. *Dig Liver Dis.* 2018;50:1012-1018. https://doi.org/10.1016/j.dld.2018.06.024

26. Halliday JS, Djordjevic J, Lust M, et al. A unique clinical phenotype of primary sclerosing cholangitis associated with Crohn's disease. *J Crohn's Colitis.* 2012;6:174-181. https://doi.org/10.1016/j.jcmono.2011.07.015

27. Olsson R, Danielsson A, Järnerot G, et al. Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis. *Gastroenterology.* 1991;100(5 Pt 1):1319-1323.

28. Mitchell SA, Thysсен M, Orchard TR, Jewell DP, Fleming KA, Chapman RW. Cigarette smoking, appendectomy, and tonsillectomy as risk factors for the development of primary sclerosing cholangitis: a case control study. *Gut.* 2002;51:567-573.

29. Karlsen T-H, Schrumpf E, Boberg K-M. Genetic epidemiology of primary sclerosing cholangitis. *World J Gastroenterol.* 2007;13:5421-5431.

30. Melum E, Franka A, Schramm C, et al. Genome-wide association analysis in primary sclerosing cholangitis identifies two non-HLA susceptibility loci. *Nat Genet.* 2011;43:17-19. https://doi.org/10.1038/ng.728

31. Weismüller TJ, Wedemeyer J, Kubicka S, Strassburg CP, Manns MP. The challenges in primary sclerosing cholangitis – aetiopathogenesis, autoimmunity, management and malignancy. *J Hepatol.* 2008;48:538-557. https://doi.org/10.1016/j.jhep.2008.01.020

32. Lewin M, Vilgrain V, Ozenne V, et al. Prevalence of sclerosing cholangitis in adults with autoimmune hepatitis: a prospective magnetic resonance imaging and histological study. *Hepatology.* 2009;50:528-537. https://doi.org/10.1002/hep.23024

33. Zenouzi R, Liwinski T, Yamamura J, et al. Follow-up magnetic resonance imaging/3D-magnetic resonance cholangiopancreatography in patients with primary sclerosing cholangitis: challenging for experts to interpret. *Aliment Pharmacol Ther.* 2018;48:169-178. https://doi.org/10.1111/apt.14797

34. Abdalian R, Dhar P, Jha J, Haider M, Guindí M, Heathcote EJ. Prevalence of sclerosing cholangitis in adults with autoimmune hepatitis: evaluating the role of routine magnetic resonance imaging. *Hepatology.* 2008;47:949-957. https://doi.org/10.1002/hep.22073

35. Jess T, Simonsen J, Jørgensen KT, Pedersen BV, Nielsen NM, Frisch M. Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. *Gastroenterology.* 2012;143:375-381.e1. https://doi.org/10.1053/j.gastro.2012.04.016

36. Zheng H-H, Jiang X-L. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease. *Eur J Gastroenterol Hepatol.* 2016;28:1.

37. Shah SC, Ten Hove JR, Castaneda D, et al. High risk of advanced colorectal neoplasia in patients with primary sclerosing cholangitis associated with inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2018;16:1106-1113.e3. https://doi.org/10.1016/j.cgh.2018.01.023

38. Karagiannis P, Gilbert AE, Nestle FO, Karagiannis SN. IgG4 antibodies and cancer-associated inflammation: insights into a novel mechanism of immune escape. *Oncoimmunology.* 2013;2:e24889. https://doi.org/10.4161/onci.24889

39. Raina A, Yadav D, Regueiro M, et al. Mucosal IgG4 cell infiltration in ulcerative colitis is linked to disease activity and primary sclerosing cholangitis. *Inflamm Bowel Dis.* 2013;19:1232-1237. https://doi.org/10.1097/MIB.0b013e318281344d

40. Pardi DS, Loftus EV, Kremers WK, Keach J, Lindor KD. Ursodeoxycholic acid as a chemopreventive agent in patients with ulcerative colitis and primary sclerosing cholangitis. *Gastroenterology.* 2003;124:889-893. https://doi.org/10.1053/gast.2003.50156

41. Eaton JE, Silveira MG, Pardi DS, et al. High-dose ursodeoxycholic acid is associated with the development of colorectal neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. *Am J Gastroenterol.* 2011;106:1638-1645. https://doi.org/10.1038/ajg.2011.156

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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