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Primary Sclerosing Cholangitis:

Epidemiological Aspects,
Prevalence of Elevated IgG4 Levels,
and Quality of Life

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ABSTRACT

Primary Sclerosing Cholangitis: Epidemiological Aspects, Prevalence of Elevated IgG4 Levels, and Quality of Life

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Background and Aims: Primary sclerosing cholangitis (PSC) is a rare cholestatic disease with considerable associated morbidity and mortality. The reported transplant-free survival has ranged between 12-18 years. Epidemiological data and information on health related quality of life (HRQL) in patients with PSC are scarce and mostly provided from referral centers. Liver transplantation (OLT) is the only curative treatment. However, steroid responsiveness has been reported in a subgroup of PSC patients with elevated serum IgG4 values. The aim of this thesis was to investigate the incidence and prevalence of PSC and the risk of malignancy and OLT or death in patients with PSC in a population-based setting in Västra Götaland, Sweden. We also aimed to assess HRQL and the prevalence of elevated serum IgG4 in patients with PSC in the Västra Götaland PSC cohort merged with an English and a German PSC cohort respectively.

Results: The incidence rate of PSC diagnosed during the study period in Västra Götaland Sweden was 1.22 per 100 000 person-years. The incidence of PSC increased by 3% per year (95% confidence interval (CI) 0.01 to 6.20). Thirty- four out of 345 (10%) patients with PSC had elevated serum IgG4 values. A previous history of pancreatitis, intra- and extrahepatic biliary involvement and jaundice were associated with elevated IgG4 in multivariate analysis. Mortality in PSC patients was four times higher (Standardized Mortality Ratio (SMR) 4.20; 95% CI 3.01-5.69) compared with the background population in Västra Götaland. Standardized incidence ratio (SIR) for cholangiocarcinoma (CCA) was 868 (95% CI 505-1390), whereas the SIR for colorectal cancer was not significantly increased compared with the general population. Age, female gender, jaundice, cholangitis and bilirubin were associated with an increased risk of liver-related death or OLT, whereas high age was a risk factor for CCA. Elevated serum IgG4 values was not a risk factor for death or OLT (relative risk (RR) = 0.59, 95% CI (0.28-1.22) or CCA (RR= 0.45, 95% CI (0.06-3.35). Patients with PSC had significantly lower scores from several areas of the short-form 36 (SF-36), compared with controls. Age (β=-0.62 to -0.21, $p<0.05$) and systemic symptoms (β=3.84-15.94, $p<0.05$) such as pruritus were associated with lower scores in physical domains, whereas large duct disease with lower scores in vitality domain of the SF-36 (β= -7.10, $P<0.05$).

Conclusions: The incidence of PSC increased significantly in Västra Götaland during 1992-2005 and the observed prevalence is the highest reported to date. The prevalence of elevated serum IgG4 was similar to that reported in previous studies. The SMR and SIR for hepatobiliary cancer were similar to what has been reported previously in another Swedish study. An unexpected find was that the risk of colorectal cancer was not higher than in the background population. In contrast to previous studies, the prognosis was similar in patients with elevated and normal serum IgG4 values. HRQL was poorer in patients with PSC compared to controls and non life-threatening symptoms such as pruritus were associated with impaired HRQL.

Keywords: Primary sclerosing cholangitis, incidence, mortality, liver transplantation, IgG4, health related quality of life, Västra Götaland, hepatobiliary cancer.

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Caminante son tus huellas	Walker, your footsteps
el camino y nada más;	are the path and nothing more
Caminante, no hay camino,	Walker, there is no path,
se hace camino al andar,	the path is made by walking.
y al volver la vista atrás	By walking one makes the path,
se ve la senda que nunca	*and upon glancing behind,*
se ha de volver a pisar.	*one sees the pathway,*
Caminante no hay camino	*that never will be trod again.*
Sino estelas en la mar	Walker, there is no path,
	Only wakes upon the sea.

Antonio Machado

LIST OF PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I Incidence and prevalence of primary sclerosing cholangitis in a defined adult population in Sweden.

Björn Lindkvist, Maria Benito de Valle, Bo Gullberg, Einar Björnsson.

Hepatology 2010; 52 (2): 571-577.

II Mortality and cancer risk related to primary sclerosing cholangitis in a Swedish population-based cohort.

Maria Benito de Valle, Einar Björnsson, Björn Lindkvist.

Liver International 2011; 32 (3): 441-448

III Factors that reduce health-related quality of life in patients with primary sclerosing cholangitis.

Maria Benito de Valle, Monira Rahman, Björn Lindkvist, Einar Björnsson, Roger Chapman, Evangelos Kalaitzakis.

Clinical Gastroenterology and Hepatology 2012; 10 (7):769-775.

IV The impact of elevated serum IgG4 levels in patients with primary sclerosing cholangitis

Maria Benito de Valle, Tobias Muller, Einar Björnsson, Morgan Otten, Martin Volkmann, Olaf Guckelberger, Bertram Wiedenmann, Riadh Sadik, Eckart Schott, Mats Andersson, Thomas Berg, Björn Lindkvist .

Manuscript.

CONTENTS

ABBREVIATIONS

PSC	Primary Sclerosing Cholangitis
IBD	Inflammatory bowel disease
UC	Ulcerative colitis
CCA	Cholangiocarcinoma
OLT	Liver transplantation
IAC	Immunoglobulin-G4 associated cholangitis
HRQL	Health related quality of life
PBC	Primary biliary cirrhosis
ICD	International Classification of Diseases
MRCP	Magnetic resonance cholangiopancreatography
ERCP	Endoscopic retrograde cholangiopancreatography
PET	Positron emission tomography
AIP	Autoimmune pancreatitis
SF-36	Short-Form 36
CLDQ	Chronic liver Disease Questionnaire
FIS	Fatigue Impact Scale
HAD	Hospital Anxiety Depression
AAPC	Annual average percentage change
CI	Confidence interval
IRR	Incidence rate ratio
SMR	Standardized Mortality Rate
SIR	Standardized Incidence Rate
RR	Relative risk

INTRODUCTION

First described by Smith and Loe in 1965 (1), primary sclerosing cholangitis (PSC) is a chronic progressive disorder of unknown etiology characterized by chronic inflammation and stricture formation of the biliary tree. The diagnosis is usually made within the third and fourth decades of life. PSC has a male dominance with a male to female ratio of 2:1. Approximately 75% of patients with PSC have associated inflammatory bowel disease (IBD) (2-4) and about 5% of patients with ulcerative colitis (UC) will develop PSC (5).

Knowledge about PSC epidemiology is mostly provided from referral centers, with a risk of selection bias (3, 4, 6, 7). Small population-based studies have reported incidence and prevalence rates of 0.9-1.3 per 100 000 person-years and 8.5-13.6 per 100 000 persons respectively (8-11).

The clinical course is variable and unpredictable, some patients being asymptomatic for years and others progressing to liver failure and cirrhosis (3, 4, 12). PSC is considered a premalignant condition, most of the studies have reported a cumulative incidence of cholangiocarcinoma (CCA) between 7% and 14% (3, 4, 13-15).

There is no medical treatment for PSC and liver transplantation (OLT) is the only curative treatment. However, steroid responsiveness has been described in a subset of PSC patients with elevated serum IgG4 (16, 17). The entity has been named immunoglobulin G4-associated cholangitis (IAC) and is characterized by elevated serum IgG4, lymphoplasmacytic cell infiltration in the involved organs and both biochemical and biliary strictures steroid responsiveness (16-18).

Several studies have reported impaired quality of life (HRQL) in patients with different chronic liver disease (19-21). Data about quality of life in patients with PSC are scarce, provided from tertiary centers and the results have been discordant (20-23).

1. ETIOLOGY AND PATHOPHYSIOLOGY

PSC is likely to be caused by complex interactions between multiple genetic variants and environmental factors (24). A genetic susceptibility is supported by the familial occurrence of PSC and association with HLA B8 and HLA DR3 (25, 26) . The etiology of PSC is unknown, possible causative mechanisms are immunologic and non- immunologic (infectious, toxins and ischemia). Three studies have suggested that cigarette smoking may protect against the development of PSC (24, 27, 28). Moreover, this protective effect was seen in patients with and without IBD.

The 2:1 male- to- female gender ratio and the relatively poor response of the disease to immunosuppression suggest that PSC is not a classic autoimmune disease. However, the association of PSC with IBD, other autoimmune diseases and humoral and cellular immune abnormalities supports the immunologic theory. A common pathogenetic agent for PSC and IBD has been suggested, although the PSC-UC association is still not entirely understood. Thus, PSC can occur several years after colectomy and IBD can develop several years after OLT (29, 30). It has been hypothesized that bacterial antigens searching the portal vein through an increased intestinal permeability because of the inflamed colon could trigger an immune response. However, there are no clinical studies supporting this hypothesis. Patients with PSC do not have increased intestinal permeability in the small bowel and no evidence of small bowel bacterial overgrowth has been found (31).

Antineutrophil cytoplasmic antibodies have been detected in 85% of patients with PSC (32) being and unrelated to the presence of IBD. Cholangiocytes seem to be the targets of immune attack. One study found a significantly higher number of autoantibodies against antigens on biliary epithelial cells in patients with PSC compared with primary biliary cirrhosis (PBC), autoimmune hepatitis and control patients (33). Bile duct injury in PSC is characterized by significant periductal fibrosis leading to obliterating fibrosis of the bile ducts. The pathogenesis of bile duct destruction is unknown.

2. PSC, INCIDENCE AND PREVALENCE

Research on PSC epidemiology is provided mostly from referral centers. Four small population-based studies have reported incidence rates of 0.9-1.3 per 100 000 person-years (8-11). Data on the incidence of PSC in Asia and South Europe are scarce (34, 35). Although PSC is a rare disease, two previous studies from the US and the UK have reported trends to increased incidence (8, 36).

To accurately investigate the incidence of PSC, it is important to define the population at risk and be able to review clinical data through good retrieval of medical records. The International Classification of Diseases (ICD) nine and tenth codes are not exclusive for PSC, they include all forms of cholangitis and careful validation of PSC cases is mandatory. Card et al identified PSC cases through the General Practice Database Research, which gives an estimate of PSC incidence in primary care but not in the general population. A Spanish study sent questionnaires to gastroenterologists and hepatologists, with a response rate of 69% (35). The incidence rate reported by the above- mentioned studies was considerably lower than that previously found, 0.41 and 0.04/ 100 000 person-years respectively (35, 36). Case ascertainment methodology might explain differences in the results compared to studies from Scandinavia, North America and Wales (8, 10, 11). Table 1 summarizes studies investigating the incidence of PSC. The need for larger population-based studies has been pointed out by several investigators (8, 11).

Västra Götaland is a county located in the south-west of Sweden. From a medical care perspective, a defined population of about 1.5 million is served by one university hospital and seven regional hospitals. Exact age- and sex-stratified population statistics are available. All OLT in the region are performed at Sahlgrenska University Hospital, Gothenburg and no patients with PSC are referred to hospitals outside the region. This allows complete retrieval of cases with PSC and exact population statistics are available.

Previous studies have reported a PSC prevalence ranging from 8.5-13.6 per 100 000 person. Screening of asymptomatic IBD patients and mortality rates might have influenced the increased prevalence of PSC.

3. CLINICAL PRESENTATION

Up to 40% of PSC patients have been reported to be asymptomatic in recent reports (4) as opposed to 10 to 25% in earlier series (2, 6, 37, 38). The increase availability of no invasive diagnostic methods (magnetic resonance cholangiopancreatography, (MRCP)), screening of patients with IBD with pathological liver tests and methodological differences explain the increasing rate of patients with PSC diagnosed as asymptomatic. Approximately 8% have normal liver tests. Typical symptoms include right upper quadrant abdominal discomfort, pruritus, and weight loss (4). Fatigue was considered a common symptom in PSC during the 80s. However in a Swedish study, the prevalence of fatigue was significantly lower in PSC patients compared to –age and –sex matched subjects from the general population and did not differ from patients with IBD (23). In several patients with IBD, elevated alkaline phosphatase levels point to the PSC diagnosis, given this close association. Episodes of cholangitis accompanied by jaundice are uncommon at presentation. Not infrequently, the diagnosis is made after endoscopic retrograde cholangiopancreatography (ERCP) for suspected symptomatic gallstone disease (39). Common findings in abdominal ultrasound are hepatomegaly (44-55%) and splenomegaly. Only 2-4% patients have ascites and 2-6% have a history of variceal bleeding prior to diagnosis (3, 4, 40, 41).

4. DIAGNOSIS

Summary box 1.

Mayo Clinic diagnosis criteria:

. Cholestatic disorder, including elevated alkaline phosphatase ≥6 months

. Characteristic radiographic appearance of PSC and/or

. Histologic features consistent with PSC

. Exclusion of secondary cholangitis (previous bile injury, biliary neoplasm, immunodeficiency-associated cholangiopathy, choledocolitiasis or ischemia)

Typical cholangiographic findings are multifocal strictures and dilatation giving a characteristic beaded appearance. Approximately 5% have small duct PSC, an entity characterized by a lack of evidence of biliary tract disease on cholangiography but histopathology findings typical for PSC: concentric rings of connective tissue around bile ducts, known as the "onion ring" appearance (42). ERCP has previously been considered the golden standard for PSC diagnosis. However, because of associated complications (pancreatitis, perforation, biliary sepsis, bleeding and aspiration), MRCP has been used with increasing frequency as a non-invasive alternative to ERCP, permitting a high accurate visualization of the biliary tree (43). Angulo et al reported better visualization of the intrahepatic biliary tree with MRCP compared to ERCP (44), whereas difficulties in early PSC, cirrhosis, and in the differentiation of CCA, Caroli's disease and secondary sclerosing cholangitis using MRCP have been described (45). In a meta-analysis of 456 subjects, the sensitivity and specificity of MRCP for detecting PSC were 0.86 and 0.94 respectively (46). MRCP was compared to a previous ERCP in four out of six included studies in the above- mentioned meta-analysis and to ERCP or percutan transhepatic cholangiography in two of six included studies (46). ERCP is nowadays reserved for

cases with a suspicion of PSC despite negative findings on MRCP, cases with a need for diagnostic sampling or therapeutic intervention in the biliary intervention and in cases with cirrhosis.

5. NATURAL HISTORY

5.1 Mortality and liver transplantation

Survival has been shown to be reduced in both symptomatic and asymptomatic PSC patients (47, 48). Also, the inherent risk of CCA that affects 10-20% of PSC patients contributes considerably to mortality rates. Typically, the combined end-point death or OLT is reached after 12-18 years (7, 15, 49). A 10-year survival of 65% has been reported in two different studies (8, 10) and a threefold increased risk of mortality among PSC patients was found in a register-based study from the UK (36). A more favorable prognosis has been observed among patients with small duct compared to those with large duct PSC (50-52). A Swedish study investigated long- term outcomes and survival of all PSC patients included in three previous small studies (50-53). Thus, among 83 patients with small duct PSC, transplant-free survival was significantly longer in patients with small duct compared to those with large duct PSC (13 versus 10 years) (53). However, 23% of patients with small duct progressed to large duct PSC (53).

The clinical course of PSC is often unpredictable, making decisions about timing for OLT a difficult challenge. Patients with PSC complications such as repeated septic cholangitis or intractable pruritus do not meet Model of End Stage Liver disease criteria for OLT. Furthermore, there is no sensitive and specific enough diagnostic tool for CCA, which occurs among 10-20% of PSC patients. On the other hand, preventive OLT is not indicated. Indications for OLT are summarized in summary box 2 (54).

Summary box 2.

Indications for liver transplantation in PSC

End-stage liver disease	. Chronic liver failure .Complications of portal hypertension .Impaired quality of life
Special indications despite a low MELD score (≤ 17)	. Intractable pruritus .Recurrent or refractory bacterial cholangitis . Severe extra-hepatic biliary obstruction that precludes operative repair .Uncontrolled peristomal variceal bleeding . Limited stage peripheral or hilar cholangiocarcinoma filling the Mayo protocol criteria (55, 56)

5.2 Risk factors for death and liver transplantation

The progression of PSC is variable and difficult to predict. Several studies have investigated prognostic factors associated with worse prognosis in order to improve timing for OLT. Most of these studies have employed Cox proportional hazard models to assess survival. Age has been identified as an independent risk factor for death or OLT in all these models (2-4, 6, 7, 15) and bilirubin with the exception of the King College case series (2-4, 7, 15). Only the last mentioned study here has reported alkaline phosphatase as a prognostic factor (6). Transient elevated serum bilirubin levels in patients with PSC can be related to an episode of cholangitis or to a dominant biliary stricture. In order to improve the Cox regression model, a German study included persistent elevated bilirubin levels instead, which is more accurate than isolated bilirubin values (3). The results of the study were concordant with previous reports.

Most early prognostic models have included histological stadium and this variable has been associated with worse prognosis (2, 4, 6). However, because of sample error and reproducibility difficulty, this variable has not been included in more contemporary studies. Some authors have reported an association between splenomegaly and hepatomegaly and death or OLT (2, 3, 6, 49). Information about whether histology and imaging findings were added in the prognostic models at the time of PSC diagnosis or at follow-up is lacking in these studies.

All these models are time-fixed models, taking into account the value of a variable at one single point in time. In order to assess short-term prognosis, a multicenter European study, used a time-dependent model. Bilirubin, age and albumin were identified as prognostic factors in both the time-fixed and time-dependent models (57). A stronger association between bilirubin and poor prognosis was reported in the time-dependent model than in the time-fixed model.

The value of all these prognostic models is limited due to the clinical of PSC and confounding factors, such as biliary stones and CCA. Also, they are difficult for bedside use. In clinical practice, available tools are the Child Pugh classification, Model of end stage liver disease and PSC Mayo risk score. Child Pugh Classification has been validated in patients with liver cirrhosis (58, 59), whereas the Mayo model was developed and validated based on patients with a wide range of disease severity (47). The PSC Mayo risk score provides more valid survival information at early stages of PSC (47, 60). Age, bilirubin, aspartate aminotransferase and a previous history of bleeding esophageal varices are the variables included in the PSC Mayo risk score.

6. MALIGNANCIES

CCA is the most dreadful PSC complication. Approximately half of patients with PSC plus CCA are diagnosed within one year after PSC diagnosis (14). The majority of the tumors are localized at the hilum of the liver and fibrolamellar cancer is the most frequent type (61). Biliary dysplasia seems to precede the occurrence of CCA (62). Chronic exposure to accumulated bile acids because of chronic cholestasis and inflammatory molecules (e.g. IL-6) have been proposed as carcinogenic agents (63).

The reported accumulated risk for CCA ranges from 3-36% depending on the population, sample size, length of follow up and the methods used to establish diagnosis (3, 6, 12, 49, 64, 65). The largest cohort including 604 Swedish patients with PSC reported a 2% incidence of hepatobiliary cancer during the first year after PSC diagnosis (13). Thereafter an annual incidence rate of 0.5%-1.5% has been reported (13, 66). Bergqvist et al found a 160 times higher risk of hepatobiliary malignancies. Gallbladder and hepatocellular carcinoma among patients with PSC have also been reported (67-69). In a study including 134 PSC patients under transplantation investigations, 4% of all PSC patients developed hepatocellular cancer (67). All cases had advanced liver cirrhosis (67).

The diagnosis of CCA is a clinical challenge, with no diagnostic tool sensitive and specific enough to detect CCA at an early stage. Methods for early detection have been studied, using tumor markers (CA 19-9, CEA), cytological brushings during ERCP, and positron emission tomography (PET), but only PET methodology has been evaluated prospectively in PSC patients on the liver transplant list (70). Up to 50% of dominant biliary strictures are benign and it is difficult to distinguish between benign and malignant biliary strictures (3, 71). Combination of two radiologic methods (ultrasound, MRCP, ERCP, computerized tomography) is usually necessary for the diagnosis of CCA (72). A study from the Mayo Clinic including 23 patients with CCA found the following overall positive predictive values 40%, 38%, 48%, 23% and 21% for magnetic resonance image, computerized tomography, ultrasound, ERCP and MRCP (72). Combining MRCP and Magnetic Resonance Image can yield a sensitivity that is comparable (89%) to that of ERCP (91%) (72). The specificity of brush cytology for the diagnosis of CCA in PSC is high, whereas the sensitivity varies between 18%-40% (72-75).
Clinical deterioration, elevated serum bilirubin, variceal bleeding, smoking, alcohol consumption and longer IBD duration have been suggested as risk factors for CCA in PSC patients (14, 64, 66, 76, 77).

Patients with PSC are also at increased risk of colorectal dysplasia and cancer. Annual surveillance colonoscopies with colon biopsies are recommended (78). In a case-control study, the reported cumulative risk of colorectal dysplasia or cancer was 9%, 31% and 50% after 10, 20 and 25 years of UC duration in 40 patients with PSC and UC, compared with 2%, 5% and 10% for 80 patients with

UC and without PSC (79). A almost fivefold increased risk of colorectal dysplasia or colorectal cancer in patients with PSC and UC compared to patients with UC was found in a meta-analysis (80).

The risk of proximal cancer is particularly increased and cancer is diagnosed at more advanced stage (81). The increased risk for colon cancer remains after OLT, a study reported a fourfold increased risk for colon cancer compared with pre-transplantation risk (82).

7. IMMUNOGLOBULIN-G4 CHOLANGITIS

Steroid-responsive biliary strictures similar to those observed in patients with PSC have mostly been reported in association with autoimmune pancreatitis (AIP) (83, 84). AIP is a form of chronic pancreatitis characterized by high serum levels of IgG4, typical features on imaging and histology and response to steroid treatment (85, 86). Other organs involvement is also characteristic of AIP, i.e. biliary tract involvement has been described in 17% of cases (84). In case the intra-or extrahepatic biliary tract is involved without pancreas involvement, the condition has been named immunoglobulin-G4 associated cholangitis (IAC) (18). Table 2 illustrates IAC diagnostic criteria. Considerable overlap exists between AIP and IAC. A retrospective study from the Mayo Clinic identified 53 IAC cases through a database of patients with AIP (17).

The clinical picture of IAC is similar to classic PSC but with elevated IgG4 in serum and characteristic IgG4 plasma cells infiltration in the involved organs (17, 18). In contrast to classic PSC, patients with IAC are older at diagnosis and IBD has in most cases been found less frequently (50-75%) (17, 31, 87). Patients with IAC usually present with obstructive jaundice due to involvement of the distal common bile duct or associated AIP (17, 18). Nakazawa et al compared cholangiography findings between patients with PSC and AIP; long stenosis, segmental stricture and long stricture with pre-stenotic dilatation were significantly more common in patients with AIP (88).

Steroid responsiveness has been reported in two studies from the Mayo Clinic (16, 17). Resolution of biliary strictures and normalization of liver enzymes were observed by Ghazale et al in 60% of treated

patients (17). In another study from the Mayo Clinic, 18 out of 24 patients responded to steroids but 50% of treated patients reported steroid side-effects (16). Proximal biliary strictures and elevated serum IgG4 values were identified as predictors for IAC relapse (16, 17).

Patients with PSC and elevated IgG4 seemed to have a more advanced liver disease in terms of higher bilirubin levels and Mayo score and rate of liver cirrhosis up to 50% (16, 87). Also, shorter time to OLT among PSC patients with elevated IgG4 compared to those with normal values has been observed by two retrospective studies from the Mayo Clinic (87, 89).

Studies investigating the prevalence of elevated serum IgG4 in patients with PSC are from tertiary centers and no previous studies have addressed this in a population-based cohort.

8. QUALITY OF LIFE AND LIVER DISEASE

Health-related quality of life (HRQL) is impaired in patients with chronic liver disease (21, 22). Worse HRQL among patients with chronic liver disease compared to the general population and similar to that in patients with other chronic diseases has been reported (21). These findings were confirmed particularly in patients with cholestatic liver diseases (20). Few patients with PSC have been included in these studies (20-22). A study including two North European PSC cohorts from tertiary centers found no significant differences in "patients general well-being" between PSC patients and those with IBD (23). Liver disease severity has been associated with impaired HRQL in patients with chronic liver diseases in general, particularly in patients with cholestatic liver diseases and cirrhosis (20, 21, 90). Among patients with liver cirrhosis, HRQL is considerably more impaired in patients with hepatocellular disease etiology compared to those with a cholestatic disease (21). Non life-threatening symptoms, such as muscle cramps in patients with liver cirrhosis and pruritus in patients with PSC, have been associated with impaired HRQL (20, 90). Older age, medications, comorbidities and psychiatric diagnosis have also been reported as predictors of HRQL (21, 90, 91).

There is a lack of population-based studies assessing HRQL with liver specific instruments in patients with PSC. Patients with PSC may have impaired HRQL because of disease complications, symptoms of concurrent IBD, specific PSC symptoms such as pruritus and ongoing psychological distress concerning the risk for CCA or colon cancer. The aim of paper III was to include the psychosocial aspect of PSC in the thesis.

9. FATIGUE IN CHOLESTATIC LIVER DISEASES

Fatigue is a debilitating symptom and has been extensively studied in patients with PBC (92-95). Initially, fatigue was described as a characteristic PBC symptom, the prevalence ranging between 8 and 81% (92-94). However, in a more contemporary study, fatigue in patients with PBC did not differ compared with those with IBD and irritable bowel syndrome (95). Data about the prevalence of fatigue among patients with PSC are provided by only two referral centers, from Gothenburg and Oxford. In this study, fatigue was not considered a symptom related to PSC (23). In this study, fatigue was not considered a symptom related to PSC (23).

In both conditions, PBC and PSC, a correlation between fatigue and depression has been observed (23, 92, 94). On contrary, liver disease severity was not related to fatigue (23, 95).

AIMS OF THE THESIS

We specifically wanted to study:

7. The incidence and prevalence of PSC in a population-based cohort.
8. The temporal trends in the incidence of PSC.
9. The Standardized Incidence rates (SIR) for cancer and the Standardized Mortality Rates (SMR) in relation to PSC in the established population-based cohort.
10. Risk factors present at the time of PSC diagnosis that predicted increased risk of hepatobiliary cancer or the combined end-point liver-related death or OLT.
11. HRQL and its potential determinants in two well-defined European cohorts of patients with PSC.
12. The prevalence of fatigue and its relation to HRQL in patients with PSC from these two European population-based cohorts.
13. The prevalence of elevated IgG4 levels in serum in two European PSC cohorts and to assess the clinical features at PSC diagnosis associated with elevated IgG4 levels.
14. Whether positive IgG4 status in patients with PSC is a risk factor for death, OLT and CCA.

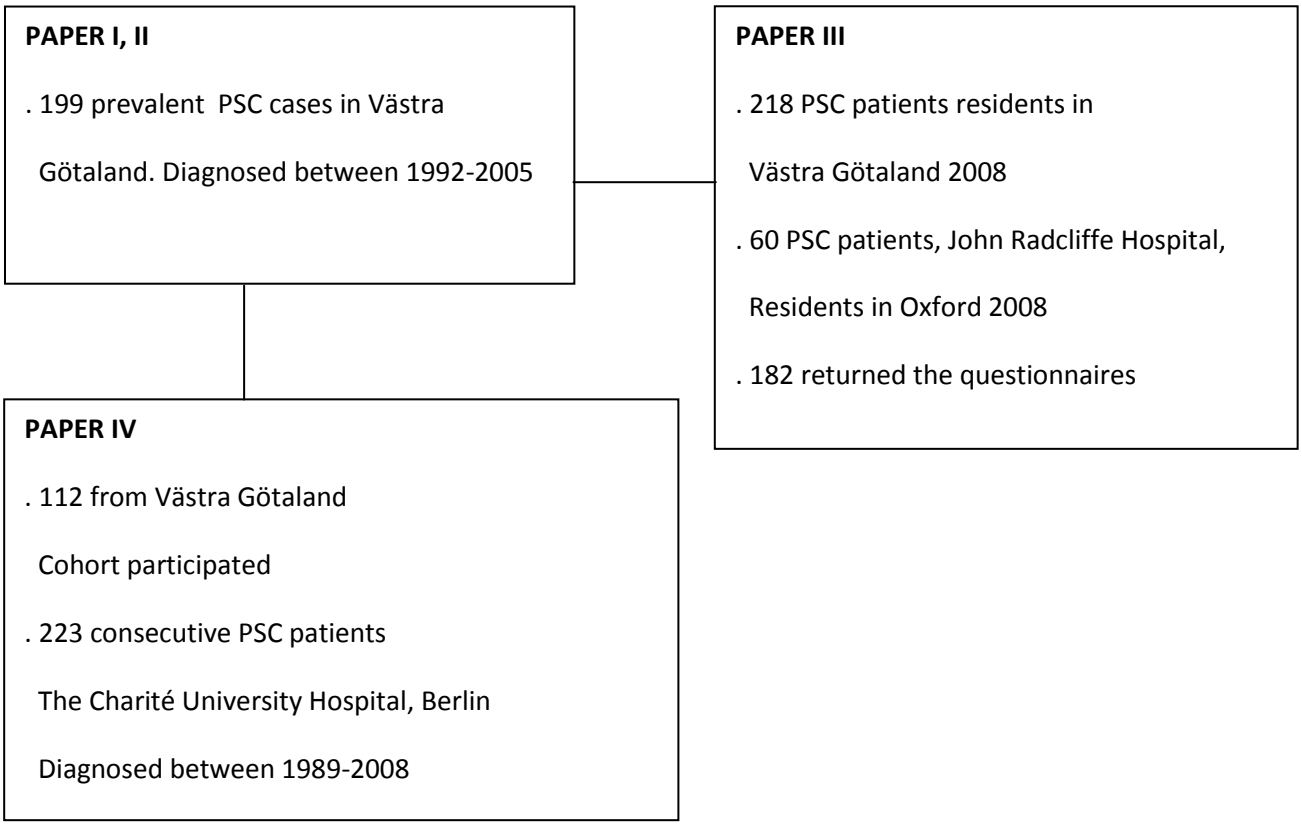
MATERIAL AND METHODS

The studies were performed according to the Declaration of Helsinki and were approved by the Gothenburg University Ethics Committee. Studies III and IV were also approved by the ethics committee of Milton Keynes in England and The Charité university hospital in Berlin.

1. SUBJECTS

Summary box 3 illustrates the study design of this project. PSC patients included in paper I and II came from eight hospitals in Västra Götaland county. Cases with PSC diagnosis during the study period 1992 to 2005 were included. Two other European PSC cohorts from Oxford (England) and Berlin (Germany) were included in studies III and IV.

Summary Box 3. Description of the project design.



All patients with PSC from paper I and patients with PSC from the outpatient's clinic at in the John Radcliffe Hepatology center in Oxford, residents in Västra Götaland and Oxford respectively in 2008 were included in paper III. In addition, 19 PSC patients diagnosed between 2007 and 2008 from Västra Götaland were invited to participate in the study. The John Radcliffe Hospital is a tertiary hepatology center in the UK renowned for PSC patient care. Table 3 illustrates differences between both cohorts.

Table 3. Results, paper III.
Comparisons of general characteristics between the Swedish and English PSC cohorts.

The previously established cohort in paper I of 199 prevalent PSC cases was included in paper IV. The German cohort comprehended a consecutive series of 233 patients with PSC diagnosed between 1989-2008 at the Charité university hospital in Berlin, a tertiary care center that serves a population of 3 million inhabitants.

Table 4. Results, paper IV.

General characteristics in a Swedish and German PSC cohorts.

2. CASE ASCERTAINMENT

Cases were identified from in- and out-patient diagnosis registers from all hospitals in the region using a computerized search for relevant codes according to the International Classification of Diseases (ICD), ninth and tenth revision (codes 576 and K830, respectively). The computerized search was extended to the end of 2006, i.e. one year beyond the end of the study period in order to not miss cases with an uncertain diagnosis at the end of the study period. Only subjects aged ≥ 18 years were considered, no diagnostic searches were performed in pediatric clinics. The diagnosis of large duct PSC was defined using the Mayo criteria (Summary box 1, in the Introduction). Cases were defined as small duct PSC when no evidence for biliary tract disease was detected on cholangiography but histopathology from liver biopsy showed features of PSC and criterion 1 and 3 were present.

3. DATA COLLECTION

Clinical data at diagnosis, laboratory findings, extension of biliary involvement, date of first biochemical sign or symptom of PSC, a previous history of pancreatitis and associated IBD were extracted from clinical records. Cases of PSC were classified as either or not related to IBD and large or small duct PSC.

Annual age stratified, data on the population of Västra Götaland were obtained from Statistics Sweden (www.scb.se). The National Register at Statistics Sweden was used to identify patients who resided outside Västra Götaland at the time of diagnosis or who moved out of Västra Götaland during the study period and to obtain dates of death.

Serum blood samples were collected at the first visit for the German cohort and in 2008 for the Swedish. IgG4 concentration was determined by nephelometry. The normal value range for individuals over 18 years is 8.0-140.0 mg/dl. Patients with serum IgG4 concentrations of > 140mg/dl were classified as IgG4 positive.

Questionnaires (III)

All patients were sent a letter asking them to participate in the study. Those who accepted were sent the study questionnaires. A reminder letter was sent 2-6 weeks later to those who had not responded. The questionnaire booklet contained questions on work, marital status, and education as well as the following questionnaires:

Short-Form 36 (SF-36)

This 36-item instrument was used to assess HRQL (physical, emotional, and social functioning) (96). The SF-36 is scored from 0 to 100, with higher scores indicating better HRQL. The SF-36 has previously been used for the assessment of HRQL in patients with chronic liver disease (90, 91, 97). An age- (2-year age interval) and gender-matched reference sample (n= 364), randomly drawn from the Swedish SF-36 normative database (n= 8930), was used as a control group (98).

Chronic Liver Disease Questionnaire (CLDQ)

The CLDQ is a liver disease-specific HRQL questionnaire that consists of 29 items divided into six domains: abdominal symptoms, activity, emotional function, fatigue, systemic symptoms and worry. Summary scores for each domain range from 1 (most impairment) to 7 (least impairment). Patients with a CLDQ domain score of < 4 (i.e. symptoms more frequent than "some of the time") were considered to have significant symptoms.

Fatigue Impact Scale (FIS)

The Fatigue Impact Scale was initially developed and validated for use in patients with chronic fatigue syndrome (99) and PBC (100). To provide a control group from the general population for comparison of fatigue between the two patient groups, a random sample of 2000 subjects (20-75 years of age) from the population in Gothenburg, Sweden were sent the FIS by mail. A total of 858 subjects from the general population returned the questionnaire (23, 95). From this group of subjects from the general population, two sex-and age-matched controls were randomly assigned to each PSC patient.

Patients were classified as fatigued if they had a FIS score of > 2SD compared to the sex- and age-matched controls.

Hospital Anxiety and Depression (HAD) scale

The HAD scale was used to assess psychological distress. Each item uses a 4-grade scale (0-3) with subscales for anxiety (7 items) and depression (7 items). Higher scores indicate higher levels of anxiety and depression (101). Normal values from the Swedish population are available (102).

4. FOLLOW-UP

Follow- up started at the time of PSC diagnosis. Subjects were followed up until the date of an event, i.e. cancer diagnosis or death or until end of follow- up. The follow-up time frame was March 2008 for paper II and December 2008 and December 2010 for the German and Swedish cohorts respectively included in paper IV.

The Swedish PSC database was linked to the Swedish Cause of Death and Tumor Registries. A high coverage of cancer diagnosis has previously been demonstrated in the Swedish Cancer Register (103). Cause of death was validated by review of clinical files and autopsy reports. Information on incident cancer diagnosis was retrieved by review of clinical files including radiology, pathology and autopsy reports. For the German cohort, information about death, liver transplantation or cancer was retrieved from the medical records.

Hepatobiliary cancer was defined as any primary cancer arising in the liver, bile ducts or gallbladder. CCA included all primary cancer arising from the bile ducts. In order to avoid exclusion of PSC related cancer due to delayed diagnosis, cancers diagnosed within 6 months after OLT were included as incident cases. Subjects with severe dysplasia in the colonic mucosa were included in the colorectal cancer group. Information on colectomy was obtained in the review of clinical files. A second line of data capturing was provided by cross linking of the PSC database to the patient registry at the Swedish National Board of Health and Welfare searching for surgical operation codes related to any kind of colonic resection.

5. STATISTICS

Point prevalence of PSC was calculated from the number of cases of PSC aged ≥ 18 years, residing in Västra Götaland on 31 December 2005. Patients who were diagnosed outside Västra Götaland and moved into the region before this date were included in this analysis. Incident cases of PSC were defined as patients ≥ 18 years of age who fulfilled the criteria for PSC and resided in Västra Götaland at the time of diagnosis. Changes in age and sex composition of the background population were adjusted by using the annual age- and sex- specific population of Västra Götaland as a denominator in all incidence rate calculations. Crude incidence was calculated as the average annual incidence 1992-2005. Poisson regression was used to analyze temporal, age- and sex-associated effects on the overall incidence rate of PSC and specific incidence rate of large duct PSC, and PSC with or without IBD. Average annual percentage change (AAPC) with a 95% confidence interval (CI) was obtained by multiplying incidence rate ratios (IRR) related to year of diagnosis obtained in the adjusted Poisson model by 100.

Data on vital status for the Swedish PSC cohort were available until the end of April 2010 and the analysis of crude Standardized Mortality Ratio (SMR) was therefore extended to that date. Subjects were censored at the time for OLT in all analysis of Standardized Incidence Ratio (SIR). The Kaplan-Meier method was used to calculate life table estimates for 5- and 10- year transplant- free survival and cancer incidence. In addition, the log-rank test was used to compare transplant-free survival curves between PSC patients with positive and negative IgG4 status.

Cox proportional hazards analysis was used to estimate relative risks (RR) with 95% CI for incident malignancies and the combined endpoint for liver-related death and OLT. Death of any cause and OLT was the combined endpoint used in paper IV. Risk of hepatobiliary cancer was assessed in two different ways: with and without exclusion of cases diagnosed within one year after PSC diagnosis (paper II). Time since PSC diagnosis was used as the underlying time scale in all Cox regression analyses. Age (in decades), sex, IBD, extension of biliary involvement, symptoms at diagnosis, bilirubin (in quartiles) and treatment with ursodeoxycholic acid were entered in univariate analysis

(paper II), whereas IgG4 status was the variable entered for paper IV. Factors that were associated with the risk of incident hepatobiliary cancer or liver-related death or OLT respectively with a p-value of 0.1 or less in the univariate analysis were entered in the adjusted model. By multivariate analysis, age was associated with increased risk of hepatobiliary cancer, whereas age, female sex, cholangitis and bilirubin were independent risk factors for liver related death or OLT. Thus, these variables were entered in the adjusted model to assess the risk for CCA, death or OLT respectively in relation to IgG 4 status (paper IV).

Logistic regression was used in order to identify factors independently associated with HRQL, as assessed by the SF-36 domain and summary scores (paper III) and clinical features at the time of PSC diagnosis that predict positive IgG4 status (paper IV).

6. VALIDATION OF THE SWEDISH VERSION OF THE CHRONIC LIVER DISEASE QUESTIONNAIRE

Previously, Liver disease- specific HRQL instruments (CLDQ) were available in English (104), German (105) and Spanish (106) but not in Swedish. Thus, we conducted a study to test a Swedish version of the CLDQ for validity and reliability (107). A total of 80 adult clinically stable patients with chronic liver disease were enrolled. A forward-backward translation of the original American-English version of the CLDQ (104) was performed. Internal consistency was assessed by means of the Cronbach's α coefficient and convergent validity by means of the Spearman's coefficient between CLDQ scores and relevant SF-36, HAD, GSRS and FIS domains scores. Retest reliability was assessed by means of the intraclass correlation coefficient. All tests were two-tailed and conducted at a 5% significance level. In case of multiple comparisons, the significance level was set at 1‰.

The Swedish version of CLDQ (107) showed good convergent validity, as demonstrated by the correlations between its domains and the validation instruments used, and moderate to high internal consistency and reproducibility. Discriminant validity was also good, as patients with cirrhosis versus those without cirrhosis had significantly lower scores in all CLDQ domains.

RESULTS

1. GENERAL CHARACTERISTICS

1.1 Prevalent PSC cases (I,II)

Between 1992 and 2005, a total of 199 incident and prevalent cases of PSC were detected in Västra Götaland. Mean age at diagnosis was 38 years, 76% of cases had associated IBD. Data on IBD duration was available in 81% of all cases and 11% were diagnosed after PSC diagnosis. Ninety three patients (46%) were symptomatic at the time of diagnosis, the most common symptoms being jaundice (24%) and abdominal pain (25%). The proportions of patients with extra- and intrahepatic, intrahepatic biliary tree involvement and small duct disease 58%, 31% and 10% respectively. Among patients with small-duct disease, one out of 20 progressed to large-duct disease and died of liver failure.

1.2 Quality of life PSC cohort (III)

Two hundred and eighteen PSC patients in Västra Götaland, Sweden and 60 in Oxfordshire, UK were identified and asked to fill in the questionnaires. Completed questionnaires were returned by a total of 182 patients, giving a response rate of 65% (69% in Sweden and 55% in England). Twenty-two patients (12%) had received a liver transplant due to PSC. Patients were older at the time of PSC diagnosis compared to the PSC cohort from paper I (50 versus 38 years), a similar proportion of patients to that reported in paper I and II had associated IBD (79%). Comorbidities were present in 146 (91%) patients, with arterial hypertension being the most common (62%). Regarding liver disease severity, the mean Mayo score was 0.34 and among patients with liver cirrhosis (8%), 6% had decompensated liver disease.

1.3 IgG4 PSC cohort (IV)

Prevalence of concomitant IBD was lower (53 versus 71%), the percentage of subjects with a previous history of pancreatitis was higher (21 versus 5%) and symptomatic disease was more common in IgG4 positive subjects (82 versus 30%) compared to those with negative IgG4 status. Jaundice was the most

common symptom at presentation, 74% of IgG4 positive patients suffered from jaundice at presentation compared to 12% of IgG4 negative patients. Combined involvement of intra- and extra hepatic bile duct were the typical cholangiografic findings in IgG4 positive patients, present in 82% of cases, compared to only 20% of IgG4 negative subjects. Bilirubin and alkaline phosphatase levels were significantly higher in IgG4 positive cases compared to the group with normal IgG4 values.

2. INCIDENCE AND PREVALENCE (I)

2.1Crude incidence and prevalence

The mean crude annual incidence in 1992-2005. Among men and women the incidence was 1.78 and 0.69 respectively, in the corresponding population. The point prevalence of PSC in the same population was 16.2 (23.7 among men and 8.9 among women) per 100 000, on 31 December 2005.

2.2 Time trends in the overall incidence of PSC

The overall incidence of PSC increased statistically significantly in the total adult population (AAPC 3.06 (95%CI: 0.01 to 6.20)), which equals an increase of 35.1 percent (95% CI 0.06-82.5) over a 10-year period. Sex- stratified analysis showed tendencies towards increasing trends in both men (AAPC 2.13 (95% CI: -1.35 to 6.08)) and women (AAPC 4.98 (95% CI: -0.46 to 10.72)) but neither of these tendencies were statistically significant. Trends in age- standardized sex- stratified PSC incidence are presented in Figure 1.

2.3 Stratified time trends

Diverging trends were observed for the incidence of PSC related to IBD when comparing men and women. In women, there was a statistically significant increase in the incidence of PSC related to IBD (AAPC 7.01 (95% CI: 0.24 to 14.24) and the incidence of large-duct disease (AAPC 6.32; 95% CI 0.03-13.02). In men, the incidence of PSC without IBD increased statistically significantly (AAPC 9.69, 95% CI: 0.82 to 19.33) as did the incidence of small-duct disease (AAPC 17.88, 95% CI 0.95-40.25).

2.4 The effects of age on the incidence of PSC

The age-related effects on the incidence of PSC are depicted in Figure 2. Age had a strong and statistically significant influence on the incidence of PSC related to IBD, small and large duct PSC with a decreasing incidence with increasing age. There was no statistically significant effect of age on the incidence of small duct PSC and PSC without IBD. These findings were consistent in both sexes.

Figure 1. Results, paper I.
Trends in age standardized sex stratified PSC.

Figure 2. Results, paper II.
Age specific incidence of PSC in Västra Götaland between 1992-2006

3. MORTALITY AND LIVER TRANSPLANTATION (II, IV)

3.1 Transplant-free survival

At follow- up in 2008 (paper II), information was available on 194 patients. Five had moved outside the region and were lost to follow-up. Twenty-nine patients (13.6%) died at a median follow- up of 4 years (range 0-11), whereas 25 (11.7%) received a liver transplant at a median follow up of 2 years (range 0-12). Transplant-free survival at five- and ten- year follow-up was 81% (95% CI 75-87%) and 70% (95% CI 63-78%) respectively (Figure 3). Among patients with small-duct PSC, one out of 20 progressed to large-duct PSC and died of liver failure.

For the merged Swedish and German cohort (paper IV), follow-up was available for 260 (75%) patients. The median follow-up time from PSC diagnosis was 8 years (range 0-29) for the whole cohort. The proportion of German patients who received a liver transplant was significantly higher compared to Swedish patients (28% versus 9%). Time to OLT or death did not differ significantly between patients with elevated and normal IgG4 (14 versus 18 years, p=0.71) (Figure 4). A slightly lower percentage of patients with negative IgG4 status had died at follow- up compared to those with positive IgG4 status (6% versus 9%, p= 0.51).

Figure 3. Results, paper II.

Liver transplant free survival in 199 PSC patients. Tick marks indicate censored subjects.

Figure 4. Results, paper IV.

Kaplan-Meier curve illustrates differences in transplant-free survival between PSC patients with elevated and normal IgG4 values (log-rank test p= 0.47).

3.2 Risk factors for death, liver related death or liver transplantation (II, IV)

There was a four-fold increased risk of mortality (SMR 4.20; 95% CI 3.01-5.69) compared to the general population in Västra Götaland. Censoring subjects undergoing OLT at the time of operation gave similar results.

By univariate analysis, age, female gender, extra hepatic bile duct involvement, symptomatic disease, jaundice, cholangitis and bilirubin in the highest quartile were associated with the risk of liver- related death or OLT. These variables were entered in the multivariate analysis with the exception of jaundice given the close relationship between jaundice and bilirubin. Age, female gender, cholangitis, jaundice and bilirubin in the highest quartile were statistically significantly associated with the risk of liver related death or OLT in the adjusted model. The strongest association was found for bilirubin (RR

3.95; 95% CI 1.46-10.75), highest versus lowest quartile) and cholangitis (RR 2.56; 95% CI 1.20-5.64), for presence versus absence of cholangitis).

IgG4 status was not associated with increased risk of death (RR 0.51, 95% CI (0.21-1.23)) or the combined end-point death or OLT (RR 0.59, 95% CI (0.28-1.22)).

4. CANCER AND RISK FACTORS (paper II, IV)

Overall, 29 incident malignancies were identified in the PSC cohort. Seven out of 21 of all hepatobiliary cancer were diagnosed within one year after PSC diagnosis. Five out of seven patients had concomitant IBD, all but one had been diagnosed PSC at a young age. In patients diagnosed with cancer within one year after PSC diagnosis, four ERCP and three MRCP showed typical signs of PSC.

There was a four-fold increased risk of any malignancy compared to the general population in Västra Götaland (SIR 4.17; 95% CI 2.79-5.99). However, the risk of cancer regardless of site was not significantly increased compared to the general population when hepatobiliary cancers were excluded (SIR for all sites excluding hepatobiliary cancer 1.12; 95% CI 0.48-2.21). SIR for hepatobiliary cancer was 177 (95% CI 110-271) and for CCA 868 (95% CI 505-1390). IBD duration at PSC diagnosis as a continuous variable in years was not associated with the risk of hepatobiliary cancer (RR 1.03; 95% CI 0.99-1.97; p= 0.09), data not shown.

As mentioned in the methods section, the risk of hepatobiliary cancer was analyzed in two different ways. Age was significantly associated with the risk of hepatobiliary cancer (RR 1.40, 95% CI (1.01-1.95) per decade, p= 0.04) when all cases were included in the analysis. After exclusion of hepatobiliary cancer identified within one year of PSC diagnosis, cholangitis was a prognostic factor for hepatobiliary cancer (RR 9.24, 95% CI 2.13-40.0; p= 0.003). Positive IgG4 status was not associated with increased risk of CCA (RR = 0.45, 95% CI 0.06-3.35; p=0.3).

Two subjects with colorectal cancer were identified. SIR for colorectal cancer was not statistically significantly increased in PSC subjects compared with the general population.

5. QUALITY OF LIFE

4.1 Health-related quality of life

Patients with PSC had significantly lower scores in all SF-36 domains compared with the general population, with the exception of the physical functioning and bodily pain domains (Figure 5). Patients who had undergone OLT did not report significantly different HRQL compared to controls ($p>0.05$) with the exception of general health SF-36 domain (59 versus 71 respectively, $p<0.05$).

Age was found to be negatively related to all SF-36 physical domain scores and to physical component summary (PCS) score ($r= -0.09$ to -0.49, $p< 0.05$) and positively related to SF-36 mental health, role emotional, and mental component summary (MCS) scores ($r= 0.09$-0.22, $p<0.05$). Patients with large-duct PSC, compared with those with small-duct PSC, had lower SF-36 vitality, social functioning, mental health and MCS ($p<0.05$ for all) scores. Severity of liver disease was related to HRQL, because patients with cirrhosis had lower SF-36 physical functioning, role functional, general health, mental health and PCS scores compared with non-cirrhotic patients ($p<.05$ for all). All CLDQ domain scores were related to SF-36 PCS and MCS ($r= 0.23$-0.75, $p<0.01$).

Exclusion of patients with CCA (n=2) did not change the results of the analyses presented above (data not shown).

Figure 5. Results, paper III.

HRQL in patients with PSC who had not received a transplant (n=160) compared with controls (n=364) as assessed by SF-36 (mean, 95% confidence intervals). * $P < 0.05$.

4.2 Fatigue

Fatigue, as assessed by the FIS, did not differ significantly between PSC patients and controls (Figure 6). Patients who had undergone OLT did not report significantly different fatigue levels compared to the rest of the cohort or controls (significant fatigue according to the total FIS score in 5.3% PSC patients without prior OLT, 5.3% in PSC patients who had received a transplant, and 4.7% in controls, $p> 0.05$).

Figure 6. Results, paper III.

Proportion of patients with PSC who had not received a transplant (n= 160) and controls (n=320) with significant fatigue as assessed by FIS (%, 95% confidence intervals). P >.05 for all.

4.3 Psychological distress

The proportion of subjects with significant or borderline depression, as assessed by the HAD, did not differ between patients and controls (9% versus 15%, p= 0.06). The same was true for anxiety (9% versus 6%, p=0 .4).

4.4 Factors associated with impaired quality of life

In the first stage, age was found to have a negative impact on two out of four physical SF-36 domains, whereas serum alkaline phosphatase concentration was negatively associated with three mental SF-36 domains. Large duct, as opposed to small-duct PSC, was related to lower vitality and mental health scores. However, liver disease severity (Mayo Risk score, presence of cirrhosis), comorbid illness,

including IBD, ursodeoxycholic acid treatment, or duration of follow-up were not found to be major predictors of HRQL in these patients.

In the second stage, subjective symptoms as assessed by the CLDQ were included in the linear regression analysis. Serum alkaline phosphatase levels were excluded from this (and the next) stage to avoid potential confounding with pruritus and other symptoms. Significant fatigue according to CLDQ was found to be an independent predictor for all physical SF-36 domains, PCS and two mental domains. Not unexpectedly, emotional function, as assessed by the CLDQ, was associated with lower scores in all mental SF-36 domains. Systemic symptoms were independently related to all physical SF-36 domains, with the exception of general health.

In the third stage of the analysis, each specific symptom score (question numbers 3,6, 21, 23 and 27 on the CLDQ) was included in the regression analysis for SF-36 domains that in the second stage were found to be independently related to the CLDQ systemic symptom domain (i.e. physical functioning, role functional, bodily pain, and PCS). Pruritus was identified as an independent predictor of the SF-36 bodily pain (β= 9.3, $p<0.01$), and role functioning (β=-15.1, p=.01) domains and the SF-36 PCS (β=-3.38, P=.02), whereas, not unexpectedly, the CLDQ bodily pain domain score was related to SF-36 bodily pain domain (β= -31.7, $p<0.01$) as well as the SF-36 PCS (β=-6.76, $p<0.01$).

DISCUSSION

The main results in the present project will be briefly summarized below and later compared to other findings in the literature.

PSC is a rare disease but with a considerable morbidity and mortality, although, few population-based studies on PSC have been conducted. In the present project, we have investigated epidemiological aspects and HRQL of PSC in a population-based setting.

The incidence of PSC increased significantly with an AAPC of 3% under the study period and the prevalence of 16 per 100 000 person is the highest reported to date. The prevalence of elevated serum IgG4 in patients with PSC was similar to what has been previously reported by tertiary centers. Mortality risk was four times higher among PSC patients compared to the background population in Västra Götaland and a considerably increased risk for hepatobiliary cancer (SIR 177) has been confirmed in a population-based PSC setting. An unexpected finding was that the risk of CRC was not increased compared with the background population. Risk factors associated with OLT or death did not differ from previous studies from referral centers, with the exception of female sex. In contrast to previous studies, the prognosis was similar in patients with elevated and normal serum IgG4 values. HRQL was poorer in patients with PSC compared to controls and non- life-threatening symptoms such as pruritus were associated with impaired HRQL. Taking our findings into consideration we confirm a high morbidity and mortality of PSC in a population-based PSC setting, report an increasing incidence and impaired HRQL in a population-based setting.

1. INCIDENCE AND PREVALENCE

In paper I, we investigated the incidence and prevalence of PSC in an adult population-based setting. We found a crude incidence of 1.22 per 100 000 person-year, which is among the highest to date. IBD

was associated with PSC in 76% of cases and the highest IBD incidence rates have been described in Northern countries (108). Thus, not surprisingly, the incidence rate reported in paper I is similar to that previously described in a Norwegian study (1.3 per 100 000 person-years) (10) and slightly higher than that from two North American studies (0.9 per 100 000 person-year) (8, 9). It is important to mention that the Canadian study included pediatric PSC cases (9), and the remaining population-based studies do not state whether a search for PSC patients was conducted in pediatric clinic registries (8, 10, 11, 36, 109) . Pediatric cases were not included in our cohort. The incidence of PSC was nearly five times higher in the pediatric population compared to the adult population in the study by Kaplan et al (9). On the other hand, PSC in children seems to be a different entity compared to PSC in the adult population. Evidence suggests that overlap syndrome of autoimmune hepatitis and PSC is significantly more common in children than adults and defects in the ABCB4 (MDR3) gene have been found in children with small duct disease (110, 111).

Case ascertainment can also have influenced incidence rates estimates since ICD diagnosis codes according to the ninth and tenth version are not specific for PSC. Interestingly, in a recently published meta-analysis the method of case ascertainment did not contribute to the heterogeneity observed between the studies (112). This meta-analysis, included eight studies investigating the incidence of PSC. The overall incidence rate estimate was 0.77 (0.45-1.09) per 100 000 person-years at risk, a slightly higher incidence rate was found (1.00 per 100 000 person-years at risk) when only population-based studies were considered.

1.1 Trends in incidence

The overall incidence of PSC increased significantly in the total adult population with an Annual Average Percent Change (AAPC) of 3.06 (95% CI 0.01-6.20) which equals an increase of 35% (10%-82%) over a ten-years period. One possible explanation is that the incidence of IBD, the major risk factor for PSC, may have increased during the study period. In paper I, this theory may be supported for women with PSC and IBD but not for the men. Unfortunately, information about IBD incidence

trends in Västra Götaland, specifically over the last decades, was not available. However, a Danish study found a significant increase in the incidence of IBD from 2003 to 2005 but no differences in sex-stratified incidence of IBD were observed (113). Other contributing factors are worth mentioning. One of them is the above- mentioned shift in the PSC diagnostic work-up from ERCP to MRCP. Also, the increasing use of biological and immunosuppressive therapies may have lead to detection bias of PSC over the past ten years. Since these medicines can induce liver toxicity, liver tests are routinely screened and followed up in patients under this treatment. Consequently, the increased awareness of PSC disease and the use of biological and immunosuppressive therapies have contributed to the increased incidence of PSC.

1.2 Stratified incidence

The only previous study investigating the ratio between large and small duct PSC included the pediatric population. This study reported a five times higher incidence of large duct compared with small duct PSC (9). We found significant trends in different subtypes of PSC with an increase of small duct PSC and PSC not associated with IBD in men and large duct PSC and IBD-associated PSC in women. The number of patients in each subgroup was however small and no firm conclusions can be drawn based on these findings. Further multicenter studies in order to increase the sample size are warranted to confirm the results. It is important to clarify PSC subtypes, since small duct disease patients have a better prognosis than those with large duct disease and associated IBD implies an increased risk of colorectal cancer.

Not surprisingly, the association between age and the overall incidence of PSC was statistically significant. However, stratified analysis revealed that this association was only present in IBD-associated PSC; the incidence of PSC without IBD was not associated with age. Supporting these findings, the reported mean peak for IBD has been between 16 and 25 years with no significant peaks later in life (113).

1.3 Prevalence

Previous studies from northern Europe and US have reported PSC prevalence ranging from 8.5-13.6 per 100 000 person (8, 10, 11). In paper I, the PSC prevalence rate was 16 per 100 000 person-year, which is slightly higher and the highest prevalence reported to date. In general, prevalence rates are influenced by incidence and mortality rates. Overall, in studies reporting similar incidence rates than that reported in paper I, prevalence estimates did not differ considerably from our results. Given the small number of patients included in those studies and different follow-up times, comparisons of mortality rates are not appropriate.

In paper IV, we found a prevalence of PSC patients with an elevated serum IgG4 of 10%, similar to that reported from referral centers in the US (16, 87). For the population-based Swedish sub-cohort, the prevalence was slightly lower (6%). A possible explanation for this difference is that more aggressive cases can have been missed in the Swedish cohort since serum IgG4 was measured after PSC diagnosis (16, 87). However, in the two previous studies from the US, serum IgG4 was also measured after PSC diagnosis indicating that referral bias is a more likely explanation . Overall, the prevalence of IAC seems to be underestimated since elevated serum IgG4 values and lymphoplasmacytic infiltration in liver explants from PSC patients have been found in approximately one fourth of all transplanted patients (89).

Although the aim of paper IV was to assess the prevalence of elevated IgG4 in patients with PSC, the clinical characteristics associated with IgG4 status were those reported to be associated with IAC (17). Elevated serum IgG4 can be found in patients with PSC and other conditions such as CCA, choledocolithiasis and pancreatic cancer without evidence for IAC (114, 115) and normal values have been observed in patients with IAC. The reported sensitivity of serum IgG4 in patients with IAC (74%) is similar to that found in patients with AIP, but the specificity remains unclear. Since patients with IAC respond to steroid treatment, it is important to recognize this entity. For further confirmation of IAC, histology is the golden standard in diagnostic work-up and other organ involvement supports

the diagnosis. Thus, studies assessing histology, radiological findings, other organ involvement at the time of PSC diagnosis and steroid challenge are warranted in the future.

2. NATURAL HISTORY OF PSC

2.1 Mortality

Previous studies investigating PSC survival have defined the start- and end-point in different ways. Some studies have defined start point as the first symptom or pathological liver test compatible with PSC (6, 49) whereas others chose the first pathological cholangiography (3, 4, 7). In the present project, the later definition was used. Thus, survival can be underestimated in paper II and IV given the time delay between pathological liver tests and the confirmed PSC diagnosis by cholangiography and/-or liver biopsy.

A fourfold increased risk of death related to PSC compared to the background population was observed in paper II. Most of previous studies on PSC have reported case series mortality without a defined background population, which does not allow estimates of SMR (2-4, 6, 7, 49). Results similar to our findings with a threefold increased mortality rate were recently reported in a UK-based population (36). However, that was a register-based study without individual case validation introducing a risk of misclassification bias. We also found a similar ten- year transplant-free survival to that previously reported by two referral centers (71% versus 65%) (2, 8). Thus, a high mortality rate associated to PSC has been confirmed in a large unselected PSC subset in paper II.

Although liver-related death defined the end-point in paper II, we were also able to report all causes of death. Overall 28 out of 36 (78%) deaths were liver- related, whereas in 23% of cases the cause of death was not liver related. It is noteworthy that in two cases death was related to PSC, one patient died because of colorectal cancer with associated IBD and another after pancreas surgery. In the latter case, pathology could not confirm the initially suspected pancreatic cancer. This patient probably had AIP.

Two previous Swedish and Dutch studies have reported that malignancy accounted for 44% of mortality in PSC patients (13, 15). In agreement, in paper II, malignancy was the main cause of death in 47% of cases. However, 17 out of 18 were CCA and only one case of CRC was found. In contrast, in the Dutch study CCA and CRC accounted for 24% and 11% of mortality respectively. The low SIR of colorectal cancer found in paper II explains differences in the results.

2.2 Risk factors for death and liver transplantation

The aim of the paper II study was to investigate risk factors at the time of PSC diagnosis associated with OLT or death. In the Västra Götaland PSC cohort, 90% of cases had typical PSC findings on cholangiography. According to available guidelines from Europe and America (EASLD, AASLD), liver biopsy is indicated in case PSC is still suspected despite normal cholangiography. Since abdominal imaging allowing diagnosis of hepatomegaly or splenomegaly was not routinely performed at PSC diagnosis in our cohort, these variables were not included in the analysis either.

In accordance with previous studies from referral centers in the US and Europe, age and bilirubin were associated with a poor prognosis in a population-based setting (4, 6, 38, 49). Whether older age represents long- time undiagnosed PSC is unclear. An interesting finding in paper II is that females had a worse prognosis than males. To our knowledge, only one previous study has identified female sex as a risk factor for OLT or death, but only by the univariate analysis (38). In general, prognostic models identify clinical variables which predict for the whole PSC group but the information may be less valuable at the individual level. The implications of our findings in paper II in the clinical praxis would be that PSC patients being diagnosed at an older age, with elevated bilirubin and female gender, should be followed more intensively. PSC has usually a quiescent course and clinical parameters used in the prognostic models represent different disease stages. Thus, the time-dependent model proposed previously by a Norwegian group is more appropriate for short-time prognosis (57). In the future, long-term assessment of endoscopic therapy effects on survival would also be of value. Recently a study including 65 PSC patients who underwent repeated endoscopic balloon dilatation of dominant

strictures reported a better five- year survival rate than that predicted by the Mayo score (85% versus 65%) (116). However, this study, as all other studies of endoscopic therapy in PSC, was uncontrolled and retrospective. Thus, there is no proof that endoscopic therapy has any effect on prognosis in PSC. Genetic analysis should also be included in future studies, i.e. genetic variants of the pregnane X receptor may lead to a more aggressive course in PSC in animal models of cholestasis (117).

In conclusion, a more holistic prognostic model including time-dependent prognostic models, assessment of endoscopic therapy in randomized prospective studies and genetic analysis might shed light on risk factors associated with poor prognosis in PSC patients.

3. MALIGNANCIES

Malignancy risk is reported as SIR, which is one of the strengths in paper II. The intention with this approach was to investigate the previously reported increased malignancy risk among PSC patients in a population-based PSC cohort (13). Using the same definition of hepatobiliary malignancies and statistical tools permits comparisons between both studies.

One third of all hepatobiliary cancers were diagnosed within one year after PSC diagnosis, which is similar to that reported by Bergqvist et al (37%) and lower than that found in a multicenter European study (50%) (14). Thus, the presence of symptoms in PSC patients recently diagnosed should be investigated intensively to rule out hepatobiliary cancer.

Overall, a fourfold increased risk of malignancy was observed among PSC patients compared to the background population, which is slightly lower than that reported by Bergqvist et al (13). We found a SIR of 177 for hepatobiliary cancer, which is similar to 160 reported in the previous Swedish study. A weakness in our study is the unknown autopsy rate, in contrast to 74% autopsies in Bergqvist et al (13). As a consequence, the prevalence of hepatobiliary cancers in our cohort may have been underestimated. In contrast to the above- mentioned study, no increased risk of pancreatic cancer related to PSC was detected in paper II, whereas Bergqvist et al found a 14-fold increased risk for

pancreatic cancer. Since histology obtained in autopsy may ultimately differentiate these two types of cancer, misclassification of them in our study cannot be excluded.

In paper IV, the proportion of patients that developed CCA was similar in PSC patients with elevated IgG4 values compared to those with normal IgG4 values (6% versus 7%). This is a novel finding, in previous studies no evidence for CCA was shown among patients with PSC and elevated serum IgG4 (16, 87). Björnsson et al reported two cases with elevated serum IgG4 and suspected CCA, but histology confirmed AIP (16). Contrary to the above-mentioned studies, information about PSC disease duration was available and follow-up was long enough to permit evaluation of CCA risk. Interestingly, most of patients with IAC had previously surgically treated for suspected biliary malignancies. Consequently, it is important to identify patients with IAC in order to avoid unnecessary surgeries after thorough investigations to exclude CCA since patients with IAC respond well to steroids.

3.1 Risk factors of cholangiocarcinoma

In paper II, risk factors of hepatobiliary cancers were analyzed in two different ways: including all cases and excluding cases diagnosed within one year after PSC diagnosis. To our knowledge, only one previous multicenter European study has investigated risk factors as mentioned above, finding that after exclusion of 24 cases of CCA in patients with PSC diagnosed within one year, jaundice was not longer associated with an increased risk of CCA (14). Age has been previously identified as a prognostic factor for CCA by some research groups (4, 15), whereas others could not confirm this association (66, 118). In paper II, age was a prognostic factor for hepatobiliary cancer in both analysis.

It has been suggested that longstanding undiagnosed PSC may explain the association between older age and the large proportion of CCA diagnosed within one year after PSC diagnosis. However, concomitant cirrhosis has been reported in only 20% of patients with CCA (119) and a long PSC disease duration does not seem to be a prerequisite for the development of CCA (13, 14, 118). Only one case-control study from a transplant center found evidence for more advanced liver disease among

patients with PSC and CCA compared to those without CCA (66). In that study, esophageal varices was an independent predictor for CCA (66).

Further prospective studies investigating prognostic factors for CCA related to PSC disease duration are warranted to identify risk factors in the short and long term after PSC diagnosis.

Three previous studies have indicated that a long IBD duration may be a risk factor for CCA (14, 120, 121), This could not be confirmed in paper II. It has to be mentioned that in 11% of cases in our cohort, IBD was diagnosed after PSC and IBD duration was unknown in 20%. Thus, in 30% of cases this variable could not be assessed.

Although a similar proportion of PSC patients with elevated and normal serum IgG4 levels developed CCA (7% versus 6%), IgG4 status was not a risk factor for CCA. Because the most aggressive cases of PSC patients can have been missed in the Swedish sub-cohort and because of the small sample size, the results should be interpreted with caution. However, the lack of an association between IgG4 status and these end-points was also observed when the analysis was restricted to only the German cohort where IgG4 status was measured at first visit.

3.2 Colorectal cancer

An unexpected finding in paper II was that the risk of colorectal cancer did not differ significantly between patients with PSC and the background population (SIR 2.87; 95% CI 0.33-10.4). In contrast to our findings, a SIR for colorectal cancer of 17.1 was reported by Bergqvist et al and an accumulated ten year incidence of colorectal cancer of 14% by Claessen et al (13, 15). These studies included older PSC cohorts with inclusion periods from 1970 to 1998 and from 1980 to-2006 respectively. The management of IBD has changed substantially during the last twenty years with increasingly active medical treatment and the implementation of endoscopic surveillance programs. In fact, a large study including IBD patients from three Swedish cohorts who were followed up until 2004 reported a

significant decrease of mortality due to CRC and a tendency towards a decline in the incidence of colorectal cancer (122).

In paper II, patients were censored at the time of colectomy, making a bias in this regard unlikely. In contrast to Bergqvist et al's study (13), colorectal dysplasia was not defined as a case in paper II. However, reclassification of colorectal dysplasia as cases in our study still did not result in significantly increased SIR levels for colorectal cancer.

In paper IV, 52% of patients with elevated serum IgG4 had concomitant IBD, which is similar to that previously reported. We did not find any case of colorectal cancer in patients with elevated serum IgG4. Data on IgG4 systemic disease involving the colon are scarce. Positive IgG4 immunostaining has been demonstrated in patients with AIP and diagnosis UC (123), but remains unexplored in PSC patients with elevated serum IgG4. Further studies with a control group without IBD and elevated serum IgG4 to investigate whether this subgroup have an increased risk of CRC are warranted.

4. QUALITY OF LIFE

We found a worse HRQL among patients with PSC compared to the general population in accordance with 2 previous studies from referral centers (20, 22). All mental SF-36 domains and MCS scores were significantly lower in PSC patients compared to controls, whereas no differences were found between the groups regarding MCS. Thus, mental health was more impaired than physical health. In agreement, a previous study found poorer mental health as assessed by the CLDQ in patients with cholestatic liver diseases compared to patients with other chronic diseases (20). However, the significance of this finding is unclear because neither depression nor anxiety, as assessed by the HAD, was more common in patients with PSC compared with the general population. In our cohort, clinical depression was found in 2% of patients, which is similar to the proportion of patients with PSC diagnosed with depression in a previous study using a structured psychiatric interview technique (124). A possible explanation of our results is the influence of an undiagnosed psychiatric disease since patients in both cohorts were not prospectively evaluated by a psychiatric interview.

Several of our findings are worth mentioning. Liver disease severity was not associated with poorer HRQL, which is in contrast to previous reports in patients with cholestatic liver disease (20, 21). A possible explanation could be that previous studies enrolled 39-61% patients with PSC having cirrhosis, compared to 8% in our cohort. In contrast to those mentioned studies, histology was not assessed. Thus, an underestimation of liver cirrhosis in paper III cannot be excluded. Associated IBD was either a predictor of impaired HRQL in paper III in accordance with previous studies from referral centers (23, 125). However, as mentioned above the lack of a control group with PSC without IBD hampers interpretations.

We found a negative correlation between age and physical domains. This was an expected finding since age has a negative influence on physical health (96) and has been reported previously (19). Associated comorbidities have been identified as predictors of HRQL in patients with different chronic liver diseases and cirrhosis (90, 91). This could not be confirmed in paper III. However, previous studies have assessed the number of comorbidities, whereas in paper III, the Charlson' comorbidity index was used. Furthermore, more severe comorbidities in terms of associated cardiovascular disease were observed in one of the mentioned studies compared to paper III (25% versus 3%) (91).

Pruritus is an important clinical outcome. In fact, OLT may be indicated in patients with severe pruritus refractory to medical treatment. In paper III, we confirm that pruritus is a major determinant of HRQL in PSC patients in accordance with previous studies (20, 21). Since pruritus is a devastating symptom that can lead to sleeplessness and psychological distress one would expect an influence on mental domains. However, pruritus was only associated with physical health in paper III.

Paper III is the first study investigating HRQL in different PSC subtypes. We found that HRQL was reduced in patients with large-duct disease compared with those with small-duct disease. This emphasizes that HRQL complements clinical outcomes. Patients with large- duct disease have a worse outcome in terms of survival, development of CCA and HRQL (50). Further studies should confirm our findings.

We found no differences in HRQL between PSC patients who received a liver transplant and those who did not. Since the study was not designed to address this issue, the cohort was not followed up longitudinally which limits comparisons with a previous study reporting improvement of HRQL among patients with PBC and PSC one year after OLT (22).

5. FATIGUE

Fatigue contains psychological and physical aspects and it has been recognized as a hallmark in patients with hepatocellular disease and liver cirrhosis. In paper III, fatigue was not a specific symptom of PSC in accordance with a previous study from two referral centers (23). However, it seems to be an important symptom in a small group of PSC patients and 11% of patients had significant fatigue as assessed by CLDQ. Selection bias could be argued, since only 8% had liver cirrhosis. Theoretically, encephalopathy can cause lethargy and fatigue. However, previous studies could not show a significant association between liver tests, Mayo PBC score or histology and fatigue (23, 93-95). Former studies reported fatigue as a typical symptom of PBC (92-94). However, assigned controls in those studies were healthy blood donors, historical controls and patients with AIH. In our study, controls were assigned from the same normative database as the one used by Björnsson et al (23). A selection bias in the previously mentioned Swedish study and paper III cannot be excluded, since the response rate among controls was 44%.

5. METHODOLOGICAL ISSUES

The intention was to capture all PSC cases diagnosed in the adults between 1992-2005 in Västra Götaland. A register search was performed in the medicine and surgery departments. Since no patients with PSC are referred outside the region and all OLT are performed at Sahlgrenska University Hospital, we are confident that paper I and II are population-based studies. Strengths of the present project are the sample size and the standardized validation of all cases. Detection bias is a possible source of error. An example of this is when diagnostic tools for the detection of a disease are altered.

Imaging of the bile tree is a cornerstone in the diagnosis of PSC and ERCP has previously been the standard method for obtaining a cholangiogram in a patient with suspected PSC. However, diagnostic ERCP has been successively replaced by MRCP during the study period due to increasing availability and lower risk of complications related to the latter method. If the threshold for when a cholangiogram should be obtained in patients with suspected PSC has decreased as a consequence of the less invasive nature of MRCP, a detection bias needs to be considered. However, in our study, the diagnostic delay (i.e. the time from the first biochemical sign or symptom of the disease until the time when the diagnosis is established) was constant over the entire study period. Although detection bias cannot be excluded completely, it is unlikely that it is important enough to have had any significant impact on the observed trends.

The increasing use of MRCP may also have lead to misclassification bias, because subtle changes in the large bile ducts can be difficult to detect by MRCP leading to an illusory change in the ratio between the incidence of large and small duct PSC. We observed a significantly increasing incidence of small duct PSC in men and a non-significant decreasing trend in women in this study. A misclassification cannot explain these findings since the same diagnostic work- up was used in both sexes.

Cholangiography findings were not systematically reevaluated, which is a limitation of this project. Inclusion of cholangiography findings as a risk factor for poor prognosis would have given a more complete picture. Unfortunately, this was not possible.

In paper II, we aimed to study risk factors associated with mortality, OLT and malignancy. The PSC database was linked to the Cause of death and Tumor registers. Through these linkages, patients who died or cancer cases diagnosed outside Västra Götaland hospitals could be captured. A drawback in this study was the unknown rate of autopsies, which might have underestimated the prevalence of hepatobiliary cancer.

Västra Götalands PSC cohort was merged with a British and German cohorts respectively in order to increase the sample size in paper III and IV. Although paper III includes patients from a referral

center, The John Radcliffe Hospital is well renowned for the care of PSC patients. Furthermore, PSC patients with an address outside Oxford were excluded. The response rate was intermediate (68%) which can imply detection bias. A strength in paper III is the use of a validated HRQL liver-specific instrument which can capture differences in early and advanced liver disease. Although the study includes two northern European PSC cohorts, assigned controls were from the Swedish normative database. However, similar values in SF-36 domains and summary scores have been found in the normative Swedish and English population (98, 126). In contrast to previous studies, controls with other chronic diseases or IBD could not be included. Another shortcoming is the fact that data were collected retrospectively, whereas questionnaires were collected prospectively. Since liver function tests fluctuate in PSC, they could have worsened at the time the questionnaires were completed. The study was cross-sectional which limits evaluation if disease progression influences changes in HRQL.

Strengths in paper IV are that it is the first European study assessing the prevalence of elevated IgG4 among patients with PSC and the long-term follow-up. However, only the Swedish part of the study applied a population-based recruitment and the participation rate in this sub-cohort was low (119/199, 56%). Possible reasons for the low participation rate in this sub-cohort was that blood tests were taken at each community hospital and many patients considered the distance too far. However, selection bias cannot be excluded. The German sub-cohort included 233 consecutive PSC patients. The prevalence of PSC specifically in Germany has not been studied previously. The German cohort was from North of Germany (Hannover) and given the previously described North-South IBD prevalence (127), we could extrapolate the prevalence found in Västra Götaland for PSC patients to the German cohort. In that case, approximately 50% of PSC patients diagnosed during 1989-1998 were included in the study.

CONCLUSIONS

From the studies presented in this thesis it is concluded that:

. The incidence of PSC during 1992-2005 was 1.22/100 000 person- years and increased by a 3% AAPC which equals a 35% incidence increase over a ten-year period. The prevalence was 16.2/100 000 person, the highest reported rate to date. Thus, the burden of PSC seems more considerable than previously estimated.

. Mortality risk in the PSC cohort was four times higher compared with the population in Västra Götaland during the study period. Age, female gender, jaundice, cholangitis and bilirubin were significantly associated with the risk of liver-related death or OLT.

. We confirm a considerable increased risk of CCA in a population-based PSC setting, finding a similar SIR (177) for CCA to that reported by a previous Swedish study. Age was associated with increased risk for CCA.

. HRQL was impaired in an unselected PSC population. Age and systemic symptoms were associated with physical domains, whereas large duct disease correlated with mental domains.

. Non life-threatening symptoms, such as pruritus were major determinants of impaired HRQL.

. Confirming findings from a previous Swedish study, fatigue was not a specific symptom of PSC. However, fatigue as assessed by CLDQ was an important symptom in 11% of PSC patients.

. The prevalence of PSC patients with elevated IgG4 in the whole cohort was 10%. That is similar to that previously reported from tertiary centers. A slightly lower prevalence was found in the population-based sub cohort.

. Jaundice, intra- and extrahepatic biliary tree involvement and a previous history of pancreatitis were associated with positive IgG4 status.

. In contrast to previous reports, prognosis in patients with PSC and elevated IgG4 values did not differ from those with normal IgG4 value.

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POPULÄR VETENSKAPLIG SAMMANFATTNING

Bakgrund och syfte

Primär skleroserande kolangit (PSC) är en ovanlig kronisk leversjukdom som kännetecknas av tilltagande ärrbildning av gallträdet vilket i en stor del av fallen leder till avancerad leversvikt. Sjukdomen debuterar vanligen i 20-30 årsåldern och män drabbas oftare än kvinnor. Mellan 70-80% av alla patienter med PSC lider även av inflammatorisk tarmsjukdom. Cirka 10-20% av alla patienter kommer att någon gång under livet utveckla cancer i gallgångarna och de med associerade inflammatorisk tarmsjukdom löper också en förhöjd risk för cancer i tjocktarmen. Medicinsk behandling saknas, levertransplantation är den enda botande behandling och PSC är en av de vanligaste diagnoserna bland patienter som genomgår levertransplantation i Sverige. Nyligen har en ny sjukdomsentitet, sk immunoglobulin G4 (IgG4) associerad kolangit, beskrivits. Detta är en form av kolangit som liknar PSC men som också uppvisar förhöjda nivåer av IgG4 i blodet och förbättring efter kortisonbehandling.

Nedsatt livskvalité har påvisats i ett flertal studier hos patienter med kronisk leversjukdom, men kunskapen om livskvalité hos patienter med PSC är begränsad.

De kunskaper vi idag har om PSCs epidemiologi, hur vanligt det är med förhöjda IgG4 nivåer vid PSC och livskvalitet hos patienter med PSC kommer i stor utsträckning från fallserie rapporter från högspecialiserade klinider. En potentiell felkälla i denna typ av studier är att det finns en risk att de patienter som ses vid dessa kliniker inte är representativa för alla patienter med PSC. Studier som baseras på samtliga fall av en sjukdom från en given backgrundspopulation undviker detta problem men få populationsbaserade studier av PSC har hittintills publicerats.

Västra Götaland har många goda förutsättningar för att kunna genomföra en populationsbaserad epidemiologisk studie av PSC med god kvalitet. Populationen är tillräckligt stor (1,5 miljoner) för att generera ett antal PSC fall som är stort nog för att tillåta analyser av trender i incidens, det finns begränsat antal sjukhus som diagnostiserar och följer upp patienter med PSC och dessa har diagnosregister som sträcker sig långt bak i tiden. Generellt i Sverige finns dessutom mycket goda möjligheter att via personnummer koppla en databas över patienter med PSC till tumör- och dödsorsaksregister för att undersöka hur det gått för patienterna.

Huvudsyfte med denna avhandling var att undersöka epidemiologiska aspekter av PSC i en populations-baserad studie i Västra Götaland. Projektet hade följande delmål:

. Att undersöka incidens, trender i incidens och prevalens av PSC .

. Att undersöka mortalitet och risk för cancer hos individer med PSC.

. Att undersöka faktorer vid diagnos av PSC som är kopplade till ökad risk för död, levertransplantation eller cancer.

. Att undersöka livskvalitet hos patienter med PSC samt faktorer associerad med lägre livskvalitet.

. Att undersöka förekomsten av förhöjda nivåer av IgG4 hos patienter med PSC och vilken betydelse detta har för risken för död, levertransplantation eller cancer.

Genomförandet och resultat

Fall av PSC har identiferats genom sökning av diagnosregister vid samtliga medicin- och kirurgkliniker i Västra Götalands PSC under perioden 1992-2006. Tilgängliga journalhandlingar har reviderats och diagnosen har omprövats för att säkertställa att alla inkluderade fall möter generellt accepterade diagnoskriterier. Relevanta kliniska data så som kön, ålder, datum för PSC diagnos, död och sista uppföljningsdatum, röntgenfynd, förekomst av inflammatorisk tarmsjukdom och uppgifter eventuella cancerdiagnoser fördes in i databasen. Hur det sedan gick för patienterna har undersökts genom att identifiera individer som genomgått levertransplantation i register vid Sahlgrenska Universitetssjukhuset transplantationsklinik, de som insjuknat med cancer i tumörregistret och de som avlidit i dödsorsaksregistret. Samtliga patienter md PSC diagnos i Västra Götaland vid studiens genomförande 2008 kallades till provtagning för IgG4 analys. Frågeformulär som undersöker generell och leverrelaterad livskvalitet, ångest och depression samt trötthet skickades per post till samtliga patienter. Som kontrollmaterial användes friska individer från en tidigare insamlad svensk databas.

För de studier som rör livskvalitet och IgG4-nivåer har den svenska kohorten slagits samman med en tysk PSC-kohort och för studien som rör livskvalitet har den svenska databasen kombinerats med en brittisk kohort.

Incidensen (antal insjuknanden per år dividerat med antalet individer i befolkningen) av PSC var i medeltal 1,22 fall/ 100 000 invånare och år och ökade signifikant under den studerade perioden. Vid studiens slut var prevalensen av PSC 16,2 fall per år/ 100 000 invånare. Incidensen ökade med 3% årligen, vilket innebär en ökning på 35% under en tioårsperiod. Hos kvinnor ökade incidensen av PSC som drabbar stora gallgångar och PSC associerad med inflammatorisk tarmsjukdom, medan hos män ökade incidensen av PSC som engagerar små gallgångar och PSC utan associerad inflammatorisk tarmsjukdom. Incidensen av PSC i både stora och små gallgångar samt PSC relaterad till

inflammatorisk tarmsjukdom sjönk med ökande ålder. Trettio fyra av 345 (10%) PSC patienter hade förhöjda IgG4 nivåer i blodet. Gulsot, samtidigt engagemang av gallgångar i och utanför levern och en tidigare episod av bukspottskörtelinflammation var associerade med förhöjda IgG4 nivåer i blodet.

Risken för död var 4,2 ggr högre hos individer med PSC i jämförelse med den övriga befolkningen i Västra Götaland och risken för gallgångscancer var nästan 900 ggr förhöjd. Hälften av all cancer i lever och gallgångar upptäcktes inom ett år efter PSC diagnosen. I motsats till vad som rapporterats i en tidigare studie, fann vi inte någon ökad risk för cancer i tjocktarmen hos patienter med PSC. Högt bilirubin, tidigare episod av kolangit, kvinnlig kön och hög ålder var associerade med ökad risk för död eller levertransplantation, medan hög ålder var relaterad till ökad risk för cancer i gallgångarna. Patienter med PSC och förhöjda IgG4 nivåer löpte inte någon ökad risk för död, levertransplantation eller gallgångscancer.

Patienter med PSC hade lägre livskvalitet än kontroller. Hög ålder och systemiska symtom i allmänhet och klåda i synnerhet var associerade med lägre poäng i de delar av livskvalitetsenkäten som undersöker fysisk välbefinnande, medan engagemang av stora gallgångarna var relaterad med lägre poäng för mental välbefinnande. Andel patienter med signifikant trötthet, depression eller ångest skilde sig inte mellan patienter och kontroller.

Slutsatser

Incidensen och prevalensen av PSC är högre än vad som rapporterats i tidigare studier och ökade signifikant under studieperioden. Detta innebär att den samhälleliga bördan relaterad till denna sjukdom är större än vad tidigare uppskattats.

Detta innebär en högre sjukdomsbörda än den som tidigare har uppskattats. Andel patienter med förhöjda IgG4 nivåer i blodet var i samma nivå som vad som rapporterats i tidigare studier.

Risk för död var fyra gånger högre hos patienter med PSC i jämförelse med den övriga befolkningen i Västra Götaland och den markant ökade risken för cancer i lever och gallgångar som beskrivits i tidigare studier kunde bekräftas i våran populations-baserad kohort. I motsats till vad som tidigare rapporterats fann vi dock inte att patienter med PSC och förhöjda IgG4 nivåer hade sämre prognos än de med normala IgG4 värdena.

Patienter med PSC hade nedsatt livskvalitet jämfört med den friska kontrollgruppen. Hög ålder, engagemang av stora gallgångar och systemiska symtom var faktorer som var associerade med lägre livskvalitet.

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