Review

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Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: A systematic review

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Summary

Objective: Studies on the epidemiology of primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) show variable outcome. We aimed at systematically reviewing the incidence and prevalence rates, as well as geographical distribution and temporal trends of PSC and PBC.

Data sources: A systematic search of literature was performed in Medline and EMBASE (search last conducted January 10th, 2011).

Study selection: Population-based epidemiological studies reporting incidence and/or prevalence rates for PSC or PBC in a defined geographical area of at least 100,000 adult inhabitants were considered relevant.

Data extraction: Study area, study period, number of patients, number of inhabitants, incidence per 100,000 inhabitants per year, prevalence per 100,000 inhabitants, method of case-finding, method of case-ascertainment, male/female ratio and in case of PSC, occurrence of inflammatory bowel diseases (IBD) were extracted from retrieved articles.

Results: The literature search yielded 2286 abstracts of which 31 articles fulfilled all inclusion criteria. Studies varied in size from 10 to 770 patients in catchment areas from 100,312 to 19,230,000 inhabitants. The incidence and prevalence rates for PSC range from 0 to 1.3 per 100,000 inhabitants/year and 0–16.2 per 100,000 inhabitants, respectively. PBC incidence rates range from 0.33 to 5.8 per 100,000 inhabitants/year and prevalence rates range from 1.91 to 40.2 per 100,000 inhabitants; prevalence rates are increasing in time.

Conclusions: Incidence and prevalence rates of both PSC and PBC vary widely and seem to be increasing. True population-based studies are scarce and therefore large population-based studies combining meticulous case-finding and case-ascertainment strategies are necessary.

Keywords: Primary sclerosing cholangitis; Primary biliary cirrhosis; Epidemiology; Incidence; Prevalence.

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Abbreviations: PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; IBD, inflammatory bowel disease; UDCA, ursodeoxycolic acid; MOOSE, Meta-analysis Of Observational Studies in Epidemiology; ICD, International Classification of Diseases; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography; AMA, antimitochondrial antibodies.

Introduction

Primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) are enigmatic cholestatic liver diseases ultimately resulting in cirrhosis and liver failure. Both diseases are considered complex genetic diseases, but the etiopathogenesis is still unknown [1,2]. PSC is more common in men than in women (2:1) and can occur at any age with a peak incidence around 40. PSC is strongly associated with inflammatory bowel diseases (IBD), most often ulcerative colitis, and patients have an increased risk for developing colorectal and hepatobiliary malignancies [3,4]. The course of PSC is highly variable with reported median survival rates until liver transplantation or death from 12 to 18 years [5]. PBC on the other hand predominantly affects middle aged or elderly women (1:9). Common symptoms associated with PSC and PBC are pruritus, fatigue and upper abdominal discomfort. However, more than 50% of patients are asymptomatic at time of diagnosis [6,7]. Multifocal strictures and dilatations of the intra- and/or extra-hepatic bile ducts seen on cholangiography are hallmarks of PSC, although these can also be found in secondary sclerosing cholangitis due to cholelithiasis, biliary surgery, IgG4-associated cholangitis or various other causes [8]. Antimitochondrial antibodies directed against the E2 subunit of the pyruvate dehydrogenase complex are a sensitive serological hallmark of PBC [9]. Ursodeoxycholic acid (UDCA) improves serum liver tests, histologic features and survival of PBC patients [10–12]. In PSC, the beneficial role of UDCA in disease progression and survival is still unproven [13,14]. Several studies have investigated the epidemiology of both diseases, using different case-finding and case-ascertainment strategies. The reported incidence and prevalence figures show quite some variation, depending on the applied search strategy, the population under study, and the scrutiny of case-finding and ascertainment. We aimed at systematically reviewing the literature on incidence and prevalence rates and temporal trends for PSC and PBC.

Methods

Literature search

A systematic search of the medical literature was performed using the checklist proposed by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group with assistance of a clinical librarian, in peer-reviewed medical databases Medline and EMBASE (search last conducted January 10th, 2011) [15]. The following strategy was used to search Medline: (((“Cholangitis, Sclerosing”[Mesh]) OR (primary sclerosing cholangitis*[tiab]) OR (“liver cirrhosis,

biliary"[Mesh]) OR (primary biliary cirrhosis*[tiab])) AND (("epidemiology"[subheading]) OR (epidemiol*[tiab]) OR ("Incidence"[Mesh]) OR (incidenc*[tiab]) OR (prevalen*[tiab]) OR ("prevalence"[Mesh]))).

The following strategy was used to search EMBASE: (((exp primary sclerosing cholangitis) OR (primary sclerosing cholangitis.ti,ab.) OR (exp primary biliary cirrhosis) OR (primary biliary cirrhosis.ti,ab.)) AND ((exp EPIDEMIOLOGY/) OR (epidemiol*.ti,ab.) OR (exp INCIDENCE/) OR (incidenc*.ti,ab.) OR (prevalen*ti,ab.) OR (exp PREVALENCE/))).

Selection criteria

Two authors (KB and CYP) independently screened title and abstract of identified articles. Population-based epidemiological studies depicting incidence and/or prevalence rates for PSC or PBC in a defined geographical area of at least 100,000 adult inhabitants were considered relevant. Full articles of potentially relevant studies were retrieved for further analysis. Disagreement was resolved by discussion. Review articles were excluded from both search strategies. There were no language restrictions.

Data extraction

The following data were extracted and analyzed per study: study area, study period, number of patients, number of inhabitants, incidence per 100,000 inhabitants per year, prevalence per 100,000 inhabitants, method of case-finding, method of case-ascertainment, male/female ratio and in case of PSC, occurrence of inflammatory bowel diseases. When the full text of an article was missing, the corresponding author was asked to provide complementary data.

Quality assessment

Appraisal of study quality was based on (1) definition of studied population, (2) case-finding method and (3) case-ascertainment criteria. The study quality was considered 'good' when a case-finding method combined several hospital databases in a defined catchment area and when a well-directed case-ascertainment was performed using established diagnostic criteria. Quality was considered 'moderate' when the case-finding strategy was insufficient with a reasonable chance to miss cases or case-ascertainment was not performed by an expert panel using established diagnostic criteria. The quality of a study was considered 'poor' when case-finding or case-ascertainment had not been performed.

Results

The search yielded 2286 abstracts of which 30 articles in English and one in Norwegian were eligible for inclusion. Two thousand two hundred and twenty three articles were excluded based on title and abstract. For the remaining 63 articles, reasons for exclusion are depicted in Fig. 1.

Study characteristics

Of included articles, 19 reported incidence or prevalence rates in Europe [16–34], seven in North-America [35–41], three in Asia [42–44], and two in Australia [45,46]. Studies varied in size from 10 to 770 patients in catchment areas from 100,312 to 19,230,000 inhabitants.

Various sources had been used for case-finding purposes. In 17 studies, a search was performed in a medical record database using the International Classification of Diseases (ICD) or a similar diagnosis coding system. Other sources were laboratory databases, pathology databases, personal registry of physicians, radiological databases, hospital billing system and death certificates. Of the 31 included studies, 13 (41.9%) used one source for case-finding, three studies (9.7%) used two sources, seven studies (22.6%) used three sources, five studies (16.1%) used four sources, two studies (6.5%) used five sources and one study (3.2%) combined six sources for case-finding. An overview is given in Tables 1 and 2. A quality assessment of case-finding and case-ascertainment methods is presented in Table 3. Studies of good quality are highlighted in Tables 1 and 2 and incidence and prevalence rates are shown in Figs. 2 and 3.

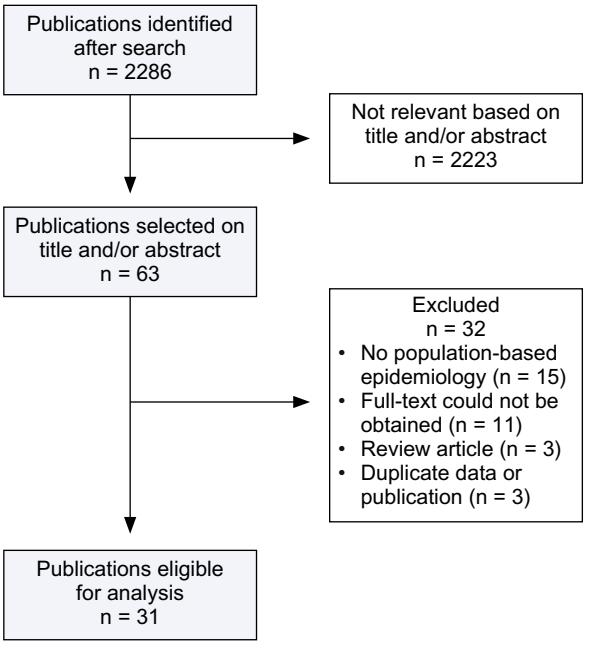

Fig. 1. Flowchart study selection.

PSC

Eleven studies on the epidemiology of PSC from 1984 till 2005 were identified of which four fulfilled quality criteria for both case-ascertainment and case-finding. Three were performed in North America between 1976 and 2005, reporting incidence rates ranging from 0 to 0.92 per 100,000 inhabitants per year [37,39,40]. In Alaska, no PSC patients were identified between 1984 and 2000 [37]. In Canada, 49 PSC patients were diagnosed in a 5-year period in a population of 1,112,521 corresponding to an incidence rate of 0.92 per 100,000 inhabitants per year [40]. One prospective population-based study from Norway included 17 newly diagnosed PSC patients in a 10-year period, between 1986 and 1995, resulting in an incidence rate of 1.31 per 100,000, still the highest incidence rate for PSC found worldwide [27].

Eight studies reported the proportion of concomitant IBD in PSC patients ranging from 20% in Singapore up to 76% in Sweden [27,31–34,39,40,44]. When combining studies that met all quality criteria, the average proportion of IBD in PSC patients was 70% (67–73%) [27,39,40]. Temporal trends in PSC incidence were reported in four studies, all of which demonstrated increasing incidence rates in time [31,34,40,32].

PBC

Twenty-four studies describing incidence and/or prevalence rates between 1972 and 2007 for PBC were identified. When considering studies of good quality only, the lowest and highest incidence rates for PBC were both found in Newcastle Upon Tyne, United

Table 1. Incidence and prevalence of primary sclerosing cholangitis.

Study, [Ref.] Country	Period	No. of patients	Population	Case-finding	Case-ascertainment[a]	Incidence[§] (95% CI)	Prevalence[§] (95% CI)	IBD (%)	Male (%)
Escorsell *et al.*, [31] Spain	1984-1988	43	19,230,000	Personal registry gastroenterologists and hepatologists	I + II + III + IV	0.07	0.22	47	60
Berdal *et al.*, [24] Akershus, Norway	1985-1994	12	180,000	ICD-9	III	0.7	5.6	n.a.	58
Byron *et al.*, [35] Winnipeg, Canada	1987-1994	39	650,000	All clinical records referral center	II + III + VI or II + IV + VI	n.a.	6.5	n.a.	n.a.
Boberg *et al.*, [27] Oslo, Norway	1986-1995	17	130,000	Prospective registration	II + III + IV	1.3 (0.8-2.1)	8.5 (2.8-14.2)	71	71
Ang *et al.*, [44] Changi, Singapore	1989-1998	10	750,000	10 consecutive patients	III + IV	n.a.	1.3	20	90
Bambha *et al.*, [39] Olmsted County, US	1976-2000	22	?	Medical records linkage system, pathology reports, laboratory reports, IBD research records	I + II + III + V or I + II + IV + V	0.9	13.6	73	68
Hurlburt *et al.*, [37] Alaska, US	1984-2000	0	100,312	All clinical records, ICD-9	III	0	0	n.a.	n.a.
Card *et al.*, [32] UK	1987-2002	223	2,027,909	General Practice Research Database	n.a.	0.41 (0.34-0.48)	3.85 (3.04-4.80)	48	63.5
Kingham *et al.*, [33] Swansea, UK	1984-2003	46	251,000	Prospective registration	I + II + III + IV	0.91	12.7	62	62
Lindkvist *et al.*, [34] Västra Götaland, Sweden	1992-2005	199	1,492,000	ICD-9 and ICD-10	II + III + V	1.22	16.2	76	71
Kaplan *et al.*, [40] Alberta, Canada	2000-2005	49	1,112,521	ERCP database, review of MRCPs, pathology database, ICD-9, ICD-10	II + III + V or II + IV + V	0.92	n.a.	67	55

Studies fulfilling all quality criteria regarding (1) definition of studied population, (2) case-finding method, and (3) case-ascertainment criteria are highlighted in blue.
[a]Case-ascertainment criteria: I, clinical features; II, serum AP↑ ⩾6 months; III, ERCP or MRCP; IV, liver biopsy; V, no signs of secondary sclerosing cholangitis; VI, inflammatory bowel disease.
[§]Per 100,000 inhabitants.
ICD, International Classification of Diseases; IBD, inflammatory bowel disease; ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography; n.a., not available; ?, unknown.

Kingdom, 0.9 per 100,000 inhabitants per year in 1977 and 5.8 per 100,000 inhabitants per year in 1994, respectively [16,26]. The highest prevalence rate for PBC of 40.2 per 100,000 age- and sex-matched inhabitants was found in 1995 in Olmsted County, Minnesota, USA [36]. When combining studies, the mean proportion of female patients was 92% (76–100%). All eight studies depicting yearly prevalence rates for several consecutive years reported increased prevalence rates in time (Fig. 4) [19,22,23,25–27,30,38].

Key Points

- Incidence and prevalence rates for both PSC and PBC vary widely and seem to be increasing in time
- The incidence and prevalence rates for PSC range from 0-1.3 per 100,000 inhabitants/year and 0-16.2 per 100,000 inhabitants, respectively
- For PBC, the incidence and prevalence rates range from 0.33-5.8 per 100,000 inhabitants/year and 1.91-40.2 per 100,000 inhabitants, respectively
- Most epidemiological studies are performed in the Western world and true population-based studies are scarce. Proper epidemiological data may help to identify etiologic factors for these complex diseases. Hence, large population-based studies are warranted

Discussion

This systematic review yielded a wide range in incidence and prevalence rates as well as study quality for PSC and PBC in Europe, North America, Asia and Australia. The incidence and prevalence rates for PSC range from 0 to 1.3 per 100,000 inhabitants/year and 0–16.2 per 100,000 inhabitants, respectively. In case of PBC, incidence rates range from 0.33 to 5.8 per 100,000 inhabitants/year and prevalence rates range from 1.91 to 40.2 per 100,000 inhabitants. Several causes may underlie the differences found. Improvement of diagnostic tools, increasing disease awareness, and digitalized patient registration likely contributed to the rising incidence and prevalence rates. In 1970, gastroenterologists were able for the first time to successfully cannulate the papilla of Vater and selectively intubate the ducts using a duodenoscope with omnidirectional angulation, the first ERCP [47]. A disadvantage of ERCP is the risk of pancreatitis, bleeding or perforation. More than 20 years after the introduction of ERCP, MRCP was introduced making it possible to visualize the intra- and extra-hepatic ducts without the risks associated with ERCP [48]. The introduction of MRCP lowered the threshold for diagnostic imaging and may have resulted in a higher frequency of cholangiographies diagnosing PSC. In 1965, antimitochondrial antibodies were identified as the most important serological marker for PBC [49]. At that time there was no effective treatment available, but that changed in 1982 when the first trials were initiated administering UDCA at a dose of 13–15 mg/kg daily, with good

Table 2. Incidence and prevalence of primary biliary cirrhosis.

Study, [Ref.] country	Period	No. of patients	Population	Case-finding	Case-ascertainment[b]	Incidence[§] (95% CI)	Prevalence[§] (95% CI)	Male (%)
Hamlyn *et al.*, [16] Newcastle upon Tyne, UK	1972-1977	117	2,080,000	Personal registry physicians, positive AMA results, death certificates	I + IIb + III	0.9	n.a.	7
Triger *et al.*, [17] Sheffield, UK	1977-1979	34	520,000	Personal registry physicians, positive AMA results	I + IIb + III	0.58	5.4	6
Danielsson *et al.*, [18] Northern Sweden	1973-1982	111	570,000	Personal registry physicians, hospital patient registry, positive AMA results	I + IIb or I + IIb + III	1.3	15.1	14
Eriksson *et al.*, [19] Malmö, Sweden	1973-1982	33	240,000	Autopsy reports	I + IIb + III	2.4	9.6	24
Löfgren *et al.*, [20] Örebro, Sweden	1976-1983	18	164,063	Positive AMA results	I + IIb + III	1.4	12.8	22
Almdal *et al.*, [21] Denmark	1981-1985	233	5,100,000	Hospital admission registry	-	0.9	n.a.	24
Myszor *et al.*, [22] Newcastle, UK	1965-1987	411	1,920,000	Hospital admission registry, positive AMA results, personal registry physicians	I + IIb + III or I + IIb	1.98	15.35	10
Witt-Sullivan *et al.*, [41] Ontario, Canada	1986-1988	225	?	Personal registry physicians	I + III	0.33	2.24	n.a.
Watson *et al.*, [45] Victoria, Australia	1990-1991	84	4,390,000	Personal registry physicians, hospital discharge registry, positive AMA results	I + IIb + III or I + IIb	n.a.	1.91	8
Remmel *et al.*, [23] Estonia	1973-1992	69	1,526,177	Personal registry physicians, positive AMA results	I + IIb + III	0.39	2.69	5
Berdal *et al.*, [24] Akershus, Norway	1985-1994	21	180,000	ICD-9	I + IIb + III	1.2	12	0
James *et al.*, [25] North-East England, UK	1987-1994	770	2,052,668	Personal registry physicians, ICD-9, ICD-10, positive AMA results, death certificates	I + IIb + III or I + IIb	3.22	33.46	8
Metcalf *et al.*, [26] Newcastle upon Tyne, UK	1987-1994	160	285,310	Personal registry physicians, ICD-9, positive AMA results, death certificates, liver pathology reports	I + IIb + III or I + IIb	5.8	39.2	10
Byron *et al.*, [35] Winnipeg, Manitoba, Canada	1987-1994	52	650,000	All clinical records referral center	I + IIb + IV	n.a.	8	n.a.
Kim *et al.*, [36] Olmsted County, US	1975-1995	46	?	Medical record database, pathology database, positive AMA results	I + II or I + III	2.7	40.2	11
Boberg *et al.*, [27] Oslo, Norway	1986-1995	21	130,000	Prospective registration	I + II + III or I + II + IV	1.6 (1.0-2.5)	14.6 (7.1-11.1)	24
Rautiainen *et al.*, [28] Finland	1988-1999	545	2,972,189	ICD-9, ICD-10, pathology registry, personal registry physicians, discharge database transplantation unit	I + IIb + III	1.7 (1.5-2.0)	18.0 (17.2-18.9)	13
Hurlburt *et al.*, [37] Alaska, US	1984-2000	18	100,312	All clinical records, ICD-9	I + IIb + III	n.a.	16	0
Eaton *et al.*, [29] Denmark	1977-2001	666	5,472,032	ICD-8, ICD-10	-	n.a.	12	n.a.
Pla *et al.*, [30] Sabadell, Spain	1990-2002	87	389,758	Prospective registration, personal registry physicians, pathology registry, positive AMA results, hospital medical record system	I + II + III	1.72	19.5	3
Sood *et al.*, [46] Victoria, Australia	1990-2002	249	4,880,000	Personal registry physicians, database liver transplantation unit, medical record search, positive AMA results	I + IIb + III	n.a.	5.1	11
Myers *et al.*, [38] Alberta, Canada	1996-2002	137	1,100,000	Physician claims database, inpatient discharge abstract database, ambulatory care classification system detabase	I + IIb + III	3.03	22.7	17
Delgado *et al.*, [42] Southern, Israel	1993-2004	47	826,000	Personal registry physicians, liver transplantation registry, ICD-9, positive AMA results, pathology registry, autopsy certificates	I + II + III	n.a.	5.5	0
Chong *et al.*, [43] Brunei Darussalam	2007	10	390,000	Hepatology clinics register, pathology register, pharmacy database	I + IIb + III	1.0	2.6	0

Studies fulfilling all quality criteria regarding (1) definition of studied population, (2) case-finding method, and (3) case-ascertainment criteria are highlighted in blue.
[b]Case-ascertainment criteria: I, AMA; IIa, serum AP↑ ⩾6 months; IIb, cholestatic liver parameters; III, liver biopsy; IV, IgM↑.
[§]Per 100,000 inhabitants.
AMA, antimitochondrial antibodies; ICD, International Classification of Diseases; n.a., not available; ?, unknown.

Table 3. Quality assessment of all included studies.

Study, yr [Ref.]	Definition of study population	Case-finding	Case-ascertainment
Chong *et al.*, 2010 [43]	+	+	+
Myers *et al.*, 2009 [38]	+	+	+
Kaplan *et al.*, 2007 [40]	+	+	+
Pla *et al.*, 2007 [30]	+	+	+
Rautiainen *et al.*, 2007 [28]	+	+	+
Delgado *et al.*, 2005 [42]	+	+	+
Bambha *et al.*, 2003 [39]	+	+	+
Hurlburt *et al.*, 2002 [37]	+	+	+
Kim *et al.*, 2000 [36]	+	+	+
James *et al.*, 1999 [25]	+	+	+
Boberg *et al.*, 1998 [27]	+	+	+
Metcalf *et al.*, 1997 [26]	+	+	+
Danielsson *et al.*, 1990 [18]	+	+	+
Myszor *et al.*, 1990 [22]	+	+	+
Hamlyn *et al.*, 1983 [16]	+	+	+
Lindkvist *et al.*, 2010 [34]	+	±	+
Sood *et al.*, 2004 [46]	+	±	+
Berdal *et al.*, 1998 [24]	+	±	+
Remmel *et al.*, 1995 [23]	+	±	+
Watson *et al.*, 1995 [45]	+	±	+
Löfgren *et al.*, 1985 [20]	+	±	+
Triger *et al.*, 1980 [17]	+	±	+
Kingham *et al.*, 2004 [33]	+	?	+
Byron *et al.*, 1996 [35]	+	-	+
Eriksson *et al.*, 1984 [19]	+	?	+
Card *et al.*, 2008 [32]	+	±	-
Eaton *et al.*, 2007 [29]	+	±	-
Ang *et al.*, 2002 [44]	+	?	±
Almdal *et al.*, 1991 [21]	+	-	-
Witt-Sullivan *et al.*,1990 [41]	-	-	±
Escorsell *et al.*,1994 [31]	-	-	±

+, good; ±, moderate; -, absent or poor; ?, unknown.
Studies are ranged according to quality assessment score and year of publication with last published highest.
Scoring studies on top.

results [50]. Improvement of diagnostic tools and disposition of therapeutic modalities likely play a role in increasing prevalence over time, but may also contribute to global differences since these tools and therapies are not equally distributed around the world.

The introduction of computers in healthcare has been a big leap forward in clinical epidemiological research. Case-finding became easier and more accurate after the introduction of digitalized laboratory and pathology databases. Although some studies in the seventies and eighties seemed well performed, the increase in incidence and prevalence rates, especially for PBC, is in all probability partly attributable to a more exhaustive case-finding strategy using computer databases. The method stated by Metcalf

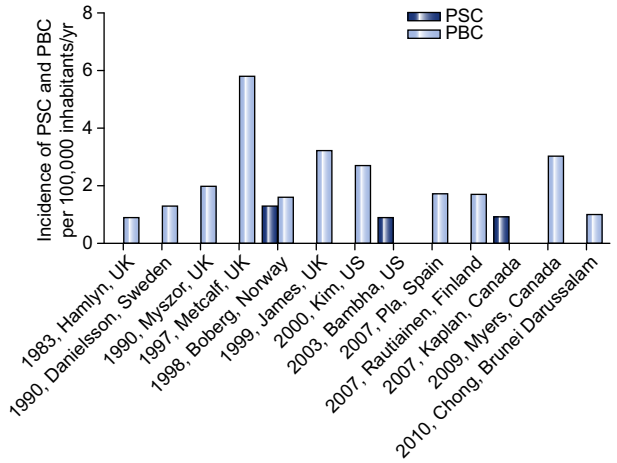

Fig. 2. Incidence of primary sclerosing cholangitis and primary biliary cirrhosis (considering high quality studies only).

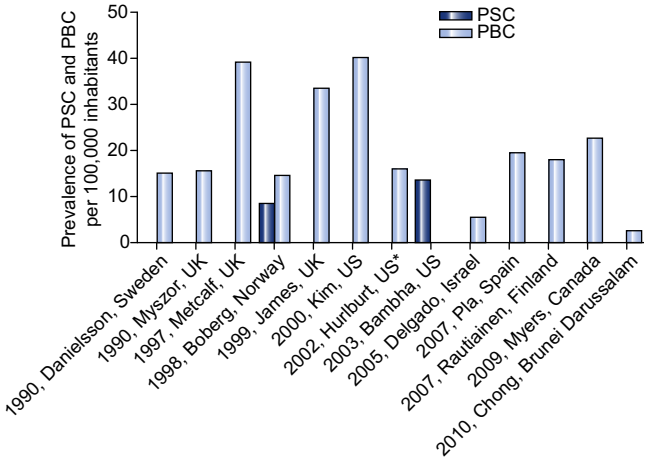

Fig. 3. Prevalence of primary sclerosing cholangitis and primary biliary cirrhosis (considering high quality studies only). *No PSC patients during a 17-year study period.

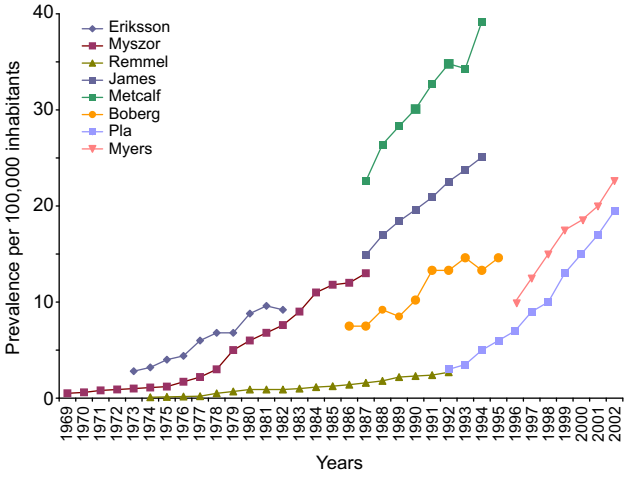

Fig. 4. Temporal trends in PBC prevalence.

and James already published in 1997 is an excellent example of a meticulous case-finding strategy and has set a standard for subsequent studies [51]. These guidelines include: stringent case inclusion criteria; definition of date of disease onset; well-defined study period, area and population; multiple case finding methods and rigorous tracing of all possible cases [51]. Temporal trends may partly be explained by these technological developments and case-finding strategies, yet increasing incidence and prevalence rates in time are even observed within studies. Other factors like the ones discussed below, may play a role in increasing incidence and prevalence rates and geographical differences.

PSC

Although true population-based studies are lacking for PSC, two factors seem to play a significant role in the global distribution of the disease: a variable frequency of IBD around the world and differences in HLA-susceptibility among ethnic groups causing population differences. A recent review combining 47 studies concerning the epidemiology of Crohn's disease showed a wide variety in incidence and prevalence rates with the highest numbers found in Northern Europe, New Zealand and North America, and lowest numbers in South America, Africa and Asia [52]. Recently, a large PSC cohort listed for liver transplantation in the United States was clinically and genetically investigated. The authors were able to demonstrate that the risk of being listed for liver transplantation is significantly associated with ancestral origin and that phenotype differences in PSC exist across ethnicities [53].

Based on these reports, the genetic background seems to play a significant role in the etiology and global distribution of the disease. Unfortunately, no population-based epidemiological studies were performed in Africa or Asia. One study from Singapore falls short in proper case-finding method, hence it is difficult to draw conclusions [44]. Three out of four of the highest scoring studies were performed in North America. An outlier among these well-conducted studies in North America is a study published in 2002 [37]. Clinical records of all cases of autoimmune liver disease at the Alaska Native Medical Center from 1983 till June 2000 were reviewed. Only one referral center in a population of 100,312 provides a solid foundation for an epidemiological study, even though the authors estimate that 10–20% of Alaska natives seek medical care outside the health care delivery system. Strikingly, no PSC patients were found in a 17-year period. A possible explanation may be the low incidence of inflammatory bowel disease in this population consisting of Eskimo's, Aleuts and Indians.

With a catchment area of 19,230,000 inhabitants, the study of Escorsell *et al.* in Spain between 1984 and 1988 is the largest ever conducted [31]. Unfortunately, the case-finding and case-ascertainment method based on a questionnaire sent to gastroenterologists and hepatologists is insufficient for population-based epidemiology.

Recently, a systematic review and meta-analysis of the incidence of PSC has been published. Six population-based studies form North America and Europe resulted in a combined incidence rate of 1.0 (0.82–1.17) per 100,000 inhabitants [54]. Incidence rates did not differ when stratified for continent. However, the study from the Alaska Native Medical Center was not included in this analysis.

PBC

Between 1972 and 2007, 23 articles have been published describing incidence and prevalence of PBC. Since the introduction of the guidelines for proper epidemiological studies by Metcalf and James in 1997, the quality of studies improved [51]. The highest incidence and prevalence rates to date have been found in Olmsted County, USA, and Newcastle upon Tyne, UK, pointing towards possible geographic or genetic risk factors. However, until 2005 no studies were performed outside the Western world. In 2005, the first study from the Middle East was published, identifying 47 women in Southern Israel resulting in an overall prevalence rate of 5.5 per 100,000 inhabitants, a 7-fold lower prevalence rate compared to the UK and USA [42]. Five years later, an even lower prevalence rate was found in Brunei Darussalam, Southeast Asia [43]. Ten patients were identified in a catchment area of 390,000 inhabitants. Strikingly, the prevalence rate in the Chinese population was almost twice as high as in the Malay population (4.1 per 100,000 and 2.3 per 100,000, respectively), though the small number of patients is a limitation of the study. Notable differences in sex ratio were found. At present, it remains unclear whether there is a true variation in sex ratio among populations of different geographical areas with different ethnic backgrounds or if this is a consequence of varying study quality.The current hypothesis regarding etiology is that PBC is a complex genetic autoimmune disease, meaning that a combination of genetic susceptibility and environmental factors triggers disease. Besides infectious and life-style factors, several environmental triggers for PBC have been suggested in the last thirty years and these may partly account for differences in geographical distribution. Triger published a study in 1980 revealing a cluster of PBC patients in Sheffield, UK [17]. Almost all patients in this cluster received water from a single water source. However, chemical analysis of the water did not unravel a potential trigger. Twenty years later, another study from the UK showed strong variations in geographical distribution of patients in Northeast England, but this distribution could not be explained by geographical or demographic features [55]. In New York, a significant association between a cluster of PBC patients and superfund toxic waste sites contaminated with volatile aromatic hydrocarbons and trichloroethylene was identified, supporting the hypothesis that environmental toxins play a role in development of PBC [56]. In conclusion, incidence and prevalence rates of both PSC and PBC vary widely and seem to be increasing. True population-based epidemiological studies are scarce, especially in PSC, so it is unclear whether these are true variations or due to methodological differences. Proper worldwide epidemiological data may help identifying etiologic factors for these complex diseases. Hence, large population-based studies combining meticulous case-finding and case-ascertainment strategies as stated by Metcalf and James are necessary and may provide clues as to possible genetic background and environmental risk factors for these chronic cholestatic diseases.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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