UNIVERSITY OF CALGARY

Validity of Administrative Data for the Diagnosis of Primary Sclerosing Cholangitis: A Population-Based Study

By

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Validity of Administrative Data for the Diagnosis of Primary Sclerosing Cholangitis: A Population-Based Study" submitted by Natalie Molodecky in partial fulfilment of the requirements for the degree of Master of Science (Epidemiology).

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CONTRIBUTIONS OF AUTHORS

[1] Molodecky NA, Kareemi H, Parab R, et al. Incidence of Primary Sclerosing Cholangitis: A Systematic Review and Meta-Analysis. *Hepatology.* 2011;53(5):1590-1599. Copyright © 2011, American Association for the Study of Liver Diseases.

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Ms Molodecky participated in conceiving the study concept and design, acquisition of data, analysis and interpretation of data, drafting manuscript, and statistical analysis.

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Mr. Kareemi participated in the collection of data.

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[2]Molodecky NA, Myers RP, Barkema HW, Quan H, Kaplan GG. Validity of Administrative Data for the Diagnosis of Primary Sclerosing Cholangitis: A Population-Based Study. *Liver Int.* 2011;31(5):712-720.

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TABLE OF CONTENTS

CHAPTER ONE: INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown etiology. It is characterised by chronic inflammation, destruction, and fibrosis of the intra- and/or extra-hepatic biliary tree. The aberrant inflammatory response ultimately leads to cirrhosis, end-stage liver disease, and need for liver transplantation.[3] PSC is strongly associated with the inflammatory bowel diseases (IBDs), particularly ulcerative colitis (UC).[3] Approximately 2-7.5% of UC patients will have PSC, while 70-80% of PSC patients will have UC or Crohn's Disease (CD).[3-6] Currently, there are no therapies that improve the natural history of PSC.[7] Liver transplantation is the only life-extending therapy for patients with end-stage PSC;[8] however, PSC frequently recurs after liver transplantation.[9-10] There is a nearly threefold increase in mortality for those who develop PSC compared to non-PSC patients.[11] The median survival time for PSC patients is between 9 to 12 years from diagnosis;[4] however, disease course is variable from one patient to another.[4, 8] PSC patients are at increased risk for malignancies, such as cholangiocarcinoma and cancers of the pancreas, gallbladder, liver and colon.[8]

PSC poses a significant burden on the health care system because of high mortality, morbidity, and necessity for liver transplantation. Despite the severity of this condition, few epidemiologic studies have investigated the incidence and prevalence of PSC.[11-17] Incidence rates of 0.04 to 1.3 per 100,000 and prevalence of 0.22 to 12.7 per 100,000 have been noted.[11-17] These estimates are likely influenced by selection and referral biases as some studies investigating the epidemiology of PSC have not been population based[11, 14] and have used tertiary referral centres.[18-22] Estimates from studies that identified cases through physician surveys[14] are likely underestimated and those from studies that used

administrative databases without validating the PSC diagnosis[11] likely misrepresent the epidemiology of PSC.

The relative paucity of population-based data on the epidemiology of PSC may be largely due to the difficulty in ascertaining cases and limited investment; both of which are consequences of the rarity of this disease. However, evidence suggests that the incidence of PSC may be increasing.[1] This increase in PSC incidence may be a direct result of its link with IBD, as recent evidence suggests that the incidence of IBD is still increasing in many regions of the world.[23-27] Moreover, the observed increase may be due to improvements in diagnostic abilities of physicians and diagnostic tools, such as non-invasive imaging studies,[28-29] or increasing use of biologic therapies (e.g. infliximab) and immunosuppressants (e.g. azathioprine and methotrexate).[30-32] Additional studies are necessary to resolve these issues; however, the decrease in power in carrying out these analyses may hinder the finding of statistical evidence when studying uncommon diseases such as PSC.

Administrative databases could be useful in studying the epidemiology of PSC. The benefits of administrative databases include their relatively low cost, broad geographic coverage, large sample sizes and near complete capture of health care utilization, allowing for adequate power to study PSC. Administrative databases are often population-based, and data recording is independent, which maximizes external validity and minimizes non-responder, recall, and selection biases. Moreover, the use of administrative databases enables assessment of research subjects over longer periods of follow up and minimizes losses over time. Finally, with the data having already been collected, research is less time-consuming than equivalent work involving primary data collection.

Although there are many strengths of using large administrative databases to study PSC, some important weaknesses associated with their use must be considered. The primary purpose of administrative databases is not for research purposes but to collect information on health services such as clinical care, administration, and fees. As a result, desired information may not be available or may be inaccurately recorded. This may lead to misclassification biases in studies using administrative databases without validation for accuracy. Although aadministrative data have been validated for many conditions[33], there is no information regarding the validity of the diagnostic code for PSC in administrative databases. Additionally, PSC does not have a distinct code, as the disease is listed under the diagnostic field code of 576.1 in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and K83.0 in the Tenth Revision (ICD-10). This code includes more common acute conditions such as ascending cholangitis, a bacterial infection of the biliary tract that primarily occurs as a result of gallstones.[34] The validity of the code for PSC is essential to ensure that valid conclusions are drawn from research studies using administrative data.

Therefore, the objectives of this thesis project were: (1) to conduct a systematic review with meta-analysis of the incidence of PSC; and 2) to determine the validity of administrative data for a diagnosis of PSC and to generate coding algorithms and a predictive model for the identification of PSC patients using administrative data.

CHAPTER TWO: LITERATURE REVIEW

PSC poses a significant burden on the health care system because of high mortality, morbidity, and necessity for liver transplantation.[7, 8] Despite the severity of this condition, few population-based epidemiologic studies have investigated the incidence of PSC.[35-42] Most studies that have described the epidemiology of PSC used data from tertiary referral centers[18-22], which may be limited by a referral bias. While several studies describing the incidence of PSC have been published, they have not been systematically summarized. The objectives of this study were to conduct a systematic review with meta-analysis of the incidence of PSC and provide recommendations for future studies describing the epidemiology of this disease. Insight into the incidence of PSC is important in describing the burden of disease and may shed light on its etiology.

(MANUSCRIPT)

Incidence of Primary Sclerosing Cholangitis: A Systematic Review and Meta-Analysis. Molodecky NA, Kareemi H, Parab R, et al. *Hepatology.* 2011;53(5):1590-1599.

CHAPTER THREE: METHODS

The relative paucity of incidence studies of PSC identified through the systematic review was likely due, in part, to the difficulty in ascertaining cases of PSC and the limited investment in rare diseases. Administrative databases could be useful in studying the epidemiology of PSC; however, there is no information regarding the validity of the diagnostic code in administrative databases. Additionally, PSC does not have a distinct code, as the disease is listed under the diagnostic field code of 576.1 in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and K83.0 in the Tenth Revision (ICD-10). This code includes more common acute conditions such as ascending cholangitis, a bacterial infection of the biliary tract that primarily occurs as a result of gallstones.[34]

The purpose of this study was to assess the validity of the code for PSC in administrative data and generate a coding algorithm that may help specifically identify PSC patients. If this administrative data is accurate, and/or a valid coding algorithm can be generated to improve accuracy, this information may be used to more precisely track the epidemiology, risk factors, and clinical outcomes of PSC using administrative databases.

(MANUSCRIPT)

Validity of administrative data for the diagnosis of primary sclerosing cholangitis: a population-based study. Molodecky NA, Myers RP, Barkema HW, Quan H, Kaplan GG. *Liver Int.* 2011;31(5):712-720.

CHAPTER FOUR: CONCLUSION

PSC is a rare disease of unknown etiology. Despite its low prevalence, the burden of disease is substantial due to the lack of effective therapeutic options, and high rate of complications, which predominantly affect young patients. Few population-based epidemiologic studies have investigated the incidence of PSC and as a result the epidemiology of this disease remains poorly defined.

Here we present a comprehensive overview of the incidence of PSC. The overall incidence of PSC was 0.77 per 100,000 person-years at risk. The incidence was largely unchanged in multiple stratified analyses exploring study characteristics (e.g. case ascertainment). The median age at diagnosis of PSC was 41 years, with males having nearly two-fold risk of developing PSC compared with females. The pooled proportion of IBD in PSC cases was 67%, consistent with previous reports. Sensitivity analysis considering only population-based studies increased the IR estimate to 1.00 per 100,000 person-years at risk. Since population-based studies provide a more accurate and reliable estimate of the rate of disease, the IR of 1.00 per 100,000 is likely more representative of the true incidence of PSC.

Additionally, the meta-analysis identified a relative paucity of population-based data of PSC, which is likely due, in part, to the difficulty in ascertaining cases of PSC and limited investment in this disease. Administrative databases could be useful in studying the epidemiology of PSC; however, there is no information regarding the validity of the diagnostic code in administrative databases. The purpose of the subsequent study was to

assess the validity of the code for PSC in administrative data and generate a coding algorithm that may help specifically identify PSC patients.

This study used chart data to assess the accuracy and validity of ICD-9-CM and ICD-10 administrative data for the coding of PSC. The initial Se of 84% and PPV of 7% of the PSC diagnostic code indicated a poor ability to discern true from false PSC cases in administrative data. We attempted to develop an algorithm that would enable the identification of a cohort of true PSC cases. Through multiple algorithms and sensitivity analyses, the PPVs remained quite low with fluctuating Se estimates. Overall, we were not able to develop an ICD-9 or -10 based algorithm that could be used in administrative databases to identify a PSC cohort for population-based epidemiological research. While identifying true PSC cases from administrative data was not possible, these methods may be used as an initial screening tool to narrow down the search of identifying PSC cases. Though, ultimately PSC requires a distinct ICD code from ascending cholangitis to be adequately used for epidemiological research.

Through communication of our findings with the Canadian Institute for Health Information (CIHI), a specific code to uniquely identify PSC will be implemented in the 2012 revision of ICD-10-CA. Applying this change to ICD-11 will enable other populations to study PSC. Currently there are discussions between the World Health Organization Family of International Classifications (WHO-FIC), CIHI, and our team at the University of Calgary regarding global implementation of a specific code for PSC in the next ICD revision.

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CHAPTER SIX: REVISED ICD-10-CA CODE FOR PSC

Table 1. Revised ICD-10-CA code for PSC.

ICD-10-CA	Description
K83.0	Cholangitis *Excludes:* cholangitic liver abscess (K75.0)
K83.00	Primary sclerosing cholangitis
K83.01	Secondary sclerosing cholangitis Use additional code to identify the underlying disease
K83.02	Ascending cholangitis Cholangitis: • Infectious, infective • Suppurative *Excludes:* Cholangitis with choledocholithiasis (K80.3-, K80.4-)
K83.08	Other and unspecified cholangitis Cholangitis: • NOS • recurrent

Note: Revised ICD-10-CA codes for K80.0 cannot be implemented until April 1, 2012.

CHAPTER SEVEN: REVIEWER COMMENTS

02-Jan-2011

Re: Validity of Administrative Data for the Diagnosis of Primary Sclerosing Cholangitis (PSC): A Population-Based Study.

Dear Dr. Kaplan,

We are delighted to inform you that we have received a positive report on your paper. The referee(s), the associate editor and editor-in-chief agree that the paper is well written and will greatly contribute to the journal.

You will see from the referees' reports that your manuscript requires only a minimal amount of modification. We would like you to follow the point brought forward by reviewer 1 in regard to a code for secondary sclerosing cholangitis. We will speed up our analysis of the revision by completing the editorial handling as soon as possible.

We appreciate your interest in Liver International and especially appreciate your patience. We look forward to receiving your revision.

Yours Sincerely

Dr. Peter Fickert
Associate Editor

Dr. Samuel Lee
Editor-in-Chief Liver International

Reviewer: 1
Comments to the Author
This is a relatively simple study, with an expected outcome- the current coding of PSC is clearly inadequate and needs updating. The authors clearly show this as one would predict. However they go on to ensure that a necessary change is proposed to the ICD coding system, and appears to be likely implemented in 2012. I have no specific comments but would say if there is going to be a code for PSC, it would make sense to have one for secondary sclerosing cholangitis!

Reviewer: 2

Comments to the Author

The manuscript "Validity of Administrative Data for the Diagnosis of Primary Sclerosing Cholangitis (PSC): A Population-Based Study." describes the difficulty finding PSC patients from available in- and outpatient databases. Current coding of PSC is not useful for identifying subjects with true PSC from databases with a low positive predictive value. This finding probably reflects the experience of many scientists in the field who have tried to identify patients with PSC. The subject is of interest, since correctly identifying patients with a rare disease such as PSC is important for research as well as treatment purposes. The study seems to be well conducted although the findings cannot be generalized to other settings, as mentioned by the authors.

CHAPTER EIGHT: PUBLICATIONS IN MASTER'S DEGREE

- **Molodecky NA**, Kareemi H, Parab R, Barkema HW, Quan H, Myers RP, Kaplan GG. The incidence of PSC: a systematic review and meta-analysis. *Hepatology* 2011; 53(5):1590-9.
- **Molodecky NA**, Myers RP, Barkema HW, Quan H, and Kaplan GG. Validity of Administrative Data for the Diagnosis of Primary Sclerosing Cholangitis. *Liver International* 2011; 31(5):712-20.
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- **Molodecky NA,** Soon IS, Rabi D, Ghali W, Barkema HW, Kaplan GG. The relationship between urban environment and inflammatory bowel disease: a systematic review and meta-analysis. [Submitted for publication to *British Medical Journal*].
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- Quan S, **Molodecky NA**, Frolkis A, Proulx MC, Lang E, Myers RP, Kaplan GG. Validity of Administrative Data for Identifying Hospitalizations for Upper Gastrointestinal Bleeding Secondary to Peptic Ulcer Disease. [Preparing to submit for publication].
- Ferris MC, Kaplan B, **Molodecky NA**, Soon I, Dixon E, Kaplan GG. The Dynamic Global Incidence of Acute Appendicitis: A Systematic Review of International Temporal Trends. [Preparing to submit for publication].

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CLINICAL STUDIES

Validity of administrative data for the diagnosis of primary sclerosing cholangitis: a population-based study

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Keywords
algorithms – positive predictive value – primary sclerosing cholangitis – sensitivity – validation

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Abstract

Background/Aims: Administrative databases could be useful in studying the epidemiology of primary sclerosing cholangitis (PSC); however, there is no information regarding the validity of the diagnostic code in administrative databases. The aims of this study were to determine the validity of administrative data for a diagnosis of PSC and generate algorithms for the identification of PSC patients. *Methods:* The sensitivity (Se) and positive predictive value (PPV) of a PSC diagnosis based on administrative data from 2000 to 2003 were determined through chart review data. Algorithms were developed by considering variables associated with PSC and coding details. A logistic regression model was constructed using covariates associated with PSC. Based on this model, each subject was assigned a probability of having PSC. A cutoff value was selected that maximized the Se and specificity (Sp) of correctly predicting PSC cases. *Results:* In the administrative data, the initial Se and PPV were 83.7 and 7.2% respectively. The optimal algorithm included one PSC code and one inflammatory bowel disease code and had Se 56% and PPV 59%. Overall, the algorithms yielded inadequate PPV and Se estimates to identify a cohort of true PSC cases. The predictive model was constructed using six covariates. For this model, the area under the receiver operating characteristic curve was 93.5%. A cutoff of 0.0729 was used, which maximized the Se 81.9% and Sp 90.7%; however, the PPV was 41.0%. *Conclusion:* An algorithm for the identification of true PSC cases from administrative data was not possible. We recommend that PSC receives a distinct ICD code from ascending cholangitis.

Background

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown aetiology. It is characterized by chronic inflammation, destruction and fibrosis of the intra- and/or extra-hepatic biliary tree. The aberrant inflammatory response ultimately leads to cirrhosis, end-stage liver disease and the need for liver transplantation (1). PSC is strongly associated with inflammatory bowel diseases (IBDs), particularly ulcerative colitis (UC) (1). Approximately 2–7.5% of UC patients will have PSC, while 70–80% of PSC patients will have UC or Crohn's disease (1–4). Currently, there are no therapies that improve the natural history of PSC (5). Liver transplantation is the only life-extending therapy for patients with end-stage PSC (6); however, PSC frequently recurs after liver transplantation (7, 8). There is a nearly three-fold increase in mortality for those who develop PSC compared with non-PSC patients (9). The median survival time for PSC patients is between 9 and 12 years from diagnosis (2); however, disease course is variable from one patient to another (2, 6). PSC patients are at an increased risk for malignancies, such as cholangiocarcinoma and cancers of the pancreas, gallbladder, liver and colon (6).

Primary sclerosing cholangitis poses a significant burden on the health care system because of high mortality, morbidity and the necessity for liver transplantation. Despite the severity of this condition, few epidemiological studies have investigated the incidence and prevalence of PSC (9–15). Incidence rates of 0.04–1.3 per 100 000 and prevalence of 0.22–12.7 per 100 000 have been observed (9–15). These estimates are likely influenced by selection and referral biases, as some studies investigating the epidemiology of PSC have not been population based (9, 12) and have used tertiary referral centres (16–20). Estimates from studies that identified cases through physician surveys are likely underestimated (12) and those from studies that used administrative databases without validating the PSC diagnosis (9) likely misrepresent the epidemiology of PSC.

Administrative databases could be useful in studying the epidemiology of PSC; however, there is no information regarding the validity of the diagnostic code in administrative databases. Additionally, PSC does not have a distinct code, as the disease is listed under the diagnostic field code of 576.1 in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and K83.0 in the Tenth Revision (ICD-10). This code includes more common acute conditions such as ascending cholangitis, a bacterial infection of the biliary tract that primarily occurs as a result of gallstones (21).

The purpose of this study was to assess the validity of the code for PSC in administrative data and generate a coding algorithm that may help specifically identify PSC patients. If this administrative data is accurate, and/or a valid coding algorithm can be generated to improve accuracy, this information may be used to track more precisely the epidemiology, risk factors and clinical outcomes of PSC using administrative databases.

The objectives of the study were (i) to determine the validity of administrative data for a diagnosis of PSC; (ii) to generate coding algorithms and a predictive model for the identification of PSC patients using administrative data.

Methods

Study time period

The 2000–2003 fiscal period was selected. Since 1 April 2002, inpatient and ambulatory care contacts have been coded according to ICD-10-CA. Selecting this time period enabled the assessment of both ICD-9-CM and ICD-10-CA codes. Physician claims data were not available after 31 March 2003; therefore, this was selected as the endpoint of our study period. Population-based data were extracted from fiscal years 1999–2003 to allow for an additional 1-year period to ensure capture of all relevant clinical variables (e.g. IBD).

Study populations and data sources

Two study populations were identified (i) through chart review; (ii) from administrative databases.

Chart review study population and data sources for validation

The true PSC study population was defined as all residents of the Calgary Health Region (CHR) with a diagnosis of PSC during fiscal 2000–2003. This included both prevalent and incident cases. The diagnosis of PSC was based on previously published criteria (11) (i) chronically elevated liver enzymes; (ii) standard endoscopic or radiological evidence of PSC on endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP); (iii) liver biopsy consistent with histological characteristics of PSC in the absence of cholangiographical evidence; (iv) exclusion of secondary causes of cholangitis. The index date of PSC was defined by the first ERCP, MRCP or liver biopsy consistent with PSC.

All inpatient and outpatient medical records identified by the following four data sources were manually assessed for confirmation of the PSC diagnosis (14): (i) Endoscopy Database (EndoPro); (ii) Radiology Database; (iii) Liver Pathology Database; (iv) Regional Hepatologists and Gastroenterologists. EndoPro captures information of all ERCPs performed in the CHR since 2000. The Radiology Database contains information of all radiographical procedures, including MRCPs performed in the CHR since 2000. The Liver Pathology Database stores the results from all liver biopsies performed in the CHR from 1998 onwards. All regional hepatologists and gastroenterologists reviewed their billing records for ICD-9-CM and ICD-10-CA codes for PSC. From these data sources, a set of individuals who were confirmed to have PSC was compiled (14).

Administrative database study population and data sources

This study population consisted of PSC cases in the CHR between fiscal years 2000 and 2003. All patient contacts/claims with a diagnostic field coded 576.1 of the ICD-9-CM or K83.0 of the ICD-10-CA were extracted. A single contact or claim with one of these codes defined a potential PSC case.

Population-based data for the CHR were extracted for fiscal years 1999–2003 using three health service databases from Alberta Health Services: (i) Physician Claims (PC) Database; (ii) Canadian Institute for Health Information (CIHI) Inpatient Discharge Abstract Database (DAD); (iii) Ambulatory Care Classification System (ACCS) Database. The PC database captures claims submitted for payment by Alberta physicians for services provided to registrants of the Alberta Health Care Insurance Plan (AHCIP). The CIHI DAD captures all hospitalizations in Canada (excluding Quebec) and contains patient demographical, comorbidity, procedure and mortality information. Rates of agreement from reabstraction studies are $> 95\%$ for demographical data and range from 75 to 96% for most responsible diagnostic codes (22). The ACCS database captures all information on facility-based ambulatory care including clinic and emergency department visits, same-day surgery and day procedures. These databases can be linked using the AHCIP Registry, which contains unique personal health numbers (PHN) for all those included in the AHCIP. All residents of Alberta and their dependents are eligible for this government-administered universal health plan. Over 99% of Alberta residents participate in the plan (23).

Statistical analysis

Algorithms

Using data obtained from the review of clinical records as the gold standard, the assessment of the sensitivity (Se)

and positive predictive value (PPV) and their 95% confidence intervals (95% CIs) of a PSC diagnosis was calculated based on administrative data. Se was defined as the proportion of true PSC cases identified from the chart review that were recorded in administrative data. The PPV was defined as the proportion of PSC cases identified in the administrative data that were true PSC cases. Algorithms were developed by considering demographical and clinical variables associated with PSC and PSC coding details in order to maximize the PPV while maintaining a high Se. The variables associated with PSC that were extracted for both study populations for fiscal years 1999–2003, included (i) age at diagnosis; (ii) sex; (iii) prevalence of IBD; (iv) diagnostic procedures (i.e. liver biopsy, ERCP, MRCP); (v) diseases associated with secondary cholangitis (i.e. cholelithiasis, disorders of the bile duct); (vi) complications (i.e. cholangiocarcinoma, hepatocellular carcinoma, liver transplantation, malignancy) (Appendix A). The coding details extracted included: (i) number of PSC codes; (ii) timing between PSC codes. Coding details were extracted because PSC is a chronic condition requiring more frequent healthcare visits than the more common acute conditions within the same code.

Sensitivity analyses were conducted for: (i) incident cases; (ii) incident cases with confirmed IBD; (iii) cases with a PSC diagnosis before fiscal year 2002; (iv) adult cases ($\geq$18 years of age); (v) exclusion of in-hospital mortality cases.

Predictive model

Based on the true PSC cases, a logistic regression model using covariates associated with PSC was constructed. Based on this predictive model, each subject with a PSC code was assigned a probability of having PSC. The Se and specificity (Sp) estimates for all possible cutoff values were represented graphically with a receiver operating characteristic (ROC) curve for the predictive model. A cutoff value was selected that maximized the Se and Sp of correctly predicting true PSC cases. Subjects with predicted probabilities above the cutoff were classified as true PSC cases and those below were classified as false cases.

Results

Sensitivity and positive predictive value

A total of 86 true PSC cases were identified from chart review, 39 of which were incident cases. Seven incident and seven prevalent PSC cases were not identified within the administrative data resulting in an Se of 83.7% (95% CI: 74.2%, 90.8%). In the three administrative databases, 998 potential cases were identified. When considering 72 were true PSC cases, the PPV was 7.2% (95% CI: 5.7%, 9.0%). Of the 14 PSC cases not captured within the administrative data, two had PHNs not identified in the CHR registry, one of which was an incident case. The remaining 12 were captured in the registry but did not have PSC codes, six of which were incident cases. One of the prevalent PSC cases was misclassified as having primary biliary cirrhosis (PBC). Of the total number of unique individuals identified in the administrative databases, 67 died in hospital, only one of which was a true PSC case. The number of cases and subject demographics are presented in Table 1.

Algorithms

Eleven variables associated with PSC were considered, and the corresponding Se and PPVs estimates were calculated (Table 2). The algorithm that considered only cases with at least one PSC code and one IBD code for all three databases combined had Se 59% (95% CI: 48%, 70%) and PPV 56% (95% CI: 45%, 66%). The Se and PPV estimates for all other variables were considerably lower. The physician claims database had the greatest balance of Se and PPV

Table 1. Number of cases (true primary sclerosing cholangitis and false primary sclerosing cholangitis) identified by source, patient demographics and coding details

Characteristics/coding details	All databases		Ambulatory Care Classification System Database		Physician Claims Database		Inpatient Database	
Case type	True PSC	False PSC	True PSC	False PSC	True PSC	False PSC	True PSC	False PSC
Total cases captured	72	926	49	432	59	527	37	379
Males [*n* (%)]	40 (55.6)	320 (34.6)	34 (69.4)	217 (50.2)	34 (57.6)	122 (23.1)	27 (73.0)	184 (48.5)
Median age [years (IQR)]	41 (30, 56)	63 (47, 76)	46 (29, 60)	64 (48, 78)	38 (29, 54)	62 (44, 75)	38 (27, 50)	67 (52, 79)
Total PSC contacts	525	2128	167	531	280	1137	78	460
No. of cases with one contact [*n* (%)]	10 (13.9)	522 (56.4)	23 (46.9)	366 (84.7)	16 (27.1)	307 (58.3)	15 (40.5)	335 (88.4)
Total contacts for cases with $\geq$two contacts	515	1606	144	165	264	830	63	125
Number of in-hospital deaths	1	66	NA	NA	NA	NA	1	66

IQR, interquartile range; NA, not applicable; PSC, primary sclerosing cholangitis.

Table 2. Sensitivity and positive predictive value estimates for algorithms including variables associated with primary sclerosing cholangitis for all cases

	All Databases		Ambulatory Care Classification System Database		Physician Claims Database		Inpatient Database	
Characteristics	PPV % (*n*)	Se % (*n*)	PPV % (*n*)	Se % (*n*)	PPV % (*n*)	Se % (*n*)	PPV % (*n*)	Se % (*n*)
IBD	**56.0 (51/91)**	**59.3 (51/86)**	**77.8 (28/36)**	**32.6 (28/86)**	**58.6 (41/70)**	**47.7 (41/86)**	**70.6 (24/34)**	**27.9 (24/86)**
Crohn's disease	56.7 (34/60)	39.5 (34/86)	78.9 (15/19)	17.4 (15/86)	59.6 (28/47)	32.6 (28/86)	62.5 (10/16)	11.6 (10/86)
Ulcerative colitis	65.6 (40/61)	46.5 (40/86)	79.2 (19/24)	22.1 (19/86)	68.1 (32/47)	37.2 (32/86)	80.0 (16/20)	18.6 (16/86)
All diagnostic procedures	**15.0 (47/313)**	**54.7 (47/86)**	**21.2 (39/185)**	**45.3 (39/86)**	**NA**	**NA**	**11.1 (19/171)**	**22.1 (19/86)**
Liver biopsy	27.7 (18/65)	20.9 (18/86)	50.0 (9/18)	10.5 (9/86)	NA	NA	18.0 (9/50)	10.5 (9/86)
ERCP	11.2 (26/233)	30.2 (26/86)	16.3 (23/141)	26.7 (23/86)	NA	NA	5.5 (6/109)	7.0 (6/86)
MRCP	26.1 (29/111)	33.7 (29/86)	34.8 (23/66)	26.7 (23/86)	NA	NA	24.1 (14/58)	16.3 (14/86)
Secondary cholangitis	**5.6 (17/304)**	**19.8 (17/86)**	**4.6 (30/658)**	**34.9 (30/86)**	**7.1 (44/616)**	**51.2 (44/86)**	**6.6 (46/698)**	**53.5 (46/86)**
Cholelithiasis	10.0 (52/521)	60.5 (52/86)	7.8 (65/836)	75.6 (65/86)	8.5 (58/684)	67.4 (58/86)	7.7 (64/829)	74.4 (64/86)
Disorders of bile duct*	3.9 (19/485)	22.1 (19/86)	4.5 (31/694)	36.0 (31/86)	6.0 (49/823)	57.0 (49/86)	6.3 (48/758)	55.8 (48/86)
Complications	**10.5 (29/275)**	**33.7 (29/86)**	**16.2 (16/99)**	**18.6 (16/86)**	**15.3 (27/176)**	**31.4 (27/86)**	**9.8 (12/123)**	**14.0 (12/86)**
Cholangiocarcinoma	7.2 (5/69)	5.8 (5/86)	13.6 (3/22)	3.5 (3/86)	11.9 (5/42)	5.8 (5/86)	12.5 (4/32)	4.7 (4/86)
Hepatocellular carcinoma	23.2 (13/56)	15.1 (13/86)	20.0 (1/5)	1.2 (1/86)	16.7 (12/72)	14.0 (12/86)	0	0
Liver transplantation	40.0 (12/30)	14.0 (12/86)	50.0 (11/22)	12.8 (11/86)	50.0 (10/20)	11.6 (10/86)	50.0 (8/16)	9.3 (8/86)
Malignancy†	9.2 (24/260)	27.9 (24/86)	8.6 (7/81)	8.1 (7/86)	13.1 (22/168)	25.6 (22/86)	4.6 (5/109)	5.8 (5/86)

*Includes obstruction, perforation or fistula of bile duct; spasm of sphincter of Oddi; biliary cyst; other diseases of biliary tract; various bile duct procedures (see Appendix A).

†Includes various malignant neoplasms (see Appendix A). Bold characteristics and corresponding estimates are the totals/summaries of the characteristics and corresponding estimates below them.

ERCP, endoscopic retrograde cholangiopancreatographies; IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiopancreatographies; NA, not applicable; PPV, positive predictive value; Se, sensitivity.

Table 3. Sensitivity and positive predictive value estimates for algorithms including primary sclerosing cholangitis coding details for all databases

	All data		Within 1 year from first code		Within 2 years from first code		Within 3 years from first code	
Diagnostic criterion	PPV % (*n*)	Se % (*n*)	PPV % (*n*)	Se % (*n*)	PPV % (*n*)	Se % (*n*)	PPV % (*n*)	Se % (*n*)
≥1 contact	7.2 (72/998)	83.7 (72/86)	7.2 (72/998)	83.7 (72/86)	7.2 (72/998)	83.7 (72/86)	7.2 (72/998)	83.7 (72/86)
≥2 contacts	13.3 (62/466)	72.1 (62/86)	12.7 (35/375)	40.7 (35/86)	14.2 (41/289)	47.7 (41/86)	15.8 (47/298)	54.7 (47/86)
≥3 contacts	17.3 (47/272)	54.7 (47/86)	13.3 (22/165)	25.6 (22/86)	15.7 (28/178)	32.6 (28/86)	18.2 (34/187)	39.5 (34/86)
≥4 contacts	22.4 (38/170)	44.2 (38/86)	15.5 (18/116)	20.9 (18/86)	16.3 (20/123)	23.3 (20/86)	21.1 (28/133)	32.6 (28/86)
≥5 contacts	25.4 (30/118)	34.9 (30/86)	17.3 (17/98)	19.8 (17/86)	18.3 (19/104)	22.1 (19/86)	20.9 (23/110)	26.7 (23/86)

PPV, positive predictive value; Se, sensitivity.

estimates, while the ACCS and inpatient databases had lower Se but much higher PPVs (Table 2).

Algorithms considering the number of PSC contacts/claims were assessed with respect to PPV and Se (Table 3). Increasing the number of contacts considered in the 4-year period increased the PPV estimates, however, at great expense to the Se. The ACCS database greatly improved the discrimination between true and false PSC cases with a PPV of 82% (95% CI: 48%, 98%) when at least five contacts were considered; however, the Se fell to 10% (95% CI: 5%, 19%) indicating a poor ability to capture true cases (Appendix B). Stratifying the number of codes into time intervals from first PSC code did not greatly change the estimates of PPV and Se (Table 3 and Appendix C).

Sensitivity analyses were developed that considered the number of PSC contacts/claims within the 4-year study period for various PSC sub-groups. When considering only incident PSC cases, both the Se and PPV estimates decreased (Table 4). Estimates ranged from 82% (95% CI: 66%, 92%) with at least one contact to 46% (95% CI 30%, 63%) with at least three contacts. The PPV

Table 4. Sensitivity and positive predictive value estimates for sensitivity analyses

Diagnostic criterion	Considering only incident PSC cases		Considering only incident PSC cases with confirmed IBD		Considering only cases with diagnosis prior to fiscal year 2002		Considering only adults (≥18 years)		Considering only adults (≥18 years) and excluding in-hospital deaths	
	PPV % (*n*)	Se % (*n*)	PPV % (*n*)	Se % (*n*)	PPV % (*n*)	Se % (*n*)	PPV % (*n*)	Se % (*n*)	PPV % (*n*)	Se % (*n*)
≥1 contact	3.3 (32/958)	82.1 (32/39)	37.5 (24/64)	61.5 (24/39)	7.0 (39/558)	62.9 (39/62)	7.1 (69/972)	83.1 (69/83)	7.5 (68/905)	81.9 (68/83)
≥2 contacts	6.0 (26/430)	66.7 (26/39)	44.4 (20/45)	51.3 (20/39)	13.6 (37/273)	59.7 (37/62)	13.1 (59/449)	71.1 (59/83)	14.3 (58/407)	69.9 (58/83)
≥3 contacts	7.4 (18/243)	46.2 (18/39)	43.8 (14/32)	35.9 (14/39)	18.7 (31/166)	50.0 (31/62)	17.4 (45/258)	54.2 (45/83)	18.8 (44/234)	53.0 (44/234)
≥4 contacts	9.0 (13/145)	33.3 (13/39)	57.9 (11/19)	28.2 (11/39)	26.9 (28/104)	45.2 (28/62)	22.7 (37/163)	44.6 (37/83)	23.5 (36/153)	43.4 (36/153)
≥5 contacts	7.4 (7/95)	17.9 (7/39)	46.7 (7/15)	17.9 (7/39)	31.1 (23/74)	37.1 (23/62)	25.7 (29/113)	34.9 (29/83)	26.7 (28/105)	33.7 (28/105)

IBD, inflammatory bowel disease; PPV, positive predictive value; PSC, primary sclerosing cholangitis; Se, sensitivity.

estimates were low. Combining PSC coding details for incident cases with a confirmed diagnosis of IBD greatly increased the PPV while maintaining a relatively high Se estimate (Table 4). Considering only those cases with at least four PSC contacts and confirmed IBD the PPV was 58% (95% CI: 33%, 80%). Although this value indicates a relatively poor ability in discriminating between true and false PSC cases, it was higher than estimates from algorithms in many of the previous analyses. The PPV and corresponding Se estimate for at least two contacts were 44% (95% CI: 30%, 60%) and 51% (95% CI: 35%, 68%) respectively. A Se analysis was performed considering only cases with their first PSC code before fiscal 2002, allowing a sufficient period of time for accrual of multiple PSC codes and the assessment of differences between ICD-9-CM and ICD-10-CA (Table 4). The PPV estimates were similar to those from the previous algorithms; however, the Se estimates were much lower. Similar results to the initial analyses were demonstrated when considering only adult patients (Table 4). When all in-hospital deaths were removed, the PPV estimates slightly increased while the Se estimates slightly decreased.

Predictive model

The predictive model was constructed based on the following six covariates (Table 5): (i) sex; (ii) age (continuous); (iii) IBD; (iv) biopsy; (v) cholelithiasis; (vi) presence of at least two PSC codes. This model was restricted to those of age > 5 years, which was the youngest age of the true PSC cases from the gold standard. For this model, the area under the ROC curve was 93.5%. Based on this model, the estimated probabilities of PSC were much higher for true PSC cases than for false PSC cases. A cutoff of 0.0729 was used, which maximized the Se and Sp, with estimates of 81.9 and 90.7%, respectively; however, the PPV of this model was 41.0%. Selecting a cutoff of 0.20 decreased the Se to 70.8% while increasing the Sp and PPV, with estimates of 96.5 and 61.5% respectively.

Table 5. Variables used in predictive model to identify true positive predictive value cases

Variables	Coefficient	Standard error	*P*-value
Male	0.7364003	0.3385648	0.03
IBD	3.230578	0.3480381	< 0.001
Age	−0.025693	0.0095345	0.007
Biopsy	1.098129	0.4593777	0.017
Cholelithiasis	−0.8709009	0.364019	0.017
≥2 PSC contacts	1.71407	0.4047091	< 0.001
Constant	−3.399987	0.6235593	< 0.001

IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis.

Discussion

This study used chart data to assess the accuracy and validity of ICD-9-CM and ICD-10-CA administrative data for the coding of PSC. The initial Se of 84% and PPV of 7% of the PSC diagnostic code indicated a poor ability to discern true from false PSC cases in administrative data. We attempted to develop an algorithm that would enable the identification of a cohort of true PSC cases. Through multiple algorithms and sensitivity analyses, the PPVs remained quite low with fluctuating Se estimates. There appeared to be trade-offs between PPV and Se, whereby algorithms with higher PPVs had lower Se estimates. When at least five contacts were considered in the ACCS database, we surpassed the bottom threshold of 80% PPV; however, the Se of this algorithm was poor. While identifying true PSC cases from administrative data was not possible, these methods may be used as an initial screening tool to narrow

down the search of identifying PSC cases. Although, ultimately PSC requires a distinct ICD code from ascending cholangitis to be adequately used for epidemiological research.

A predictive model was constructed based on subject characteristics to identify a cohort of PSC cases for future study of risk factors and clinical outcomes. The following covariates were included in the model after assessment of significance and predictive ability: sex, age, IBD, liver biopsy, cholelithiasis and at least two PSC contacts. This model had an area under the ROC curve of 93%, and was therefore able to accurately predict true and false PSC cases. However, the PPV remained low because of the low prevalence of PSC in the administrative data.

We were not able to identify a population-based cohort of true PSC cases by developing an algorithm or predictive model that maximized the PPV while maintaining a high Se. However, these methods could be used for defining a cohort of true PSC cases if the objective was not to define the epidemiology of disease. For example, these methods could be used as an initial screening tool to narrow down the search of identifying PSC cases for chart review validation. This would save time and cost in carrying out population-based studies on PSC.

One recommendation for more accurate PSC identification in administrative data would be to implement a specific ICD-11 code. This would greatly increase the validity of the diagnostic code and would enable the development of an algorithm to identify PSC cases. An algorithm used to identify a cohort of cases with PBC, a similar chronic liver condition, in administrative data was validated for fiscal years 1994–2002 (24). The authors were able to reliably identify patients with PBC, with Se and PPV estimates of 94 and 73% respectively. The accurate identification of PBC cases was possible because of the low proportion of false cases (10%) resulting from PBC having a specific ICD-10 code. Through communication of our findings with the CIHI, a specific code to uniquely identify PSC will be implemented in the 2012 revision of ICD-10-CA (Appendix D). Applying this change to ICD-11 will enable other populations to study PSC.

Some limitations of this study must be recognized. Firstly, the gold standard was developed through a search of multiple databases followed by chart review. Although the Se and Sp of the databases have not been investigated, using a multimethod approach enabled us to be confident that all PSC cases in the CHR were captured. Secondly, owing to the absence of an unselected control group, Sp and negative predictive values could not be determined. However, owing to the rare incidence of PSC [~1.0 per 100 000 person-years (14)], the Sp and negative predictive values are likely high. Thirdly, it must be observed that the validity of the diagnostic code for PSC may have changed since our study time period as physicians were fee for service during this time and are now mostly on alternative reimbursement plans. Owing to the increased incentive for physicians to accurately code on the fee for service plan, the validity of the PSC code during our study time period is likely higher than the current validity. Fourthly, our algorithm may lack generalizability to other countries with different administrative databases and data collection practices. However, other countries are able to use these algorithms as a starting point for validating their own administrative databases. Fifthly, challenges inherent in using administrative databases must be mentioned. The validity of diagnostic and procedural codes used in the analysis may not be accurate. IBD has been validated in administrative data and five IBD diagnostic codes are required to ensure a correct diagnosis (25). Owing to the small number of true PSC cases and the relatively short time interval considered, it was not possible to look at multiple codes of both PSC and IBD. Sixthly, there is no valid and complete drug database in Alberta, which may have enabled the development of an algorithm to identify PSC cases. Although there is no medication proven effective for PSC, current drugs are aimed at treating symptoms and managing complications. One such drug that is common for cases with PSC is ursodeoxycholic acid, which improves the liver function profile (26). Other data centres with complete drug databases may be useful in studying this rare condition.

Overall, we were not able to develop an ICD-9- or 10-based algorithm that could be used in administrative databases to identify a PSC cohort for population-based epidemiological research. Consequently, current epidemiological research should be limited to settings where the diagnosis of PSC can be confirmed outside of an administrative database. A distinct code for PSC will be included in the 2012 revision of ICD-10-CA. Widespread use of this code would enable global study of PSC.

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Appendix A

Table A1. Diagnostic and procedural codes extracted

	ICD-9-CM Diagnostic code	ICD-9-CM Procedural code	ICD-10-CA Diagnostic code	ICD-10-CA Procedural code
Tests and procedures				
ERCP		51.10, 51.11, 52.13		3.OG.10.^^, 2.OE.10^^
MRCP		88.97		3.OT.40.^^
Liver biopsy		50.11, 50.12, 50.91		2.OA.71.^^
Comorbidities				
Crohn's disease	555.x		K50.x	
Ulcerative colitis	556.x		K51.x	
Malignancy	140.0–208.9		C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x	
Secondary cholangitis				
Cholelithiasis	574.x	51.2x	K80.x	1.09.89.^^
Other disorders of bile duct	576.2–576.9, 751.61	51.4x, 51.51, 51.81, 51.84, 51.88, 51.96, 51.98, 87.51	K83.x	1.OE.38.^^, 1.OE.50.^^, 1.OE.52.^^, 1.OE.54.^^, 1.OE.55.^^, 1.OE.57.^^, 1.OE.59.^^, 2.OE.28.^^, 2.OE.70.^^, 2.OE.71.^^,
Complications				
Cholangiocarcinoma	155.1, 156.x		C22.1, C24.0, C24.8–9	
Hepatocellular carcinoma	155.0		C22.0	
Liver transplantation	V42.7	50.5x	Z94.4, T86.4	1.OA.85.^^

ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography.

Appendix B

Table B1. Sensitivity and positive predictive value estimates for algorithms including primary sclerosing cholangitis coding details

	Physician Claims Database		Inpatient Database		Ambulatory Care Classification System Database	
Diagnostic criterion	PPV % (*n*)	Se % (*n*)	PPV % (*n*)	Se % (*n*)	PPV % (*n*)	Se % (*n*)
≥1 contact/claim	10 (59/586)	69 (59/86)	9 (37/416)	43 (37/86)	10 (49/481)	57 (49/86)
≥2 contacts/claims	16 (43/263)	50 (43/86)	33 (22/66)	26 (22/86)	28 (26/92)	30 (26/86)
≥3 contacts/claims	23 (32/138)	37 (32/86)	38 (9/24)	10 (9/86)	44 (18/41)	21 (18/86)
≥4 contacts/claims	27 (26/97)	30 (26/86)	40 (4/10)	5 (4/86)	68 (13/19)	15 (13/86)
≥5 contacts/claims	26 (19/73)	22 (19/86)	29 (2/7)	2 (2/86)	82 (9/11)	10 (9/86)

PPV, positive predictive value; Se, sensitivity.

Appendix C

Table C1. Sensitivity and positive predictive value estimates for algorithms including primary sclerosing cholangitis coding details and time interval from first PSC code

	Physicians Claims Database		Inpatient Database		Ambulatory Care Classification System Database	
Interval between contacts	PPV % (*n*)	Se % (*n*)	PPV % (*n*)	Se % (*n*)	PPV % (*n*)	Se % (*n*)
Within 1 year from first code						
≥1 contact/claim	10 (59/586)	69 (59/86)	9 (37/416)	43 (37/86)	10 (49/481)	57 (49/86)
≥2 contacts/claim	11 (37/326)	43 (37/86)	33 (22/67)	26 (22/86)	23 (19/81)	22 (19/86)
≥3 contacts/claim	9 (19/202)	22 (19/86)	36 (9/25)	10 (9/86)	39 (11/28)	13 (11/86)
≥4 contacts/claim	9 (11/125)	13 (11/86)	40 (4/10)	5 (4/86)	64 (7/11)	8 (7/86)
≥5 contacts/claim	11 (9/80)	10 (9/86)	29 (2/7)	2 (2/86)	100 (5/5)	6 (5/86)
Within 2 years from first code						
≥1 contact/claim	10 (59/586)	69 (59/86)	9 (37/416)	43 (37/86)	10 (49/481)	57 (49/86)
≥2 contacts/claim	13 (44/351)	51 (44/86)	33 (22/67)	26 (22/86)	24 (21/88)	24 (21/86)
≥3 contacts/claim	14 (32/236)	37 (32/86)	36 (9/25)	10 (9/86)	41 (14/34)	16 (14/86)
≥4 contacts/claim	12 (18/154)	21 (18/86)	40 (4/10)	5 (4/86)	57 (8/14)	9 (8/86)
≥5 contacts/claim	15 (16/109)	19 (16/86)	29 (2/7)	2 (2/86)	75 (6/8)	7 (6/86)

Table C1. Continued

	Physicians Claims Database		Inpatient Database		Ambulatory Care Classification System Database	
Interval between contacts	PPV % (*n*)	Se % (*n*)	PPV % (*n*)	Se % (*n*)	PPV % (*n*)	Se % (*n*)
Within 3 years from first code						
≥1 contact/claim	10 (59/586)	69 (59/86)	9 (37/416)	43 (37/86)	10 (49/481)	57 (49/86)
≥2 contacts/claim	13 (45/339)	52 (45/86)	33 (22/67)	26 (22/86)	27 (25/94)	29 (25/86)
≥3 contacts/claim	15 (34/226)	40 (34/86)	36 (9/25)	10 (9/86)	44 (18/41)	21 (18/86)
≥4 contacts/claim	16 (24/148)	28 (24/86)	40 (4/10)	5 (4/86)	67 (12/18)	14 (12/86)
≥5 contacts/claim	19 (19/102)	22 (19/86)	29 (2/7)	2 (2/86)	80 (8/10)	9 (8/86)

PPV, positive predictive value; Se, sensitivity.

Appendix D

Table D1. Revised ICD-10-CA code for primary sclerosing cholangitis

ICD-10-CA	Description
K83.0	Cholangitis *Excludes:* cholangitic liver abscess (K75.0)
K83.00	Primary sclerosing cholangitis
K83.01	Secondary sclerosing cholangitis Use additional code to identify the underlying disease
K83.02	Ascending cholangitis Cholangitis: Infectious, infective Suppurative *Excludes:*cholangitis with choledocholithiasis (K80.3, K80.4)
K83.08	Other and unspecified cholangitis Cholangitis: NOS Recurrent

Revised ICD-10-CA codes for K80.0 cannot be implemented until 1 April 2012.

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Incidence of Primary Sclerosing Cholangitis: a Systematic Review and Meta-Analysis

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Incidence studies of primary sclerosing cholangitis (PSC) are important for describing the disease's burden and for shedding light on the disease's etiology. The purposes of this study were to conduct a systematic review of the incidence studies of PSC with a meta-analysis and to investigate possible geographic variations and temporal trends in the incidence of the disease. A systematic literature search of MEDLINE (1950-2010) and Embase (1980-2010) was conducted to identify studies investigating the incidence of PSC. The incidence of PSC was summarized with an incidence rate (IR) and 95% confidence intervals. The test of heterogeneity was performed with the *Q* statistic. Secondary variables extracted from the articles included the following: the method of case ascertainment, the country, the time period, the age, the male/female incidence rate ratio (IRR), and the incidence of PSC subtypes (small-duct or large-duct PSC and inflammatory bowel disease). Stratified and sensitivity analyses were performed to explore heterogeneity between studies and to assess effects of study quality. Time trends were used to explore differences in the incidence across time. The search retrieved 1669 potentially eligible citations; 8 studies met the inclusion criteria. According to a random-effects model, the pooled IR was 0.77 (0.45-1.09) per 100,000 person-years. However, significant heterogeneity was observed between studies ($P < 0.001$). Sensitivity analyses excluding non–population-based studies increased the overall IR to 1.00 (0.82-1.17) and eliminated the heterogeneity between studies ($P = 0.08$). The IRR for males versus females was 1.70 (1.34-2.07), and the median age was 41 years (35-47 years). All studies investigating time trends reported an overall increase in the incidence of PSC. *Conclusion:* The incidence of PSC is similar in North American and European countries and continues to increase over time. Incidence data from developing countries are lacking, and this limits our understanding of the global incidence of PSC. (HEPATOLOGY 2011;53:1590-1599)

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of an unknown etiology that is characterized by chronic inflammation, destruction, and fibrosis of the intrahepatic and/or extrahepatic biliary tree. This aberrant inflammatory response may ultimately lead to cirrhosis, end-stage liver disease, and the need for liver transplantation.[1] Furthermore, PSC patients are at a considerably higher

Abbreviations: AAPC, average annual percentage change; CI, confidence interval; GPRD, General Practice Research Database; IBD, inflammatory bowel disease; ICD, International Classification of Diseases*; IR, incidence rate; IRR, incidence rate ratio; MOOSE, Meta-Analysis of Observational Studies in Epidemiology; N/A, not available; PSC, primary sclerosing cholangitis; SE, standard error.*

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risk of developing colon cancer and cholangiocarcinoma.[1-3] Studies have shown a strong association between PSC and inflammatory bowel diseases (IBDs); this is particularly true for ulcerative colitis.[1] Approximately 2% to 7.5% of patients with ulcerative colitis have PSC, whereas 70% to 80% of PSC patients have ulcerative colitis or Crohn's disease.[1,4-6] The disease predominantly affects males,[1] and the diagnosis is commonly made in the third or fourth decade of life.[5] Epidemiological studies have reported that the incidence of PSC ranges from 0.04 to 1.30 per 100,000 person-years. Although the incidence of PSC is low, recent evidence suggests that it has increased in the last few decades.[7-9]

PSC poses a significant burden to the health care system because of its high mortality and morbidity rates and the need for liver transplantation.[2,10] Despite the severity of this condition, few population-based epidemiological studies have investigated the incidence of PSC.[7-9,11-15] Most studies that have described the epidemiology of PSC have used data from tertiary referral centers,[16-20] and these data may be limited by a referral bias. Although several studies describing the incidence of PSC have been published, they have not been systematically summarized. The objectives of our study were to conduct a systematic review of the incidence of PSC with a meta-analysis and to provide recommendations for future studies describing the epidemiology of this disease. Insight into the incidence of PSC is important in describing the burden of the disease and may shed light on its etiology.

Patients and Methods

Search Strategy. We conducted a systematic literature search with a predetermined protocol that was in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE),[21] which studied the quality of reporting.[21] We searched MEDLINE (1950 to June 2010) and Embase (1980 to June 2010) for studies investigating the incidence of PSC. The search strategy is outlined in detail in Appendix I. The search was not limited by language or to human subjects. The reference lists of relevant articles were also reviewed.

Selection Criteria. Two reviewers (N.A.M. and H.K.) identified articles eligible for further review by performing an initial screening of identified abstracts and titles. Abstracts were eliminated if they were not observational and did not investigate the epidemiology of PSC. Studies that did not report original data (e.g., review articles) were also excluded. The full text of the remaining articles was retrieved and systematically reviewed according to the inclusion and exclusion criteria. Articles were included if they reported an incidence rate (IR) of PSC or enough information to calculate the IR. Disagreements between reviewers were resolved by consensus with third-party experts (R.P.M. and G.G.K.).

Data Extraction. Two reviewers independently extracted data for each study. The variable of interest was the incidence of PSC. The IR per 100,000 person-years with 95% confidence intervals (CIs) was documented for the overall study period and for individual years when they were reported. Secondary variables extracted from the articles included the following: the method of case ascertainment (i.e., a patient registry or administrative database), the country of origin, the study time period, the median age and range, the male/female incidence rate ratio (IRR), the incidence of small-duct and large-duct PSC, the percentage of PSC cases with IBD, and information on key indicators of study quality from MOOSE.[21]

Statistical Analysis. The incidence of PSC was summarized with an IR, which was defined as the number of cases in a population per 100,000 person-years at risk in the population. IRs adjusted for confounding factors were selected over unadjusted IRs. The standard errors (SEs) and 95% CIs for the IRs were estimated under the assumption of a Poisson distribution. The ratio of males to females was summarized with an IRR, which was defined as the IR of PSC in males over the IR of PSC in females. When the IRR was not reported but the number of male and female incident PSC cases and the total study population were included, the IRR was calculated under the assumption that the background population was 50% male. Heterogeneity was assessed with the Q statistic (5% level), and meta-analyses were performed with random-effects models because of the presence of heterogeneity between studies. Stratified analyses and meta-regression were performed according to the methods of case ascertainment (i.e., administrative data versus patient registry data) and the region of publication (i.e., North America versus Europe). The study time periods were not stratified because there was considerable overlap between them. Temporal trends were calculated with Joinpoint regression analysis,[22] by which, through a series of permutations, tests were performed to assess whether the addition of joinpoints resulted in statistically significant linear changes in the direction or magnitude of the rates in comparison with a linear line. Two joinpoints at most were considered. The parameter estimate used to summarize the

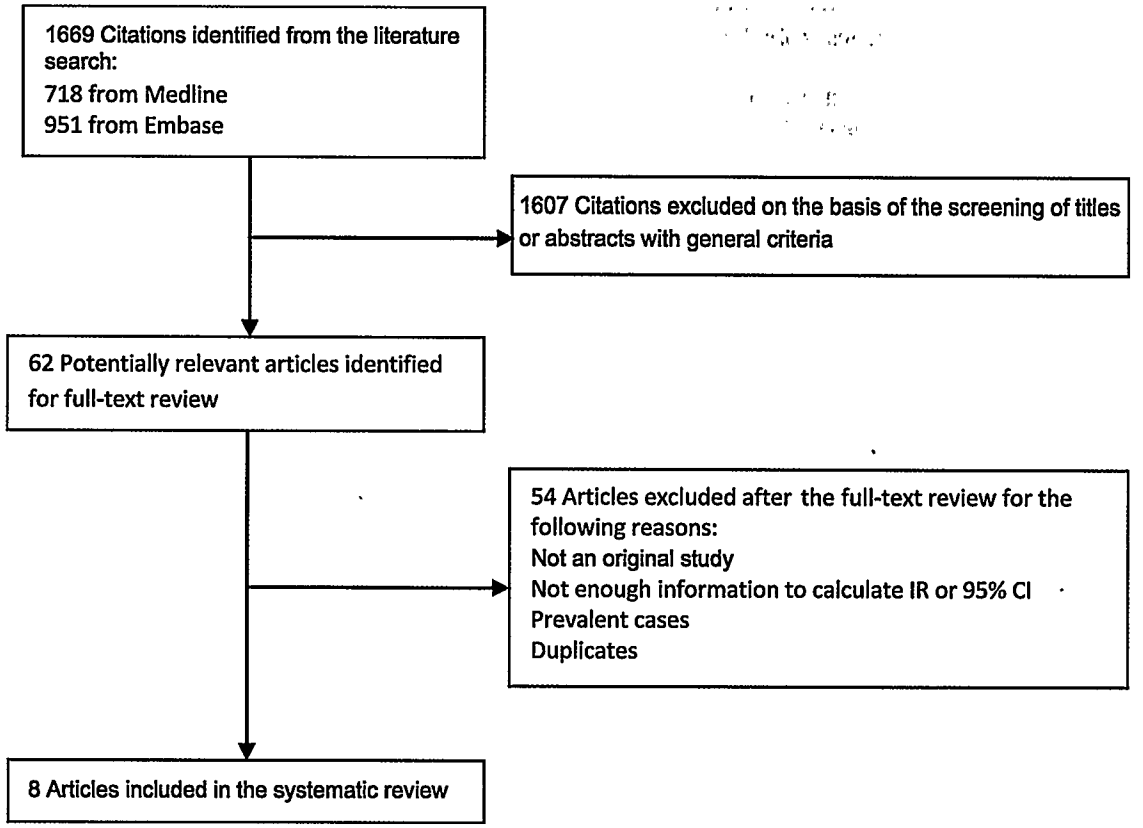

Fig. 1. Literature search results.

trend over the fixed interval was the average annual percentage change (AAPC) according to a generalized log-linear model that assumed a Poisson distribution. Sensitivity analyses were conducted by the exclusion of studies that were not population-based because this was considered the most important difference in the quality of the studies. The possibility of publication bias was assessed with the Begg test.

Results

Literature Search. The search retrieved 718 and 951 citations from MEDLINE and Embase, respectively; 1607 of these citations were excluded after an initial screening based on titles and abstracts, and this left 62 articles for the full-text review (Fig. 1). The observed agreement between reviewers for the eligibility of articles during the initial screening was 92% (κ = 0.85). Upon the full-text review of the 62 articles, 54 were excluded for reasons listed in Fig. 1, and this left 8 studies for final inclusion in the systematic review.[7-9,11-15] The agreement between reviewers for the eligibility of articles was 100% (κ = 1). Characteristics of the eight included studies are shown in Table 1.

Epidemiology and Demographics. The eight studies identified from the literature search that met our inclusion criteria were pooled to give an overall IR estimate of 0.77 (0.45-1.09) per 100,000 person-years at risk (Fig. 2). Statistically significant heterogeneity was observed between studies (Q statistic = 403.53, $P \leq 0.001$). Two studies reported the incidence of large-duct PSC versus small-duct PSC. Kaplan et al.[11] found a 5-fold higher rate, whereas Lindkvist et al.[9] found a 9-fold higher rate of large-duct PSC versus small-duct PSC. No evidence of publication bias was found (Begg test: $z = -1.12$, $P = 0.262$).

The proportion of male incident PSC cases versus female incident PSC cases was reported in all eight studies. The IRR for males versus females was pooled to give an overall IRR estimate of 1.70 (1.34-2.07; Fig. 3). When we analyzed only those studies that reported IRRs without the assumption of a 50% male background population, the pooled IRR was 1.84 (1.18-2.51). In eight studies that reported the age at diagnosis, the pooled median age was 41 years (range = 35-47 years; Fig. 4). Six studies reported the proportion of incident PSC cases with a diagnosis of IBD. When these were pooled, the proportion of IBD in PSC cases was 68% (58%-77%; Fig. 5).

Table 1. Summary of Studies Including the Incidence of PSC

Author	Publication Year	Country (Region)	Study Period	Source of Cases	Population-Based	Method of Case Ascertainment (Comments)	PSC Cases, n	Person-Years	Age at Diagnosis (Years), Median (Range)	Male/Female, n (%)/IRR	PSC IR (per 100,000 Person-Years)	IBD With PSC, n (%)	AAPC, % (95% CI)
Kaplan et al.[11]	2007	Canada (Calgary)	2000-2005	Patient registry	Yes	Retrospective cohort	49	5,562,605	41 (29-60)‡	27/22 (55)/ 1.24 (0.82-1.81)	0.92 (0.68-1.21)	36 (74)	6.0**,‖
Kingham et al.[12]	2004	United Kingdom (South Wales)	1984-2003	Patient registry	Yes	Prospective cohort	46	5,020,000	52 (11-80)††	33/20 (62)/ 1.65 (0.92-3.03)†,††	0.91 (0.67-1.22)	33 (62)††	N/A
Bambha et al.[13]	2003	United States (Olmsted County, MN)	1976-2000	Administrative database	Yes	Medical record linkage system	22	2,444,444	40 (34-50)‡	15/7 (68)/ 2.31 (0.89-6.71)	0.90 (0.56-1.36)	16 (73)	N/A
Berdal et al.[15]	1998	Norway (Akershus)	1985-1994	Administrative database	Yes	ICD codes (validated by a review of medical records)	12	1,800,000	43§ (32-64)	7/5 (58)/ 1.40 (0.38-5.59)†	0.7 (0.34-1.16)	N/A	N/A
Lindkvist et al.[9]¶	2010	Sweden (Vastra Gotaland)	1992-2005	Administrative database	Yes	ICD codes (validated by a review of medical records)	199	16,311,475	38.5 (18-77)	142/57 (71)/ 2.58 (1.88-3.57)	1.22 (1.06-1.40)	152 (76)	3.06‖ (0.01-6.20)
Boberg et al.[14]¶	1998	Norway (Aker University Hospital catchment area)	1986-1995	Patient registry	Yes	Prospective cohort	17	1,300,000	37 (14-67)	12/5 (71)/ 2.40 (0.79-8.70)†	1.3 (0.8-2.1)	12 (71)	N/A
Escorsell et al.[7]*	1994	Spain (nationwide)	1984-1988	Patient registry	No	Questionnaire (responses from 69.7% of centers in the region)	37	96,200,000	42.3§ (12-75)#	26/17 (60)#/ 1.53 (0.80-3.00)†	0.04 (0.03-0.05)	20 (47)#	27.2‖
Card et al.[8]*	2008	United Kingdom (nationwide)	1991-2001	Administrative database	No	GPRD (not fully population-based and not validated for PSC)	149	36,341,463	55 (5-94)	1.85 (1.33-2.59)	0.41 (0.34-0.48)	N/A	4.1

*The study was excluded from the sensitivity analysis because it was not population-based.
†Fifty percent of the study population was assumed to be male.
‡Interquartile range.
§Mean age.
‖Statistically significant increase.
¶Only adults (≥18 years).
#Based on 43 PSC cases (incident and prevalent).
**Unpublished data.
††Based on 53 incident cases (7 were outside the population and were not included in the incidence calculation).

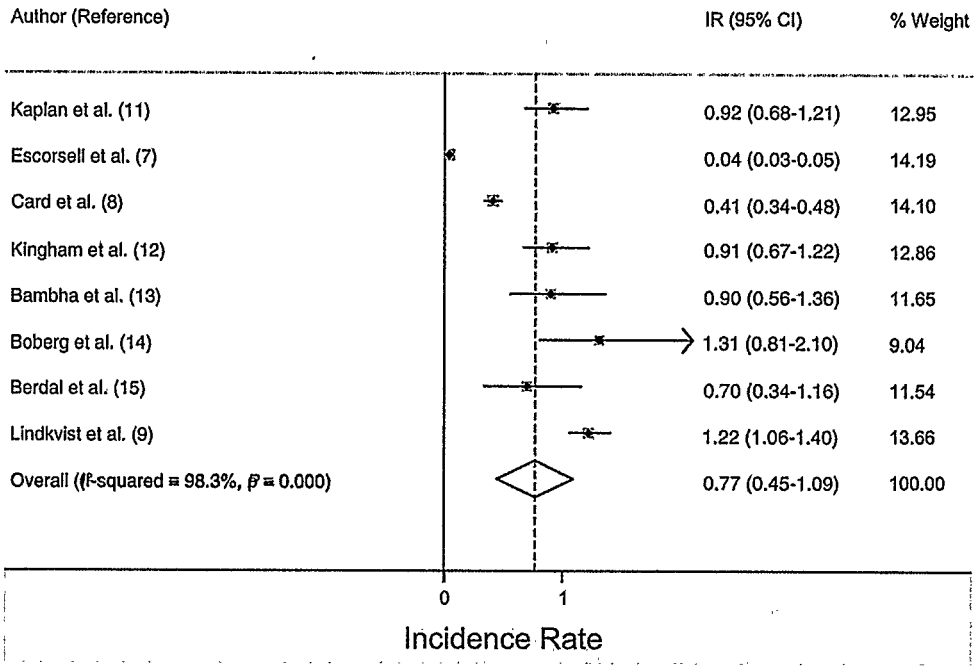

Fig. 2. Pooled IR estimates of PSC per 100,000 person-years at risk. Weights are from random-effects analysis.

The source of case ascertainment varied between studies, with four studies using administrative databases and four using patient registries (Table 1). The IR of PSC did not significantly differ between the two methods when a meta-regression was performed ($P = 0.845$; Table 2). The eight included studies were conducted in North America and Europe. The two studies from North America[11,13] had similar estimates and gave a pooled IR of 0.91 (0.69-1.14) per 100,000 person-years at risk. Studies from Europe[9,12,14,15] had a lower pooled estimate of 0.72 (0.36-1.08); however, meta-regression analysis revealed no statistically significant difference between regions ($P = 0.636$).

Temporal Trends in PSC Incidence. Five studies investigated temporal trends in PSC incidence[7-9,11] (Table 2). Four studies reported estimates for the trends; three of these demonstrated statistically significant increases at the 5% level [AAPC = 6.0%[11] (unpublished data), AAPC = 27.2%,[7] and AAPC = 3.1%[9]]. In the last study, a significant increase of 35.1% over a 10-year period was reported ($P = 0.05$).

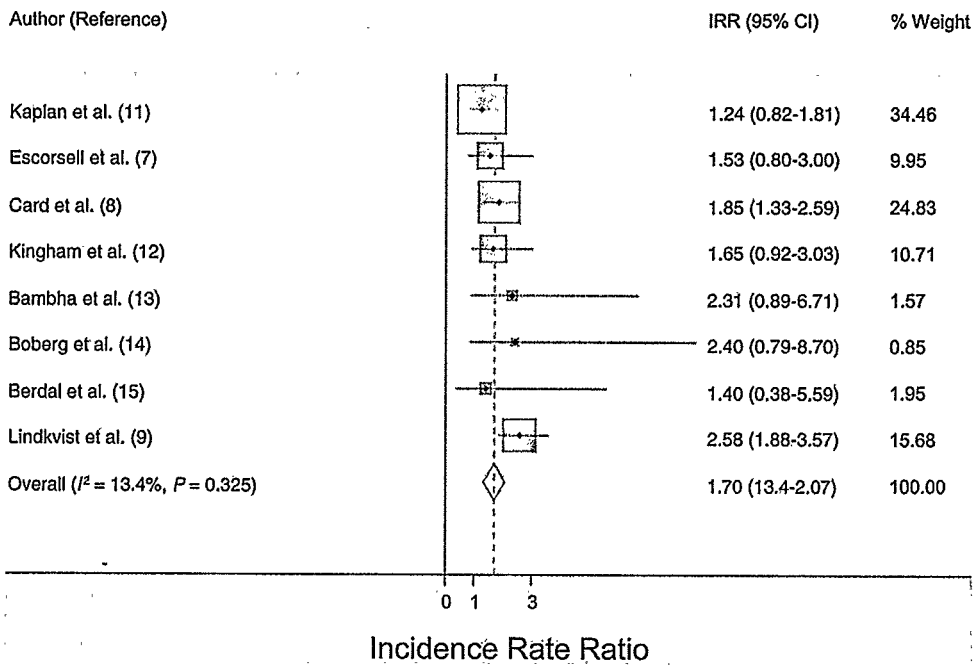

Fig. 3. IRRs of PSC for males versus females. Weights are from random-effects analysis.

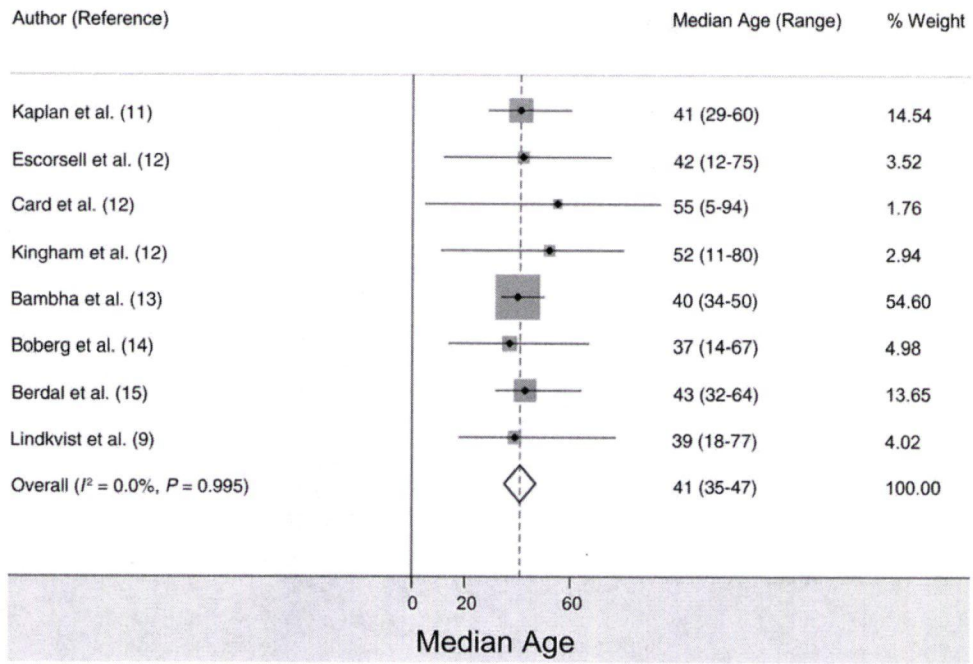

Fig. 4. Median ages in years for patients with a diagnosis of PSC. Weights are from random-effects analysis.

Another study reported a tendency toward increasing incidence; however, a statistically significant result was not found (AAPC = 4.1%).[8] The study that did not report an estimate for the trend found a significant trend toward increasing incidence in men but not women ($P < 0.01$ and $P = 0.6$, respectively) when the overall study time period was considered.[13] One study reported time trends for different subtypes of PSC but failed to find a statistically significant increase when either small-duct or large-duct PSC or PSC with or without IBD was considered.[9]

Sensitivity Analysis. The exclusion of the two studies that were not fully population-based increased the pooled IR of PSC to 1.00 (0.82-1.17) per 100,000 person-years at risk (Fig. 6). When only these six studies were considered, statistically significant heterogeneity was not observed (Q statistic = 9.72, $P = 0.08$). The pooled IRR for males versus females did not significantly change when these studies were excluded; the estimated value was 1.77 (1.15-2.38). The median age remained the same; however, higher pooled estimates were found for the different methods of case ascertainment and the study regions (Table 2).

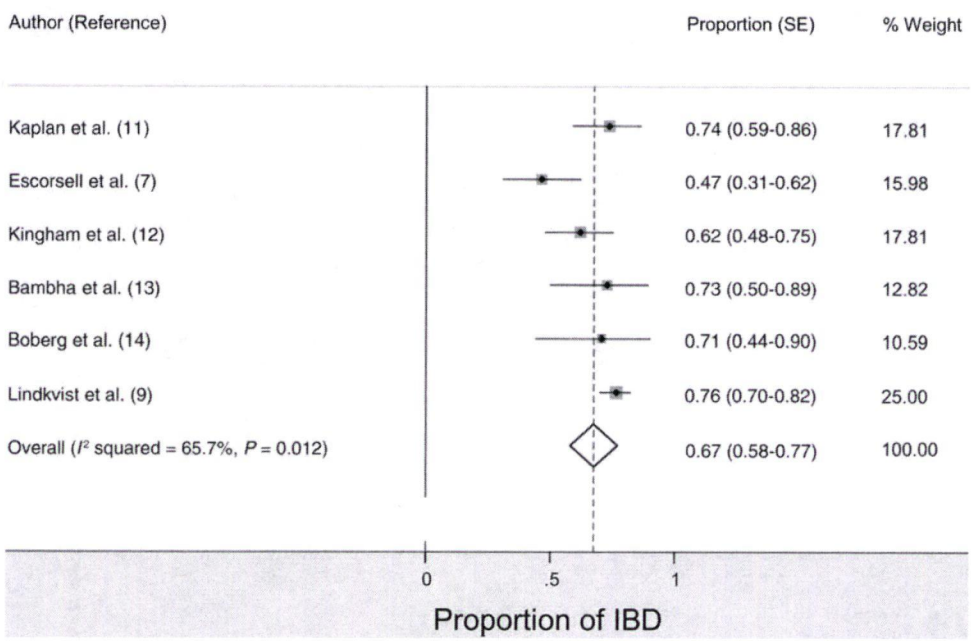

Fig. 5. Proportions of incident PSC cases with IBD. Weights are from random-effects analysis.

Table 2. Demographic, Epidemiological, and Study Quality Data With Stratified Analyses for Studies Exploring the Incidence of PSC

Analysis	Characteristic	Studies, n	Measure	Meta-Regression *P* Value
Primary				
Epidemiology	IR	8	IR (95% CI): 0.77 (0.45-1.09)	N/A
Demographics	Male/female ratio	8	IRR (95% CI): 1.70 (1.34-2.07)	
	Male/female ratio*	4	IRR (95% CI): 1.84 (1.18-2.51)	
	Age	8	Median (range): 41 years (35-47 years)	
	IBD	6	% (SE): 67 (58-77)	
Stratified				
Method of case ascertainment	Administrative database	4	IR (95% CI): 0.76 (0.11-1.41)	0.845
	Patient registry	4	IR (95% CI): 0.81 (0.30-1.31)	
Region of study	North America	2	IR (95% CI): 0.91 (0.69-1.14)	0.636
	Europe	6	IR (95% CI): 0.72 (0.36-1.08)	
Sensitivity				
Epidemiology	IR	6	IR (95% CI): 1.00 (0.82-1.17)	N/A
Demographics	Male/female ratio	6	IRR (95% CI): 1.77 (1.15-2.38)	
	Male/female ratio*	3	IRR (95% CI): 1.91 (0.79-3.03)	
	Age	6	Median (range): 41 years (35-47 years)	
	IBD	5	% (SE): 74 (69-79)	
Method of case ascertainment	Administrative database	3	IR (95% CI): 0.98 (0.65-1.32)	0.914
	Patient registry	3	IR (95% CI): 0.95 (0.76-1.13)	
Region of study	North America	2	IR (95% CI): 0.91 (0.69-1.14)	0.581
	Europe	4	IR (95% CI): 1.03 (0.77-1.29)	

Abbreviation: N/A, not available.
*Studies assuming that the study population was 50% male were excluded.

Discussion

PSC is a rare disease of unknown etiology. Despite its low prevalence, the burden of disease is substantial because of the lack of effective therapeutic options and the high rate of complications, which predominantly affect young patients. Few population-based epidemiological studies have investigated the incidence of PSC, and as a result, the epidemiology of this disease remains poorly defined. Here we present a comprehensive overview of the incidence of PSC. The overall incidence of PSC was 0.77 per 100,000 person-years at risk. The incidence was largely unchanged in multiple stratified analyses exploring study characteristics (e.g., case ascertainment). The median age at the diagnosis of PSC was 41 years, with males having a nearly 2-fold greater risk of developing PSC versus females. The pooled proportion of IBD in PSC cases was 67%, and this was consistent with previous reports. Sensitivity

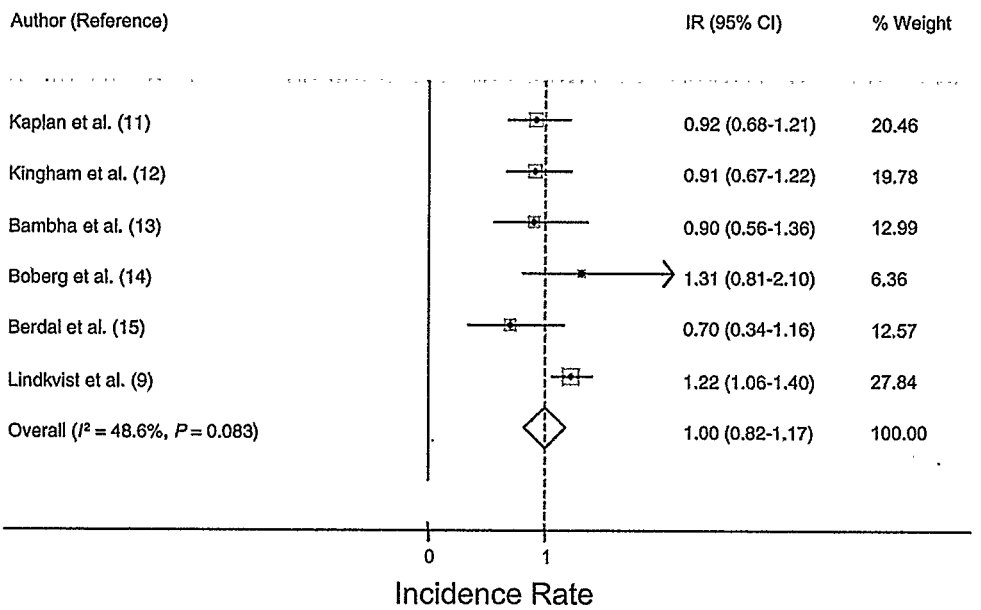

Fig. 6. Pooled IR estimates of PSC per 100,000 person-years at risk for population-based studies. Weights are from random-effects analysis.

analysis considering only population-based studies increased the IR estimate to 1.00 per 100,000 person-years at risk. Because population-based studies provide a more accurate and reliable estimate of the rate of disease, the IR of 1.00 per 100,000 is likely more representative of the true incidence of PSC.

Heterogeneity was observed between studies exploring the incidence of PSC. This heterogeneity may be explained by differences in the geographic region, differences in the study design (e.g., the method of case ascertainment), and intrinsic biases associated with observational studies. A stratified analysis was conducted to assess IRs in different geographic regions. All the studies originated from either North America or Europe. When stratification was performed by continent, no differences in IRs were found. Regional similarities in IRs may be due to the fact that the studies originated from countries that were comparable in ethnicity, the prevalence of IBD, and the rates of IBD susceptibility genes.[23,24] Data were lacking for regions of low IBD prevalence (e.g., the developing world), so we could not explore the incidence of PSC in these areas. Because the incidence and prevalence of IBD are highest in North America[25,26] and Europe,[27] PSC estimates from these studies may overestimate the global health burden. Additionally, we explored whether the method of case ascertainment contributed to the heterogeneity observed between studies. IRs did not differ between studies using administrative databases and studies using patient registries, and this indicated the robustness of these incidence estimates. Ideally, we would have explored whether the year of study contributed to the heterogeneity observed between studies; however, the considerable overlap of the time periods prevented this analysis. Additionally, we would have investigated the differences in the incidence of small-duct PSC versus large-duct PSC; however, only two studies stratified their results by the different types of PSC. Differentiating PSC subtypes is important because small-duct PSC has a more benign prognosis than large-duct PSC.[11,28] Thus, future population-based studies are required to characterize the incidence of the different subtypes of PSC.

Sensitivity analysis excluding studies that were not population-based revealed no statistically significant heterogeneity. The inconsistency of heterogeneity was likely due to the much smaller IR estimates and the larger overall study populations in two of the studies that were not population-based. The study by Escorsell et al.[7] ascertained cases through a questionnaire circulated to gastroenterologists and hepatologists in 33 hospitals throughout Spain; however, only 69.7% of the centers responded. Because of the non–population-based nature of this study and the common under-reporting by physicians, the IR was likely largely underestimated. The study by Card et al.[8] ascertained cases through the General Practice Research Database (GPRD). The GPRD is not population-based; therefore, its incidence estimate represents that of the GPRD and not the general population. Moreover, the code for PSC was not validated, and this poses additional challenges to its validity. These two studies were not fully comparable with the other studies included in the analysis.

The incidence of PSC appears to be increasing; however, additional studies are necessary to confirm this observation. This increase in PSC incidence may be a direct result of its link to IBD because recent evidence suggests that the incidence of IBD is still increasing in many regions of the world.[26,29-32] Studies investigating the incidence of PSC with and without IBD may help to resolve this issue; however, the decrease in power when these analyses are conducted may hinder the finding of statistical evidence. One study reported time trends in PSC with and without IBD but failed to find a statistically significant increase.[9] Additionally, the observed increase may be due to improvements in the diagnostic abilities of physicians and diagnostic tools such as noninvasive imaging (i.e., magnetic resonance cholangiopancreatography).[33,34] Magnetic resonance cholangiopancreatography permits fast and highly accurate imaging of the biliary tree and has been used with increasing frequency as a noninvasive alternative to endoscopic retrograde cholangiopancreatography.[33,35-37] Furthermore, the increasing use of biological therapies (e.g., infliximab) and immunosuppressants (e.g., azathioprine and methotrexate), particularly in those with IBD,[38-40] may have contributed to the greater detection of PSC over time. Biologics and immunosuppressants have been associated with drug-induced liver complications, hepatobiliary disease, and liver toxicity[41,42]; therefore, the routine screening of liver function profiles for individuals taking these therapies has increased. Studies investigating the incidence of PSC should consider assessments of diagnostic tool utilization over time. Moreover, this increase in incidence may be a result of biases in observational studies. In particular, the study by Escorsell et al.[7] had an unrealistically high AAPC of 27%. Many factors likely contributed to the obvious bias of this estimate. The population estimate used to calculate the incidence was taken from the end of the study period. An increase in the study population (i.e., 12 regions in Spain)[43] over the time interval

would have overestimated the increase in IR. Additionally, because of the retrospective nature of the study and the need for physicians to respond to a questionnaire, the response rate could have been lower for earlier time periods. Finally, detection bias could have been more pronounced at the end of the study period because of the increased availability and use of diagnostic technologies.

The relative paucity of incidence studies of PSC was likely secondary to the difficulty of ascertaining cases of PSC, particularly from administrative databases. Administrative databases have the potential to introduce misclassification errors for rare diseases such as PSC. For example, PSC does not have a distinct *International Classification of Diseases* (ICD) code (ninth or tenth revision) and instead is listed under *cholangitis*, which includes much more common acute conditions such as ascending cholangitis. This leads to the incorrect classification of PSC incidence with administrative databases in which ICD coding is used without validation.

Limitations of our systematic review should be considered. First, the number of studies included in the stratified analyses was relatively small, so the incidence of PSC in these strata may not be accurately represented. Second, the quality of the studies was not always optimal; this was shown by the inconsistent methods of case ascertainment. Third, because of the lack of data provided by each study for comprehensively studying the demographics and time trends of the incidence of PSC, secondary calculations were required. Fourth, our systematic review was limited to incidence data and not to prevalence data. Although prevalence may be helpful in describing the disease burden, it is a static measure of the proportion of PSC cases in a population and is, therefore, influenced by mortality. Because patients with PSC have a high mortality rate, with survival rates likely differing by the population, our interest was in summarizing the rate at which new PSC cases occurred. Finally, the results of the meta-analysis should be interpreted with caution because data pooling does not address the intrinsic biases of observational studies. Despite these limitations, this review provides a comprehensive summary of the current literature. The meta-analysis identified important deficiencies in the literature, so future studies should be conducted to address the paucity of data as well as study design and quality issues.

The objective of this review was to help us to estimate the public health burden of PSC; the meta-analysis demonstrated that the IR of PSC was 0.77 per 100,000 person-years at risk with a slightly higher estimate of 1.00 per 100,000 person-years when only population-based studies were considered. We feel that because of the increased quality of population-based studies, the latter estimate better reflects the true incidence of PSC. Additionally, the meta-analysis identified important study limitations; thus, future studies should be properly designed with high-quality and systematic methods of case ascertainment and should explore the incidence of both small-duct PSC and large-duct PSC. Furthermore, additional studies need to evaluate whether the incidence of PSC is truly increasing by analyzing the incidence of PSC with and without IBD as well as the utilization of diagnostic tools concurrently with the incidence of PSC. Finally, the meta-analysis highlights that researchers should continue to explore the incidence of PSC, particularly in the developing world.

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