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Title:

Increasing prevalence of primary biliary cholangitis in Victoria, Australia

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Background and Aim:

The prevalence of primary biliary cholangitis (PBC) reported in different countries varies significantly and in some parts of the world appears to be increasing. The aim of this study was to determine the 2013 prevalence of PBC in Victoria, Australia, and to determine the time trend by comparing it to previous studies undertaken in 1991 and 2002.

Methods:

Four case-finding methods were used to identify cases of PBC in Victoria. 1. Physicians' survey; 2. Tertiary hospital search; 3. Liver Transplant Database search; 4. Private Pathology Anti-Mitochondrial Antibody (AMA) search.

Results:

The prevalence of PBC in Victoria Australia is 189.0 per million using all four methods. The average annual increase in prevalence from 1991 to 2013 was 7.7 per million per year. Using the same case finding methods as the 1991 Victorian prevalence study (methods 1, 2), the prevalence of PBC increased from 19.1 per million in 1991 to 49.4 per million in 2002 ($p < 0.001$) and to 80.7 per million in 2013 ($p < 0.001$.)

Conclusions:

The current prevalence of PBC in Victoria is significantly higher than previously reported. The use of private pathology-based case-finding methods is important in identifying the maximum number of PBC cases.

Keywords: primary biliary cirrhosis, autoimmune liver disease, epidemiology

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Introduction

Primary biliary cholangitis (PBC) is a chronic progressive cholestatic liver disease that predominantly affects women over the age of 40. It is characterised by the immune mediated destruction of small and medium sized intrahepatic bile ducts. The aetiology of PBC is thought to be a combination of genetic and environmental factors. The serological signature of PBC, the anti-mitochondrial antibody (AMA), is a highly disease specific antibody that is present in 90-95% of PBC patients.¹

The disease was previously known as Primary Biliary Cirrhosis but has had a nomenclature change recently, as the majority of patients diagnosed in the current era are not cirrhotic. Currently, a large percentage of PBC patients are asymptomatic at diagnosis and are detected because of abnormal liver biochemistry obtained for other reasons.²

In the majority of patients the disease is responsive to Ursodeoxycholic acid (UDCA), a hydrophilic non-toxic bile acid. Life expectancy is not reduced in this group of patients. However, in those presenting with advanced disease the condition is often progressive despite medical therapy and liver transplantation is often required to prevent premature death. PBC is the third most common indication for liver transplantation in Europe³ and the ninth most common indication in Victoria, Australia.⁴

There is a marked geographical variation in prevalence of PBC. One of the highest reported rates of PBC, 251 per million of population,⁵ was found in the UK, while much lower rates have been reported in Australia (51 per million in 2002⁶) and New Zealand (99 per million in 2008⁷.)

There is a wide variation in case finding methods in PBC prevalence studies. The previously mentioned PBC prevalence studies in Northern England⁵ and New Zealand⁷ both employed multiple case finding methods although there was considerable variation in methodology between the studies. However, these differences in methodology are unlikely to explain all the variation in disease prevalence. Considering the shared ethnic backgrounds of the Australian, New Zealand, and UK

populations, the variation in disease prevalence has provided evidence that there may be important environmental factors influencing the disease aetiology.

Over the last 30 years, there have been two prevalence studies of PBC undertaken in Victoria, Australia. The first was undertaken in 1991 and reported an extremely low prevalence of 19 per million.⁸ A study performed 11 years later in 2002,⁶ revealed a marked increase in prevalence to 51 per million. This current study aims to define the 2013 prevalence of PBC in Victoria and to examine the time trend relative to these previous studies. We also aimed to explore the utility of an additional case finding method, private pathology AMA testing, in identifying additional cases.

Methods

Criteria for the diagnosis of PBC

Patients fulfilling the diagnosis of definite or probable PBC were included in this study. Definite PBC was defined as the presence of liver histology compatible with PBC from liver biopsy findings, cholestatic liver function tests (elevation of serum alkaline phosphatase) and an AMA titre of at least 1:40.⁹ Probable PBC was defined as patients fulfilling two of these three diagnostic criteria.

Study population and period

The census date applied to this study was 1 January 2013. The source population was the state of Victoria, Australia. Patient postcodes were collected to confirm residence within Victoria, excluding interstate cases being treated in Victoria. Population statistics were obtained from the Australian Bureau of Statistics. The population of Victoria at the time of the study was 5.35 million, including 2.49 million women aged over 40 years, the population most at risk of PBC.

Case ascertainment

Four separate methods were used to identify patients with PBC. Method 1 (physicians' survey) and method 2 (tertiary hospital search) were the same as those employed in the 1991 Victorian prevalence study.⁸ The 2002 Victorian prevalence study⁶ used the former two methods as well as method 3 (liver transplant database search.)

Method 1: Physicians' survey

A survey was sent by mail to all registered gastroenterologists and hepatologists in Victoria. For each patient with PBC under their care, the physician was asked to complete a questionnaire which included the patient's first and last initial, along with the patient's postcode, country of birth, date of presentation, AMA titre, liver function test results and liver biopsy results, if available. Physicians who did not respond were further contacted by telephone calls, e-mails, and further letters to encourage their participation.

Method 2: Tertiary hospital search

The second method included a medical record search for cases of PBC recorded between 1 January 2003 and 1 January 2013, at Victoria's seven major teaching hospitals (Austin Hospital, Eastern Health, Royal Melbourne Hospital, Alfred Hospital, Western Hospital, Monash Medical Centre and St Vincent's Hospital.) This involved searching for a coded diagnosis of PBC through medical records, as well as a search for patients in whom a positive AMA result had been obtained during this period. The previously described questionnaire was completed for each patient identified as either probable or definite PBC by either the hospital medical record or AMA search.

Method 3: Liver Transplant Database search

For the third method, we undertook a search of the Victorian Liver Transplant Unit database, based at the Austin Hospital (Heidelberg, Victoria). This unit is responsible for all liver transplants performed in the state of Victoria and has a database of all patients referred for consideration of liver transplantation. All identified patients had their medical records reviewed and a questionnaire completed. Patients who had received a liver transplant prior to the census date of 1 January 2013 were excluded.

Method 4: Private Pathology AMA search

A fourth and new case finding method was used in this study. It involved surveying private pathology company databases for patients with positive AMA results. This method was employed to capture cases that are seen predominantly in the private sector and thus may be missed by methods 1-3. In those with positive AMA, liver function test results were also collected to determine which patients fulfilled the criteria for probable PBC. Patient age, sex, date of birth and postcode were also collected in this cohort. In Australia, approximately 60% of all pathology services are provided by the private sector.¹⁰ The private pathology sector, at the time of the census date, was made up largely of three publicly listed companies, Sonic Healthcare Ltd, Primary Healthcare Ltd and Clinical Laboratories Pty Ltd. These three companies all agreed to contribute data for the study. These companies together provide approximately 80% of all private pathology in Australia.¹⁰

Patient initials, date of birth, and postcode were used to identify and remove duplicate patients. All data was entered into a secure Microsoft Access database. The project had ethics approval from the Austin Health Human Research Ethics Committee as well as those of the other six tertiary hospitals in Victoria.

Statistical analysis

Prevalence estimates were age-standardised to the 2011 Australian population (most recent census prior to the prevalence date), using the direct method.

Differences in prevalence between time points and between case finding methods in 2013 were assessed by Poisson regression, estimating prevalence ratios (PR) and 95% confidence intervals (CI). Differences in sex ratio between groups were assessed by including a product term between sex and the respective covariate (year or method) denoting the significance of the difference in sex ratio between groups. Statistical analyses were conducted in STATA/SE 15.0 (StataCorp, College Park, USA.)

Results

In total, we identified 1,012 cases of PBC who were resident in Victoria, with 187 classified as having definite PBC and 825 probable. One hundred and thirteen out of 143 (79.0%) registered gastroenterologists/hepatologists in Victoria responded to the physicians' survey. In the physicians' survey, a total of 176 PBC patients were identified. The tertiary hospital search identified another 261 patients. Eleven further patients were identified through the Liver Transplant Unit database search. Using our fourth novel case finding method, the private pathology AMA search, an additional 579 cases were identified (Figure 1.) In total, 89 cases (9%) were identified by multiple methods. Table 1 shows the overall cohort characteristics and by each case ascertainment method.

2013 PBC prevalence

The prevalence of PBC in 2013 using method 1 (physicians' survey) and 2 (tertiary hospital search) was 80.7 per million (Table 2). Including method 3 (liver transplant database search) increased the estimated prevalence to 82.6 per million and including method 4 (private pathology AMA search) increased the prevalence to 189.0 per million. The female to male ratio was 7:1. The mean age of males was 67.8 (± 13.9) years and females 63.4 (± 12.8) years. Figure 2 shows the prevalence of PBC by age in our patient cohort.

PBC prevalence over time

The prevalence of PBC in Victoria significantly increased over the three time-points assessed, regardless of the ascertainment methods employed (Table 2.) Using only the case finding methods employed in the 1991 study (methods 1 and 2; physicians' survey and hospital record search) there was a significant increase in prevalence, increasing 2.6-fold to 2002 and 4.2-fold to 2013. Using the three methods used in the 2002 study (physicians' survey, tertiary hospital search, and liver transplant database search) there was a 1.6-fold increase from 2002 to 2013. Using all four ascertainment methods, including the private pathology AMA search, the prevalence was markedly higher – 189 per million – over double that found using just the 3-method ascertainment, and 3.7 times higher that found in 2002 (Figure 3.)

The average annual increase in disease prevalence from 1991 to 2013 was 7.7 per million per year (95% CI: 5.74-8.12). The average annual increase for females was 3.8 per million per year (95% CI:

1.99-5.22) compared with 1.4 per million per year (95% CI: 3.17-11.55) for males (Figure 4.) The prevalence in women greater than 40 years was 336 per million.

Discussion

This study identified a prevalence of PBC in Victoria, Australia in 2013 of 82.6 using the three methods from the 2002 study and 189 per million using all four case finding methods. We found a 4.2 fold increase from 1991 and a 1.62 fold increase from 2002 in this study using the original case finding methods from these two studies (two and three methods respectively.)

In this present study we employed a novel case-finding method of searching private pathology company databases for positive AMA and cholestatic liver function tests (method 4.) This additional method identified 55% of all of the cases. Method 1 (physicians' survey) and 2 (tertiary hospital search) identified 44% and method 3 (liver transplant database search) identified only 1% of the cases. This demonstrates the importance of incorporating pathology services that are utilised by primary health care in future studies of PBC prevalence. In Australia, pathology services are quite distinctly separated between public hospitals and primary health services. In public hospitals, pathology is generally provided by in-house services; however, in general and private specialist practice, the vast majority of pathology is provided by the three large companies who provided data for this study.

Currently PBC is most often diagnosed early in the natural history of the disease and therefore managed in the community.¹¹ This contrasts with previous decades where the majority of patients with were diagnosed with advanced liver disease.¹² These historic cohorts of patients with advanced disease were more likely to be managed within the public hospital system or at least in the hands of specialist gastroenterologists. Indeed in our 1991 survey, the majority of the patients were described as being symptomatic at diagnosis. This drift in management from hospital-centric to being based largely in primary care reinforces the utility of incorporating case-finding methodologies that identify the large group of patients managed solely in private or general practice.

There was an increase in prevalence from 51 per million in 2002 to 189 per million in 2013 and even if cases identified by method 4 are excluded there was a 1.62 fold increase to 82.6 per million. This increased prevalence may reflect increased awareness of the condition by medical practitioners and therefore more frequent diagnosis. Other potential explanations may include increasing patient

longevity and earlier diagnosis. It is also possible that disease incidence is increasing. Increased PBC prevalence has also been observed in northeast England where, over a 7-year period, there was a greater than 1.5-fold increase in prevalence from 149 per million in 1987 to 251 per million in 1994 using the same case-finding methods.⁵ A rise in prevalence was also demonstrated in a Canadian study where the prevalence rose greater than 2-fold from 100 per million in 1996 to 227 per million in 2002, again using the same case finding methods in both studies.¹³

One of the other hypotheses to explain this increase in disease prevalence is related to reduced sun exposure and vitamin D levels. It has been proposed that many autoimmune diseases are modulated by vitamin D¹⁴ which has known immunomodulatory effects on a number of immune cells involved in adaptive immunity including T lymphocytes, B lymphocytes and dendritic cells.¹⁵ The expression of vitamin D receptor by these immune cells and subsequent production of 1,25-dihydroxycholecalciferol (1,25(OH)₂D₃) has been shown to suppress autoimmunity in several autoimmune diseases.¹⁶ There is some evidence to suggest an association between PBC and decreased vitamin D.¹⁷ Sood *et al* demonstrated that for women aged greater than 40 years, the group most at risk of PBC, the prevalence of the disease was significantly greater for women who had been born in the UK and had migrated to Victoria, compared with those women who were Australian born.⁶ Given the similarity in ethnicity between the British and Victorian populations, this suggests that some environmental factor in Victoria offers a degree of protection from PBC. This most obvious environmental difference between the two locations is sun exposure. There is also evidence that Australians themselves are reducing the amount of sun exposure due to effective SunSmart campaigns over the last two decades to reduce the incidence of skin cancer,¹⁸ and that nearly one third of adults in Australia are vitamin D deficient.¹⁹ Therefore, the increased prevalence may be related to a decrease in sun exposure and lower vitamin D levels. However, this remains a hypothesis and needs to be explored in future studies.

There is also evidence to suggest that the prevalence of Multiple Sclerosis in Victoria²⁰ is increasing and that there is a high incidence of inflammatory bowel disease in Geelong, Victoria amongst the highest reported in the international literature.²¹ Therefore it is also plausible that Vitamin D or another environmental factor is playing a role in the rates of other autoimmune diseases in Victoria.

Although we have improved patient identification in this study with expanded methodologies it is likely that cases have still been missed. Rural and regional cases may have been under-represented as

only 16% of cases were diagnosed living in rural/regional areas yet 32% of Victoria's population was living in rural /regional areas in 2013.²² Each method of case ascertainment may have slightly under-represented the total case number. The first method, the physicians' survey, had a 79% response rate and thus there may have been cases missed by this method. The second method involved an extensive search for cases at all tertiary hospitals; this included searching for coding of PBC diagnosis in hospital medical records and for positive AMA results. At one Victorian hospital, The Alfred hospital, positive AMA results could only be obtained for the period 2009-2013 due to inability to search a pre-existing database. Thus, to ensure that cases were not missed, a search of liver biopsy results from 2003-2013 was performed. This yielded four additional cases from 2003-2009 and no extra cases from 2009-2013. The Liver Transplant Unit database search (method 3) was likely to be complete; however, this contributed only a small number of cases to this study (1%). We had expected to find more overlap between the four case-finding methods. However, given the private pathology AMA search was likely to have identified cases that are seen mainly in the private sector, it is not surprising that there was not a large percentage of cases that overlapped with the tertiary hospital search and the Austin Hospital's Liver Transplant Unit database search.

One of the limitations of this study is that Method 4, the private pathology AMA search, is likely to be an overestimate of PBC cases as the diagnosis of probable PBC was made with one positive AMA result and one set of cholestatic liver function tests. We acknowledge that this is likely to have potentially overestimated PBC cases. It is also important to point out that this fourth method would not have included cases that had pathology testing at the other small private pathology companies, although given they cover only 20% of private pathology testing in Victoria, this is unlikely to have had a significant impact on the overall prevalence.

In this current study, the disease prevalence in women older than 40 years (the group at greatest risk of this disease) was 336 per million compared with 188 per million in 2002. This translates to PBC developing in one in 2,986 women in this age group. This marked increase in disease prevalence in Victoria emphasises the need for awareness of the condition by general practitioners. Early diagnosis is crucial as the condition has an excellent prognosis when UDCA therapy is initiated before cirrhosis is established.²³ In addition, the recent data demonstrating efficacy of Obeticholic acid for patients who fail UDCA or can't tolerate the drug,²⁴ reinforces the need for early diagnosis.

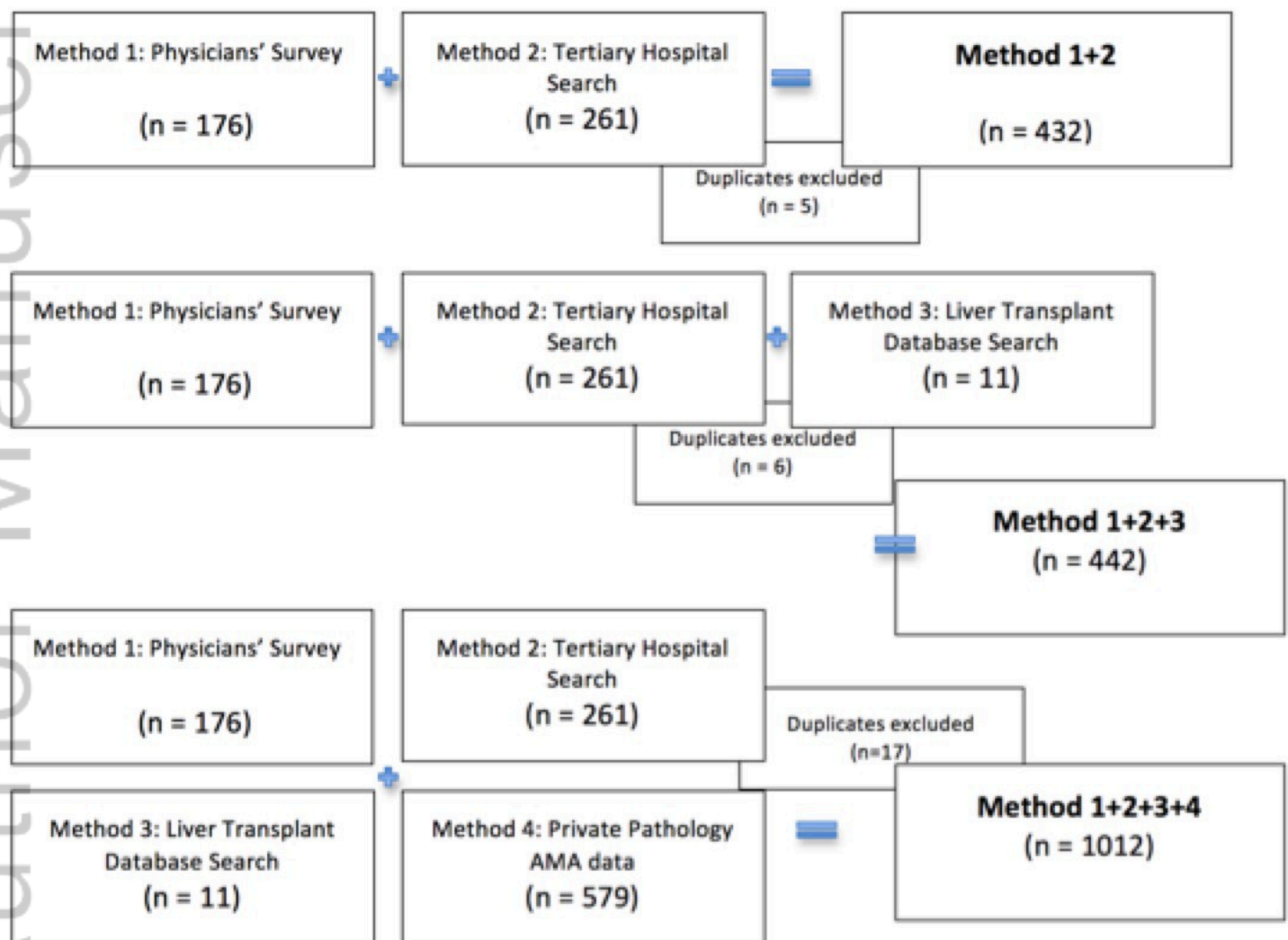
In conclusion, this study reveals a marked increase in the prevalence of PBC in Victoria, Australia. Once considered an extremely rare disease in Australia, this is no longer the case. Although the increase in disease prevalence in Victoria and other populations may have several possible explanations, it is tantalising to hypothesise that this may be partly due to changes in existing environmental triggers. The addition of a case-finding method that sensitively penetrates into primary health care and which identified a large percentage of cases has important implications for future PBC epidemiological studies.

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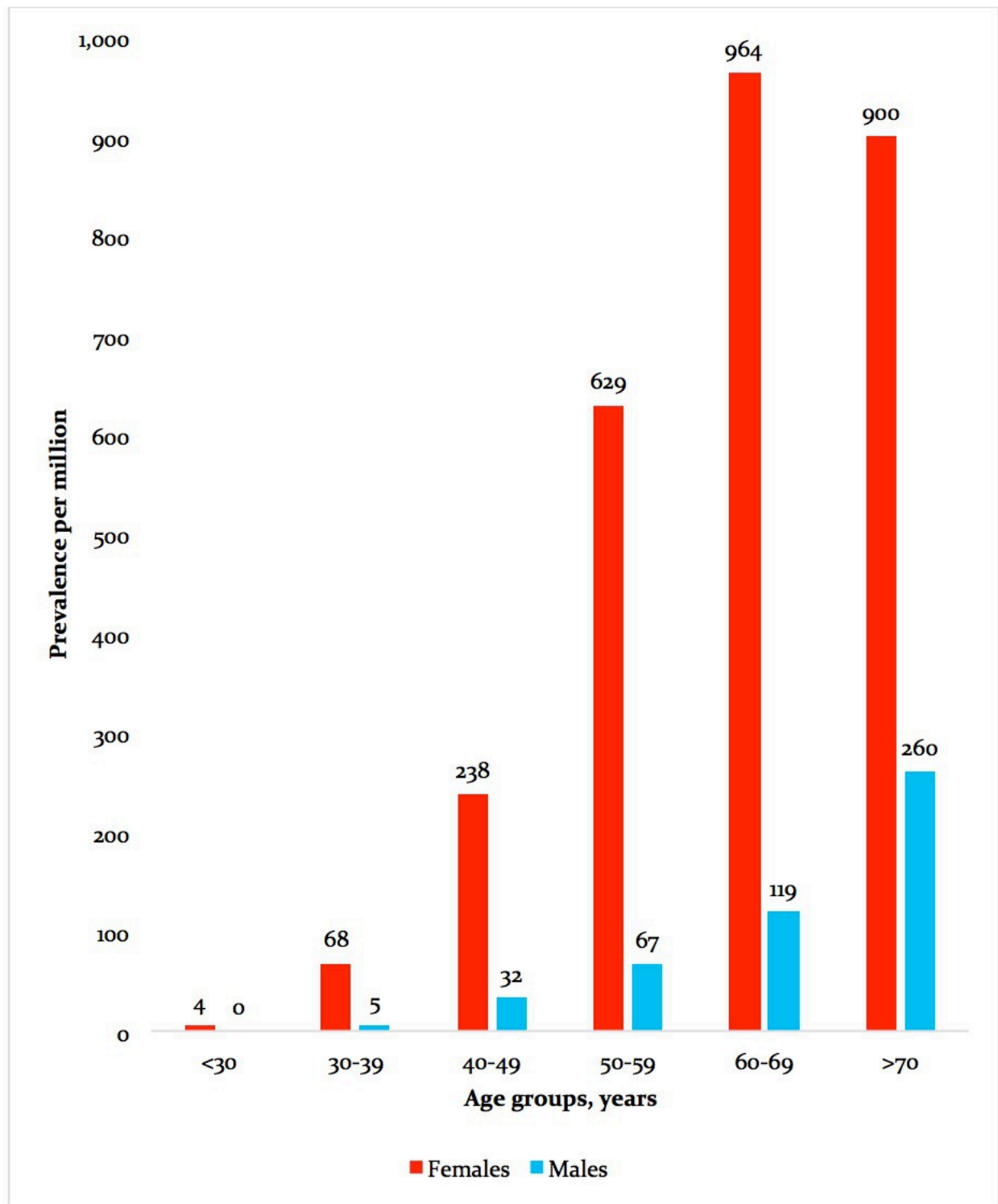
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Figure 1. Case identification using the four different case ascertainment methods.



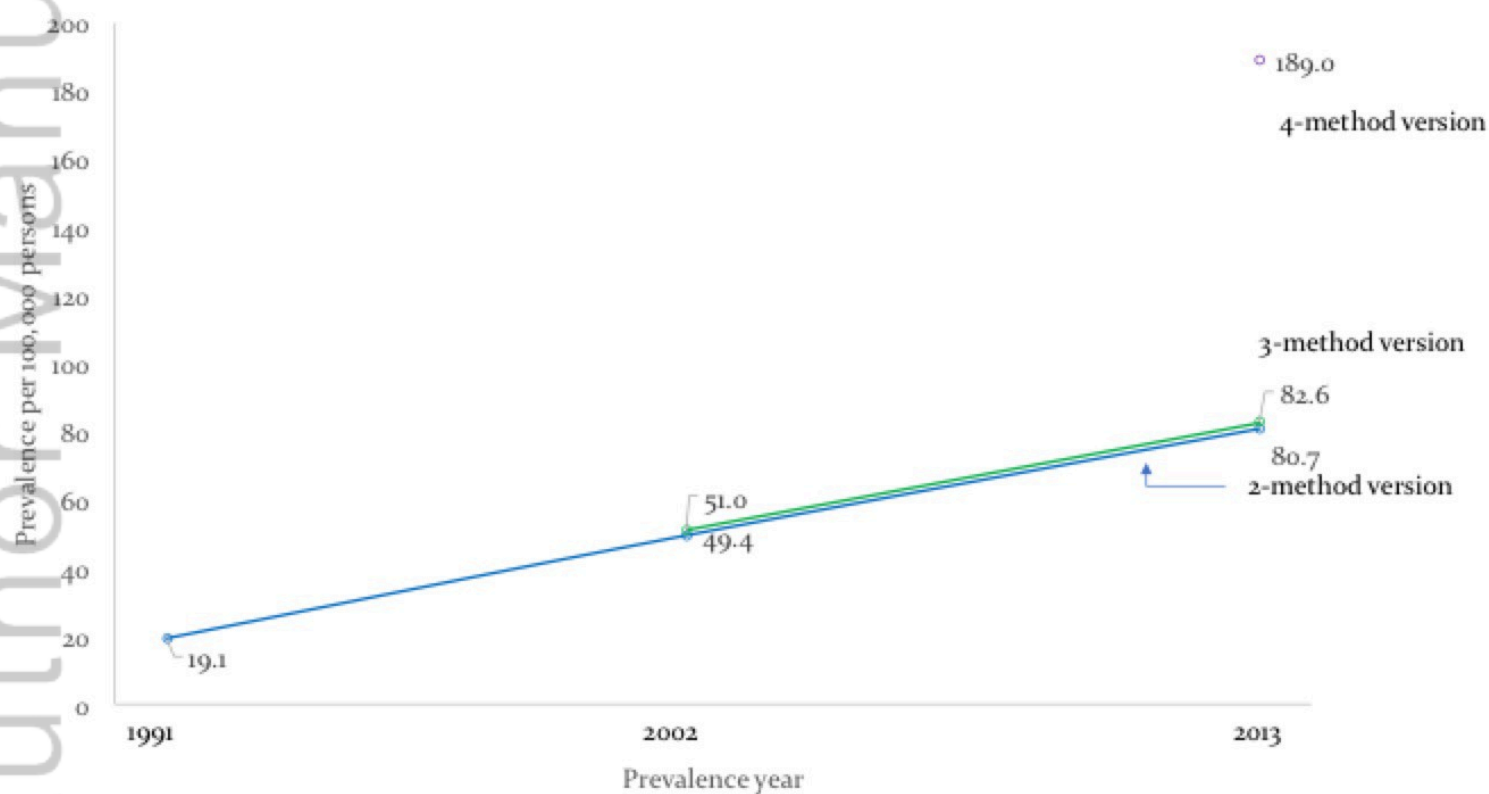
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Figure 2. 2013 prevalence estimates (using four case-finding methods) by age and stratified by sex.



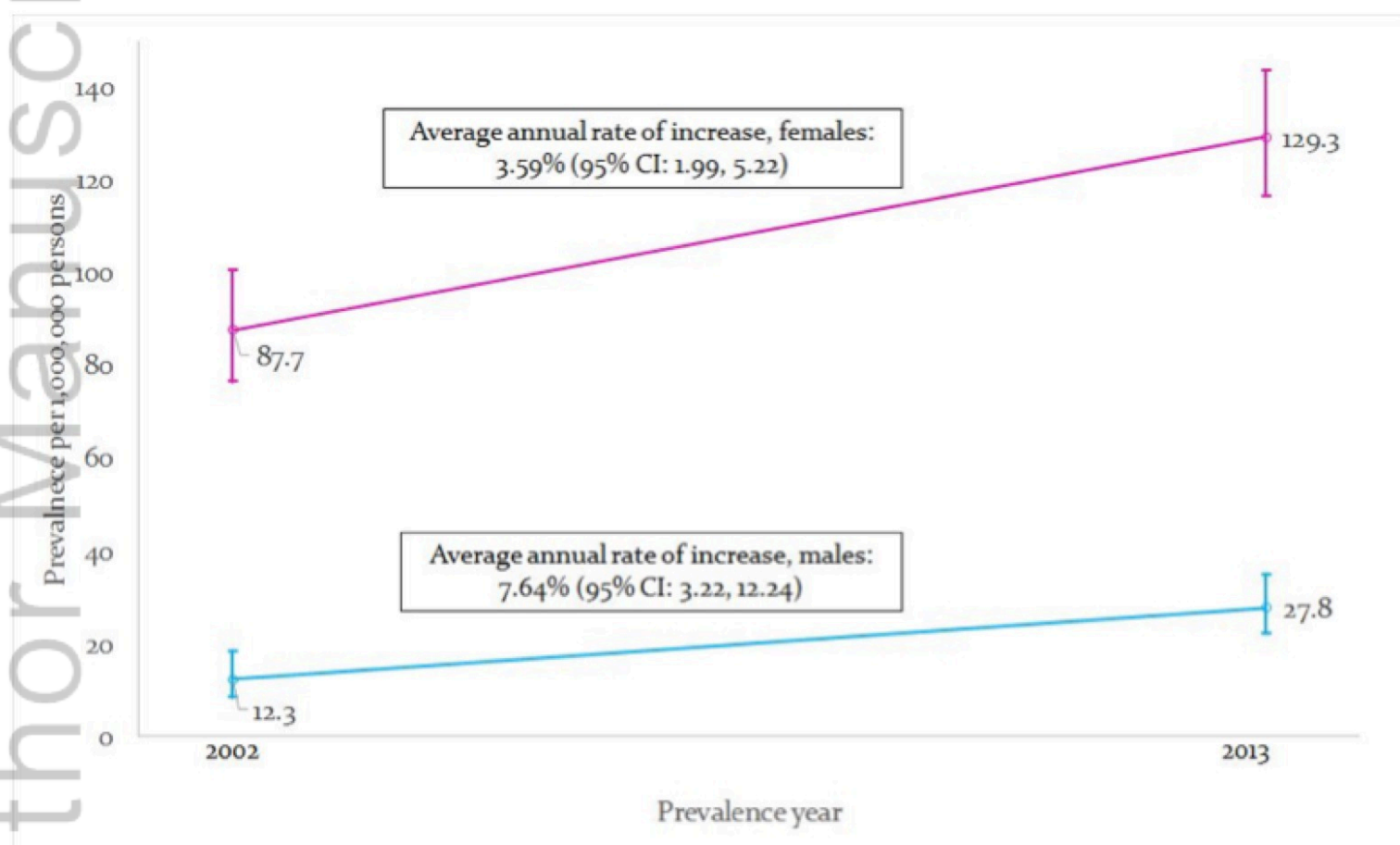
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Figure 3. Estimated PBC prevalence comparing 2, 3 and 4 case ascertainment methods.



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Figure 4. Sex Specific prevalence estimates over time.



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