Published in final edited form as:
Dig Liver Dis. 2013 July ; 45(7): 589–594. doi:10.1016/j.dld.2013.01.028.

Questionnaire Based Assessment of Risk Factors for Primary Biliary Cirrhosis

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Abstract

Background—Primary Biliary Cirrhosis is a cholestatic liver disease characterized by immune-mediated destruction of bile ducts. Its pathogenesis is largely unknown, although complex interactions between environment and genetic predisposition are proposed.

Aims—Identify disease risk factors using a detailed patient questionnaire and compare study findings to 3 published reports.

Methods—Questionnaire data were prospectively collected from 522 cases and 616 controls of the Mayo Clinic Primary Biliary Cirrhosis Genetic Epidemiology Registry. Case and control responses were compared using logistic regression, adjusting for recruitment age, sex, and education level.

Results—Cases reported ever regularly smoking cigarettes more frequently than controls ($P < 0.001$). History of urinary tract infection (UTI) was similar between groups; however, cases reported multiple UTIs more commonly than controls ($P < 0.001$). Frequency of other autoimmune disease was higher in cases than controls ($P < 0.001$). As well, prevalence of primary biliary cirrhosis among first-degree relatives was higher in case families than control families ($P < 0.001$).

Conclusions—Our study confirms prior reported risk factors associated with disease risk. Given the potential importance of gene and environment interactions, further examination of environmental risk factors considering genetic background may provide new insight into primary biliary cirrhosis pathogenesis.

Keywords

autoimmune; tobacco; cholestasis

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INTRODUCTION

Primary Biliary Cirrhosis (PBC) is an idiopathic cholestatic disease of the liver that affects predominantly women. PBC is characterized by immune-mediated destruction of the interlobular bile ducts leading to cholestasis and liver cirrhosis.[1] To date, the pathogenesis of PBC remains elusive, but is likely a result of complex interactions between genetic alleles and environmental exposures.[1,2] Such interactions could ultimately alter immune tolerance to self-antigens, potentially leading to chronic inflammatory destruction of intrahepatic bile ducts.

The role of environmental exposure in the pathogenesis of PBC is evidenced by increased disease prevalence in certain geographical locations and seasonal variations of disease diagnosis.[3,4] Moreover, a number of studies have also suggested various microorganisms and chemicals as other potential ecologic cues.[5–9] Recently, multiple genome-wide association studies have identified 22 loci that confer increased risk of disease illustrating the role of genetics beyond the evidence of high concordance among monozygotic twins[10] and familial aggregation of disease.[11,12]

The identification of reproducible risk factors for PBC is essential to better understand disease pathogenesis and to improve future treatment. In the past 10 years, studies from the United States, United Kingdom, and France have reported a few factors that consistently associate with increased risk of PBC including family history, smoking, and multiple urinary tract infections.[13–15] The impact of risk varies among these studies, likely the result of inherent biases associated with the case-control design and the protracted presentation of clinical symptoms from true disease onset. A future approach incorporating environmental and genetic data may also prove informative.

In this study, we aimed to discover novel risk factors for PBC as well as consolidate data regarding known PBC risk factors from previous studies. To accomplish this, we assessed information on demographics, environmental exposures, and lifestyles; as well as personal and familial medical history using a self-administered questionnaire, which was sent to enrollees of the using the *Mayo Clinic PBC Genetic Epidemiology* (MCPGE) *Registry*, which includes PBC cases and clinic-based controls. Comparison of our data with prior studies will not only support published findings, but also provide validation of our cases for the future pursuit of genetic and environmental interactions that possibly confer increased risk of disease.

METHODS

PBC Cases and Controls

The first 522 cases with PBC and 616 controls who completed questionnaire data as part of the MCPGE Registry were included in this study. Details regarding the establishment of the MCPGE Registry have been described previously.[16] The diagnosis of PBC was based on clinically accepted standards including a history of six or more months of biochemical cholestasis, the presence of AMA in serum, and compatible liver biopsies of patients with no evidence of other known liver disease. The diagnosis of “AMA negative” PBC was made on the basis of chronic (i.e., six or more months) biochemical cholestasis and compatible liver biopsies in the absence of detectable AMA in serum. The control group was recruited from the Mayo Clinic Division of General Internal Medicine. The Mayo Clinic Investigational Review Board approved all study methods and study participants provided written informed consent.

Questionnaire Development, Distribution, and Collection

The questionnaire was developed by the Mayo Clinic Survey Center. It collects information regarding demographics, anthropometric features, education, lifestyle and environmental exposures as well as extensive personal and familial medical history. The survey consists of 70 primary questions and 300 secondary queries covering thirty-seven pages. This study instrument was given directly or mailed to consented participants along with a pre-paid return envelope. In the case of study participants who did not return the first questionnaire, a second questionnaire was mailed within two months of the initial contact. Study questionnaires were completed by 522/616 cases (85%) and 616/734 controls (84%) between January 2004 and March 2010.

Data Entry and Statistical analysis

Questionnaire responses were double entered into a SAS database. Each question was summarized by descriptive statistics for both PBC cases and controls. Considering that age, sex, and education level significantly differed between cases and controls, descriptive statistics were adjusted to reflect PBC case distributions by weighting the control data according to the proportions of PBC cases in each combination of age, sex, and education category. This adjustment allows visual comparison of the descriptive statistics between cases and controls, and provides consistency with P-values for testing the differences in case/control status. The P-values were calculated from a multivariable logistic regression model that included the questionnaire item, age, sex, and education. The method of generalized estimating equations was utilized to compare the effects of having family history of PBC between cases and controls in first-degree and second-degree relatives. Each family member was included in analysis, the endpoint was PBC or another autoimmune disease, and the independent variable was proband status (i.e., family member was from a PBC case or control family). This method takes into account the relatedness in family members. Lastly, a multivariable logistic model was fit where variables were selected using a forwards model selection approach with adjustment for age, sex, and education. The analysis was run using SAS 9.2 (SAS Institute Inc., Cary, NC), and a P-value of 0.05 was considered significant.

RESULTS

Demographics

Demographic indices of PBC cases and controls are shown in Table 1. A majority of cases were female (91%), Caucasian (97%), and AMA positive (90%, data not shown). The median age of PBC diagnosis was 55 years with a median age at enrollment of 59.8 in cases and 60.2 in controls ($P = 0.06$). Education level was significantly different between the 2 groups, with controls reporting higher education with professional training beyond college more often than PBC cases (31% vs. 18%).

Medical History

History of other reported autoimmune disease (celiac sprue, Sjögren's syndrome, Raynaud's syndrome, rheumatoid arthritis, or autoimmune hepatitis) was higher in PBC cases compared to controls ($P < 0.001$), with Sjögren's syndrome (14% vs. 1%, $P < 0.001$), Raynaud's syndrome (13% vs. 4%, $P < 0.001$) and autoimmune hepatitis (7 % vs. 0%, $P < 0.001$) individually more frequent among PBC cases (Table 2). History of urinary tract infection (UTI) did not differ between the two groups (39% vs. 37%, $P = 0.41$). However, reporting multiple episodes of UTI, defined as having more than 1 episode per year, was more common among cases than controls (29% vs. 19%, $P < 0.001$). No difference in frequency of surgery between cases and controls was found for the majority of the assessed

surgical procedures. However, cholecystectomy (34% vs. 17%, $P < 0.001$) and tonsillectomy (51% vs. 44%, $P = 0.01$) were more common among cases. Moreover, the difference in tonsillectomy rate was even more significant when limited to those having the procedure during childhood (<19 years old) (45% vs. 36%, $P = 0.001$). PBC cases reported higher rates of symptomatic gastroesophageal reflux (39% vs. 28%, $P < 0.001$), thyroid disease (28% vs. 20%, $P < 0.001$), and cholelithiasis (32% vs. 19%, $P < 0.001$) than controls. The frequencies of other assessed diseases did not differ between the groups and are provided in supplemental Table S2.

History of Childhood Diseases and Immunizations

The history of reported childhood diseases and immunizations for cases and controls are shown in Table 3. PBC cases reported significantly more episodes of measles than controls (64% vs. 56%, $P = 0.01$), despite no significant difference of measles vaccination. More so, the rate of small pox vaccination was higher in cases compared to controls (65% vs. 57%, $P = 0.01$), whereas the rate of rubella vaccination was higher in the controls compared to the cases (37% vs. 29%, P = 0.05).

Gynecologic and Reproductive History

The reproductive history of the 474 female PBC cases and 460 controls enrolled in this study was assessed (Table 4). The median age at menarche and menstrual cessation of the case and control groups were similar. As well, no significant difference between cases and controls in regards to number of pregnancies, age of first pregnancy, and number of live births was found. However, PBC cases more frequently reported symptomatic pruritus during pregnancy (14% vs. 6%, $P = 0.01$). Though the frequencies of birth control pill use, hormone replacement therapy, and age of menopause were similar between PBC cases and controls, the duration of oral contraceptive use was significantly less in cases (29% vs. 20%, $P = 0.02$).

Family History

We assessed history of PBC in first-degree relatives (FDRs) and second-degree relatives (SDRs) of PBC cases and controls. The 522 PBC-pedigrees included 3,860 FDRs and 5,737 SDRs, whereas the 616 control-pedigrees consisted of 4,133 FDRs and 6,252 SDRs. The PBC case families had a higher overall prevalence of PBC among the FDRs than the control families (1.3% vs. 0.2%, $P < 0.001$). However, the reports of PBC among SDRs were exceedingly rare in both case and control families and not statistically different (0.2% vs. 0%, $P = 0.15$). Among other autoimmunities, autoimmune thyroid disease was more commonly reported in relatives of PBC cases (FDRs: 6.5% vs. 4.4%, $P = 0.003$; SDRs: 2.3% vs. 0.7%, $P < 0.001$).

Health, Lifestyle, and Environmental Exposures

A history of regular cigarette smoking, defined as lifetime smoking of more than 100 cigarettes, was reported by 53% of PBC cases compared to 40% of controls ($P < 0.001$). The total duration as a regular smoker was slightly longer among PBC cases compared to controls (22.0 years vs. 21.0 years, $P = 0.04$), with a median of 10.5 pack-years smoked by cases prior to the diagnosis to PBC (Table 5). Both the age when individuals started smoking and current smoking status were not found to be significantly different between the groups.

A history of second-hand smoke exposure was investigated by assessing the frequency and duration of contact with smokers both at home and at work. Lifetime exposure to second-hand smoke at home (81% vs. 73%, $P = 0.01$) was significantly higher in PBC cases

compared to controls. There was no difference between the groups in regards to exposure at work, although among the exposed, the total number of years of second-hand smoke was higher in the cases ($P < 0.001$).

The control group more often than cases reported any history of alcohol consumption or active drinking ($P = 0.03$, $P < 0.001$). For individuals that ever consumed alcohol, the duration of consumption was found to be lower among cases than controls (29.5 years vs. 35.0 years, $P < 0.001$). The consumption of caffeinated beverages (i.e., coffee, tea and soda) by the two groups was also assessed, and no difference in the frequency or duration of consumption was found (data not shown).

In regards to potential toxic exposures, there was no evidence of more frequent exposure to or duration of pesticides use (i.e., farm use, commercial application, utility in home or garden) in cases compared to controls (data not shown).

PBC cases reported having worse overall health during the 12 months prior to completing the questionnaire ($P < 0.001$) (supplemental Table S1). The frequency of moderate and vigorous physical activity was found to be lower among cases compared to controls ($P < 0.001$), yet there was no significant difference in the overall intensity of daily physical activity reported by the groups. Moreover, the frequency of physical activity during leisure time was found to be significantly less among cases compared to controls ($P < 0.001$).

We found no difference in the reported use of fat/oils in cooking between the groups (data not shown). However, cases reported less consumption of fruit and vegetables ($P = 0.002$, and $P < 0.001$, respectively) and also utilized one-a-day vitamins less frequently compared to the control group ($P = 0.03$) (data not shown).

Multivariable Analysis

A multivariable logistic regression model predicting cases was created using a forward model selection approach after adjusting for age, sex, and education level (supplemental Table S3). A history of regular smoking (OR: 1.56, $P < 0.001$), autoimmune hepatitis (OR: 2.86, $P = 0.002$), Raynaud's syndrome (OR: 2.86, $P < 0.001$), Sjögren's syndrome (OR: 7.62, $P < 0.001$), and measles infection (OR: 1.49, $P = 0.005$) remained significantly associated with increased risk for the development of PBC.

DISCUSSION

Using the MCPGE Registry we have conducted the largest single-center case-control study evaluating PBC risk factors to date. Our findings of family history of PBC, personal history of autoimmune disease, smoking, and multiple urinary tract infections were significant risk factors for disease development support three proceeding observational studies.[13–15] Direct comparison of case-control studies can be a challenging given the variability among the tools utilized to collect epidemiologic risk factor data. We have provided an extensive comparison of existing study data for PBC risk between three prior studies and our own (Table 6).

Our cases appeared to be similar to the prior studies in terms of sex makeup (91% female), median age of PBC diagnosis (55 years), and median age at time of questionnaire completion (59.8 years).[13–15] As expected, autoimmune disease (celiac sprue, Sjögren's, Raynaud's, RA, or AIH) were reported more by PBC cases than controls (Table 2). Unlike the Corpechot study[15], we could not denote the timing of autoimmune disease onset, but our findings do support previously identified Sjögren's syndrome (14%), Raynaud's syndrome (13%) and autoimmune hepatitis (7 %) as the most frequently associated autoimmune

diseases among PBC cases (Table 2). In terms of other medical history, we observed more frequent symptomatic gastroesophageal reflux (GERD) (39%) and multiple urinary tract infections (UTIs) (29%) in cases vs. controls. Although not always clearly defined, a history of multiple UTIs has been demonstrated in all three prior studies (Table 6). This uniformity strongly supports a possible infectious hypothesis as a contributor for disease development.[17] We also showed that cases undergo tonsillectomy at any age (51%) and before the age of 19 years (45%) more frequently than controls. These findings were congruent with both the Gershwin[13] and Prince[14] studies. Overall, our findings do suggest that recurrent infections could contribute to development of PBC, possibly through altered immune tolerance mechanisms.

We assessed vaccinations similarly to Corpechot, but we are the only study to assess the frequency of childhood illnesses in cases and controls. As seen in Table 3, we observed significantly higher rates of immunization for small pox in PBC cases vs. controls, whereas rubella immunization rates were significantly lower in cases. The Corpechot study[15] reported statistically significantly lower vaccination rates in PBC cases for all vaccinations as well for individual vaccinations including tetanus, influenza, poliomyelitis, and pertussis. However, our data do not replicate these findings. Interestingly, despite a similar vaccination rate of measles between groups, we did find significantly more history of measles within the cases than controls (Table 3) that remained statistically different in the multivariate model (supplemental Table S3). This unique finding supports a possible role of a maladaptive immune response underlying PBC, however the result should be interpreted with caution given the self-reporting nature of the survey. Nonetheless, this phenomenon is also supported by recent PBC candidate genes studies, which have implicated multiple genetic loci, many with significant overlap of other autoimmune disorders and associated with immune tolerance and response pathways.[12]

Our study verifies prior reports of significant history of smoking[13–15] associating with PBC risk (Table 6). In addition, we also showed that cases smoked cigarettes for significantly more years on a regular basis than controls (Table 5). Our findings strongly reaffirm prior reports of a clear association of smoking and PBC development, but may also underline an important aspect of disease modification. A recent retrospective study from the United States reported that smoking may accelerate PBC progression based on data that frequency and amount of regular smoking (i.e., number of pack-years) were significantly associated with advanced histological disease stage (i.e., stage III/IV) at disease presentation.[18]

We also assessed second-hand smoke exposure at home and work. We found that PBC cases were more frequently exposed to second-hand smoke at home, but the total years of exposure were not different between cases and controls (Table 5). In contrast, the reported frequencies of second-hand smoke exposure at work was similar between cases and controls, but the duration of exposure was higher in the cases (data not shown). This finding suggests that perhaps the exposure to various chemical components of cigarette smoke, even passively, may confer an elevated risk for PBC. In the home, cases were more likely to have prolonged and continuous exposures to various components of cigarettes than at work, thereby requiring less time to accumulate the overall risk. The findings from our survey support the hypothesis of an effect of inhaled substances from tobacco on the alteration of immune tolerance, which has been suggested for other autoimmune diseases.[19]

We also examined the familial history of PBC within pedigrees of the 522 PBC cases and 616 controls. We found that the risk for developing PBC was 5.7 times higher among FDRs of PBC cases compared to FDRs of controls. There was no statistical difference of PBC between the SDRs of cases and controls. However, the controls did not report any cases of PBC within SDRs, whereas cases reported PBC frequency in SDRs at 0.2%. This is the first

study wherein not only FDRs, but also SDRs of PBC cases and controls were assessed for PBC. The increased frequency of PBC among FDRs, but not SDRs, of affected probands strongly supports the genetic contribution to PBC.

To our knowledge, this is the first study to explore the dietary habits and activity level of PBC cases. In addition to reporting poorer overall health in the prior 12 months, cases were less likely to be involved in physical activity during leisure time. Our study also demonstrates PBC cases consume vegetables, fruits, and one-a-day vitamins less frequently than controls (supplemental Table S2). At this point, it is difficult to dissect the mechanism by which poor lifestyle choices and dietary habits contribute to PBC. However, our findings suggest diet and lifestyle could be patient modifiable factors that likely impact disease development and progression. Nonetheless, future studies are required to confirm these novel observations and examine their potential effect on patient outcomes.

Previous studies have reported relatively similar results regarding various reproductive factors associated with PBC.[13–15] Notably, a small epidemiologic study showed that PBC patients have had more pregnancies in comparison to controls, but this has not been reproduced.[20] We found age of menstruation or menopause onset, number of pregnancies, number of live births, and age at first or last pregnancy, were not different between cases and controls (Table 4). Similar to Corpechot[15], our univariate analysis showed that longer use of oral contraceptives may be protective against PBC. Indeed, Alvaro *et al.*, has shown an altered distribution of estrogen receptors in liver samples of patients with different stages of PBC.[21] However, further studies are necessary to understand the potential roles of hormonal fluctuations, fetal microchimerism, and pregnancy in the pathogenesis of PBC. Similar to prior studies[15], itching during pregnancy was found to occur more frequently among PBC cases compared to controls suggesting that hormonal fluctuations during pregnancy may unmask a tendency for intrahepatic cholestasis.

Similar to prior observational PBC studies, there are limitations of our investigation. Our study is comparatively moderate in size and a majority of the patients of the MCPGE Registry are referral cases to our medical center and therefore, may represent individuals with more medical comorbidities. However, the MCPGE Registry survey was an extensive measure of demographics, anthropometric features, education, lifestyle, environmental exposures, and extensive personal and familial medical history.

In conclusion, this study reports on the association between a number of risk factors and PBC from a tertiary medical center using a case-control study design. This was a complementary investigation aimed at confirming formerly reported risk factors of PBC as well as examining ones not previously assessed by utilizing a different epidemiologic survey. Our data suggest that history and duration of smoking, second-hand smoke exposure, autoimmune disease, multiple urinary tract infections, and having a first- (but not a second-) degree relative with PBC are associated with increased PBC risk. In the future, an enhanced assessment of PBC pathogenesis will require evaluation of the interaction between environmental risks (i.e., non-genetic) along with genetic variables. Given that the MCPGE Registry confirms the known risk factors of PBC and is directly linked to a biospecimen repository, we are strongly positioned to pursue gene environment interaction studies that may better elucidate the pathogenesis and progression of PBC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are thankful to the PBC patients and controls of this study.

Support: This research was supported by grants to Dr. Lazaridis from the NIH (RO1 DK80670) and A. J. and Sigismunda Palumbo Charitable Trust, as well as a grant to Dr. Lammert from the American Liver Foundation.

Abbreviations

AIH	Autoimmune hepatitis
AMA	anti-mitochondrial antibodies
FDR	first-degree relative
MCPGE Registry	Mayo Clinic PBC Genetic Epidemiology Registry
PBC	primary biliary cirrhosis
SDR	second-degree relative
SLE	systemic lupus erythematosus
UTI	urinary tract infection

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Table 1

Demographics of Primary Biliary Cirrhosis cases and controls.

	PBC	Controls	P-value
Sex (female)	474 (91%)	460 (75%)	< 0.001
Median age at enrollment (years)[#]	59.8 (27.9 – 84.6)	60.2 (23.0 – 84.3)	0.06
Median age at diagnosis (years)[#]	55.0 (25.0 – 85.0)	--	
Education Level			
High School or Less	156 (30%)	115 (19%)	< 0.001
College/vocational school	269 (52%)	307 (50%)	
Professional training beyond college	94 (18%)	189 (31%)	
Race (Caucasian)	97%	99%	0.08[*]

PBC: Primary Biliary Cirrhosis

[*] adjusted for age at time of recruitment, gender, and education

[#] variables summarized as median (min - max)

Table 2

Autoimmune disease in Primary Biliary Cirrhosis cases and controls.

	PBC	Controls	P-value*
Autoimmune hepatitis	7%	0%	< 0.001
Celiac sprue	1%	0%	0.16
Raynaud's syndrome	13%	4%	< 0.001
Rheumatoid arthritis	8%	7%	0.12
Sjögren's syndrome	14%	1%	< 0.001
Diabetes Mellitus diagnosed before age 21	1%	0%	0.29
Diagnosis of any autoimmune disease (Celiac sprue, Sjögren's, Raynaud's syndrome, Rheumatoid arthritis or Autoimmune hepatitis)	33%	11%	< 0.001

PBC: Primary Biliary Cirrhosis

*adjusted for age at time of recruitment, gender, and education

Table 3

Childhood disease and immunizations in Primary Biliary Cirrhosis cases and controls.

	PBC	Controls	P-value*
Childhood diseases			
Chickenpox	70%	70%	0.98
Measles	64%	56%	0.01
Mumps	54%	53%	0.78
Rheumatic fever	4%	4%	0.35
Rubella (i.e. German measles)	30%	30%	0.74
Immunizations			
Influenza	73%	76%	0.42
Measles	38%	43%	0.32
Mumps	31%	39%	0.06
Rubella (i.e. German measles)	29%	37%	0.05
Smallpox	65%	57%	0.01
Pertussis	43%	43%	0.8
Pneumococcal	45%	42%	0.23
Polio	79%	82%	0.37

PBC: Primary Biliary Cirrhosis

* adjusted for age at time of recruitment, gender, and education

Table 4

Gynecologic and reproductive history of female Primary Biliary Cirrhosis cases and controls.

	PBC	Controls	P-value*
Median age at first menarche#	13.0 (9.0 – 17.0)	13.0 (8.0 – 19.0)	0.84
Median age menstruation ceased#	48.0 (21.0 – 59.0)	48.0 (20.0 – 65.0)	0.56
Ever pregnant	90%	88%	0.27
Median number of pregnancies#	3.0 (0.0 – 10.0)	3.0 (0.0 – 15.0)	0.7
Median number of live births#	2.0 (0.0 – 7.0)	2.0 (0.0 – 9.0)	0.11
Median age at first pregnancy#	21.5 (15.0 – 46.0)	22.0 (14.0 – 37.0)	0.29
Pruritus during pregnancy	14%	6%	0.01
Oral contraceptives			
Ever taken contraceptives	75%	75%	0.82
Median age of contraceptive start#	21.0 (12.0 – 45.0)	21.0 (14.0 – 45.0)	0.07
Number of years using contraceptives			0.02
Less than 1 year	17%	10%	
1–5 years	35%	39%	
6–10 years	27%	22%	
11 or more years	20%	29%	
Hormone replacement therapy			
Ever taken hormone replacement	64%	61%	0.15
Median age hormone replacement started#	49.0 (14.0 – 69.0)	48.0 (15.0 – 70.0)	0.11

PBC: Primary Biliary Cirrhosis

*adjusted for age at time of recruitment and education

#variables summarized as median (min - max)

Table 5

Smoking history of Primary Biliary Cirrhosis cases and controls.

	PBC	Controls	P-value*
Smoking			
Ever regularly smoked cigarettes	53%	40%	< 0.001
Median age started smoking#	18.0 (10.0 – 58.0)	18.0 (12.0 – 50.0)	0.34
Currently smoking cigarettes regularly	14%	13%	0.29
Median years as regular smoker#	22.0 (1.0 – 56.0)	21.0 (0.0 – 60.0)	0.04
Median number pack years prior to PBC diagnosis#	10.5 (0.3 – 88.0)	--	
Second-Hand Smoke Exposure			
Ever lived with a smoker	81%	73%	0.01
Ever worked with a smoker	55%	50%	0.24

PBC: Primary Biliary Cirrhosis

*adjusted for age at time of recruitment, gender, and education

#variables summarized as median (min - max)

Table 6

Summary of odds ratios from published Primary Biliary Cirrhosis case-control risk factor studies: familial, medical, and reproductive measures.

	Corpechot[15]	Prince[14]	Gershwin[13]	MCPGE Registry
PBC cases	*222*	*318 Epidemiological Cases* * *2,258 Foundation Cases* **	*1,032*	*522*
Controls	*509*	*2,438*	*1,041*	*616*
Family history of PBC	*OR = 6.8 (FDR)*	OR = 2.3 * OR = 4.4 **	*OR = 10.7 (FDR)* OR = 12.1	OR = 5.7 (FDR)
Sjögren syndrome	*OR = 11.9*	n/a	OR = 22.7	OR = 10.2 ($P < 0.001$)
Family history of Sjögren syndrome	NS	n/a	*OR = 5.8*	n/a
Raynaud syndrome	*OR = 7.2*	n/a	OR = 5.7	OR = 3.8 ($P < 0.001$)
History of autoimmune disease	OR = 6	n/a	OR = 3.2	OR = 4.2 ($P < 0.001$)
Tobacco				
Current	OR = 1.7	OR = 1.5 *, OR = 1.4 **	OR = 2	OR = 1.4 ($P = 0.29$)
Significant history	NS	*OR = 1.6**, *OR = 1.5*** OR = 1.6 *, OR = 1.6 **	*OR = 1.6*	OR = 1.6 ($P < 0.001$)
Second-hand exposure	OR = 3.5	n/a	n/a	OR = 1.6 ($P = 0.01$)
Urinary tract infections	*OR =2.7*	*OR = 2.1**, *OR = 1.8*** OR = 2.4 *, OR = 1.7 **	*OR = 1.5* OR = 1.4	OR = 1.7 ($P < 0.001$)
Tonsillectomy	NS	*OR = 2.4**, *OR = 1.7*** NS *, OR = 1.7 **	OR = 1.3	OR = 1.5 ($P = 0.001$)
Cholecystectomy	OR = 1.8	n/a	OR = 1.8	OR = 2.6 ($P < 0.001$)
Any type vaccine	OR = 0.4	n/a	n/a	n/a
Tetanus vaccine	OR = 0.3	n/a	n/a	n/a
Influenza vaccine	OR = 0.3 n/a	n/a n/a	n/a n/a	OR = 0.9 ($P = 0.42$) OR = 1.4 ($P = 0.01$)
Measles				
OCP	*OR = 0.6* OR = 0.7	n/a	NS	OR = 1.0 ($P = 0.82$)
HRT	NS	n/a	*OR = 1.5* OR = 1.6	OR = 1.2 ($P = 0.15$)

	Corpechot[15]	Prince[14]	Gershwin[13]	MCPGE Registry
Pregnancy pruritus	*OR = 3.9*	*OR = NS**, *OR = 2.1*** OR = 2.1*, OR = 2.2**	n/a	OR = 2.0 (*P* = 0.01)
Abortion	*OR = 2*	n/a	n/a	n/a

PBC: Primary Biliary Cirrhosis

OR: Odds Ratio

MCPGE Registry: Mayo Clinic PBC Genetic Epidemiology Registry

FDR: Analysis included first-degree relatives only

OCP: Oral Contraceptive Pills

HRT: Hormone replacement therapy

NS: Not statistically significant

n/a: not available for analysis

Italics: Odds ratio calculated from associated study multivariate analysis

* Epidemiologic cases[14]

** Foundation cases[14]