Autoimmune Hepatitis and Immune-Mediated Cholestatic Liver Diseases

16

Albert J. Czaja

Abstract

Autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis are immune-mediated chronic liver diseases of uncertain cause that have a global distribution and highly variable occurrence. The goals of this review are to describe the epidemiological studies that have identified the populations at risk, estimated the incidence and prevalence of each disease, suggested environmental and genetic bases for their occurrence, and indicated trends that should direct the allocation of healthcare resources and investigational efforts. Population-based epidemiological studies have described patterns of susceptibility for each liver disease that reflect predilections for certain age groups, gender, geographical regions, and ethnic background. Familial studies and genetic analyses have implicated a genetic predisposition for each disease, and population-based studies have suggested associations with triggering agents, including pollutants, xenobiotics, viruses, bacteria, and the intestinal microbiome. Variations in prevalence between ethnic groups within regions or between countries may reflect differences in early diagnosis, management, and outcome, and the increasing incidence of these diseases in certain regions and ethnic groups may help identify pivotal etiological factors that might be modified. Population-based epidemiological studies are lacking in China, India, and developing countries, and they are needed to complete the global perspective of these diseases and their consequences. In conclusion, autoimmune hepatitis and the immune-mediated cholangiopathies are rare, but they constitute a global healthcare burden that is increasing in certain geographical regions and ethnic groups. Populations at risk and susceptibility factors must continue to be characterized, and interventions must be tailored to meet individual and regional needs.

A. J. Czaja
Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine and Science, Rochester, MN, USA
e-mail: czaja.albert@mayo.edu

R. J. Wong, R. G. Gish (eds.), *Clinical Epidemiology of Chronic Liver Diseases*,
https://doi.org/10.1007/978-3-319-94355-8_16

Keywords
Autoimmune hepatitis · Primary biliary cholangitis · Primary sclerosing cholangitis · Epidemiology

16.1 Introduction

Population-based epidemiological studies are essential for understanding the genetic susceptibilities and the possible antigenic triggers of autoimmune liver disease [1, 2]. They are also necessary to correctly allocate resources for improving the early diagnosis and management of this disease category [3]. Autoimmune liver disease encompasses acute and chronic forms of liver injury that are defined by cell- and antibody-mediated immune responses that lack a definable etiological agent [4]. They may have variable clinical phenotypes and severity, but they all tend to be persistent, progressive, and variably responsive to current therapies. Autoimmune hepatitis is the prototypic autoimmune liver disease, and primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) complete the disease category. Variant phenotypes also exist in which the features of autoimmune hepatitis can be intermixed with those of PBC or PSC [5–7]. The lack of codified diagnostic criteria for these variant or overlap syndromes and uncertainty about their pathogenic basis have limited the performance of epidemiological studies that clarify their disease burden.

Autoimmune liver disease is a consequence of misdirected and dysregulated immune responses against self-antigens in a genetically susceptible individual [4]. The triggering antigens may reflect molecular mimicry between environmental or infectious agents and normal proteins within the liver [8]. Chronic or repeated exposures to these extrinsic agents may break immune tolerance of these normal self-proteins, and liver-infiltrating, antigen-sensitized, cytotoxic T lymphocytes may initiate and sustain hepatic injury [4, 9, 10]. The class II molecules of the major histocompatibility complex (MHC) can contribute to the presentation of antigens, sensitization of T helper lymphocytes, and differentiation of the activated immune cells along cytokine-mediated pathways that result in cellular- and antibody-dependent immune responses [11–16]. Genetic factors outside the MHC, including polymorphisms of genes that influence the production of various cytokines and immune modulators, may also affect the propensity for tissue damage and its severity [17, 18]. Epigenetic factors that influence the transcriptional activity of regulatory genes without altering the sequence of deoxyribonucleic acid (DNA) can unbalance homeostatic mechanisms that maintain immune tolerance of self-antigens, alter susceptibility for immune-mediated disease, and create an inheritable trait that has transgenerational consequences [19–21].

Autoimmune liver disease has a global distribution, and its occurrence varies between ethnic groups within the same geographical region, in different age groups, and in different countries [1, 22]. The diversity of individual susceptibilities for

autoimmune liver disease may reflect genetic and epigenetic differences and variations in the nature and duration of exposure to environmental and microbial antigens within a specific age range or geographical location [21, 23]. Region-specific environmental antigens may derive from water and food sources, industrial pollutants, or toxic waste sites [24], and the microbial antigens may be indigenous infectious agents [25] or region-specific microflora within the intestinal microbiome that are affected by factors such as diet, sanitation, socioeconomic status, and antibiotic exposure [26–32]. Epigenetic alterations in gene activity can be induced by these environmental factors [33, 34], and they can influence the risk for immune-mediated disease in individuals and their progeny in different geographical regions and ethnicities [35]. Population-based epidemiological studies are key mechanisms by which to identify these antigenic sources and develop management strategies that impact on disease occurrence.

Autoimmune liver disease constitutes only a fraction of patients with chronic liver disease, but it affects most individuals during productive phases of life [3]. Accordingly, its indirect costs due to years of productive life lost may far exceed its direct costs for medical care [3]. Furthermore, the recognition of differences in liver-related mortality among different ethnic groups in the same geographical region can direct efforts to understand and improve outcomes [36]. Hispanics in the United States have an overall liver-related mortality that is 49% higher than in non-Hispanic whites (13.7 cases per 100,000 persons versus 9.2 cases per 100,000 persons) and 82% higher than in African Americans (13.7 cases per 100,000 persons versus 7.5 cases per 100,000 persons) [37]. The proper allocation of medical resources, the formulation of healthcare policies, and the direction of future investigation in the autoimmune liver diseases require epidemiological studies that define the burden of each disease type in the general population and in different ethnic groups within that population.

The goals of this review are to describe the epidemiology of autoimmune hepatitis, PBC and PSC and to indicate how continued strengthening of this knowledge base can clarify pathogenic mechanisms, identify at risk subgroups, and direct the allocation of healthcare resources and future investigational efforts.

16.2 Epidemiology of Autoimmune Hepatitis

Population-based studies that have estimated the incidence and prevalence of autoimmune hepatitis have been performed in Alaska [38], Australia [39], Denmark [40], southern Israel [41], the Netherlands [42], New Zealand [43], Norway [44], Singapore [45], Spain [46, 47], and Sweden [48]. Population-based studies within the United States have been performed mainly in the pediatric population [49] (Table 16.1). These assessments have indicated the rarity of autoimmune hepatitis (defined as an annual incidence less than 50 cases per 100,000 persons [50]) and the regional variability of its occurrence [38–42, 45]. Countries with healthcare systems that provide universal access, systematic data accumulation, and prescribed follow-up examinations (Sweden, Netherlands, Denmark, Norway, and New Zealand) have

Table 16.1 Incidence and prevalence of autoimmune hepatitis in different regions (lowest to highest annual incidence)

Geographical region	Annual incidence per 100,000 persons	Prevalence per 100,000 persons
Canada (children) [52, 53] (2000–2009)	0.23	2.4, non-First Nations children 9.9, First Nations children
United States (children) [49] (1986–2011)	0.4	3.0
Singapore [45]	Not reported	4.0 (similar in Chinese, Malaysian, and Indian subgroups)
Australia (Capital Territory) [39]	Not reported	8.0
Israel (southern) [41]	0.67	11.0
Spain (Sagunto/Valencia) [46, 47]	0.83–1.07 (women, 1.37–1.96; men, −0.12 to 0.26) (increasing incidence in women)	11.61 (women, 19.17; men, 3.66)
Sweden [48]	0.85	10.7
Netherlands [42]	1.1 (increasing incidence over 10 years)	18.3
Denmark [40] (1994–2012)	1.68 (rising incidence from 1.37 to 2.33)	23.9 (women, 34.6; men, 13.0)
Norway (Oslo) [44]	1.9	16.9
New Zealand (Canterbury Region) [43] (2001–2007)	2.0 (1.7, age-standardized) (stable incidence over 6 years)	24.5 (18.9, age-standardized)
Alaska (native population) [38]	Not reported	42.9

Numbers in brackets are references

performed the strongest population-based evaluations [51]. They have also been able to describe changes in occurrence, phenotype, and mortality, albeit mainly in homogeneous white populations.

16.2.1 Annual Incidence of Autoimmune Hepatitis

The annual incidence of autoimmune hepatitis in adults ranges from 0.67 cases per 100,000 persons in southern Israel [41] to 2.0 cases per 100,000 persons in the Canterbury Region of New Zealand (95% confidence interval [CI]: 0.8–3.3 per 100,000) (Table 16.1). The annual incidence of autoimmune hepatitis in Canadian children was 0.23 cases per 100,000 persons between 2000 and 2009 [52], and it was 0.4 cases per 100,000 persons in children residing in the United States (Utah) between 1986 and 2011 [49].

Two studies evaluating temporal trends have suggested that the incidence of autoimmune hepatitis has been increasing in the adult populations of Spain [46, 47] and Denmark [40] over 10–18 years, whereas a third study in New Zealand has

suggested a stable incidence over a 6 year period from 2001 to 2007 [43]. Temporal trends may reflect changes in the methods of case-recognition, but they may also indicate a true increase in disease occurrence that warrants additional scrutiny. The wide range in incidence may reflect variations in the type and frequency of antigenic exposures, differences in genetic predispositions, or the effects of gender-specific (possibly hormonal) modifiers of the immune response [1, 4].

16.2.2 Prevalence of Autoimmune Hepatitis

The prevalence of autoimmune hepatitis in adults ranges from 4.0 cases per 100,000 persons in Singapore (with a similar prevalence in the Chinese, Malaysian and Indian subpopulations) [45] to 42.9 cases per 100,000 persons in Alaskan natives [38] (Table 16.1). The prevalence of autoimmune hepatitis in Alaskan natives is 1.7-fold greater than the highest reported prevalence of autoimmune hepatitis elsewhere [38]. In children, the prevalence of autoimmune hepatitis is 3.0 cases per 100,000 persons in Utah [49] and 2.4 cases per 100,000 persons in the non-native children of British Columbia, Canada [49, 53]. In contrast, the prevalence of autoimmune hepatitis in the First Nations (Aboriginal) children of British Columbia (9.9 cases per 100,000 persons) is nearly fourfold greater than that of the non-native children within this same geographical region (2.4 cases per 100,000 persons) [53].

The differences in prevalence between children and adults from different geographical regions and between children within the same geographical region suggest that predispositions for autoimmune hepatitis may be associated with age-related antigenic exposures and hereditary or culturally-specific factors. Other differences in prevalence among populations with autoimmune hepatitis have less apparent associations. Whereas the prevalence of autoimmune hepatitis is similar in Sweden and Spain (10.7–11.6 cases per 100,000 persons) [46–48], it is higher in Norway, the Netherlands, and Denmark (16.9–23.9 case per 100,000 persons) despite similarly predominant white adult populations, geographical proximity, and availability of tertiary medical care [40, 42, 44] (Table 16.1).

16.2.3 Variations of Phenotype in Different Geographical Regions and Ethnic Groups

The phenotype of autoimmune hepatitis can vary between different ethnic groups and geographical regions [1]. Autoimmune hepatitis is characterized by its inflammatory nature, and codified diagnostic criteria and scoring systems have been refined to exclude prominent cholestatic features [54–56]. In Alaskan natives [38], Somalians [57], and individuals from the Middle East [58] who have autoimmune hepatitis, clinical, laboratory, and histological changes of cholestasis are common (57–67%) (Table 16.2).

In the United Kingdom, 50% of children with autoimmune hepatitis have cholangiographic changes that suggest an autoimmune sclerosing cholangitis [59],

Table 16.2 Regional and ethnic differences in phenotypic manifestations of autoimmune hepatitis

Variable feature	Manifestations	Regional or ethnic differences
Age	Children and adults in same geographical region have different frequencies of AIH [40, 43, 49, 52] Adults in different countries have different ages of disease onset [40, 42] Peak age shift to elderly adults [40, 43]	Highest prevalence in adults [40, 42, 43, 49, 52] Peak age (New Zealand), 60 years [43] Peak age (Denmark), 70 years [40] Median age (Netherlands), 43–48 years [42]
Gender	Female predilection varies in different countries [38, 40, 41, 44, 45, 47]	Young Somalian men affected [57] Unusual high female frequency in Alaskan natives and southern Israelis (91–95%) [38, 41] F:M ratio (Singapore), 11:1 [45] F:M ratio (USA, Europe), 2.6–5.2:1 [40, 44, 47, 63]
Cholestasis	Clinical, laboratory or histological findings of cholestasis [38, 57, 58]	Present in 57–67% of Alaskan natives, Somalians, Middle Easterners [38, 57, 58] Unusual in white North American and European adults [54, 55]
Autoimmune sclerosing cholangitis	Focal strictures and dilations by cholangiography in otherwise classical AIH [59]	Present in 50% of British children with AIH [59] Present in 21% of Utah children with AIH [49] Rare in North American and European adults (1–10%) unless CUC present (44%) [60–62]
Antibodies	Variable frequencies of serological markers of AIH in children and adults between countries [52, 67, 70, 71, 73]	Anti-LKM1 occur mainly in children [66] • 13% of Canadian children with AIH [52] • 38% of British children with AIH [59, 67] • 1% in American adults [68, 69] Alaskan natives versus American adults • Anti-dsDNA, 48% versus 23–34% [70, 71] • ANCA, 38% versus 96% [70, 72] • Anti-Ro, 11% versus 40% [70, 73, 74] Japanese versus American adults • Anti-Ro, 62% versus 38% [73]

AIH autoimmune hepatitis, *ANCA* anti-neutrophil cytoplasmic antibodies, *anti-dsDNA* antibodies to double-stranded deoxyribonucleic acid, *anti-LKM1* antibodies to liver kidney microsome type 1, *anti-Ro* antibodies to ribonucleoprotein, *CUC* chronic ulcerative colitis, *F:M ratio* female-to-male ratio, *USA* United States of America
Numbers in brackets are references

whereas in the United States (Utah), only 21% of children with autoimmune hepatitis have features of autoimmune sclerosing cholangitis [49] (Table 16.2). The overall incidence of autoimmune sclerosing cholangitis in Utah is 0.1 cases per 100,000 persons, and the prevalence is 0.6 cases per 100,000 persons [49]. Cholangiographic changes of sclerosing cholangitis (focal biliary strictures and dilations) are even less frequent (2–10%) in white North American and European adults with autoimmune hepatitis [60, 61] unless they have concurrent chronic ulcerative colitis [62].

Autoimmune hepatitis has had a female propensity in all countries with the possible exception of Somalia where the disease appears to affect young males [57] (Table 16.2). Among Alaskan natives, 91% of patients with autoimmune hepatitis are women [38], and in southern Israel, 95% of patients are women [41]. The female-to-male ratio in Singapore is 11:1 [45]. In contrast, women constitute 72–78% of patients with autoimmune hepatitis in Denmark [40], Sweden [48], the Netherlands [42], and the United States [63], and the prevalence of autoimmune hepatitis in northern Europe is only 2.6–5.2 times greater in women than in men [40, 44, 46, 47]. Women may also have a predilection to have concurrent immune diseases more commonly than men in white North American and European populations [64, 65].

Autoimmune hepatitis affects all ages, but its prevalence is higher in adults than children [40, 42–44, 49, 52] (Table 16.2). Furthermore, the age of onset in adults may be shifting from the young and middle-aged populations to the elderly. In New Zealand, the peak age at presentation was in the sixth decade, and 72% of patients presented after the age of 40 years [43]. In Denmark, the peak incidence of autoimmune hepatitis in both genders was at the age of 70 years [40]. In contrast, the peak incidence of autoimmune hepatitis in the Netherlands was in the middle age range. The median age at presentation was 48 years in Dutch women and 43 years in Dutch men [42].

The serological manifestations of autoimmune hepatitis can also vary between age ranges, ethnic groups, and countries [1] (Table 16.2). Antibodies to liver kidney microsome type 1 (anti-LKM1) occur mainly in children with autoimmune hepatitis [66]. They are detected in 13–38% of children with autoimmune hepatitis in the United Kingdom [59, 67] and in Canada [52], but they are present in only 1% of North American adults with autoimmune hepatitis [68, 69]. In Alaskan natives with autoimmune hepatitis, there is a higher frequency of antibodies to double stranded deoxyribonucleic acid (anti-dsDNA) (48% versus 23–34% depending on the assay) than in white North American patients [70, 71], and the frequencies of antineutrophil cytoplasmic antibodies (ANCA) (38% versus 96%) [70, 72] and antibodies to ribonucleoprotein (anti-Ro) are lower (11% versus 40%) [70, 73, 74]. In contrast, antibodies to Ro are detected more commonly in Japanese patients with autoimmune hepatitis than in North American patients (62% versus 38%, $P < 0.0001$) [73].

Plasma cells that stain for immunoglobulin G4 (IgG4) and number more than 5 per high power field are present in the liver tissue of 3–35% of patients with autoimmune hepatitis [75–77]. These patients have been classified as having IgG4-associated

autoimmune hepatitis, and they commonly, but not invariably, have increased serum levels of IgG4 [76–78]. The frequency of IgG4-associated autoimmune hepatitis varies with the stringency of the diagnostic criteria. Application of the most stringent criteria (definite autoimmune hepatitis by international criteria, ≥10 IgG4-staining plasma cells/high power field, and serum IgG4 level ≥135 mg/dL) has recognized the variant form in only 3.3% of patients with autoimmune hepatitis [76, 78].

IgG4-associated autoimmune hepatitis may represent a variant clinical phenotype of autoimmune hepatitis that is within a spectrum of IgG4-related diseases that includes autoimmune pancreatitis and IgG4-associated cholangitis [79]. Liver injury is recognized in 60–70% of patients with autoimmune pancreatitis, and the associated IgG4-hepatopathy is characterized by IgG4-staining plasma cells near the portal vein, portal inflammation, portal sclerosis, bile duct damage, lobular hepatitis, and cholestasis [76, 78]. The features of IgG4-associated autoimmune hepatitis have typical histological findings of autoimmune hepatitis except for the prominent infiltration of IgG4-staining plasma cells [76].

IgG4-associated autoimmune hepatitis has been described mainly in Japan and China, and all experiences have emphasized responsiveness to conventional glucocorticoid therapy [75–77, 80]. The *de novo* occurrence of IgG4-associated autoimmune hepatitis after liver transplantation [80], the absence of relapse after drug withdrawal [77], the development of autoimmune pancreatitis 2 years after diagnosis in one patient [81], and the occurrence of IgG4-associated cholangitis 5 years later in another patient [76] are clinical vignettes that emphasize the uncertain nature and consequences of this variant [76].

Patients with IgG4-associated autoimmune hepatitis have higher serum immunoglobulin E (IgE) levels than patients with classical autoimmune hepatitis, and this finding suggests that the IgG4-associated autoimmune hepatitis may be triggered by antigens that generate an allergic response [76]. Both IgG4 and IgE are immune responses that have been recognized in allergic reactions [82, 83], and they are mediated by IL-10-secreting regulatory T cells which are abundant in autoimmune pancreatitis and IgG4-associated cholangitis [84]. The IgG4-staining histological phenotype of autoimmune hepatitis may reflect an allergic reaction to environmental antigens in a genetically-predisposed individual. Epidemiological studies are required to clarify the global distribution of IgG4-associated autoimmune hepatitis and the antigenic exposures associated with this variant form of autoimmune hepatitis.

16.2.4 Variations in Liver-Related Mortality in Different Geographical Regions and Ethnic Groups

Mortality rates can vary between ethnic groups and geographical regions, and these differences may reflect variable access to medical care, promptness of diagnosis and treatment, frequency of cirrhosis at presentation, type of treatment administered, diligence of follow-up, frequency of co-morbidities (concurrent diseases, alcohol intake), and socioeconomic status [1]. Regional- and ethnic-specific differences in the intrinsic

behavior of the liver disease cannot be excluded, but they are more difficult to discover beneath an overlay of cultural, economic, and healthcare disparity [1]. Furthermore, the liver-related death burden may be underestimated in population studies that apply only one diagnostic category of the International Classification of Diseases (ICD). Liver-specific descriptors, such as hepatic encephalopathy, hepatorenal syndrome, and liver malignancy, must also be included in all outcome analyses [85].

Liver-related mortality can vary in different ethnic groups within the same geographical region [1]. Liver failure is more common at presentation in African-Americans with autoimmune hepatitis than in white American adults (38% versus 9%) [86] (Table 16.3). African-Americans with autoimmune hepatitis are younger at diagnosis than white Americans; they have cirrhosis more frequently (57–85% versus 38%); they require liver transplantation more often (51% versus 23%); and their overall mortality is significantly higher (24% versus 6%), especially in black

Table 16.3 Regional and ethnic differences in outcomes of autoimmune hepatitis

Outcomes	Findings	Regional or ethnic differences
Liver-related mortality	Different between ethnic groups in same region [86] Different between geographical regions [40, 41, 45, 95–97]	African-American versus white American adults • Liver failure at presentation, 38% versus 9% [86] • Mortality, 24% versus 6% [86] • Highest mortality in black males [86] Regional differences in mortality • 10 years, 7–10.3% in Europe, Israel, USA [40, 41, 95, 96] • 5 years, 29% in Singapore [45] • <3 years (mean, 15.7 ± 17 months), 25% in India [97]
Cirrhosis	Different in ethnic groups in same region [86] Different between geographical regions [40, 41, 45, 95–97] Differences may reflect disease severity, genetic predisposition, or socioeconomic status [86]	African-Americans versus white Americans • Younger at presentation [86] • Cirrhosis at presentation, 57–85% versus 38% [86, 87] Regional differences in cirrhosis at presentation • 42% in Singapore [45] • 76% in India [97] • 12–29% in Europe, Israel, USA [40–42, 96] Mortality hazard (1st year), 3.25 (95% CI: 2.25–4.7) [40]
Liver transplantation	Differences may reflect disease severity, delayed diagnosis, or limited access to medical care [86, 92]	African-Americans versus white Americans • Liver transplantation indicated, 51% versus 23% [86] • Access to transplantation may be less [92, 94]

(continued)

Table 16.3 (continued)

Outcomes	Findings	Regional or ethnic differences
Hepatocellular carcinoma	Differences may reflect limited access to treatment in ethnic groups of same or different region [89–94] Referral bias in tertiary medical centers may over-estimate occurrence [100]	African-Americans versus white Americans • Higher mortality with localized HCC [88, 89] • Lower frequency of liver transplantation [94] Regional differences in occurrence • 0.8 cases per 1000 person-years in Denmark [40] • 0.7% 10 year cumulative risk in Denmark [40] • 1% frequency (median, 6 years) in Netherlands [42] • 1 case per 965 person-years in USA [99] • 10.9 cases per 1000 person-years in UK [100] Male predominant except in UK [40, 42, 98, 100] Develops in cirrhosis only except in UK [40, 98, 100]

CI confidence interval, *HCC* hepatocellular carcinoma, *UK* United Kingdom, *USA* United States of America
Numbers in brackets are references

males [86, 87]. African-Americans also have a higher mortality associated with small, non-metastatic hepatocellular carcinoma [88, 89]. These findings may reflect a more aggressive autoimmune hepatitis, possibly because of different antigenic triggers or genetic predispositions in the black population, or they could reflect cultural or socioeconomic differences between the white and black populations that prevent early diagnosis and limit access to medical interventions, especially liver transplantation [90–94].

Liver-related mortality can also vary in different geographical regions. Autoimmune hepatitis has a 10-year all-cause mortality of 26.4% in Denmark (95% CI: 23.7–29.1%), but only 38.6% of the known causes of death are liver-related [40] (Table 16.3). The estimated 10-year liver-related mortality in Denmark is 10.2% and similar to the 10-year liver-related mortality of 9% in the United Kingdom [95], 10.3% in southern Israel [41], and 7% in North America [96]. In each of these non-Asian countries, the mortality estimates are lower than the 5-year liver-related mortality of 29% in Singapore [45] and the overall mortality of 25% in India during a mean observation period of only 15.7 ± 17 months [97].

The presence of cirrhosis at presentation in 42% of the patients in Singapore [45] and 76% of the patients in India [97] may explain the differences in mortality (Table 16.3). Cirrhosis at presentation occurs in only 12–29% of patients with autoimmune hepatitis in Denmark [40], southern Israel [41], the Netherlands [42], and the United States [96], and it has a greater mortality hazard during the first year after

diagnosis than the absence of cirrhosis (mortality hazard of cirrhosis, 3.25; 95% CI: 2.25–4.70) [40].

Hepatocellular carcinoma has an incidence of 0.8 cases per 1000 person-years (95% CI: 0.3–1.5) in Denmark, especially in men with cirrhosis, and the 10-year cumulative risk of hepatocellular carcinoma has been 0.7% (95% CI: 0.3–1.5) [40] (Table 16.3). These findings are similar to those in the Netherlands where the frequency of hepatocellular carcinoma has been 1% during a median observation interval of 6 years [42]. In the United States, hepatocellular carcinoma has developed only in patients with longstanding cirrhosis (≥5 years duration) [98]; it has been male predominant [98]; and its incidence has been 1 per 965 person-years [99]. In the United Kingdom, hepatocellular carcinoma has occurred at a rate of 10.9 cases per 1000 patient-years or 1.1% per year [100]. It has affected 3.4% of patients without cirrhosis, and it has developed equally in men and women (6.4% versus 6.1%) [100]. The study in the United Kingdom was performed in a tertiary medical center, and it may have reflected referral bias associated with more advanced and severe autoimmune hepatitis than encountered elsewhere.

16.2.5 Variations of Genetic Predisposition in Different Geographical Regions and Ethnic Groups

Autoimmune hepatitis has a complex genetic predisposition that can vary in children and adults within the same geographical region and between adults in different regions [11]. Autoimmune hepatitis does not have a causative gene, but a constellation of normal genes within and outside the MHC may favor immune reactivity. Familial occurrence is rare (0.2% in Brazil [101] and 0.3% in the Netherlands [42]), but monozygotic (not dizygotic) twins have been affected [42]. Furthermore, 42% of first-degree relatives in the Netherlands have had other autoimmune diseases (rheumatoid arthritis, type 1 diabetes, and autoimmune thyroid disease) [42]. The antibodies associated with autoimmune hepatitis have been uncommon in first degree relatives of juvenile patients in Britain, but the frequency of the human leukocyte antigen (HLA) DRB1*0301, which has been associated with autoimmunity, has been similar in both populations [102]. These findings suggest a familial propensity for immune reactivity.

16.2.5.1 Genetic Susceptibilities Within the MHC

Genes within the MHC encode the antigen-binding groove of the class II MHC molecules, and they can affect the presentation of antigens and the nature of the autoreactive response [11]. *DRB1*0301* and *DRB1*0401* are the principal susceptibility alleles in white North American and European adults with autoimmune hepatitis [103, 104] (Table 16.4). Each allele encodes a six amino acid sequence (leucine-leucine-glutamic acid-glutamine-lysine-arginine) at positions DRβ67–72 of the antigen binding groove, and this sequence has been associated with the occurrence of autoimmune hepatitis in these adult populations [103, 105].

Table 16.4 Ethnic differences in genetic factors for autoimmune hepatitis

Genetic factors	Principal associations in ethnic groups with autoimmune hepatitis	Clinical associations
Alleles inside MHC	White North American and European adults • *DRB1*0301* and *DRB1*0401* [103, 104] Japanese, Chinese, Mexicans, South Koreans • *DRB1*0404* and *DRB1*0405* [106–110] Argentina, Brazil, Venezuela, Peru • *DRB1*1301* (children) [111–115] • *DRB1*0405* (adults) [23] • *DRB1*1301*, *DRB1*0405*, *DQB1*02*, *DQB1*0603* (meta-analysis) [116] North American and European children • *DQB1*0201* [122, 123] • Linked with *DRB1*07*, *DRB1*03* [123]	*DRB1*03 and DRB1*04 alleles* • Encode similar amino acid sequences in class II MHC molecules [11, 103, 105] • May present similar triggering antigens [4] *DRB1*1301* • Encodes different amino acid sequence than *DRB1*03* and *DRB1*04* alleles in class II MHC molecules [11, 117] • Affects mainly children [23, 111] • Associated with HAV infection [25] • May favor viral triggers [4] *DQB1*0201*, *DRB1*07* and *DRB1*03* • Associated with anti-LKM1 [122, 123] • Affects mainly children [122, 123] • May favor CYP2D6 or homologous viral epitopes [128, 129]
Variants outside MHC	North American adults • *CTLA-4* [131, 135] • *TNFRSF (Fas)* [137] • *TNFA* [138, 139] European and Chinese adults • *Vitamin D receptor* (*VDR*) [140, 141] European adults • *SH2B3* [104] • *CARD10* [104] Japanese adults • *TNFRSF (Fas)* [136] • *STAT4* [142] South American children and adults • *TGF-β1* [18]	Controversial pathogenic significance [134] Statistical associations in small cohorts [132] Not disease-specific [17, 130–132] Uncertain functional differences between variants of same gene [4] Variable presence in ethnic groups [131, 133] No direct comparisons between ethnicities [1] Constellations may be more important than any single variant [4, 11]

CARD10 caspase recruitment domain family member 10 gene, *CTLA-4* cytotoxic T lymphocyte antigen-4 gene, *MHC* major histocompatibility complex, *SH2B3* Scr homology 2 adaptor protein 3 gene, *STAT4* signal transducer and activator of transcription 4 gene, *TGF-β1* transforming growth factor-beta 1 gene, *TNFA* tumor necrosis factor-α gene, *TNFRSF* tumor necrosis factor receptor super-family (Fas) gene
Numbers in brackets are references

*DRB1*0404* and *DRB1*0405* are the principal susceptibility alleles in Japan [106, 107], mainland China [108], and Mexico [109], and *DRB1*0405* and *DQB1*0401* are the main susceptibility alleles in South Korea [110] (Table 16.4). The *DRB1*0404* and *DRB1*0405* alleles differ from the *DRB1*0301* and *DRB1*0401* alleles by encoding an arginine for lysine at the DRβ71 position. This substitution of

a similarly structured and charged amino acid for lysine would not greatly alter antigen selection and presentation by the class II MHC molecules. Accordingly, the autoimmune hepatitis associated with the alleles, *DRB1*0301*, *DRB1*0401*, *DRB1*0404* and *DRB1*0405*, could be triggered in different geographical regions and ethnic groups by antigens with homologous epitopes [4].

In contrast, *DRB1*1301* is the principal susceptibility allele in Argentina [23, 111], Brazil [112, 113], Venezuela [114], and Peru [115], and *DRB1*0405*, *DQB1*02*, and *DQB1*0603* have also been implicated by meta-analysis [116] (Table 16.4). Children with autoimmune hepatitis in Argentina have mainly *DRB1*1301* [111], whereas adults with autoimmune hepatitis in Argentina have mainly *DRB1*0405* [23]. *DRB1*1301* encodes a different amino acid sequence (isoleucine-leucine-glutamic acid-aspartic acid-glutamic acid-arginine) between positions DRβ67–72 than the *DRB1*03* and *DRB1*04* alleles, and this sequence would change the steric and electrostatic properties of the antigen binding groove of the class II MHC molecules [117].

The substitution of the negatively charged aspartic acid and glutamic acid at positions DRβ70 and 71 within the antigen binding groove suggest that the autoimmune hepatitis in South American children with *DRB1*1301* is triggered by antigens different than those encountered in South American, North American, and European adults who have mainly *DRB1*03* and *DRB1*04* alleles. The association of protracted hepatitis A virus infection in patients with *DRB1*1301* [25] has supported speculation that the hepatitis A virus is a cause of autoimmune hepatitis, especially in areas like South America that are endemic for the virus [118–121]. This hypothesis might also extend elsewhere to other infectious agents that are more common in children than adults.

*DQB1*0201* has been proposed as the principal susceptibility allele of autoimmune hepatitis that is characterized by the presence of anti-LKM1 [122, 123] (Table 16.4). This allele is in strong linkage disequilibrium with *DRB1*07* and *DRB1*03* [123], and HLA DRB1*07 has been associated with this type of autoimmune hepatitis in Brazil [112, 113, 124, 125], Britain [126], and Germany [127]. The cytochrome P450 2D6 (CYP2D6) is the target antigen of anti-LKM1, and it has homologies with peptide sequences in the hepatitis C virus, cytomegalovirus, and herpes simplex type 1 virus [128, 129]. The autoimmune hepatitis characterized by anti-LKM1 in European children may be a reflection of exposures to indigenous infectious or environmental agents that mimic CYP2D6. Susceptibility might be enhanced by alleles of the MHC that favor presentation of these antigens.

16.2.5.2 Genetic Susceptibilities Outside the MHC

Genetic polymorphisms outside the MHC are not antigen-directed, and they may modify the immune response and modulate the mechanisms of tissue damage and repair in a fashion that is not disease-specific [17, 130–132]. They are frequently present in non-hepatic immune-mediated diseases, and they are commonly absent in the same immune-mediated disease but in different ethnic groups [131, 133]. Accordingly, their presence is not essential for disease occurrence, and their true role in autoimmune hepatitis has been unclear and controversial [134].

Polymorphisms of the *cytotoxic T lymphocyte antigen-4 gene* (*CTLA-4*) [131, 135], *Fas* gene (*tumor necrosis factor receptor super-family [TNFRSF] gene*) [136, 137], *tumor necrosis factor-α* (*TNFA**2) *gene* [138, 139], *vitamin D receptor* (*VDR*) *gene* [140, 141], *signal transducer and activator of transcription 4* (*STAT4) gene* [142], *transforming growth factor-beta 1 (TGF-β1) gene* [18], the *Scr homology 2 adaptor protein 3 (SH2B3) gene* [104], and the *caspase recruitment domain family member 10* (*CARD10) gene* [104] have been implicated as genetic factors in autoimmune hepatitis (Table 16.4). Each has been described in region- and ethnic-specific cohorts; each has been implicated by statistical association of varying strength; and none has an established role in the occurrence or manifestations of autoimmune hepatitis. A constellation of polymorphisms may be a more critical determinant of the phenotype and behavior of autoimmune hepatitis in different populations than a single prime variant.

16.2.5.3 Genetic Associations with Clinical Course

The alleles within the MHC have been associated with differences in the phenotype and behavior of autoimmune hepatitis in patients of the same or different ethnicity [11]. *DRB1*0301* has been associated with an earlier age of onset, more severe disease, higher frequency of treatment failure, and greater requirement for liver transplantation than patients with *DRB1*0401* in white North American and European adults [16, 64, 105, 143]. In contrast, patients with *DRB1*0401* are more commonly women, have concurrent immune diseases more frequently, respond better to immunosuppressive therapy, and are older at disease onset than patients with *DRB1*0301* [16, 64, 105]. Elderly patients (aged ≥60 years) have *DRB1*0401* more often than young adults (aged ≤30 years), and they respond better to immunosuppressive therapy despite having a greater frequency of cirrhosis at presentation [144, 145].

*DRB1*0301* is rare in the Japanese population, and *DRB1*0405* is the principal susceptibility allele for autoimmune hepatitis [106, 146, 147]. Japanese patients with autoimmune hepatitis are typically women with late onset disease, few or no symptoms, mild disease severity, responsiveness to treatment, and favorable long-term prognosis [148–150]. In this ethnic group, the common association of *DRB1*0405* with autoimmune hepatitis and the almost complete absence of *DRB1*0301* in the general population may have shaped a disease phenotype that is similar to that of women in western countries who also have *DRB1*04* alleles. Genome wide association studies (GWAS) in diverse geographical regions and ethnic groups may be able to identify other genetic factors that influence outcome and help individualize management strategies.

16.2.6 Possible Epigenetic Changes Affecting Predisposition and Outcome

Micro-ribonucleic acids (miRNAs) are regulatory molecules that exert an epigenetic effect on the transcriptional activity of genes by binding with the messenger RNA (mRNA) produced by the gene and marking it for degradation by an RNA-induced silencing complex (RISC) [151, 152]. This gene silencing effect can repress

the activity of protein-encoding genes, and it may alter the expressions of pro- and anti-inflammatory genes in autoimmune liver disease [21]. Serum levels of the miRNAs miR-21 and miR-122 have fluctuated with the serum ALT concentrations in Japanese patients with autoimmune hepatitis, and the circulating level of miR-21 has correlated with the histological grade of inflammation [153].

miRNAs have organ but not disease specificity, and their association with inflammatory activity in autoimmune hepatitis suggests that they may affect susceptibility and outcome. The expression of miRNAs is influenced by genetic factors, and the genes expressing the miRNAs themselves can be affected by epigenetic mechanisms that may be cued from the environment [154, 155]. Epidemiological studies are required to determine if differences in clinical phenotype and outcome in diverse populations can be ascribed to variations in the expression of miRNAs as a result of genetic variation or environmental cues.

Vitamin D deficiency occurs in 51–92% of patients with non-cholestatic chronic liver disease [156–158] and 81% of Turkish patients with autoimmune hepatitis [159]. Low serum levels of 25-hydroxyvitamin D3 may result from impaired liver hydroxylation of the skin-derived vitamin D3 [156, 157] or impaired synthesis, absorption, or consumption of vitamin D3 [160]. Variations in sun exposure, seasonal climate, diet, and contact with toxins that alter the metabolic activity of P450 cytochromes can promote vitamin D deficiency and perturb the immunomodulatory actions of vitamin D [161].

Vitamin D has diverse immunomodulatory effects on the innate and adaptive immune systems [162–164], and the vitamin D receptor (VDR) is expressed on multiple cell types [165, 166]. Furthermore, the hydroxylating enzyme (25-hydroxyvitamin D-1α hydroxylase) that converts inactive 25-hydroxyvitamin D3 to the active 1,25-dihydroxyvitamin D3 is not restricted to the kidney. The expression of 25-hydroxyvitamin D-1α hydroxylase can be induced in diverse cell types, and the hydroxylating enzyme can activate vitamin D outside the kidney [167, 168].

The activated 1,25-dihydroxyvitamin D3 can in turn interact with the vitamin D response element (VDRE) in regulatory genes, and it can modulate the immune response by exerting an epigenetic effect on the transcriptional activity of the targeted gene [169]. Genetic factors can affect the structure and avidity of the VDR, and differences in vitamin D availability and metabolism may also affect susceptibility to autoimmune hepatitis and its clinical phenotype in diverse populations [140, 141]. Population-based epidemiological studies will be pivotal in determining the impact of vitamin D deficiency and epigenetic changes on the distribution and consequences of autoimmune hepatitis.

16.3 Epidemiology of Primary Biliary Cholangitis

Primary biliary cholangitis is a progressive chronic liver disease in which the biliary epithelial cells rather than the hepatocytes are the primary targets of the immune response [170]. Clinical, laboratory, and histological changes (bile duct injury, destruction or loss) define a cholestatic phenotype that typifies PBC and distinguishes it from autoimmune hepatitis [171]. Importantly, the classical cholestatic

components can be absent at presentation [172] or intermixed with features of autoimmune hepatitis (overlap syndrome) [6]. Furthermore, many patients may be asymptomatic and escape early detection [173, 174]. For these reasons, population-based epidemiological studies of PBC can be influenced greatly by the level of clinical expertise within the community being scrutinized [175].

16.3.1 Annual Incidence of Primary Biliary Cholangitis

The annual incidence of PBC has ranged from 0 to <1 case per 100,000 persons in Brunei, Darussalem [176] and Estonia [177] to 3.2 cases per 100,000 persons in Newcastle, United Kingdom [178, 179] (Table 16.5). Olmsted County, Minnesota (2.7 cases per 100,000 persons) [180], Calgary, Canada (3.03 cases per 100,000 persons) [181], and Newcastle, United Kingdom (3.2 cases per 100,000 persons) [178, 179] have reported an annual incidence of PBC that is almost twofold greater than the annual incidence of PBC in Denmark (1.14 cases per 100,000 persons) [182], Sweden (1.4 cases per 100,000 persons) [173], Norway (1.6 cases per 100,000 persons) [44], Italy (1.67 cases per 100,000 persons) [182], and Spain (1.72 cases per 100,000 persons) [183]. Furthermore, the annual incidence of PBC in Olmsted

Table 16.5 Incidence and prevalence of primary biliary cholangitis in different regions (lowest to highest annual incidence)

Geographical region	Annual incidence per 100,000 persons	Prevalence per 100,000 persons
Australia (Victoria) [194, 198]	Not reported	1.9–5.1 (Australian-born, 3.72; Italian-born, 19.9; Greek-born, 20.8; British-born, 14.1)
Brunei, Darussalem [176, 306]	0–1	2.6 (Malaysian, 2.3; Chinese, 4.1)
Estonia [177]	0.23	2.69
Japan [175, 195]	Not reported	2.7–5.4
China (southern) [196]	Not reported	4.92 (15.6 in women aged >40 years)
Israel (southern) [197]	Not reported	5.5
Denmark [182]	1.14	11.5
Sweden [173]	1.4	12.8
Norway (Oslo) [44]	1.6	14.6
Italy (Lombardia) [182]	1.67	16 (increasing prevalence)
Spain (Sabadell) [183]	1.72	19.5
United States (Olmsted County, Minnesota) [180]	2.7 (women, 4.5; men, 0.7) (stable for 20 years)	40.2 (women, 65.4; men, 12.1)
Canada (Calgary) [181]	3.03 (women, 4.84; men, 1.04) (stable from 1996 to 2003)	22.7 (increased from 10 over 6 years)
United Kingdom (Newcastle) [178, 179, 199]	3.2 (increased from 2.3 over 7 years)	25.1 (increased from 14.9 over 7 years)

Numbers in brackets are references

County, Calgary, and Newcastle is almost 14-fold greater than the annual incidence of PBC in Estonia (0.23 cases per 100,000 persons) [177]. Importantly, each region with the highest annual incidence of PBC (Olmsted County, Minnesota, Calgary, Canada, and Newcastle, United Kingdom) has an academic medical center with a long-standing interest and expertise in PBC.

The annual incidence of PBC has been stable for 7 years in Calgary, Canada [181] and for 20 years in Olmsted County, Minnesota [180], but it has increased in Newcastle, United Kingdom (2.3–3.2 cases per 100,000 persons over 7 years) [178, 179] (Table 16.5). In adults aged ≥20 years in Newcastle, the annual incidence has increased from 3.1 to 4.3 cases per 100,000 persons, and in women aged ≥40 years, it has increased from 9.1 to 10 cases per 100,000 women [179]. These trends have not been statistically significant, but they have been consistent in each analyzed subgroup. Since the three regions with the highest annual incidence of PBC have academic medical centers with similar interest and expertise in PBC, the increasing annual incidence of PBC in one area is unlikely to reflect a difference in case detection. Continued separation of the Newcastle region from the other two regions would suggest a newly introduced environmental factor for PBC or a changing population by age, gender or genetic composition.

The annual incidence of PBC in women has been 4.5 cases per 100,000 persons in Olmsted County, Minnesota [180] and 4.84 cases per 100,000 persons in Calgary, Canada [181]. The annual incidence of PBC in women has been 4.6- to 6.4-fold greater than in men residing in these same regions (Table 16.5). The female-to-male ratio of patients with PBC has been 2.3:1 in Lombardia, Italy [182], 4.2:1 in Denmark [182], and 9–10:1 in most other studies [50, 175, 184]. The bases for the female predisposition for PBC and the variable sex ratios in different regions are unclear [170]. Recent studies have suggested that the composition of the intestinal microbiome can influence the immune response in PBC [185–188]. The intestinal microflora may also contribute to gender bias by influencing serum sex hormone levels and altering the antigenic stimuli that modulate the immune response [32, 189, 190].

The annual incidence of PBC is highly dependent on age, and in Calgary, the highest incidence is among individuals aged 60–79 years (annual incidence, 6.3 cases per 100,000 persons) [181]. Primary biliary cholangitis does not affect children, and the absence of childhood PBC also distinguishes it from autoimmune hepatitis and PSC [59, 67, 191–193]. The bases for protection against PBC in children are unknown, and this uncertainty must generate speculation about the pathogenic role of post-pubescent female hormones, infections, environmental factors, and age-related changes in the intestinal microbiome [32, 170].

16.3.2 Prevalence of Primary Biliary Cholangitis

The prevalence of PBC ranges from 1.9 cases per 100,000 persons in Victoria, Australia [194] to 40.2 cases per 100,000 persons in Olmsted County, Minnesota [180]. Asian countries (Japan [195] and China [196]) and southern Israel [197] have a prevalence of PBC that is one third the prevalence of PBC in Europe and one fifth

the prevalence in North America (Table 16.5). In contrast, Australia, whose population is descended mainly from European settlers, has a lower prevalence of PBC than Europe, North America, Asia and southern Israel [194, 198]. Prevalence has been 5.4-fold higher in women than men in the United States (65.4 cases per 100,000 women versus 12.1 cases per 100,000 men) [180], and it has been 15-fold higher in patients aged 60–79 years than in patients aged 20–39 years in Canada (57.3 cases per 100,000 persons versus 3.8 cases per 100,000 persons) [181].

Australian-born women aged ≥24 years have a prevalence of 5.1 cases per 100,000 persons (95% CI: 3.75–6.79) [194], but this estimate is still lower than that reported in Europe [44, 173, 178, 179, 182, 183], North America [180, 181], and Japan [195] (Table 16.5). Australian-born individuals also have a lower prevalence of PBC (3.72 cases per 100,000 persons) compared to individuals who have migrated to Australia from Britain (14.1 cases per 100,000 persons), Italy (19.9 cases per 1000,000 persons), and Greece (20.8 cases per 100,000 persons) [198]. Genetic factors are unlikely to be the basis for protection from PBC since most Australians are descended from British and European settlers [194] whose native populations have had a higher prevalence of PBC than native Victorians [179, 198]. These findings have justified speculation that individuals in Australia are protected from PBC because they lack an environmental factor encountered elsewhere [194, 198].

The prevalence of PBC has increased by more than twofold over a 6 year period in Calgary, Canada (from 10 to 22.7 cases per 100,000 persons) and by 1.7-fold over a 7 year period in Newcastle, United Kingdom [178, 179, 199] (Table 16.5). The prevalence may also have increased in Lombardia, Italy [182]. An increasing prevalence of PBC in certain regions suggests that the disease is being recognized at earlier asymptomatic stages and individuals with the disease are living longer [179]. Whereas greater recognition of the disease can be a consequence of improved case-detection, improved survival may relate to changes in the behavior, management or cause of the disease.

16.3.3 Variations in Liver-Related Mortality in Different Geographical Regions

The number of liver transplants performed in patients with PBC has been decreasing [3, 200], and this finding suggests that earlier detection and improved management have had an impact on prevalence. This possibility has not been established (or excluded) by comparisons of mortality between regions with rising and stable prevalence of PBC. The annual mortality of PBC in Calgary, Canada has been 3.4%; the standardized mortality ratio (SMR) has been 2.1 (95% CI: 1.2–3.4); the frequency of liver transplantation over 5.8 years (range, 10 days–10.9 years) has been 4.4%; and the 5- and 10-year survivals have been 83% and 73%, respectively [181]. The 5- and 10-year survivals of women with PBC in Calgary are 87% and 80%, respectively, compared to those of men (64% and 0%, respectively). Calgary has had a greater increase in prevalence of PBC than Newcastle, England and Lombardia, Italy. Survival has also been better in this region.

The SMR for PBC has been 2.85 (95% CI: 2.54–3.19) in Newcastle, United Kingdom [179], and the 5- and 10-year survivals have been 70% and 61%, respectively, in Lombardia Italy [182]. Women with PBC in Lombardia have had 5- and 10-year survivals of 77% and 67%, respectively, compared to those of men (55% and 47%, respectively). In contrast, the estimated 10-year survival of PBC in Olmsted County, Minnesota, which has had a stable prevalence of PBC for 20 years, is 59% [180]. Countering the suggestion that increased survival is a basis for increasing prevalence of PBC in certain communities is the lack of statistically valid comparisons of survival between the regions of interest.

The marked predilection of women for PBC [50, 175, 177, 180, 182], the lower occurrence but higher mortality of men than women with the disease [181, 182], the relative protection of native-born Australians from PBC [194, 198], and the sparing of children [170] are epidemiological observations that lack an explanation, and these findings should direct future investigations.

16.3.4 Environmental Factors and the Occurrence of Primary Biliary Cholangitis

Environmental agents and conditions have been implicated as risk factors for PBC, and they may help explain the clustering of cases in certain areas within the same geographical region [201, 202].

16.3.4.1 Tobacco Smoking

Tobacco smoking has been strongly implicated as an environmental risk factor for PBC (Table 16.6). Regular smoking and a history of previous smoking have been more frequent in patients with PBC than control populations [203–209], and patients with PBC have had a higher frequency of persistent passive exposure to tobacco smoke [209, 210]. Furthermore, smoking history and the amount of tobacco consumed have been associated with advanced hepatic fibrosis [211, 212]. Smoking intensity, defined by the number of pack-years, has been higher in patients with advanced hepatic fibrosis (stages 3 and 4) than in patients without these histological findings, and the likelihood of advanced hepatic fibrosis at presentation has increased by 5% (95% CI: 1.3–8.7%) for each increase in pack-year exposure [212]. Smoking has also been more frequent in other immune-mediated diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), and Graves' disease [213]. These observations have supported concerns that tobacco smoke has deleterious effects on the immune system.

Smokers in general have increased plasma levels of the pro-inflammatory cytokines, interleukin (IL)-1, IL-6, IL-8, and interferon-gamma (IFN-γ) [214–216]. The anti-inflammatory cytokine, IL-10, is also increased, but plasma IFN-γ (not IL-10) levels are higher in female smokers than male smokers [208, 217]. The predominance of IFN-γ in women in conjunction with other pro-inflammatory cytokines favor a type 1 cytokine pathway of lymphocyte differentiation and proliferation in

Table 16.6 Environmental risk factors for primary biliary cholangitis

Risk factor	Possible mechanism(s)	Evidence
Cigarette smoking	Releases polycyclic aromatic hydrocarbons (including benzene) and ROS [216, 222, 223] Pro-inflammatory cytokines increased [215] Protective dendritic cell functions less [220] Risk of infection increased [220] Xenobiotic transformation of mitochondrial antigen into neo-antigen [216, 224]	History of smoking associated with PBC [205] Regular smoking more common in PBC [209] More lifetime exposure to second hand smoke [209] Associated with advanced fibrosis [211, 212] Dose-dependent effect on fibrosis risk [212] Linked to RA, SLE, MS, Graves' disease [213]
Toxic waste exposure	Possible exposures to benzene, trichloroethylene, and other aromatic and halogenated hydrocarbons [227] Toxic liver injury may trigger autoreactive immune response [227]	Increased frequency of PBC on liver transplant list in zip code areas in or adjacent to Superfund toxic waste sites in New York [227]
Water source	Soft water, low fluoride levels found [226] Uncertain pathogenic effects [216]	PBC >10-fold more common in areas of Sheffield, England receiving water from one reservoir [184]
Nail polish Hair dye	May alter or complex with self-proteins changing structure to induce immune response (xenobiotic effect) [228]	Controlled interview-based study showed increased association with PBC [205]
HRT	Uncertain pathogenic effect [233] Improves liver tests in PBC [234]	HRT use more frequent in PBC [205] May be prescribed more commonly [205]
Urban living	Presumed exposure to industrial pollution, infectious agents, toxic waste [230]	Associated with higher prevalence than in rural community [230]
Seasonality	May relate to seasonal infections, pollutants, exercises, diets, sunlight/UV exposure [235]	Peak diagnosis of PBC in northeast England during month of June [235]

HRT hormonal replacement therapy, *MS* multiple sclerosis, *PBC* primary biliary cholangitis, *RA* rheumatoid arthritis, *ROS* reactive oxygen species, *SLE* systemic lupus erythematosus, *UV* ultraviolet
Numbers in brackets are references

PBC [218]. Predominance of the type 1 cytokine pathway can in turn promote hepatic fibrosis [219]. Tobacco smoking can also suppress the secretion of cytokines, IL-12 and IL-23, by dendritic cells and weaken the immune response to bacterial lipopolysaccharide [220]. A compromised immune defense could favor the occurrence of infections that might also trigger PBC [220]. Chronic expression of IFN-γ in a mouse model can produce an autoimmune cholangitis with female predominance that mimics human PBC [221].

Numerous other cytotoxic agents are also inhaled during tobacco smoking, including nicotine, polycyclic aromatic hydrocarbons (benzene), and reactive oxygen species (ROS) [222, 223]. Chemical transformation of benzene through halogenation can have a xenobiotic effect, and it may contribute to the development of PBC by altering mitochondrial antigens and inducing an autoreactive response [224]. ROS may also contribute by altering mitochondrial function, inducing apoptosis, provoking nitrosative stress, and stimulating hepatic fibrosis [225].

16.3.4.2 Water Sources, Toxic Waste Sites, Nail Polish, and Hormonal Replacement Therapy

The unusual occurrence of PBC in certain areas within a geographical region has supported the concept that a toxic agent might predispose to the disease by exerting a xenobiotic effect [24, 224, 226, 227]. Xenobiotics are foreign substances (chemicals, drugs, and pollutants) that are not naturally produced or consumed. Their introduction into the system is usually fortuitous and unsuspected, and they can have deleterious consequences. The mitochondrial component, pyruvate dehydrogenase complex-E2 (PDC-E2), can be altered *in vitro* by a xenobiotic [224, 228], and this molecular alteration could create a neo-antigen that enhances or extends an autoreactive response [229]. Modification of the PDC-E2 peptide with 2-octynoic acid induces a greater reactivity against PBC sera than against control sera, and the use of 2-octynoic acid in perfumes, lipstick, and food colorings ensures ample opportunity for environmental exposure to this xenobiotic [224].

Epidemiological studies have supported the concept of a xenobiotic effect in PBC (Table 16.6). A single water source in Sheffield, England has supplied an area in which the prevalence of PBC has been >10-fold higher than the prevalence of PBC in areas supplied by other water sources [226]. Neighborhoods in close proximity to a toxic waste site have had more patients with PBC awaiting liver transplantation than other neighborhoods of New York [227], and case-control studies have indicated a statistical association between the occurrence of PBC and yearly exposures to nail polish ($P < 0.0001$) and hair dye ($P = 0.04$) [205]. The higher prevalence of PBC in urban communities (14.4 cases per 100,000 persons) than in rural communities (3.7 cases per 100,000 persons) supports speculation that PBC-causing xenobiotics are more plentiful in the urban environment [230].

Drugs may also exert a xenobiotic effect or cause drug-induced liver injury which may in turn promote a pro-inflammatory immune response [231]. A case-control study by questionnaire has demonstrated a statistically higher frequency of hormonal replacement therapy (HRT) in patients with PBC than in unaffected women [205] (Table 16.6). The pathogenic significance of this finding remains speculative since HRT is frequently prescribed in PBC as part of a management strategy to prevent or improve osteoporosis [232]. Estrogen receptors are present in the biliary epithelial cells of patients with PBC (in contrast to normal liver), but they disappear in advanced stages and their role in disease progression is unclear [233]. Furthermore, estradiol therapy has actually improved liver tests in PBC [234].

16.3.4.3 Seasonal Variation

The diagnosis of PBC has a seasonality that may influence its detection at early stages and its prognosis (Table 16.6). The symptoms of PBC have been recognized most commonly in the Spring and early Summer in northeast England [230, 235], and the peak month for diagnosing PBC in this region has been June [235]. Furthermore, the distribution of patients with survivals >10 years has had a similar seasonality that has not been evident in the distribution of patients with survivals <5 years [235]. These findings have suggested that the summer occurrence of symptoms may have contributed to an early diagnosis of PBC that in turn favored an improved survival.

The seasonality of the diagnosis of PBC in northeast England could not be attributed to changes in the number of patients attending medical clinics or admitted to hospital, and a transient seasonal factor with a short lag time between exposure and effect has been suspected [235, 236]. Infections [237–241] and air pollutants whose occurrence can vary with weather conditions [242, 243] have been prime considerations, but other seasonal factors (activities, dietary adjustments, and exposure to sunlight and ultraviolet radiation) cannot be overlooked. Similar epidemiological studies have not been performed in other countries to assess the regional specificity of the observations.

16.3.5 Infectious Agents and the Occurrence of Primary Biliary Cholangitis

Infectious agents may trigger an immune-mediated disease by sensitizing immune cells to peptide sequences within the pathogen that resemble those within the host (molecular mimicry) [9, 244]. They may also cause tissue damage, create or expose neo-antigens within the host, and promote a pro-inflammatory immune response that breaks self-tolerance [4]. Some infectious agents may metabolize xenobiotics, and these metabolic products may then alter the immunogenicity of normal host proteins (xenobiotic effect) [238]. An infectious etiology has long been considered in PBC [245–247], and this speculation has been supported by several epidemiological studies. *Escherichia coli* has been the most commonly implicated organism, and it induces the expression of antibodies to PDC-E2 and histological changes of cholangitis in a mouse model [244]. Multiple other pathogens have also been proposed [247], but only *Novoshingobium aromaticivorans* [238, 241, 248, 249] and β-retrovirus [250–254] have been well studied.

16.3.5.1 *Escherichia coli* and Urinary Tract Infections

Escherichia coli and PDC-E2 have structural similarities, and these homologies between the pathogen and the host (molecular mimicry) may generate a promiscuous immune response that breaks self-tolerance of PDC-E2 and triggers PBC [9, 244, 255, 256] (Table 16.7). In the United Kingdom, the frequency of urinary tract infection (UTI) has been higher in women with PBC (19%) than in women with

Table 16.7 Infectious agents and the occurrence of primary biliary cholangitis

Infectious agent	Laboratory evidence	Clinical evidence
Escherichia coli	Structural homologies with PDC-E2 [9] Induces antibodies to PDC-E2 and cholangitis in mouse model [244]	UTIs more common in PBC [257, 258] Most UTIs caused by *E. coli* [257] Multiple UTIs are risk factors [259] Association exists across regions [209, 210]
Novoshingobium aromaticivorans	Metabolizes xenobiotics [238] Two homologies with PDC-E2 [241] PBC sera reactive against bacteria [238] Infected mice develop cholangitis [244]	PBC sera react to bacterial proteins [240] Reactivity consistent with AMA [240] FDRs may also react (1.2%) [240] Bacteria in 25% PBC fecal specimens [240]
Human β-retrovirus	Viral sequences in diseased livers [251] Exogenous virus signature [251] Retroviral antibodies in serum [250] Retroviral sequences in genome [253] Virus-like particles in biliary cells [237]	Better after anti-retroviral therapy [254] Retroviral infection not in all PBC [252] Retrovirus not disease-specific [262]
Less robust candidates • Epstein-Barr virus • *Mycobacterium gordonae* • *Helicobacter pylori* • *Chlamydia pneumoniae* • *Mycoplasma pneumoniae*	Increased EBV DNA in PBMC, liver tissue, and saliva of PBC patients [263] PBC sera react against *M. gordonae* [264] *M. gordonae* and AMA cross-react [264] *H. pylori* in PBC liver tissue [265] *C. pneumoniae* antigen and RNA in PBC liver tissue [266] PDC subunits on mycoplasma [267] Reactivity to mycoplasma in PBC [267]	No epidemiological studies or treatment trials [247]

AMA antimitochondrial antibodies, *EBV DNA* Epstein-Barr virus deoxyribonucleic acid, *FDRs* first degree relatives, *PBC* primary biliary cholangitis, *PBMC* peripheral blood mononuclear cells, *PDC-E2* pyruvate dehydrogenase complex E2 subunits, *RNA* ribonucleic acid, *UTIs* urinary tract infections
Numbers in brackets are references

other chronic liver (7%) or non-liver (8%) diseases, and most UTIs have been caused by *Escherichia coli* [257, 258]. Furthermore, most women with PBC have had multiple, often asymptomatic UTIs that have disappeared and re-appeared spontaneously in patterns unaffected by antibiotic therapy [259].

Similar associations between UTIs and PBC have been recognized in the United States [205, 209, 216] and France [210] (Table 16.7). Multiple UTIs have been common in women with PBC (>1 episode per year in the United States [209] to >5 episodes per lifetime in France [210]), and the infections have occurred mainly before the diagnosis of PBC [260]. The highest adjusted odds ratio (OR) for the occurrence of PBC (OR: 2.60 [1.02–6.63]) has been in British women aged

<55 years who have had pyelonephritis 5 years prior to the diagnosis of PBC [260]. Animal studies have supported the epidemiological findings by demonstrating the development of autoimmune cholangitis and antimitochondrial antibodies (AMA) in genetically susceptible mice after infection with *Escherichia coli* [244].

16.3.5.2 *Novoshingobium aromaticivorans*

Novoshingobium aromaticivorans is an alphaproteobacterium. Alphaproteobacteria are ubiquitous, gram-negative, non-spore-forming, rod-shaped, aerobic organisms that are found mainly in soil sediments [239]. *Novoshingobium aromaticivorans* degrades aromatic compounds which may then act as xenobiotics, and it also activates environmental estrogens [238, 241] (Table 16.7). Two lipoylated proteins within *Novoshingobium aromaticivorans* have homology with PDC-E2, and sera from patients with PBC have uniformly reacted against these bacterial proteins in titers 100- to 1000-fold higher than against *Escherichia coli* [238]. Furthermore, genetically-modified mice infected with *Novoshingobium aromaticivorans* have developed biliary changes, albeit less severe than in mice infected with *Escherichia coli* [244].

In Iceland, the sera of patients with PBC have reacted against the proteins of *Novoshingobium aromaticivorans* in a fashion consistent with their AMA status, and the one of 85 first-degree relatives (1.2%) who had AMA also had reactivity to the proteins of *Novoshingobium aromaticivorans* [239, 240] (Table 16.7). *Novoshingobium aromaticivorans* has been isolated in 25% of fecal specimens from patients with PBC, but it has also been recovered with similar frequency in healthy individuals from the same household (26%) and healthy individuals from different households (27%) [238].

There have been no epidemiological studies within the same geographical region or between regions to define the distribution or clustering of PBC that is associated with *Novoshingobium aromaticivorans*. Furthermore, there have been no studies that suggest routes of bacterial transmission, identify genetic, ethnic or age-related predispositions, characterize the clinical phenotype, or determine differences in outcome. Causal relationships are difficult to establish by demonstrating molecular mimicries in the laboratory, coincident colonization of comparable frequency in patients and healthy individuals, and compatible but nonspecific biliary changes in genetically-modified animal models.

16.3.5.3 Human β-Retrovirus

Human β-retrovirus emerged as an etiological consideration in PBC when explorative studies in the livers of patients with PBC failed to demonstrate bacterial infection [254]. Subsequent studies using subtractive hybridization techniques found viral sequences in the diseased livers that were consistent with an exogenous virus that had nucleotide similarities with a β-retrovirus associated with breast cancer in mice [251] (Table 16.7). Later studies in PBC demonstrated retroviral antibodies in serum samples [250], virus-like particles in biliary epithelial cells [237], and retroviral sequences in the genome of biliary epithelium [253]. Biochemical responses to a treatment combination of reverse transcriptase

inhibitor and protease inhibitor in patients with PBC provided a proof of principle that retrovirus might cause PBC [254, 261].

Subsequent studies have challenged the role of β-retrovirus in PBC. Immunological and molecular evidence of retroviral infection has been absent in one study [252], and retrovirus has been detected in liver diseases other than PBC in another study [262] (Table 16.7). Furthermore, the frequency of retroviral detection has been higher in other liver diseases than in PBC (27% versus 12%) [262]. There have been no epidemiological studies demonstrating the incidence, prevalence, distribution and consequences of human β-retroviral infection in PBC, and the pathogenic relationship between this viral agent and PBC remains uncertain.

16.3.5.4 Other Infectious Candidates

Epstein-Barr virus (EBV) [263], *Mycobacterium gordonae* [264], *Helicobacter pylori* [265], *Chlamydia pneumoniae* [266], and *Mycoplasma pneumoniae* [267] have all been proposed as causative agents of PBC, but none has been validated or aggressively pursued [247] (Table 16.7). Infection may be a consequence of chronic liver disease rather than its cause. Furthermore, the burden of infection with one or more organisms may be the critical factor triggering the disease rather than any individual agent [268].

16.3.6 Variations in Genetic Predisposition in Different Geographical Regions and Ethnic Groups

Epidemiological studies have implicated genetic factors in the occurrence of PBC [269–271], and these observations have been supported by genome-wide association studies in North American, European, and Japanese cohorts [272–275]. PBC has occurred in 5 of 8 monozygotic twin sets within families that have had at least one index case of PBC, and it has not occurred in 8 dizygotic twin sets selected by the same criteria [270] (Table 16.8). The concordance rate of 0.63 among individuals that have genetic identity and shared environmental background (monozygotic twins) contrasts with the absence of disease in individuals that lack genetic identity but have shared environmental background (dizygotic twins). The findings strongly implicate genetic factors in the occurrence of PBC, and they are supported by other studies of familial occurrence.

PBC has clustered in families, including 5 of 8 sisters of Palestinian origin [202], and familial occurrence has been documented in 0.72% of first degree relatives in Newcastle, England [276]; 1% in Brazil [277]; 1.3% in London, England [278]; 5.1–5.8% in different regions of Japan [269, 279]; 6.4% in New York, New York [280]; and 9.9% in Crete, Greece [271] (Table 16.8). First degree family members may also manifest autoantibodies, hypergammaglobulinemia, and extrahepatic autoimmune diseases that suggest a genetic propensity for immune reactivity. AMA have been demonstrated in 13% of first degree relatives in Olmsted County, Minnesota [281] and 18.8% in Larissa, Greece [282]. Immune mediated diseases of

Table 16.8 Genetic associations with primary biliary cholangitis

Sources	Principal associations	Clinical implications
Twin studies	PBC in 5 of 8 MZ twin sets [270] PBC in 0 of 8 DZ twin sets [270] High concordance with genetic identity (0.63) [270]	Genetic identity a risk factor [270] Shared environment less critical [270]
Familial occurrence	PBC in 5 of 8 Palestinian sisters [202] PBC in 0.72–10% of FDR [271, 276] AMA in 13–19% of FDR [281, 282] Autoimmune diseases in 4–14% of FDR [277, 283] PBC in 1.2% of offspring [276]	Hereditary propensity for PBC [280] Low penetrance of genotype [276]
HLA associations	*DRB1*08-DQB1*0402* haplotype [285] Extends weakly to *DPB1*0301* in British [285] Extends weakly to *DPB1*0501* in Japanese [285] DRB1, DQA1, DQB1 loci by GWAS [275, 287, 288]	Contributory not causative [275] Weak association [285]
Non-HLA associations	Located on chromosomes 6p21.3 and 2q [275] *IL-12A, IL-12RB2* are major factors [289] *CTLA-4* implicated [17, 130]	Lack disease specificity [275] Modulate immune reactivity [290]

AMA antimitochondrial antibodies, *CTLA-4* cytotoxic T lymphocyte antigen-4 gene, *DZ* dizygotic, *FDR* first degree relatives, *HLA* human leukocyte antigen, *IL* interleukin, *MZ* monozygotic, *PBC* primary biliary cholangitis
Numbers in brackets are references

a non-liver nature have also been present in 4% of first degree relatives in Brazil [277] and 14% of first degree relatives in Newcastle, England [283].

These findings are consistent with a hereditary propensity for the development of PBC, but they do not indicate a disease-related genotype of strong penetrance (Table 16.8). Only 1.2% of the offspring of PBC patients develop PBC [276], and the frequency of first degree relatives developing PBC is only 0.7% in the absence of AMA [284]. First degree relatives have a greater frequency of developing PBC if they express AMA (24%), but only if the serum alkaline phosphatase level is also increased [284]. The occurrence of PBC may be favored by hereditary factors, but other infectious, toxic or environmental agents may be necessary to trigger the disease. The variations in the occurrence of PBC, its laboratory manifestations, and other immune-mediated diseases in first degree relatives from different geographical regions and ethnic groups support these considerations.

PBC has been associated with the *DRB1*08-DQB1*0402* haplotype, and this haplotype extends weakly to include *DPB1*0301* in British patients and *DPB1*0501* in Japanese patients [285] (Table 16.8). Polymorphisms of genes that can affect the immune response in PBC are located on chromosomes 6p21.3 and 2q [286], and a polymorphism of the *cytotoxic T lymphocyte antigen-4* (*CTLA-4*) *gene* has been

implicated in PBC [17, 130]. Genome wide association studies have demonstrated genetic associations in PBC within and outside the MHC, and at least 27 risk loci unrelated to the human leukocyte antigen (HLA) have been associated with PBC [275, 287, 288]. The HLA variants that have been described in PBC by GWAS are at DRB1, DQA1 and DQB1 loci, and the non-HLA loci have been mainly genes that affect the production of IL-12 and the family of cytokines that modulate immune reactivity [275]. Variants of *IL-12A* and *IL-12RB2* have had strong associations with PBC [289], and they encode subunits on $CD4^+$ T lymphocytes that induce molecular signaling pathways that promote the immune response [275, 290]. These loci have not been disease-specific, have been shared in other immune-mediated diseases, and can vary in different ethnic groups. They probably constitute a genetic background that favors immune reactivity after exposure to one or more environmental or infectious agents.

16.3.7 Possible Epigenetic Changes Affecting Predisposition and Outcome

Epigenetic changes that affect the expression of the chemokine receptor CXCR3 may influence the migration of activated T lymphocytes and natural killer (NK) cells to sites of liver injury in PBC [291], and the miRNAs miR-451a and miR-642a-3p may silence immune regulatory genes and contribute to disease severity [292]. Demethylation of the DNA molecule enwrapped with histones within the nucleosomes of chromatin can enhance the accessibility of transcription factors to DNA binding sites, increase the activity of ribonucleic acid polymerase (RNAP), and promote the transcriptional activity of immunomodulatory genes [21, 293, 294]. In PBC, the CXCR3 gene promoter in the X chromosome of $CD4^+$ T lymphocytes is demethylated [291], and this epigenetic change may affect the migration of liver-infiltrating inflammatory cells and the severity of PBC [295]. Similarly, the over-expression of miR-451a and miR-642a-3p in exosomes isolated from the plasma of patients with PBC may silence anti-inflammatory genes and increase disease severity as described in patients with rheumatoid arthritis [296]. Epigenetic changes are under-evaluated factors in the autoimmune liver diseases, and they may be affected by environmental cues, inherited as stable traits, and help shape susceptibility and phenotypic diversity.

16.4 Epidemiology of Primary Sclerosing Cholangitis

The epidemiology of PSC has been difficult to study because its diagnosis has been dependent on evolving criteria and techniques [297–303]. Older studies may not have applied the same diagnostic tools or had the same interpretative expertise as more recent studies [61], and the same diagnostic methods may not have been applied uniformly in all centers in the same study or in different studies. Furthermore, certain aspects of the disease, such as small duct PSC [304], PSC unrelated to inflammatory bowel disease [305], PSC in children [192] and asymptomatic PSC [303], may have

been overlooked in some medical centers. Consequently, variations in the incidence and prevalence of PSC between studies in different regions may reflect differences in diagnostic methods and case identification rather than actual regional differences in the occurrence of the disease. These interpretive difficulties may be more pronounced in population-based studies of PSC than in population-based studies of autoimmune hepatitis and PBC [306].

16.4.1 Annual Incidence of Primary Sclerosing Cholangitis

The annual incidence of PSC has ranged from 0 cases per 100,000 persons among Alaskan natives [38, 307] to 1.3 cases per 100,000 persons in Norway [44] (Table 16.9). The most recent studies in Sweden (1992–2005) [305] and the Netherlands (2008–2011) [308] indicate a more than twofold difference in the annual incidence of PSC between the countries (1.22 cases per 100,000 persons in Sweden versus 0.5 cases per 100,000 cases in the Netherlands). Swedish men have a threefold higher incidence of PSC than Dutch men (1.78 cases per 100,000 persons versus 0.6 cases per 100,000 persons), whereas Swedish women have a 1.7-fold higher incidence of PSC than Dutch women (0.69 cases per 100,000 persons versus 0.4 cases per 100,000 persons) [305, 308].

The United Kingdom [309, 310], the Netherlands [308]), the United States [311, 312] and Canada [313] have annual incidences of PSC that are less than 1 case per 100,000 persons (0.41–0.91 cases per 100,000 persons in the United Kingdom, 0.5 cases per 100,000 persons in the Netherlands, 0.41–0.9 cases per 100,000 persons in the United States, and 0.92 cases per 100,000 persons in Canada) (Table 16.9). Spain is an exception among the European countries as the annual incidence of PSC was only 0.07 cases per 100,000 persons in a questionnaire study performed between 1984 and 1988 [314]. Small duct PSC has an incidence of 0.15 cases per 100,000 persons in Calgary, Canada, whereas the overall incidence of PSC in this region is more than sixfold greater at 0.92 cases per 100,000 persons [313].

In contrast to the European and North American experiences, the Scandinavian countries (Sweden, Norway) have an annual incidence of PSC that is greater than 1 case per 100,000 persons (1.22 cases per 100,000 persons in Sweden and 1.31 cases per 100,000 persons in Norway), and the incidences are similar to each other despite differences in the time intervals of each study [44, 305] (Table 16.9). In all studies, PSC has been more common in men than women, and in the few pediatric studies, children have been less commonly affected than adults. The annual incidence of PSC among children in the United States (Utah) is 0.2 cases per 100,000 persons [49], and this incidence is lower than the annual incidence of 0.9 cases per 100,000 persons among adults in the United States (Olmsted County, Minnesota) [311]. The annual incidence of PSC in Canadian children is 0.23 cases per 100,000 persons, and it is also lower than the annual incidence of PSC in Canadian adults (1.11 cases per 100,000 persons) [313]. The similar incidence of PSC in the children of Utah and Canada suggests that possible differences in ethnicity or cultural background were inconsequential.

Table 16.9 Incidence and prevalence of primary sclerosing cholangitis in different regions (lowest to highest annual incidence)

Geographical region	Annual incidence Per 100,000 persons	Prevalence Per 100,000 persons
Alaska (Natives) [38, 307] (1984–2000)	0	Not reported
Spain [314] (1984–1988)	0.07 Increased from 0.02 to 0.07 over 5 years	0.22 (December 31, 1988) Increased from 0.08 to 0.22 over 5 years
United States (Utah) [49] (1986–2011)	0.2 (children)	1.5 (children)
United Kingdom [309, 310] (1991–2001 and 1984–2003)	0.41–0.91 No significant increase over 10 years	3.85 (2001)–12.7 (July 1, 2003) United Kingdom versus South Wales
Netherlands [308] (2008–2011)	0.5 (men, 0.6; women, 0.4) 0.25, female adolescents 0.93, men aged 40–49 years	6.0 (January 1, 2008) Increasing prevalence (possible greater frequency of IBD)
United States [311, 312] (1991–2000 and 2000–2006)	0.41–0.9 (men, 0.45–1.25; women, 0.37–0.54) No increase in men or women	4.03 (men, 4.92; women, 3.19) to 13.6 (men, 20.9; women, 6.3) California versus Minnesota
Canada (Calgary) [313] (2000–2005)	0.92 (adults, 1.11; children, 0.23) Small duct PSC, 0.15	Not reported
Japan [367] (2007)	Not reported	0.95 (2007)
Sweden [305] (1992–2005)	1.22 (men, 1.78; women, 0.69) Increased overall AAPC, 3.06 Increased AAPC for women: • IBD-associated PSC, 7.01 • Large duct PSC, 6.32 Increased AAPC for men: • Non-IBD related, 9.69 • Small duct PSC, 17.88	16.2 (December 31, 2005) (men, 23.7; women, 8.9)
Norway [44, 315] (1986–1995)	0.7–1.31	5.6–8.5 (December 31, 1995)

AAPC average annual percentage change, *IBD* inflammatory bowel disease, *PSC* primary sclerosing cholangitis
Numbers in brackets are references

A meta-analysis restricted to eight population-based studies [44, 305, 309–311, 313–315] has estimated the overall annual incidence of PSC as 1.0 case per 100,000 persons [316]. The incidence of PSC was considered to be similar in North America and Europe, and the incidence ratio for males versus females was 1.7 (range, 1.34–2.07). The median age at diagnosis was 41 years (range, 35–47 years), and the frequency of concurrent inflammatory bowel disease was 67%. Importantly, the average annual percentage change (AAPC) in the incidence of PSC had increased in four studies, ranging from 3.06% to 27.2% [316]. A population-based study in

Sweden has indicated that the AAPC for large duct PSC has increased by 6.32% in women and that the AAPC for small duct PSC has increased by 17.88% in men [305] (Table 16.9).

The disparities between studies may reflect differences in the time intervals of each study, the methods that were applied for detection of PSC, and the level of expertise and interest in PSC among the participating institutions. Alternatively, the disparities may reflect true differences in susceptibility to the disease. Predispositions for PSC may be influenced by genetic factors [15, 132, 317–326], exposure to environmental agents [327–329], alterations in the intestinal microbiome [330–332], and the presence of inflammatory bowel disease, especially ulcerative colitis [333, 334]. These predisposing factors may vary among age groups, races, and regions within a country or between countries [321].

Inflammatory bowel disease (IBD), mainly ulcerative colitis, has been present in 67–80% of patients with PSC in Europe and North America [311, 316, 335], and men with PSC have had IBD more commonly than women with PSC in the United States (73% versus women 52%) [312]. Since 2.4–7.5% of patients with IBD have PSC [303, 336, 337], an increasing frequency of IBD in a population may impact on the annual incidence of PSC in that region. The annual incidence of ulcerative colitis has increased from 22.1 cases per 100,000 persons in Finland to 27.4 cases per 100,000 persons from 2001 to 2007 [338]. The annual incidence of ulcerative colitis is also higher in Finnish men than women (27.8 cases per 100,000 persons versus 21.9 cases per 100,000 persons). An increasing frequency of men with ulcerative colitis may explain in part an increasing annual incidence of PSC in some regions. An increase in the annual incidence of IBD has also been reported in Denmark [339] and suggested in the Netherlands [308].

16.4.2 Prevalence of Primary Sclerosing Cholangitis

The prevalence of PSC has been as low as 0.22 cases per 100,000 persons in Spain [314] to as high as 16.2 cases per 100,000 persons in Sweden [305] (Table 16.9). Sweden (16.2 cases per 100,000 persons) [305], Olmsted County, Minnesota in the United States (13.6 persons per 100,000 persons) [311], and Norway (8.5 cases per 100,000 persons) [44] have had the highest prevalence of the disease, and these regions have also had tertiary medical centers with long-standing expertise and interest in PSC. Men have had a 2.7-fold greater prevalence of PSC than women in Sweden [305] and a 3.3-fold greater prevalence in Olmsted County, Minnesota [311].

Prevalence in a geographic region has not closely reflected the incidence of the disease in that region (Table 16.9). Countries with similar annual incidences of PSC (United Kingdom [309] and the Netherlands [308], and Sweden [305] and Norway [44]) have had 1.9–2.3-fold differences in prevalence. A striking increase in the prevalence of PSC in Spain from 0.08 cases per 100,000 persons to 0.22 cases per 100,000 persons over a 5 year period may have reflected improved case

detection [314], but a more recent population-based study in the Netherlands using current diagnostic criteria and methods has also suggested that the prevalence of PSC is increasing [308]. A factor that may account for this apparent increase in prevalence is improved survival through early diagnosis and the availability of liver transplantation.

16.4.3 Variations in Clinical Phenotype

16.4.3.1 Variant ("Overlap") Syndromes

PSC may have clinical features that resemble autoimmune hepatitis or PBC [340], and the mixed manifestations may be present concurrently [341, 342] or emerge later [343–346]. Features reminiscent of autoimmune hepatitis are present in 4–54% of patients with PSC [347, 348], and cholangiographic features of PSC are present in 2–10% of patients with autoimmune hepatitis [60, 61]. The frequency that findings of PSC and PBC coexist is estimated at 0.76% based on the presence of a mixed syndrome in two of 261 patients with autoimmune liver disease [346]. The diagnostic criteria for the variant ("overlap") syndromes of PSC have not been codified, and treatment recommendations are based on weak clinical evidence [6, 7, 301, 349]. Immunosuppressive therapy (prednisone or prednisolone with azathioprine) in combination with ursodeoxycholic acid has been recommended by the European Association for the Study of the Liver (EASL) [350] and the American Association for the Study of Liver Diseases (AASLD) [301]. The epidemiology of the variant syndromes of PSC is unknown.

16.4.3.2 IgG4-Associated Cholangitis

IgG4-associated cholangitis has cholangiographic features that are indistinguishable from those of PSC [351, 352]. The inflammatory lesions usually involve the extrahepatic, hilar, and perihilar bile ducts by cholangiography [352], but histological examination of the liver can indicate small bile duct damage in 26% [353]. The histological manifestations of small bile duct injury are most common (80%) in patients with intrahepatic strictures [353], and the histological spectrum includes portal inflammation, >10 IgG4-staining plasma cells, and distinctive portal-based fibro-inflammatory micro-nodules composed of fibroblasts, plasma cells, lymphocytes, and eosinophils [354, 355].

IgG4-associated cholangitis is within the spectrum of IgG4-related diseases that have been characterized as fibro-inflammatory processes with a dense lymphoplasmacytic infiltrate enriched with IgG4-staining plasma cells, storiform fibrosis, and obliterative phlebitis [355, 356]. The IgG4-related diseases have affected the colon, salivary glands, periorbital tissues, kidneys, lungs, thyroid, prostate, skin, and pericardium in addition to the pancreas, liver, and biliary tract [356]. The diagnostic criteria of the Japan Biliary Association for IgG4-associated cholangitis include coexistence of IgG4-related disease outside the biliary tract [357]. The other criteria are characteristic cholangiographic changes, elevated serum IgG4 level, and typical histopathological findings.

Autoimmune pancreatitis occurs in 19–92% of patients with IgG4-associated cholangitis, depending in part on the presence or absence of jaundice [351, 358], and the lungs, kidneys, colon, mesentery, retroperitoneum, and salivary glands may also be involved [359]. A lymphoplasmacytic infiltrate that contains >50 IgG4-staining plasma cells/high power field may involve the colon in patients with IgG4-associated cholangitis and mimic ulcerative colitis [359–361]. IgG4-related colitis should be differentiated from the ulcerative colitis more frequently associated with PSC.

Serum IgG4 levels are increased in 74–90% of patients with IgG4-associated cholangitis (versus 9–15% in patients with PSC) [358, 359, 362], and a ratio of serum IgG4/IgG1 >0.24 has been proposed as a feature distinguishing IgG4-associated cholangitis from PSC [359]. IgG4-associated cholangitis must be distinguished from PSC and cholangiocarcinoma [363], and its characteristic responsiveness to glucocorticoid therapy can be a distinguishing feature and another criterion for its diagnosis [357]. The epidemiology of the IgG4-related diseases is unknown, albeit the early reports of this disease have been mainly from Japan.

16.4.4 Variations in Outcomes of Primary Sclerosing Cholangitis in Different Age Groups

The estimated median survival from diagnosis to liver transplantation or death from PSC was 21.2 years in a population-based study from the Netherlands, and the duration of transplant-free survival was 20.6 years [308]. Small duct PSC was associated with a better survival than large duct PSC, and the main causes of death were cholangiocarcinoma (32%), liver failure (18%), complications of liver transplantation (9%), and colorectal carcinoma (8%) [308].

The median transplant-free survival for pediatric patients with PSC has been 12.7 years, and overall survival has been shorter than in an age- and gender-matched population [364]. Small duct PSC may be more common in children than adults (36% versus 6–11%), but the shorter transplant-free survival for children than adults suggests differences in the stage of PSC at diagnosis or the aggressiveness of the liver disease [365]. The 5-year survival with the native liver in children has been 80%, and the 10-year survival after liver transplantation has been 89%. Unlike PSC in adults, the PSC in children has not been complicated by cholangiocarcinoma [364, 365].

Survival in adults has been better in studies based on population-based cohorts that are not weighted by disease severity compared to studies from tertiary medical centers where referrals for advanced disease are likely (median survival, 21.3 years in population-based cohorts versus 13.2 years in cohorts from tertiary referral centers) [308]. These observations may also apply to the pediatric experiences which are mainly derived from referral institutions [59, 192, 364, 365]. Variations in the prevalence of PSC among countries with a similar incidence of the disease may reflect differences in the severity and stage of the disease at presentation which may in turn vary with the nature of the medical centers participating in the study.

16.4.5 Variations in the Occurrence of PSC in Different Geographic Regions and Ethnic Groups

Population-based epidemiological studies of PSC have been sparse in developing countries and different ethnic groups. PSC has been described in Japan [366, 367], India [368], and Singapore [369], and the major phenotypic difference between the PSC of Asia and western countries has been a lower frequency of concurrent IBD in Asia. PSC has been associated with IBD in only 20% of patients in Singapore [369], 37% in Japan [366], and 50% in India [368]. A questionnaire-based epidemiological study in Japan in 2007 (which excluded sclerosing cholangitis associated with immunoglobulin-4) estimated the prevalence of PSC as 0.95 cases per 100,000 persons [367]. This prevalence was at least fourfold lower than in western countries (Table 16.9). The basis for this disparity remains uncertain, albeit a lower frequency of IBD in these countries may have contributed.

Disparities in the occurrence of PSC have also been recognized in certain regions within the same country, and ethnic diversity may have been a contributing factor. The prevalence of PSC has been 3.3-fold greater in a region of the United Kingdom (South Wales) [310] than in the entire country [309], and the annual incidence (0.41 versus 0.91 cases per 100,000 persons) and overall prevalence (4.03 versus 13.6 cases per 100,000 persons) of PSC have varied in different regions of the United States (northern California [312] versus Olmsted County, Minnesota [311]).

Non-Hispanic whites in northern California (Oakland) account for 80% of the cases of IBD [312, 370]. African Americans account for 16% of cases, and Asians account for 9% [312, 370]. These ethnic variations in the occurrence of IBD may explain in part the regional differences in the occurrence of PSC. Importantly, the occurrence of IBD may not closely correlate with the occurrence of PSC as each disease has genetic factors that are independent of each other [319, 320]. Well-designed, population-based epidemiological studies are required to understand the regional differences within the same country.

16.4.6 External and Internal Environmental Factors in Primary Sclerosing Cholangitis

The major external environmental risk factor that has been implicated in PSC has been non-smoking (Table 16.10). Four case control studies have indicated that patients with PSC are more commonly non-smokers than healthy control subjects (66–70% versus 39–47%) [327–329, 371]. Furthermore, the odds ratio for PSC in current smokers compared to never-smokers is reduced (odds ratio, 0.13–0.21). The decreased odds for PSC in current and former smokers has been independent of the presence or absence of IBD, and a systemic protective effect of smoking on the occurrence of PSC has been proposed [327, 371]. Tonsillectomy has also been associated with a decreased risk of PSC [329], whereas the protective effect of appendectomy that had been proposed for ulcerative colitis [372] has not been recognized in PSC [328, 329, 371].

Investigational scrutiny has also focused on the intestinal microbiome as a reservoir of microbial antigens, metabolic products, and activated immune cells that could affect susceptibility to IBD and PSC [32] (Table 16.10). Biliary epithelial cells in PSC express toll-like receptors (TLR4 and TLR9) that can respond to bacterial-derived lipopolysaccharide and produce pro-inflammatory cytokines [331, 373]; atypical perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) are directed against β-tubulin which cross-reacts with an intestinal bacterial antigen (FtsZ) [330]; and commensal bacteria in a murine model of PSC are protective against the disease [332]. Preliminary translational studies have supported the potential pathogenic role of the intestinal microbiome by demonstrating clinical and laboratory improvement in patients with PSC after antibiotic therapy [374]. The internal environment may be more important than the external environment in modulating the occurrence of this disease and affecting its distribution among different ethnic groups and countries [375].

16.4.7 Genetic Factors in the Occurrence of Primary Sclerosing Cholangitis

The disparities in the occurrence of PSC between age-groups, different ethnicities, and various countries may be a consequence of genetic factors that favor or protect against IBD or PSC (Table 16.10). The frequency of PSC among first degree relatives is 0.7%, and it is 1.5% among siblings [376]. Three percent of patients with PSC have first degree relatives with PSC, and this occurrence is almost 100-fold greater than in the general population [376]. The risk of PSC in first degree relatives is independent of the presence of IBD, and the genetic factors associated with PSC have been different than those associated with IBD by high resolution typing of *DRB1* and *DQB1* loci [319]. These observations support a genetic basis for PSC, and they suggest a complex genetic disease that lacks a single genetic determinant.

PSC has been associated with HLA DRB1*03 and HLA B8 [377, 378], and haplotypes containing *DRB3*0101-DRB1*0301* and *DRB3*0101-DRB1*1301* have been proposed as risk factors for the disease [318] (Table 16.10). Furthermore, the haplotype containing *DRB1*04-DQB1*0501* has been associated with protection from the disease [318, 378]. Genome wide association studies have found the strongest associations with PSC near *HLA-B* at chromosome 6p21, and it has also implicated alleles outside the HLA complex at chromosome 13q31 [12, 336].

HLA associations with HLA B8 and HLA DRB1*13 have been identified as risk factors for PSC in patients listed for liver transplantation, and HLA DRB1*04 has been protective [321] (Table 16.10). African Americans were at greater risk for liver transplantation than European Americans (odds ratio, 1.323; 95% CI: 1.221–1.438), and they had HLA B8 more commonly than the HLA B8-DRB1*03 linkage disequilibrium found in European Americans. These observations introduced the possibility that refinements in HLA typing might be able to distinguish ethnic differences in susceptibility to PSC. Such differences might explain in part regional variations in the occurrence of PSC and support future studies designed to discover triggering antigens in different age groups, ethnic populations, and geographical regions.

Table 16.10 Risk factors for primary sclerosing cholangitis

Risk factor	Presumed mechanism	Evidence
Non-smoking	Smoking may be protective against IBD [327, 371] Actions uncertain [327]	More non-smokers in PSC than controls [327–329, 371] Independent of protective effect on IBD [327, 371]
Tonsillectomy	Uncertain [329]	Statistical association in risk survey [329]
Intestinal microbiome	Reservoir of microbial agents, metabolic products, and activated immune cells affect systemic immune responses [32]	BEC express TLR4 and TLR9 [373] BEC respond to bacterial LPS [331, 373] BEC produce pro-inflammatory cytokines [331, 373] pANCA cross-react with microbial antigen [330] Commensal intestinal bacteria protective [332] Antibiotic therapy improves patients [374]
IBD	Disordered intestinal microbiome (dysbiosis) [32] Increased intestinal permeability to microbial antigens and gut-derived immune cells [32]	Present in 67–80% of patients with PSC [311, 316, 335] Different genetic risk factors than PSC [320] More frequent in men with or without PSC [312, 338] Increasing frequency in certain countries [308, 338, 339] May be basis for increasing frequency of PSC [338, 339]
Family history	Genetic predisposition with low penetrance [376]	PSC in 0.7% of FDRs and 1.5% of siblings [376] 3% of patients with PSC have FDRs with PSC [376]
Genetic predisposition	Complex genetic disease associated with susceptibility loci within and outside MHC [12, 322, 325]	Associated with HLA DRB1*03 and HLA B8 [377] HLA DRB1*04 protective [321, 378] *DRB3*0101-DRB1*0301* and *DRB3*0101-DRB1*1301* are susceptibility haplotypes [318] *DRB1*04-DQB1*0501* is protective haplotype [318] Associated with *HLA-B* locus at chromosome 6p21 and non-HLA alleles on chromosome 13q31 by GWAS [12]

BEC biliary epithelial cells, *FDRs* first degree relatives, *GWAS* genome-wide association studies, *HLA* human leukocyte antigen, *IBD* inflammatory bowel disease, *LPS* lipopolysaccharide, *MHC* major histocompatibility complex, *PSC* primary sclerosing cholangitis, *TLR* toll-like receptors
Numbers in brackets are references

16.4.8 Possible Epigenetic Changes Affecting Predisposition and Outcome

Patients with PSC have 21 miRNAs that are differentially expressed, and miR-200c is the principal distinguishing marker [379]. miR-200c is down-regulated in PSC compared to healthy individuals but up-regulated in patients with cholangiocarcinoma. The miRNAs associated with PSC may influence the actions of diverse regulatory genes that may include anti- and pro-inflammatory genes and tumor suppressors. Aberrant DNA methylation has been described in the genes of patients with cholangiocarcinoma and PSC [380], and these epigenetic changes might be clues to the mechanisms of malignant transformation in PSC and the identity of

biomarkers that reflect this propensity [381]. The genes regulating the expression of the miRNAs are subject to epigenetic factors that may be influenced by inheritable traits or environmental cues, and these epigenetic changes could contribute to variations in disease behavior between individuals, populations or geographical regions.

16.5 Overview

Autoimmune hepatitis, PBC and PSC are rare chronic liver diseases (annual incidence, <50 cases per 100,000 persons), but they are persistent, progressive, and variably responsive to current management strategies. They can affect individuals in their most productive phases of life, and their societal costs may be high. Misdirected immune-mediated mechanisms and regulatory pathways have been implicated in their occurrence, and a constellation of genetic factors may influence susceptibility to the disease and outcome.

Variant (overlap) syndromes have also been described in which patients with autoimmune hepatitis may have features similar to those of PBC or PSC, and patients with PBC or PSC may have features similar to those of autoimmune hepatitis [5, 6]. The pathogenic bases for these variant syndromes are uncertain; diagnostic criteria have not been codified; and their inclusion within the classical disease categories based on their predominant component remains controversial [349]. These variant syndromes may confound epidemiological studies of the classical immune-mediated liver diseases. They may also re-shape the understanding of host-dependent mechanisms and pathogenic pathways of autoimmunity and help explain regional differences in the occurrence, clinical phenotype, and outcomes of autoimmune hepatitis, PBC and PSC.

Population-based epidemiological studies have indicated that autoimmune hepatitis, PBC, and PSC can occur with different frequencies in different geographical regions, ethnic groups, and age-ranges and that the incidence and prevalence of each disease may be increasing in certain regions. The etiological triggers for autoimmune hepatitis, PBC and PSC are uncertain, but the preferential emergence of these diseases in certain populations and their clustering in certain locations suggests that environmental and infectious agents are critical factors in genetically predisposed individuals.

Variations in the incidence of the disease in different regions and ethnic groups should direct investigations that define genetic susceptibility factors and etiological agents, and variations in prevalence should direct evaluations of management strategies that impact on immediate and long-term survival. Population-based studies have been lacking in developing countries, and they have also been deficient in describing the burden, distribution, and trends of autoimmune hepatitis and the variant syndromes world-wide. Epidemiological studies that fill these current gaps in knowledge are essential to design pertinent investigational protocols, appropriately allocate resources, and impel changes in healthcare policy and practice.

Acknowledgments This review did not receive financial support from a funding agency or institution, and Albert J. Czaja, MD has no conflict of interests to declare.

Table of Landmark Literature

Study title and authors	Study design	Summary results	Main limitations
Ngu JH et al. J Gastroenterol Hepatol 2010;25:1681–86	Population-based study of AIH in Canterbury, New Zealand	• Peak age in sixth decade • Ethnic-specificity	• Tertiary referral center over-representative
Gronbaek L, et al. J Hepatol 2014;60:612–17	Population-based study of AIH using Danish National Patient Registry	• Cirrhosis in 28% • Incidence increasing • Prognosis improving	• Uncertain uniformity of diagnostic criteria
Van Gerven NM, et al. Scand J Gastroenterol 2014;49:1245–54	Population-based study of AIH in the Netherlands	• Concurrent immune diseases in 26%	• Incomplete datasets • Diagnostic uncertainties
Sood S, et al. Gastroenterology 2004;127:470–5	Population-based studies of PBC in Victoria, Australia	• Victorians protected • Absent environmental trigger possible	• Inconsistent case finding methods used
Myers RP, et al. Hepatology 2009;50:1884–92	Population-based study of PBC in Calgary, Canada	• Increasing prevalence • Need for better therapy	• Risk factors unavailable • Incomplete datasets
Gershwin ME, et al. Hepatology 2005;42:1194–1202	Large case-controlled interview-based study of PBC	• Risk factors of family history, UTIs, past smoking, and HRT	• Patients highly selected • Dependent on patient's recall and understanding
Bambha K, et al. Gastroenterology 2003;125:1364–69	Population-based study of PSC in U.S. community	• Male predominance • 73% of PSC with IBD • Poor overall survival	• Uncertain case discovery
Molodecky NA, et al. Hepatology 2011;53:1590–99	Meta-analysis of 8 mainly population-based studies of PSC	• Incidence increasing	• Small number of studies • No prevalence data
Boonstra K, et al. Hepatology 2013;58:2045–55	Population-based study of PSC in the Netherlands	• Lower survival in tertiary referral centers • CRC increased	• Incomplete datasets • Uncertain case discovery

AIH autoimmune hepatitis, *CRC* colorectal cancer, *HRT* hormone replacement therapy, *IBD* inflammatory bowel disease, *PBC* primary biliary cholangitis, *PSC* primary sclerosing cholangitis, *UTIs* urinary tract infections

References

1. Czaja AJ. Autoimmune hepatitis in diverse ethnic populations and geographical regions. Expert Rev Gastroenterol Hepatol. 2013;7:365–85.
2. Czaja AJ. Review article: next-generation transformative advances in the pathogenesis and management of autoimmune hepatitis. Aliment Pharmacol Ther. 2017;46:920–37.
3. Kim WR, Brown RS Jr, Terrault NA, El-Serag H. Burden of liver disease in the United States: summary of a workshop. Hepatology. 2002;36:227–42.
4. Czaja AJ. Transitioning from idiopathic to explainable autoimmune hepatitis. Dig Dis Sci. 2015;60:2881–900.
5. Czaja AJ. The variant forms of autoimmune hepatitis. Ann Intern Med. 1996;125:588–98.
6. Czaja AJ. The overlap syndromes of autoimmune hepatitis. Dig Dis Sci. 2013;58:326–43.
7. Czaja AJ. Cholestatic phenotypes of autoimmune hepatitis. Clin Gastroenterol Hepatol. 2014;12:1430–8.
8. Oldstone MB. Molecular mimicry, microbial infection, and autoimmune disease: evolution of the concept. Curr Top Microbiol Immunol. 2005;296:1–17.
9. Bogdanos DP, Baum H, Grasso A, Okamoto M, Butler P, Ma Y, et al. Microbial mimics are major targets of crossreactivity with human pyruvate dehydrogenase in primary biliary cirrhosis. J Hepatol. 2004;40:31–9.
10. Czaja AJ. Autoimmune hepatitis. Part A: pathogenesis. Expert Rev Gastroenterol Hepatol. 2007;1:113–28.
11. Czaja AJ. Genetic factors affecting the occurrence, clinical phenotype, and outcome of autoimmune hepatitis. Clin Gastroenterol Hepatol. 2008;6:379–88.
12. Karlsen TH, Franke A, Melum E, Kaser A, Hov JR, Balschun T, et al. Genome-wide association analysis in primary sclerosing cholangitis. Gastroenterology. 2010;138:1102–11.
13. Hirschfield GM, Invernizzi P. Progress in the genetics of primary biliary cirrhosis. Semin Liver Dis. 2011;31:147–56.
14. Hirschfield GM, Chapman RW, Karlsen TH, Lammert F, Lazaridis KN, Mason AL. The genetics of complex cholestatic disorders. Gastroenterology. 2013;144:1357–74.
15. Berntsen NL, Klingenberg O, Juran BD, Benito de Valle M, Lindkvist B, Lazaridis KN, et al. Association between HLA haplotypes and increased serum levels of IgG4 in patients with primary sclerosing cholangitis. Gastroenterology. 2015;148:924–27.e2.
16. van Gerven NM, de Boer YS, Zwiers A, Verwer BJ, Drenth JP, van Hoek B, et al. HLA-DRB1*03:01 and HLA-DRB1*04:01 modify the presentation and outcome in autoimmune hepatitis type-1. Genes Immun. 2015;16:247–52.
17. Juran BD, Atkinson EJ, Schlicht EM, Fridley BL, Lazaridis KN. Primary biliary cirrhosis is associated with a genetic variant in the 3′ flanking region of the CTLA4 gene. Gastroenterology. 2008;135:1200–6.
18. Paladino N, Flores AC, Fainboim H, Schroder T, Cuarterolo M, Lezama C, et al. The most severe forms of type I autoimmune hepatitis are associated with genetically determined levels of TGF-beta1. Clin Immunol. 2010;134:305–12.
19. Mann DA. Epigenetics in liver disease. Hepatology. 2014;60:1418–25.
20. Jeffries MA, Sawalha AH. Autoimmune disease in the epigenetic era: how has epigenetics changed our understanding of disease and how can we expect the field to evolve? Expert Rev Clin Immunol. 2015;11:45–58.
21. Czaja AJ. Epigenetic changes and their implications in autoimmune hepatitis. Eur J Clin Investig. 2018;48:e12899.
22. Czaja AJ. Global disparities and their implications in the occurrence and outcome of autoimmune hepatitis. Dig Dis Sci. 2017;62:2277–92.
23. Pando M, Larriba J, Fernandez GC, Fainboim H, Ciocca M, Ramonet M, et al. Pediatric and adult forms of type I autoimmune hepatitis in Argentina: evidence for differential genetic predisposition. Hepatology. 1999;30:1374–80.

24. Smyk D, Mytilinaiou MG, Rigopoulou EI, Bogdanos DP. PBC triggers in water reservoirs, coal mining areas and waste disposal sites: from Newcastle to New York. Dis Markers. 2010;29:337–44.
25. Fainboim L, Canero Velasco MC, Marcos CY, Ciocca M, Roy A, Theiler G, et al. Protracted, but not acute, hepatitis A virus infection is strongly associated with HLA-DRB*1301, a marker for pediatric autoimmune hepatitis. Hepatology. 2001;33:1512–7.
26. Henao-Mejia J, Elinav E, Thaiss CA, Licona-Limon P, Flavell RA. Role of the intestinal microbiome in liver disease. J Autoimmun. 2013;46:66–73.
27. Barin JG, Tobias LD, Peterson DA. The microbiome and autoimmune disease: report from a Noel R. Rose Colloquium. Clin Immunol. 2015;159:183–8.
28. Chong CW, Ahmad AF, Lim YA, Teh CS, Yap IK, Lee SC, et al. Effect of ethnicity and socioeconomic variation to the gut microbiota composition among pre-adolescent in Malaysia. Sci Rep. 2015;5:13338.
29. Francino MP. Antibiotics and the human gut microbiome: dysbioses and accumulation of resistances. Front Microbiol. 2015;6:1543.
30. Lin R, Zhou L, Zhang J, Wang B. Abnormal intestinal permeability and microbiota in patients with autoimmune hepatitis. Int J Clin Exp Pathol. 2015;8:5153–60.
31. Miller GE, Engen PA, Gillevet PM, Shaikh M, Sikaroodi M, Forsyth CB, et al. Lower neighborhood socioeconomic status associated with reduced diversity of the colonic microbiota in healthy adults. PLoS One. 2016;11:e0148952.
32. Czaja AJ. Factoring the intestinal microbiome into the pathogenesis of autoimmune hepatitis. World J Gastroenterol. 2016;22:9257–78.
33. Javierre BM, Hernando H, Ballestar E. Environmental triggers and epigenetic deregulation in autoimmune disease. Discov Med. 2011;12:535–45.
34. Canas CA, Canas F, Bonilla-Abadia F, Ospina FE, Tobon GJ. Epigenetics changes associated to environmental triggers in autoimmunity. Autoimmunity. 2016;49:1–11.
35. Heyn H, Moran S, Hernando-Herraez I, Sayols S, Gomez A, Sandoval J, et al. DNA methylation contributes to natural human variation. Genome Res. 2013;23:1363–72.
36. Morales LS, Lara M, Kington RS, Valdez RO, Escarce JJ. Socioeconomic, cultural, and behavioral factors affecting Hispanic health outcomes. J Health Care Poor Underserved. 2002;13:477–503.
37. Carrion AF, Ghanta R, Carrasquillo O, Martin P. Chronic liver disease in the Hispanic population of the United States. Clin Gastroenterol Hepatol. 2011;9:834–41.
38. Hurlburt KJ, McMahon BJ, Deubner H, Hsu-Trawinski B, Williams JL, Kowdley KV. Prevalence of autoimmune liver disease in Alaska Natives. Am J Gastroenterol. 2002;97:2402–7.
39. Haider AS, Kaye G, Thomson A. Autoimmune hepatitis in a demographically isolated area of Australia. Intern Med J. 2010;40:281–5.
40. Gronbaek L, Vilstrup H, Jepsen P. Autoimmune hepatitis in Denmark: incidence, prevalence, prognosis, and causes of death. A nationwide registry-based cohort study. J Hepatol. 2014;60:612–7.
41. Delgado JS, Vodonos A, Malnick S, Kriger O, Wilkof-Segev R, Delgado B, et al. Autoimmune hepatitis in southern Israel: a 15-year multicenter study. J Dig Dis. 2013;14:611–8.
42. van Gerven NM, Verwer BJ, Witte BI, van Erpecum KJ, van Buuren HR, Maijers I, et al. Epidemiology and clinical characteristics of autoimmune hepatitis in the Netherlands. Scand J Gastroenterol. 2014;49:1245–54.
43. Ngu JH, Bechly K, Chapman BA, Burt MJ, Barclay ML, Gearry RB, et al. Population-based epidemiology study of autoimmune hepatitis: a disease of older women? J Gastroenterol Hepatol. 2010;25:1681–6.
44. Boberg KM, Aadland E, Jahnsen J, Raknerud N, Stiris M, Bell H. Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. Scand J Gastroenterol. 1998;33:99–103.

45. Lee YM, Teo EK, Ng TM, Khor C, Fock KM. Autoimmune hepatitis in Singapore: a rare syndrome affecting middle-aged women. J Gastroenterol Hepatol. 2001;16:1384–9.
46. Primo J, Merino C, Fernandez J, Moles JR, Llorca P, Hinojosa J. [Incidence and prevalence of autoimmune hepatitis in the area of the Hospital de Sagunto (Spain)]. Gastroenterol Hepatol. 2004;27:239–43.
47. Primo J, Maroto N, Martinez M, Anton MD, Zaragoza A, Giner R, et al. Incidence of adult form of autoimmune hepatitis in Valencia (Spain). Acta Gastroenterol Belg. 2009;72:402–6.
48. Werner M, Prytz H, Ohlsson B, Almer S, Bjornsson E, Bergquist A, et al. Epidemiology and the initial presentation of autoimmune hepatitis in Sweden: a nationwide study. Scand J Gastroenterol. 2008;43:1232–40.
49. Deneau M, Jensen MK, Holmen J, Williams MS, Book LS, Guthery SL. Primary sclerosing cholangitis, autoimmune hepatitis, and overlap in Utah children: epidemiology and natural history. Hepatology. 2013;58:1392–400.
50. Griffiths L, Dyson JK, Jones DE. The new epidemiology of primary biliary cirrhosis. Semin Liver Dis. 2014;34:318–28.
51. Bjornsson ES, Ekbom A. Scandinavian epidemiological research in gastroenterology and hepatology. Scand J Gastroenterol. 2015;50:636–48.
52. Jimenez-Rivera C, Ling SC, Ahmed N, Yap J, Aglipay M, Barrowman N, et al. Incidence and characteristics of autoimmune hepatitis. Pediatrics. 2015;136:e1237–48.
53. Chung HV, Riley M, Ho JK, Leung B, Jevon GP, Arbour LT, et al. Retrospective review of pediatric and adult autoimmune hepatitis in two quaternary care centres in British Columbia: increased prevalence seen in British Columbia's First Nations community. Can J Gastroenterol. 2007;21:565–8.
54. Czaja AJ, Carpenter HA. Validation of scoring system for diagnosis of autoimmune hepatitis. Dig Dis Sci. 1996;41:305–14.
55. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International Autoimmune Hepatitis Group report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol. 1999;31:929–38.
56. Czaja AJ. Performance parameters of the diagnostic scoring systems for autoimmune hepatitis. Hepatology. 2008;48:1540–8.
57. D'Souza R, Sinnott P, Glynn MJ, Sabin CA, Foster GR. An unusual form of autoimmune hepatitis in young Somalian men. Liver Int. 2005;25:325–30.
58. Zolfino T, Heneghan MA, Norris S, Harrison PM, Portmann BC, McFarlane IG. Characteristics of autoimmune hepatitis in patients who are not of European Caucasoid ethnic origin. Gut. 2002;50:713–7.
59. Gregorio GV, Portmann B, Karani J, Harrison P, Donaldson PT, Vergani D, et al. Autoimmune hepatitis/sclerosing cholangitis overlap syndrome in childhood: a 16-year prospective study. Hepatology. 2001;33:544–53.
60. Abdalian R, Dhar P, Jhaveri K, Haider M, Guindi M, Heathcote EJ. Prevalence of sclerosing cholangitis in adults with autoimmune hepatitis: evaluating the role of routine magnetic resonance imaging. Hepatology. 2008;47:949–57.
61. Lewin M, Vilgrain V, Ozenne V, Lemoine M, Wendum D, Paradis V, et al. Prevalence of sclerosing cholangitis in adults with autoimmune hepatitis: a prospective magnetic resonance imaging and histological study. Hepatology. 2009;50:528–37.
62. Perdigoto R, Carpenter HA, Czaja AJ. Frequency and significance of chronic ulcerative colitis in severe corticosteroid-treated autoimmune hepatitis. J Hepatol. 1992;14:325–31.
63. Czaja AJ, Carpenter HA, Santrach PJ, Moore SB, Taswell HF, Homburger HA. Evidence against hepatitis viruses as important causes of severe autoimmune hepatitis in the United States. J Hepatol. 1993;18:342–52.
64. Czaja AJ, Carpenter HA, Santrach PJ, Moore SB. Significance of HLA DR4 in type 1 autoimmune hepatitis. Gastroenterology. 1993;105:1502–7.
65. Czaja AJ, dos Santos RM, Porto A, Santrach PJ, Moore SB. Immune phenotype of chronic liver disease. Dig Dis Sci. 1998;43:2149–55.

66. Homberg JC, Abuaf N, Bernard O, Islam S, Alvarez F, Khalil SH, et al. Chronic active hepatitis associated with antiliver/kidney microsome antibody type 1: a second type of "autoimmune" hepatitis. Hepatology. 1987;7:1333–9.
67. Gregorio GV, Portmann B, Reid F, Donaldson PT, Doherty DG, McCartney M, et al. Autoimmune hepatitis in childhood: a 20-year experience. Hepatology. 1997;25:541–7.
68. Czaja AJ, Manns MP, Homburger HA. Frequency and significance of antibodies to liver/kidney microsome type 1 in adults with chronic active hepatitis. Gastroenterology. 1992;103:1290–5.
69. Czaja AJ. Performance parameters of the conventional serological markers for autoimmune hepatitis. Dig Dis Sci. 2011;56:545–54.
70. Ferucci ED, Choromanski TL, Hurlburt KJ, Livingston S, Plotnik J, Manns MP, et al. Autoimmune hepatitis in the Alaska Native population: autoantibody profile and HLA associations. Liver Int. 2014;34:1241–9.
71. Czaja AJ, Morshed SA, Parveen S, Nishioka M. Antibodies to single-stranded and double-stranded DNA in antinuclear antibody-positive type 1-autoimmune hepatitis. Hepatology. 1997;26:567–72.
72. Targan SR, Landers C, Vidrich A, Czaja AJ. High-titer antineutrophil cytoplasmic antibodies in type-1 autoimmune hepatitis. Gastroenterology. 1995;108:1159–66.
73. Parveen S, Morshed SA, Arima K, Nishioka M, Czaja AJ, Chow WC, et al. Antibodies to Ro/La, Cenp-B, and snRNPs antigens in autoimmune hepatitis of North America versus Asia: patterns of immunofluorescence, ELISA reactivities, and HLA association. Dig Dis Sci. 1998;43:1322–31.
74. Montano-Loza AJ, Shums Z, Norman GL, Czaja AJ. Prognostic implications of antibodies to Ro/SSA and soluble liver antigen in type 1 autoimmune hepatitis. Liver Int. 2012;32:85–92.
75. Umemura T, Zen Y, Hamano H, Ichijo T, Kawa S, Nakanuma Y, et al. IgG4 associated autoimmune hepatitis: a differential diagnosis for classical autoimmune hepatitis. Gut. 2007;56:1471–2.
76. Umemura T, Zen Y, Hamano H, Joshita S, Ichijo T, Yoshizawa K, et al. Clinical significance of immunoglobulin G4-associated autoimmune hepatitis. J Gastroenterol. 2011;46(Suppl 1):48–55.
77. Chung H, Watanabe T, Kudo M, Maenishi O, Wakatsuki Y, Chiba T. Identification and characterization of IgG4-associated autoimmune hepatitis. Liver Int. 2010;30:222–31.
78. Yada N, Kudo M, Chung H, Watanabe T. Autoimmune hepatitis and immunoglobulin g4-associated autoimmune hepatitis. Dig Dis. 2013;31:415–20.
79. Umemura T, Zen Y, Hamano H, Kawa S, Nakanuma Y, Kiyosawa K. Immunoglobin G4-hepatopathy: association of immunoglobin G4-bearing plasma cells in liver with autoimmune pancreatitis. Hepatology. 2007;46:463–71.
80. Zhao XY, Rakhda MI, Wang TI, Jia JD. Immunoglobulin G4-associated de novo autoimmune hepatitis after liver transplantation for chronic hepatitis B- and C-related cirrhosis and hepatocellular carcinoma: a case report with literature review. Transplant Proc. 2013;45:824–7.
81. Ishizu Y, Ishigami M, Kuzuya T, Honda T, Hayashi K, Nakano I, et al. Immunoglobulin G4-associated autoimmune hepatitis later complicated by autoimmune pancreatitis: a case report. Hepatol Res. 2016;46:601–6.
82. Jeannin P, Lecoanet S, Delneste Y, Gauchat JF, Bonnefoy JY. IgE versus IgG4 production can be differentially regulated by IL-10. J Immunol. 1998;160:3555–61.
83. Meiler F, Klunker S, Zimmermann M, Akdis CA, Akdis M. Distinct regulation of IgE, IgG4 and IgA by T regulatory cells and toll-like receptors. Allergy. 2008;63:1455–63.
84. Zen Y, Fujii T, Harada K, Kawano M, Yamada K, Takahira M, et al. Th2 and regulatory immune reactions are increased in immunoglobin G4-related sclerosing pancreatitis and cholangitis. Hepatology. 2007;45:1538–46.
85. Asrani SK, Larson JJ, Yawn B, Therneau TM, Kim WR. Underestimation of liver-related mortality in the United States. Gastroenterology. 2013;145:375–82. e2
86. Verma S, Torbenson M, Thuluvath PJ. The impact of ethnicity on the natural history of autoimmune hepatitis. Hepatology. 2007;46:1828–35.

87. Lim KN, Casanova RL, Boyer TD, Bruno CJ. Autoimmune hepatitis in African Americans: presenting features and response to therapy. Am J Gastroenterol. 2001;96:3390–4.
88. Wong RJ, Corley DA. Survival differences by race/ethnicity and treatment for localized hepatocellular carcinoma within the United States. Dig Dis Sci. 2009;54:2031–9.
89. Mathur AK, Osborne NH, Lynch RJ, Ghaferi AA, Dimick JB, Sonnenday CJ. Racial/ethnic disparities in access to care and survival for patients with early-stage hepatocellular carcinoma. Arch Surg. 2010;145:1158–63.
90. Mathur AK, Sonnenday CJ, Merion RM. Race and ethnicity in access to and outcomes of liver transplantation: a critical literature review. Am J Transplant. 2009;9:2662–8.
91. Mathur AK, Schaubel DE, Gong Q, Guidinger MK, Merion RM. Racial and ethnic disparities in access to liver transplantation. Liver Transpl. 2010;16:1033–40.
92. Yu JC, Neugut AI, Wang S, Jacobson JS, Ferrante L, Khungar V, et al. Racial and insurance disparities in the receipt of transplant among patients with hepatocellular carcinoma. Cancer. 2010;116:1801–9.
93. Harvin JA, Van Buren G, Tsao K, Cen P, Ko TC, Wray CJ. Hepatocellular carcinoma survival in uninsured and underinsured patients. J Surg Res. 2011;166:189–93.
94. Siegel AB, McBride RB, El-Serag HB, Hershman DL, Brown RS Jr, Renz JF, et al. Racial disparities in utilization of liver transplantation for hepatocellular carcinoma in the United States, 1998–2002. Am J Gastroenterol. 2008;103:120–7.
95. Hoeroldt B, McFarlane E, Dube A, Basumani P, Karajeh M, Campbell MJ, et al. Long-term outcomes of patients with autoimmune hepatitis managed at a nontransplant center. Gastroenterology. 2011;140:1980–9.
96. Roberts SK, Therneau TM, Czaja AJ. Prognosis of histological cirrhosis in type 1 autoimmune hepatitis. Gastroenterology. 1996;110:848–57.
97. Gupta R, Agarwal SR, Jain M, Malhotra V, Sarin SK. Autoimmune hepatitis in the Indian subcontinent: 7 years experience. J Gastroenterol Hepatol. 2001;16:1144–8.
98. Montano-Loza AJ, Carpenter HA, Czaja AJ. Predictive factors for hepatocellular carcinoma in type 1 autoimmune hepatitis. Am J Gastroenterol. 2008;103:1944–51.
99. Park SZ, Nagorney DM, Czaja AJ. Hepatocellular carcinoma in autoimmune hepatitis. Dig Dis Sci. 2000;45:1944–8.
100. Yeoman AD, Al-Chalabi T, Karani JB, Quaglia A, Devlin J, Mieli-Vergani G, et al. Evaluation of risk factors in the development of hepatocellular carcinoma in autoimmune hepatitis: implications for follow-up and screening. Hepatology. 2008;48:863–70.
101. Findor JA, Sorda JA, Daruich JR, Manero EF. Familial association in autoimmune liver disease. Medicina (B Aires). 2002;62:241–4.
102. Wang P, Su H, Underhill J, Blackmore LJ, Longhi MS, Grammatikopoulos T, et al. Autoantibody and human leukocyte antigen profiles in children with autoimmune liver disease and their first-degree relatives. J Pediatr Gastroenterol Nutr. 2014;58:457–62.
103. Strettell MD, Donaldson PT, Thomson LJ, Santrach PJ, Moore SB, Czaja AJ, et al. Allelic basis for HLA-encoded susceptibility to type 1 autoimmune hepatitis. Gastroenterology. 1997;112:2028–35.
104. de Boer YS, van Gerven NM, Zwiers A, Verwer BJ, van Hoek B, van Erpecum KJ, et al. Genome-wide association study identifies variants associated with autoimmune hepatitis type 1. Gastroenterology. 2014;147:443–52.
105. Czaja AJ, Strettell MD, Thomson LJ, Santrach PJ, Moore SB, Donaldson PT, et al. Associations between alleles of the major histocompatibility complex and type 1 autoimmune hepatitis. Hepatology. 1997;25:317–23.
106. Yoshizawa K, Ota M, Katsuyama Y, Ichijo T, Matsumoto A, Tanaka E, et al. Genetic analysis of the HLA region of Japanese patients with type 1 autoimmune hepatitis. J Hepatol. 2005;42:578–84.
107. Yoshizawa K, Umemura T, Ota M. Genetic background of autoimmune hepatitis in Japan. J Gastroenterol. 2011;46(Suppl 1):42–7.
108. Qiu DK, Ma X. Relationship between human leukocyte antigen-DRB1 and autoimmune hepatitis type I in Chinese patients. J Gastroenterol Hepatol. 2003;18:63–7.

109. Vazquez-Garcia MN, Alaez C, Olivo A, Debaz H, Perez-Luque E, Burguete A, et al. MHC class II sequences of susceptibility and protection in Mexicans with autoimmune hepatitis. J Hepatol. 1998;28:985–90.
110. Lim YS, Oh HB, Choi SE, Kwon OJ, Heo YS, Lee HC, et al. Susceptibility to type 1 autoimmune hepatitis is associated with shared amino acid sequences at positions 70–74 of the HLA-DRB1 molecule. J Hepatol. 2008;48:133–9.
111. Fainboim L, Marcos Y, Pando M, Capucchio M, Reyes GB, Galoppo C, et al. Chronic active autoimmune hepatitis in children. Strong association with a particular HLA-DR6 (DRB1*1301) haplotype. Hum Immunol. 1994;41:146–50.
112. Goldberg AC, Bittencourt PL, Mougin B, Cancado EL, Porta G, Carrilho F, et al. Analysis of HLA haplotypes in autoimmune hepatitis type 1: identifying the major susceptibility locus. Hum Immunol. 2001;62:165–9.
113. Czaja AJ, Souto EO, Bittencourt PL, Cancado EL, Porta G, Goldberg AC, et al. Clinical distinctions and pathogenic implications of type 1 autoimmune hepatitis in Brazil and the United States. J Hepatol. 2002;37:302–8.
114. Fortes Mdel P, Machado IV, Gil G, Fernandez-Mestre M, Dagher L, Leon RV, et al. Genetic contribution of major histocompatibility complex class II region to type 1 autoimmune hepatitis susceptibility in Venezuela. Liver Int. 2007;27:1409–16.
115. Padilla M, Mayorga R, Carrasco F, Bedregal T, Bobadilla F, Rondon C, et al. Liver transplantation for autoimmune hepatitis in Peru: outcomes and recurrence. Ann Hepatol. 2012;11:222–7.
116. Duarte-Rey C, Pardo AL, Rodriguez-Velosa Y, Mantilla RD, Anaya JM, Rojas-Villarraga A. HLA class II association with autoimmune hepatitis in Latin America: a meta-analysis. Autoimmun Rev. 2009;8:325–31.
117. Schreuder GM, Hurley CK, Marsh SG, Lau M, Maiers M, Kollman C, et al. The HLA dictionary 2001: a summary of HLA-A, -B, -C, -DRB1/3/4/5, -DQB1 alleles and their association with serologically defined HLA-A, -B, -C, -DR, and -DQ antigens. Hum Immunol. 2001;62:826–49.
118. Vento S, Garofano T, Di Perri G, Dolci L, Concia E, Bassetti D. Identification of hepatitis A virus as a trigger for autoimmune chronic hepatitis type 1 in susceptible individuals. Lancet. 1991;337:1183–7.
119. Huppertz HI, Treichel U, Gassel AM, Jeschke R, Meyer zum Buschenfelde KH. Autoimmune hepatitis following hepatitis A virus infection. J Hepatol. 1995;23:204–8.
120. Tabak F, Ozdemir F, Tabak O, Erer B, Tahan V, Ozaras R. Autoimmune hepatitis induced by the prolonged hepatitis A virus infection. Ann Hepatol. 2008;7:177–9.
121. Elfaramawy AA, Elhossiny RM, Abbas AA, Aziz HM. HLA-DRB1 as a risk factor in children with autoimmune hepatitis and its relation to hepatitis A infection. Ital J Pediatr. 2010;36:73.
122. Djilali-Saiah I, Renous R, Caillat-Zucman S, Debray D, Alvarez F. Linkage disequilibrium between HLA class II region and autoimmune hepatitis in pediatric patients. J Hepatol. 2004;40:904–9.
123. Djilali-Saiah I, Fakhfakh A, Louafi H, Caillat-Zucman S, Debray D, Alvarez F. HLA class II influences humoral autoimmunity in patients with type 2 autoimmune hepatitis. J Hepatol. 2006;45:844–50.
124. Bittencourt PL, Goldberg AC, Cancado EL, Porta G, Carrilho FJ, Farias AQ, et al. Genetic heterogeneity in susceptibility to autoimmune hepatitis types 1 and 2. Am J Gastroenterol. 1999;94:1906–13.
125. Goldberg AC, Bittencourt PL, Oliveira LC, Ramasawmy R, Marin ML, Palacios SA, et al. Autoimmune hepatitis in Brazil: an overview. Scand J Immunol. 2007;66:208–16.
126. Ma Y, Bogdanos DP, Hussain MJ, Underhill J, Bansal S, Longhi MS, et al. Polyclonal T-cell responses to cytochrome P450IID6 are associated with disease activity in autoimmune hepatitis type 2. Gastroenterology. 2006;130:868–82.
127. Czaja AJ, Kruger M, Santrach PJ, Moore SB, Manns MP. Genetic distinctions between types 1 and 2 autoimmune hepatitis. Am J Gastroenterol. 1997;92:2197–200.

128. Manns MP, Griffin KJ, Sullivan KF, Johnson EF. LKM-1 autoantibodies recognize a short linear sequence in P450IID6, a cytochrome P-450 monooxygenase. J Clin Invest. 1991;88:1370–8.
129. Kerkar N, Choudhuri K, Ma Y, Mahmoud A, Bogdanos DP, Muratori L, et al. Cytochrome P4502D6(193–212): a new immunodominant epitope and target of virus/self cross-reactivity in liver kidney microsomal autoantibody type 1-positive liver disease. J Immunol. 2003;170:1481–9.
130. Agarwal K, Jones DE, Daly AK, James OF, Vaidya B, Pearce S, et al. CTLA-4 gene polymorphism confers susceptibility to primary biliary cirrhosis. J Hepatol. 2000;32:538–41.
131. Agarwal K, Czaja AJ, Jones DE, Donaldson PT. Cytotoxic T lymphocyte antigen-4 (CTLA-4) gene polymorphisms and susceptibility to type 1 autoimmune hepatitis. Hepatology. 2000;31:49–53.
132. Mells GF, Kaser A, Karlsen TH. Novel insights into autoimmune liver diseases provided by genome-wide association studies. J Autoimmun. 2013;46:41–54.
133. Bittencourt PL, Palacios SA, Cancado EL, Porta G, Carrilho FJ, Laudanna AA, et al. Cytotoxic T lymphocyte antigen-4 gene polymorphisms do not confer susceptibility to autoimmune hepatitis types 1 and 2 in Brazil. Am J Gastroenterol. 2003;98:1616–20.
134. Tang J, Zhou C, Zhang ZJ, Zheng SS. Association of polymorphisms in non-classic MHC genes with susceptibility to autoimmune hepatitis. Hepatobiliary Pancreat Dis Int. 2012;11:125–31.
135. Djilali-Saiah I, Ouellette P, Caillat-Zucman S, Debray D, Kohn JI, Alvarez F. CTLA-4/CD 28 region polymorphisms in children from families with autoimmune hepatitis. Hum Immunol. 2001;62:1356–62.
136. Hiraide A, Imazeki F, Yokosuka O, Kanda T, Kojima H, Fukai K, et al. Fas polymorphisms influence susceptibility to autoimmune hepatitis. Am J Gastroenterol. 2005;100:1322–9.
137. Agarwal K, Czaja AJ, Donaldson PT. A functional Fas promoter polymorphism is associated with a severe phenotype in type 1 autoimmune hepatitis characterized by early development of cirrhosis. Tissue Antigens. 2007;69:227–35.
138. Cookson S, Constantini PK, Clare M, Underhill JA, Bernal W, Czaja AJ, et al. Frequency and nature of cytokine gene polymorphisms in type 1 autoimmune hepatitis. Hepatology. 1999;30:851–6.
139. Li S, Huang X, Zhong H, Chen Z, Peng Q, Deng Y, et al. Tumour necrosis factor alpha (TNF-alpha) genetic polymorphisms and the risk of autoimmune liver disease: a meta-analysis. J Genet. 2013;92:617–28.
140. Vogel A, Strassburg CP, Manns MP. Genetic association of vitamin D receptor polymorphisms with primary biliary cirrhosis and autoimmune hepatitis. Hepatology. 2002;35:126–31.
141. Fan L, Tu X, Zhu Y, Zhou L, Pfeiffer T, Feltens R, et al. Genetic association of vitamin D receptor polymorphisms with autoimmune hepatitis and primary biliary cirrhosis in the Chinese. J Gastroenterol Hepatol. 2005;20:249–55.
142. Migita K, Nakamura M, Abiru S, Jiuchi Y, Nagaoka S, Komori A, et al. Association of STAT4 polymorphisms with susceptibility to type-1 autoimmune hepatitis in the Japanese population. PLoS One. 2013;8:e71382.
143. Sanchez-Urdazpal L, Czaja AJ, van Hoek B, Krom RA, Wiesner RH. Prognostic features and role of liver transplantation in severe corticosteroid-treated autoimmune chronic active hepatitis. Hepatology. 1992;15:215–21.
144. Czaja AJ, Carpenter HA. Distinctive clinical phenotype and treatment outcome of type 1 autoimmune hepatitis in the elderly. Hepatology. 2006;43:532–8.
145. Czaja AJ. Clinical features, differential diagnosis and treatment of autoimmune hepatitis in the elderly. Drugs Aging. 2008;25:219–39.
146. Seki T, Kiyosawa K, Inoko H, Ota M. Association of autoimmune hepatitis with HLA-Bw54 and DR4 in Japanese patients. Hepatology. 1990;12:1300–4.
147. Seki T, Ota M, Furuta S, Fukushima H, Kondo T, Hino K, et al. HLA class II molecules and autoimmune hepatitis susceptibility in Japanese patients. Gastroenterology. 1992;103:1041–7.

148. Nakamura K, Yoneda M, Yokohama S, Tamori K, Sato Y, Aso K, et al. Efficacy of ursodeoxycholic acid in Japanese patients with type 1 autoimmune hepatitis. J Gastroenterol Hepatol. 1998;13:490–5.
149. Miyake Y, Iwasaki Y, Takaki A, Kobashi H, Sakaguchi K, Shiratori Y. Clinical features of Japanese elderly patients with type 1 autoimmune hepatitis. Intern Med. 2007;46:1945–9.
150. Abe M, Mashiba T, Zeniya M, Yamamoto K, Onji M, Tsubouchi H. Present status of autoimmune hepatitis in Japan: a nationwide survey. J Gastroenterol. 2011;46:1136–41.
151. Pratt AJ, MacRae IJ. The RNA-induced silencing complex: a versatile gene-silencing machine. J Biol Chem. 2009;284:17897–901.
152. Ambros V. microRNAs: tiny regulators with great potential. Cell. 2001;107:823–6.
153. Migita K, Komori A, Kozuru H, Jiuchi Y, Nakamura M, Yasunami M, et al. Circulating microRNA profiles in patients with type-1 autoimmune hepatitis. PLoS One. 2015;10:e0136908.
154. Han L, Witmer PD, Casey E, Valle D, Sukumar S. DNA methylation regulates MicroRNA expression. Cancer Biol Ther. 2007;6:1284–8.
155. Tang JT, Wang JL, Du W, Hong J, Zhao SL, Wang YC, et al. MicroRNA 345, a methylation-sensitive microRNA is involved in cell proliferation and invasion in human colorectal cancer. Carcinogenesis. 2011;32:1207–15.
156. Fisher L, Fisher A. Vitamin D and parathyroid hormone in outpatients with noncholestatic chronic liver disease. Clin Gastroenterol Hepatol. 2007;5:513–20.
157. Miroliaee A, Nasiri-Toosi M, Khalilzadeh O, Esteghamati A, Abdollahi A, Mazloumi M. Disturbances of parathyroid hormone-vitamin D axis in non-cholestatic chronic liver disease: a cross-sectional study. Hepatol Int. 2010;4:634–40.
158. Stokes CS, Volmer DA, Grunhage F, Lammert F. Vitamin D in chronic liver disease. Liver Int. 2013;33:338–52.
159. Efe C, Kav T, Aydin C, Cengiz M, Imga NN, Purnak T, et al. Low serum vitamin D levels are associated with severe histological features and poor response to therapy in patients with autoimmune hepatitis. Dig Dis Sci. 2014;59:3035–42.
160. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357:266–81.
161. Ohyama Y, Yamasaki T. Eight cytochrome P450s catalyze vitamin D metabolism. Front Biosci. 2004;9:3007–18.
162. Lemire JM. Immunomodulatory role of 1,25-dihydroxyvitamin D3. J Cell Biochem. 1992;49:26–31.
163. Adams JS, Hewison M. Unexpected actions of vitamin D: new perspectives on the regulation of innate and adaptive immunity. Nat Clin Pract Endocrinol Metab. 2008;4:80–90.
164. Luong KV, Nguyen LT. The role of vitamin D in autoimmune hepatitis. J Clin Med Res. 2013;5:407–15.
165. Provvedini DM, Tsoukas CD, Deftos LJ, Manolagas SC. 1,25-dihydroxyvitamin D3 receptors in human leukocytes. Science. 1983;221:1181–3.
166. Bhalla AK, Amento EP, Clemens TL, Holick MF, Krane SM. Specific high-affinity receptors for 1,25-dihydroxyvitamin D3 in human peripheral blood mononuclear cells: presence in monocytes and induction in T lymphocytes following activation. J Clin Endocrinol Metab. 1983;57:1308–10.
167. Barbour GL, Coburn JW, Slatopolsky E, Norman AW, Horst RL. Hypercalcemia in an anephric patient with sarcoidosis: evidence for extrarenal generation of 1,25-dihydroxyvitamin D. N Engl J Med. 1981;305:440–3.
168. Adams JS, Sharma OP, Gacad MA, Singer FR. Metabolism of 25-hydroxyvitamin D3 by cultured pulmonary alveolar macrophages in sarcoidosis. J Clin Invest. 1983;72:1856–60.
169. Kim S, Shevde NK, Pike JW. 1,25-dihydroxyvitamin D3 stimulates cyclic vitamin D receptor/retinoid X receptor DNA-binding, co-activator recruitment, and histone acetylation in intact osteoblasts. J Bone Miner Res. 2005;20:305–17.
170. Gershwin ME, Ansari AA, Mackay IR, Nakanuma Y, Nishio A, Rowley MJ, et al. Primary biliary cirrhosis: an orchestrated immune response against epithelial cells. Immunol Rev. 2000;174:210–25.

171. Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ. AASLD Practice Guidelines. Primary biliary cirrhosis. Hepatology. 2009;50:291–308.
172. Lindgren S, Glaumann H, Almer S, Bergquist A, Bjornsson E, Broome U, et al. Transitions between variant forms of primary biliary cirrhosis during long-term follow-up. Eur J Intern Med. 2009;20:398–402.
173. Lofgren J, Jarnerot G, Danielsson D, Hemdal I. Incidence and prevalence of primary biliary cirrhosis in a defined population in Sweden. Scand J Gastroenterol. 1985;20:647–50.
174. Prince MI, Chetwynd A, Craig WL, Metcalf JV, James OF. Asymptomatic primary biliary cirrhosis: clinical features, prognosis, and symptom progression in a large population based cohort. Gut. 2004;53:865–70.
175. Podda M, Selmi C, Lleo A, Moroni L, Invernizzi P. The limitations and hidden gems of the epidemiology of primary biliary cirrhosis. J Autoimmun. 2013;46:81–7.
176. Chong VH, Telisinghe PU, Jalihal A. Primary biliary cirrhosis in Brunei Darussalam. Hepatobiliary Pancreat Dis Int. 2010;9:622–8.
177. Remmel T, Remmel H, Uibo R, Salupere V. Primary biliary cirrhosis in Estonia. With special reference to incidence, prevalence, clinical features, and outcome. Scand J Gastroenterol. 1995;30:367–71.
178. Metcalf JV, Bhopal RS, Gray J, Howel D, James OF. Incidence and prevalence of primary biliary cirrhosis in the city of Newcastle upon Tyne, England. Int J Epidemiol. 1997;26:830–6.
179. James OF, Bhopal R, Howel D, Gray J, Burt AD, Metcalf JV. Primary biliary cirrhosis once rare, now common in the United Kingdom? Hepatology. 1999;30:390–4.
180. Kim WR, Lindor KD, Locke GR 3rd, Therneau TM, Homburger HA, Batts KP, et al. Epidemiology and natural history of primary biliary cirrhosis in a US community. Gastroenterology. 2000;119:1631–6.
181. Myers RP, Shaheen AA, Fong A, Burak KW, Wan A, Swain MG, et al. Epidemiology and natural history of primary biliary cirrhosis in a Canadian health region: a population-based study. Hepatology. 2009;50:1884–92.
182. Lleo A, Jepsen P, Morenghi E, Carbone M, Moroni L, Battezzati PM, et al. Evolving trends in female to male incidence and male mortality of primary biliary cholangitis. Sci Rep. 2016;6:25906.
183. Pla X, Vergara M, Gil M, Dalmau B, Cistero B, Bella RM, et al. Incidence, prevalence and clinical course of primary biliary cirrhosis in a Spanish community. Eur J Gastroenterol Hepatol. 2007;19:859–64.
184. Triger DR, Berg PA, Rodes J. Epidemiology of primary biliary cirrhosis. Liver. 1984;4:195–200.
185. Mao TK, Lian ZX, Selmi C, Ichiki Y, Ashwood P, Ansari AA, et al. Altered monocyte responses to defined TLR ligands in patients with primary biliary cirrhosis. Hepatology. 2005;42:802–8.
186. Kikuchi K, Lian ZX, Yang GX, Ansari AA, Ikehara S, Kaplan M, et al. Bacterial CpG induces hyper-IgM production in CD27(+) memory B cells in primary biliary cirrhosis. Gastroenterology. 2005;128:304–12.
187. Honda Y, Yamagiwa S, Matsuda Y, Takamura M, Ichida T, Aoyagi Y. Altered expression of TLR homolog RP105 on monocytes hypersensitive to LPS in patients with primary biliary cirrhosis. J Hepatol. 2007;47:404–11.
188. Shimoda S, Harada K, Niiro H, Shirabe K, Taketomi A, Maehara Y, et al. Interaction between Toll-like receptors and natural killer cells in the destruction of bile ducts in primary biliary cirrhosis. Hepatology. 2011;53:1270–81.
189. Yurkovetskiy L, Burrows M, Khan AA, Graham L, Volchkov P, Becker L, et al. Gender bias in autoimmunity is influenced by microbiota. Immunity. 2013;39:400–12.
190. Markle JG, Frank DN, Mortin-Toth S, Robertson CE, Feazel LM, Rolle-Kampczyk U, et al. Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. Science. 2013;339:1084–8.

191. Chavhan GB, Roberts E, Moineddin R, Babyn PS, Manson DE. Primary sclerosing cholangitis in children: utility of magnetic resonance cholangiopancreatography. Pediatr Radiol. 2008;38:868–73.
192. Kerkar N, Miloh T. Sclerosing cholangitis: pediatric perspective. Curr Gastroenterol Rep. 2010;12:195–202.
193. Roberts EA. Autoimmune hepatitis from the paediatric perspective. Liver Int. 2011;31:1424–31.
194. Watson RG, Angus PW, Dewar M, Goss B, Sewell RB, Smallwood RA. Low prevalence of primary biliary cirrhosis in Victoria, Australia. Melbourne Liver Group. Gut. 1995;36:927–30.
195. Inoue K, Hirohara J, Nakano T, Seki T, Sasaki H, Higuchi K, et al. Prediction of prognosis of primary biliary cirrhosis in Japan. Liver. 1995;15:70–7.
196. Liu H, Liu Y, Wang L, Xu D, Lin B, Zhong R, et al. Prevalence of primary biliary cirrhosis in adults referring hospital for annual health check-up in Southern China. BMC Gastroenterol. 2010;10:100.
197. Delgado J, Sperber AD, Novack V, Delgado B, Edelman L, Gaspar N, et al. The epidemiology of primary biliary cirrhosis in southern Israel. Isr Med Assoc J. 2005;7:717–21.
198. Sood S, Gow PJ, Christie JM, Angus PW. Epidemiology of primary biliary cirrhosis in Victoria, Australia: high prevalence in migrant populations. Gastroenterology. 2004;127:470–5.
199. Myszor M, James OF. The epidemiology of primary biliary cirrhosis in north-east England: an increasingly common disease? Q J Med. 1990;75:377–85.
200. Ilyas JA, O'Mahony CA, Vierling JM. Liver transplantation in autoimmune liver diseases. Best Pract Res Clin Gastroenterol. 2011;25:765–82.
201. Invernizzi P. Geoepidemiology of autoimmune liver diseases. J Autoimmun. 2010;34:J300–6.
202. Abu-Mouch S, Selmi C, Benson GD, Kenny TP, Invernizzi P, Zuin M, et al. Geographic clusters of primary biliary cirrhosis. Clin Dev Immunol. 2003;10:127–31.
203. Howel D, Fischbacher CM, Bhopal RS, Gray J, Metcalf JV, James OF. An exploratory population-based case-control study of primary biliary cirrhosis. Hepatology. 2000;31:1055–60.
204. Parikh-Patel A, Gold EB, Worman H, Krivy KE, Gershwin ME. Risk factors for primary biliary cirrhosis in a cohort of patients from the united states. Hepatology. 2001;33:16–21.
205. Gershwin ME, Selmi C, Worman HJ, Gold EB, Watnik M, Utts J, et al. Risk factors and comorbidities in primary biliary cirrhosis: a controlled interview-based study of 1032 patients. Hepatology. 2005;42:1194–202.
206. Prince MI, Ducker SJ, James OF. Case-control studies of risk factors for primary biliary cirrhosis in two United Kingdom populations. Gut. 2010;59:508–12.
207. Liang Y, Yang Z, Zhong R. Smoking, family history and urinary tract infection are associated with primary biliary cirrhosis: a meta-analysis. Hepatol Res. 2011;41:572–8.
208. Smyk DS, Rigopoulou EI, Muratori L, Burroughs AK, Bogdanos DP. Smoking as a risk factor for autoimmune liver disease: what we can learn from primary biliary cirrhosis. Ann Hepatol. 2012;11:7–14.
209. Lammert C, Nguyen DL, Juran BD, Schlicht E, Larson JJ, Atkinson EJ, et al. Questionnaire based assessment of risk factors for primary biliary cirrhosis. Dig Liver Dis. 2013;45:589–94.
210. Corpechot C, Chretien Y, Chazouilleres O, Poupon R. Demographic, lifestyle, medical and familial factors associated with primary biliary cirrhosis. J Hepatol. 2010;53:162–9.
211. Zein CO, Beatty K, Post AB, Logan L, Debanne S, McCullough AJ. Smoking and increased severity of hepatic fibrosis in primary biliary cirrhosis: a cross validated retrospective assessment. Hepatology. 2006;44:1564–71.
212. Corpechot C, Gaouar F, Chretien Y, Johanet C, Chazouilleres O, Poupon R. Smoking as an independent risk factor of liver fibrosis in primary biliary cirrhosis. J Hepatol. 2012;56:218–24.
213. Costenbader KH, Karlson EW. Cigarette smoking and autoimmune disease: what can we learn from epidemiology? Lupus. 2006;15:737–45.

214. Glossop JR, Dawes PT, Mattey DL. Association between cigarette smoking and release of tumour necrosis factor alpha and its soluble receptors by peripheral blood mononuclear cells in patients with rheumatoid arthritis. Rheumatology (Oxford). 2006;45:1223–9.
215. Arnson Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. J Autoimmun. 2010;34:J258–65.
216. Juran BD, Lazaridis KN. Environmental factors in primary biliary cirrhosis. Semin Liver Dis. 2014;34:265–72.
217. Whetzel CA, Corwin EJ, Klein LC. Disruption in Th1/Th2 immune response in young adult smokers. Addict Behav. 2007;32:1–8.
218. Harada K, Van de Water J, Leung PS, Coppel RL, Ansari A, Nakanuma Y, et al. In situ nucleic acid hybridization of cytokines in primary biliary cirrhosis: predominance of the Th1 subset. Hepatology. 1997;25:791–6.
219. Montano-Loza AJ, Thandassery RB, Czaja AJ. Targeting hepatic fibrosis in autoimmune hepatitis. Dig Dis Sci. 2016;61:3118–39.
220. Kroening PR, Barnes TW, Pease L, Limper A, Kita H, Vassallo R. Cigarette smoke-induced oxidative stress suppresses generation of dendritic cell IL-12 and IL-23 through ERK-dependent pathways. J Immunol. 2008;181:1536–47.
221. Bae HR, Leung PS, Tsuneyama K, Valencia JC, Hodge DL, Kim S, et al. Chronic expression of interferon-gamma leads to murine autoimmune cholangitis with a female predominance. Hepatology. 2016;64:1189–201.
222. Bluhm AL, Weinstein J, Sousa JA. Free radicals in tobacco smoke. Nature. 1971;229:500.
223. Pryor WA, Stone K. Oxidants in cigarette smoke. Radicals, hydrogen peroxide, peroxynitrate, and peroxynitrite. Ann N Y Acad Sci. 1993;686:12–27; discussion 27–8.
224. Amano K, Leung PS, Rieger R, Quan C, Wang X, Marik J, et al. Chemical xenobiotics and mitochondrial autoantigens in primary biliary cirrhosis: identification of antibodies against a common environmental, cosmetic, and food additive, 2-octynoic acid. J Immunol. 2005;174:5874–83.
225. Czaja AJ. Nature and implications of oxidative and nitrosative stresses in autoimmune hepatitis. Dig Dis Sci. 2016;61:2784–803.
226. Triger DR. Primary biliary cirrhosis: an epidemiological study. Br Med J. 1980;281:772–5.
227. Ala A, Stanca CM, Bu-Ghanim M, Ahmado I, Branch AD, Schiano TD, et al. Increased prevalence of primary biliary cirrhosis near Superfund toxic waste sites. Hepatology. 2006;43:525–31.
228. Walden HR, Kirby JA, Yeaman SJ, Gray J, Jones DE, Palmer JM. Xenobiotic incorporation into pyruvate dehydrogenase complex can occur via the exogenous lipoylation pathway. Hepatology. 2008;48:1874–84.
229. Yeaman SJ, Kirby JA, Jones DE. Autoreactive responses to pyruvate dehydrogenase complex in the pathogenesis of primary biliary cirrhosis. Immunol Rev. 2000;174:238–49.
230. Hamlyn AN, Macklon AF, James O. Primary biliary cirrhosis: geographical clustering and symptomatic onset seasonality. Gut. 1983;24:940–5.
231. Czaja AJ. Drug-induced autoimmune-like hepatitis. Dig Dis Sci. 2011;56:958–76.
232. Menon KV, Angulo P, Boe GM, Lindor KD. Safety and efficacy of estrogen therapy in preventing bone loss in primary biliary cirrhosis. Am J Gastroenterol. 2003;98:889–92.
233. Alvaro D, Invernizzi P, Onori P, Franchitto A, De Santis A, Crosignani A, et al. Estrogen receptors in cholangiocytes and the progression of primary biliary cirrhosis. J Hepatol. 2004;41:905–12.
234. Guattery JM, Faloon WW. Effect of estradiol upon serum enzymes in primary biliary cirrhosis. Hepatology. 1987;7:737–42.
235. McNally RJ, James PW, Ducker S, James OF. Seasonal variation in the patient diagnosis of primary biliary cirrhosis: further evidence for an environmental component to etiology. Hepatology. 2011;54:2099–103.
236. McNally RJ, Ducker S, James OF. Are transient environmental agents involved in the cause of primary biliary cirrhosis? Evidence from space-time clustering analysis. Hepatology. 2009;50:1169–74.

237. Xu L, Shen Z, Guo L, Fodera B, Keogh A, Joplin R, et al. Does a betaretrovirus infection trigger primary biliary cirrhosis? Proc Natl Acad Sci U S A. 2003;100:8454–9.
238. Selmi C, Balkwill DL, Invernizzi P, Ansari AA, Coppel RL, Podda M, et al. Patients with primary biliary cirrhosis react against a ubiquitous xenobiotic-metabolizing bacterium. Hepatology. 2003;38:1250–7.
239. Kaplan MM. Novosphingobium aromaticivorans: a potential initiator of primary biliary cirrhosis. Am J Gastroenterol. 2004;99:2147–9.
240. Olafsson S, Gudjonsson H, Selmi C, Amano K, Invernizzi P, Podda M, et al. Antimitochondrial antibodies and reactivity to N. aromaticivorans proteins in Icelandic patients with primary biliary cirrhosis and their relatives. Am J Gastroenterol. 2004;99:2143–6.
241. Padgett KA, Selmi C, Kenny TP, Leung PS, Balkwill DL, Ansari AA, et al. Phylogenetic and immunological definition of four lipoylated proteins from Novosphingobium aromaticivorans, implications for primary biliary cirrhosis. J Autoimmun. 2005;24:209–19.
242. Zabiegala B, Urbanowicz M, Namiesnik J, Gorecki T. Spatial and seasonal patterns of benzene, toluene, ethylbenzene, and xylenes in the Gdansk, Poland and surrounding areas determined using radiello passive samplers. J Environ Qual. 2010;39:896–906.
243. Tiwari V, Hanai Y, Masunaga S. Ambient levels of volatile organic compounds in the vicinity of petrochemical industrial area of Yokohama, Japan. Air Qual Atmos Health. 2010;3:65–75.
244. Wang JJ, Yang GX, Zhang WC, Lu L, Tsuneyama K, Kronenberg M, et al. *Escherichia coli* infection induces autoimmune cholangitis and anti-mitochondrial antibodies in non-obese diabetic (NOD).B6 (Idd10/Idd18) mice. Clin Exp Immunol. 2014;175:192–201.
245. Haydon GH, Neuberger J. PBC: an infectious disease? Gut. 2000;47:586–8.
246. Kumagi T, Abe M, Ikeda Y, Hiasa Y. Infection as a risk factor in the pathogenesis of primary biliary cirrhosis: pros and cons. Dis Markers. 2010;29:313–21.
247. Koutsoumpas AL, Kriese S, Rigopoulou EI. Popular and unpopular infectious agents linked to primary biliary cirrhosis. Auto Immun Highlights. 2012;3:95–104.
248. Mattner J, Savage PB, Leung P, Oertelt SS, Wang V, Trivedi O, et al. Liver autoimmunity triggered by microbial activation of natural killer T cells. Cell Host Microbe. 2008;3:304–15.
249. Mohammed JP, Mattner J. Autoimmune disease triggered by infection with alphaproteobacteria. Expert Rev Clin Immunol. 2009;5:369–79.
250. Mason AL, Xu L, Guo L, Munoz S, Jaspan JB, Bryer-Ash M, et al. Detection of retroviral antibodies in primary biliary cirrhosis and other idiopathic biliary disorders. Lancet. 1998;351:1620–4.
251. Xu L, Sakalian M, Shen Z, Loss G, Neuberger J, Mason A. Cloning the human betaretrovirus proviral genome from patients with primary biliary cirrhosis. Hepatology. 2004;39:151–6.
252. Selmi C, Ross SR, Ansari AA, Invernizzi P, Podda M, Coppel RL, et al. Lack of immunological or molecular evidence for a role of mouse mammary tumor retrovirus in primary biliary cirrhosis. Gastroenterology. 2004;127:493–501.
253. Wang W, Indik S, Wasilenko ST, Faschinger A, Carpenter EJ, Tian Z, et al. Frequent proviral integration of the human betaretrovirus in biliary epithelium of patients with autoimmune and idiopathic liver disease. Aliment Pharmacol Ther. 2015;41:393–405.
254. Lytvyak E, Montano-Loza AJ, Mason AL. Combination antiretroviral studies for patients with primary biliary cirrhosis. World J Gastroenterol. 2016;22:349–60.
255. Hopf U, Moller B, Stemerowicz R, Lobeck H, Rodloff A, Freudenberg M, et al. Relation between *Escherichia coli* R(rough)-forms in gut, lipid A in liver, and primary biliary cirrhosis. Lancet. 1989;2:1419–22.
256. Bogdanos DP, Baum H, Butler P, Rigopoulou EI, Davies ET, Ma Y, et al. Association between the primary biliary cirrhosis specific anti-sp100 antibodies and recurrent urinary tract infection. Dig Liver Dis. 2003;35:801–5.
257. Burroughs AK, Rosenstein IJ, Epstein O, Hamilton-Miller JM, Brumfitt W, Sherlock S. Bacteriuria and primary biliary cirrhosis. Gut. 1984;25:133–7.
258. Smyk DS, Bogdanos DP, Kriese S, Billinis C, Burroughs AK, Rigopoulou EI. Urinary tract infection as a risk factor for autoimmune liver disease: from bench to bedside. Clin Res Hepatol Gastroenterol. 2012;36:110–21.

259. Butler P, Hamilton-Miller JM, McIntyre N, Burroughs AK. Natural history of bacteriuria in women with primary biliary cirrhosis and the effect of antimicrobial therapy in symptomatic and asymptomatic groups. Gut. 1995;36:931–4.
260. Varyani FK, West J, Card TR. An increased risk of urinary tract infection precedes development of primary biliary cirrhosis. BMC Gastroenterol. 2011;11:95.
261. Mason A, Xu L, Neuberger J. Proof of principal studies to assess the role of the human betaretrovirus in patients with primary biliary cirrhosis. Am J Gastroenterol. 2004;99:2499–500.
262. Johal H, Scott GM, Jones R, Camaris C, Riordan S, Rawlinson WD. Mouse mammary tumour virus-like virus (MMTV-LV) is present within the liver in a wide range of hepatic disorders and unrelated to nuclear p53 expression or hepatocarcinogenesis. J Hepatol. 2009;50:548–54.
263. Morshed SA, Nishioka M, Saito I, Komiyama K, Moro I. Increased expression of Epstein-Barr virus in primary biliary cirrhosis patients. Gastroenterol Jpn. 1992;27:751–8.
264. Vilagut L, Pares A, Vinas O, Vila J, Jimenez de Anta MT, Rodes J. Antibodies to mycobacterial 65-kD heat shock protein cross-react with the main mitochondrial antigens in patients with primary biliary cirrhosis. Eur J Clin Investig. 1997;27:667–72.
265. Nilsson HO, Taneera J, Castedal M, Glatz E, Olsson R, Wadstrom T. Identification of *Helicobacter pylori* and other *Helicobacter* species by PCR, hybridization, and partial DNA sequencing in human liver samples from patients with primary sclerosing cholangitis or primary biliary cirrhosis. J Clin Microbiol. 2000;38:1072–6.
266. Abdulkarim AS, Petrovic LM, Kim WR, Angulo P, Lloyd RV, Lindor KD. Primary biliary cirrhosis: an infectious disease caused by Chlamydia pneumoniae? J Hepatol. 2004;40:380–4.
267. Berg CP, Kannan TR, Klein R, Gregor M, Baseman JB, Wesselborg S, et al. Mycoplasma antigens as a possible trigger for the induction of antimitochondrial antibodies in primary biliary cirrhosis. Liver Int. 2009;29:797–809.
268. Shapira Y, Agmon-Levin N, Renaudineau Y, Porat-Katz BS, Barzilai O, Ram M, et al. Serum markers of infections in patients with primary biliary cirrhosis: evidence of infection burden. Exp Mol Pathol. 2012;93:386–90.
269. Tsuji K, Watanabe Y, Van De Water J, Nakanishi T, Kajiyama G, Parikh-Patel A, et al. Familial primary biliary cirrhosis in Hiroshima. J Autoimmun. 1999;13:171–8.
270. Selmi C, Mayo MJ, Bach N, Ishibashi H, Invernizzi P, Gish RG, et al. Primary biliary cirrhosis in monozygotic and dizygotic twins: genetics, epigenetics, and environment. Gastroenterology. 2004;127:485–92.
271. Mantaka A, Koulentaki M, Chlouverakis G, Enele-Melono JM, Darivianaki A, Tzardi M, et al. Primary biliary cirrhosis in a genetically homogeneous population: disease associations and familial occurrence rates. BMC Gastroenterol. 2012;12:110.
272. Nakamura M, Nishida N, Kawashima M, Aiba Y, Tanaka A, Yasunami M, et al. Genome-wide association study identifies TNFSF15 and POU2AF1 as susceptibility loci for primary biliary cirrhosis in the Japanese population. Am J Hum Genet. 2012;91:721–8.
273. Liu X, Invernizzi P, Lu Y, Kosoy R, Lu Y, Bianchi I, et al. Genome-wide meta-analyses identify three loci associated with primary biliary cirrhosis. Nat Genet. 2010;42:658–60.
274. Mells GF, Floyd JA, Morley KI, Cordell HJ, Franklin CS, Shin SY, et al. Genome-wide association study identifies 12 new susceptibility loci for primary biliary cirrhosis. Nat Genet. 2011;43:329–32.
275. Gulamhusein AF, Juran BD, Lazaridis KN. Genome-wide association studies in primary biliary cirrhosis. Semin Liver Dis. 2015;35:392–401.
276. Jones DE, Watt FE, Metcalf JV, Bassendine MF, James OF. Familial primary biliary cirrhosis reassessed: a geographically-based population study. J Hepatol. 1999;30:402–7.
277. Bittencourt PL, Farias AQ, Abrantes-Lemos CP, Goncalves LL, Goncalves PL, Magalhaes EP, et al. Prevalence of immune disturbances and chronic liver disease in family members of patients with primary biliary cirrhosis. J Gastroenterol Hepatol. 2004;19:873–8.
278. Brind AM, Bray GP, Portmann BC, Williams R. Prevalence and pattern of familial disease in primary biliary cirrhosis. Gut. 1995;36:615–7.
279. Yanagisawa M, Takagi H, Takahashi H, Uehara M, Otsuka T, Yuasa K, et al. Familial clustering and genetic background of primary biliary cirrhosis in Japan. Dig Dis Sci. 2010;55:2651–8.

280. Bach N, Schaffner F. Familial primary biliary cirrhosis. J Hepatol. 1994;20:698–701.
281. Lazaridis KN, Juran BD, Boe GM, Slusser JP, de Andrade M, Homburger HA, et al. Increased prevalence of antimitochondrial antibodies in first-degree relatives of patients with primary biliary cirrhosis. Hepatology. 2007;46:785–92.
282. Zografos TA, Gatselis N, Zachou K, Liaskos C, Gabeta S, Koukoulis GK, et al. Primary biliary cirrhosis-specific autoantibodies in first degree relatives of Greek primary biliary cirrhosis patients. World J Gastroenterol. 2012;18:4721–8.
283. Watt FE, James OF, Jones DE. Patterns of autoimmunity in primary biliary cirrhosis patients and their families: a population-based cohort study. Q J Med. 2004;97:397–406.
284. Gulamhusein AF, Juran BD, Atkinson EJ, McCauley B, Schlicht E, Lazaridis KN. Low incidence of primary biliary cirrhosis (PBC) in the first-degree relatives of PBC probands after 8 years of follow-up. Liver Int. 2016;36:1378–82.
285. Underhill JA, Donaldson PT, Doherty DG, Manabe K, Williams R. HLA DPB polymorphism in primary sclerosing cholangitis and primary biliary cirrhosis. Hepatology. 1995;21:959–62.
286. Jones DE, Donaldson PT. Genetic factors in the pathogenesis of primary biliary cirrhosis. Clin Liver Dis. 2003;7:841–64.
287. Webb GJ, Siminovitch KA, Hirschfield GM. The immunogenetics of primary biliary cirrhosis: a comprehensive review. J Autoimmun. 2015;64:42–52.
288. Cordell HJ, Han Y, Mells GF, Li Y, Hirschfield GM, Greene CS, et al. International genome-wide meta-analysis identifies new primary biliary cirrhosis risk loci and targetable pathogenic pathways. Nat Commun. 2015;6:8019.
289. Hirschfield GM, Liu X, Xu C, Lu Y, Xie G, Lu Y, et al. Primary biliary cirrhosis associated with HLA, IL12A, and IL12RB2 variants. N Engl J Med. 2009;360:2544–55.
290. van Wanrooij RL, Zwiers A, Kraal G, Bouma G. Genetic variations in interleukin-12 related genes in immune-mediated diseases. J Autoimmun. 2012;39:359–68.
291. Lleo A, Zhang W, Zhao M, Tan Y, Bernuzzi F, Zhu B, et al. DNA methylation profiling of the X chromosome reveals an aberrant demethylation on CXCR3 promoter in primary biliary cirrhosis. Clin Epigenetics. 2015;7:61.
292. Tomiyama T, Yang GX, Zhao M, Zhang W, Tanaka H, Wang J, et al. The modulation of co-stimulatory molecules by circulating exosomes in primary biliary cirrhosis. Cell Mol Immunol. 2017;14:276–84.
293. Sydow JF, Cramer P. RNA polymerase fidelity and transcriptional proofreading. Curr Opin Struct Biol. 2009;19:732–9.
294. Tough DF, Prinjha RK. Immune disease-associated variants in gene enhancers point to BET epigenetic mechanisms for therapeutic intervention. Epigenomics. 2017;9:573–84.
295. Marra F, Tacke F. Roles for chemokines in liver disease. Gastroenterology. 2014;147:577–94.
296. Smigielska-Czepiel K, van den Berg A, Jellema P, van der Lei RJ, Bijzet J, Kluiver J, et al. Comprehensive analysis of miRNA expression in T-cell subsets of rheumatoid arthritis patients reveals defined signatures of naive and memory Tregs. Genes Immun. 2014;15:115–25.
297. Bartholomew LG, Cain JC, Woolner LB, Utz DC, Ferris DO. Sclerosing cholangitis: its possible association with Riedel's struma and fibrous retroperitonitis. Report of two cases. N Engl J Med. 1963;269:8–12.
298. Geubel AP, Baggenstoss AH, Summerskill WH. Responses to treatment can differentiate chronic active liver disease with cholangitic features from the primary biliary cirrhosis syndrome. Gastroenterology. 1976;71:444–9.
299. Wiesner RH, LaRusso NF. Clinicopathologic features of the syndrome of primary sclerosing cholangitis. Gastroenterology. 1980;79:200–6.
300. Ludwig J, Barham SS, LaRusso NF, Elveback LR, Wiesner RH, McCall JT. Morphologic features of chronic hepatitis associated with primary sclerosing cholangitis and chronic ulcerative colitis. Hepatology. 1981;1:632–40.
301. Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, et al. Diagnosis and management of primary sclerosing cholangitis. Hepatology. 2010;51:660–78.
302. Lindor KD, Kowdley KV, Harrison ME. ACG Clinical Guideline: primary sclerosing cholangitis. Am J Gastroenterol. 2015;110:646–59.

303. Lunder AK, Hov JR, Borthne A, Gleditsch J, Johannesen G, Tveit K, et al. Prevalence of sclerosing cholangitis detected by magnetic resonance cholangiography in patients with long-term inflammatory bowel disease. Gastroenterology. 2016;151:660–69.e4.
304. Angulo P, Maor-Kendler Y, Lindor KD. Small-duct primary sclerosing cholangitis: a long-term follow-up study. Hepatology. 2002;35:1494–500.
305. Lindkvist B, Benito de Valle M, Gullberg B, Bjornsson E. Incidence and prevalence of primary sclerosing cholangitis in a defined adult population in Sweden. Hepatology. 2010;52:571–7.
306. Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. J Hepatol. 2012;56:1181–8.
307. Jepsen P, Gronbaek L, Vilstrup H. Worldwide incidence of autoimmune liver disease. Dig Dis. 2015;33(Suppl 2):2–12.
308. Boonstra K, Weersma RK, van Erpecum KJ, Rauws EA, Spanier BW, Poen AC, et al. Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. Hepatology. 2013;58:2045–55.
309. Card TR, Solaymani-Dodaran M, West J. Incidence and mortality of primary sclerosing cholangitis in the UK: a population-based cohort study. J Hepatol. 2008;48:939–44.
310. Kingham JG, Kochar N, Gravenor MB. Incidence, clinical patterns, and outcomes of primary sclerosing cholangitis in South Wales, United Kingdom. Gastroenterology. 2004;126:1929–30.
311. Bambha K, Kim WR, Talwalkar J, Torgerson H, Benson JT, Therneau TM, et al. Incidence, clinical spectrum, and outcomes of primary sclerosing cholangitis in a United States community. Gastroenterology. 2003;125:1364–9.
312. Toy E, Balasubramanian S, Selmi C, Li CS, Bowlus CL. The prevalence, incidence and natural history of primary sclerosing cholangitis in an ethnically diverse population. BMC Gastroenterol. 2011;11:83.
313. Kaplan GG, Laupland KB, Butzner D, Urbanski SJ, Lee SS. The burden of large and small duct primary sclerosing cholangitis in adults and children: a population-based analysis. Am J Gastroenterol. 2007;102:1042–9.
314. Escorsell A, Pares A, Rodes J, Solis-Herruzo JA, Miras M, de la Morena E. Epidemiology of primary sclerosing cholangitis in Spain. Spanish Association for the Study of the Liver. J Hepatol. 1994;21:787–91.
315. Berdal JE, Ebbesen J, Rydning A. [Incidence and prevalence of autoimmune liver diseases]. Tidsskr Nor Laegeforen. 1998;118:4517–9.
316. Molodecky NA, Kareemi H, Parab R, Barkema HW, Quan H, Myers RP, et al. Incidence of primary sclerosing cholangitis: a systematic review and meta-analysis. Hepatology. 2011;53:1590–9.
317. Norris S, Kondeatis E, Collins R, Satsangi J, Clare M, Chapman R, et al. Mapping MHC-encoded susceptibility and resistance in primary sclerosing cholangitis: the role of MICA polymorphism. Gastroenterology. 2001;120:1475–82.
318. Donaldson PT, Norris S. Evaluation of the role of MHC class II alleles, haplotypes and selected amino acid sequences in primary sclerosing cholangitis. Autoimmunity. 2002;35:555–64.
319. Karlsen TH, Boberg KM, Vatn M, Bergquist A, Hampe J, Schrumpf E, et al. Different HLA class II associations in ulcerative colitis patients with and without primary sclerosing cholangitis. Genes Immun. 2007;8:275–8.
320. Karlsen TH, Hampe J, Wiencke K, Schrumpf E, Thorsby E, Lie BA, et al. Genetic polymorphisms associated with inflammatory bowel disease do not confer risk for primary sclerosing cholangitis. Am J Gastroenterol. 2007;102:115–21.
321. Bowlus CL, Li CS, Karlsen TH, Lie BA, Selmi C. Primary sclerosing cholangitis in genetically diverse populations listed for liver transplantation: unique clinical and human leukocyte antigen associations. Liver Transpl. 2010;16:1324–30.
322. Hov JR, Lleo A, Selmi C, Woldseth B, Fabris L, Strazzabosco M, et al. Genetic associations in Italian primary sclerosing cholangitis: heterogeneity across Europe defines a critical role for HLA-C. J Hepatol. 2010;52:712–7.

323. Juran BD, Atkinson EJ, Schlicht EM, Larson JJ, Ellinghaus D, Franke A, et al. Genetic polymorphisms of matrix metalloproteinase 3 in primary sclerosing cholangitis. Liver Int. 2011;31:785–91.
324. Friedrich K, Rupp C, Hov JR, Steinebrunner N, Weiss KH, Stiehl A, et al. A frequent PNPLA3 variant is a sex specific disease modifier in PSC patients with bile duct stenosis. PLoS One. 2013;8:e58734.
325. Liu JZ, Hov JR, Folseraas T, Ellinghaus E, Rushbrook SM, Doncheva NT, et al. Dense genotyping of immune-related disease regions identifies nine new risk loci for primary sclerosing cholangitis. Nat Genet. 2013;45:670–5.
326. Spurkland A, Saarinen S, Boberg KM, Mitchell S, Broome U, Caballeria L, et al. HLA class II haplotypes in primary sclerosing cholangitis patients from five European populations. Tissue Antigens. 1999;53:459–69.
327. Loftus EV Jr, Sandborn WJ, Tremaine WJ, Mahoney DW, Zinsmeister AR, Offord KP, et al. Primary sclerosing cholangitis is associated with nonsmoking: a case-control study. Gastroenterology. 1996;110:1496–502.
328. van Erpecum KJ, Smits SJ, van de Meeberg PC, Linn FH, Wolfhagen FH, vanBerge-Henegouwen GP, et al. Risk of primary sclerosing cholangitis is associated with nonsmoking behavior. Gastroenterology. 1996;110:1503–6.
329. Mitchell SA, Thyssen M, Orchard TR, Jewell DP, Fleming KA, Chapman RW. Cigarette smoking, appendectomy, and tonsillectomy as risk factors for the development of primary sclerosing cholangitis: a case control study. Gut. 2002;51:567–73.
330. Terjung B, Sohne J, Lechtenberg B, Gottwein J, Muennich M, Herzog V, et al. p-ANCAs in autoimmune liver disorders recognise human beta-tubulin isotype 5 and cross-react with microbial protein FtsZ. Gut. 2010;59:808–16.
331. Mueller T, Beutler C, Pico AH, Shibolet O, Pratt DS, Pascher A, et al. Enhanced innate immune responsiveness and intolerance to intestinal endotoxins in human biliary epithelial cells contributes to chronic cholangitis. Liver Int. 2011;31:1574–88.
332. Tabibian JH, O'Hara SP, Trussoni CE, Tietz PS, Splinter PL, Mounajjed T, et al. Absence of the intestinal microbiota exacerbates hepatobiliary disease in a murine model of primary sclerosing cholangitis. Hepatology. 2016;63:185–96.
333. Fausa O, Schrumpf E, Elgjo K. Relationship of inflammatory bowel disease and primary sclerosing cholangitis. Semin Liver Dis. 1991;11:31–9.
334. Schrumpf E, Fausa O, Kolmannskog F, Elgjo K, Ritland S, Gjone E. Sclerosing cholangitis in ulcerative colitis. A follow-up study. Scand J Gastroenterol. 1982;17:33–9.
335. Talwalkar JA, Lindor KD. Primary sclerosing cholangitis. Inflamm Bowel Dis. 2005;11:62–72.
336. Melum E, Franke A, Schramm C, Weismuller TJ, Gotthardt DN, Offner FA, et al. Genome-wide association analysis in primary sclerosing cholangitis identifies two non-HLA susceptibility loci. Nat Genet. 2011;43:17–9.
337. Saich R, Chapman R. Primary sclerosing cholangitis, autoimmune hepatitis and overlap syndromes in inflammatory bowel disease. World J Gastroenterol. 2008;14:331–7.
338. Jussila A, Virta LJ, Kautiainen H, Rekiaro M, Nieminen U, Farkkila MA. Increasing incidence of inflammatory bowel diseases between 2000 and 2007: a nationwide register study in Finland. Inflamm Bowel Dis. 2012;18:555–61.
339. Vind I, Riis L, Jess T, Knudsen E, Pedersen N, Elkjaer M, et al. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003–2005: a population-based study from the Danish Crohn colitis database. Am J Gastroenterol. 2006;101:1274–82.
340. Culver EL, Chapman RW. Systematic review: management options for primary sclerosing cholangitis and its variant forms—IgG4-associated cholangitis and overlap with autoimmune hepatitis. Aliment Pharmacol Ther. 2011;33:1273–91.
341. Luth S, Kanzler S, Frenzel C, Kasper HU, Dienes HP, Schramm C, et al. Characteristics and long-term prognosis of the autoimmune hepatitis/primary sclerosing cholangitis overlap syndrome. J Clin Gastroenterol. 2009;43:75–80.

342. Oliveira EM, Oliveira PM, Becker V, Dellavance A, Andrade LE, Lanzoni V, et al. Overlapping of primary biliary cirrhosis and small duct primary sclerosing cholangitis: first case report. J Clin Med Res. 2012;4:429–33.
343. McNair AN, Moloney M, Portmann BC, Williams R, McFarlane IG. Autoimmune hepatitis overlapping with primary sclerosing cholangitis in five cases. Am J Gastroenterol. 1998;93:777–84.
344. Burak KW, Urbanski SJ, Swain MG. A case of coexisting primary biliary cirrhosis and primary sclerosing cholangitis: a new overlap of autoimmune liver diseases. Dig Dis Sci. 2001;46:2043–7.
345. Abdo AA, Bain VG, Kichian K, Lee SS. Evolution of autoimmune hepatitis to primary sclerosing cholangitis: a sequential syndrome. Hepatology. 2002;36:1393–9.
346. Kingham JG, Abbasi A. Co-existence of primary biliary cirrhosis and primary sclerosing cholangitis: a rare overlap syndrome put in perspective. Eur J Gastroenterol Hepatol. 2005;17:1077–80.
347. Czaja AJ. Frequency and nature of the variant syndromes of autoimmune liver disease. Hepatology. 1998;28:360–5.
348. Kaya M, Angulo P, Lindor KD. Overlap of autoimmune hepatitis and primary sclerosing cholangitis: an evaluation of a modified scoring system. J Hepatol. 2000;33:537–42.
349. Boberg KM, Chapman RW, Hirschfield GM, Lohse AW, Manns MP, Schrumpf E. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. J Hepatol. 2011;54:374–85.
350. Beuers U, Boberg KM, Chapman RW, Chazouilleres O, Invernizzi P, Jones DEJ, et al. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol. 2009;51:237–67.
351. Bjornsson E, Chari S, Silveira M, Gossard A, Takahashi N, Smyrk T, et al. Primary sclerosing cholangitis associated with elevated immunoglobulin G4: clinical characteristics and response to therapy. Am J Ther. 2011;18:198–205.
352. Okazaki K, Uchida K, Koyabu M, Miyoshi H, Ikeura T, Takaoka M. IgG4 cholangiopathy: current concept, diagnosis, and pathogenesis. J Hepatol. 2014;61:690–5.
353. Naitoh I, Zen Y, Nakazawa T, Ando T, Hayashi K, Okumura F, et al. Small bile duct involvement in IgG4-related sclerosing cholangitis: liver biopsy and cholangiography correlation. J Gastroenterol. 2011;46:269–76.
354. Deshpande V, Sainani NI, Chung RT, Pratt DS, Mentha G, Rubbia-Brandt L, et al. IgG4-associated cholangitis: a comparative histological and immunophenotypic study with primary sclerosing cholangitis on liver biopsy material. Mod Pathol. 2009;22:1287–95.
355. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol. 2012;25:1181–92.
356. Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med. 2012;366:539–51.
357. Ohara H, Okazaki K, Tsubouchi H, Inui K, Kawa S, Kamisawa T, et al. Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012. J Hepatobiliary Pancreat Sci. 2012;19:536–42.
358. Ghazale A, Chari ST, Zhang L, Smyrk TC, Takahashi N, Levy MJ, et al. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. Gastroenterology. 2008;134:706–15.
359. Boonstra K, Culver EL, de Buy Wenniger LM, van Heerde MJ, van Erpecum KJ, Poen AC, et al. Serum immunoglobulin G4 and immunoglobulin G1 for distinguishing immunoglobulin G4-associated cholangitis from primary sclerosing cholangitis. Hepatology. 2014;59:1954–63.
360. Dastis SN, Latinne D, Sempoux C, Geubel AP. Ulcerative colitis associated with IgG4 cholangitis: similar features in two HLA identical siblings. J Hepatol. 2009;51:601–5.
361. Narula N, Vasudev M, Marshall JK. IgG(4)-related sclerosing disease: a novel mimic of inflammatory bowel disease. Dig Dis Sci. 2010;55:3047–51.
362. Mendes FD, Jorgensen R, Keach J, Katzmann JA, Smyrk T, Donlinger J, et al. Elevated serum IgG4 concentration in patients with primary sclerosing cholangitis. Am J Gastroenterol. 2006;101:2070–5.

363. Oh HC, Kim MH, Lee KT, Lee JK, Moon SH, Song TJ, et al. Clinical clues to suspicion of IgG4-associated sclerosing cholangitis disguised as primary sclerosing cholangitis or hilar cholangiocarcinoma. J Gastroenterol Hepatol. 2010;25:1831–7.
364. Feldstein AE, Perrault J, El-Youssif M, Lindor KD, Freese DK, Angulo P. Primary sclerosing cholangitis in children: a long-term follow-up study. Hepatology. 2003;38:210–7.
365. Miloh T, Arnon R, Shneider B, Suchy F, Kerkar N. A retrospective single-center review of primary sclerosing cholangitis in children. Clin Gastroenterol Hepatol. 2009;7:239–45.
366. Takikawa H, Takamori Y, Tanaka A, Kurihara H, Nakanuma Y. Analysis of 388 cases of primary sclerosing cholangitis in Japan; presence of a subgroup without pancreatic involvement in older patients. Hepatol Res. 2004;29:153–9.
367. Tanaka A, Takikawa H. Geoepidemiology of primary sclerosing cholangitis: a critical review. J Autoimmun. 2013;46:35–40.
368. Kochhar R, Goenka MK, Das K, Nagi B, Bhasin DK, Chawla YK, et al. Primary sclerosing cholangitis: an experience from India. J Gastroenterol Hepatol. 1996;11:429–33.
369. Ang TL, Fock KM, Ng TM, Teo EK, Chua TS, Tan JY. Clinical profile of primary sclerosing cholangitis in Singapore. J Gastroenterol Hepatol. 2002;17:908–13.
370. Hiatt RA, Kaufman L. Epidemiology of inflammatory bowel disease in a defined northern California population. West J Med. 1988;149:541–6.
371. Boonstra K, de Vries EM, van Geloven N, van Erpecum KJ, Spanier M, Poen AC, et al. Risk factors for primary sclerosing cholangitis. Liver Int. 2016;36:84–91.
372. Rutgeerts P, D'Haens G, Hiele M, Geboes K, Vantrappen G. Appendectomy protects against ulcerative colitis. Gastroenterology. 1994;106:1251–3.
373. Karrar A, Broome U, Sodergren T, Jaksch M, Bergquist A, Bjornstedt M, et al. Biliary epithelial cell antibodies link adaptive and innate immune responses in primary sclerosing cholangitis. Gastroenterology. 2007;132:1504–14.
374. Tabibian JH, Weeding E, Jorgensen RA, Petz JL, Keach JC, Talwalkar JA, et al. Randomised clinical trial: vancomycin or metronidazole in patients with primary sclerosing cholangitis—a pilot study. Aliment Pharmacol Ther. 2013;37:604–12.
375. Tabibian JH, Talwalkar JA, Lindor KD. Role of the microbiota and antibiotics in primary sclerosing cholangitis. Biomed Res Int. 2013;2013:389537.
376. Bergquist A, Lindberg G, Saarinen S, Broome U. Increased prevalence of primary sclerosing cholangitis among first-degree relatives. J Hepatol. 2005;42:252–6.
377. Schrumpf E, Fausa O, Forre O, Dobloug JH, Ritland S, Thorsby E. HLA antigens and immunoregulatory T cells in ulcerative colitis associated with hepatobiliary disease. Scand J Gastroenterol. 1982;17:187–91.
378. Czaja AJ, Santrach PJ, Breanndan Moore S. Shared genetic risk factors in autoimmune liver disease. Dig Dis Sci. 2001;46:140–7.
379. Bernuzzi F, Marabita F, Lleo A, Carbone M, Mirolo M, Marzioni M, et al. Serum microRNAs as novel biomarkers for primary sclerosing cholangitis and cholangiocarcinoma. Clin Exp Immunol. 2016;185:61–71.
380. Timmer MR, Beuers U, Fockens P, Ponsioen CY, Rauws EA, Wang KK, et al. Genetic and epigenetic abnormalities in primary sclerosing cholangitis-associated cholangiocarcinoma. Inflamm Bowel Dis. 2013;19:1789–97.
381. Andresen K, Boberg KM, Vedeld HM, Honne H, Hektoen M, Wadsworth CA, et al. Novel target genes and a valid biomarker panel identified for cholangiocarcinoma. Epigenetics. 2012;7:1249–57.