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Progress in Liver Cancer Associated to Autoimmune Liver Disease

Danlin Wang[1,2], Liang Song[1], Lei Guan[2], Yi Lu[1,2], Ying Han[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China
[2]National Clinical Research Center for Digestive Diseases and Xijing Hospital of Digestive Diseases, Xijing Hospital, Air Force Military Medical University, Xi'an, Shaanxi, 710032, China
Correspondence Author

Abstract: ***Autoimmune liver diseases (AILDs) are a group of liver diseases caused by abnormal autoimmune responses of the body, mainly including three main types: autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) [1]. Although the three diseases differ in their clinical manifestations and pathological mechanism, their common feature is the abnormal attack of the immune system on the liver tissue, resulting in impaired liver function. Primary liver cancer is considered the sixth most commonly diagnosed type of cancer worldwide, and it is also the third leading cause of death. The disease mainly includes hepatocellular carcinoma (HCC), intrahepatic cholangiocellular carcinoma (ICC) and other special types of liver cancer [2, 3]. There is a correlation between autoimmune liver disease and liver cancer, which has attracted wide attention from the medical community in recent years. Previous studies have reported that patients with AILDs will have a 3.6 times increased risk of developing cancer, while the risk of death from cancer will increase by 2.48 times. In addition to hepatobiliary cancer, several studies have further revealed that AILDs may also be complicated by colorectal cancer, hematological malignancies, pancreatic cancer, and skin cancer [4]. Therefore, this article will review the epidemiology, pathogenesis, risk factors, treatment prognosis and preventive surveillance of liver cancer associated with autoimmune liver disease.***

Keywords: Autoimmune liver disease-related liver cancer, Autoimmune hepatitis, Primary biliary cholangitis, Primary sclerosing cholangitis.

1. Introduction

Autoimmune liver disease (AILDs) is a group of chronic non-suppurative inflammation of the liver mediated by the autoimmune system. The damage of hepatobiliary cells causes cholestasis, and the disease can progress to cirrhosis and primary liver cancer. AILDs include autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitisb (PSC). Autoimmune hepatitis mainly shows the inflammation and damage of the liver parenchymal cells, primary biliary cholangitis is characterized by chronic intrahepatic cholestasis, causing the bile duct inside the liver, and primary sclerosing cholangitis is characterized by idiopathic hepatic and external biliary inflammation and fibrosis, characterized by stenosis and sclerosis of the bile duct [1].

Primary liver cancer is one of the most common malignant tumors in the world, with the incidence and mortality of the sixth and third of malignant tumors respectively. Primary liver cancer mainly includes hepatocellular carcinoma (HCC), intrahepatic cholangiellular carcinoma (ICC) and other types. Among them, HCC accounts for 75% -85% of all cases, and the number of new cases and deaths is about 840,000 and 780,000 per year, while ICC accounts for only 10%-15% [2]. HCC is considered to be the most common primary liver malignancy tumor in the world, with high degree of malignancy, strong infiltration and metametastasis, and limited treatment methods, and its long-term efficacy depends on early diagnosis and early treatment [3,4]. In the etiology of primary liver cancer, HBV infection is still predominant, but with the increasing incidence of AILDs, it has become an important etiology that cannot be ignored in primary liver cancer [5].

Autoimmune liver disease-related liver cancer is that developed based on long-term autoimmune liver disease. AILD can lead to cirrhosis, liver and extrahepatic malignancies, liver failure and even death. The past has been that AILDs do not progress to liver cancer, but studies have found that the incidence of liver cancer is higher when patients with AILDs progress to cirrhosis. Increasing evidence also indicates that although the incidence of AIH and PBC patients is low compared to other liver diseases, the risk of AILDs progressing to hepatobiliary malignancy gradually increases with the increasing incidence of autoimmune liver diseases.

2. Epidemiology

2.1 AIH-associated Liver Cancer

AIH is a type of hepatic inflammatory lesions based on autoimmune response, characterized by elevated serum transaminase, IgG levels and several positive autoantibodies. The pathogenesis is not clear, which may be related to the genetic susceptibility and environmental factors that trigger the immune system to its own hepatocyte antigen and produce immune response [6]. In the Asian region, the incidence and prevalence of AIH were 1.31/100,000 and 12.99/1010,000, respectively, and the incidence and prevalence were higher in women than in men [7]. The incidence of HCC among patients with AIH is reported to be about 4.0‰, twice that of the general population [8]. Due to different regions and population, the incidence of HCC in AIH patients is also different, with Europe, Asia and North America having 2.37‰, 6.18‰ and 2.97‰ respectively, while the incidence was higher than that in women (4.05‰vs3.44‰) [9,10]. According to a Danish cohort study of 2904 patients with AIH, a 20-year increased risk of developing HCC compared with the control group. A UK study of 1008 AIH patients for 18 years showed that 10-year cumulative all-cause mortality and

liver-related mortality (including HCC) were 31.9% and 10.5%, respectively. A prospective study from King's College London showed that HCC represented 6.2% in the AIH population and 12.3% in patients with cirrhosis, with an incidence of 1.1% per year [11]. Recently, an international multicenter retrospective cohort study published by Colapietro et al [12]. They mainly studied the incidence and risk factors of HCC in AIH patients, including a total of 1428 AIH patients in North America and Europe. A total of 24 patients (about 1.7%) developed HCC during the follow-up period, with an incidence of 1.44/1000 person-years, which was still lower than the incidence of HCC in patients with HBV or HCV infection (12-15/1000 person-years) [13,14].

2.2 PBC-associated Liver Cancer

PBC is a chronic intrahepatic cholestatic liver disease with the main lesion site in the small intrahepatic bile duct, and chronic progressive non-suppurative inflammation mediated by autoimmunity. Its pathogenesis is related to the body's autoimmune response against bile duct epithelial cells. Most patients have skin pruritus, jaundice, fatigue and other manifestations, and specific antibodies such as anti-mitochondrial antibodies can be detected in the serum. Liver cirrhosis and related complications can occur with the progression of the disease. A meta-analysis by Professor Yamini Natarajan et al. included 29 clinical studies and 22615 PBC patients, which showed that the incidence of HCC in PBC patients was about 4.17‰, similar to AIH, the cancer rate of PBC patients with liver cirrhosis was significantly increased (15.7‰), and the cancer rate in men was more than 2 times that of women (9.82‰vs3.82‰) [15]. It is also reported that all-cause mortality and liver-related mortality or liver transplant rates in PBC patients are higher in men than in women [16]. Therefore, although the incidence of autoimmune liver disease is low in men, the mortality rate and cancer rate are higher than those in women [11]. A recent meta-analysis showed that the incidence of PBC-associated HCC in Asia was 5.77/1000 (human. Year), the incidence of HCC associated with PBC in North America is 5.10/1000 (human. Years) were similar but higher than the European incidence of 2.67/1000 (human. Year) [17]. In New Zealand, a population-based study by Canterbury et al. found a standardised incidence ratio (SIR) of all cancers in PBC patients of 1.6, indicating an increased risk of cancer in this population [9]. Furthermore, a meta-analysis of cohort studies showed an overall relative cancer risk of 3.64 in patients with autoimmune liver disease including PBC, underscoring the increased cancer risk in these patients, which also focused on identifying new molecular and pathways involved in PBC-related liver injury [16]. Shackel et al used cDNA array analysis to identify [7], a differentially expressed gene important in inflammation, fibrosis, proliferation, signaling, apoptosis and oxidative stress in PBC. This approach provides insights into the pathogenesis of PBC and the potential therapeutic targets for this disease.

2.3 PSC-associated Liver Cancer

Primary sclerosing cholangitis mainly involves the intrahepatic and extrahepatic bile ducts, leading to chronic cholestatic disease characterized by progressive stenosis and fibrosis of the bile duct, with rapid progression and high degree of malignancy. In addition to the manifestations of cholestasis, patients may also have intestinal diseases such as inflammatory bowel disease, and the development of the disease can lead to liver cirrhosis, liver failure and other serious consequences [18, 19]. A recent large multicentre study by the International PSC Study Group in more than 7000 PSC patients showed that the disease is equally common in women and men [20, 21].

PSC is considered precancerous, and the cause of death in 40%-50% of patients with PSC is associated with malignancy. The PSC patients have a significantly increased risk of developing primary liver cancer, cholangiocarcinoma, pancreatic cancer, and colorectal cancer compared with the general population [22]. After an average of 5.7 years of follow-up of 604 PSC patients, the incidence of hepatocellular carcinoma was approximately 1.5%, cholangiocarcinoma was approximately 13%, and pancreatic cancer was 14 times that of the general population [18,19]. In a Swedish study of 604 patients with PSC, HCC was found in 4% of liver transplants (4 out of 92 transplanted livers) [23]. In two Dutch studies, including 590 and 211 patients, no cases of HCC were reported during the follow-up or in the transplanted liver [18, 24]. A recent UK study found PSC in IBD during 10-year follow-up and found that the incidence of HCC in PSC / IBD was 1.8% (47 / 2588). In addition, a study of 830 patients from the United States reported a high incidence of HCC cases in PSC, with 20 patients (2.5%) diagnosed with HCC during a median follow-up period of 9.5 years [20, 25]. All the patients with HCC had liver cirrhosis. The higher incidence of HCC may be related to the longer follow-up time in this study. Although HCC in patients with PSC, these two studies highlight the need for monitoring of HCC in patients with PSC.

Overall, AILDs especially AIH and PBC increase the risk of HCC, although lower risk compared to other liver diseases, but significantly increased risk of HCC when patients develop cirrhosis. Currently, HCC monitoring in patients with PBC and AIH with cirrhosis has been supported in the guidelines for early diagnosis and early detection.

3. Nosogenesis

Continuous hepatic inflammation caused by AILDs can activate hepatic stellate cells and promote excessive deposition of extracellular matrix, leading to the continuous progression of liver fibrosis and destroying the normal tissue structure of the liver. In AIH, autoimmune reactions cause repeated hepatocyte injury, necrosis and regeneration, increasing the risk of genetic mutation accumulation; PBC patients with long-term bile duct damage, cholestasis, causing chronic inflammation and oxidative stress can induce abnormal proliferation of hepatocytes; progressive fibrosis and stenosis in PSC patients, also prone to cholestasis and chronic inflammation, creating a suitable microenvironment for tumor development [26]. In addition, AILDs-related immune regulation disorders, such as cytokine imbalance, may also participate in the occurrence and development of liver cancer cells.

The molecular mechanism of the development and development of liver cancer is still unclear, and the increased

incidence of liver cancer in patients with AILDs may be related to liver inflammation, long-term hepatocellular injury, autoimmune response, cholestasis, genetic susceptibility and other factors. Liver inflammation can trigger oxidative stress, damage cellular DNA, cause gene mutations and increase the risk of liver cancer. Abnormal autoimmune response leads to immune cells mistakenly attack liver cells, unbalanced immune regulation, and persistence of inflammation. Cholestasis can lead to hepatocellular injury and dysplasia of bile duct epithelial cells, which may develop into cholangiocarcinoma [27, 28]. Genetic susceptibility, such as genetic mutations and familial aggregation phenomenon, also increases the risk of liver cancer [28].

Recent Xiamen university research team reported that the liver cancer initiation cells glycogenolysis key enzyme glucose-6-phosphatase is often down, to increase glycogen storage, accumulation of glycogen through liquid phase separation pathway to promote malignant tumor, and eliminate glycogen accumulation can reduce the incidence of malignant tumor [29]. Therefore, intracellular glycogen accumulation may also be one of the mechanisms underlying the development and development of HCC. Chronic inflammation of the liver caused by various etiologies leads to increased levels of inhibitory cytokines within the liver, such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β). These cytokines have potent immunosuppressive effects and are able to suppress the response of the immune system, thus creating favorable conditions for the growth and spread of tumor cells [28]. Moreover, the liver is in chronic contact with the gut microbiota, and this unique physiological environment may lead to a relatively inactive immune response within the liver. This immune tolerance property of the liver, may provide a place for tumor cells to grow, making tumors more likely to form and develop in the liver. Therefore, understanding these complex interactions is essential for developing effective preventive and therapeutic strategies.

Autoimmune responses play key roles in tumorigenesis. In a cohort study of 478753 participants, Ming-Ming He et al found that immune-mediated disease was associated with increased cancer risk, especially the excessive activation of IL-12 and IL-23 signaling prompted abnormal TH 1 and TH-17 immune responses, leading to chronic inflammation, and the IL-23/TH-17 /IL-17 axis may lead to weakened barrier function in the local mucosa of the skin and intestine and lungs and suppressed anti-tumor immune surveillance [30]. Although growing evidence suggests a role of immune components and the gut microbiome in cancer development, more studies are needed to elucidate these associations. Moreover, HLA-G functions as an immunomodulatory molecule in a variety of diseases, including cancer progression. Regulation of HLA-G expression may become a therapy for related diseases. Studies show that HLA-G plays a key role in the control of autoimmune diseases, and its molecular level and polymorphisms are associated with disease susceptibility and severity [31]. Finally, homeostasis of the gut-hepatic axis is essential to prevent hepatocellular injury and liver tumors, and Farnesoid X receptor (FXR) is a ligand-activated transcription factor that is highly expressed in the liver and intestine. In addition to the regulation of bile acid levels, lipid, and glucose metabolism, FXR is also involved in the regulation of liver regeneration, liver inflammation, tumor suppressor genes, and liver fibrosis [32,33].

Mc Gee et al. Study based on SEER registry data showed that the risk of hepatobiliary cancer increased significantly after several autoimmune diseases, with primary biliary cirrhosis and hepatocellular carcinoma (odds ratio (OR) of 31.33,95% confidence interval (CI) of 23.63 to 41.56) [33,34]. In addition, other studies suggest that some patients may have specific genetic mutations or genetic polymorphisms, making them more susceptible to autoimmune liver disease, and increasing the risk of liver cancer during the development of the disease. For example, some genes related to immune regulation, cell cycle regulation, and DNA repair are mutated or have polymorphisms, which may affect the body's control of autoimmune response and the ability to repair after liver damage, thus playing an important role in the pathogenesis of liver cancer related to autoimmune liver disease [27,34].

Cholestasis makes the components of bile (such as bile salts, bilirubin, etc.) accumulate in the liver, and these substances can produce toxic effects on liver cells and bile duct epithelial cells, leading to cell damage [35, 36]. And in the autoimmune liver diseases such as primary biliary cholangitis and primary sclerosing cholangitis, cholestasis exists. For example, high concentrations of bile salts can destroy the integrity of the cell membrane, causing intracellular ionic imbalance and organelle dysfunction, which can then trigger apoptosis or necrosis. Cholestasis also stimulates bile duct epithelial cells. Prolonged proliferation of bile duct epithelial cells may develop abnormalities and form atypical hyperplasia, a premalignant state. With the passage of time and the synergistic effects of other factors (such as inflammation, genetic factors, etc.), these atypical hyperplasia of bile duct epithelial cells may further become cholangiocarcinoma, which can develop into liver cancer in some cases, or its presence may also act as a local adverse factor to promote the occurrence of liver cancer [2, 37].

4. Hazards

4.1 AIH-associated Liver Cancer

For patients with autoimmune hepatitis, long-term liver inflammatory activities, repeated hepatocyte damage and repair process may lead to the accumulation of hepatocyte gene mutations, thus increasing the incidence of liver cancer. In particular, those patients with poor disease control, persistent inflammation, and progression to the stage of cirrhosis have a relatively higher risk of developing liver cancer [8]. The development of AIH-associated HCC is influenced by several factors, including age, gender, diabetes, AIH relapse, ALT abnormalities, long-term immunosuppressive therapy, treatment failure, and cirrhosis [8, 9].

Older patients are more likely to develop cirrhosis, thus increasing the risk of HCC. Male patients had a higher incidence of HCC than women, twice as, and deteriorated faster [9]. The reason for this may be that male patients have higher BMI values, smoking and drinking rate, and higher iron load, and the presence of these factors promotes tumorigenesis. Differences in gender hormone levels and

autoimmune systems may also be responsible for the increase in cancer rates [38]. Diabetes mellitus, as a complication of AIH treatment, may promote HCC development. Alcohol use can increase the HCC risk by six-fold. Repeated recurrence of AIH and persistent ALT abnormalities are also associated with HCC development [39, 40]. Previous studies reported that the decreased survival of patients with AIH was mainly related to the onset of cirrhosis at diagnosis or during follow-up or persistent inflammatory activity during follow-up, leading to liver-related death, including the development of HCC. Patients with recurrent liver inflammation, portal hypertension, and immunosuppressants for more than three years have an increased risk of HCC [41]. Immunosuppressive therapy is the main means of AIH treatment, which may cause cytokine disorder and lymphocyte defects in the body, increase the chance of tumor cells to escape immune surveillance, and long-term use may increase the risk of HCC. Treatment failure is more likely to be a risk factor for HCC than immunosuppressive treatment itself. Although most patients with AIH respond well to immunosuppressive therapy, they can progress to liver cirrhosis and liver failure if left untreated or poorly responded. Progress to cirrhosis can lead to an increased risk of liver-related complications and shorter survival [42].

The incidence of HCC in AIH patients with cirrhosis was about 10.07/1000. In a study including 93 AIH patients, 92 patients already had cirrhosis at the time of the diagnosis of HCC, so cirrhosis was considered necessary for the development of HCC in patients with AIH [43]. This is in line with the basic incidence of liver cancer, 85%-95% of liver cancer patients have the basis of cirrhosis [10]. As an independent risk factor for HCC associated with AIH, cirrhosis significantly increased in the incidence of HCC, and the longer the duration of cirrhosis, the higher the risk of HCC. Patients with AIH with cirrhosis for more than a decade have a significantly increased probability of developing HCC. Although patients with AIH without cirrhosis can also develop HCC, the probability is already very low.

4.2 PBC-associated Liver Cancer

Primary bile duct-induced cholangitis mainly affects the small bile ducts in the liver, causing non-suppurative inflammation and cholestasis. With the development of the disease to the late onset of cirrhosis, the liver microenvironment changes caused by cholestasis, such as bile duct epithelial cell hyperplasia, chronic inflammatory cells, such as infiltration, provide a suitable "soil" for the occurrence of liver cancer. May play a role in the development and development of liver cancer. Related studies have shown that the risk of liver cancer in PBC patients is several times higher than that in the general population [16].

Biochemical non-response is an important risk factor for HCC in PBC. Palak J Trivedi Professor and colleagues observed 4565 patients with PBC up to 40 years and found that the probability of biochemical failure (Paris I standard) after taking ursodeoxycholic acid (ursodeoxycholic acid, UDCA) occurred significantly increased in HCC (6.6‰vs1.4‰, $p<0.0001$). The study also found that men, elevated aspartate transaminotransferase, stage or stage PBC, liver decompensation, and thrombocytopenia were all risk factors for HCC in PBC [44]. Although taking UDCA can theoretically delay the development of cirrhosis and thus reduce the incidence of HCC, the incidence of HCC is not significantly different between patients taking UDCA and not taking PBC [15]. Male gender and late histological stages have been reported to be independently associated with the development of HCC. In addition, an international cohort study demonstrated that biochemical non-response (not met Paris-II) at one year of UDCA treatment significantly increased the risk of HCC. Recent studies have summarized other risk factors associated with HCC in PBC, including smoking, older age, portal hypertension, thrombocytopenia, viral infection, diabetes, obesity, and alcohol consumption [45].

4.3 PSC-associated Liver Cancer

The risk of liver cancer in patients with primary sclerosing cholangitis also cannot be ignored. The interaction of various factors, such as chronic inflammation of the bile duct, poor bile drainage caused by bile duct stenosis and complicated intestinal diseases, makes the liver be in a bad pathological state for a long time and promote the occurrence of liver cancer. Moreover, once such patients develop liver cancer, the prognosis is often poor due to the complexity of their bile duct lesions [18, 19].

A large multicentre cohort study reported an incidence of 10% of intrahepatic cholangiocellular carcinoma in patients with PSC [19]. Combined inflammatory bowel disease is a risk factor for malignancy in PSC patients, while 21%-80% of PSC patients have combined inflammatory bowel disease, and the longer the onset, the higher the incidence of tumors [20, 21]. Hyperlipidemia and obesity are considered potential risk factors for malignant tumors in patients with primary sclerosing cholangitis (PSC) [22]. Specifically, hyperlipidemia may lead to disordered lipid metabolism in the body, thus increasing the risk of cell carcinogenesis. And obesity, as a chronic inflammatory state, may also promote tumor development and progression through various mechanisms. Therefore, controlling blood lipid levels and maintaining a healthy body weight are important to reduce the risk of malignancies in PSC patients.

5. Treatment and Prognosis

The main purpose of autoimmune liver disease is to control liver inflammation, delay the progression of disease, and prevent the occurrence of cirrhosis and complications. For autoimmune hepatitis, drugs such as glucocorticoids and immunosuppressive agents are often used. Patients with primary biliary cholangitis may use drugs such as ursodeoxycholic acid to improve cholestasis. Primary sclerosing cholangitis is currently relatively difficult to treat, some patients can try to use immunosuppressor agents, but the effect is limited. In order to prevent autoimmune liver cancer, while the primary disease should be actively treated and the disease is stable; on the other hand, patients should maintain a healthy lifestyle, such as smoking cessation, alcohol restriction, reasonable diet, and proper exercise. For patients who have already developed cirrhosis, measures such as antiviral therapy (if associated viral infection) can be considered according to the specific situation to further reduce

the risk of liver cancer [46].

Patients with AILDs have the following clinical features: low AFP level, small maximum tumor diameter, and most in Barcelona stage A and B. In terms of treatment methods, most patients choose conservative treatment and hepatic artery embolization chemotherapy, while a small number of patients choose surgical resection or liver transplantation. The treatment modality for AILDs-related liver cancer is currently controversial. After local treatment such as radiofrequency ablation and embolic intervention, the necrotic tissue may release autoantigens, which has the possibility of aggravating the patient's condition [47]. Although partial liver resection can remove the tumor tissue, the trauma is large and only suitable for patients with good early liver function. Which treatment method is more beneficial to AILDs-HCC patients still needs to be verified by a multicentre, large-sample, randomized controlled trial. At present, it has been clear that liver transplantation can significantly prolong the survival of patients, because liver transplantation can improve the liver function of patients, and patients with liver transplantation are generally better, so the prognosis of liver transplant patients is better [48].

AILDs related liver cancer patients overall prognosis than other causes (such as hepatitis b, hepatitis C related liver cancer) liver cancer patients may be more complex and relatively poor, on the one hand is due to the existence of AILD itself liver lesions affected the treatment tolerance and effect, on the other hand is such patients with liver cancer after treatment needs to balance AILD condition, limiting the application of some treatment. The mean survival time of patients with AIH related HCC was 14 ± 12 months and that with PBC was 8.4 ± 14 months, significantly less than patients with HCC of other etiology [48, 49]. In the study of risk factors affecting the patient prognosis, multivariate regression analysis showed that AFP level and number of tumors were independent risk factors affecting the prognosis [44].

6. Prevention and Monitoring

Over the past 15 years, despite tremendous advances in the treatment of liver cancer, the prognosis of liver cancer patients has only improved slightly. Partial liver resection, radiofrequency elimination, liver transplantation are only used for patients with early liver cancer, so regular follow-up, early diagnosis and early treatment are still an effective means to improve the prognosis of patients with liver cancer. Although some scholars believe that regular follow-up monitoring is necessary only when the incidence of liver cancer is more than 1.5%. But considering that this cut-off value is derived from other liver diseases, it has not been validated in patients with AILDs. In addition, it has been reported that patients with AILDs with regular imaging examination also have a good prognosis after developing liver cancer [50]. Therefore, the American Association for the Study of Liver Disease (AASLD) recommends that men and patients with cirrhosis should have B-ultrasound or CT tests every 6 months to monitor the occurrence of liver cancer. For patients without confirmed cirrhosis, follow-up monitoring should also be performed: lower platelet count reduction, Mayo risk score greater than 4.1, and liver transient elasticity value greater than 17 kPa [51].

For patients with AILDs, especially a long course, moderate and severe liver fibrosis, cirrhosis, and other liver cancer risk factors (such as older, male, have a family history of liver cancer, etc.) of individuals, should be listed as a key monitoring object, regular liver cancer related screening, such as liver ultrasound and serum AFP (AFP) detection, in order to early detection of signs of liver cancer. For some high-risk patients, such as those with persistent inflammatory activity, and other risk factors such as diabetes mellitus. Risk stratification was performed according to the specific conditions of AILDs patients, such as disease type (AIH, PBC, PSC), liver fibrosis stage, and degree of inflammatory activity. For example, PSC patients with cirrhosis have a higher risk of liver cancer. The monitoring time interval of such patients can be appropriately shortened, and the examination means can be more comprehensive, so as to realize individualized monitoring scheme, improve the efficiency of early detection of liver cancer, and improve the long-term prognosis of patients [49-51].

7. Development Trend of AILDs-related Liver Cancer

Although HBV is still the main cause of liver cancer, the number of HBV and HCV infections is decreasing in decline with the great achievements in the prevention and control of viral hepatitis in China. But the incidence and prevalence of autoimmune liver disease are rising. Therefore, AILDs related to liver cancer should be paid attention to accordingly. The National hepatitis B in 2014 showed that the HBsAg carriage rate in people under 30 and 15 years old decreased from 10.1% and 10.8% in 1992 to 4.4% and 0.8%, respectively. The vaccination rate of hepatitis A vaccine and hepatitis B vaccine among school-age children in China has been in the world's leading level [49]. It can be believed that we can basically achieve the goal of eliminating the public health threat of viral hepatitis in WHO 2030.An in-depth analysis of the global burden of liver cancer data found that the incidence and number of cases of liver cancer increased significantly from 1990 to 2017, and the causes of liver cancer are also evolving [3].

It is foreseeable that in the near future, non-alcoholic fatty liver disease, diabetes and AILDs will become the main cause of liver cancer, and the number of cases of AILDs-related liver cancer will also increase. AILDs are considered rare diseases, but a growing number of research data suggest that the incidence and prevalence of AILDs are rising, and that the actual prevalence may be much higher than expected [41]. Due to the different levels of understanding of AILDs in hospitals at all levels and the uneven diagnosis and treatment techniques, the diagnosis and treatment rates of AILDs are lower than the average level. Most patients with AILDs cannot get early standard treatment, which greatly increases the risk of liver cancer in AILDs patients. Therefore, improving the awareness of autoimmune liver disease, preventing monitoring and conducting multicenter clinical research to obtain the true and accurate prevalence of AILDs incidence, and increasing the study of AILDs-related liver cancer should be put on the agenda as soon as possible.

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