MINI-REVIEW

Genetic Factors, Viral Infection, Other Factors and Liver Cancer: An Update on Current Progress

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Abstract

Primary liver cancer is one of the most common cancers at the global level, accounting for half of all cancers in some undeveloped countries. This disease tends to occur in livers damaged through alcohol abuse, or chronic infection with hepatitis B and C, on a background of cirrhosis. Various cancer-causing substances are associated with primary liver cancer, including certain pesticides and such chemicals as vinyl chloride and arsenic. The strong association between HBV infection and liver cancer is well documented in epidemiological studies. It is generally acknowledged that the virus is involved through long term chronic infection, frequently associated with cirrhosis, suggesting a nonspecific mechanism triggered by the immune response. Chronic inflammation of liver, continuous cell death, abnormal cell growth, would increase the occurrence rate of genetic alterations and risk of disease. However, the statistics indicated that only about one fifth of HBV carries would develop HCC in lifetime, suggesting that individual variation in genome would also influence the susceptibility of HCC. The goal of this review is to highlight present level of knowledge on the role of viral infection and genetic variation in the development of liver cancer.

Keywords: Viral infection - genetic variation - liver cancer

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Introduction

Primary liver cancer is cancer that forms in the tissues of the liver and it is one of the most common cancers in global range. Due to the poor prognosis and the low rate of long term survival, it also placed heavy burden on the government and the family of patients. At present, liver cancer is more prevalent in male population than females, with it mostly affecting people over 50. The latest data from IARC showed that the estimated death cases caused by primary liver cancer in both genders were 478,000 and 217,000 in worldwide, respectively (International Agency for Research on Cancer, 2009). The distribution of primary liver cancer also indicated that the incidence and mortality vary between geographical regions. The highest liver cancer rates are observed in East and South-East Asia and in Middle and Western Africa, in contrast, the corresponding measures are low in South Central and Western Asia, as well as Northern and Eastern Europe (Jemal et al., 2011). Additionally, this disease accounts for half of all cancers in some undeveloped countries. This is mainly because of the prevalence of hepatitis, caused by contagious viruses, that predisposes a person to liver cancer.

According to the SEER Cancer Statistics Review 1975-2008 released by National Cancer Institute (Howlader et al., 2011) , the incidence rate of liver cancer in male and female in the United States were 11.2 and 3.9, respectively. Interestingly, we also observed a significant difference between races, the highest rate observed among male of Asian/Pacific Islander, reached 22.1. Trend in China has been less well documented and the absence of authentic data on incidence and mortality make it more difficult to evaluate the epidemiological trend in detail. Nonetheless, the ministry of health has provided the access of mortality of liver cancer in 1973-1975, 1990-1992 and 2004-2005, and constant increases were observed in both genders (Ministry of Health of the People's Republic of China, 2010).

This disease tends to occur in livers damaged by alcohol abuse (Kono et al., 1987) chronic infection with hepatitis B (Beasley et al., 1981) and C (Saito et al., 1990) and cirrhosis (Adami et al., 1992). Various cancer-causing substances are associated with primary liver cancer, including certain pesticides (Zhao et al., 2011) and such chemicals as vinyl chloride (Du et al., 1998) and arsenic (Liaw et al., 2008). Although great progress has been made in those above-mentioned factors, however, the association between genetic factors and disease risk has remained unclear. This article reviews the current progress on the association study on liver cancer risk, such as biologic, genetic factors potentially related to liver cancer susceptibility.

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HBV Infection

The association between HBV infection and liver cancer is well documented in epidemiological study. Patients with chronic infection maintain elevated risk of hepatocelluar carcinoma, especially in those cases with active liver disease and cirrhosis. A report published in 2006 showed that HBV infection accounts for about 60% of the total liver cancer occurrence in developing countries and about 23% in developed countries (Parkin, 2006). In additional, a large scale investigation suggested that only 29% of liver cancer patients had no marker of either HBV or HCV infection from six European Liver Centers (International Agency for Research on Cancer, 2008) , and these two infections together are responsible for more than 70% of liver cancer cases worldwide (Cougot et al., 2005).

The mechanism of HBV chronic infection involved cancer development has already been investigated by various molecular studies, and great progress and solid evidence have acquired. It is generally acknowledged that HBV involves in the development of liver cancer through long time of chronic infection, frequently associated with cirrhosis, suggesting a nonspecific mechanism triggered by the immune response. Chronic inflammation of liver, continuous cell death, abnormal cell growth, would increase the occurrence rate of genetic alterations and risk of disease (Nakamoto et al., 1998). Further efforts indicated that the incorporation of HBV DNA into the host genome can play as precursor to liver cancer. The viral DNA encodes four types of genes all have been detected in the tissue specimen of HCC cases (Shafritz et al., 1981).

Some studies suggested that HBV genetic variability may influence the risk of liver cancer, however, this opinion is still remain questioned. The distribution of HBV genotypes is also different in the geographical regions. A study conducted in China has demonstrated that infection by HBV genotype B and C are associated with an excessive risk of hepatocellular carcinoma (Liu et al., 2009). An investigator (Chan et al., 2004) established a cohort among hepatitis B patients in Hong Kong, after 1664 person years of follow up, an adjusted relative risk of 2.84 (95%CI=1.05-7.72; p=0.040) for HBV genotype C infection was calculated by performing multivariate analysis. Furthermore, the result of bimolecular assays suggested that substitutions and deletion of nucleotides of HBV genome, including G1317A, T1341 C/A/G and pre-S2 deletion may lead to elevated risk of developing hepatocelluar carcinoma, on the other hand, those mutations may capable of serving as the predictor of liver cancer among patients with genotype C chronic hepatitis (Zhang et al., 2007). The latest approach by using Mboll PCR restriction analysis also identified a novel mutation in pre-S2, it is reported that F141L mutation was significantly related to HCC, even in comparison to live cirrhosis among 241 Korean patients (Mun et al., 2011). As for pre-S deletion, it was (Gao et al., 2007) reported that these mutations were more commonly found in the patients with HCC that in the chronic hepatitis B or asymptomatic carrier, suggesting pre-S deletion might involved in HBV-related hepatocarinogenesis. Mutations in basal core promoter may also involved in the development of carcinoma, the result of direct sequencing revealed that mutations including A1896, A1899 and multiple mutations T1762/A1764+A1896, T1762/A1764+A1899, and T1762/A1764+A1896+A1899 were more common in cirrhotic hepatocellular carcinoma group and non-cirrhotic hepatocellular carcinoma than chronic hepatitis B patients (Zheng et al., 2011). Moreover, a study with 37 patients and 38 controls has been performed and reported G1613A and C1653T double mutations were more prevalent in patients with HCC, thus, those mutations may serve as makers in predicting HCC development (Tatsukawa et al., 2011). Being compared with both carriers of inactive virus (25%) or patients with chronic hepatitis(35%), the frequency of T1653 mutation in box alpha, the rate among patients with HCC (70%) was significantly higher, suggesting it would lead to elevated risk of HCC (Ito et al., 2006).

Due to shared modes of transmission, the HBV/HCV coinfection possesses considerable rate among high risk population in some endemic areas. In general, approximately 2–10% of anti-HCV-positive cases were also identified as HBsAg positive by applying serological test. According to laboratory studies conducted before, the interaction between HBV and HCV was more frequently characterized by an inhibition of HBV caused by HCV (Jardi et al., 2001). However, it is believed that the coinfected cases tend to experience more severe liver damage, a higher possibility of liver cirrhosis and a higher incidence of HCC. However, the present conclusion on this issue is still remains inconsistent. A meta-analysis with 59 studies suggested that the coinfection for HCC risk was not significantly higher than monoinfection (Cho et al., 2011), while a latest cohort study found that multiplicative synergistic effect of coinfection with 6,694 participants (Oh et al., 2012). The hazard ratio of developing HCC was 115.0 (95%CI=32.5-407.3) in dually-infected subjects, and 17.1 (95%CI=8.4-34.8) in HBV and 10.4 (95%CI=4.9-22.1) in HCV monoinfeted subjects when being compared with the dual-negative subjects.

Viral load can serve as the measure of severity of HBV infection and tracking viral load is used to predict the outcome of infected cases. A retrospective study conducted among Taiwan population (Liu et al., 2006) demonstrated that if the HBV load is greater than 105 copies/ml, the odd ratio for HCC risk would reach 2.5 (95%CI=1.1-5.7), furthermore, the author also observed a lower odd ratio of 2.3 between HCC risk and HBV load among noncirrhotic hepatocellular carcinoma patients (Liu et al., 2006). A case-cohort study in Taiwan revealed that high viral load can cause HCC and low viral load (<4.39 log copies/ml) was associated with sustained normalization of ALT levels and decreased risk of this disease (Wu et al., 2008). Similarly, a research performed in Hong Kong (Chan et al., 2008) also reported positive association between high HBV load and HCC risk with a hazard ratio of 1.62 among Hong Kong population. A research conducted in Gambia found that, the high HBV DNA levels were strongly associated with HCC and the OR reached 38.8 after adjustment (Mendy et al, 2010), and more and more evidence demonstrated that the suppression of HBV may significantly reduce the risk of

HCC. Interestingly, HBV load has no significant difference between patients with early HCC and those with non-early HCC (Chu et al., 2012), however, the positive association of higher load and cancer risk remained constant when being compared with previous studies.

It is universally acknowledged that antiviral therapy against HBV infection would suppress virus level and improve outcomes. However, due to the cost and adverse effect occurred, it may not be generally accepted and performed in every patients with chronic infection. As for the HCC patients, it is reported that interferon treatment was capable of suppressing tumor growth (Zhang et al., 2009; Zhuang et al., 2010) and improving survivals (Qu et al., 2010) among HCC patients, and this findings were validated by various researches, including cell assays (Yang et al., 2008; Yin et al., 2011; Li et al., 2012). The effect of interferon treatment on the prevention of HCC development among cases with chronic infection remains inconclusive, multiple studies confirmed the protective effect among hepatitis C (Soga et al., 2005; Yu et al., 2006; Hung et al., 2011), however, a Japanese study (Imai et al., 2010) reported that the protective effect generated by applying interferon only limited to patients with chronic hepatitis C aged and over and was also limited to the subjects maintaining SVR when 6 months-IFN was given. The protective effect of interferon is still unclear among patients with HBV infection as well, an investigator in Taiwan (Lin et al., 2007) observed that only in patients with pre-existing cirrhosis, however, a meta-analysis in 2009 (Yang et al., 2009) suggests that the IFN is capable of preventing or delaying the development of HCC with a RR of 0.59. Similarly, a meta-analysis (Miyake et al., 2009) with the data of eight studies and the preventive effects were observed, and they were stronger in Asian population. In contrast, latest meta-analysis for randomized controlled trials (Zhang et al., 2011) demonstrated the cancer risk did not significantly reduced by IFN therapy, so the anti-tumor effects of INF still requires further validation.

Genetic Variation

It is generally agreed that HBV infection plays key role in HCC development, however, the statistics indicated that only about one fifth of HBV carries would develop HCC in lifetime, suggesting that individual variation in genome would also influence the susceptibility of HCC. P53 tumor suppressor gene is of extreme importance of maintaining genomic integrity and stability, thus malfunction of p53 was associated with increased cellular proliferation. A study conducted in Morocco revealed that the mutation of p53 codon72 would significantly increase the cancer risk and the OR for the Pro/Pro genotype was 2.304 (Ezzikouri et al., 2007). A case-control study (Yoon et al., 2008) was performed among subjects with chronic hepatitis B infection and observed a greater OR of codon72, furthermore, the results that combined MDM2 SNP309 and codon72 together, the OR was 20.78, suggesting the existence of synergistic effect. A newly published study in Turkish population also observed the positive association between this mutation and cancer risk with an OR of 3.20, moreover, the significant risk can be detected in male group and HBV group in stratified analysis (Sümbül et al., 2012). According to the result of the latest analysis which pooled data from eleven individual case-control studies, this polymorphism is associated with excessive risk of liver cancer, and the association is greater among Caucasians than other races (Lv et al., 2013).

Growing evidence reveals that IL-6 may play an important role in developing HCC and over expression of it would elevate the cancer risk. A case-control study conducted in Turkey (Ataseven et al., 2006) measured the IL-6 serum level among 70 subjects in total, and found that the serum level was correlated with the disease advancement. The latest epidemiological approach performed in Italy observed similar trend between IL-6 serum level and HCC, furthermore, the G carriers of -174G/C polymorphism had higher IL-6 serum level in HCC patients than that of subjects with LC (Giannitrapani et al., 2011). Polymorphisms in TNF-alpha may change the regulation of immune cells and malfunction of itself. It is reported that TNF-alpha was associated with multiple kinds of cancer, including liver cancer. Protective effect of -863 C allele was observed among Thai population, however, -308 was found to be non-significantly related with cancer risk (Kummee et al., 2007). In contrast, a study performed among Turkish population (Akkiz et al. 2009) reported a positive association between -308 polymorphism and risk of developing HCC in the Turkish population, to be precise, the OR for the mutation was 4.75 (95%CI=2.25-9.82). Currently, the association between HCC susceptibility and polymorphisms of TNF-alpha still remains inconsistent. Lately, it was reported that both 2 polymorphisms mentioned above had no statistical association with the risk of HCC in Han Chinese population (Chen et al., 2011).

To current knowledge of medical research, EGFR is a transmembrane tyrosine kinase whose activation drives signal transduction pathways affecting cellular proliferation, cell motility and apoptosis (Jorissen et al., 2003). Combined the data retrieve from many studies, the frequency of over expression of EGFR among HCC patients was about 40% to 70%. An epidemiological study (Li et al., 2010) was conducted to assess the risk of EGFR variants, the statistical analysis indicated that EGF 61GG was the risk factor of HCC, additionally, with the immuno-histochemical test, about 59.09% of HCC tissues tested showed EGF protein expression. Study conducted among patients with cirrhosis (Tanabe et al., 2008) shared same result, the subjects with G/G genotype have 4-fold risk when being compared with those with A/A genotype. It is quite expectable that the G/G carries had significant higher expression of EGF than other genotypes, those results remained constant when being compared with French group. Among HBV infected Chinese population, G/G genotype still maintains the excessive risk of HCC with an OR of 2.76 (Chen et al., 2011), A molecular study was conducted to further verify the association and found that G allele was positively correlated with the serum level of EGF (Abu Dayyeh et al., 2011).

DNA is the carrier of genetic information with encoded sequence and basis of gene expression, so maintaining the integrity of DNA molecules would be vital to the

survival and physiological function of the cell. DNA can be damaged by many sorts of mutagens, such as viral infection, base analog, ultraviolet light, ionizing radiation and the free oxygen radicals generated from cellular metabolism. Therefore, mutations that occur in DNA repair genes are strongly related with excessive cancer risks in human. Although great advancement has been made in the association studies of polymorphisms in repair genes and breast (Antoniou et al., 2010), colorectal (Wei et al. 2011) and lung cancer (López-Cima et al., 2007), however, the research focus on liver cancer was infrequently published. Codon 399 in XRCC1 was investigated among Taiwanese population (Yu et al., 2003), and both positive association and dose-dependent relationship for early-onset HCC were observed. The results of a study conducted in Guangxi province also consistent with an increased OR of 2.47 among subjects with aflatoxin B-related HCC, suggesting XRCC1 would affect the cancer risk, especially in those having high-level of long-term AFB1 exposure(Long et al., 2006). Subsequently, Researchers in China (Long et al., 2011) further investigated the role of codon 399 in AFB-related HCC, and the correlation between this specific mutation in XRCC1 and AFB1-DNA adducts level was obtained. Two meta-analyses showed inconsistent result with previously mentioned studies, it is demonstrated that in over all scale, variant in codon 399 was non-significantly associated with HCC risk, stratified the subjects for races, region and nations, the result remained negative (Liu et al., 2011; Wu et al.,2013).

Genome-wide association study, also known as whole genome association study, allow researchers to sample 500,000 or more SNPs from each subject in a study capturing variation uniformly across the genome. To address, these studies have identified risk and protective factors for asthma, cancer, diabetes, heart disease, and other human differences. A GWAS performed in HBV carries with HCC and HBV carriers without HCC among 715 Chinese study subjects and found that an intronic SNP in KIF1B on Chromosome 1p36.22 was strongly related with HBV-related HCC. This result was further validated in subsequent 5 replicated studies with independent samples, consisting of 1,962 cases with HCC, 1,430 control subjects and 159 family trios. Additional evidence in this study demonstrated that KIF1B-, UBE4B or PGD-related pathways might be involved in the development of cancer (Zhang et al., 2010). Kumar et al conducted GWAS in subjects with HCV-induced HCC and HCV-negative controls of Japanese origin, after further verification with additional samples, a previously unidentified locus in 5' flanking region of MICA on 6p21.33 was confirmed to be the risk factor of HCV-induced HCC, and this SNP was also been proved to play a role in the progression from HCV to HCC (Kumar et al., 2011). Systematic review conducted recently showed the significant reduced risk among Chinese population and other population with large-sample size, while no association detected in the small size cohorts (Wang et al., 2013). However, no significant association between K1F1B SNP and HCC risk was reported from latest publication (Spipong et al., 2013). It may indicated that other possible mechanisms or pathways involved in the progress of developing HCC.

Obesity and Diabetes Mellitus

Several studies has been conducted and identified DM as a potential risk factor for HCC, however, so far there is no consensus reached if it can act as an independent role in the etiology of HCC. The OR of HCC among subjects with both HCV infection and DM was 11.601 when being compared with the DM-free subjects (Hung et al.,2010), subsequently, prospective study with 1,470 subjects was conducted and found that the risk effect of DM was selective and only can be observed among those with chronic hepatitis C without cirrhosis after eradication of HCV (Hung et al., 2011). Animal testing in Swiss-Webster mice also confirmed the positive association and biological evidence was obtained (Lemke et al., 2008). As seen in the study conducted in the United States (Hassan MM et al., 2010), the adjusted OR of DM related to HCC risk was 4.2, furthermore, they also found that the risk would increase with the diabetes duration. Interestingly, the treatment against diabetes was also capable of changing the cancer risk, dietary control and sulfonylureas or insulin were related with excessive risk, whereas biguanides or thiazolidinediones was inversely associated with HCC. Investigators (Gao et al., 2010) observed same statistical association among Chinese population with an OR of 4.88, similarly, a case-control study with a total of 6275 eligible subjects found that the prevalence of diabetes is higher among HCC patients without cirrhosis than among those with cirrhosis. Additionally, the association has also been found among female individuals, further stratified the female subjects with the status of cirrhosis, the OR has become greater (Li et al., 2012). In order to eliminate the effect of viral infection, a case-control study was conducted among Italian subjects (Polesel et al., 2009) to evaluate the independent impact of DM, the result indicated that the risk induced by DM persists with or without HBV/HCV infection. Investigators conducted a prospective study and a nested case-control study among same Chinese population in Singapore (Koh et al., 2013), the exposure of DM at baseline was associated positively with a hazard ratio of 2.14 (95%CI=1.69-2.71). The association was tended to be equally strong after adjustment between genders. Interestingly, the magnitude of risk caused by DM has grown stronger among hepatitis B and C infection free subjects than those with HBV or HCV infection. Latest meta-analysis of 25 cohort studies reported DM was correlated with an elevated incidence of HCC, when being compared with subjects without DM. After the controlling of potential cofounders, the association still remained with significance (Wang et al., 2012). To summarize, these findings demonstrated above are strongly support the positive association between DM and excessive risk of HCC. Obesity now represents a crucial public health issue with a stable increase in global range. With the progress of medical research, it has been identified as independent risk of various cancers, the association between obesity and HCC has also been proposed. The case-control study with 185 HCC cases and 404 control subjects found that population with obesity has

a 3.5-fold risk of HCC when being compared with those with normal BMI (Polesel et al., 2009). A meat-analysis of ten cohort studies was performed to identify the role of obesity with the results of previous studies (Saunders et al., 2010). Seven cohorts reported positive association between obesity and HCC risk, while two reported no association and one found they were inversely related. Animal experiment has further verified the positive association between obesity and HCC risk (Thompson et al., 2013), high fat diet was capable of promoting the formation of HCC both in the absence or presence of a known hepatocarcinogen among mice. Although the results were inconsistent, however, the overall evidence still suggests the presence of positive association. In addition, a cohort study conducted among Taiwanese population (Loomba et al., 2013) demonstrated that the interaction between obesity and alcohol consumption may manifests as synergistic effect. With or without adjustment for several confounding factors, the hazard ratios were 7.19 in unadjusted analysis and 3.82 in multivariable adjusted analysis.

Micro RNA Expression

Micro RNA is a kind of endogenous non-coding RNA, universally can be detected in animals, plants and viruses. It has been proved that micro RNA plays important roles in the development, proliferation, differentiation and apoptosis of organism through complementary binding with target mRNA. In mammalian, the miRNA complementarity to its mRNA target is not perfect with some mismatched bases, which means one miRNA can target many different sites on the same mRNA or on many different mRNAs (Lewis et al., 2005). Researches performed in global range indicated that miRNA is closely related in cancer development, including prostate cancer (Porkka et al., 2007), breast cancer (Ma et al., 2007), and HCC (Meng et al., 2007).

454 sequencing developed by Roche was performed and 314,000 miRNAs from HCC and more than 268,000 from adjacent normal liver were successfully identified. Further analysis indicated that miR-21 and miR-122 are potential biomarkers for prediction of HCC (Mizuguchi et al., 2011). Researchers (Burchard et al., 2010) conducted the study on the function of miR-122 and found that, miR-122 was significantly under-expressed in HCC and consequently the expression of miR-122 seed-matched genes was elevated. In additional, miR-122 can also serve as a parameter for survival among patients with HCC, the results generated by using TaqMan MiRNA assay indicated that patients with greater mi-R122 level have longer overall survival than those with lower miR-122 serum concentration with a hazard ratio of 0.440 (Köberle et al., 2013) . In vivo validation suggested that the loss if miR-122 alone can up-regulated seed-matched genes and down-regulated mitochondrially localized genes that are critical for metabolic functions. Thus, the association between miR-122 related mitochondrial metabolism and HCC development requires further investigation.

Micro RNA has also been suspected with the alteration of sensitivity of certain anti-tumor treatments. A biological study aimed to reveal the function of miR-21 has been conducted in Japanese population and found that, this specific micro RNA is capable of lowering the effects of IFN-α/5-FU by applying Annexin V assay. On the other hand, transfection of anti-miR-21 rendered HCC cells sensitive to IFN-α/5-FU (Tomimaru et al., 2010). However, another study (Bihere et al., 2011) applied qRT-PCR on the serum samples of 62 CHC patients, 29 patients with CHC and HCC and 19 healthy controls, the results showed that miR-21 levels were correlated with standard liver parameters, histological grading and staging of CHC. Being compared with healthy control, the serum levels of mi-R21 in patients with CHC were significantly higher, but evidence also revealed that there was no difference between patients with CHC and CHC-associated HCC. Thus, miR-21 level can be served as the marker for necroinflammatory activity, but can not distinguish the patients with HCV from HCV-related HCC. Cellular assay conducted recently revealed that miR-21 inhibits PTEN and hSulf-1 expression in HCC cells. The suppression of PTEN and hSulf-1 would enhance the activity of HCC cell proliferation and promote the tumor growth in vivo (Bao et al., 2013). Based on these findings, it can be inferred that miR-21 may involve and regulate the HCC cellular proliferation, and targeted treatment can be developed in future.

Some researches revealed that some specific micro-RNAs are capable of suppressing the development of HCC and serve as anti-tumor factors. Compared with normal counterparts, the expression of miR-101 was decreased in HCC tissues. Besides, miR-101 could sensitize hepatoma cell lines to serum starvation and chemotherapeutic drug-induced apoptosis. Furthermore, miR-101 also can suppress the expression of Mcl-1 and reduce the protein level of Mcl-1, whereas the miR-101 inhibitor up-regulated Mcl-1 expression and inhibited cell apoptosis (Su et al., 2009). Evidence from the study conducted by researchers in China (Zhang et al., 2010) showed that miR-22 also maintains the function of suppressing tumourigenicity and cell proliferation. The results of qRT-PCR demonstrated that miR-22 expression was down-regulated in HCC tissue sample when being compared with normal counterparts. In detail, miR-22 expression can significantly inhibit HCC cell proliferation and tumourigenicity. HDAC4 which involves in the cancer development was identified as a target gene of miR-122. The expression of HDAC4 has been proved to be inversely correlated with miR-122. Taken these findings together, it can be assumed that miR-22 may can be applied in the cancer therapy against HCC.

Developing early detection method of HCC based on micro RNA has become hot subject and great progress has been made. Rreal time qPCR was performed in the serum samples of eligible subjects and miR-855-5p was selected for further analysis (Gui et al., 2011). The statistical analysis showed this micro RNA yield an AUC of 0.904 with 90.53% sensitivity and 79.17% specificity in differing liver pathologies from healthy controls. Same experimental method has also been applied in the samples retrieved from 3 independent cohorts with 934 subjects in total (Zhou et al., 2011). With the results of

Logistics regression model and AUC, a micro RNA panel (mi-R122, miR-192, miR-233, miR-26a, miR-27a and miR-801) with high diagnostic accuracy was obtained with an AUC of 0.864. The performance of micro RNA panel remains steady and satisfactory with the variation of disease status and has also been proved that was capable of discriminating HCC from healthy control, CHB and LC. These advances in miRNA research provided a novel availability of early diagnosis and maintained greater both sensitivity and specificity than AFP test, however, miRNA-based screening still requires further validation with large sample size and long term observation.

Conclusion

The impact and involvement of chronic infection, alcohol abuse and some known factors has been confirmed by various studies. The chronic HBV infection are accounted for a certain part of HCC incidence, therefore, the most effective way to prevent it is applying HBV vaccine among general population. According to the distribution of HCC in global range, the vaccination program against HBV must be further strengthened in undeveloped countries. Anti-viral therapy could possibly reduce the occurrence of HCC among individuals chronic infection and should be promoted appropriately. What need to emphasize is that, the interactions between host immune status, viral infection, and genetic variation were still remain undetermined and less investigated, further investigation should be performed, and high-throughput technology combined with larger sample size and well designed study is definitely required to solve the issue.

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