# Prevention of Hepatitis B Virus Infection and Liver Cancer

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## 1 Introduction

Hepatocellular carcinoma (HCC) is one of the leading cancer in the world (Parkin et al. 2001). Because of its high fatality (overall ratio of mortality to incidence of 0.93), liver cancer is one of the five most common causes of death from cancer worldwide. According to the 2018 global report from World Health Organization (WHO), liver cancer is the sixth most common cancer and the fourth most common cause of cancer death (WHO 2018). Persistent infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is associated with approximately 90% of HCC. Evidence from epidemiology, case control study, animal experiments, molecular biology all support the important oncogenic role, either directly or indirectly, of HBV and HCV in HCC. As evidenced by the large population infected with HBV in the developing world, HBV remains the most prevalent oncogenic virus for HCC in humans. HBV is estimated to cause around 55–70% of HCC worldwide, while HCV accounts for around 25% of HCC (Bosch and Ribes 2002). Liver cirrhosis is a common precancerous lesion, accounting for approximately 80% of patients with HCC, including children (Hsu et al. 1983). This sequel usually results from severe liver injury caused by chronic HBV or HCV infection.

The World Health Assembly calls for the elimination of viral hepatitis as a public health threat by 2030 to reduce new infections by 90% and mortality by 65% compared with the 2015 baseline (WHO 2017). Among the proposed strategies to eliminate viral hepatitis, prevention is the most important and cost-effective way to be conducted to achieve the goal.

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## 2 Disease Burden of HCC

According to the 2018 Cancer, today's report from the International Agency for Research on Cancer (IARC), WHO, liver cancer cases accounts for 4.7% of all new cancer cases and 8.2% of all cancer death cases (IARC, WHO 2018). Approximately, 257 million people (3.5% of the world population) in year 2015 are living with HBV infection. Hepatitis B resulted in 887,000 deaths, mostly from complications (mainly liver cirrhosis and HCC) (WHO 2019). High incidence areas of HCC are mainly in developing regions, such as Eastern and South-Eastern Asia, Middle, and Western Africa. The African (6.1%) and Western Pacific regions (6.2%) had the highest prevalence (WHO 2017). The geographical distribution of the mortality rates is similar to that observed for incidence.

Even in the same country, different ethnic group may have varied incidence of HCC. The annual incidence of HCC in Alaskan Eskimo males was 11.2 per 100,000, five times that of white males in the USA (Heyward et al. 1981). The world geographic distribution of HCC overlaps well with that of the distribution for chronic HBV infection (Beasley 1982). Regions with a high prevalence of HBV infection also have high rates of HCC. HBV causes 60–80% of the primary liver cancer, which accounts for one of the five major cancer deaths particularly in areas highly prevalent for HBV infection, such as Eastern and South-Eastern Asia, the Pacific Rim, and the Northen Africa (Bosch and Ribes 2002; IARC, WHO 2018). The southern parts of Eastern and Central Europe, the Amazon basin, the Middle East, and the Indian subcontinent are also areas with high prevalence of HBV infection and HCC (Lavanchy 2004; WHO 2019).

## 3 Transmission Routes of Hepatitis B Virus Infection

The age and source of primary HBV infection are important factors affecting the outcome of HBV infection. Maternal serum HBsAg and hepatitis B e antigen (HBeAg) status affect the outcome of HBV infection in their offspring. In Asia and many other endemic areas, before the era of universal HBV immunization, perinatal transmission through HBsAg carrier mothers accounts for 40–50% of HBsAg carriers. Irrespective of the extent of HBsAg carrier rate in the population, around 85–90% of the infants of HBeAg seropositive carrier mothers became HBsAg carriers (Stevens et al. 1975). In endemic areas, HBV infection occurs mainly during infancy and early childhood. In contrast to the infection in adults, HBV infection during early childhood results in a much higher rate of persistent infection and long-term serious complications, such as liver cirrhosis and HCC.

## 4 Chronic Hepatitis B Virus Infection and Liver Cancer

Liver injury caused by chronic HBV infection is the most important initiation event of hepatocarcinogenesis (Bruix et al. 2004). The role of HBV in tumor formation appears to be complex and may involve both direct and indirect mechanisms of carcinogenesis (Grisham 2001; Villanueva 2007). The outcome of persistent HBV infection is affected by the interaction of host, viral, and environmental factors (Table 1).

### 4.1 Viral (HBV) Risk Factors for HCC

Chronic HBV infection with persistent positive serum HBsAg is the most important determinant for HCC. A prospective general population study of 22, 707 men in Taiwan showed that the incidence of HCC among subjects with chronic HBV infection is much higher than among non-HBsAg carriers during long-term follow-up. The relative risk is 66. These findings support the hypothesis that HBV has a primary role in the etiology of HCC (Beasley et al. 1981).

HBeAg is a marker of active HBV replication. Chronic HBV-infected subjects with prolonged high HBV replication levels or positive HBeAg after 30 years of age have a higher risk of developing HCC during follow-up. Those HBsAg carriers with persistent seropositive HBeAg have 3–6 times more risk of developing HCC than those with negative serum HBeAg (Yang et al. 2002) (Table 1). Higher HBV

**Table 1** Summary of Risk Factors for Progression to HCC in HBV-Infected Individuals

| Risk factors | High risk/Low risk | References |
|---|---|---|
| Viral factors | | |
| 1. HBsAg | Positive/negative = 66/1 | Beasley et al. (1981) |
| 2. HBeAg in HBsAg-positive persons | Positive/negative = 60/10 | Yang et al. (2002) |
| 3. HBV DNA level | High {[$>10^6$]/$10^5$ ~ $10^6$/[$10^4$ ~ $<10^5$]}/ | Chen et al. (2006) |
| 4. HBV genotype | Low [$<10^4$] copies/ml = 11/9/3/1 [C or D]/[A or B] | Tseng et al. (2012) |
| Host factors | | |
| 1. Age | >40/<40 years = 2–12/1 | Chen et al. (2008), Tseng et al. (2012) |
| 2. Age at HBeAg seroconversion | Older (>40 years)/younger (<30 years) = 5/1 | Chen et al. (2010) |
| 3. Gender | Male/female = 2–4/1 | Ni et al. (1991), Schafer and Sorrell (1999) |
| 4. Family HCC history | Positive/negative = 2–3/1 | Turati et al. (2012) |
| 5. Liver cirrhosis | Yes/no = 12/1 | Yu et al. (1997) |
| 6. Maternal HBsAg | Positive/negative = 30/1 | Chang et al. (2009) |
| **Other factors** | Yes/no = 1–2/1 | Yu et al. (1997), Jee et al. (2004) |
| Smoking | Yes/no = 1–2/1 | Yu et al. (1997), Jee et al. (2004) |
| Habitual Alcohol | | |

DNA levels predict higher rates of HCC in those with chronic HBV infection. In comparison to those with serum HBV DNA level $<10^4$ copies/ml, those with greater serum HBV DNA levels [$10^4 \sim <10^5$], [$10^5 \sim 10^6$], or [$>10^6$] copies/ml have a higher risk of HCC [2.7, 8.9, or 10.7] during long-term follow-up (Chen et al. 2006).

There are at least ten genotypes of HBV identified with geographic variation.

Those with HBV genotype C or D infection has a high risk of developing HCC than those infected with genotype A or B HBV (Tseng et al. 2012). In Alaska, those infected with genotype F have a higher risk of HCC than other genotypes (Livingston et al. 2007).

The presence of pre-S mutants carries a high risk of HCC in HBV carriers and was proposed to play a potential role in HBV-related hepatocarcinogensis (Wang et al. 2006). Subjects infected with HBV core promoter mutants were reported to have a higher risk of developing HCC.

## 4.2 Host Factors for HCC (Table 1)

Older age (>40 yrs) is a risk factor for HCC development (Tseng et al. 2012; Chen et al. 2008). It is very likely due to the accumulation of genetic alterations with gain or loss of genes and liver injury with time during chronic HBV infection. HCC patients are mostly (around 80%) anti-HBe seropositive at diagnosis (Chien et al. 1981). This implies that HCC occurs after long-term HBV infection and liver injury, and that the patients have seroconverted to anti-HBe. Chronic HBV-infected patients with delayed HBeAg seroconversion after age 40 have significantly higher risk of developing HCC (hazard ratio 5.22), in comparison with patients with HBeAg seroconversion before age 30 (Chen et al. 2010).

There is a strong male predominance in HBV-related HCC, with a male to female ratio of 2 $\sim$ 4:1, even in children (Ni et al. 1991; Schafer and Sorrell 1999), but the mechanisms are not fully understood. The higher activity of androgen pathway functions as a tumor-promoting factor in male hepatocarcinogenesis, and the higher activity of the estrogen pathway functions as a tumor-suppressing factor in female hepatocarcinogenesis (Yeh and Chen 2012). Male predominance of HCC occurs even among young children aged 6–9 years, a possible oncogenic activation of RNA-binding motif on Y chromosome (RBMY) gene may help to explain the male predominance of HCC in children (Chua et al. 2015).

Liver cirrhosis is a pre-cancer lesion for HCC (Yu et al. 1997). Cirrhotic HBV carriers have a 3–8% annual rate of developing HCC. Those with positive HCC family history have a higher risk of HCC in comparison to those without a positive history of HCC. Familial clustering of HCC suggests the role of genetic predisposing factors in addition to the intra-familial transmission of HBV infection (Chang et al. 1984). In a meta-analysis, the pooled relative risk for family history of liver cancer was 2.50 (95% CI, 2.06–3.03) (Turati et al. 2012) (Table 1).

### 4.3 Maternal Effect

Those with positive maternal serum HBsAg have a 30 times higher risk of developing HCC than those with negative maternal HBsAg (Chang et al. 2009). HBeAg is a soluble antigen produced by HBV. It can cross the placenta barrier from the mother to the infant. Transplacental HBeAg from the mother induces a specific unresponsiveness of helper T cells to HBeAg and HBcAg in neonates born to HBeAg-positive HBsAg carrier mothers (Hsu et al. 1992). This may help to explain why 85–90% of the infants of HBeAg-positive carrier mothers became persistently infected (Beasley et al. 1977).

### 4.4 Environmental/Life Style Factors

Smoking, habitual alcohol drinking, and in some regions aflatoxin exposure are factors which were related to higher risk of HCC (Yu et al. 1997; Jee et al. 2004; Chen et al. 2008).

## 5 Strategies of Liver Cancer Prevention

The prognosis of HCC is grave, unless it is detected early and complete resection or ablation is performed. Even in such cases, *de novo* recurrence of HCC is always a problem. Prevention is thus the best way toward the control of HCC. There are three levels of liver cancer prevention, i.e., primary, secondary, and tertiary prevention of liver cancer (Fig. 1).

Primary prevention by universal infant vaccination to block both mother-to-infant and horizontal transmission of HBV infection is the most effective and safe way to prevent HCC. Secondary prevention using antiviral therapy for chronic hepatitis B is aimed at reducing viral replication, liver injury, and fibrosis, shown by the normalization of the liver enzymes, HBeAg clearance, and reduction of HBV DNA levels. Tertiary prevention of HCC using antiviral therapy targeting the subject of successfully treated HCC patients is aimed to prevent the recurrence of HCC.

Other strategies to prevent HCC are also proposed, such as blood and injection safety, prevention of high-risk behavior, changes in environment and/or diet, and liver transplantation for precancerous lesion (e.g., liver cirrhosis) may also be helpful to prevent HBV infection and related liver cancer. In addition, etiology-specific and generic candidate HCC chemoprevention strategies for high-risk subjects, including statins, antidiabetic drugs, selective molecular targeted agents, and dietary and nutritional substances were also reported (Jacobson et al. 1997; Egner et al. 2001; Athuluri-Divakar and Hoshida 2018). Some studies revealed that the use of concomitant medications with statin and nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin could reduce the risk of HCC

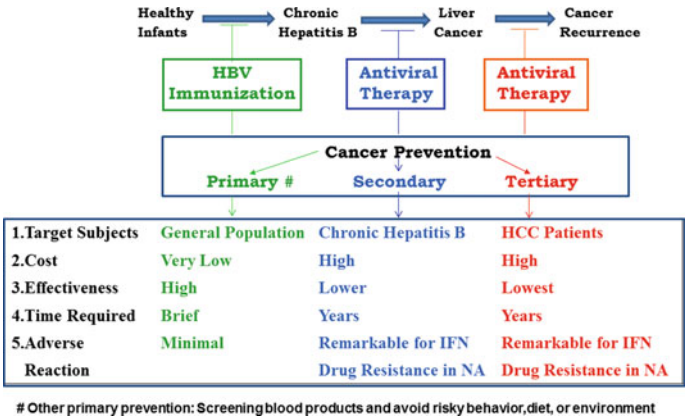


**Fig. 1** Strategies for primary, secondary, and tertiary prevention of liver cancer. HBV immunization is the most effective way. For persons who have been infected by hepatitis virus, antiviral therapy may delay or reduce the risk of developing HCC in a minor degree. The effect of other strategies such as chemoprevention and avoidance of risky behavior is still not confirmed and under investigation. HBV = hepatitis B virus; IFN = interferon; NA = nucleos(t)ide analogue

recurrence in patients receiving curative HCC resection, regardless of HBV status (Wu et al. 2012; Lee et al. 2016). However, the effects of those chemoprevention strategies on reducing the risk of HCC recurrence should be further confirmed.

## 6 Primary Prevention of Hepatitis B Virus Infection by Immunization

### 6.1 Universal Hepatitis B Vaccination in Infancy

Currently, there are mainly tree strategies of universal immunization programs in the world, depending on the resources and prevalence of HBV infection. (Table 2) In countries with adequate resources, such as the USA, pregnant women are screened for HBsAg but not HBeAg. It is recommended that every infant receives three doses of HBV vaccine. In addition, infants of all HBsAg-positive mothers, regardless of HBeAg status, also receive HBIG within 24 h after birth (Shepard et al. 2006). This strategy saves the cost and the procedure of maternal HBeAg screening but increases the cost of HBIG, which is very expensive.

The first universal hepatitis B vaccination program in the world was launched in Taiwan since July 1984 (Chen et al. 1987). Pregnant women were screened for both serum HBsAg and HBeAg. Infants of HBeAg and HBsAg double positive mothers received HBIG within 24 h after birth (Strategy II).

To save the cost of screening and HBIG, some countries with intermediate/low prevalence of chronic HBV infection or inadequate resources do not screen

**Table 2** Current pregnant women screening and universal infant hepatitis B virus (HBV) immunoprophylaxis strategies in different countries and proposed surveillance program for high-risk children with breakthrough infection linked to the specific strategies

| Strategy type | Pregnant women screening | | Neonatal immunization[a] | | |
|---|---|---|---|---|---|
| | HBsAg | HBeAg | HBV vaccine | HBIG to children of HBsAg (+)/HBeAg (−) mothers | HBIG to children of HBsAg (+)/HBeAg (+) mothers |
| I | Yes | No | Yes | Yes | Yes |
| II[b] | Yes | Yes | Yes | No | Yes |
| III | No | No | Yes | No | No |

[a]Examples of applied countries: Strategy type I: USA, Italy, Korea; Strategy type II: Taiwan, Singapore; Strategy type III: Thailand

[b]In Strategy type II, either simultaneous or sequential HBsAg and HBeAg tests can be applied. All pregnant women are screened for HBsAg and HBeAg at the same time; or all pregnant women are screened for HBsAg, while HBeAg is tested only in those positive for HBsAg; the former strategy is time saving and the latter is budget saving

pregnant women and all infants receive three doses of HBV vaccines without HBIG. Using this strategy, the cost of maternal screening and HBIG can be saved. The efficacy of preventing the infants from chronic infection seems satisfactory (Poovorawan et al. 1989).

## 6.2 Effect of HBV Vaccination on the Reduction of HBV Infection and Related Complications

HBV vaccine has been part of the WHO global immunization resulting in major declines in acute and chronic HBV infection. Approximately, 90–95% the incidence of chronic HBV infection in children has been reduced in areas where universal HBV vaccination in infancy has been successfully introduced. After the universal vaccination program of HBV, the rate of chronic HBV infection was reduced to approximately one-tenth of that before the vaccination program in the vaccinated infants worldwide. Fulminant or acute hepatitis also has been reduced.

Serial epidemiologic surveys of serum HBV markers were conducted in Taiwan (Hsu et al. 1986; Chen et al. 1996; Ni et al. 2001, 2007, 2016). The HBsAg carrier rate decreased significantly from around 10% before the vaccination program to 0.6–0.7% afterward in vaccinated children younger than 20 years of age. Similar effect has also been observed in many other countries (Whittle et al. 2002; Jang et al. 2001), where universal vaccination programs have been successfully conducted. The HBV vaccination program has indeed reduced both the perinatal and horizontal transmission of HBV worldwide (Da Villa et al. 1995; Whittle et al. 2002). In the reports from Gambia and Korea, universal vaccination programs have also been quite successful. The hepatitis B carrier rate has fallen from 5 to 10% to

less than 1% demonstrating that universal vaccination in infancy is more effective than selective immunization for high-risk groups (Montesano 2011).

Worldwide in 2015, the estimated prevalence of HBV infection in children under five years of age was around 1.3%, compared with approximately 4.7% in the pre-vaccination era (WHO 2019). The low incidence of chronic HBV infection in children under five years of age at present can be attributed to the widespread use of hepatitis B vaccine.

## 6.3 Effect of Liver Cancer Prevention by Immunization Against Hepatitis B Virus Infection (Table 3)

Current therapies for HCC are not satisfactory. Even with early detection and therapy for HCC, recurrence or newly developed HCC is often a troublesome problem during long-term follow-up. Therefore, vaccination is the best way to prevent HBV infection and HCC.

HCC in children is closely related to HBV infection and the characteristics are similar to HCC in adults (Chang et al. 1989). In comparison to most other parts of the world, Taiwan has a high prevalence of HBV infection and HCC in children. Children with HCC in Taiwan are nearly 100% HBsAg seropositive, and most (86%) of them are HBeAg negative. Maternal HBsAg of HCC children are mostly

**Table 3** Incidence rates of HCC among children 6–19 years old and adults 20–26 years old, born before versus after universal HBV vaccination program

| Age at diagnosis, year | HBV vaccination | Year | Hepatocellular carcinoma | | |
|---|---|---|---|---|---|
| | | | No. of HCCs | Incidence rate (per $10^5$ person years) | Rate ratio (95% CI) |
| Taiwan | | Birth year | | | |
| 6–19 | No | 1963–1984 | 447 | 0.57 | 1.00 (referent) |
| | Yes | 1984–2005 | 114 | 0.18 | 0.31 |
| 20–26 | No<br>Yes | 1956–1984<br>1984–1991 | 896<br>52 | 1.33<br>0.56 | 1.00 (referent)<br>0.42 |
| Khon Kaen | (Thailand) | Birth year | | | |
| >5–18 | No | Before 1990 | 15 | 0.097 | 1.00 (referent) |
| | Yes | After 1990 | 3 | 0.024 | 0.25 |
| Alaska | (USA) | Diagnostic year | | | |
| <20 | No | 1969–1984 | | 0.7–2.6 | |
| | Yes | 1984–1988 | | 2.9 | |
| | Yes | 1989–2008 | | 0.0–1.4 | |

1. Taiwan-Chang et al. (2016); 2. Thailand-Wichajarn et al. (2008); 3. Alaska- McMahon et al. (2011)

(94%) positive. Most (80%) of the non-tumor portion has liver cirrhosis. Integration of HBV genome into host genome was demonstrated in the HCC tissues in children (Chang et al. 1991). The histological features of HCC in children are very similar to that in adults.

The reduction in HBV infection after the launch of universal hepatitis B vaccination program in July 1984 in Taiwan has had a dramatic effect on the reduction of HCC incidence in children. The rate ratio of the annual incidence of HCC in children and adolescents of 6–19 years old was significantly reduced from 1.00 in those born before the vaccination program to 0.31 in those born afterward (Chang et al. 1997; Chang et al. 2000; Chang et al. 2005; Chang et al. 2009). The cancer prevention effect by the universal HBV vaccine program has been further extended to young adults of 20–26 years old after 27 years of the vaccination program (Chang et al. 2016) (Table 3).

Approximately, 90% of the mothers of the HCC children with known serum HBsAg status were positive for HBsAg. This provides strong evidence of perinatal transmission of maternal HBV as the main route of HBV transmission in HCC children born after the immunization era and was not effectively eliminated by the HBV immunization program (Chang et al 2009).

The incidence of HCC diagnosed during 1985–2007 at Khon Kaen region is significantly lower in Thai children under 18 years old who receive hepatitis B vaccine at birth (year of birth after 1990) than unvaccinated children. The age-standardized incidence rates (ASRs) for liver cancer in children >10 years of age were significantly reduced from 0.88 per million in non-vaccinated to 0.07 per million in vaccinated children (Wichajarn et al. 2008).

Alaska Native people experience the highest rates of acute and chronic HBV infection and HCC in the USA. Universal newborn HBV vaccination coupled with mass screening and immunization of susceptible Alaska Natives has eliminated HCC among Alaska Native children. The incidence of HCC in persons <20 years decreased from 3/100,000 in 1984–1988 to zero in 1995–1999 and no HCC cases have occurred since 1999 (McMahon et al. 2011).

## 7 Secondary and Tertiary Prevention of Hepatitis B Related HCC

Secondary prevention of HCC uses antiviral agents with either type 1 interferon to induce immune responses or with nucleos(t)ide analogues (NA) to suppress viral replication. Studies have shown that a finite course of conventional interferon-α (IFN) therapy may provide long-term benefit for reducing the progression of liver fibrosis and the development of cirrhosis and HCC (Lin et al. 2007; Miyake et al. 2009; Yang et al. 2009; Wong et al. 2010). Yet significant reduction of HCC was only observed in patients with preexisting cirrhosis and HBeAg seroconverters. Some other meta-analysis revealed inconsistent or no significant reduction of HCC risk after interferon therapy (Lai and Yuen 2013; Cammà et al. 2001; Miyake et al. 2009).

Long-term therapy with nucleos(t)ide analogues may reduce disease progression of chronic hepatitis B, improve fibrosis, and lower the risk of HCC. A multicentered prospective randomized controlled trial of antiviral therapy using the first generation NA (lamivudine) was conducted in Asian patients with HBV-related cirrhosis. HCC was lower (3.9%) in lamivudine-treated patients than in 7.4% of placebo controls after a median follow-up of 32 months ($P = 0.047$) (Liaw et al. 2004). Subsequent meta-analysis confirms that NA treatment reduces but does not eliminate the risk of hepatocellular carcinoma (Thursz et al. 2014).

In patients receiving first-generation NAs with low genetic barrier to drug resistance, the risk of HCC remained higher in patients with resistance-related virological breakthrough than those with sustained virological response (Liaw 2013). Recent studies further illustrated the effect of reducing HBV-related HCC by NAs with high potency and minimal drug resistance [i.e., entecavir (ETV) and tenofovir desoproxial fumarate (TDF)]. Long-term ETV treatment effect was more prominent in patients at higher risk of HCC (with cirrhosis, older age and had more active disease) than younger patients and those without cirrhosis (Hosaka et al. 2013; Su et al. 2016; Wu et al. 2014; Papatheodoridis et al. 2017; Hsu et al. 2018). Suppression of viral replication in non-cirrhosis may reduce the risk of HCC, but since the risk of HCC is not as high as in cirrhosis patients, the magnitude of the risk reduction is less remarkable (Sherman 2013).

For HCC patients who have been treated successfully by surgery, liver transplantation, or local therapy, tertiary prevention of HCC using antiviral therapy against HBV or HCV may potentially prevent late tumor recurrence (Breitenstein et al. 2009). Yet further study is needed to confirm its efficacy.

## 8 Problems to Be Solved in Liver Cancer Prevention

The risk of developing HCC for vaccinated cohorts was significantly associated with incomplete HBV vaccination and maternal HBsAg or HBeAg seropositivity (Chang et al. 2005; Chang et al. 2009). Failure to prevent HCC by HBV vaccination results mostly from unsuccessful control of HBV transmission from highly infectious mothers. To eradicate HBV infection and its related diseases, we have to overcome the difficulties that hinder the success of universal HBV vaccination.

### 8.1 Low Coverage Rate of Universal Infant HBV Vaccination

Increasing uptake of HBV vaccine was noted globally year by year. In 2015, global coverage with the three doses of hepatitis B vaccine in infancy reached 84% (WHO 2017). However, in some countries such as in Southeast Asia and Africa, due to inadequate resources, failure to attract national government fund delays the integration of HBV vaccination into the EPI program. Even with integration into the

EPI program, the coverage rate is still inadequate. One main reason is that the parents still have to pay for the HBV vaccines in those countries.

In 1992, WHO recommended that all countries with a high burden of HBV-related diseases should introduce hepatitis B vaccine in their routine infant immunization programs by 1995 and that all countries do so by 1997 (Kane 1996). In 1996, an additional target was added, that is, an 80% reduction in the incidence of new hepatitis B carriers among children worldwide by 2001 (Kane and Brooks 2002). This is particularly urgent in areas where HBV infection and HCC are prevalent.

How to reduce the cost of the vaccine and to increase funds for HBV vaccination to help children of endemic areas with poor economic conditions are important issues to solve for the eradication of HBV infection and its related liver cancer. The Global Alliance for Vaccines and Immunization (GAVI), established in 1999, has contributed in helping the developing countries to increase the coverage of HBV vaccination.

## 8.2 Poor Compliance Caused by Anxiety to the Adverse Effects of Vaccination or Ignorance

In countries with adequate resources, the ignorance of the parents/guardians or an antivaccine mentality drives some of the people to refuse vaccination. Opposition to vaccination may be reduced by clarification of the vaccine-related side effects. Clarification of this question may help to eliminate opposition to vaccination, which hampers the effort of HBV vaccination and, hence, the goal of eradication of HBV and its related liver diseases (Halsey et al. 1999). Education and propagation of the benefits of HBV vaccination will enhance the motivation of the public and the governments to accept HBV vaccination, even in low prevalence areas.

## 8.3 Breakthrough Infection or Non-responsiveness in Vacinees

Causes of break through infection or non-responders include high maternal viral load (Lee et al. 1986), intrauterine infection (Tang et al. 1998; Lin et al. 1987), surface gene mutants (Hsu et al. 1999; Hsu et al. 2004; Hsu et al. 2010), poor compliance, genetic hypo-responsiveness, and immune-compromised status. A positive maternal HBsAg serostatus was found in 89% of the HBsAg seropositive subjects born after the launch of the HBV vaccination program in Taiwan (Ni YH et al. 2007). Maternal transmission is the primary reason for breakthrough HBV infection and is the challenge that needs to be addressed in future vaccination programs. Risk factors of failure include a high level of maternal HBV DNA, uterine contraction and placental leakage during the process of delivery, and low level of maternal anti-HBc (Lin et al. 1991; Chang et al. 1996). Mother-to-infant transmission is the major cause of HBV infection among immunized children.

Among 2356 Taiwan children born to HBsAg-positive mothers and identified through prenatal maternal screening, children born to HBeAg-positive mothers are at greatest risk for chronic HBV infection (9.26%), in spite of HBIG injection <24 h after birth and full course of HBV vaccination in infancy (Chen et al. 2012).

Intrauterine HBV infection, though infrequent, is a possible reason for vaccine failure. Although immunoprophylaxis for HBV infection is very successful, still around 2.4% of infants of HBeAg-positive mothers already had detectable HBsAg in the serum at birth or shortly after birth (Tang et al. 1998) and persisted to 12 months of age and later. They become HBsAg carriers despite complete immunoprophylaxis.

The rate of HBsAg gene mutants in HBsAg carriers born after the vaccination program is increasing with time. The rate of HBV surface gene mutation was 7.8%, 17.8%, 28.1%, and 23.8%, respectively, among those seropositive for HBV DNA, at before, and 5, 10, and 15 years after the launch of the HBV vaccination program (Hsu et al. 1999; Hsu et al. 2010). Fortunately, it remained stationary (22.6%) at 20 years after the vaccination program. HBV vaccine covering surface gene mutant proteins is still not urgently needed for routine HBV immunization at present, but careful and continuous monitoring for the surface gene mutants is needed.

Vaccine hypo-responsiveness or non-responsiveness may occur in immunocompromised host, or in genetically hypo-responders or non-responders to HBV vaccine. Before receiving immunosuppressant or organ transplantation, hepatitis B markers and anti-HBs need to be monitored routinely. Hepatitis B vaccination should be given to those with inadequate anti-HBs levels. A double dose of HBV vaccine can be given to hypo-responders to enhance the vaccine response. Further development of a better vaccine is needed for non-responders to conventional HBV vaccine.

## 8.4 Problems of Secondary Prevention Using Current Antiviral Therapy

Current antiviral therapies and immune modulating agents did not reach a high sustained response rate. It is difficult to eliminate cccDNA even in those with sustained virologic response; therefore, HBV cannot be eradicated from the hosts in the majority of treated cases with a high viral relapse rate after discontinuation of NAs. Although the newer nucleos(t)ide has much lower resistance rates, the problem of drug resistance still exists after prolonged use. Newer safe therapeutic agents which can permanently eradiate HBV from the host are needed.

The oncogenic process starts early in patients with chronic HBV infection, even in childhood (Chang et al. 1991). A cirrhotic (or severely injured) liver may contain many clones of cells carrying genetic abnormalities and integration of HBV genome into the host that predispose to cancer. Stopping the oncogenic process, by suppressing viral replication, at a late stage, such as in cirrhosis, may reduce or delay, but not eliminate HCC occurrence.

## 9 Strategies Toward a Successful Control of HBV-Related HCC

Primary prevention by universal vaccination is most cost effective toward a successful control of HBV infection and its complications. Yet currently, there are several problems remained to be solved. The most important strategy is to provide effective primary prevention to every infant for a better control of HBV infection globally, include further increasing the world coverage rates of HBV vaccine, and better methods to act against breakthrough HBV infection/vaccine non-responsiveness. It is extremely important to find ways to reduce the cost of HBV vaccines and to increase funding for HBV vaccination of children living in developing countries endemic of HBV infection. It is particularly urgent in areas where HBV infection and HCC are prevalent.

Increasing efforts are required to eliminate acute and chronic hepatitis B. Due to the competition of other new vaccines, HBV has not captured sufficient attention from policymakers, advocacy groups, or the general public. This is a major challenge for the future (van Herck et al. 2008). It is very important to persuade and support the policy makers of countries that still have no universal HBV vaccination program to establish a program and to encourage the countries which already have a program to increase the coverage rates. A comprehensive public health prevention program should include prevention, detection, and control of HBV infections and its related complications, and evaluation of the effectiveness of prevention activities (Lavanchy 2008).

### 9.1 Prevention of Breakthrough HBV Infection

Further investigation into the mechanisms of breakthrough HBV infection or non-responders is crucial for setting effective strategies to prevent breakthrough infection of HBV. Current HBV vaccine has induced good immune response and protection against HBV infection in most vaccinees. Yet approximately, 10% breakthrough infection rate occurs in high-risk infants of HBsAg carrier mothers with positive HBeAg and/or high viral load.

Nucleos(t)ide analogue treatment during pregnancy was used attempting to prevent perinatal transmission of HBV infection. A pilot study included 8 highly viremic (HBV DNA $\geq 1.2 \times 10^9$ copies/mL) mothers treated with lamivudine per day during the last month of pregnancy. At 12 months old, 12.5% in the lamivudine group and 28% in the control group were still HBsAg and HBV DNA positive (van Zonneveld et al. 2003). Another clinical trials using lamivudine mg per day were given from 34 weeks of gestation to four weeks after delivery for HBsAg seropoitive highly viremic mothers (Xu et al. 2009) demonstrated a reduction of HBsAg seropositive rate in the infants of the treated group (18%) in comparison to infants of the control group (39%) at week 52. Another study recruited mothers with positive HBeAg and HBV DNA $>1.0 \times 10^7$ copies/ml.

The incidence of perinatal transmission was lower in the infants that completed follow-up born to the telbivudine-treated mothers than to the controls (0% vs. 8%; $p = 0.002$) (Han et al. 2011).

Tenofovir is considered a preferred choice because of its antiviral potency, more safety data in pregnant women, and lower rates of resistance. A prospective well-controlled trial in Taiwan recruiting pregnant women with HBV DNA $\geq$7.5 log 10 IU/mL has shown a reduction of HBsAg positivity of infants from 10.71 to 1.54% ($P = 0.0481$), with an odds ratio of 0.10 ($P = 0.0434$) in the tenofovir treated group (Chen et al. 2015).

Whether the development of new HBV vaccines against surface antigen gene mutants, and better vaccines for immune-compromised individuals may further reduce the incidence of new HBV infections requires further investigation.

## 9.2 Screening High-Risk Subjects and Provide Secondary Prevention of HCC

HBsAg carriers are at high risk for HCC. Screening for serum HBsAg is the first step to early detect the high-risk persons for HBV-related HCC screening. With limited resources, the priority target subjects to be screened are illustrated in Fig. 2. They should be screened for HBsAg, and if positive, screening for HCC. Subjects with an HBsAg carrier mother or HBsAg carrier family member(s) are particularly at higher risk of chronic HBV infection and HCC. Screening HBsAg among pregnant women is helpful to give antiviral therapy during third trimester for highly

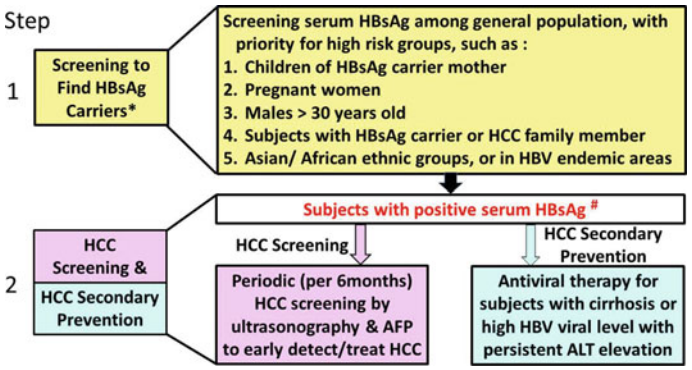


**Fig. 2** Screening for HBsAg and secondary prevention of hepatocellular carcinoma. HBsAg carriers are at high risk of developing HCC. So the first step is screening to find HBsAg seropositive persons. *HBsAg carriers are subjects with chronic HBV infection. #Subjects with positive HBsAg, particularly those with special high risk of HCC, i.e., males >40 years, positive HCC family history, cirrhosis, high viral load with persistent abnormal ALT levels, are the priority target groups to receive periodic HCC screening and secondary prevention of HCC

infectious pregnant women to interrupt mother-to-infant transmission. Furthermore, those with positive HBsAg can be followed up regularly to screen or secondarily prevent HCC.

The HCC risk is higher in HBsAg carriers who are males, over 40 years old, with liver cirrhosis, a family history of HCC, or high HBV DNA >10,000 copies/mL (Table 1). For those high-risk subjects, periodic (every fix months) screening of HCC by ultrasonography and alpha-fetoprotein (AFP) is recommended. For those who are living in areas where ultrasound is not readily available, periodic screening with AFP should be considered (Bruix and Sherman 2005).

Secondary prevention of HCC can be considered in high HCC risk patients with chronic HBV infection, such as those with liver cirrhosis, or with high HBV DNA levels and persistent or intermittent abnormal ALT levels. If the future novel antiviral agent(s) is safe and could eradiate HBV, it can be given to patients with chronic HBV infection as early as possible even during childhood (Chang 2013). Potential new therapies including drugs targeting virus (inhibit viral entry, interfere RNA or viral assembly/ encapsidation, or HBsAg production or viral secretion), or targeting host immune system to enhance innate immunity or to restore HBV specific T cell and B cell responses (Kapoor and Kottilil 2014; Serigado et al. 2017; Coffin and Lee 2015; Yang and Bertoletti 2016).

## 10 Implication in Other Cancer Prevention and Future Prospects

Prevention is the best way to control cancer. Prevention of liver cancer by hepatitis B vaccination is the first successful example of cancer preventive vaccine in human. With the universal hepatitis B vaccination program starting from neonates in most countries in the world, HBV infection and its complications will be further reduced in this century. It is expected that an effective decline in the incidence of HCC in adults will be achieved in the near future. Furthermore, the impact of HBV vaccination on the control of hepatitis B and its related diseases can be extrapolated to other infectious agent-related cancers.

Besides vaccination, addition of hepatitis B immunoglobulin immediately after birth and even antiviral agent during the third trimester of pregnancy to block mother-to-infant transmission of HBV are existing or possible emerging strategies to enhance the prevention efficacy of HBV infection and its related liver cancer. Safe novel antiviral agent with high rate of HBV eradiation is anticipated for better secondary prevention of HCC in patients with chronic HBV infection.

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