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Hepatitis B

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Researchers Find a More Accurate Blood Test for Liver Cancer

To date, doctors have relied on a lab test that measures alpha fetoprotein (AFP) levels in blood to identify liver cancer in patients infected with the hepatitis B virus (HBV), but this test can be inaccurate and may not reveal liver tumors until it's too late for treatment.

Chinese researchers measured Golgi protein 73 (GP73) levels in the blood to see if increases in this protein, which appears to be released at high levels when liver cancer occurs, would be a more accurate test for cancer.

They compared GP73 and AFP levels in 4,217 subjects, includ-

ing 1,690 healthy adults, 337 people infected with HBV, 512 patients with cirrhosis (severe liver scarring of the liver), 789 patients with liver cancer, 61 patients with liver lesions, 206 patients with benign liver lesions, and 622 patients with non-liver cancers.

Their findings, published in the October 2010 issue of the journal *Gut*, showed that elevated GP73 levels (exceeding 8.5 relative units) were found in liver cancer patients more frequently than were elevated AFP levels.

"The sensitivity and specificity of GP73," for liver cancer were 74.6% and 97.4%, compared with 58.2% and 85.3% for AFP. The GP73 level was significantly increased in patients with liver

cancer compared with the healthy control group.

"Although GP73 levels in HBV carriers and patients with cirrhosis were somewhat elevated, they were much lower than in patients with liver cancer," researchers noted.

GP73 decreased after liver tumors were removed surgically, and then increased when cancer recurred. GP73 levels were only moderately increased when non-liver cancers were present.

"GP73 is an accurate marker for the detection of liver cancer and its recurrence after surgery, with higher sensitivity and specificity than AFP," researchers wrote. "Clinical implementation of serum GP73 measurement as a standard test for liver cancer is recommended."

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Physicians Failing to Screen Asian-American Patients for HBV and Liver Cancer

University of California at San Francisco researchers screened 109 physicians—mostly primary care providers—to see how many screened their patients for HBV infection and liver cancer. About 24% of these physicians' patients were Asian-American and at high risk for hepatitis B infection.

Only 76% of the providers reported they had screened more than half of their Asian-American patients for HBV and 43% had vaccinated more than half of their patients. While 94% of these physicians knew Asian-American patients were at elevated risk of liver disease and cancer resulting from HBV infection, only 79% had screened more than half of their Asian-American patients for liver cancer.

An estimated 10% of Asian-Americans are believed to be chronically infected with hepatitis B, especially if they are immigrants from Asia.

Physicians who had higher screening and

immunization rates were familiar with medical guidelines that recommend it, and were aggressive about vaccinating at-risk patients, according to the report published in the November issue of the journal of *Digestive Diseases and Sciences*.

HBV and cancer screening rates and HBV vaccination of Asian-Americans by physicians is “suboptimal,” the researchers wrote. “Provider education is essential in increasing rates of HBV and liver cancer screening among Asian-Americans.”

Experts Explore Risks of Breastfeeding and Antiviral Use in Mother-to-Child HBV Transmission

While many consider breastfeeding by HBV-infected mothers to be safe, research is inconclusive and experts are uncertain at what point babies born to infected mothers become infected with HBV—whether it's before or during birth process or afterwards, such as during breastfeeding.

Bulgarian researchers studied mother-to-child infection, and also the

safety of antiviral use by breastfeeding mothers. Their findings, published in the October 2010 *World Journal of Gastroenterology*, are inconclusive but shed more light into mother-to-child infections, which cause an estimated half of all chronic HBV infections worldwide.

While maternal screening programs and immediate immunization of newborns with the hepatitis B vaccine have reduced infection of newborns by 95%, mother-to-child infection (called vertical transmission) is still responsible for significant HBV infection.

When are infants infected before birth?

Researchers have assumed that before labor, the infant is safely protected from HBV by the placenta. But when mothers have high viral load, many suspect that HBV may cross the placenta and infect the fetus. For example, even when infants are immediately immunized at birth, 8.5% of infants born to women with high viral load (higher than 100,000,000 HBV DNA copies per mL) become chronically infected.

Because of this, doctors are urging use of antivirals during the third trimester to reduce viral load in women who are positive for the hepatitis B “e” antigen (HBeAg) and have high viral loads.

Experts speculate that infants may become infected during the birth process, due to possible transfusion of the mother's blood to the fetus during contractions or if a membrane ruptures and the fetus is exposed to infected secretions, blood or other fluids from the genital tract.

Is breastfeeding safe?

There are few studies that compare breast-fed to formula-fed infants born to infected mothers. The studies reviewed by these researchers found no increased HBV infection risk from breastfeeding, but most of these studies did not continue to follow the children into early childhood.

Researchers have found not only hepatitis B surface antigen (HBsAg), but also HBeAg and HBV DNA in breast milk. HBV DNA was found in 81.25% of Chinese mothers' breast milk if HBsAg and HBeAg were both positive and

in 45.24% if HBeAg was negative.

On the plus side, breast milk provides infants with a number of bioactive proteins. Lactoferrin, for example, is a major human milk protein with antibacterial power.

Lactoferrin also has antiviral activity against the hepatitis C virus, cytomegalovirus, herpes simplex virus, rotavirus, adenovirus and human immunodeficiency virus (HIV). Recently, lactoferrin and iron- and zinc-saturated lactoferrin was found to inhibit HBV DNA.

“There have not been sufficient studies that can even partially explain the possible effect of breastfeeding on eventual prevention of (vertical transmission) of HBV,” the researchers wrote. Studies of HIV transmission through breastfeeding found that when breastfeeding was inconsistent, the risk of HIV transmission increased, perhaps because of breast engorgement or some other irritation.

“It remains unclear if the situation with HBV is similar and (this) could be a subject of future research,” they noted. This issue is important for regions with

high HBV prevalence where promotion of exclusive breastfeeding is vital for child health.

Currently, the American Academy of Pediatrics recommends breastfeeding despite maternal HBV infection when newborns have been immunized at birth and received hepatitis B immune globulin (HBIG).

If antivirals are administered to pregnant women to lower viral load, is it safe to breastfeed?

The antivirals that a mother takes to reduce her viral load during pregnancy and safeguard her health pass into breast milk. But to date, there are few studies that establish if antivirals in breast milk are safe for infants.

A recent study of lamivudine (Epivir-HBV) antiviral treatment in HIV-infected mothers who nursed their infants for six months after birth found notable amounts of the antiviral in breast milk at birth, but the level tapered off and reached undetectable levels after six months.

Another study of HIV mothers found neutropenia (a decline in white blood cells that fight infection) in 15.9% of infants born

to antiviral-treated mothers at one month of age, compared to 3.7% in an unexposed group.

Based on the HIV studies, “... We might reconsider stopping the preemptive antiviral therapy (used to lower viral load during pregnancy) during breast feeding if there is a high risk of HBV hepatitis flare (to the mother),” researchers wrote.

Recently, the antiviral tenofovir (Viread) has been recommended for use in pregnant women. Given tenofovir’s low rate of drug resistance, it may be the better antiviral to use in pregnant and nursing women, researchers suggest, even though there have been no human studies on tenofovir treatment and breast milk.

The small amounts of tenofovir (found in breast milk in animal studies) are very unlikely to cause viral resistance, they wrote.

“To the best of our knowledge, a relevant study regarding drug levels in human breast milk and possible effects in breastfed infants has still

not been published,” they concluded.

HBsAg Levels Provide Early Indicator If Interferon Is Working

HBeAg-positive patients who experience a 60% decline in HBsAg after 12 weeks of pegylated interferon treatment are more likely to seroconvert and lose HBeAg and develop “e” antibodies after treatment according to a study by South Korean researchers, published in the January 2011 issue of the *Journal of Medical Virology*.

Researchers monitored HBV DNA and HBsAg levels in 37 HBeAg-positive patients receiving 48 weeks of pegylated interferon, and then followed them for another 48 weeks.

Average HBsAg levels at start of treatment and at week 96 were 6,218 international units per milliliter (IU/mL) and 4,038 IU/mL respectively. The average HBV DNA levels declined 2.1-fold and alanine aminotransferase (ALT) levels, which increase when there is liver cell damage, dropped from 173 to 102 by week 96.

Researchers suggest doctors monitor HBsAg levels in this patient group to determine as early as possible whether interferon is effective, given its expense and high rate of side effects, which include depression.

HBV Mutations Can Dramatically Increase Liver Cancer Risk

Mutations in the HBsAg (called the preS region) and in the core promoter region of the HBV appear to greatly increase the risk of liver cancer in patients infected with HBV genotypes or strains B and C, according to a report by Chinese researchers published in the *Journal of Medical Virology*.

Researchers studied the HBV genotypes and mutations in 140 HBV-infected patients with cancer and 280 infected patients without cancer.

Among the mutations identified, 23 in genotype C and 6 in genotype B were associated with an increased risk of cancer. Their analysis showed that genotype, viral load, and preS and core promoter mutations increased cancer risk in those

with genotype C and B.

Forty-eight percent of patients with liver cancer had preS and core promoter mutations. Only 4.3% of patients without cancer had those mutations.

“Conclusively, (these mutations are) associated independently with liver cancer,” researchers wrote.

“Further prospective studies are needed to confirm the role of these mutations in the development of liver cancer.”

In another article in this journal, South Korean researchers identified mutations in the HBV’s X protein as also contributing to increased rates of liver cancer in patients with HBV genotype C.

They followed 267 patients with differing degrees of HBV infection and liver damage and found mutations in the X protein were higher in patients with severe liver disease or liver cancer.

Entecavir Effective in Preventing HBV Reactivation During Cancer Treatments

Even when HBV infection is inactive—with low viral load and average ALT levels—treatment with

cancer-fighting drugs that suppress the immune system can cause a dangerous resurgence of hepatitis B.

Researchers are experimenting with using antivirals in these HBV-infected cancer patients as a way to preemptively prevent an infection recurrence during cancer treatment.

German researchers treated four patients, whose HBV had rebounded as a result of immune-suppressing cancer treatment, with entecavir (Baraclude) to see how effective it was in reducing hepatitis B reactivation. Entecavir effectively suppressed HBV and all patients experienced a rapid improvement without side effects. In three patients, HBsAg levels became undetectable after two months.

“Entecavir seems to be an effective and safe treatment for HBV reactivation,” researchers wrote in the November 2010 issue of the *World Journal of Gastroenterology*. “Monitoring of quantitative HBsAg might be an additional useful tool to monitor treatment response.”

Researchers Identify Lab Test That Detects HBsAg with Mutations

Mutations in HBsAg can cloak or hide HBV infection in donated blood or in patients undergoing lab tests for hepatitis B. Researchers have been trying to develop more sensitive tests that can identify HBV in blood, even when HBsAg mutations are present.

Recently, a team of European researchers tested 147 blood samples containing HBsAg with varying mutations with two generations of a commercial HBsAg test (Enzygnost® HBsAg 5.0 and 6.0, Siemens Healthcare Diagnostics Products) to see which test was more effective.

The second test was more accurate in identifying HBsAg with mutations.

“The results showed that modifications in design of the assay (test) improved considerably the ability of the test to detect HBsAg mutants, and that difficulties in detecting such HBV variants should not be expected with the routine use of the test in diagnostic laboratories and in blood transfusion centers,” researchers wrote

in the *Journal of Medical Virology*.

Lowering Viral Load Helps Immune System's Killer Cells to Fight Infection

Dutch researchers recently reported in the *Journal of Hepatology* that when viral load declines, the immune system's natural killer cells become more effective in containing the HBV infection through T cells that target specific viruses.

The researchers compared natural killer cells from 40 chronic HBV patients with killer cells from 25 healthy individuals. They also tracked changes in killer cells in 15 HBV patients who were successfully treated with entecavir and experienced a decline in viral load.

Natural killer cell numbers did not dramatically differ between HBV patients and control subjects, but the HBV infection somehow hampered the killer cells' ability to identify the virus and fight the infection.

Entecavir treatment, which lowered viral load, partially restored the ability of killer cells to fight infection as viral load declined. And,

as viral load declined, the effectiveness of the killer cells increased.

Researchers recommended more studies into natural killer cells to see if eventually they could be strengthened in order to completely eradicate chronic HBV infections.

Accelerated Hepatitis B Vaccine Schedule Boosts Immunization Rates Among Drug Users

The number of injecting drug users (IDUs) who receive all three doses of the hepatitis B vaccine can be increased using an accelerated, two-month vaccination schedule and modest financial incentives, according to a report by U.S. researchers published in the November edition of the *Journal of Infectious Diseases*.

The hepatitis B vaccine is usually administered in three doses over a six-month period. However, the percentage of IDUs who have been vaccinated is low in comparison to other groups, despite the fact that they are at high risk of infection.

Researchers from the Drugs, AIDS, STDs, and Hepatitis (DASH)

project followed 1,260 IDUs over two years after they were divided into four groups.

- Group 1 received the standard hepatitis B vaccination schedule (month 0, month 1, month 6) and standard health information about HIV.
- Group 2 had the regular vaccination schedule and received health information that also included information about the benefits of HBV immunization.
- Group 3 received an accelerated vaccination schedule (three injections within two months), and standard health information.
- And Group 4 received the accelerated vaccine schedule with the enhanced information.

Among the IDUs in the study, 75% who received the vaccine over two months completed all three doses, compared to 66% in the six-month vaccine program. Providing enhanced information about hepatitis B did not have an impact on vaccination rates.

Use of speedball—an injected mixture of heroin and cocaine and being homeless were also associated with

lower vaccine completion rates.

Six months after the program began, individuals who had received all three accelerated doses in the first two months were significantly more likely to have protective antibodies against hepatitis B (62%), than those awaiting their third dose (49%).

The vaccine was provided for free, and a small financial incentive was provided to encourage IDUs to come to the clinics so all three doses could be administered.

“Straightforward payment for receipt of immunizations may be not only ethically sound but also an economically sensible way to use public health resources,” the researchers noted.

The researchers concluded that their research could provide a model for future HIV or hepatitis C vaccine trials and also provides information on the effectiveness of accelerated vaccination schedules for increasing immunization of IDUs.

