Blue Faery Bestows Two Awards to Fight Liver Cancer

Blue Faery: The Adrienne Wilson Liver Cancer Association is proud to announce the third annual Blue Faery Award (BFA) for Excellence in Liver Cancer Research. Primary liver cancer, also known as hepatocellular carcinoma (HCC), is the third leading cause of cancer deaths worldwide. Blue Faery created the award to recognise medical professionals who develop innovative research in the fight against HCC, which currently has no cure.

This year, for the first time, the BFA was given to two outstanding recipients. Dr William B Coleman, Director of Graduate Studies at University of North Carolina School of Medicine, researches pre-cancerous cells in the liver as a possible cause of HCC with the goal of targeting these cells before cancer starts. Dr Hashem B El-Serag, Chief of Gastroenterology and Hepatology at Baylor College of Medicine, focuses on public health awareness and early detection of the disease to give liver cancer patients the best chance of survival. Blue Faery felt with their different approaches to fighting liver cancer, Dr Coleman and Dr El-Serag are equally deserving of the BFA thus two separate awards will be given out.

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Epidemiology and Surveillance of Hepatocellular Carcinoma

Liver cancer is the fifth most common cancer in men and the seventh in women, worldwide (522,000 and 225,000 cases, ~8% and 6.5% of all cases, respectively). Hepatocellular carcinoma (HCC) accounts for 85-90% of all primary liver cancers, with a median survival of less than one year [1]. HCC incidence during the past two decades has more than tripled in the United States (US), where it is the fastest increasing cause of cancer-related deaths.

The highest age HCC incidence rates are reported from countries in Southeast Asia endemic for HBV infection (North/South Korea, China, Vietnam). China alone sees more than 55% of all primary liver cancer worldwide (40 per 100,000 in males, 15 per 100,000 in females). Other high-incidence areas include sub-Saharan African countries, e.g., Cameroon and Mozambique. In general, Southern Europe countries (Italy, Greece) have medium incidence rates (>10 per 100,000). Intermediate incidence areas (age adjusted rates 5-10 per 100,000) include the United Kingdom (UK, where cholangiocarcinoma is the commonest primary liver cancer), US, France and Germany. Low-incidence areas include South and Central America, Europe – excluding the Mediterranean countries – and North America (age adjusted rates in males: <6 per 100,000).

Encouraging downward trends are emerging in some high-rate areas including China and Japan. Conversely, substantial increases in HCC mortality rates have been observed in areas previously considered low incidence in North America, Europe, and Oceania. Here, HCV is the commonest etiologic risk factor, accounting for ~50% of cases.

Demographic Features and Risk Factors

HCC is rare before 40 and peaks around age 70. In low-risk populations (US, Canada, UK), the highest age-specific rates occur at age 75 plus. However, in Qidong, China, where HCC rates are among the world's highest, age-specific incidence rates among males rise until age 45 and then plateau. There is a striking male HCC predominance, with the highest male:female ratios in high HCC incidence areas. Sex hormones have been linked with HCC development [2]. High serum testosterone levels have been associated with HCC risk in nested case-control studies among HBV carriers in Taiwan and Shanghai [3]. HCC incidence also varies amongst different populations in the same region: Incidence in individuals of Asian/Pacific Islander ethnicity in the U.S. were almost three times higher than in whites (age standardised rates 11.7 and 3.9 respectively), with Hispanics and blacks in between these two extremes (8.0 and 7.0 respectively). The variable age-, sex-, and race-specific patterns in different geographic regions are likely related to differences in the dominant hepatitis virus in the population and age at viral infection.

Risk factors include HBV, HCV, alcohol, aflatoxin, possibly obesity and diabetes. HBV with HCV account for 80-90% of HCC worldwide mendelian disorders (e.g., Wilson's disease) and unknown etiology account for a minor proportion. Most risk factors promote formation of cirrhosis, found in 80-90% of patients The risk of developing HCC in cirrhotics is ~30% in HCV patients in Japan and 17% in the West, 21% in hemochromatosis, 15% in HBV cirrhosis, 8% in alcoholic cirrhosis and 4% in biliary cirrhosis [4].

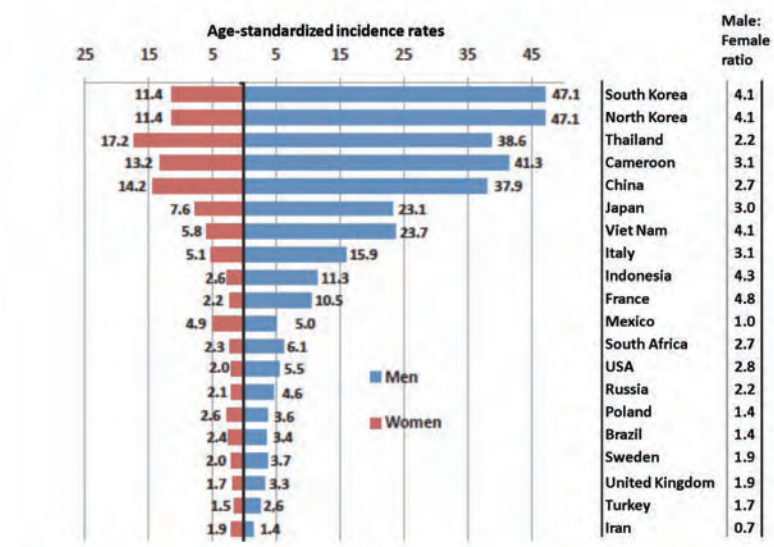
HBV

Globally 350 million people are chronically infected by HBVwith the infection accounting for about ~50% of HCC cases with considerable regional variation (70% in South Korea, 10-15% in Japan, 3% in Sweden, 9% in the United States, 55% in Greece) [5]. The lifetime HCC risk for somebody with chronic HBV infection is 10-25%. HBV is a notorious HCC cause in the absence of cirrhosis; however, the majority (70%-90%) of HBV-related HCC develops in cirrhotic livers [1]. Factors which increase risk among HBV carriers include male sex, older age, longer infection duration, family history, aflatoxin exposure, alcohol, tobacco, co-infection (HCV, delta hepatitis). A Taiwanese randomised controlled trial in patients with chronic HBV who had cirrhosis reported a significant reduction of HCC in patients treated with lamivudine compared to placebo (3.9% vs. 7.4%, hazard ratio, 0.49; P=0.047) [7].

Dietary Aflatoxin

Aflatoxins are carcinogenic mycotoxins produced by Aspergillus molds growing on grains, corn, peanuts and fermented soy beans in sub-Saharan Africa and

Figure 1: Age-standardised incidence rates of primary liver cancer, per 100,000 population at risk.



Source: GLOBOCAN 2002. The Age-Standardised Rate is calculated using the 1960 world standard population.

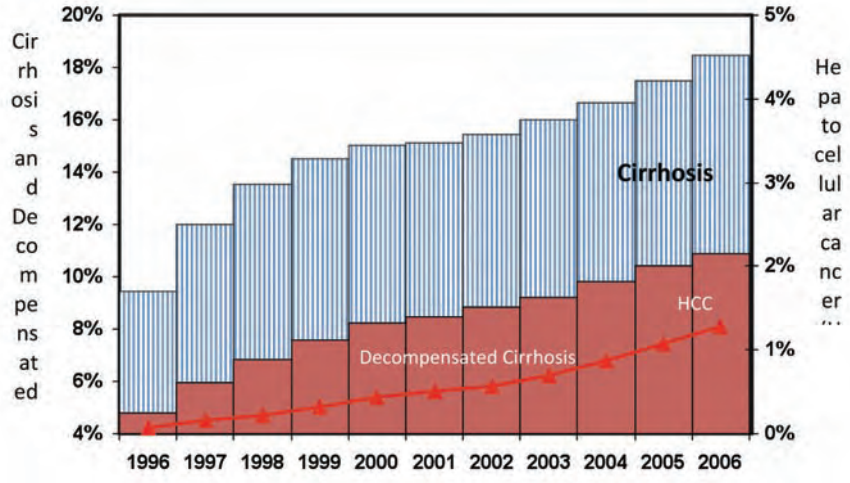


Figure 2: Prevalence of cirrhosis, decompensated cirrhosis, and hepatocellular cancer in HCV-infected patients seen in VA hospital during 1996-2006.

eastern Asia. The active catabolite AFB1-exo-8,9-epoxide, binds to DNA and produces a characteristic mutation in the p53 tumor suppressor gene. which has been detected in 30-60% of HCC tumors in aflatoxin endemic areas HBV infected individuals exposed to aflatoxin have a higher liver cancer risk, suggesting synergism between the two Efforts have been launched to eliminate AFB1 exposure of HBV carriers in China and Africa.

HCV

The global HCV prevalence is ~2%. Markers of HCV infection are found in variable proportions of HCC cases; e.g., 45-65% in Italy, 80-90% in Japan HCC risk is increased 15-20 fold in HCV-infected patients compared with HCV-negative controls [8]. The rate of HCC development in HCV-infected persons ranges from 1 to 3% after 30 years chronic infection. HCV increases HCC risk by promoting fibrosis and eventually cirrhosis. In HCV-infected patients, factors related to host and environment / lifestyle appear more important than viral factors in determining progression to cirrhosis. These include: older age overall, older age at HCV acquisition, male sex, heavy alcohol intake (>50 g/day), diabetes, obesity, and co-infection with HIV or HBV[9]. In the US, the prevalence of individuals infected with HCV for 30 years or longer has been increasing; with concomitant increases in cirrhosis and HCC as shown in studies from the Department of Veteran Affairs [10] (Figure 2).

Alcohol

Heavy alcohol intake (>50-70 g/day for several years) is a well-established HCC risk factor. There is evidence for a synergistic effect of alcohol with HCV or HBV, probably in promoting cirrhosis [8].

Fatty Liver Disease

Many studies fail to identify a major risk factor for chronic liver disease or HCC for up to 30-40% of patients. Non-alcoholic fatty liver disease (NAFLD), including its more advanced form non-alcoholic steatohepatitis (NASH), has been proposed as the etiologic factor for cryptogenic HCC.

The few population-based cohort studies of patients with NAFLD/NASH provide some evidence [11] but histological confirmation is difficult because NAFLD presence can be obscured by full blown cirrhosis. Indirect evidence to the NAFLD–HCC association is provided by multiple cross-sectional and case-control studies showing significantly higher prevalence of obesity and diabetes among patients with cryptogenic cirrhosis compared to controls with other causes of liver disease [12]. However, it is clear that development of cirrhosis related to NASH signals a considerable increase in HCC risk. While the progression of NAFLD/NASH to cirrhosis and NAFLD/NASH-related HCC may very well be infrequent, given the high prevalence, obesity and diabetes could still contribute a large number of HCC cases.

Obesity and Diabetes

Up to 90% of all obese individuals (BMI >30 kg/m^2) and up to 70% of people with diabetes have some type of fatty liver. In a large prospective cohort study (>900,000 individuals, US) followed over 16-years, liver cancer mortality was 4.5 higher in men with a BMI >35 and 1.7 higher in women with a BMI >35 compared to normal-weight individuals. Studies from Sweden and Denmark found a 2-3-fold increased HCC risk in obese men and women compared to those with normal BMI [13,14]. Type 2 diabetes, has been proposed to be a risk factor for both chronic liver disease and HCC. Several case control studies found a statistically significant association with 50% to 100% increased HCC risk in the presence of diabetes. However, reverse causality is a concern because in some cases diabetes might itself be a result of cirrhosis. A few cohort studies, better suited to evaluate temporality, have been conducted, showing that individuals with type 2 diabetes had on average a doubled risk to develop HCC [15].

Diet

The role of diet, except for alcohol and coffee drinking, in HCC etiology is largely unknown. Epidemiological studies previously reported coffee reduces risk of elevated liver enzymes and of cirrhosis, while animal studies suggest that coffee reduces liver carcinogenesis. Coffee drinking has also been associated with reduced insulin levels and reduced risk of type 2 diabetes, in itself considered to be an HCC risk factor. Both case-control and cohort studies conducted in Japan and Southern Europe reported a significantly reduced risk of HCC with increased coffee consumption [16].

HCC Surveillance

There is good evidence for the efficacy of HCC surveillance in HBV-infected patients.

A placebo controlled randomised study of ~19,000 HBV-infected patients showed that HCC surveillance with both abdominal ultrasound and serum AFP repeated at 6-month intervals resulted in a 37% reduction in HCC-related mortality. During a 16-year follow-up period, a population-based surveillance program in Alaska among HBV-infected patients using serum annual alpha-fetoprotein (AFP) reported significantly longer 5-year survival among patients who received surveillance compared to historical controls (42% vs. 0%, respectively) [17]. Several non-randomised trials and observational cohort and case-control studies have reported that patients who undergo HCC surveillance are diagnosed at an earlier stage of HCC, are more likely to receive potentially curative therapy, and have a significant reduction in cancer mortality compared to patients with symptomatic HCC [18].

Practice guidelines from the American Association of the Study of Liver Diseases and the European Association for the Study of the Liver have recommended HCC surveillance for patients at a high risk of developing HCC [19]. These include those with cirrhosis or chronic HBV infection irrespective of cirrhosis. Surveillance is not recommended in patients with HCV without cirrhosis.

Liver ultrasound is recommended as the primary surveillance modality, with a sensitivity of 60% and a specificity of 85-90%. The recommended interval between surveillance tests is six months. Serum AFP measurement is also commonly used for surveillance because it is inexpensive, simple to perform and widely available. However AFP alone is not recommended due to its low sensitivity and specificity: At a serum cutoff level of 20ng/mL, AFP has low sensitivity ranging from 25%-65% for detecting HCC [20].

Computed axial tomography (CT) and magnetic resonance imaging (MRI) scans have not been tested for surveillance, but are the main diagnostic and confirmatory tests for HCC. Disease hallmarks are arterial enhancement, followed by delayed hypointensity of the tumor in the portal venous and delayed phases. HCC diagnosis in a patient with cirrhosis can be confidently established with biopsy if a focal hepatic mass > 2 cm is identified with CT or MRI that shows typical features.

The extent of utilising HCC surveillance in clinical practice is low In our recent study among 13,002 HCV-infected veterans with cirrhosis (1998-2005), only 12% received annual surveillance in the three years following their cirrhosis diagnosis, and less than 50% received a surveillance test in the first year [21]. The low utilisation of HCC surveillance likely reflects a combination of cognitive (knowledge of guidelines, new therapeutic options) as well as logistical factors, such as the need for repeated testing over relatively short periods of time, somewhat complicated diagnostic evaluation, and the limited availability of liver transplant centers. These factors are likely obstacles facing the implementation of any effective HCC surveillance program.

Summary

HBV continues to be the major HCC risk factor worldwide, although its importance will most likely decrease during the coming decades due to the widespread use of the HBV vaccine in newborns in HBV endemic and HCC high-incidence areas. HCV has been the dominant viral cause in HCC in North America, some Western countries and Japan. In the U.S., HCV-related HCC is expected to continue at a rapid pace for the next few decades. Obesity and diabetes are increasing at a fast pace and if established as HCC risk (co)factors, they will account for more cases in the future.

Few practice guidelines recommend that ultrasound based HCC surveillance should be considered in patients with cirrhosis or advanced hepatic fibrosis irrespective of etiology, and in adult patients with HBV irrespective of cirrhosis. ■

Blue Faery: The Adrienne Wilson Liver Cancer Association is proud to announce the call for submissions and nominations for the fourth annual Blue Faery Award (BFA) for Excellence in Liver Cancer Research. Primary liver cancer, also known as hepatocellular carcinoma (HCC), is the third leading cause of cancer deaths worldwide. Blue Faery created the award to recognize medical professionals who develop innovative research in the fight against HCC, which currently has no cure. Additional information about the 2012 BFA can be found on Blue Faery's Web site www.bluefaery.org. Applications and nominations are due January 31, 2012.

Founded in 2002, Blue Faery is the only nonprofit organization in the United States solely devoted to fighting HCC. The mission of Blue Faery is to prevent, treat and cure primary liver cancer, specifically hepatocellular carcinoma, through research, education and advocacy. Blue Faery has also developed an HCC patient education brochure for liver cancer patients, their families and their healthcare providers. The free brochure, which is also available in Chinese and in Spanish, is currently distributed in 30 treatment centers across the nation.

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