

The other major classes of biomarkers used in studies of HCC are biomarkers of exposure to environmental, lifestyle or dietary carcinogens, biomarkers of oxidative stress and early biologic response. In addition, studies of genetic susceptibility have studied polymorphisms in a number of pathways and their role in HCC risk. The biomarkers of exposure include the measurement of carcinogens in urine and carcinogen-DNA and protein adducts. Examples are measurement of aflatoxin and polycyclic aromatic hydrocarbon metabolites, and DNA and protein adducts. Biomarkers of oxidative stress include urinary isoprostanes and 8-oxodeoxyguanosine and oxidized plasma proteins. Most of these assays are immunologic although the use of high performance liquid chromatograph (HPLC) as well as gas chromatography/mass spectroscopy (GC/MS) have been utilized. In nested case-control studies, many of these markers are associated with elevated risk. For example, elevated aflatoxin and polycyclic aromatic hydrocarbon-albumin adducts, aflatoxin metabolites in urine and urinary isoprostanes were observed in baseline samples from those who went on to develop HCC. Biologic response markers include measurement of specific mutations in the p53 gene. These studies have demonstrated dramatic differences in mutational

spectra of HCC depending on the geographic location. Other early response markers measure tumor DNA released into the blood stream. This DNA has been shown to carry the same genetic and epigenetic changes as does the tumor. In particular, detection of mutations in p53 and methylation of a number of tumor suppressor genes including p16, RASSF1A, MGMT, etc have been analyzed. While not yet applied to HCC cases, the area of proteomic and metabolomics may also lead to useful biomarkers of HCC.

In terms of genetic susceptibility, a number of investigators are determining whether single nucleotide polymorphisms are related to HCC risk. The genes investigated to date have included those in the carcinogen metabolism, oxidative stress and DNA repair pathways. While definitive studies are still lacking, the data suggest that, in combination with environmental exposures, genetic factors may also be important in HCC risk.

The ultimate goal of these biomarker studies is the early identification of high risk individuals so that they can be targeted for enhanced screening or chemopreventive strategies.

Interplay between viral infections and genetic alterations in liver cancer

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With over 500 000 annual deaths, Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and a leading cause of death in developing countries where about 80% of the cases arise. Risk factors include chronic hepatitis infections (hepatitis B, (HBV) and hepatitis C (HCV) viruses), alcohol, dietary contaminants such as aflatoxins. The incidence shows important geographic variations, according to In southern Asia, HCC development is mainly related to the endemic Hepatitis B Virus (HBV) infection, cases with hot spot mutation in codon 249 (249ser) of TP53 tumor suppressor gene were also described and associated to a low-intermediate exposure rate to Aflatoxin B1 (AFB1). Presence of Hepatitis C Virus (HCV) infection was also detected in 12 - 17% of HCC cases. Despite the increasing number of studies identifying viral/host interactions in viro-induced HCC or describing

potential pathways for hepatocarcinogenesis, precise mechanism has not been identified so far. HBV was demonstrated to enhance hepatocarcinogenesis by different manners; HBV chronic infection is associated to active hepatitis (CAH) and cirrhosis which are hepatic complications considered as early stage for HCC development. These complications mobilise the host immune response, the resulting inflammation initiates and selects the first genetic alteration at the origin of loss of cell control. Moreover, HBV can also promote carcinogenesis through genetic instability generated by its common integration in host DNA. HBV proteins, as HBx, was proven to interact with a variety of targets in the host cell including protein or host transcription factor such as, in particular, the p53 protein or the transcription factor E4F, which is implicated in growth,

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differentiation and senescence. Specific HBV mutations or distinct HBV genotypes are associated to higher risks factors for HCC or hepatic complications leading to HCC. In summary, active HBV replication potentially disrupts

gene integrity, may lead to oncogenic activation through several parallel mechanism, and the role of each of these mechanism may vary with the molecular diversity of viral genotypes.

Hepatocellular carcinoma (HCC) biomarkers in Colombia

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The hepatocellular carcinoma (HCC) account for 70 to 85% of primary liver cancer worldwide. SouthEast Asia and sub-Saharan Africa represent the areas with the highest incidence; instead Europe and North America correspond to low incidence areas. The data available for Latin American countries show a low incidence (<3.3/100.000 inhabitants) in most of the countries including Colombia. The rate of incidence is <5.6/100.000 in Central America, Peru and Argentina and <10/100.000 in Chile and Brazil.

Major risk factors associated with HCC are chronic Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) infection, dietary aflatoxin B1 (AFB1) exposure and intake of alcohol. In fact, alcohol abuse represents a leading cause of cirrhosis, the end-stage liver disease that precedes most cases of HCC.

The prevalence of HBV and HCV infection among cirrhosis and HCC cases varies considerably within and between regions and mirrors the patterns of HBV and HCV endemicity. The World Health Organization estimates that globally, 57% of cirrhosis were attributable to either HBV (30%) or HCV (27%) infection and 78% of HCC was attributable to HBV (53%) or HCV (25%) infection. According to the 2002 worldwide mortality report, approximately 929.000 deaths from cirrhosis (446.000) and HCC (483.000) were likely due to chronic viral hepatitis infections.

In Latin America, 31% of cirrhosis cases were attributable to HBV (8%) and HCV (23%) infection and 64% of HCC cases was attributable to these chronic viral infections (HBV 43%, HCV 21%).

In Colombia, the mortality registry shows 1300 cases of liver tumors per year, which correspond to a rate of inci-

dence of 3.18/100.000 inhabitants. Additionally, there are not data available of HCC cases attributed to each one of the well-recognized risk factors. However this data does not match the number of primary hepatic tumor and cirrhosis cases expected. The prevalence of HBV infection is moderate is most part of the country, but there are some high prevalence regions. The prevalence of HCV infection in general population is unknown but some studies has been described a high prevalence in population at risk. On the other hand, the intake of alcohol beverages in the Colombian population and the evidence of contamination with AFB1 in human and animal food consumption predict a higher rate of incidence of hepatic cirrhosis and HCC cases in this country

Since 2005 we are performing the first biomarkers study in cirrhosis and HCC in Colombia. The first part of the project consisted of a retrospective study of 2000-2004 of cases of HCC diagnosed at 4 hospitals in Bogota, Cali and Medellin. The second one is a cross-sectional study of cirrhosis and HCC at a hospital in Medellin through 2005-2007.

The study will us to determine the frequency of biomarkers corresponding to two main risk factors for cirrhosis and HCC: HBV infection, HCV infection, and a third risk factor for HCC, the AFB1 exposition, in a group of patients from the three principal cities in population, infrastructure, health coverage, and technology of Colombia.

The biomarker of HBV infection (Core Ag (HBcAg)) is being evaluated by immunochemistry in paraffin embedded of HCC cases using the monoclonal antibody (Ab) NCL-HBcAg-506 (Novo-Castra®) and the kit ultravision

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