term food storage, in particular during the rain season. Thus, in these regions, most inhabitants of rural areas are highly exposed to aflatoxins, with seasonal variations reflecting the consumption of stored versus fresh foodstuff. Population-based surveys have demonstrated the presence of serum aflatoxin-albumin adducts in over 95% of the normal population in The Gambia, West Africa. Exposure starts in the perinatal period, through in utero transfer and breast-feeding, and continues throughout life, mainly from consumption of peanuts. Time patterns of aflatoxin-albumin adduct levels correlate with the seasonal availability of peanuts.

There is strong experimental evidence that aflatoxins are potent hepatocarcinogens in rodents. In humans, there are good ecological correlations between the risk of HCC and the presence of biomarkers of aflatoxin exposure in serum or in urine .The most significant carcinogenic aflatoxin is B1 (AFB1), which is the most abundant in the diet. AFB1 is metabolized in the liver by several CYP450 enzymes (mainly 1A2 and 3A4) to a reactive AFB1-8,9-exo-epoxide (Mace et al. 1997). This metabolite generates a primary DNA adduct (8-9, dihydro-8-(N7-guanyl)-9-hydroxyaflatoxin; AFB1-N7-Gua), naturally converted to two secondary lesions, an apurinic (AP) site and a stable, AFB1-formamidopyrimidine (AFB1-FAPY) adduct The latter is considered as the most mutagenic lesion (Smela et al. 2002). The sequence context of codon 249 (AGGCC) represents a site of intermediate affinity for the formation of AFB1-induced lesions. Other codons in TP53, including some codons that are "hotspots" in many cancers (codon 245, 248 and 273), have a similar or even greater affinity for AFB1 than codon 249. Thus, the selectivity for 249ser in HCC cannot be solely explained by thepreferential formation of adducts at this position and other factors must play a role to select this particular mutation as the major carcinogenic one in liver cells exposed to aflatoxins.

There is evidence that imperfect DNA repair may increase the risk of mutagenesis and carcinogenesis induced by AFB1. Higher levels of AFB1-DNA adducts have been detected in the placenta of healthy women from Tawain carrying the Gln399 allele of XRCC1, an enzyme involved in base excision repair, causing slower repair and persistence of DNA adducts. Together, these results suggests that deficient DNA repair does not explain the high prevalence of 249ser in HCC, and that biological selection may play a role to facilitate the clonal expansion of cells carrying 249ser during the development of HCC.

Occult HBV infection and HCC

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A number of risk factors appear to play a role in Hepatocellularcinoma (HCC), HBV infection being one of the most important. Chronic inflammation and cytokines are key determinants in the development of fibrosis and liver cell proliferation. HBV DNA integration into host cellular DNA, has been extensively studied and may disrupt or promote expression of cellular genes that are important in cell growth and differentiation. Moreover, expression of HBV proteins may have a direct effect on cellular functions, and some of these gene products may lead to malignant transformation. Several HBV genes have been frequently found in infected tissues including truncated pre-S2/S, hepatitis B X gene, and a novel spliced transcript of HBV (hepatitis B spliced protein). The proteins expressed from these integrated genes have been shown to have intracellular activities, including effects on cellular growth and apoptosis.

Occult hepatitis B virus (HBV) infection is characterized by persistence of HBV DNA into the tissue of hep-

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atitis B surface antigen-negative individuals. The clinical relevance of this peculiar infection, in particular, the impact of occult HBV infection in cases of HCC has been a matter of debate. Prevalence and molecular status of occult HBV in patients with HCC has been investigated in several studies. HCC patients from Italy, France, Japan, Morocco, the United States, Canada etc.....who had no detectable HBsAg in their serum have been studied. In these HBsAg-negative HCC patients, HBV DNA was detected in tumorous and/or in adjacent non tumorous liver tissue using polymerase chain reaction (PCR) in almost half of the patients, being anti-HCV positive or not. Some of the patients are positive for anti-HBc antibodies as the only marker of HBV infection, but not all. Covalently closed circular HBV DNA may be detected indicating that at least some of these patients had actively replicating HBV infections. Observational cohort study showed that, among the HBsAg-negative patients with chronic hepatitis C, HCC develops for the most part in carriers of occult HBV.

One of the markers in HCC cases, HBsAg (-), has been the presence of the HBV-X gene expression in HCC since positivity for the HBV-X protein in liver tissue in several studies reached half of the liver tissues specimens. In all studies, the significant association of occult HBV with HCC was irrespective of age, sex, and may be contemporary with hepatitis C virus infection. Both integrated viral DNA and covalently closed circular HBV genomes were detected in patients with occult HBV. Moreover, the presence of free HBV genomes was associated with persistence of viral transcription and replication: There are evidences that occult HBV is a risk factor for the development of HCC and that the potential mechanisms whereby overt HBV might induce tumour formation are mostly maintained in cases of occult infection

HCV and HCC molecular epidemiology

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iHepatitis C virus (HCV) is a member of the family Flaviviridae, responsible for the majority of the non-A non-B post-transfusion hepatitis before 1990. Around 170 millions persons in the world are thought to be infected with this virus. A high number of HCV-infected people develop cirrhosis and from these, a significant proportion progresses to hepatocellular carcinoma (HCC). Six HCV genotypes and a large number of subtypes in each genotype have been described. Infections with HCV genotype 1 are associated with the lowest therapeutic success. HCV genotypes 1, 2, and 3 have a worldwide distribution. HCV subtypes 1a and 1b are the most common genotypes in the United States and are also are predominant in Europe, while in Japan, subtype 1b is predominant. Although HCV subtypes 2a and 2b are relatively common in America, Europe, and Japan, subtype 2c is found commonly in northern Italy. HCV genotype 3a is frequent in intravenous drug abusers in Europe and the United States. HCV genotype 4 appears to be prevalent in Africa and the Middle East, and genotypes 5 and 6 seem to be confined to South Africa and Asia, respectively.

HCC accounts for approximately 6% of all human cancers. Around 500,000 to 1 million cases occur annually worldwide, with HCC being the fifth common malignancy in men and the ninth in women. HCC is frequently a consequence of infection by HBV and HCV.

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