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Hepatitis C and hepatocellular carcinoma

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ABSTRACT

Chronic hepatitis C virus infection is a well-recognized risk factor for occurrence of hepatocellular carcinoma (HCC). In Europe, Oceania and America, chronic hepatitis C and alcoholic cirrhosis are the main risk factors for HCC. In Latin America, a few retrospective and one prospective study have also shown the predominant role played by hepatitis C in this setting. Furthermore, the incidence of HCC has been increasing in industrialized countries in the last decades; partially as a consequence of the increase in HCV-related cirrhosis (as the long-term sequel of the peak of infections occurring 2-4 decades ago). The main risk factor for HCC development in patients with hepatitis C is the presence of cirrhosis. Among patients with hepatitis C and cirrhosis, the annual incidence rate of HCC ranges between 1-8%, being higher in Japan (4-8%) intermediate in Italy (2-4%) and lower in USA (1.4%). Some studies have also found that HCC may be the first complication to develop and the more frequent cause of death in the compensated HCV-associated cirrhosis. Other risk factors for HCC occurrence are older age at infection, male gender, decreased platelet count, esophageal varices, presence of porphyria cutanea tarda, liver steatosis or diabetes, infection with genotype 1b, coinfection with hepatitis B virus or with HIV and chronic alcoholism. Many studies and also meta-analysis have reported that antiviral therapy based on interferon may reduce the incidence of HCC in chronic hepatitis C, especially in patients with sustained virologic response. Patients with HCV-related cirrhosis should undergo surveillance for HCC.

Key words. Hepatocarcinoma. Risk factors for hepatocarcinoma. Cirrhosis. Incidence of hepatocarcinoma. Interferon. Coinfection.

Chronic hepatitis C virus (HCV) infection is a well-recognized risk factor for hepatocellular carcinoma (HCC). HCC is a malignant tumor that usually emerges in patients with chronic liver disease and hepatitis B, hepatitis C and alcoholic cirrhosis are the more frequent predisposing conditions.[1-4]

The incidence of HCC is highly variable across the world and it runs a parallel course with the prevalence of chronic carriers of hepatitis B virus (HBV) at each region.[2-4] Thus, in areas with high endemicity of HBV, like sub-Saharan Africa or Eastern Asia, the highest annual incidence rates of HCC are found (greater than 30/100.000 individuals) and most of patients are young adults who became infected with the virus very early at their lives, either through vertical (mother to newborn) or horizontal (between siblings) transmission. More than 80% of world cases of HCC occur in these 2 regions and China alone accounts for more than 50%.[4] In contrast, intermediate annual incidence rates (5-20/100.000 individuals) are observed in Southern European countries (Italy, Spain, Greece) and low annual incidence rates (lower than 5/100.000 individuals) in Northern European countries, Oceania and North and South America, where the rates of chronic carriers of HBV are coincidently low. In all these regions, chronic hepatitis C and alcoholic cirrhosis are the main risk factors for HCC.[5-10]

There is a difference also in the incidence trends of HCC between the Asian and some of the occidental countries. A decreasing incidence of HCC has been reported in Taiwan as a consequence of the instauration of universal hepatitis B vaccination programs;[11] and in China, due to a government program promoting dietetic changes and then a reduced exposure to the hepatocarcinogen aflatoxin B_1.[12] In contrast, many studies performed in industrialized countries (USA, United Kingdom, Italy, France and Canada) have been showing a significant increase of the incidence.[13-16] A recently published study showed that the age-adjusted HCC incidence rates tripled between 1975 and 2005 in USA.[17]

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In that country, available studies suggest that HCV infection acquired 2-4 decades ago accounts at least 50% of the observed increase in HCC.[18,19]

In Latin America, a few published studies have also showed the importance of hepatitis C and chronic alcoholism as risk factors for HCC.[20-24] Small retrospective series of patients with HCC from Mexico and Chile reported that chronic HCV infection was present in 73% and 48% of them, respectively.[21,22] A multicenter series from Brazil including 287 HCC cases (but with full serological studies available in only 132 out of them), found that hepatitis C accounted for 25%.[20] In Argentina, a retrospective multicenter study analyzed the etiology among 551 patients with HCC and showed that alcoholic cirrhosis and chronic hepatitis C were present in 76% of cases (hepatitis C in 40.5%).[23] Recently, the first prospective study aimed in investigating etiology of HCC in Latin America was performed.[24] Most of the patients were included by colleagues from Argentina, Brazil, Venezuela and Colombia. Hepatitis C was shown to be the leading risk factor for HCC, present in 38% out of 240 cases[24] (without significant differences between the countries).

RISK FACTORS FOR HCC AMONG PATIENTS WITH CHRONIC HEPATITIS C

The main risk factor for occurrence of HCC in patients with hepatitis C is the presence of cirrhosis. Almost all the patients with HCC associated with HCV have cirrhosis at the time of diagnosis. Among patients with HCV-related cirrhosis, the annual incidence of HCC ranges between 2-8%.[25] The rate is higher in Japan (4-8%),[26,27] intermediate in Italy (2-4%),[28,29] and lower in USA (1.4%).[30] The 5-year cumulative risk for HCC in patients with cirrhosis was 17% in Europe and 30% in Japan.[3] Furthermore, studies from Italy have shown that HCC was the main cause of death and the first complication to develop among compensated cirrhotic patients;[28] and, also in Japan, the development of HCC was more frequent than that of hepatic failure.[31]

The risk for HCC is much lower in patients with noncirrhotic hepatitis C. In a Japanese study, the incidence per 100 person years increased from 0.4 among those with stage F0-F1 to 1.5 in stage F2, 5.1 in stage F3 and to 6.9 in stage F4.[27] In a multicenter study from USA, that included 1005 patients, the cumulative 5-year HCC incidence was 7.0% among patients with cirrhosis and 4.1% in those with bridging fibrosis in the baseline liver biopsy. In 18% of patients with occurrence of HCC during follow-up, serial biopsies did not show progression to cirrhosis.[30] However, most of experts think that severe liver fibrosis secondary to long-lasting chronic inflammation and liver regeneration resulting from immune-mediated cell death are factors contributing to HCC development; and that a direct oncogenic role of HCV remains to be determined.[32]

Among patients with cirrhosis associated with HCV, risk factors for developing HCC can be separated in host-related, virus-related and external ones. Some host-related factors that have been independently associated with progression to HCC are older age at infection (> 50 years), male gender, decreased platelet count, esophageal varices;[3,30,33] and presence of comorbid conditions, including porphyria cutanea tarda,[34] liver steatosis [35] and diabetes.

Regarding viral-related factors, there is no evidence that viral load influences the risk for developing HCC. Considering that previous research had produced controversial results, a recent meta-analysis was performed to investigate whether genotype 1b was associated with a higher risk of HCC.[36] Authors focused on 21 studies that presented age-adjusted risk estimates for genotype 1b versus other genotypes and found that patients infected with HCV-1b had almost double the risk to develop HCC than those infected with the others [Relative Risk (95% Confidence Intervals)=1.78 (1.36-2.32)].[36]

Cohort studies from Italy and China have shown that cirrhotic patients coinfected with HCV and HBV had a 2- to 6-fold higher risk of developing HCC compared with those infected with only one virus;[37,38] and a meta-analysis of 32 case-control studies found a synergistic effect between HBV and HCV infections in causing HCC.[39] Interestingly, patients with chronic hepatitis C and an occult HBV infection (presence of HBV DNA in the liver or in serum but HBsAg negative) had also a higher risk of HCC during follow-up than those with HCV infection alone;[40] and HBV DNA was frequently detected in liver tissue of Japanese patients with a sustained virologic response to antiviral treatment for hepatitis C who developed a HCC.[41] In contrast, recent studies have shown that a past HBV infection (anti-HBc seropositivity with HBsAg negative) does not mean an additional risk for HCC, when multivariate analysis are performed.[42,43]

Coinfection with HIV may also modify the natural history of chronic hepatitis C and a faster progression to cirrhosis has been described. A retrospective study showed that anti-HIV positive patients with HCC were younger at the diagnosis time than anti-HIV negative ones; and the estimated

time from HCV infection to HCC was significantly shorter in the coinfected patients than in monoinfected ones (26.1 *vs.* 33.8 years, respectively) (p 0.002).[44]

In respect to external factors, chronic alcoholism and hepatitis C seem to have a synergistic effect in increasing risk for HCC. Case-control studies have shown that among patients with chronic hepatitis C, there is an approximately 2-fold increased risk for HCC in heavy drinkers as compared to non-drinkers;[45,46] and longitudinal studies performed in Japan have found that lifetime alcohol use was independently associated with risk for HCC in patients with hepatitis C.[26,47] Another external factor that modifies the incidence of HCC in patients with chronic hepatitis C is the effect of antiviral treatment based on interferon. A recently published meta-analysis including 20 studies (4.700 patients) showed that the risk of HCC had been reduced in treatment groups (interferon alone in 18 studies, in association with ribavirin in 2) as compared to controls [Relative Risk (95% CI), 0.43 (0.33-0.56)].[48] As expected, risk was significantly lower in patients with a sustained virologic response versus nonresponders [Relative Risk (95% CI), 0.35 (0.26-0.46)].[48] However, another recent meta-analysis (including 3.246 patients) concluded that interferon treatment prevented the development of HCC in chronic hepatitis C, even in nonresponders.[49]

SURVEILLANCE FOR HEPATOCELLULAR CARCINOMA

Patients with hepatitis C and cirrhosis should undergo surveillance for HCC. In those with bridging fibrosis, the cost-efficacy of this strategy has not been evaluated.[25] Surveillance should be performed using ultrasonography, at 6 month intervals. If nodules are detected on ultrasound, patients should undergo diagnostic algorithms suggested by recent HCC Guidelines.

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