



# Occult Hepatitis B and Other Unexplored Risk Factors for Hepatocellular Carcinoma in Latin America

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## ABSTRACT

Occult hepatitis B infection (OBI) is the presence of hepatitis B virus (HBV) DNA in the liver and/or serum ( $< 200$  IU/mL) in HBsAg-negative patients with or without serologic markers of previous viral exposure. The clinical significance of OBI is of concern in post-transfusional hepatitis B infection, hepatitis B reactivation, chronic liver disease and hepatocellular carcinoma (HCC). The diagnosis of OBI relies on the use of highly sensitive and specific laboratory techniques. Herein, comments derived from a study analyzing the frequency and characteristics of OBI in HCC Japanese patients are stated. While OBI and other causes of HCC have been highly studied in Asia and Europe, research in Latin America in these topics is limited. Several findings such as population risk groups with high prevalence of overt and OBI infection, HBV genotype F in Argentinean HCC patients, and the clinical impact of the foreign A-D genotypes suggest the need of further investigation. Additionally, alcoholism, obesity, NASH and type 2 diabetes may override the presence of OBI. Therefore, OBI diagnosis is essential. It is known that anti-HBc alone is a predictive signal of potential OBI and given the fluctuations of the HBV infection markers, testing for HBsAg and anti-HBc at baseline and follow-up is recommended. In conclusion, OBI and other causes involved in the epidemiology of HCC in Latin America are unexplored risk factors. Genome-based research is required to decipher the role of gene-environmental interactions associated with chronic liver disease. Novel algorithms to detect OBI supported by basic/applied/clinical research are also needed.

**Key words.** Risk factor. Epidemiology. Hepatocellular carcinoma. HBV genotypes. Diagnostics.

Occult HBV infection (OBI) refers to the appearance of HBV DNA in the liver and/or serum ( $< 200$  IU/mL) in HBsAg-negative patients with or without serologic markers of previous viral exposure.<sup>1,2</sup> OBI constitutes a phase of chronic hepatitis B infection in which replication-competent viruses are actively suppressed by genetic, epigenetic and post-transcriptional mechanisms.<sup>1</sup> The clinical significance of OBI is of concern in risk patients coursing with post-transfusional hepatitis B infection, hepatitis B reactivation, chronic hepatitis, and hepatocellular carcinoma (HCC).<sup>1,2</sup>

One of the main challenges for the management of OBI is the diagnosis. The detection of both HBsAg and HBV DNA is substantially reliant on the availability of highly sensitive and specific serological and molecular techniques, respectively. Worldwide, the performance of these diagnostic assays varies widely, thus, affecting the rate of

prevalence of OBI among distinct risk groups.<sup>3</sup> Consequently, conventional criteria and standardized protocols for the detection of serum/liver HBV DNA were agreed (Taormina meeting, 2008).<sup>2</sup> Thus, it was suggested that OBI positivity is confirmed by using nested polymerase chain reaction (PCR) primers annealing within at least two of the four open-reading frames of the HBV genome (S,C,P,X).

In this issue of *Annals of Hepatology*, Muto, *et al.* published the incidence and characteristics of OBI among 75 Japanese patients with HCC.<sup>4</sup> In this study, OBI was detected in 38% of cryptogenic and 25.6% of hepatitis C patients with no other detectable risk factors (alcohol, steatosis), by using a highly sensitive, in-house PCR detection system for total HBV DNA and covalently-closed circular (ccc) DNA. Other HBV markers (HBsAg, anti-HBs, anti-HBc, Anti-HBe) were also measured.