for GI symptoms and COVID-19 is not likely to be a good substitute for more traditional epidemiologic methods, search activity could still be useful as part of a more complex model. As you have concluded, Google Trends is a valuable tool, and it is our responsibility to carefully understand and refine its role in this global pandemic.

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The authors disclose no conflicts.

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Hepatocellular Carcinoma: Unraveling the Role of Occult Hepatitis B Virus Infection

Dear Editor:

We have read with great interest the study recently published by Wong et al[1] in which the authors analyzed the association between hepatocellular carcinoma (HCC) and occult hepatitis B virus infection (OBI). In the study, the authors evaluated hepatitis B surface antigen (HBsAg) negative patients with HCC and controls and found that among patients with HCC, 69.0% had OBI, as determined by polymerase chain reaction on liver or tumor tissue. On the other hand, OBI was much less frequent among the 20 individuals without HCC.[1]

More than a decade ago, using detection of HBsAg or hepatitis B anti-core antibody (HBcAb) in liver tissue, we also evaluated the association between HCC and OBI in a Brazilian cohort. At the time, we found a significantly higher rate of OBI in patients with chronic hepatitis C (CHC) and HCC, compared with those with CHC and no HCC or controls.[2] Advanced molecular biology techniques have allowed Wong at al[1] to reach beyond the correlation of OBI and HCC to demonstrate the importance of hepatitis B virus (HBV) DNA integration in liver DNA in the context of patients with OBI and HCC. The authors found that HBV DNA integration was present in 69.0% of patients with OBI and HCC and in none of the patients with OBI without HCC. Moreover, among patients with OBI and HCC with evidence of HBV DNA integration, 91.0% were non-cirrhotic, which reinforced the hypothesis that HBV DNA integration plays an important role in hepatocarcinogenesis also in patients with OBI.[1]

The contributions of the work published by Wong et al[1] are of much importance as a mechanistic exposé for HCC development. However, caution should be used when the authors suggest that patients who have resolved HBV infection, which is based on loss of HBsAg, should be tested for HBV DNA on liver tissue to identify individuals at high risk of developing HCC ("What you need to know" section).[1] This recommendation seems unjustifiable from a practical, scientific, and economic point of view, which is based on the following: (1) The authors evaluated a population with very high prevalence of HBcAb. Indeed, 72% of those tested were HBcAb positive. It is unclear whether similar findings will stand in populations with lower prevalence of HBcAb and high frequency of HBV-related HCC such as those of Africa or Latin America, as previously described by us and others.[3,4] (2) Despite the repeated statement that HBV DNA integration was not found in those without HCC, it should be kept in mind that this group included only 3 patients, a far too low number of patients to achieve any control-based conclusions. (3) The authors rightly point out in the Discussion that covalently closed circular DNA (cccDNA) is looked on as the "final cure" in those treated for HBV. However, seroconversion to negative HBsAg (functional cure) does not correlate necessarily with cccDNA negativity, and assessment of cccDNA still remains feasible in specialized laboratories only. (4) It would be economically unsustainable to submit every individual positive for HBcAb (approximately 10%–20% of the global population, depending on the estimates) to a liver biopsy and a DNA integration assay.

In summary, we praise the authors for their important contribution to the field of hepatocarcinogenesis, especially in association to hepatitis B infection. However, we believe the next efforts should be focused on understanding whether these findings apply to other populations at risk before providing patient-care recommendations that could exacerbate costs with unclear clinical benefit. In this regard, we hope studies such as our ESCALON Project[5,6] or the Texas HCC Consortium Cohort Study[7] would help to further understand HCC development in OBI and lead to the development of better screening methods for HCC.

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Reply. We thank Mattos et al[1] for their interest in our recent study on the association between hepatitis B virus (HBV) DNA integration and hepatocellular carcinoma (HCC) in hepatitis B surface antigen (HBsAg)-negative patients. Chronic hepatitis B infection is the most common cause of HCC worldwide. Although chronic hepatitis B is closely related to HCC, the role of occult hepatitis B (OBI) in HCC is less clear.

In our study, we evaluated the prevalence of HBV DNA integration in HBsAg-negative HCC patients and found that 69% of patients with OBI and HCC had HBV DNA integration.[1] Although the role of OBI and chronic hepatitis C in HCC development has been shown in previous studies,[2–5] our study highlighted the role of OBI in hepatocarcinogenesis in patients with nonviral liver diseases such as alcoholic liver disease, nonalcoholic fatty liver disease, and those with cryptogenic HCC. Furthermore, our findings suggested the potential of testing HBV DNA integration in HBsAg-negative patients.

We agree with Mattos et al[1] that the implication of detecting liver HBV DNA has certain shortcomings and limitations that should be overcome. First, as suggested by Mattos et al,[1] the findings will require further validation in larger patient cohorts, including those with a low prevalence of hepatitis B core antibody (HBcAb). In chronic hepatitis B endemic areas such as Asia, the prevalence of HBcAb positivity among HBsAg-negative individuals generally is high, ranging from 30% to 75%.[6] Globally, up to 20% of OBI patients are seronegative for HBcAb.[7] Seronegative OBI patients remain at risk for HCC, although HCC prevalence in seronegative OBI patients remains to be determined in larger cohorts. The development of HCC in seronegative OBI was best shown in the woodchuck hepatitis virus (WHV) infection model, in which 20% of woodchucks with seronegative occult WHV infection developed HCC and 90% of them had WHV DNA integration.[8] Second, because of ethical and practical problems of obtaining liver tissues from HBcAb-positive individuals, further investigations may be focused on the identification of potential serum biomarkers for HBV DNA integration and HCC and surrogate serum markers of covalently closed circular DNA (cccDNA) such as hepatitis B core–related antigen.[9,10] The intriguing associations between cccDNA, HBV DNA integration, OBI, and HCC deserve further investigations. In our study, we identified 29 HCC patients with undetectable cccDNA but detectable HBV DNA integration.[1] Because the detectability of replicative competent intrahepatic HBV DNA (ie, cccDNA) is one criterion of defining OBI,[7] it would be interesting to study this special group of patients (with undetectable cccDNA but detectable HBV DNA integration). Nevertheless, standardized and sensitive assays for the detection of cccDNA and HBV DNA integration are needed to accurately study this association as well as its implication.

We hope that our current study has added to the knowledge related to HCC development in OBI. We agree that concerted effort from nationwide or international collaborations such as the European South American Consortium to Assess Liver-Originated Neoplasia Project[11,12] and the Texas HCC Consortium Cohort Study[13] would provide more information about the development of this important global disease.

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