Editorial Commentary

Is smoking causally-associated with hepatitis B virus-related hepatocellular carcinoma?

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Hepatitis B virus (HBV) is by far the strongest risk factor for the development of hepatocellular carcinoma (HCC). This effect seems to be augmented with several environmental factors. For instance, alcohol consumption was proved to play an important role and much attention was paid to understand the underlying mechanisms (1). On the other hand, the role of smoking was less studied despite the availability of several case-control studies that associate smoking with the risk of development HCC. This might be due to lack of clear mechanistic studies explain this effect.

In 2004 after reviewing the cumulative evidence from observational studies, the International Agency for Research on Cancer (IARC) had classified HCC as one of the tobacco-related cancers (2). It was debated for a long time whether smoking is an independent risk factor for HCC development due to the potential confounding from HBV and hepatitis C virus (HCV) infection. However, several epidemiologic data resolved this debate. One meta-analysis showed that the meta-relative risk (RR) of liver cancer in current and former smokers was higher than never smokers {RR: 1.51 [95% confidence interval (CI): 1.37–1.67] and 1.12 (95% CI: 0.78–1.60), respectively (3)}. Another meta-analysis of 27 studies recruiting 4 million patients have found the pooled hazard ratio of death from liver cancer is relatively higher in current and former smokers compared to never smoker [HR: 1.45 (95% CI: 1.33–1.59) and 1.22 (95% CI: 1.11–1.34), respectively (4)]. The largest meta-analysis to date on 81 epidemiologic studies confirmed such results that smoking increases the incidence and mortality of HCC. In current smokers the odds ratio (OR) for HCC development and for mortality form HCC were 1.55 (95% CI: 1.46–1.65; P<0.00001) and 1.29 (95% CI: 1.23–1.34; P<0.00001), respectively (5).

The paramount question in the epidemiologic research of HBV was the extent of interaction between HBV and smoking in the development of HCC. This was answered by a meta-analysis that included nine studies providing results on the interaction between smoking and HBV infection (6). The risk of HCC was the highest among HBV positive smokers 21.6 (95% CI: 15.2–30.5) followed by HBV positive non-smokers 15.8 (95% CI: 9.69–25.7) and the lowest in HBV negative smokers 1.87 (95% CI: 1.30–2.69) compared to reference population, i.e., HBV negative non-smokers. The study considered this a more than additive interaction between these two risk factors (6).

This mounting evidence of synergistic effect between smoking and HBV infection in the development of HCC was actually lacking the last piece, i.e., the mechanistic underpinnings. The study conducted by Wang and his colleagues and published in *Hepatology* under the title of "Smoking and Hepatitis B Virus-Related Hepatocellular Carcinoma Risk: The Mediating Roles of Viral Load and Alanine Aminotransferase", was the first to provide mechanistic understanding for such complex relationship

between smoking and HBV in tumorigenesis of liver cancer (7). The study included a large cohort of 4,841 male HBV carriers who were followed for 22 years with health and lifestyle questionnaire survey, clinical evaluation, ultrasonography, and blood testing. Two types of analysis were conducted, first, is a nested case-control analysis of 1,465 subjects with a cumulative incidence of HCC of 14.3%. the pertinent findings of this analysis were that not only being smoker but also the intensity and duration of smoking were associated with higher viral load, increased the likelihood of alanine aminotransferase (ALT) ≥2× upper limit of normal (ULN) and severer hepatotoxicity grades. Moreover, the OR for subsequent HCC events in the smokers was 1.68 (P=0.0173) after adjustment for age and alcohol consumption. A decline in OR to 1.37 was noticed after adjustment for viral load. This means that the viral load mediated roughly one-third of the effect of smoking on the risk of HCC. Mediation analysis was non-significant for ALT alone but significant in a model comprising viral load and ALT together.

These results come in accordance to a previous retrospective analysis that compared associated risk factors between early-onset and late-onset HCC cases and age-matched controls and found that history of smoking along with elevated alpha-fetoprotein (AFP) level (>200 ng/mL) were significant risk factor to late-onset HCC in a multivariate analysis (OR 1.68, 95% CI: 1.19–2.36 and 12.0, 95% CI: 8.12–17.8, respectively) (8). In addition, smoking was not an independent risk factor for the early-onset HCC reflecting the impact of cumulative dose with time.

Another interesting aspect of this study was the haunt for mechanistic clues for the role of smoking in tumoral evolution of HCC. The authors investigated the dynamics of IFN-γ and the proportion of natural killer cells (NK), being important immune response pillars against the clearance of HBV. The ever-smokers cohort showed a further reduction of IFN-γ and the percentage of NK cells (≤22%) compared to non-smokers, this was in a dose-dependent manner. Moreover, these changes in immune profile persist even after smoking cessation.

The main strength of this study is the large sample size together with a long follow-up and the availability of genome-wide transcriptional profiles. It is not clear why authors choose to exclude females apart from low-smoking behavior. Alcohol consumption in this cohort was relatively low (around 10%) which mitigate potential confounding factor. Depending only on ALT as a biomarker of inflammation severity is a critical point as other non-invasive models showed to be plausible and it would have been better to implement more than biomarker to validate such important hypothesis that smoking increase HCC risk through prompting inflammatory state (9).

To conclude, the viral load, ALT and impairing immune response seems to be the main mediators of the role of smoking in the development of HBV-related HCC. Duration and intensity of smoking clearly aggravate this negative impact. Therefore, the emphasis on smoking prevention and cessation in hepatitis B management is crucial. Further studies shall investigate appropriate biomarkers to follow-up such patients including HBV viral load, ALT, IFN-γ and NK cells and will this be translated to an improvement of survival of such patients or not.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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