Editorial Commentary

Smoking favours hepatocellular carcinoma

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Smoking and liver cancer

Chronic hepatitis B or C virus (HBV or HCV) remained the strongest risk factor for hepatocellular carcinoma (HCC), but results of a nested case-control study in Europe showed that 47.6% of HCC was associated with smoking (1). The International Agency for Research on Cancer (IARC) showed enough evidence to classify liver cancer as a tobacco related malignancy in 2004 (2). The available knowledge on the relationship between tobacco smoking and a variety of cancers is based primarily on epidemiological evidences. Results from a meta-analysis of 81 epidemiological studies supported this association, with significant pooled ORs for HCC development of 1.55 (95% CI, 1.46–1.65) and 1.39 (95% CI, 1.26–1.52) for current and former smokers, respectively, compared to non-smokers. They identified also a dose-response effect with a significant increase in liver cancer risk for heavy smokers (OR 1.9; 95% CI, 1.68–2.14) (3). Confirming these data, Schulze *et al.* identified 8 HCC-risk-factor-specific mutational signatures, and two of them (MSig1 and MSig3) associated with tobacco exposure, suggesting a genotoxic effect of smoking. More interesting they found also a hypermutated tumor (classified alone, outside the previous signatures) characterized by a non-fibrotic liver with black anthracotic pigment deposition and by a predominance of C>T mutations resulting from the interplay between an unknown mutagenic process influencing particularly guanine bases and transcription coupled nucleotide excision repair (4). An impact of smoking on HCC development is possible and have biological substrate, according to the carcinogenic potential of various molecules with oncogenic potential such as 4-aminobiphenyl, a liver carcinogen which has been identified as a causal risk factor for liver cancer. These oncogenic compounds covalently bind to DNA creating DNA adducts, which have a central role in the carcinogenesis by causing miscoding events in critical genes (5). Smoking increases oxidative stress and release of pro-inflammatory cytokines causing inflammation (6).

Synergic effect of smoking and HBV infection

It has been also highlighted that smoking may be associated with increased HCC risk in association with other established HCC risk factors, like alcohol, obesity, diabetes and other metabolic risk factors (7). Additionally, additive synergism between smoking and HBV/HCV infection on HCC risk was showed by a recent meta-analysis of prospective cohort studies (8) (*Figure 1*). Moreover, Kolly *et al.* showed that smokers have a significant worse overall survival than non-smokers (HR 1.77, 95% CI, 1.22–2.58), particularly in the setting of viral hepatitis in which smoking is an independent predictor for survival (HR 2.99; 95% CI, 1.75–5.23) (9). Recently Wang *et al.* revealed the relationship between smoking and the development of HBV-related HCC, highlighting a role of smoking on HBV viral load and liver inflammation (10). They used two approaches: a nested case-control study assessing the mediation effect of alanine aminotransferase (ALT)

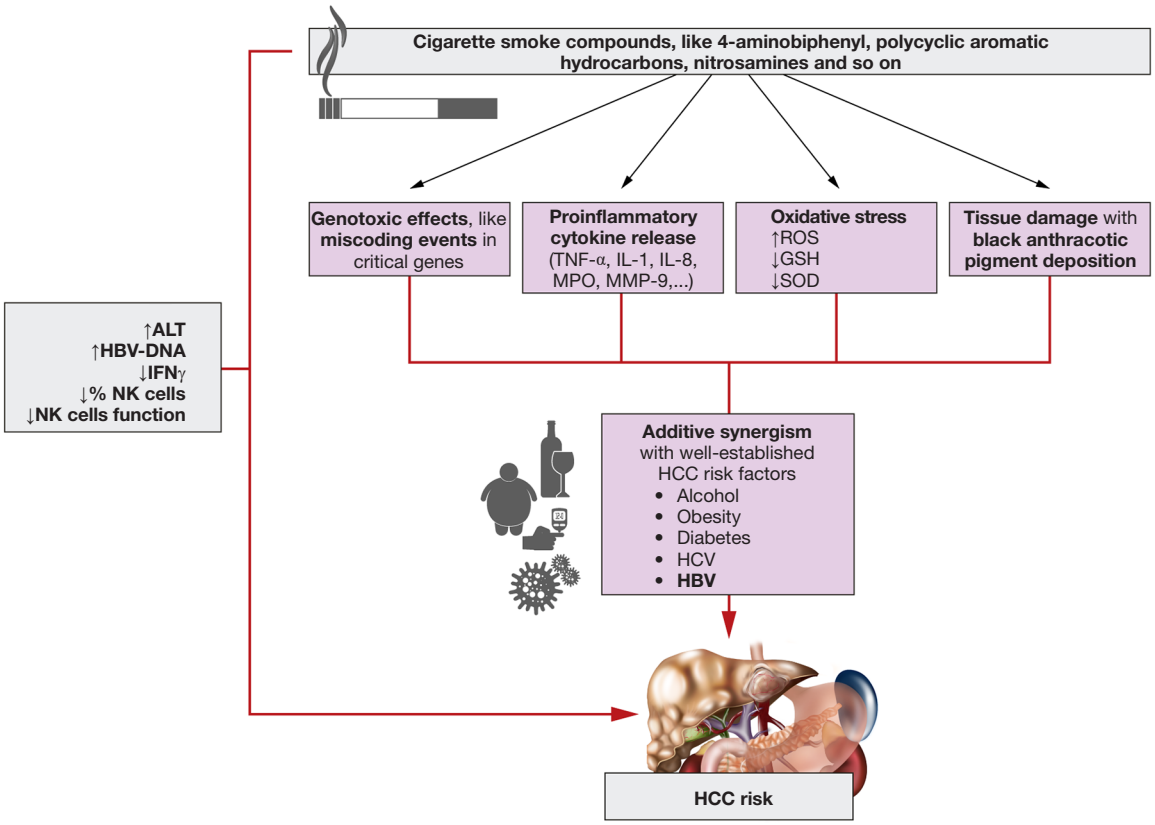

Figure 1 Synergistic carcinogenic effect of smoking and HBV on hepatocellular carcinoma risk (3-8). ALT, alanine aminotransferase; IFN, interferon; NK cells, natural killer cells; TNF, tumor necrosis factor; IL, interleukin; MPO, myeloperoxidase; MMP-9, matrix metalloproteinase-9; ROS, reactive oxygen species; GSH, glutathione; SOD, superoxide dismutase; HCC, hepatocellular carcinoma, HCV, hepatitis C virus; HBV, hepatitis B virus.

levels and viral load on the association between smoking and HCC risk, and a longitudinal analysis assessing the effects of smoking on ALT and viral load, evaluating if this association was in accordance with long-lasting immunity to infection. They noticed a dose-related effect of cumulative smoking on ALT and viral load. An association between smoking and ALT levels has been already described among HCV-infected individuals (11). They showed that smoking is associated with an adjusted OR of 1.68 for *de novo* HCC events, and the OR falls to 1.37 after adjusting for viral load. A mediation analyses highlighted that viral load mediates 31.7% of the effects of smoking on HCC risk while ALT alone is not a significant mediator.

Smoking and immune response

What is innovative in this paper is the attempt to achieve a better understanding of the effects of smoking on HBV viral load and ALT through the assessment of plasma levels of interferon (IFN)γ and of cellular immune and transcriptional profiles. They observed a dose-dependent effect of cumulative smoking exposure on IFNγ levels and on reduced percentage and function of natural killer (NK) cells in peripheral blood (*Figure 1*). Finally, they found that the combination of smoking and the decrease of NK cell fraction below 22% is associated with increased likelihood of occurring ALT ≥80 U/L and higher viral load. It was demonstrated that increased viral load mediated by smoking would induce hepatic inflammation and abnormal immunity, which has close correlation with the development of HBV-related HCC.

Future investigations

The role of elevated ALT and high viral load in HBV-related HCC is well known, and what is missing in this analysis is the effect of antiviral therapy (nucleotide/

nucleoside analogues) on smoking consequences, because antiviral drugs have long-term beneficial impact on natural course of HBV infection in terms of liver decompensation, HCC occurrence and overall survival (12). Future investigations should take into account the impact of antiviral therapy on liver disease progression, and probably a study cohort comparing subgroups of patients according to smoking/not smoking/smoking cessation ± nucleotide/nucleoside analogues therapy is mandatory to investigate if smoking cessation or not smoking at all can have a synergic effect with antiviral therapy in terms of disease progression, HCC development and mortality. Additionally, analysis of NK cells, at key time-points of the natural history of the liver disease and according to smoking habits, could be helpful to better understanding the immunological mechanisms involved on the development of HBV-related HCC in smokers *vs.* not smokers. These findings underline the importance of smoking cessation and prevention in hepatitis B management, since the increased risk of HCC in smokers is mediated by carcinogens-induced genetic changes and immunological effects on persistent viral infection and hepatocellular damage.

Conclusions

In conclusion, it is important to counsel and encourage all patients who have risk factors for HCC or patients already diagnosed with HCC to stop smoking, explaining them the potential deleterious effects on chronic liver disease and survival if they continue smoking. More efforts are required to promote smoking cessation in the overall population and specially in patients with chronic liver diseases.

Acknowledgments

None.

Footnote

Conflicts of Interest: JF Dufour: Advisory committee for Abbvie, Bayer, BMS, Fallk, Genfit, Genkyotex, Gilead, Heparegenerix, Intercept, Lilly, Merck, Novartis. M Guarino has no conflicts of interest to declare.

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