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Letter to the Editor

Comment on "Evaluation of serum interleukin-6 levels in hepatocellular carcinoma patients: a systematic review and meta-analysis"

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Dear Editor

We read with interest the recent meta-analysis by Shakiba *et al*. [1], which demonstrated that serum interleukin 6 (IL-6) levels are significantly higher in patients affected by hepatocellular carcinoma (HCC) compared to healthy controls and to patients with cirrhosis or chronic hepatitis. The authors conclude that IL-6 might play a pathogenetic role in hepatocarcinogenesis and that serum IL-6 may represent a potentially useful diagnostic biomarker. We agree with these conclusions, but we argue that a significant advance in understanding the relationship between serum IL-6 and HCC will require refining the analysis by taking into account factors that Shakiba *et al*. could not consider, the most important of which – at least in our opinion – is gender. In fact, HCC is characterized by a significant gender disparity, due to multiple mechanisms among which sex differences in MyD88-dependent IL-6 production have been considered paramount [2]. Experimental hepatocarcinogenesis data show that the administration of diethylnitrosamine (DEN) causes a larger increase in serum IL-6 in male mice than it does in female mice. Genetic ablation of IL-6 abolishes the gender differences in liver injury and the administration of estrogens to male DEN-treated mice decreases serum IL-6 concentration [2]. Estrogen-mediated inhibition of IL-6 production by Kupffer cells may thus protect females from developing liver cancer, especially among carriers of IL-6 polymorphisms associated with high production of IL-6 [3]. Consistent with this hypothesis are the results of a study conducted on patients with chronic hepatitis C, in which serum IL-6 levels predict development of HCC, but only among females, where they have a negative correlation with estradiol levels [4]. Nevertheless, others have observed that the association between high serum IL-6 concentrations and increased HCC risk depends on body mass index, and not gender [5].

In conclusion, while appreciating the attempt that Shakiba *et al*. made to give meta-analytical strength to the purported association between serum IL-6 and HCC, we wonder if further insight into this topic should not come from a re-analysis of the individual data of the studies they cite. This approach would allow them to take into account important modulating factors such as gender and body mass index.

Disclosure

Authors report no conflict of interest.

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