

IL-6, A Promising Tumor Marker and Prognostic Indicator in Patients with HCC?

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ABSTRACT

In the last decade, accumulating evidence has supported Virchow's hypothesis that cancer and inflammation are linked. Many investigators have demonstrated that the presence of a systemic inflammatory response, as evidenced by an elevated C-reactive protein (CRP) level or elevated interleukin-6 (IL-6) levels, are associated with a poor outcome in patients with many types of cancer, including hepatocellular carcinoma (HCC). In vol 134, issue 1 of the International Journal of Cancer, Ohishi *et al* have indicated that elevated serum IL-6 levels are associated with an increased HCC risk, independent of other established risk factors for HCC. They found that elevated serum IL-6 levels were associated with an increased risk of HCC, independent of HBV and HCV infection, alcohol consumption, smoking habit, BMI and radiation exposure. In subgroup analyses, they found an even stronger association between elevated serum IL-6 levels and an increased risk of HCC. The authors concluded that monitoring the serum IL-6 levels may be more useful for predicting subsequent HCC, especially among obese individuals with non-B, non-C liver disease. These findings would help clinicians to identify patients with NAFLD or NASH who potentially remain at high risk for the development of HCC.

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Key words: Hepatocellular carcinoma; Interleukin-6

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EDITORIAL

Rudolf Virchow noted a connection between cancer and inflammation in the 19th century, based on the observations that tumors often arose at the sites of chronic inflammation, and that inflammatory cells were present in biopsied tumor tissues. In the last decade, accumulating evidence has supported Virchow's hypothesis that cancer and inflammation are linked. It is estimated that underlying infections and inflammatory responses are linked to 15-20% of all deaths from cancer worldwide. These include the links between *H. pylori* and gastric cancer or MALT lymphoma, hepatitis virus and hepatocellular carcinoma (HCC), papillomavirus and cervical cancer and between autoimmune disease or inflammatory bowel disease and colon cancer^[1-3].

In the clinical setting, investigators have demonstrated that the presence of a systemic inflammatory response, as evidenced by an elevated C-reactive protein (CRP) level or elevated interleukin-6 (IL-6) levels, are associated with a poor outcome in patients with many types of cancer^[4-8].

With regard to HCC, elevated CRP levels or IL-6 levels were reported to be correlated with a poor prognosis in patients undergoing surgical resection^[9,10] or loco-regional therapy^[11,12].

Elevated CRP or IL-6 levels were also demonstrated to be associated with an increased risk of HCC in patients with diffuse type HCC^[13], chronic hepatitis B and chronic hepatitis C^[14,15]. Giannitrapani *et al*^[16] reported that the serum IL-6 levels were significantly higher in patients with HCC than those in healthy control group. Porta *et al*^[17] showed that IL-6 could be a promising tumor marker for HCC. Moreover, they showed that the diagnostic value of the IL-6 was significantly increased when combined with α -fetoprotein (AFP). Recently, Hammad *et al*^[18] indicated that the addition of IL-6, IL-17 and vitamin D to AFP could improve the prognostic ability in patients of HCC.

More recently, in vol 134, issue 1 of the International Journal of Cancer, Ohishi *et al*^[19] have indicated that elevated serum IL-6 levels are associated with an increased HCC risk, independent of other established risk factors for HCC. They investigated the association between the serum levels of CRP, IL-6 and the risk of HCC using sera collected from a prospective cohort study of atomic bomb survivors. In this nested case-control study, they found that elevated serum IL-6 levels were associated with an increased risk of HCC, independent of HBV and HCV infection, alcohol consumption, smoking habit, BMI and radiation exposure. The association of an elevated serum CRP level with an increased risk of HCC was only marginally significant. Moreover, they performed subgroup analyses to examine the association between IL-6 and the HCC risk in selected subgroups. Among obese subjects (BMI \geq 25), an even stronger association was observed between elevated serum IL-6 levels and an increased risk of HCC (all HCC; RR 3.09, non-B, non-C HCC; RR 5.01). Consequently, the authors concluded that monitoring the serum IL-6 levels in combination with established tumor markers, such as AFP or PIVKA-II, may be more useful for predicting subsequent HCC, especially among obese individuals with non-B, non-C liver disease^[19].

IL-6 is a pleiotropic inflammatory cytokine which plays an important role in regulating immune cell growth and differentiation. It is synthesized by many cell types, including T-cells, macrophages and stromal cells, in response to stimulation by tumor necrosis factor- α (TNF- α) and IL-1^[20]. The activation of the IL-6 complex activates Janus kinases (JAK) and signal transducers and activators of transcription (STATs), which regulate cell proliferation and apoptosis^[20].

With regard to HCC, Reichner *et al*^[21] demonstrated that the overexpression of IL-6 increased metastatic potential of rat HCC cells. Sakurai *et al*^[22] showed that the release of IL-1 α by necrotic hepatocytes promotes the production of IL-6, stimulates compensatory proliferation and increases hepatocarcinogenesis in the diethylnitrosamine mouse model. Meanwhile, Park *et al*^[23] demonstrated that the development of obesity-promoted HCC is dependent on the enhanced production of IL-6 and TNF via the activation of signal transducer and activator of transcription 3 (STAT3) in the diethylnitrosamine mouse model. Inhibition of STAT3 activity with several agents in HCC cells was showed to lead to the induction of apoptosis, reduction in colony-forming ability and enhanced chemosensitivity in HCC cells^[24-26]. These experimental studies support the findings by Ohishi *et al*.

The study by Ohishi *et al* indicates the role of IL-6 as a promising tumor marker for HCC, especially among obese subjects with non-B, non-C liver disease, such as non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH).

In conclusion, these findings would help clinicians to identify patients with NAFLD or NASH who potentially remain at high risk for the development of HCC.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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