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Higher Risk of Liver Cancer in People with Nonalcoholic Fatty Liver Disease Linked to High Blood Iron Levels

ALEXANDRIA, Va. – New research has found that patients with nonalcoholic fatty liver disease (NAFLD) who have high blood iron levels are at an elevated risk to develop the most common type of liver cancer, hepatocellular carcinoma (HCC). Researchers at the University of Pittsburgh will present their findings this week at The Liver Meeting Digital Experience™ held by the American Association for the Study of Liver Diseases.

Research has shown that elevated levels of iron in the blood from hereditary hemochromatosis, a disorder that causes the body to absorb too much iron, can raise the risk of HCC. However, there is little data on patients with NAFLD. HCC is a common liver condition that is estimated to affect about 25 percent of adults worldwide.

“NAFLD may contribute to the rising incidence of HCC in the U.S. However, only a small fraction of NAFLD patients eventually develop HCC. The liver is the primary reservoir of body iron. The iron overload can cause hepatotoxicity and liver damage,” said Jian-Min Yuan, MD, PhD, the senior author of the new study, the chair of cancer prevention at UPMC Hillman Cancer Center and a professor of epidemiology at the University of Pittsburgh School of Medicine. “A direct link between serum iron level and HCC risk would support a harmful role of iron elevation on HCC development in NAFLD patients.”

The researchers analyzed how elevated levels of any one of the four iron biomarkers was associated with HCC, with adjustments for age, sex, race, body mass index, type 2 diabetes history and smoking tobacco. They found that, compared with those who do not develop cancer, NALFD patients who developed HCC:

- Tend to be older, male and past or present smokers.
- Are more likely to have a history of type 2 diabetes and hypertension but lower levels of lipids.

Researchers also discovered that when it comes to links between HCC risk and iron levels in NAFLD patients:

- An elevated level of serum iron, or more than 175 mcg/dL, is associated with more than double the HCC risk of normal serum iron levels.
- A higher level of transferrin saturation, or more than 35 percent, was associated with a twofold increase in HCC risk compared with a normal transferrin saturation of 25–35 percent.

- There were no statistically significant associations between HCC risk and total iron-binding capacity.
- Elevated serum ferritin levels were not significantly associated with an increased cancer risk.

“Since HCC develops in only a small percentage of NAFLD patients, our findings — if confirmed in larger, prospective studies — may help identify patients at increased risk of developing HCC. Those patients could then be targeted for more intensive surveillance,” Yuan said. “However, since serum iron levels change constantly in response to physiologic needs, more research is needed to understand the clinical implications of persistence and magnitude of serum iron elevation, as well as the lack of association of ferritin levels with HCC risk in NAFLD patients.”

Yuan and his research team identified 47,165 patients ages 40–89 who were diagnosed with NAFLD between 2004 and 2018 using electronic health records at the University of Pittsburgh Medical Center. There were 18,569 patients who had at least one of the iron-related blood test results needed for the analysis: serum iron, transferrin saturation, total iron binding capacity or serum ferritin. After an average of 4.3 years of follow-up, 224 patients developed HCC.

Dr. Yuan’s poster entitled Elevated Serum Iron Levels Are Associated with Increased Risk of Hepatocellular Carcinoma Incidence Among Patients with Nonalcoholic Fatty Liver Disease (1048) can be viewed at The Liver Meeting Digital Experience™, Nov. 12–15, 2021. The corresponding abstract can be found in the journal HEPATOLOGY.

About AASLD
AASLD is the leading organization of clinicians and researchers committed to preventing and curing liver disease. The work of our members has laid the foundation for the development of drugs used to treat patients with viral hepatitis. Access to care and support of liver disease research are at the center of AASLD’s advocacy efforts.

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Abstract 1048: ELEVATED SERUM IRON LEVELS ARE ASSOCIATED WITH INCREASED RISK OF HEPATOCELLULAR CARCINOMA INCIDENCE AMONG PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE

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Abstract Text

Background: Iron overload due to hereditary hemochromatosis has been linked to the development of hepatocellular carcinoma (HCC) but epidemiological data on elevated iron levels in relation to the risk of developing HCC in patents with nonalcoholic fatty liver disease (NAFLD) are sparse. We determined the impact of iron indices on HCC risk in NAFLD.

Methods: We identified 47,970 patients diagnosed with NAFLD, ranging from 40-89 years of age, between 2004 and 2018 in the electronic health records (EHR) of a large US healthcare system. Among them, 19,051 had at least one measurement of serum iron, transferrin saturation, total iron binding capacity(TIBC) and serum ferritin eligible for the present analysis. After an average 4.35 years of follow-up, 192 patients developed HCC. Cox proportional hazard regression method was used to calculate hazard ratios (HRs) and the 95% confidence intervals (CIs) for HCC incidence associated with elevated levels of any one of the four iron biomarkers measured with adjustment for age, sex, race, body mass index, history of type 2 diabetes mellitus (T2DM) and tobacco smoking.

Results: NAFLD patients who developed HCC were older and more likely to be male, white, ever smokers, or having a history of T2DM, hyperlipidemia, or hypertension than NAFLD patients free of HCC (all Ps < 0.001). Compared with normal range of serum iron (75–175 mcg/dL), elevated level of serum iron (>175 mcg/dL) was associated with more than double the risk of HCC (HR = 2.44, 95% CI = 1.06-5.62) whereas reduced level of iron (< 0.001). Similarly, a higher level of transferrin saturation (>35%) was associated with a statistically significant 2-fold increased risk of HCC (HR = 2.18, 95% CI = 1.27–3.74) compared with the normal range of transferrin saturation (25-35%). There was no statistically significant association for TIBC or serum ferritin with HCC risk.

Conclusion: Elevated serum iron and transferrin saturation levels, but not ferritin levels, are significantly associated with increased risk of developing HCC in NAFLD patients. Given the potential prognostic and preventative implications of this finding, further research is warranted to study the association of iron indices on risk of developing HCC in NAFLD.