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Editorial

Hepatocellular Carcinoma – Is NAFLD Getting Stifled?

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Editorial

Hepatocellular Carcinoma (HCC) is the second leading cause of cancer death in the world among adult men. In recent years, the incidence of HCC has been escalating, especially in men [1] with a dismal 5-year survival rate at 17% [1]. The most commonly implicated risk factors are hepatitis B, hepatitis C and cirrhosis from alcohol abuse. A recently implicated but poorly understood risk factor is Nonalcoholic Fatty Liver Disease (NAFLD) and patients with NAFLD have hepatic steatosis with or without inflammation and fibrosis. Intriguingly, HCC has been shown to be the most common type of cancerin diabetics in one study [2]. The underlying pathogenesis of NAFLD is not yet clearly understood but the most commonly accepted hypothesis is insulin resistance leading to hepatic steatosis and possibly steatohepatitis [3].

Recently, Mittal et al published a retrospective cohort study in which they looked for the development of HCC without cirrhosis in veterans with NAFLD [4]. They reviewed records of 1500 veterans with verified HCC and then proceeded to classify them as those with evidence for no cirrhosis (level 1 and 2) and those with confirmed cirrhosis. Around the same time, Piscaglia et al in Italy published a prospective observational study in which they intended to assess the clinical patterns of HCC in NAFLD [5]. They followed 756 patients with either NAFLD or HCV related chronic liver disease that had HCC.

The VA study demonstrated that 194 of the 1500 patients had evidence for no cirrhosis. Interestingly, among patients with NAFLD-related HCC, 34.6% had no evidence for cirrhosis and in those patients with HCC and metabolic syndrome as the only risk factor, 32.7% patients had no evidence for cirrhosis. This is in stark contrast to viral and alcohol as risk factors where majority of patients has underlying cirrhosis at the time of diagnosis of HCC. HCC patients were likely to be older compared to those with confirmed cirrhosis with a mean age 65.5 for those with level 1 evidence of no cirrhosis and 69.7 for those with level 2 evidence of no cirrhosis and 62.6 for those with confirmed cirrhosis (p value < 0.01). At the time of diagnosis, patients with no evidence of cirrhosis were likely to have Barcelona Clinic Liver Cancer (BCLC) stage B as compared to HCC with cirrhosis (stage C Vs D). The results of the Italian study were comparable with 46.2% of patients with NAFLD-related HCC without cirrhosis as compared to 97.2% in HCV-related HCC. However, patients in this study with NAFLD-related HCC were significantly younger than patients with HCV-related HCC. Their results also showed that NAFLD patients were more likely to have advanced stage HCC with BCLC stage C compared to HCV-related HCC. Consequently, survival was significantly shorter in patients with NAFLD-HCC in HCV-HCC but seemed comparable when confounding factors were eliminated and patients were matched for tumor stage.

These studies spark interest in a recently recognized risk factor of HCC. In 2012 Rahman et al identified NAFLD without cirrhosis as a risk factor for HCC in a review of SEER (Surveillance, epidemiology and end results) database [6]. Patients with NAFLD have a more than 5-fold risk (OR 5.4; 95% CI, 3.4-8.5) of having HCC in the absence of cirrhosis than patients with HCV related HCC. HCC appeared to be common in males in both the studies consistent with prior studies defining a 2:1 risk. These studies combined both invasive and validated non-invasive method to diagnose cirrhosis in patients. More recently Ma et al identified loss of CD4+ T cell population as a risk factor for NAFLD associated HCC. In vitro and animal studies revealed increased linoleic acid exposure led to mitochondrial generation of reactive oxygen species (ROS) and apoptosis of CD4T+ cell population [7].

Several questions are generated need further research. Do we need to redefine HCC screening strategies with this new information? What are the at-risk groups within the NAFLD population? Do statins or metformin have a role in prevention of HCC in this population would also remain to be seen. These studies trigger key questions into oncogenesis with further studies warranted to identify intervention points and prevention strategies.

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