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Nonalcoholic steatohepatitis and hepatocellular carcinoma- beyond the boundaries of liver

Gupta T. NASH and HCC- beyond liver

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Abstract

The burden of non-alcoholic steatohepatitis (NASH) related hepatocellular carcinoma (HCC) is drawing attention due to emerging epidemic of obesity and metabolic syndrome and is expected to increase in near future. The antidiabetic medications, air pollutants, newer genetic mutations are latest concerns as risk factors for HCC development in patients with NASH. Though molecular signatures are very accurate, but they are not cost effective and due to logistic issues cannot be applied in larger population. We need multicentric longitudinal studies including diverse geographical areas to evaluate complex interplay of different risk factors and genetics in these patients.

Key Words: Non-alcoholic steatohepatitis; Hepatocellular carcinoma; Cirrhosis; Genetic factors; Lifestyle factors; Surveillance

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Core Tip: Nonalcoholic steatohepatitis is a metabolic liver disease which also involves multiple organs like heart, lungs, and kidneys, *etc.* Non-alcoholic steatohepatitis (NASH) may arise primarily followed by other organs or it may come late in the course of metabolic syndrome. The multidisciplinary approach is needed towards a patient with diabetes, obesity and metabolic syndrome to address all issues related to liver and heart, *etc.* Genetic and molecular signatures have provided a ray of hope for estimating

risk in these patients; however, it has many practical issues. The impact of environmental pollutants and toxins as a causative factor in NASH especially lean patient population should also be considered. We need population based studies from different geographical areas for estimation of metabolic, environmental and genetic risk factors.

TO THE EDITOR

Chrysavgis *et al*[1] have extensively reviewed the literature in non-alcoholic steatohepatitis (NASH) related hepatocellular carcinoma (HCC); its risk stratification, screening and surveillance strategies. Metabolic syndrome is a systemic disease involving heart, kidneys, lungs, and liver, *etc.* NASH is liver manifestation of metabolic syndrome. With emerging epidemic of obesity, metabolic syndrome, NASH is expected to supersede all other etiologies of liver cirrhosis as well as HCC. In various studies as discussed by Chrysavgis *et al*[1], the prevalence of HCC in non-cirrhotic non-alcoholic fatty liver disease (NAFLD) patients ranges from 15%-55%. Factors like age, male sex, concomitant smoking and alcohol intake, obesity, type 2 diabetes mellitus have shown to increase risk of HCC in non-cirrhotic NASH. Recently, use of insulin and sulfonylureas have also been shown to increase long term risk of HCC in patients of diabetes. In an Italian study[2], increased HCC risk with odds ratio of 3.7 for insulin, 1.3 for sulfonylureas and 2.1 for repaglinide was found in patients of diabetes. Even duration of treatment increased the risk for insulin but not for other therapies. The same has also been confirmed in a nationwide nested case control Korean study[3] which showed increased HCC risk with glimepiride instead of other sulfonylureas. And yet we do not have long term data for GLP-1 agonists and DPP4 inhibitors. Chinese data[4] recently showed increased association of air pollutants of particulate matter (PM) with aerodynamic diameter size PM_1, $PM_{2.5}$, PM_{10} with metabolic associated fatty liver disease. The role of intestinal dysbiosis has also been investigated in animal models and found to be associated with increased risk of NASH and HCC.

In a multicentric trial, Pinyol *et al*[5] collected samples from NASH-HCC and NASH patients and performed expression array and whole exome sequencing and compared it with HCC from non-NASH etiologies like viral/alcohol. They found *TERT* promoter, *CTNNB1*, *TP53* and *ACVR2A* most frequently to be present in NASH-HCC patients. The ACVR2A (activin type 2 receptor gene) mutation was found in higher number of patients in NASH-HCC as compared to HCC of other etiologies. The molecular signature revealed higher expression for bile acid and fatty acid signalling pathways. The Wnt/TGF-βproliferation subclass was more common in NASH-HCC. The upcoming data suggests that the molecular signature of NASH-HCC is different from HCC due to other etiologies. Collectively, NAFLD-HCC is a complex interplay of multiple factors related to unhealthy life style, environment and genetics of an individual.

The authors have included abbreviated magnetic resonance imaging (MRI) in their suggested algorithm of HCC surveillance in NAFLD due to poor window of ultrasound in obese patients. We have concerns regarding this strategy. First, large number of individuals would need surveillance, so its cost effectiveness, availability on large scale and practicality needs to be addressed; secondly, how frequently MRI would have to be repeated, this is a practical issue; thirdly, when during the clinical course of NASH, screening should be performed. Though authors have included HCC risk model as suggested by Ioannou *et al*[6] in their algorithm however, we believe that future prospective longitudinal studies are needed to determine weightage of different risk factors in determining HCC risk in patients with cirrhotic and non-cirrhotic NAFLD separately. The role of extracellular vehicles (EVs) for molecular characterization of HCC in patients of NASH may further be evaluated for HCC surveillance also. NALFD is a risk factor not only for HCC but also for colorectal and breast cancer. Instead of screening for each carcinoma separately, we need to have studies on a common platform targeting the molecular signatures in blood for surveillance of different carcinomas in body which share the pathogenetic mechanisms or pathways. The challenges involved are large population-based studies in different geographical

regions, mapping of molecular signatures and implementation. It has to be cost effective, easily accessible and readily available.

In patients of NAFLD, all-cause mortality includes mortality related to liver, heart, kidneys, and lungs, *etc.* It is time to recognise the need for multidisciplinary approach towards a patient with diabetes, obesity and metabolic syndrome to address all issues related to liver, heart, and kidneys, *etc*. Large prospective, multicentric studies including diverse geographical regions and dietary habits are needed to evaluate for risk stratification in these patients regarding need for HCC surveillance.

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