EBioMedicine 74 (2021) 103711

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Cancer surveillance in non-alcoholic fatty liver disease: A potential role for lipidomics

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ARTICLE INFO

Article History:
Received 8 November 2021
Accepted 8 November 2021

Within the past two decades, non-alcoholic fatty liver disease (NAFLD) emerged as the most prevalent chronic liver disease in western civilizations. Concerningly, this trend could recently be observed globally, especially in high-income Asia Pacific, East Asia, Latin, and Central America. Accordingly, the incidence of NAFLD-associated hepatocellular cancer (HCC) is increasing dramatically, progressively replacing other etiologies (i.e. viral hepatitis, alcoholic liver disease) and revealing the need for sufficient screening methods [1]. To date, ultrasound screening and available tumour markers are of limited sensitivity and accuracy. Especially concerning is the observation that HCC may arise in non-cirrhotic NAFLD patients, which is not considered in the current screening recommendations. The main limitation of ultrasound as a screening method for HCC is the reduced sensitivity in a predominantly obese population.

The current guidelines of the American Association for the Study of Liver Diseases (AASLD) recommend bi-annual HCC screening in patients with cirrhosis via ultrasound with or without alpha-fetoprotein (AFP) as a tumour marker [2]. Despite the evident limitations of ultrasound surveillance for the detection of early HCC lesions, additional determination of AFP is not recommended in most international guidelines due to limited sensitivity and specificity. A recent multicentric trial characterizing the utility of additional AFP determination complementary to ultrasound could clearly demonstrate an increase from 45% sensitivity in HCC early detection in ultrasound alone versus 63% for the combination of ultrasound and AFP [3]. Further modifications have been implied to utilize additional clinical features and alternative tumour markers including AFP-L3 and des-gamma carboxyprothrombin (DCP). The GALAD score (gender, age, AFP-L3, AFP, DCP) has therefore been validated in patients with NAFLD with and without cirrhosis and was found to accurately detect HCC in these individuals [4]. Another analysis conducted by Yang et al. characterized the combination of GALAD score and ultrasound vs ultrasound alone. The performance of the GALAD score was superior to ultrasound for HCC detection. The GALADUS score further enhanced the performance of the GALAD score resulting in an AUC of 0.98 (95% CI, 0.96-0.99; cutoff -0.18, sensitivity 95%, specificity 91%) [5]. While these novel scores are offering promising new paths in cancer surveillance, to date, many aspects of HCC biology and NAFLD pathophysiology have not yet been clinically evaluated for tumour detection.

We and others have previously shown that individuals with NAFLD-associated HCC display a unique microbiota composition and metabolic profile. Alterations in the gut microbiome and bile acid metabolism have been identified to be specifically associated with the stage of fibrosis and the presence of tumour in NAFLD [6]. Similarly, specific lipidomic profiles have been identified for NAFLD and its progression from non-alcoholic steatohepatitis (NASH) [7]. Addressing a potential biological function of specific lipids, Han et al. identified a hepatoprotective role of gut-derived high-density protein [8]. Lipidomics derived from plasma exosomes has recently been utilized to identify specific lipid profiles, including glycerophospholipids in patients with HCC and cirrhosis [9]. While many studies underscore the potential of lipidomics in diagnostics of NAFLD and HCC, a critical evaluation of these mechanisms as potential biomarkers in NAFLD-associated HCC is lacking.

In a recent study published in EBioMedicine by Lewinska et al., serum lipidome alterations in NAFLD and HCC have been investigated [10]. Here, lipidomics has been performed in a cohort of 249 patients with NAFLD and utilized to design a novel diagnostic score for the detection of HCC. The identified lipidome was found to be unique for NAFLD-HCC compared to other etiologies and individuals without cancer. Compared to AFP, this score was superior in detecting HCC in NAFLD patients. Metabolic alterations included upregulation of fatty acid transporters in HCC tissue and depletion of unsaturated fatty acids and acylcarnitines and represent a link between tumour biology, metabolism, and tumourigenesis. This model might easily be implied in routine diagnostics and serve as a useful addition to the available screening panel in the growing population of individuals with NAFLD upon further validation.

Contributors

Both authors were equally involved in literature search, design and writing of this commentary.

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2021.103661.

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https://doi.org/10.1016/j.ebiom.2021.103711

Declaration of Competing Interest

The authors have nothing to disclose.

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