Editorial

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NAFLD and cancer: More cause for concern?

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Non-alcoholic fatty liver disease (NAFLD) is likely to become the most prevalent liver disease in many countries,[1,2] yet clinicians are struggling to determine exactly *why* they should care about NAFLD. Is it merely a bystander – a manifestation of the metabolic syndrome resulting in cardiovascular disease – or is it a liver disease in its own right?[3]

In their cohort study from the Republic of Korea, Kim *et al.* present convincing data that patients with NAFLD, without cirrhosis, have a substantially (over 15-fold) higher incidence of hepatocellular carcinoma (HCC); that men with NAFLD have a 2-fold higher incidence of colorectal cancer; and that women with NAFLD have a 1.9-fold higher incidence of breast cancer.[4] These estimates were based on 14 incident cases of HCC, 76 incident cases of colorectal cancer, and 91 incident cases of breast cancer.

The study was based on a cohort of 25,947 subjects who had a health check-up in a tertiary hospital in Korea between September 2004 and December 2005, and were followed-up to the end of 2015. Therefore, it includes a comparable reference population, since diagnostic ascertainment was similar in the entire cohort, unlike earlier studies which used general population controls.[5] Moreover, participants with or without NAFLD were likely comparable with respect to several characteristics, such as job situation, socioeconomic status, and environmental exposures. All participants went through the same examinations for liver conditions. As many as 33.6% of the participants had NAFLD, and these NAFLD patients also had a higher body mass index, fasting glucose, LDL cholesterol, and triglyceride, as well as a higher prevalence of hypertension and diabetes, highlighting the fact that NAFLD is a manifestation of the metabolic syndrome.

These syndromic characteristics call into question whether NAFLD *caused* cancer development, or if cancer development was a result of the metabolic syndrome. When Kim *et al.* controlled for confounding by age, gender, smoking status, diabetes, hypertension, GGT, LDL cholesterol, HDL cholesterol, and triglycerides, the hazard ratio for HCC for patients with *vs.* without NAFLD fell from 25 to 17. Surprisingly, the same effect reduction was seen when they controlled for gender and age alone. In any case, an over 15-fold excess rate of HCC (and a lower confidence limit >2) indicates that NAFLD has a direct, causal effect on liver cancer, likely and largely due to its inflammatory status in the liver tissue. This conclusion is supported by the fact that the effects of diabetes, obesity, and hypertension – with relative risks in the order of two to four[6–9] – are too weak to fully explain the strong association between NAFLD and HCC. In short, there are systemic mechanisms related to the metabolic syndrome, which partly account for the huge increase in liver cancer risk among patients with NAFLD, but the key mechanism remains the inflammatory status induced by NAFLD on the liver. Thus, the relation between NAFLD and HCC can be considered causal, although given the wide confidence interval (CI) from 2 to over 100 – it remains poorly quantified.

Inference on the twofold excess rates of male colorectal and female breast cancer is more difficult. Colorectal cancer is related to diabetes, abdominal obesity (more common in men than in women), and hence to the metabolic syndrome.[10–12] Consequently, after confounder adjustment the hazard ratio for colorectal cancer for both sexes combined decreased from 2.04 to 1.45. This leaves open the issue that confounding from components of the metabolic syndrome could explain the association between NAFLD and colorectal cancer. In addition, the absence of association in women (the hazard ratio was 0.63 in females, based on 23 cases *vs.* 53 in males), and hence the lack of significant association between NAFLD and colorectal cancer in both sexes combined (HR 1.45, 95% CI 0.88–2.38) leaves any inference on causality open to discussion.

In contrast, adjustment for components of the metabolic syndrome had little effect on the hazard ratio estimates for breast cancer. This is expected, since diabetes has a limited, or no, effect on breast cancer development, and the key component of the metabolic syndrome associated with breast cancer is being overweight in post-menopause.[13,14] In stratified analyses, the association of NAFLD with breast cancer was restricted to non-obese women (BMI <25 kg/m^2). Kim *et al.* argue that, in those women, NAFLD has the same carcinogenic effect as obesity. That might be true, and can be tested. Presently, it remains uncertain whether NAFLD is a distinct cause of breast cancer.

Kim *et al.* used ultrasound to diagnose NAFLD. This adds validity to their report and is consistent with European Association for the Study of the Liver (EASL) clinical practice guidelines,[15] which further recommend that patients with abnormal liver enzymes and/or medium or high risk of fibrosis, according to the NAFLD fibrosis score or fibrosis-4 scores, should be referred to a specialist for a full workup. Kim *et al.* did find that,

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among patients with NAFLD, those with the higher fibrosis scores had a higher incidence of HCC, but not a significantly increased incidence of colorectal or breast cancer. Similarly, moderate to severe steatosis detected on ultrasound was directly related to the development of HCC only. While confirming the association and the pathogenic mechanism of NAFLD with HCC, the lack of a dose-effect relationship between markers of disease severity and rates of breast and colorectal cancer casts additional doubt on the causal effect of NAFLD on these cancer sites. It would have been a helpful addition to the paper if Kim *et al.* had compared the three groups defined by the EASL guidelines: i) abnormal liver enzymes, or steatosis and medium/high fibrosis score; ii) steatosis, normal liver enzymes, and low fibrosis score; and iii) no steatosis and normal liver enzymes. Such an analysis could have validated the diagnostic flowchart presented in the EASL guidelines.[15]

Should we screen patients with NAFLD for HCC? Well, we do not have to understand exactly what causes HCC in patients with NAFLD, as long as they are at increased risk, which they certainly are. Still the answer is undefined, given the current body of evidence, and this is consistent with current EASL and American Association for the Study of Liver Diseases guidelines.[15,16] Randomized controlled trials are necessary to determine whether screening reduces mortality in patients with NAFLD.

What is the risk of HCC in patients with NAFLD? The analysis gives the incidence rate of HCC among subjects with NAFLD (23 per 100,000 person-years), and among those without NAFLD (0.9 per 100,000 person-years). The very large confidence interval around the corresponding incidence rate ratio reflects the low number of HCC cases in the cohort (14 in the NAFLD and no NAFLD groups combined). In addition, it is impossible to estimate the risk of HCC without knowing the rate of death without HCC, the competing outcome in Kim *et al.*'s analyses.[17] It is possible, likely in fact, that Kim *et al.*'s patients with NAFLD have a higher rate of death without HCC than their non-NAFLD counterparts because of their higher prevalence of smoking, diabetes, high LDL cholesterol, *etc.* If so, the higher *rates* of colorectal cancer and breast cancer in NAFLD patients might not result in higher *risks* of those cancers.[18] For HCC, the difference in rates is so great that the absolute risk of HCC is likely be greater, too. However, it would have strengthened Kim *et al.*'s study considerably to have data on mortality without cancer.

Thus, it is now clear that patients with NAFLD have an increased risk of HCC, but their relative and absolute risk remains imprecisely quantified. It is unclear whether NAFLD increases the risk of colorectal cancer among men, and even less clear whether it increases the risk of breast cancer among women. Having more detailed patient data, such as data from liver biopsies, would have been helpful for narrowing down the subset of NAFLD patients who are at the greatest risk of developing HCC, and for clarifying the associations between NAFLD and colorectal and breast cancer. It would also have been helpful to supplement the baseline characteristics with data demonstrating how those characteristics changed during the follow-up. Importantly, despite the strong association between NAFLD and HCC development, it is unclear whether we should offer HCC surveillance to patients with NAFLD – a randomized trial should be conducted first.

Still, despite several open issues, the Korean cohort study by Kim *et al.* (1) provides relevant and valid information on the association between NAFLD and cancer risk, and evidence of its strong association with HCC. This may well become more relevant as a major cause of HCC in the future, considering our increasing control of HBV and HCV infections (*i.e.* the historic major causes of HCC) on a global population level.[19,20]

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Authors' contributions

PJ drafted the manuscript. All authors revised the manuscript for important intellectual content and approved the final manuscript.

References

[1] Armstrong MJ, Houlihan DD, Bentham L, Shaw JC, Cramb R, Olliff S, et al. Presence and severity of non-alcoholic fatty liver disease in a large prospective primary care cohort. J Hepatol 2012;56:234–240.
[2] Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: Trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2017. https://doi.org/10.1038/nrgastro.2017.109.
[3] Byrne CD, Targher G. NAFLD: A multisystem disease. J Hepatol 2015;62:S47–S64.
[4] Kim G-A, Lee HC, Choe J, Kim M-J, Lee MJ, Chang H-S, et al. Association between nonalcoholic fatty liver disease and cancer incidence rate. J Hepatol 2018;68:140–146.
[5] Sørensen HT, Mellemkjær L, Jepsen P, Thulstrup AM, Baron J, Olsen JH, et al. Risk of cancer in patients hospitalized with fatty liver: A Danish cohort study. J Clin Gastroenterol 2003;36:356–359.
[6] Turati F, Talamini R, Pelucchi C, Polesel J, Franceschi S, Crispo A, et al. Metabolic syndrome and hepatocellular carcinoma risk. Br J Cancer 2013;108:222–228.
[7] Welzel TM, Graubard BI, Zeuzem S, El-Serag HB, Davila JA, McGlynn KA. Metabolic syndrome increases the risk of primary liver cancer in the United States: A study in the SEER-Medicare database. Hepatology 2011;54:463–471.
[8] Larsson SC, Wolk A. Overweight, obesity and risk of liver cancer: A meta-analysis of cohort studies. Br J Cancer 2007;97:1005–1008.
[9] El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: A systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol 2006;4:369–380.
[10] La Vecchia C, Negri E, Decarli A, Franceschi S. Diabetes mellitus and the risk of primary liver cancer. Int J Cancer 1997;73:204–207.
[11] Pelucchi C, Negri E, Talamini R, Levi F, Giacosa A, Crispo A, et al. Metabolic syndrome is associated with colorectal cancer in men. Eur J Cancer 2010;46:1866–1872.
[12] Rosato V, Tavani A, Gracia-Lavedan E, Guino E, Castano-Vinyals G, Villanueva CM, et al. Type 2 diabetes, antidiabetic medications, and colorectal cancer risk: Two case-control studies from Italy and Spain. Front Oncol 2016;6:210.
[13] la Vecchia C, Giordano SH, Hortobagyi GN, Chabner B. Overweight, obesity, diabetes, and risk of breast cancer: Interlocking pieces of the puzzle. Oncologist 2011;16:726–729.
[14] Rosato V, Bosetti C, Talamini R, Levi F, Montella M, Giacosa A, et al. Metabolic syndrome and the risk of breast cancer in postmenopausal women. Ann Oncol 2011;22:2687–2692.
[15] European Association for the Study of the LiverEuropean Association for the Study of DiabetesEuropean Association for the Study of Obesity. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388–1402.
[16] Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease:

Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2017. https://doi.org/10.1002/hep.29367.
[17] Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: Possibilities and pitfalls. Int J Epidemiol 2012;41:861–870.
[18] Jepsen P, Vilstrup H, Andersen PK. The clinical course of cirrhosis: The importance of multistate models and competing risks analysis. Hepatology 2015;62:292–302.
[19] Bosetti C, Turati F, La Vecchia C. Hepatocellular carcinoma epidemiology. Best Pract Res Clin Gastroenterol 2014;28:753–770.
[20] Dyson J, Jaques B, Chattopadyhay D, Lochan R, Graham J, Das D, et al. Hepatocellular cancer: The impact of obesity, type 2 diabetes and a multidisciplinary team. J Hepatol 2014;60:110–117.