Editorial

Eat more natural dietary fiber and whole grains to minimize liver disease risk

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Nutritional habits in the United States have dramatically changed since the Industrial Revolution in the 18th century. However, not every 'advancement' from then to now has improved human dietary habits and health. This is evident from the rising epidemic of nutritional insufficiencies associated with the increasing prevalence of age-related diseases (1). Work from Dennis Burkett in the late 1960s was one of the first to hypothesize that refinement of grains and removal of dietary fiber could explain the regional dichotomy in disease incidence (2). Accordingly, several studies in the past 10 years have connected the inverse association between low intake of whole grain/fiber and high risk for hepatic diseases, including the most prevalent type of liver cancer, hepatocellular carcinoma (HCC) (3,4). These cohorts suggested that whole grain and fiber from cereal, but neither fruits nor vegetables, could provide the potential beneficial effects against HCC.

A recent and elegant 2021 study by Liu *et al.* complements and goes beyond these prior studies when evaluating the intake of whole grains and dietary fiber with liver cancer risk (5). Using the largest cohort to date, the authors found congruent observation that high intake of whole grains and total fiber provided a significant 22% and 31% decreased risk for HCC, respectively. Additional analysis indicated vegetables (35%) and grains (22%), but neither beans (11%) nor fruits (6%), were the best dietary fiber sources for reducing HCC risk. This observation does correlate with prior studies that fiber from fruits perhaps do not provide protection, but the current study redefines vegetables as a potential good fiber source to mitigate HCC risk.

Notably, there is a commonality between 'vegetables and grains' *vs.* 'beans and fruits'. The former sources are primarily composed of insoluble fiber whereas the latter sources mostly contain soluble fiber. Comparatively, soluble fibers are sensitive toward bacterial fermentation by the human gut microbiota, whereas insoluble fibers are resistant. With accelerating evidence of the gut microbiome and their bacterial metabolites in liver oncogenesis (6), it could be theorized that insoluble fibers may not have HCC protective properties. Rather, their inability to be metabolized by the gut microbiota limits the level of bacterial-derived metabolites that could travel from the intestine to liver and trigger tumor formation.

If this speculation on insoluble fibers is true, then this would raise a cautious discussion about the carcinogenic potential of soluble fibers via their fermentation byproducts (i.e., short chain fatty acids, SCFA). Reflecting on the Liu *et al.* study, there was no indication for soluble fibers to be tumorigenic because high fruit or bean intake did not increase HCC risk. Interestingly, a recent report highlights that fecal samples from HCC patients had significantly reduced SCFA, including butyrate, acetate, and propionate (7), but it was not clear if this would be due to low production (i.e., less fiber intake or fewer bacterial fermenters) or high absorption into enterohepatic circulation. If considering the latter possibility, the SCFA profile becomes relevant because of the stratified pro- and anti-tumorigenic potential reported for each SCFA (8-10).

This leads to discussion about total *vs.* type of soluble fiber and their associated SCFA production ratio. Soluble

fibers include inulin, pectin, β-glucans, and others where each are varied in concentration depending on the plant source. For instance, inulin is heavily present in beets and chicory root, pectin is abundant in fruits, berries, and seeds, and β-glucans is plentiful in fruits, beans, and oats. Based on their chemical structure difference, each soluble fiber is metabolized differently by distinct bacteria, and this results in various ratios of SCFA production. Inulin primarily produces butyrate, pectin is dominant toward acetate and butyrate, and β-glucans favor propionate and butyrate. The association of high total fiber intake and low HCC risk in the study by Liu *et al.* is of importance, but future research should conduct additional analysis and predictive modeling to whether the type of soluble fiber and their resulting SCFA distribution contributes to liver cancer risk in humans.

As different bacteria are responsible for butyrate, acetate, and propionate production, it is also plausible that perhaps pre-HCC patients, at least a subset, were 'predisposed' with an altered gut microbiota composition (i.e., dysbiosis) and had subsequent different fermentation capabilities that may have correlated to liver cancer risk. In perspective of this idea, our group has found alarming evidence in mice with gut microbiota dysbiosis that feeding an inulin-enriched diet favors tumor-promoting bacteria and it induced HCC, possibly through the high butyrate levels (11). This could suggest soluble fibers as nutritional liver cancer agents in the vulnerable population with gut microbiota dysbiosis. While our mouse results are preliminary, this does stipulate that more investigation is required to understand the role of dietary soluble fibers in liver cancer risk for humans.

Besides the type of dietary fiber, its manufacturing source i.e., whole (*aka* unprocessed) *vs.* refined (*aka* highly processed) is of major relevance. There is recent evidence that, when compared to whole plant-based sources, refined fiber and grains are high on the dietary inflammatory index and have an inverse association with HCC (12,13). The Liu *et al.* study analyzed primarily natural fiber from fruits and beans consumed by the participants. Future cohort studies should incorporate whole and refined foods as independent and interactive variables in their study design.

In addition to HCC, Liu *et al.* assessed the risk of intrahepatic cholangiocarcinoma (ICC, ~10–15% of liver cancer cases) with whole grain and fiber intake. Interestingly, ICC incidence was not influenced by the amount of whole grain and fiber in the diet, but future studies are certainly warranted to confirm these novel findings. It is possible that the distinction of these nutrients toward ICC risk, when compared to HCC, is based on tumor locality and the associated exposure rate to host and gut microbiota derived metabolites and their co-metabolites. Liver hepatocytes are the first to be hit with everything absorbed in the small intestine via venous blood from the portal vein. As such, compositional diversity in the human diet or lack thereof can dictate the possible production of anti-tumorigenic or pro-carcinogenic gut metabolites and thus, regulate HCC progression. The biliary tract where ICC develops, on the other hand, does not have direct contact with intestinal metabolites except for gut microbiota derived secondary bile acids that are secreted from hepatocytes to bile ducts; these metabolites have been reported to promote ICC growth (14).

Another new element to the Liu *et al.* study is the correlation between whole grain and fiber intake with chronic liver disease (CLD) mortality (i.e., fibrosis, cirrhosis, alcoholic liver diseases, and chronic hepatitis). Both whole grains and total fiber had an impressive reduction in CLD mortality by 56% and 63%, respectively. For the studied fiber sources, while fruits still showed no benefit, beans (33%) showed significant mitigation in CLD mortality alongside vegetables (45%) and grains (71%). As beans could provide protection against CLD mortality, this indicates that the soluble fiber in fruits may have some benefits, but there may be an unknown mechanism(s) to why it's not observed. Other ingredients in fruits like fructose are becoming more recognized for their pro-tumorigenic effects including in HCC (15). There might be a mechanism for which the high fructose content in fruits counteracts the benefits of soluble fiber.

The overall merits in the Liu *et al.* report is high and support the concept of HCC preventative care by means of nutritional adaptation i.e., more whole grains and dietary fiber. It would have been informative if this study also investigated the interaction of coffee with whole grains and fiber on HCC risk. Coffee is implicated to have similar benefits seen with vegetables such as activating antioxidants and probably detoxification responses by phenolic phytoceuticals. A recent report found that consumption of more than three cups of coffee per day lowered the risk of HCC (16). Of note, the Mediterranean diet is designed to provide high quantities of whole grains, dietary fiber, and polyphenols, which is associated with alleviation of non-alcoholic fatty liver disease (17). Additional investigation should explore its potential benefits against HCC. It is idealistic for future cohort studies to also consider the interaction of multiple food groups besides isolating the

individual role of one or two nutrient components that only account for a portion of the whole diet.

As the United States is becoming more malnourished with the steady decline of whole grain and fiber intake, these critical nutritional biofactors need to be properly incorporated back into the diet. The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) recommends a high dietary diversity score in terms of incorporating various non-starchy vegetables and fruits daily (18). They also propose to consume at least five servings or the equivalency of around 40 g/day of total fiber from vegetables and fruits, which is close to what Burkett advocated for >50 g/day of dietary fiber (2). Assessment herein suggests that high quantity is not the only factor to consider, where additionally the fiber type and the source between whole *vs.* refined is relevant for quality. The goal is to have a high dietary diverse score with a low inflammatory index that can collectively provide the lowest probability in developing age-related diseases, including liver cancer.

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Footnote

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References

1. Frank J, Kisters K, Stirban OA, et al. The role of biofactors in the prevention and treatment of age-related diseases. Biofactors 2021;47:522-50.
2. O'Keefe SJ. The association between dietary fibre deficiency and high-income lifestyle-associated diseases: Burkitt's hypothesis revisited. Lancet Gastroenterol Hepatol 2019;4:984-96.
3. Yang W, Ma Y, Liu Y, et al. Association of Intake of Whole Grains and Dietary Fiber With Risk of Hepatocellular Carcinoma in US Adults. JAMA Oncol 2019;5:879-86.
4. Bradbury KE, Appleby PN, Key TJ. Fruit, vegetable, and fiber intake in relation to cancer risk: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC). Am J Clin Nutr 2014;100 Suppl 1:394S-8S.
5. Liu X, Yang W, Petrick JL, et al. Higher intake of whole grains and dietary fiber are associated with lower risk of liver cancer and chronic liver disease mortality. Nat Commun 2021;12:6388.
6. Yu LX, Schwabe RF. The gut microbiome and liver cancer: mechanisms and clinical translation. Nat Rev Gastroenterol Hepatol 2017;14:527-39.
7. Zhang J, Yang S, Wang J, et al. Integrated LC-MS metabolomics with dual derivatization for quantification of FFAs in fecal samples of hepatocellular carcinoma patients. J Lipid Res 2021;62:100143.
8. Ogawa K, Yasumura S, Atarashi Y, et al. Sodium butyrate enhances Fas-mediated apoptosis of human hepatoma cells. J Hepatol 2004;40:278-84.
9. Bindels LB, Porporato P, Dewulf EM, et al. Gut microbiota-derived propionate reduces cancer cell proliferation in the liver. Br J Cancer 2012;107:1337-44.
10. Björnson E, Mukhopadhyay B, Asplund A, et al. Stratification of Hepatocellular Carcinoma Patients Based on Acetate Utilization. Cell Rep 2015;13:2014-26.
11. Singh V, Yeoh BS, Chassaing B, et al. Dysregulated Microbial Fermentation of Soluble Fiber Induces Cholestatic Liver Cancer. Cell 2018;175:679-94.e22.

12. Liu Y, Yang W, VoPham T, et al. Plant-Based and Animal-Based Low-Carbohydrate Diets and Risk of Hepatocellular Carcinoma Among US Men and Women. Hepatology 2021;73:175-85.
13. Wang XY, Fang AP, Chen PY, et al. High dietary inflammatory index scores are associated with an elevated risk of hepatocellular carcinoma in a case-control study. Food Funct 2018;9:5832-42.
14. Amonyingcharoen S, Suriyo T, Thiantanawat A, et al. Taurolithocholic acid promotes intrahepatic cholangiocarcinoma cell growth via muscarinic acetylcholine receptor and EGFR/ERK1/2 signaling pathway. Int J Oncol 2015;46:2317-26.
15. Ozawa T, Maehara N, Kai T, et al. Dietary fructose-induced hepatocellular carcinoma development manifested in mice lacking apoptosis inhibitor of macrophage (AIM). Genes Cells 2016;21:1320-32.
16. Petrick JL, Freedman ND, Graubard BI, et al. Coffee Consumption and Risk of Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma by Sex: The Liver Cancer Pooling Project. Cancer Epidemiol Biomarkers Prev 2015;24:1398-406.
17. Godos J, Federico A, Dallio M, et al. Mediterranean diet and nonalcoholic fatty liver disease: molecular mechanisms of protection. Int J Food Sci Nutr 2017;68:18-27.
18. Norat T, Aune D, Chan D, et al. Fruits and vegetables: updating the epidemiologic evidence for the WCRF/AICR lifestyle recommendations for cancer prevention. Cancer Treat Res 2014;159:35-50.

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