Response to: Perspective of the risk and molecular mechanisms of hepatocellular carcinoma after HCV eradication in the post-DAA era

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We thank Drs. Yu and Gal-Tanamy for their insightful comments regarding the challenges of surveillance for hepatocellular cancer (HCC) after successful treatment for hepatitis C (HCV) (1, 2). As they note, there are challenges at multiple levels that must be addressed to ensure that at-risk patients have access to screening tests. These complex challenges are multifactorial and include worldwide variability in access to health system resources according to economic status, patient barriers such as inability to access surveillance programs, lack of knowledge of the implications, and provider barriers(3). The widespread availability of direct-acting antiviral agents (DAAs) has dramatically simplified therapy compared to interferon-based therapies. While marginalized patients now have access to highly effective DAA therapies, additional measures will be required to ensure that appropriate post-sustained response (SVR) follow-up is implemented and stratified according to available resources.

Screening for hepatocellular carcinoma is primarily done through ultrasound imaging, however, ultrasound has suboptimal sensitivity for early-stage hepatocellular carcinoma detection(4). Moreover, non-viral liver disease is associated with poor visualization of the liver and lowers sensitivity, particularly in those with obesity, metabolic dysfunction-associated cirrhosis, and alcohol-related cirrhosis. Ultrasound surveillance is also limited by the challenges of poor adherence, barriers regarding the cost of testing, difficulty with scheduling, uncertainty as to where to obtain imaging, and transportation difficulties. Measures to improve adherence will likely improve the effectiveness of ultrasound screening but there is a clear need for novel biomarkers and other screening strategies.

Identification of improved biomarkers remains of the highest priority. The criteria for an ideal screening test should include a test performed accurately that is easily accessible with a low risk of medical or financial harm(5). Currently, alpha-fetoprotein (AFP) is the
most widely used biomarker to screen for HCC. However, AFP is not elevated in all cases of hepatocellular carcinoma with less-than-optimal sensitivity in patients with early-stage disease (32 to 49%)(6). Moreover, in inflammatory diseases such as active hepatitis C or B, AFP levels can be elevated. The addition of AFP to ultrasound surveillance does improve screening performance. There are multiple other promising biomarkers/panels including GALAD score, Doylestown plus, and mt-HBT amongst others. The GALAD score includes AFP, AFP-L3%, des-gamma-carboxy prothrombin (DCP), age, and sex, and there is currently an ongoing prospective trial to compare GALAD score to ultrasound plus AFP surveillance for HCC. Both GALAD score and Doylestown plus (age, log AFP, polyethylene glycol (PEG)-precipitated IgG, and fucosylated kininogen) have shown initial promise in the early detection of HCC though larger trials are ongoing(7).

Other promising areas of research include the use of liquid biopsies to detect tumor-specific genomic alterations in cell-free DNA. Preliminary results show that a panel of biomarkers that combines 3 methylated DNA biomarkers with AFP and sex (mt-HBT) demonstrated 82% early-stage sensitivity and 87% specificity in the diagnosis of HCC(8). This test was also more sensitive than the GALAD score or AFP. A preliminary report noted the HelioLiver Dx test, which consists of a multi-analyte blood test that combines methylated cell-free DNA markers with AFP, AFP-L3%, des-gamma-carboxy prothrombin (DCP), age and sex, was superior to ultrasound in the detection of early stage HCC(9). These blood-based biomarkers show promise in improving our ability to detect early stage HCC and will apply to those who have achieved sustained response and remain at high risk for HCC post-SVR. It will be important to address the cost of these tests which will make implementation challenging in parts of the world with limited resources. Finally, multiple risk scores have emerged to help predict the risk of HCC post-SVR and these
tools can also help determine when to enroll patients in hepatocellular carcinoma surveillance programs after achieving sustained response (10, 11).

Chemoprevention remains an important area of research for those at risk for hepatocellular carcinoma due to hepatitis C or any other etiology. A recent paper by Tsai et al demonstrated an association between reduction in HCC risk in HCV-infected individuals who failed interferon therapy and were receiving statins or metformin for metabolic complications (12). It is essential to study these and other therapies in prospective trials to determine if they reduce the risk of HCC in at risk populations(13).

The emerging literature on the identification of genetic changes and epigenetic changes associated with post-SVR HCC risk gives hope that actionable targets can be identified in at-risk individuals with targeted therapies that ameliorate epigenetic alterations that may occur during HCV infection(14). Moreover, as risk alleles are identified and validated, it may be feasible to create polygenic risk scores to better tailor HCC surveillance post-SVR and we agree that multi-omic studies will refine our understanding of the complex interplay of factors that affect the risk of HCC post-sustained response. Lifestyle interventions should also play a role in reducing the risk of HCC and at-risk patients should be counseled on improving metabolic risks, cessation of alcohol, use of coffee and other interventions(15-17). However, the single most important intervention to prevent HCC in hepatitis C patients is to administer DAA therapy and eliminate the hepatitis C infection. This includes the use of both first line and salvage therapies. We have made significant advances in our ability to treat hepatitis C and this has led to a reduction in the HCC risk in this population. Still much work remains to be done which will benefit those with hepatitis C as well as those with other chronic liver diseases at risk for hepatocellular carcinoma.
REFERENCES

13. Kwo PY. Metformin and Statins and their role in reducing Hepatocellular Carcinoma Risk: Randomized trials are needed. Clin Mol Hepatol. 2024.