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Does Cirrhosis Associated with Well Controlled Viral Hepatitis Confer a Risk for Extrahepatic Cancer?

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Chronic hepatitis B and C are major health problems globally.[1, 2] A significant proportion of patients with hepatitis B (HBV) or hepatitis C virus (HCV) infection develop liver cirrhosis, most of whom die from primary liver cancer or complications of end-stage liver disease including variceal bleeding, renal failure or infection.[3] Over the past decade, management of HBV and HCV has been revoluntionized and highly potent antiviral treatments are now available for HBV and HCV. Successful viral suppression in HBV patients and viral eradication in HCV patients with cirrhosis alters the natural history of disease by preventing death related to liver cancer and hepatic decompensation.[4] With effective antiviral treatment, there will be an increasing number of aging patients who will not experience liver related complications.

Patients with cirrhosis have a higher prevelance of diabetes, which is a well-established risk factor for cancer in cirrhotics.[5] Patients with viral hepatitis, particularly HCV, tend to have lifestyle related cancer risk factors, such as tobacco and/or alcohol use. Therefore, cirrhotic patients with viral hepatitis may be at a higher risk of malignancy than people in the general population. In additon, it is well established that HBV or HCV infection increases the risk of hematologic malignancies, particularly lymphoma.[6–8] Both viruses also create immune disturbances in the host which may affect cancer immune surveillence; correction of these immune alterations with successful antiviral therapy may be too late to prevent cancer as carcinogenesis processes may have already evolved to evade immune surveillence. Hence, while cirrhotic patients with viral hepatitis tend to have more cancer risk factors overall, there are no high quality data that describe the incidence rates of extrahepatic solid or hematologic malignancies in this patient population compared to the general population.

In this issue of *Hepatology*, Allaire and Nahon et al. report the incidence rates of cancer in cirrhotics with HBV or HCV using an ANRS CO12 CirVir cohort.[9] A total of 35 French research centers participated in this prospective cohort study sponsored by the French National Research Agency. The study included compesated Child Pugh A patients with histologic confirmation of cirrhosis. Pateints were followed for hepatocellular carcinoma (HCC) surveillance every 6 months. Clinical information including use of antiviral

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treatment, antiviral treatment responses, liver related or non-liver related outcomes including extrahepatic malignancies were prospectively monitored. The authors report the incidence rates of primary hepatic and extrahepatic malignancies compared to the cancer incidence estimate in the general population between 1980 and 2012 using 14 French tumor registries, which covers 24% of the French population. Antiviral treatment response was treated as a time dependent variable in the analysis. A total of 1,671 patients were analyzed, of whom 79% had HCV and 19% had HBV. A total of 192 primary liver and 93 extrahepatic cancers (14 lymphoid or related tissue cancers, 79 solid cancers) were diagnosed with a 5 year cumulative incidence rate of 13.4% for primary liver and 5.9% for extrahepatic cancer. Consistent with data in the literature, the standardized morbidity ratio (SMR) of primary hepatic cancer was 103 ($P<0.04$) while the SMR of extrahepatic cances was only 1.2 ($P=0.09$). When the extrahepatic cancers were separated into solid tissue cancer and lymphoid or related tissues cancer, the SMR of lymphoid or related tissue cancer was 2.03 ($P=0.02$). Next, the authors performed a subgroup analysis to investigate whether or not successful control of HBV or HCV would change the risk of primary hepatic or extrahepatic cancers. While the SMR of the primary liver cancer decreased to 51.5 ($P<0.01$), the SMR of the extrahepatic cancer actually increased to 1.56 ($P=0.01$). The SMR of the lymphoid or related tissues cancer remained high at 2.78 ($P=0.07$). Among extrahepatic solid tissue cancers, oral cancer had the highest effect size (SMR=4.97; $P= 0.005$). More than half the patients were former or current smokers and approximatley a quarter of the patients reported ongoing alcohol consumption. When patients with these risk factors were excluded, the SMR of the oral cancer decreased to 0.74 ($P=0.78$), although the SMR for lymphoid and related tissue cancer remained high at 2.08 ($P=0.02$); these observations suggest the increase in the SMR of oral cancer or other solid tissue cancers is likely due to the risk factors of tabacco and/or unhealthy alcohol use rather than an independent effect of liver cirrhosis or hepatitis virus. An effect of human papolloma virus on the oral pharyngeal cancer incidence cannot be discerned due to lack of tumor sequencing for this virus.[10] Finally, the authors investigated the cause of death among decedents. Extrahepatic cancer was the leading cause of death in decedents with successful control of virus (40%) while primary liver cancer was the leading cause in decedents without viral control (33%).

The main study finding is that cirrhotic patients with successful control of the viral hepatitis appear to be at increased risk for developing extrahepatic malignancies. The increased risk of extrahepatic solid cancers appears to be mediated by lifestyle related risk factors such as tobacco and/or alcohol use or diabetes in combination with decresed risk of liver cancer or decompensation related death. This is a well-defined large scale prospective cohort study using the ANRS CO12 CirVir database. The clear association between viral hepatitis and lymphoma, which is well-established,[6–8] increases the validity of study results. However, there are several limitations that should be taken into account when interpreting the study results. First, this study has ascertainment bias. Patients in the ANRS CO12 CirVir cohort have a different intensity of follow up as compared to the French general population. For instance, patients within the ANRS CO12 CirVir cohort had regular follow up with an experienced hepatologist every 6 months at a minimum, whereas patients in the general population would be less likely to have a similar follow up. The need for patient compliance with the follow up provides a selection factor or bias for this patient population, which can

potentially lead to an overdiagnosis of cancer in the study cohort than the general population. Second, the time period for the incidence rates of cancer were different between the the ANRS CO12 CirVir cohort and the general population. The authors used the French population cancer registry between 1980 and 2012 while ANRS CO12 CirVir cohort patients were enrolled between 2006 and 2012. If the cancer incidence in the general population has changed between 1980 and 2012, this would introduce bias especially if the index date (e.g. year of enrollment in ANRS CO12 CirVir cohort and years of general population used to estimate the malignant risk was calculated) were not matched. Third, as the authors acknwoledged, the small number of incident cancers underpowed the statistical analysis when analyzing the risk for specific types of extrahepatic solid malignacies. This is particularly true in HBV patients or patients without lifestyle related risk factors for malignancy. Therefore, the negative results in many subgroups is difficult to interpret due to the underpowered nature of this study.

What are the implications of the current study for heathcare providers and patients? Although the results of the current study do not provide specific guidance on the types of surveillance approaches appropriate for invidiual cancers, the study findings should alert clinicians to the increased possiblity of developing extrahepatic malignancy in patients with HBV or HCV assoicated cirrhosis, particulary among those with known risk factors. The data in the study will be useful to encourage lifestyle modifications in high-risk patient populations. As the number of cirrhotic patients without active HCV or HBV increases in the ensueing years, this topic will become more important. Dynamic interaction betweeen behavioral risk factors (i.e., tobacco use, alcohol use), diabetes and other metabolic risk factors, and control of viral hepatitis on the risk of hepatic and extrahepatic malignancies in cirrhotics should be carefully assessed in additional studies.

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References

1. Schweitzer A, Horn J, Mikolajczyk RT, et al. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet. 2015; 386:1546–55. [PubMed: 26231459]
2. Webster DP, Klenerman P, Dusheiko GM. Hepatitis C. Lancet. 2015; 385:1124–35. [PubMed: 25687730]
3. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol. 2006; 44:217–31. [PubMed: 16298014]
4. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. Jama. 2012; 308:2584–93. [PubMed: 23268517]
5. Yang JD, Mohamed HA, Cvinar JL, et al. Diabetes Mellitus Heightens the Risk of Hepatocellular Carcinoma Except in Patients With Hepatitis C Cirrhosis. Am J Gastroenterol. 2016; 111:1573–1580. [PubMed: 27527741]
6. Couronne L, Bachy E, Roulland S, et al. From hepatitis C virus infection to B-cell lymphoma. Ann Oncol. 2018; 29:92–100. [PubMed: 29045541]

7. Giordano TP, Henderson L, Landgren O, et al. Risk of non-Hodgkin lymphoma and lymphoproliferative precursor diseases in US veterans with hepatitis C virus. Jama. 2007; 297:2010–7. [PubMed: 17488966]

8. Marcucci F, Spada E, Mele A, et al. The association of hepatitis B virus infection with B-cell non-Hodgkin lymphoma - a review. Am J Blood Res. 2012; 2:18–28. [PubMed: 22432084]

9. Manon Allaire PN, Richard Layese, Valérie Bourcier, Carole Cagnot PM, Dominique Guyade, Stanislas Pol, Dominique Larrey VDL, Ouzan Denis, Zoulim Fabien, Roulot Dominique, et al. EXTRA HEPATIC CANCERS ARE THE LEADING CAUSE OF DEATH IN CIRRHOTIC PATIENT ACHIEVING HBV CONTROL OR HCV ERADICATION. Hepatology. 2018

10. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015; 517:576–82. [PubMed: 25631445]