HCV and Hepatocellular Carcinoma (HCC)

HCV is an established risk factor for HCC. Prospective studies have shown a significant increase in the incidence of HCC among HCV-infected compared with HCV-negative cohorts. The rate of HCC among HCV-infected persons ranges from 1% to 3% over 30 years. Similarly, HCV infection is associated with a 15- to 20-fold increase in risk for HCC compared with HCV-negative subjects in cross-sectional and case-control studies.

HCV increases the risk for HCC by inducing fibrosis and, eventually, cirrhosis. Although HCC has been reported among individuals without or with low levels of fibrosis, the risk of HCC increases with fibrosis stage; most cases of HCV-related HCC occur among patients with advanced fibrosis or cirrhosis. Once HCV-related cirrhosis is established, HCC develops at an annual rate of 1%–4%; although rates up to 8% have been reported in Japan. Risk factors for HCC include the sex of the HCV-infected individual, comorbidities (co-infection with HBV or HIV, diabetes, obesity, steatosis), viral genotype (HCV 1b), level of alcohol consumption, and age.

Treatment of HCV that results in sustained viral response can prevent HCC development. However the outcomes of treatment are different among patients without cirrhosis, with cirrhosis, or in patients who underwent resection or ablation of HCC.

Overall HCV-infection: Data from 11 randomized controlled trials (RCTs) including 1,772 patients who were analyzed in a recent metanalysis and showed that IFN significantly decreased the overall HCC incidence in HCV-infected patients [relative risk (RR)=0.39; 95% CI=0.26-0.59]. A subgroup analysis indicated that IFN decreased HCC incidence in HCV-related cirrhotic patients (RR=0.44; 95% CI=0.28-0.68); but HCC incidence in nonresponders to initial antiviral therapy was not reduced by maintenance IFN therapy (RR=0.96; 95% CI=0.59-1.56).

Maintenance: Three large prospective controlled trials of maintenance therapy have now failed to demonstrate that Peg-IFN maintenance therapy reduces complications of cirrhosis, HCC and liver-related mortality. It therefore remains uncertain if profound and persistent virologic suppression to undetectable levels of HCV RNA impacts the risk of developing HCC in patients with chronic HCV and advanced fibrosis or cirrhosis.

Treatment after HCC resection or ablation: Thirteen studies of INF-based treatment in HCC patients with ablation or resection (9 randomized trials and 4 cohort studies, total 1180 patients) were included in a meta-analysis. Surgery and ablation therapy were used in 9 and 8 studies, respectively. Interferon improved the 1-year, 2-year, and 3-year recurrence-free survival by 7.8% (95% CI 3.7-11.8%), 35.4% (95% CI 30.7-40.0%), and 14.0% (95% CI 8.6-19.4%).

HCV and Cholangiocarcinoma (CC)
HCV has been postulated as risk factors for CC.
**European Studies:** Few Western European studies reported an association between CC and both HCV and cirrhosis. A large, population-based cohort study from Denmark by Sorensen et al. examined cancer risk in 11,605 patients with cirrhosis over a mean follow-up period of 6 years, and reported a 10-fold increased risk of CC among patients with cirrhosis compared with the expected cancer cases in the general population (standardized incidence ratio of 21 versus 2). A hospital-based, case-control study in Italy by Donato et al. compared 26 intrahepatic cholangiocarcinoma (ICC) cases with 824 controls. Both HCV and HBV seropositivity was analyzed, but only HCV was significantly associated with ICC.

**US Studies:** Several US studies have shown an association between the presence of HCV and/or cirrhosis and increased risk of ICC. From The M.D. Anderson Cancer Center, a hospital-based, case-control study by Shaib et al. compared 83 patients with ICC and 163 with extrahepatic cholangiocarcinoma (ECC) to 236 controls. HCV was a significant risk factor for ICC. Cirrhosis was not analyzed as a separate variable, but 80% of HCV-positive patients had cirrhosis. For ECC, neither HCV nor HBV status was a significant risk factor. A large, population-based, case-control study by Shaib et al. of Medicare-enrolled patients compared 625 cases of ICC with 90,834 controls. In multivariate analysis, HCV was significantly associated with ICC. It was unclear if patients with HCV also had a recorded diagnostic code for cirrhosis. However, nonspecific cirrhosis was strongly associated with ICC. A similar population-based, case-control study by Welzel et al. of Medicare-enrolled patients examined risk factors for both ICC and ECC. There were 549 cases of ECC and 535 cases of ICC compared with 102,782 controls. Significant risk factors for ICC included HCV and nonspecific cirrhosis. Regarding ECC, nonspecific cirrhosis was also a risk factor, but HCV infection was not significant. A large cohort study of US veterans by El-Serag et al. examined the association between HCV and both ICC and ECC in a cohort of 146,394 HCV-infected veterans and 572,293 uninfected controls. The risk for ICC in the HCV-infected cohort, though low at 4 per 100,000 person-years, was more than double that in the controls. The risk of ECC did not differ between the HCV-infected and uninfected veterans. The association of HCV with CC is not entirely clear because of the paucity of population-based or prospective cohort studies.

There have been no studies examining the effect of antiviral HCV treatment on the risk of cholangiocarcinoma.

**References**

