Hepatocellular carcinoma is the third most common cause of cancer-related death worldwide and is therefore a major health problem (1,2). Unlike many other cancers, hepatocellular carcinoma has well-recognized risk factors that allow the identification of at-risk populations that can be targeted for screening and surveillance. The most common risk factors include chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, alcohol intake, and aflatoxin exposure (1). Worldwide, approximately 54% of hepatocellular carcinomas can be attributed to HBV infection (which affects 400 million people globally), whereas 31% can be attributed to HCV infection (which affects 170 million people), leaving approximately 15% associated with other causes of cirrhosis, such as alcoholic and nonalcoholic fatty liver disease (3,4). Other risk factors are known, such as male sex and increasing age; however, these risk factors are immutable and they only confer additional risk in the presence of underlying liver disease and not in patients who do not have liver disease. Aflatoxin exposure has long been recognized as a risk factor, but again, this is the case in patients who have chronic HBV infections. Other risk factors for hepatocellular carcinoma include smoking, diabetes, and obesity (5,6). Diabetes and obesity may act through the development of nonalcoholic fatty liver, although the link has not been definitively established. However, the mechanism whereby smoking might be a risk factor is unknown. One may speculate that carcinogens enter the bloodstream from the lungs, and when they make contact with hepatocytes primed for oncogenesis, they may induce additional genetic aberrations leading to cancer.

Increased risk of liver cancer can be assessed in terms of the risk of an individual or a population with a risk factor compared with that of an individual or population in which that particular risk factor, for example, HBV infection, is absent. For example, in the initial prospective studies, chronic HBV infection was associated with a 50- to 100-fold increased risk of developing hepatocellular carcinoma (7,8). Alternatively, incidence rates may be considered as surrogate of risk. For example, the annual incidence of hepatocellular carcinoma is 0.2%–0.6% in HBV-infected non-cirrhotic patients, 2% in HBV-infected cirrhotic patients, and 3%–8% in HCV-infected cirrhotic patients (9,10). Overall, one-third of cirrhotic patients will develop hepatocellular carcinoma during their lifetime.

In this issue of the Journal, there are two articles that report on risk factors for hepatocellular carcinoma. The first article, by Borreson et al. (11), examines the incidence of hepatocellular carcinoma in Greenlanders with chronic HBV infection. The authors confirmed that patients with chronic HBV infection had a higher overall and liver-specific mortality than the general population (8.5 times higher for hepatitis B surface antigen [HBsAg]–positive than for HBsAg-negative individuals). However, they also showed that the risk of hepatocellular carcinoma was lower among HBsAg-positive Greenlanders than in other populations throughout the world. The authors speculated that this finding might be partially explained by the prevalent HBV genotypes in Greenland: genotypes D and B6. In fact, among the different genotypes of HBV infection, genotype C has been recognized as an independent predictor of hepatocellular carcinoma development (10,12), whereas the incidence of hepatocellular carcinoma in people infected by genotype B6 has not been documented. Viral load and infection by mutants of HBV are also recognized risk factors for hepatocellular carcinoma (13), but they were not described in this study. The authors also commented that HBV infection in Greenland occurs mainly in adolescents and young adults, although they did not provide evidence for this statement. If true, this infection pattern is unlikely to account for the high chronicity rate because the likelihood of developing chronic HBV infections is highest in newborns and infants (90%) and decreases with time to be less than 1% in young adulthood. Thus, adolescent or young adult infection cannot account for the majority of chronic infections that lead to hepatocellular carcinoma. The authors also considered a number of other possibilities that might account for the difference in risk of hepatocellular carcinoma among Greenlanders chronically infected with HBV, most of which are speculative. However, one factor that probably best accounts for the lower incidence of hepatocellular carcinoma is that the cohort is relatively young. Subjects had a mean age of approximately 30–35 years at inclusion in the study, and most subjects in the cohort were in their 50s when incidence of hepatocellular carcinoma was determined. The peak age of onset of hepatocellular carcinoma in other populations is between 60 and 70 years of age. Therefore, it is possible that most hepatocellular carcinomas in the Greenlandic population are yet to occur.

The second study, from a European consortium (Trichopoulos et al. (14)) aimed to determine the attributable risk of various factors in the development of hepatocellular carcinoma. The main strength of the study was that it used a population-based cohort in which attributable fractions for development of
hepatocellular carcinoma might be amenable to primary or secondary prevention. As expected, chronic HBV (odds ratio [OR] = 9.10) and HCV infection (OR = 13.36) were important factors associated with hepatocellular carcinoma. Much lower odds ratios were identified for other known risk factors, such as obesity (OR = 2.1), alcohol intake (OR = 1.77), and current smoking (OR = 1.90). Despite the fact that there were only 115 subjects who developed hepatocellular carcinoma, a modest number for the purpose of the study, these results are consistent with those from other epidemiological studies. Interestingly, coffee intake was not associated with a decreased risk of hepatocellular carcinoma development, as previously reported (15). Nonetheless, the more remarkable and controversial data reported here was the reported fraction of attributable risk associated with various risk factors. As expected, HBV and HCV infection were associated with substantial attributable risks, at 13% and 20.9%, respectively. Somewhat surprisingly, smoking carried an attributable risk of almost 50%, a figure that challenges our current knowledge.

It is important to put these numbers into context. Attributable risk is calculated taking into account the population prevalence and the relative risk. So, if a risk factor occurs rarely in a population, even if it carries a very high risk, the attributable risk will be low. Conversely, a condition that confers only a slightly increased relative risk to an individual, if highly prevalent in the population will have a high relative risk. In this cohort, more than twice as many patients with hepatocellular carcinoma smoked as matched control subjects (40% vs 19.6%). By contrast, a wider difference was observed for the prevalence of HBV infection (14.8% vs 2.6%) and HCV infection (22.6% vs 3.1% of cancer patients and control subjects, respectively). Thus, although smoking is associated with a slightly increased relative risk, because this risk was present in a large proportion of the population, the attributable risk became substantial.

What is known from clinical and experimental studies so far is that smoking is acting as a cofactor that increases the risk of hepatocellular carcinoma development, but as a stand-alone agent, tobacco is not driving hepatocarcinogenesis. We understand that this message is reinforced with the data reported. What we should take away from this study is that among all patients with previously existing risk factors for hepatocellular carcinoma, smoking is a major contributing cofactor. Certainly, there may be some instances of hepatocellular carcinoma in smokers without any other risk factors, but because smoking often coincides with alcohol consumption or viral infection, the data should be interpreted cautiously even for those individuals. This data are compelling and we should take note. We should be counseling our patients who have other risk factors for hepatocellular carcinoma to quit smoking. Of course, there are many other health reasons to stop smoking. Here is one more.

**References**


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