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No inflammation? No cancer! Clear HBV early and live happily

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COMMENTARY ON:

Clearance of Hepatitis B Surface Antigen and Risk of Hepatocellular Carcinoma in a cohort Chronically Infected with Hepatitis B Virus. Simonetti J, Bulkow L, McMahon BJ, Homan C, Snowball M, Negus S, Williams J, Livingston SE. Hepatology. 2009 Nov 30. [Epub ahead of print]. Copyright 2009. Reprinted with permission of John Wiley and Sons, Inc.

Abstract: *Some individuals who are chronically infected with hepatitis B virus (HBV) eventually lose hepatitis B surface antigen (HBsAg). Hepatocellular carcinoma (HCC) has been demonstrated to occur in a few patients after loss of HBsAg. Neither factors associated with loss of HBsAg nor the incidence of HCC thereafter have been clearly elucidated. We performed a prospective population-based cohort study in 1271 Alaska native persons with chronic HBV infection followed for an average of 19.6 years to determine factors associated with loss of HBsAg and risk of developing HCC thereafter. HBsAg loss occurred in 158 persons for a rate of HBsAg clearance of 0.7%/year. Older age, but not sex, was associated with clearance of HBsAg, and loss of HBsAg was not associated with any particular HBV genotypes (A–D, and F) found in this population. Participants were followed for an average of 108.9 months after HBsAg loss. Six patients, two with cirrhosis and four without, developed HCC a mean of 7.3 years after HBsAg clearance (range, 2.0–15.5 years). The incidence of HCC after clearance of HBsAg was 36.8 per 100,000 per year (95% CI 13.5–80.0) which was significantly lower than the rate in those who remained HBsAg-positive (195.7 cases per 100,000 person-years of follow-up [95% CI 141.1–264.5; P < 0.001). After loss of HBsAg, HBV DNA was detected in the sera of 28 (18%) of those who cleared a median of 3.6 years after clearance. Conclusion: HCC can occur in persons with chronic hepatitis B who have lost HBsAg, even in the absence of cirrhosis. These persons should still be followed with periodic liver ultrasound to detect HCC early.*

Keywords: HBV endemicity; Hepatitis B surface antigen loss; Prognostic factors; Chronic inflammation; Cirrhosis; Hepatocellular carcinoma.

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Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDV, hepatitis Delta virus.

Chronic hepatitis B virus (HBV) infection is a leading cause of end-stage liver disease and hepatocellular carcinoma (HCC) worldwide. Spontaneous or therapy-induced hepatitis B surface antigen (HBsAg) clearance, with or without anti-HBs seroconversion, is considered a highly favorable event. However, its incidence, the facilitating factors, and the long term outcome of HBV carriers experiencing HBsAg seroclearance, are still ill defined. The article by Simonetti et al. [1] provides additional data on the rate and determinants of spontaneous HBsAg loss and prognosis after seroclearance in a population-based cohort study from the endemic area of Alaska, and highlights important differences in outcome between countries of low and high HBV endemicity.

Are there differences in the incidence and determinants (age at diagnosis, HBV genotypes) of spontaneous HBsAg clearance between chronic HBV carriers from endemic and Western regions?

The HBsAg seroclearance rate was thought to be lower in high as compared to low HBV endemic countries; however, this was likely due to insufficient length of follow-up, the longest studies in this setting being performed in Western countries [2,3]. Recent data from Taiwan indicate that when prolonging the follow-up length, the annual seroclearance rate is 1%, a figure similar to Western studies [2–4]. A common predisposing factor was older age at entry both in high and low HBV endemic regions [1,2,4], although with approximately a decade of anticipation of the age of entry in the only population-based study from the high endemic area of Alaska [1] (Table 1). As the article by Simonetti et al. [1] has shown, HBV genotypes (A–D, and F) are not associated with different rates of HBsAg seroclearance. Studies have indicated that HBsAg seroclearance is consistently associated with improvement in liver biochemistry and in liver histology (when available) and favorable long term prognosis, provided that HBsAg loss occurred at a younger age, in the absence of concurrent hepatitis C virus (HCV) or hepatitis delta virus (HDV) infection, and before the development of cirrhosis. This leads to the second, relevant question.

Does the disease progression stop after HBsAg seroconversion?

Disease progression such as HCC, decompensation or liver-related death still occurs after HBsAg seroclearance, [1,6–11] (Table 1). In

Table 1. Occurrence of hepatocellular carcinoma, decompensation and liver-related death/LT after HBsAg seroclearance in patients with chronic hepatitis B infection according to clinical status and geographic area.

Author [reference]	Geographic area	No. HBs Ag+ pts/No. pts clearing HBsAg	Mean follow-up (yrs)	Rate/yr HBsAg loss[a] (%)	Mean age at entry/mean age at HBsAg loss (yrs)	Clinical status at HBsAg loss	Mean follow-up after HBsAg loss (yrs)	No. HCC	No. decompensation	No. death/ LT
Simonetti [1]	Alaska	1271/158	19.6	0.7	21/na	Asymptomatic carriers	8.6	6 (1)	na	na
Chu [4]	Taiwan	1965/245	10.8	1.1	35/48		na	na	na	na
Manno [2]	Italy	296/59	29.1	1	36/52[b]		16[b]	0	0	0
Fattovich [3]	Italy	70/18	25.3	1	29/52[b]	Inactive carriers	8.6[b]	0	0	0
Zacharakis [5]	Greece	195/16	4.9	1.6	34/na		na	na	na	na
Chen [6]	Taiwan	na/189	na	na	na/43		5.1	2 (2)	0	1 (1)
Ahn [7]	Korea	432[c]/32	18.5	0.6[d]	na/50	Chronic hepatitis	1.6	1	na	na
Arase [8]	Japan	na[e]/164	4	na[e]	na/51		6.5	0	0	0
Yuen [9]	China	na/285	9	na	na/49	Chronic hepatitis or cirrhosis	3.0	7[f]	5	na
Fattovich [10]	Europe	309/32	5.6	0.8	45/51[b]		4.6	1 (1)	2	2 (1)
Chen [6]	Taiwan	na/29	na	na	na/54		5.1	1 (1)	4 (2)	1 (1)
Ahn [7]	Korea	432[c]/17	18.5	0.6[d]	na/50	Cirrhosis	1.6	4	na	na
Arase [8]	Japan	na[e]/67	4	na[e]	na/51		6.5	2	0	0
Tong [11]	United States	na[e]/13	15	na[e]	41/54		na	4	na	na

HCC, hepatocellular carcinoma; LT, liver transplantation; na, not available.
Number in parentheses refer to number of patients with concurrent hepatitis C virus or hepatitis delta virus infection.
[a] Patients receiving antiviral therapy were excluded from the analysis.
[b] Updated by the authors.
[c] The number of HBsAg-positive patients refers to the total study population including both subjects with chronic hepatitis and cirrhosis.
[d] The yearly rate of HBsAg loss was calculated for the total study population including both patients with chronic hepatitis and cirrhosis.
[e] Untreated patients cannot be disentangled.
[f] Six of the seven patients had cirrhosis at the time of HBsAg loss.

Asian patients with cirrhosis, HCC developed in 3–23% of cases during 1.6–6.5 years of follow-up after HBsAg clearance [6–8]. In a recent study from the United States, 35 patients with chronic hepatitis B (71% of Asian origin) were followed for a median period of 15 years after HBsAg seroclearance, and HCC developed in 4 (30%) out of 13 patients with cirrhosis at the time of the initial visit [11]. The only study, on compensated cirrhosis type B from Europe, showed that 3% of Caucasian patients developed HCC and died during a mean follow-up of 4.6 years (range 0.4–8.7) after HBsAg clearance [10]; furthermore, the only patient with HBsAg loss who developed HCC was an untreated HCV co-infected subject with persistent biochemical activity, suggesting a relevant role for HCV in the occurrence of cirrhosis and HCC [10].

On the other hand, data on the natural history of chronic HBV infection in Caucasian patients show that HCC rarely occurs in the absence of significant liver disease [2,3]. Indeed in the 30-year longitudinal study of 296 Italian inactive HBsAg carriers, none of the 59 subjects who became HBsAg negative, developed HCC or other liver-related morbidity, or mortality during a mean follow-up of 16 years after HBsAg clearance [2]. In another 25-year longitudinal study of Italian patients with chronic hepatitis B at enrollment, 18 of the 40 patients who became inactive carriers with sustained disease remission lost their HBsAg, and none of them developed HCC or died from liver-related causes during an average follow-up of 8.6 years after HBsAg loss [3].

Overall these data confirm that worldwide liver cirrhosis represents the major known risk factor for HCC and can be considered a premalignant condition even after HBsAg loss. Moreover, the reported higher risk of HCC in patients with HBsAg loss after age of 50 may merely reflect the longer duration of infection and disease of these specific patients [9,11]. The study by Simonetti et al. [1] shows that the incidence of HCC after clearance of HBsAg was significantly lower than the rate in those who remained HBsAg-positive (0.36 versus 1.9 per 100 person/year, respectively) but still remains considerably high. A possible explanation for this apparent contradiction comes from the data by Yuen et al. [9] showing that despite HBsAg seroclearance, HBV persists in the liver at low replicative and transcriptional levels allowing continuous liver inflammation, facilitating progression of disease, although at slower pace, and ultimately occurrence of HCC. As also indicated by the study of Simonetti et al. [1], the mere presence of chronic liver disease (4 out of 6 HCC cases showing chronic inflammation not yet at the cirrhotic stage) represents a potential risk for the development of HCC. Proof of concept for this comes from the data on HBV vaccination [12] showing that this not only decreased the prevalence of HBsAg in children from geographic areas of high endemicity but also dramatically reduced the incidence of HCC in this age group, thus providing the evidence that HCC is avoidable, by preventing the sequence of chronic HBV infection-chronic inflammation-liver fibrosis and eventually cirrhosis and cancer.

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