Risk and Predictors of HCC in People Less than 40 years of Age: Update from the R.E.V.E.A.L.-HBV Study

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Background

- Most patients with chronic hepatitis B (CHB)-related HCC develop this complication after the age of 40. The risk of HCC and its predictors are well documented for this group of people
- There is relatively less knowledge about the risk and predictors of HCC in CHB patients under 40 years of age
- We analysed the R.E.V.E.A.L. cohort, focusing on HCC risk in subjects less than 40 years old at enrolment, and compared the results to the HCC risk in subjects over 40 years of age

Study Population

- Source data: the R.E.V.E.A.L.-HBV study cohort (N=3,653)
  - Population-based prospective study with a mean follow-up of 11 years
  - Subjects aged 30–65 years
  - At study entry, subjects:
    1) provided informed consent;
    2) provided a serum sample which was separated on the day of collection and frozen at -70ºC;
    3) underwent a structured interview by a trained public health nurse;
    4) had an ultrasound examination
  - HBsAg-positive and anti-HCV-negative

Methods

- Laboratory tests
  - HBsAg and HBeAg: radioimmunoassay (Abbott Laboratories, North Chicago, IL, USA)
  - Anti-HCV antibodies: second-generation ELISA kits (Abbott Laboratories, North Chicago, IL, USA)
  - ALT: serum chemistry autoanalyser (Model 736, Hitachi Co., Tokyo, Japan) using commercial reagents (bioMérieux, Mercy-l'Etoile, France)
  - Serum HBV DNA level: commercial PCR kits (Cobas Amplicor, Roche Diagnostics Co., Indianapolis, IN, USA)
- Ascertainment of HCC diagnosis
  - Data linkage with computerised profiles of the National Cancer Registry and Death Certification
  - All HCC cases were confirmed as previously described[1]

1. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006: 295;65–73.

Results

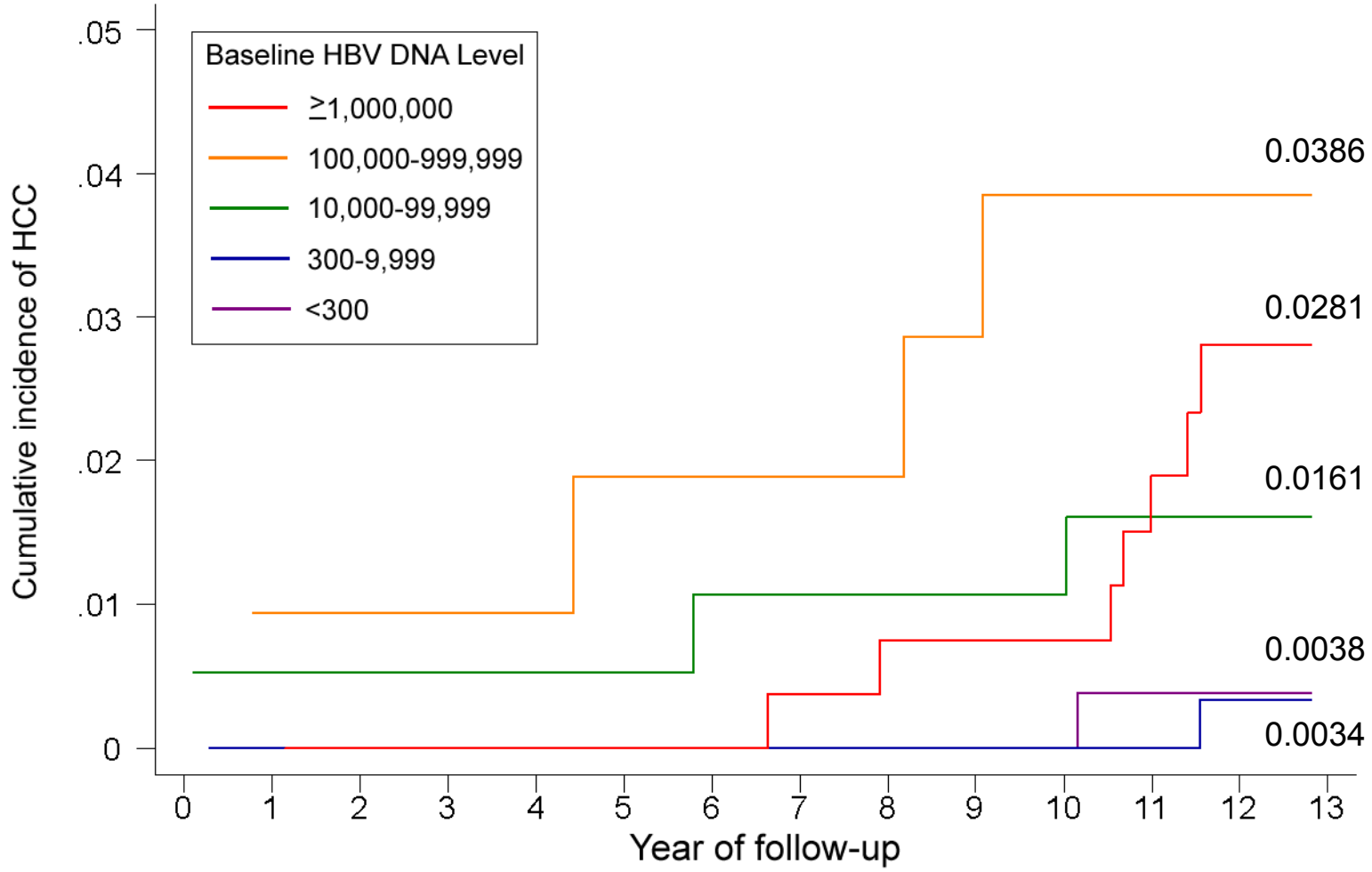
Baseline demographic and disease characteristics for all REVEAL subjects stratified by Age

	Age <40 years (n=1,216)	Age ≥40 years (n=2,437)	p-value*
Person-years of follow-up (PYFU)	14,393	27,386	<0.0001
Males, n (%)	758 (62.3)	1502 (61.6)	0.68
Number of incident HCC cases, n (%)	16 (1.3)	148 (6.1)	<0.0001
Age years, mean (median)	34.9 (35.0)	51.3 (51.0)	<0.0001
HBeAg-positive, n (%)	280 (23.0)	285 (11.7)	<0.0001
Serum ALT level, U/L <15, n (%) 15–44, n (%) ≥45, n (%)	 733 (60.3) 405 (33.3) 78 (6.4)	 1,463 (60.0) 834 (34.2) 140 (5.7)	0.66†
Cirrhosis at entry, n (%)	12 (1.0)	57 (2.3)	0.005
Cigarette smoking yes, n (%)‡	424 (34.9)	810 (33.3)	0.33
Alcohol consumption yes, n (%) §	144 (11.9)	307 (12.6)	0.52
HBV DNA level, copies/mL <300, n (%) 300–9,999, n (%) 10,000–99,999, n (%) 100,000–999,999, n (%) ≥1,000,000, n (%)	 268 (22.0) 382 (31.4) 188 (15.5) 107 (8.8) 271 (22.3)	 605 (24.8) 779 (32.0 455 (18.7) 242 (9.9) 356 (14.6)	<0.0001†
HBV genotype** B, n (%) C, n (%) B+C, n (%)	 597 (64.5) 294 (31.8) 35 (3.8)	 1,131 (61.7) 642 (35.0) 60 (3.3)	0.21

* Student's t-test for person-years of follow-up and mean age; chi-square test for other variables, † p-value for the trend, ‡ Data were not available for 3 subjects, § Data were not available for 7 subjects, ** Data were not available for 894 subjects, mostly due to undetectable HBV DNA level

Cumulative Incidence of HCC in Subjects < 40 years at enrolment

A total of sixteen subjects developed HCC for an incidence rate of 111/100,000 PYFU.



Baseline demographic and disease characteristics for subjects <40 years of age Stratified by HCC Status

	Non-HCC cases (n=1,200)	HCC cases (n=16)	p-value*
Age years, mean (median)	34.9 (35.0)	35.0 (35.0)	0.83
Males, n (%)	742 (61.8)	16 (100.0	0.0009
HBeAg-positive, n (%)	272 (22.7)	8 (50.0)	0.016
Serum ALT level, U/L <15, n (%) 15–44, n (%) ≥45, n (%)	 730 (60.8) 397 (33.1) 73 (6.1)	 3 (18.8) 8 (50.0) 5 (31.3)	<0.0001†
Cirrhosis at entry, n (%)	9 (0.8)	3 (18.8)	<0.0001
Cigarette smoking yes, n (%)‡	415 (34.6)	9 (56.3)	0.11
Alcohol consumption yes, n (%)§	140 (11.7)	4 (25.0)	0.11
HBV DNA level, copies/mL <300, n (%) 300–9,999, n (%) 10,000–99,999, n (%) 100,000–999,999, n (%) ≥1,000,000, n (%)	 267 (22.3) 381 (31.8) 185 (15.4) 103 (8.6) 264 (22.0)	 1 (6.3) 1 (6.3) 3 (18.8) 4 (25.0) 7 (43.8)	0.005†
HBV genotype** B, n (%) C, n (%) B+C, n (%)	 590 (64.8) 286 (31.4) 35 (3.8)	 7 (46.7) 8 (53.3) 0 (0.0)	0.25

* Student's t-test for mean age and chi-square test for other variables, † p-value for the trend, ‡ Data were not available for 1 subject,
§ Data were not available for 3 subjects, ** Data were not available for 290 subjects, mostly due to undetectable HBV DNA

Description of Subject with baseline HBV DNA < 300 copies/mL and new onset HCC

- 35 y/o male:
  - Serological profile at enrollment: HBsAg [+]; HBeAg [-]; anti-HCV [-]
  - Biochemical profile: At enrolment ALT 86; AST 91 (September 9th 1991)
  - BMI at enrolment: 21.8
  - No cirrhosis at enrolment but cirrhosis diagnosed in 2002
  - No alcohol consumption
  - HCC diagnosed (November 19, 2001) at age 45 confirmed by ultrasonography and CT
  - Subject only had 2 visit during study follow-up and we can not describe the serological and virological profile any further.

Table 3. Incidence rate of HCC by HBV DNA level and genotype at study entry (per 100,000 PYFU)

	Age <40 years (n=1,216)	Age ≥40 years (n=2,437)	p-value*
HBV DNA level, copies/mL			
<300	31.4	143.6	0.19
300–9,999	22.0	156.0	0.037
10,000–99,999	135.1	366.5	0.14
100,000–999,999	325.6	1,261.2	0.005
≥1,000,000	218.0	1,974.5	<0.0001
HBV genotype			
B	99.3	453.5	<0.0001
C	230.0	1,080.7	<0.0001
B+C	0.0	295.5	–

* Using exact test for two-sample Poisson rates

Table 4. Univariate Cox regression analysis of HCC for subjects <40 years of age

Variable	No. of HCC cases	Crude HR (95% CI)	p-value
Cigarette smoking			
No	7	1.0 (referent)	
Yes	9	2.5 (0.9–6.7)	0.07
Alcohol consumption			
No	12	1.0 (referent)	
Yes	4	2.6 (0.8–8.1)	0.10
HBeAg			
Negative	8	1.0 (referent)	
Positive	8	3.4 (1.3–9.0)	0.015
Serum ALT level, U/L			
<15	3	1.0 (referent)	
15–44	8	4.9 (1.3–18.6)	0.019
≥45	5	16.6 (4.0–69.4)	0.0001
Trend test			<0.0001
Liver cirrhosis at entry			
No	13	1.0 (referent)	
Yes	3	29.0 (8.2–101.9)	<0.0001
HBV DNA level, copies/mL			
<300	1	1.0 (referent)	
300–9,999	1	0.7 (0.04–11.3)	0.80
10,000–99,999	3	4.3 (0.4–41.3)	0.21
100,000–999,999	4	10.5 (1.2–94.3)	0.035
≥1,000,000	7	7.0 (0.9–56.9)	0.07
Trend test			0.032
HBV genotype			
B or B+C	7	1.0 (referent)	
C	8	2.5 (0.9–6.9)	0.08

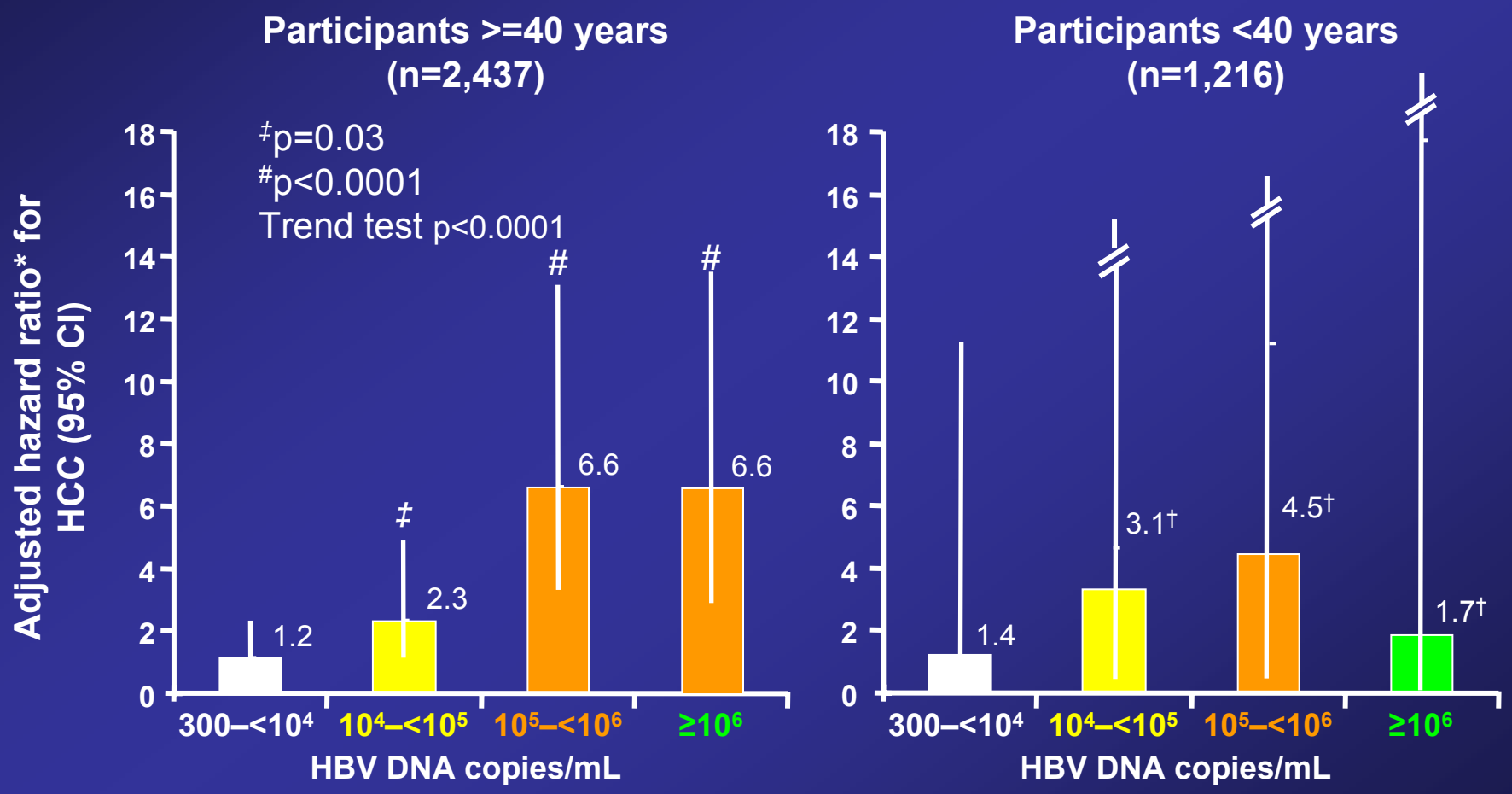
CI=confidence interval; HR = hazard ratio

Table 5. Multivariable Cox regression analysis of HCC for subjects <40 and ≥40 years of age

Variable	Age <40 years		Age ≥40 years	
	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age yrs, mean (median)	1.1 (0.9–1.3)	0.53	1.08 (1.05–1.10)	<0.0001
Cigarette smoking No Yes	 1.0 (referent) 1.6 (0.5–4.5)	 0.41	 1.0 (referent) 1.2 (0.9–1.7)	 0.28
Alcohol consumption No Yes	 1.0 (referent) 1.9 (0.6–6.6)	 0.29	 1.0 (referent) 1.8 (1.2–2.7)	 0.004
HBeAg Negative Positive	 1.0 (referent) 2.2 (0.5–10.8)	 0.31	 1.0 (referent) 2.4 (1.5–3.9)	 0.0003
Serum ALT level, U/L <15 15–44 ≥45 Trend test	 1.0 (referent) 3.0 (0.8–11.8) 8.3 (1.7–40.0)	 0.12 0.009 0.014	 1.0 (referent) 1.8 (1.2–2.6) 1.4 (0.8–2.5)	 0.004 0.19 0.032
Liver cirrhosis at entry No Yes	 1.0 (referent) 12.5 (3.1–50.3)	 0.0004	 1.0 (referent) 9.0 (5.7–14.1)	 <0.0001
HBV DNA level, copies/mL <300 300–9,999 10,000–99,999 100,000–999,999 ≥1,000,000 Trend test	 1.0 (referent) 0.7 (0.0–11.5) 3.1 (0.3–31.7) 4.5 (0.4–47.1) 1.7 (0.1–21.9)	 0.81 0.34 0.21 0.70 0.40	 1.0 (referent) 1.2 (0.5–2.6) 2.3 (1.1–5.0) 6.6 (3.2–13.7) 6.6 (3.1–14.1)	 0.72 0.031 <0.0001 <0.0001 <0.0001

CI=confidence interval; HR = hazard ratio

High HBV Viral Load as an Independent Risk Factor for HCC by Age Category



*Cox proportional hazards regression analysis. Risk is relative to HBV DNA <300 copies/mL. Risk adjusted for age, cigarette smoking, alcohol consumption, HBeAg, serum ALT, liver cirrhosis.

† 95% CI for 10^4–$<10^5$ is 0.3–31.7; 10^5–$<10^6$ is 0.4-47.1; and for $\geq 10^6$ is 0.1-21.9.

Summary

- The overall incidence rate of HCC was 111 per 100,000 PYFU for the subset of the R.E.V.E.A.L. cohort less than 40 years of age at enrolment
- All HCC cases were males; the median time to the HCC diagnosis was 9.6 years meaning that most HCC cases manifested after 40 years of age.
- Elevated serum ALT level and liver cirrhosis at entry were statistically significant independent predictors of HCC
- Increasing age, alcohol consumption, HBeAg status and increasing level of serum HBV DNA were not significantly associated with a higher risk of HCC in subjects < 40 years old.

Conclusions

- The overall risk of developing HCC in subjects below 40 years of age, over the follow-up period was low
- In this analysis, the presence of liver cirrhosis was the strongest risk predictor of HCC in subjects less than 40
- Due to the small number of HCC cases in this young age group, results from the regression model should be interpreted with caution
- The predictors of HCC in subjects less than 40 years are different from those in subjects over 40 years of age; more needs to be done to understand this population.
- Serum HBV DNA and the presence of liver cirrhosis remain the strongest predictors of HCC risk in subjects ≥40 years old