What have we learned from HBV clinical cohorts?

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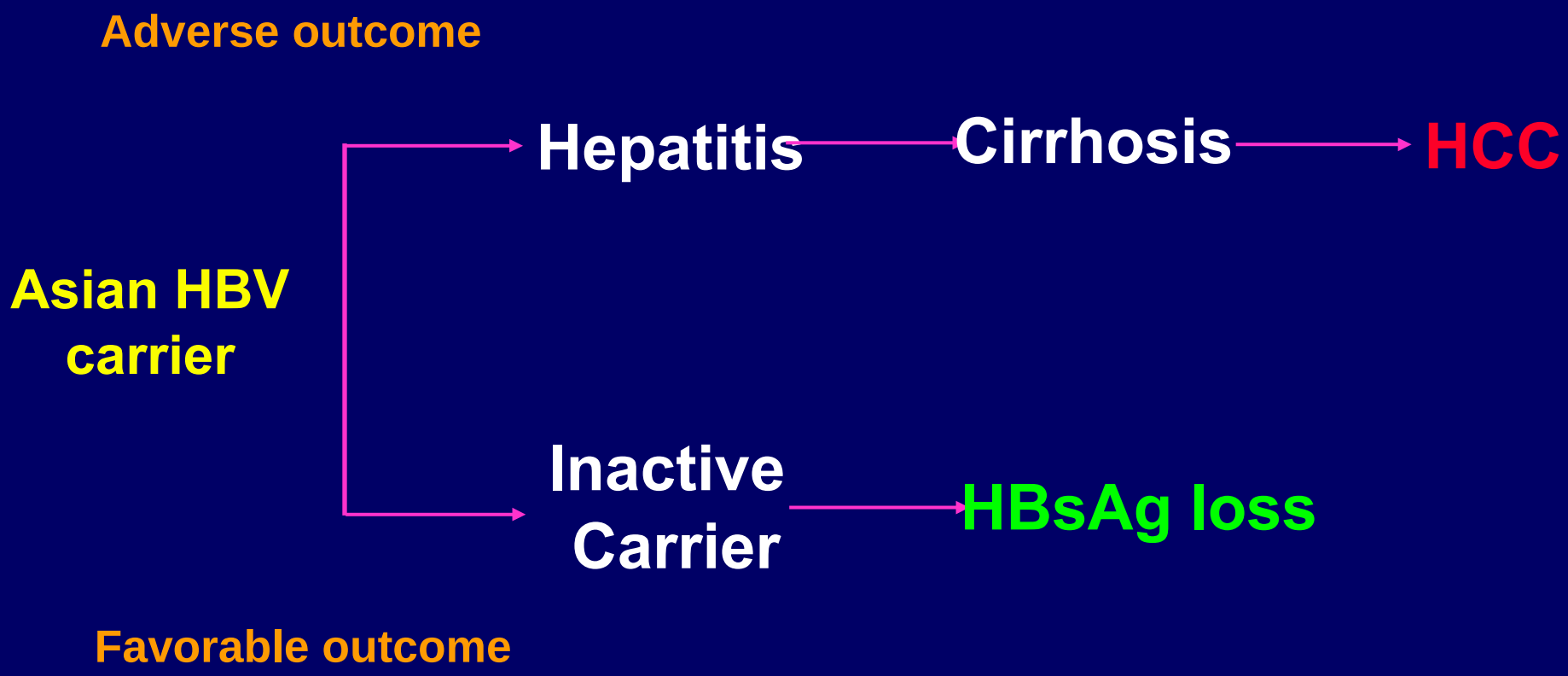
Clinical outcomes of Asian HBV carriers



What are factors affecting long-term outcomes?

Chen DS. Hepatology 2011;54:381-392.

Factors associated with disease progression in Asian HBV carriers

Viral

Persistent presence of HBeAg

Persistently high HBV-DNA level

HBV genotype C > genotype B

Core promoter mutations*

High HBsAg level**

Host

Male gender
Increasing age

Recurrent ALT flare

Persistently increased ALT levels

Cirrhosis*

Diabetes*

Environment

Heavy drinking

Cigarette smoking*

Aflatoxin*

HCV, HDV, or HIV co-infection

*Factors shown to be associated with an increases risk of HCC only. Abbreviations: ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma

** In HBV carriers with HBV DNA < 2000 IU/mL

Kwon and Lok. Nat. Rev Gastroenterol Hepatol 2011; Tseng and Kao, et al Gastroenterology 2012.

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Outline

- HBV natural history cohorts
  - REVEAL-HBV
  - SEARCH-B
  - ERADICATE-B
- Risk calculator update
- Conclusions

Summary of three HBV cohorts

Cohort	Study design	Disease stage	Number of participants	Follow-up (y)
REVEAL-HBV	Community -based cohort	Including HBeAg-positive and -negative phases	3653	11.4
SEARCH-B	Hospital-based cohort	Early HBeAg negative phase	390	7.4
ERADICATE-B	Hospital-based cohort	Including HBeAg-positive and -negative phases	2688	14.7

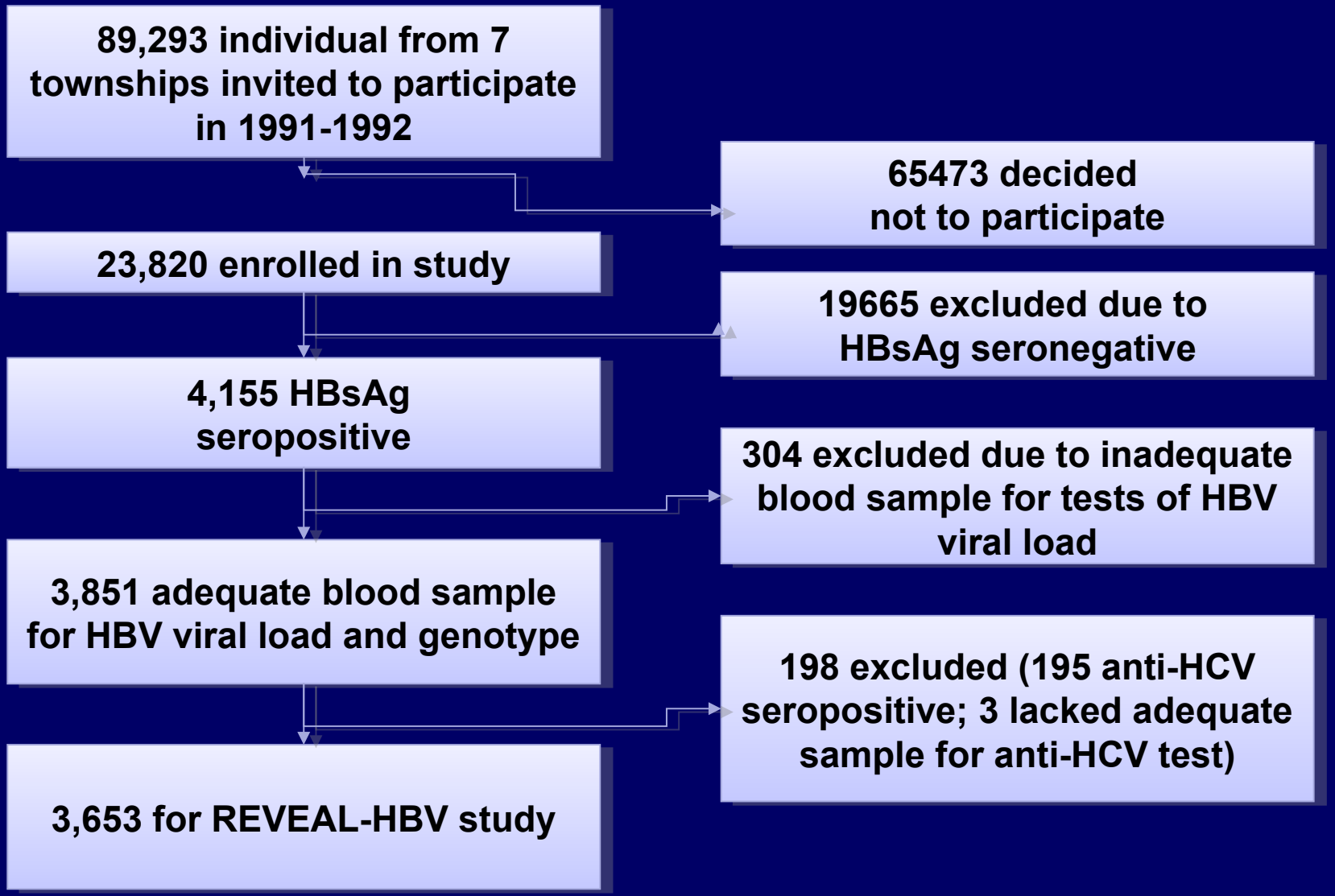
REVEAL-HBV = Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus

SEARCH-B = Study of E Antigen seRoClearance of Hepatitis B

ERADICATE-B = Elucidation of Risk fActors for DIsease Control or Advancement in Taiwanese Hepatitis B Carriers

Tseng and Kao. Tzu Chi Medical Journal 2013;25:75-81.

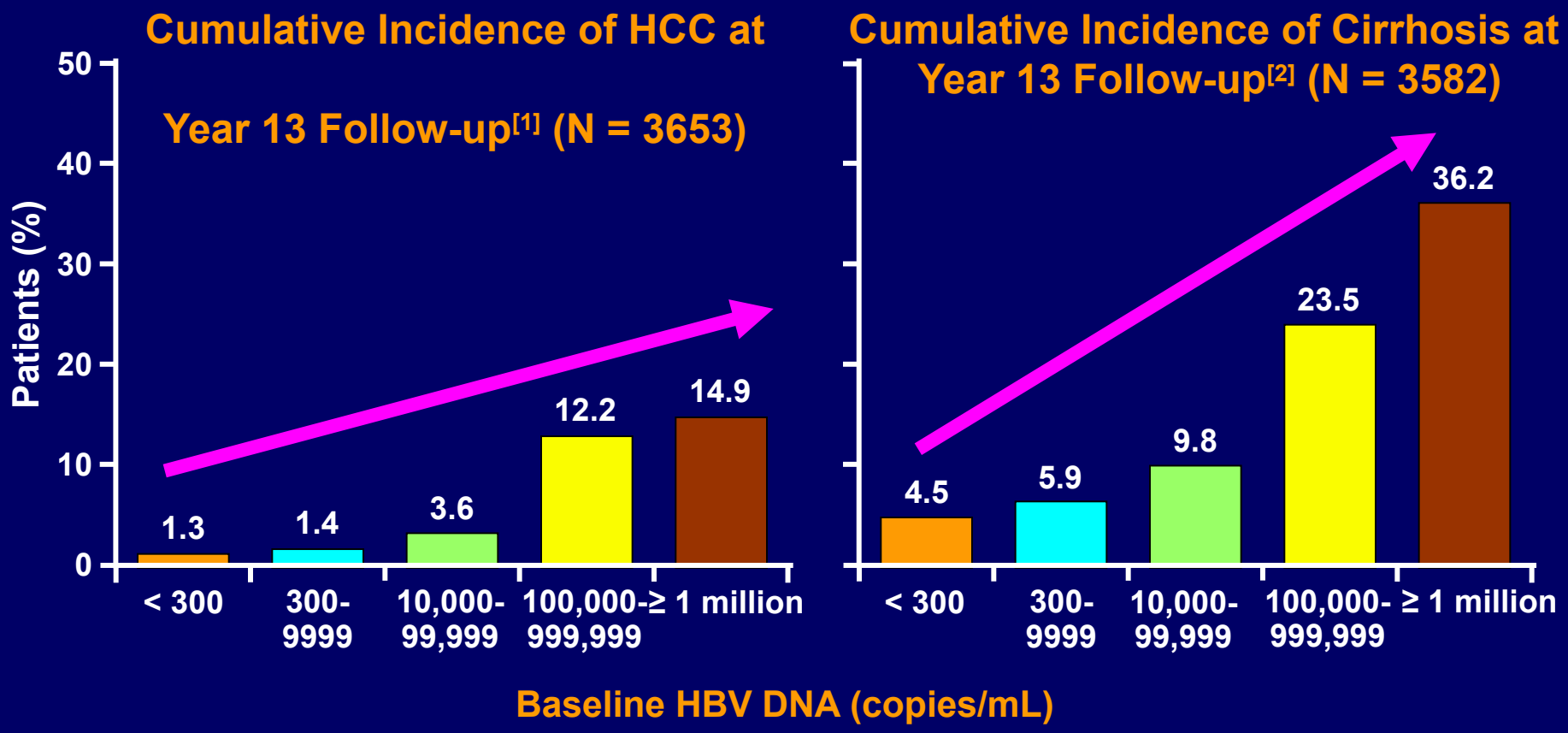
Flow of REVEAL-HBV cohort



1. Chen CJ, et al. JAMA. 2006;295:65-73.
2. Yang HI et al. JCO 2010;28:2437-2444

High baseline HBV DNA associated With increased risk of HCC and cirrhosis

REVEAL: Long-term follow-up of untreated community-based HBsAg+ve individuals in Taiwan



1. Chen CJ, et al. JAMA. 2006;295:65-73.
2. Iloeje UH, et al. Gastroenterology. 2006;130:678-686.

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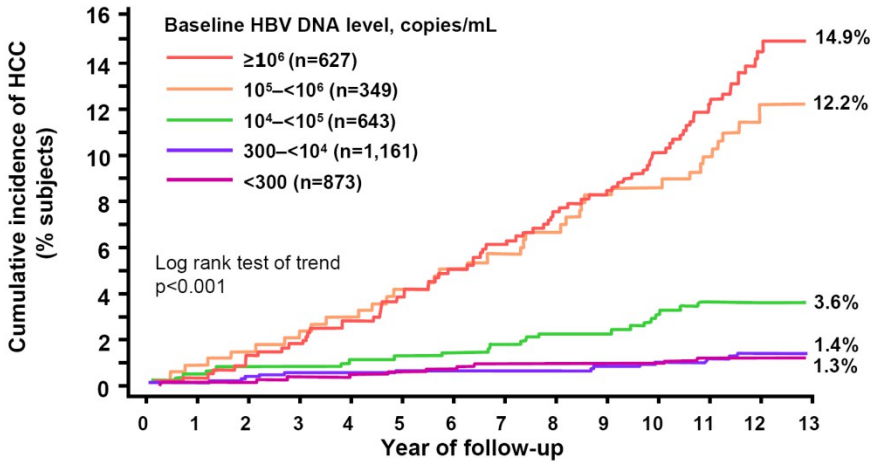
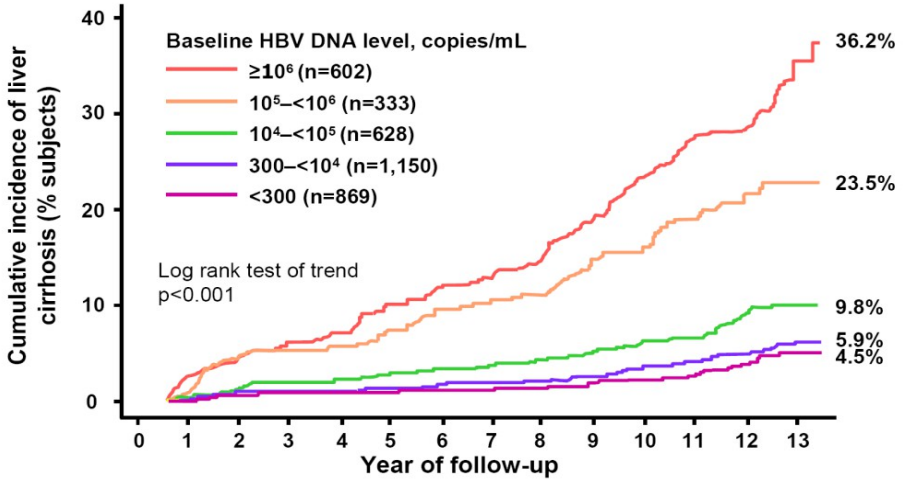
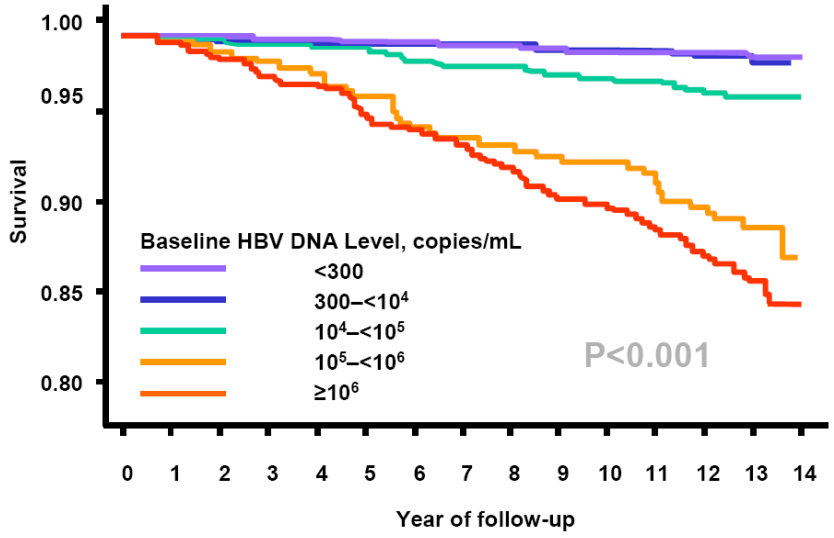
Serum HBV DNA level and liver disease progression and survival







Chen CJ et al. JAMA 2006;295:65-73.

Iloeje UH et al. Gastroenterology 2006;130:678-686.

Iloeje UH et al. Clin Gastroenterol Hepatol 2007;5:921-931.

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REVEAL-HBV: summary

- HBV viral load is a strong risk predictor for cirrhosis and HCC independent of HBeAg status, ALT level and other risk factors
- Baseline serum HBV DNA level > 10,000 copies/mL may start to increase risk of cirrhosis and HCC in HBV carriers aged 30-65 years after > 10 years of follow-up
- Patients with persistently high HBV DNA level have the highest risk
- Measurements of HBV viral load may help define which HBV carriers aged 30 years or older are at high risk for cirrhosis and HCC

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Outline

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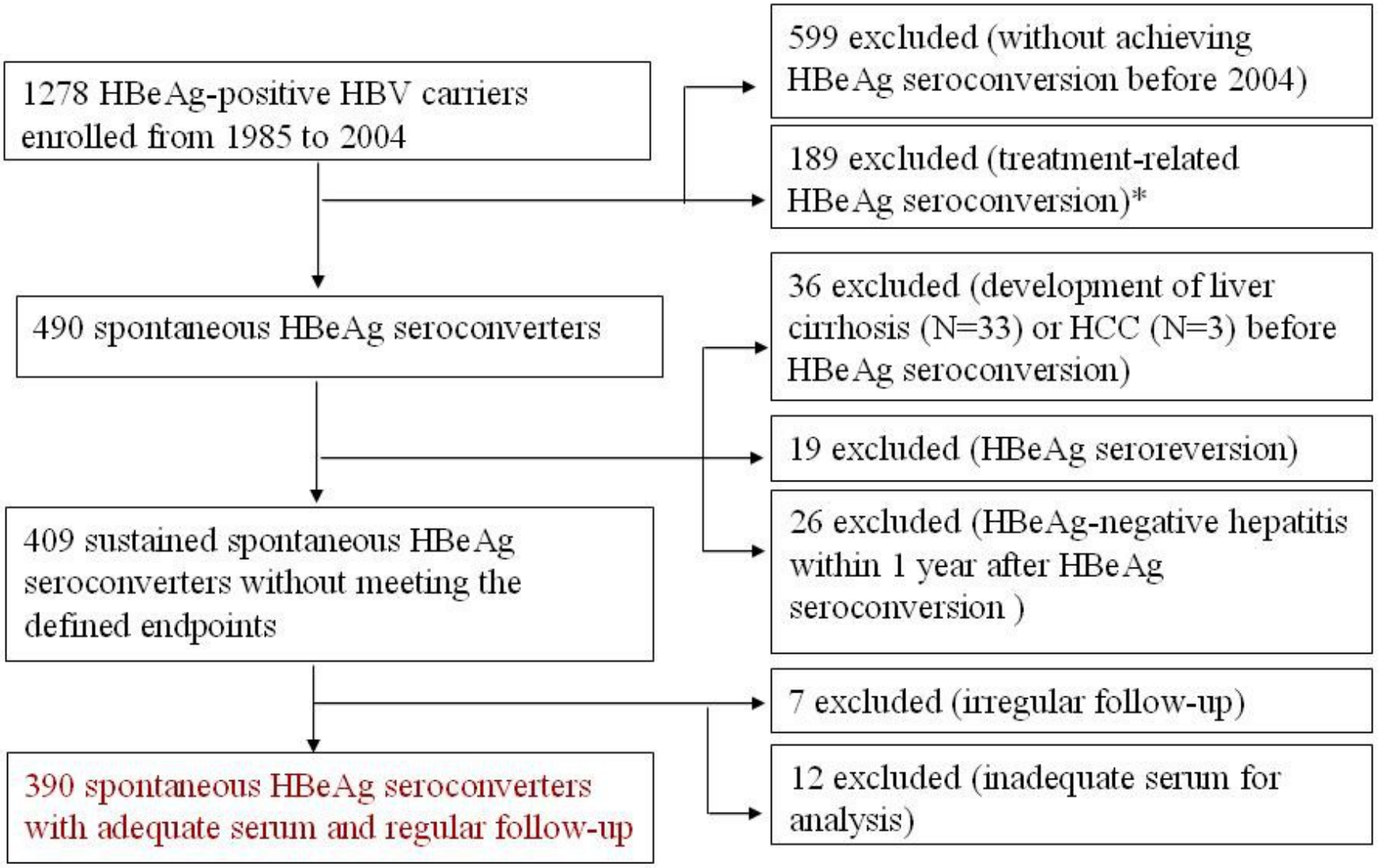
  - SEARCH-B
  - ERADICATE-B
- Risk calculator update
- Conclusions

Flow of SEARCH-B cohort



Tseng TC, Liu CJ, Kao JH et al. Gastroenterology 2011;141:517-525

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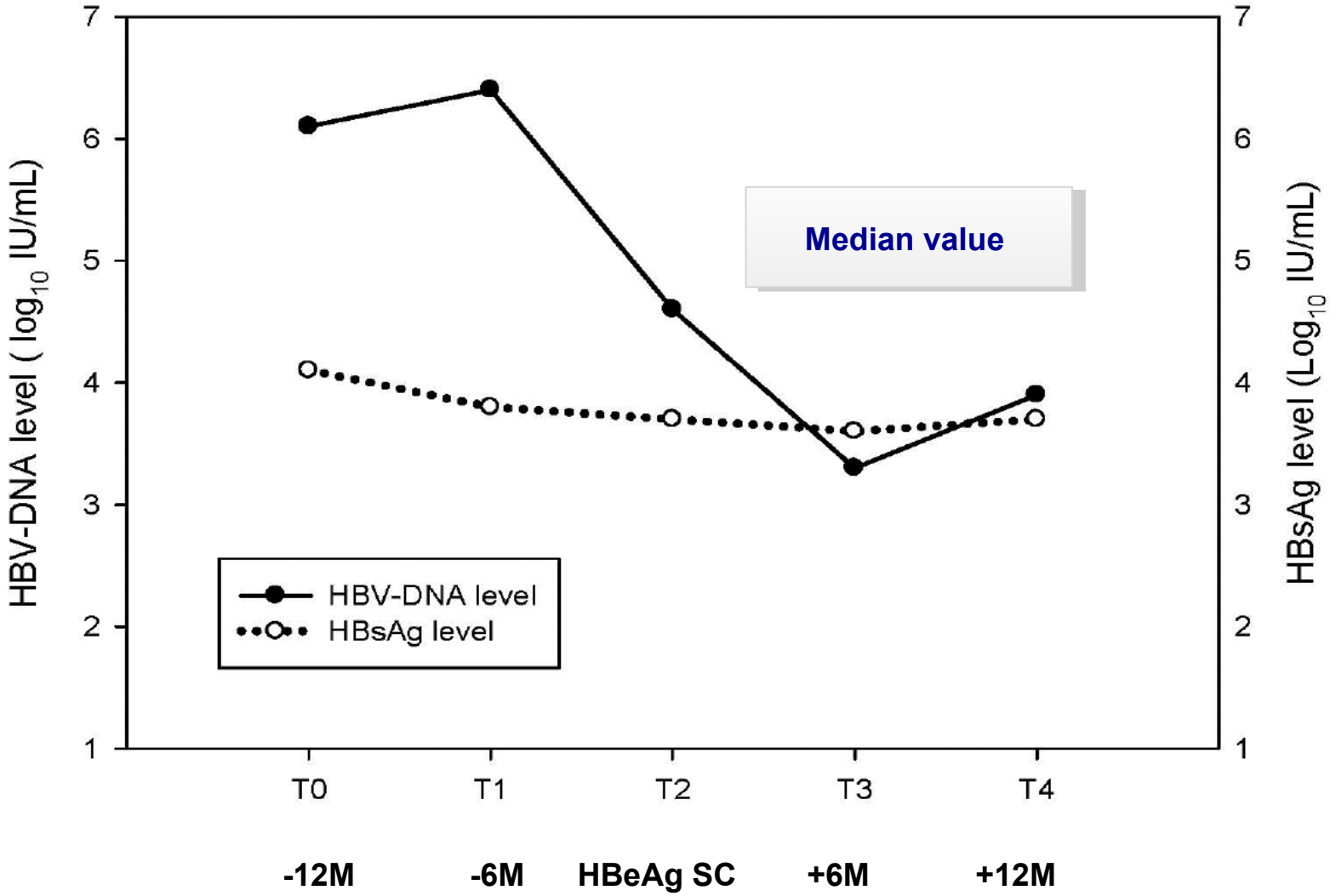
Pilot study of viral kinetics in 42 patients



Tseng TC, Liu CJ, Kao JH et al. Gastroenterology 2011;141:517-525.

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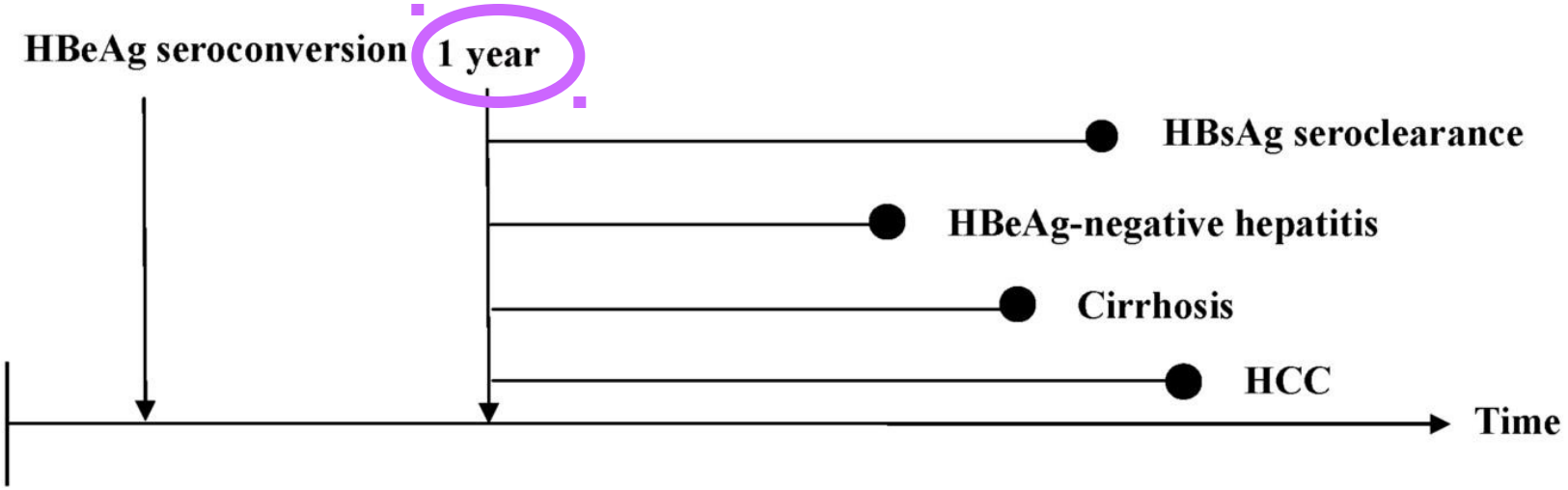
Endpoints of follow-up



- Censored at
  - Meeting each endpoints
  - End of follow-up
  - Starting anti-viral therapy

Tseng TC, Liu CJ, Kao JH et al. Gastroenterology 2011;141:517-525.

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Definition of endpoints

- **HBeAg-negative hepatitis (ENH)**
  - ALT > 80 U/L (two times the upper limit of normal)
  - HBV-DNA level >2000 IU/ml within 6 months
- **Hepatitis flare**
  - ALT elevation > 5 X ULN with a concomitant serum HBV DNA level > 2000 IU/mL
- **Cirrhosis**
  - Histologically
  - Ultrasonographic findings supplemented with clinical features
- **HCC**
  - Histology/cytology or by typical image findings in hepatic nodules > 1 cm

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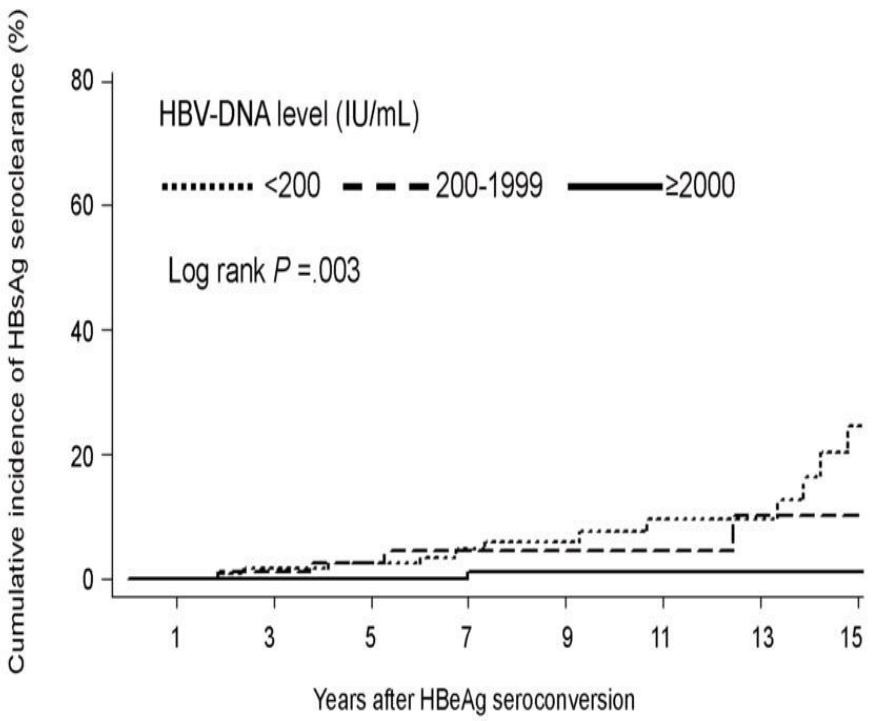
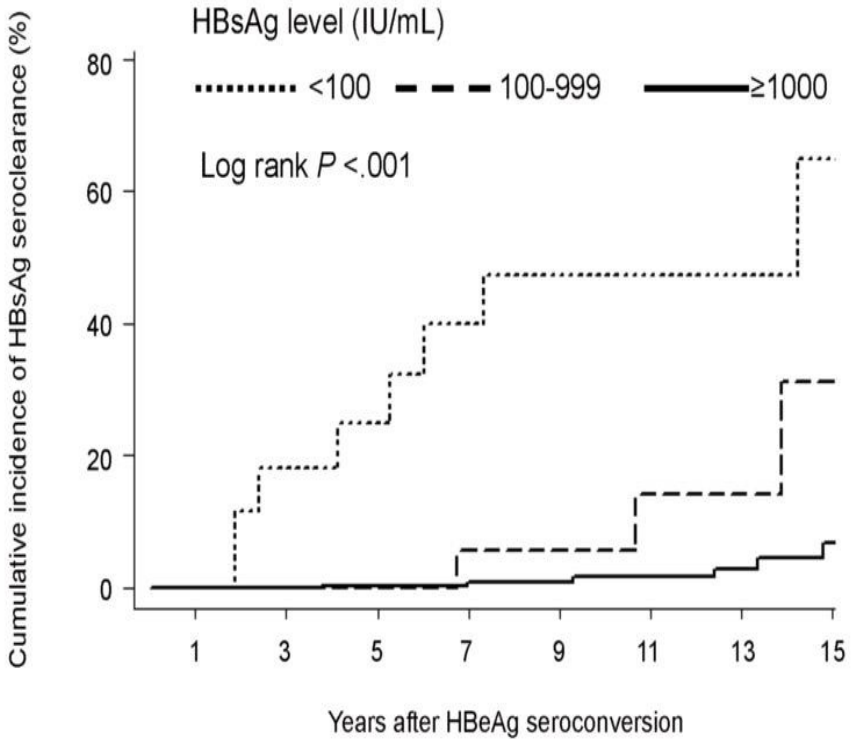
Prediction of HBsAg loss: HBV DNA vs. HBsAg



Number at risk

Serum HBV-DNA level at one year post HBeAg seroconversion (IU/mL)

<200	139	124	108	77	63	44	29	17
200-1999	100	77	56	40	33	24	13	5
≥2000	151	134	117	86	64	51	35	19



Number at risk

Serum HBsAg level at one year post HBeAg seroconversion (IU/mL)

<100	18	15	11	8	6	6	5	3
100-999	34	33	29	17	14	10	5	3
≥1000	338	290	241	178	142	104	67	37

Tseng TC, Liu CJ, Kao JH et al. Gastroenterology 2011;141:517-525.

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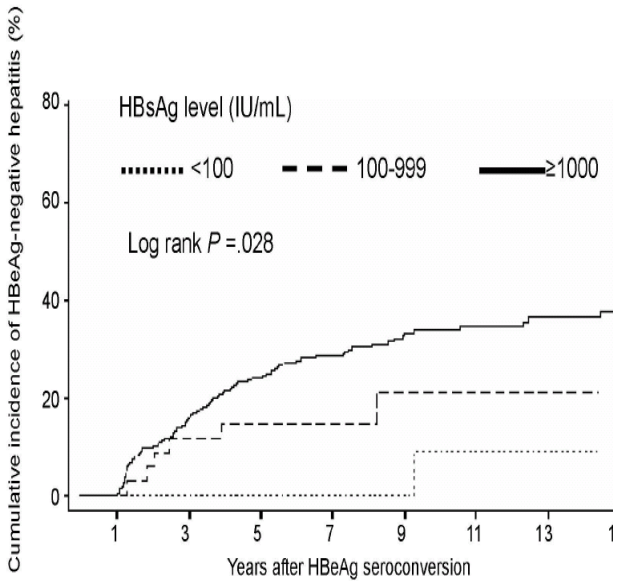
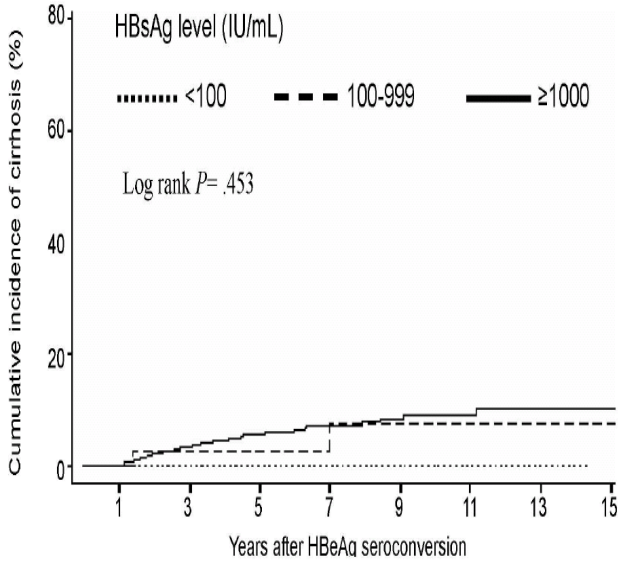
Higher HBsAg level predicts incidence of ENH, but not cirrhosis, and HCC



Number at risk

Serum HBsAg level at one year post HBeAg seroconversion (IU/mL)

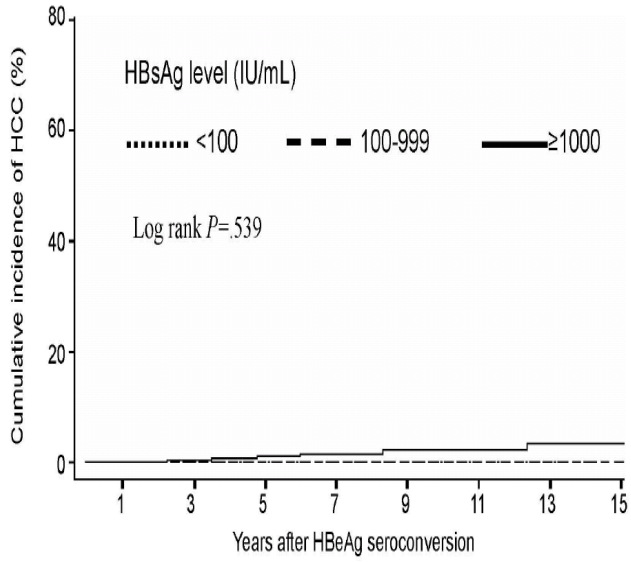
<100	18	15	14	12	11	8	8
100-999	34	30	27	17	13	7	4
≥1000	338	262	211	158	117	87	58



Number at risk

Serum HBsAg level at one year post HBeAg seroconversion (IU/mL)

<100	18	15	14	12	11	8	8	6
100-99	34	34	31	20	16	11	8	5
≥1000	338	299	258	198	147	109	74	49



Number at risk

Serum HBsAg level at one year post HBeAg seroconversion (IU/mL)

<100	18	15	14	12	11	8	8	6
100-999	34	34	32	22	18	13	9	6
≥1000	338	308	268	210	158	119	81	53

Tseng TC, Liu CJ, Kao JH et al. Gastroenterology 2011;141:517-525.

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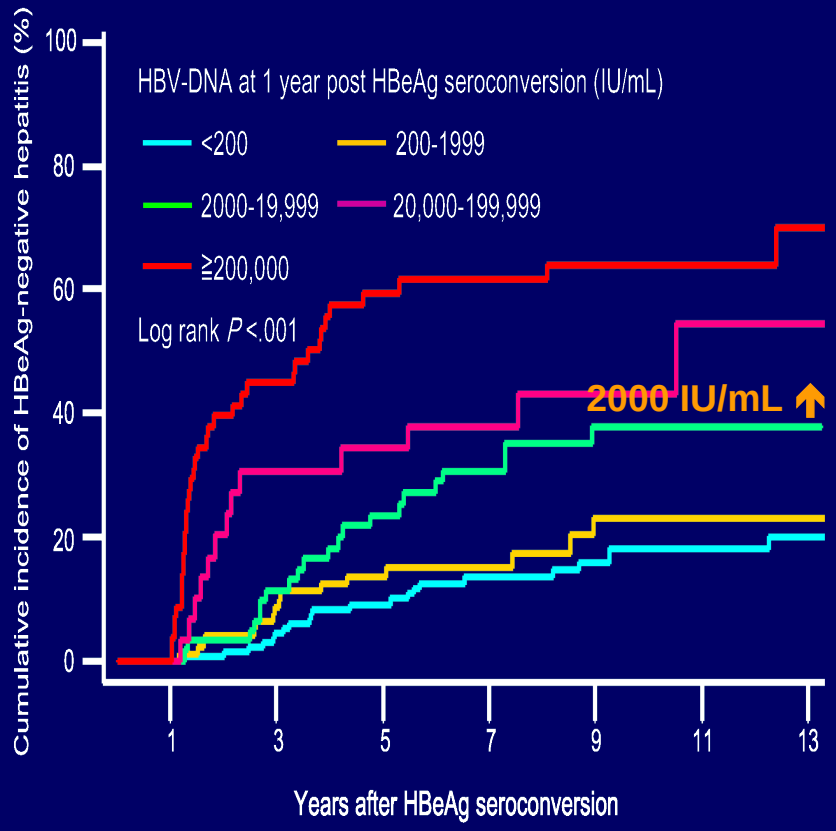
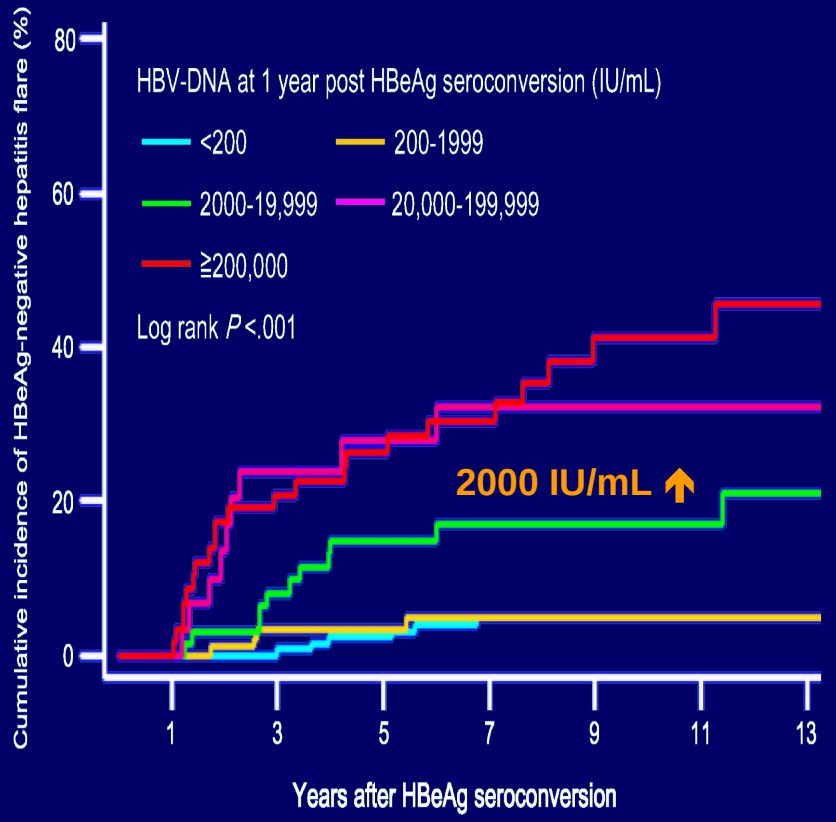
Higher HBV DNA level predicts more ENH and hepatitis flare (SEARCH-B)

HBeAg(-) hepatitis



Hepatitis f are



@ HBeAg seroconversion may not always confer favorable outcomes. Serum HBV DNA levels> 2000 IU/mL at 1 year post HBeAg seroconversion correlate with increased risk of HBeAg-negative hepatitis and hepatitis flare

Tseng and Kao et al. JID 2012;205: 54-63

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SEARCH-B: summary

- In spontaneous HBeAg seroconverters with HBV genotype B or C infection, a lower serum HBsAg level at early HBeAg-negative phase is associated a higher HBsAg loss rate
- HBsAg level <100 IU/mL predicts HBsAg loss within 6 years in spontaneous HBeAg seroconverters with HBV DNA level 200 IU/mL
- Serum HBV DNA level is better than HBsAg level in predicting disease progression in spontaneous HBeAg seroconverters

Tseng and Kao et al. Gastroenterology 2011;141:517-525.

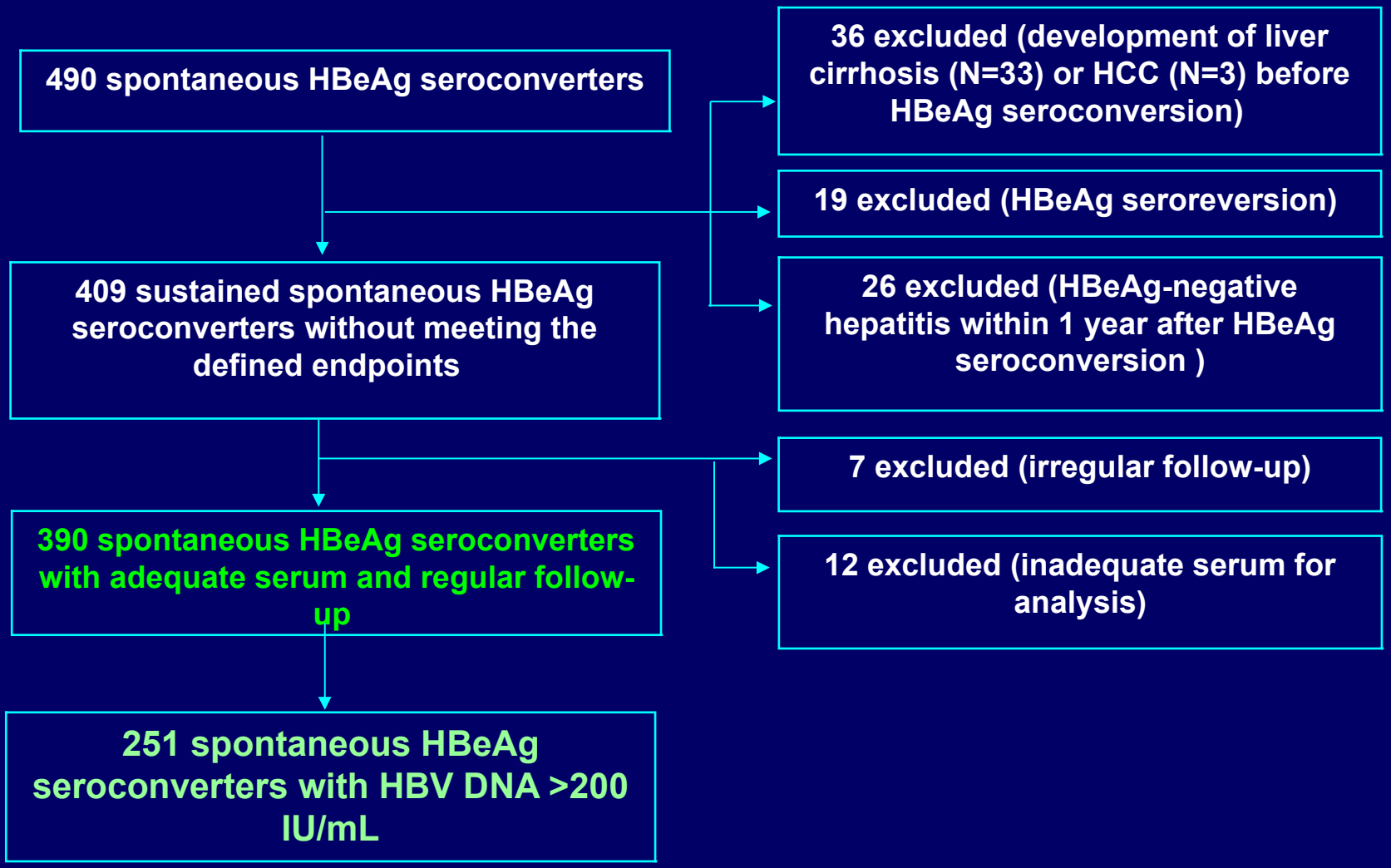
Tseng and Kao et al. JID 2012;205: 54-63

SEARCH-B: issues remained

- **Predictive value**
  - For HBsAg loss: HBsAg level is better
  - For adverse outcomes: HBV-DNA level is better
- **Explanation**
  - HBV-DNA level, compared to HBsAg level, varies within a short period time
  - HBsAg level may be a better marker for immune control of HBV
- **Future studies in natural history**
  - Predictive value of other biomarkers (e.g. viral variants)
  - Cutoff HBsAg level to define true inactive carriers
  - Role of HBsAg in stratifying risk of disease progression in patients with different viral loads

Flow of SEARCH-B subcohort

qBCPm and cirrhosis risk

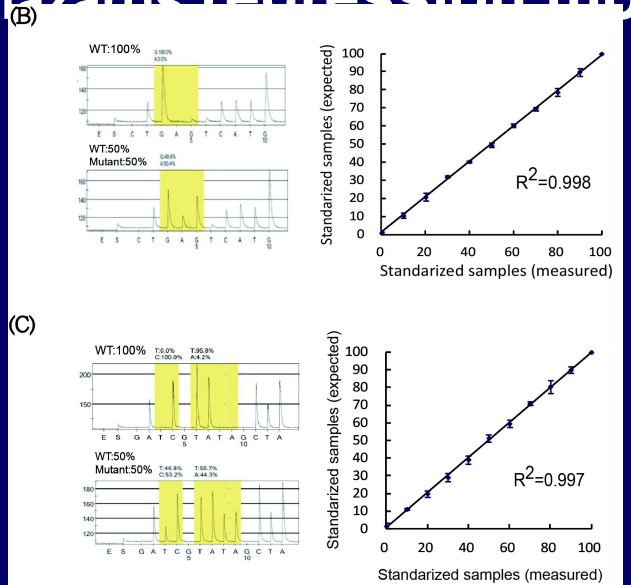


Tseng and Kao et al. Gut 2014.

Kao 2015

Methods

- **PC and BCP variations**
  - Qualitative analysis by Taqman assay (major sequence): in VL >200 IU/mL
  - Quantitative analysis by pyrosequencing: in VL >2000 IU/mL [1]
- **Statistical analysis**
  - Kaplan-Meier failure estimate
  - Cox proportional hazards regression models



1 Yang et al. Hepatology 2013; 57: 934-43

Tseng and Kao, et al. Gut 2014.

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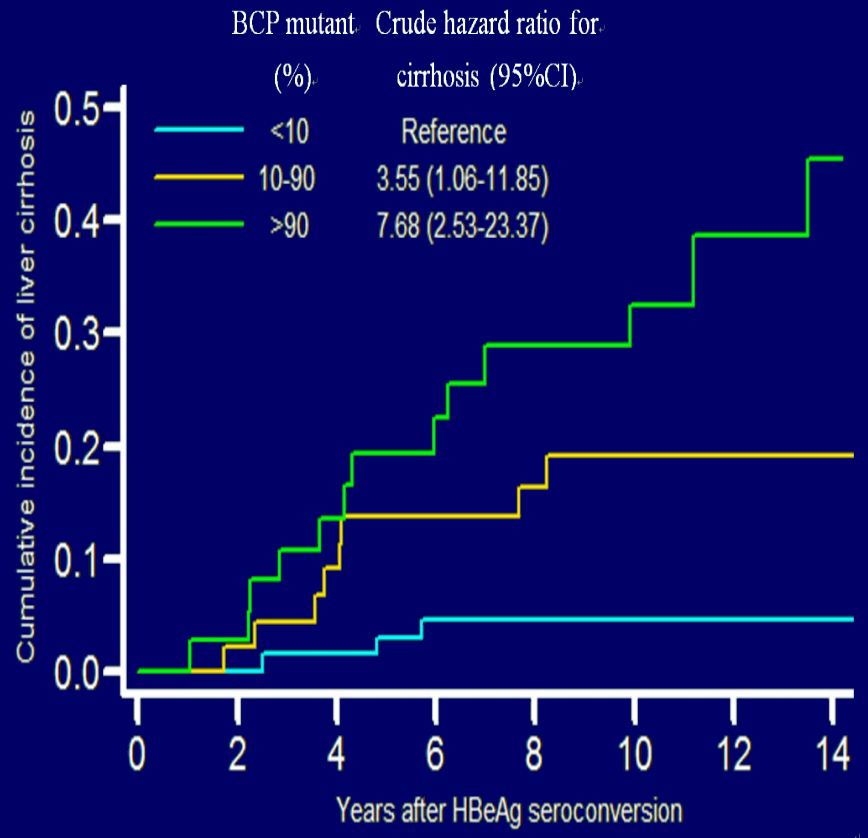
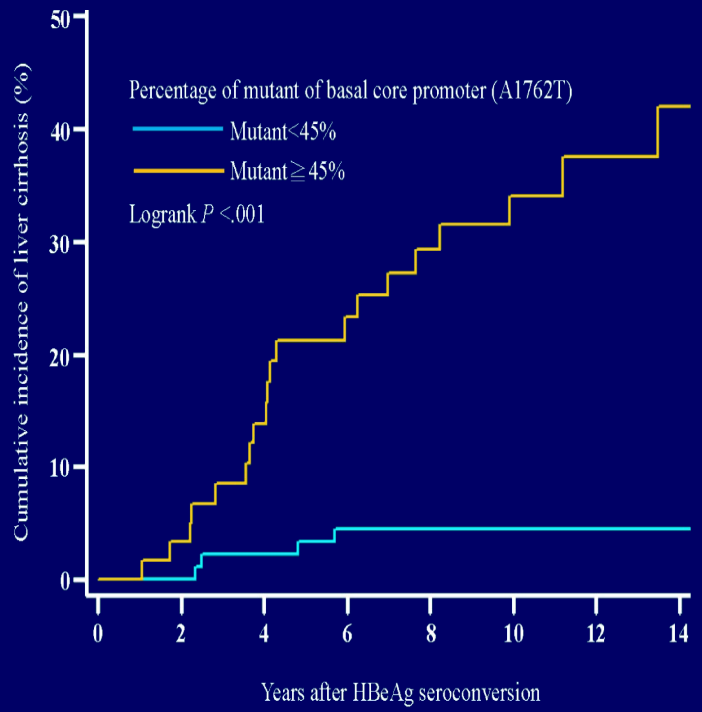
Higher BCP mutant proportion has a higher cirrhosis risk in 151 patients with HBV DNA level > 2000 IU/mL

Categorized by 10% & 90%



Categorized by 45%



Tseng and Kao et al. Gut 2014.

Kao 2015

SEARCH-B subcohort: summary

- PC/BCP variants are not associated with ENH
- A higher proportion of BCP mutant is associated with a higher risk of cirrhosis in patients with HBV DNA level > 2000 IU/mL (high viral load)

Tseng and Kao et al. Gut 2014.

Kao 2015

Outline

- HBV natural history cohorts
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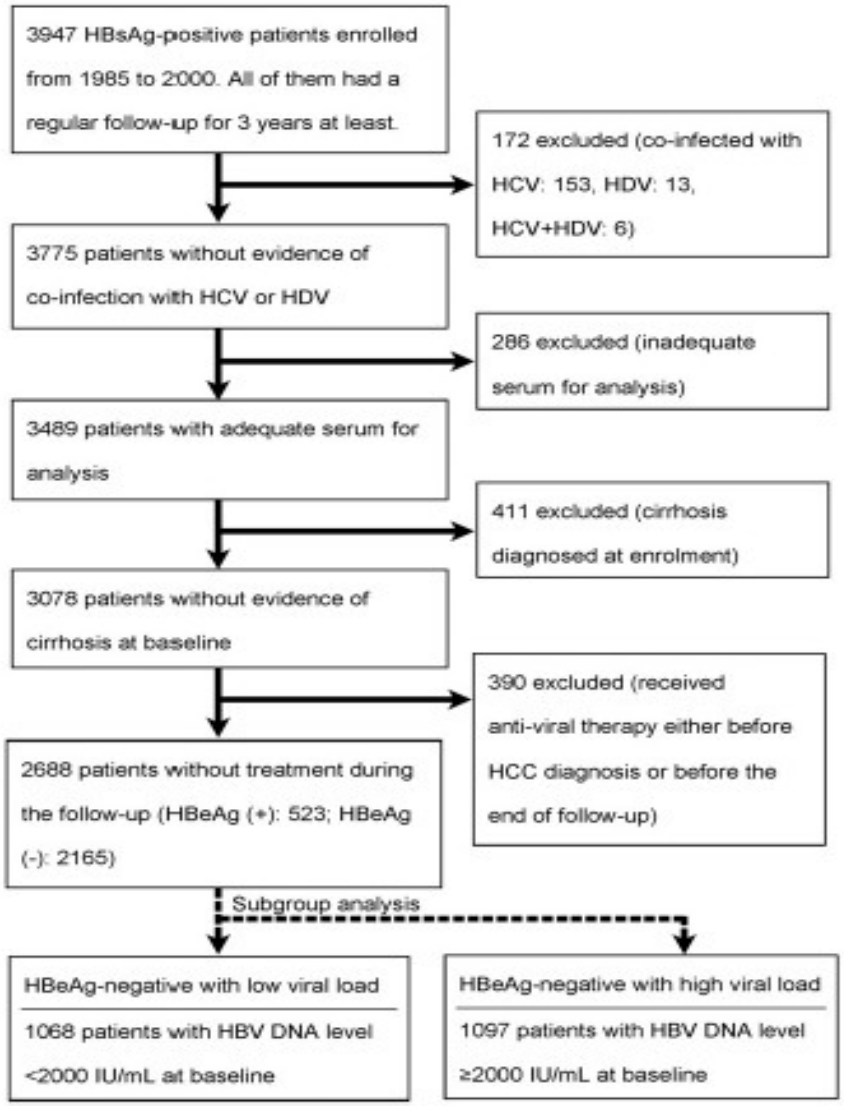
  - ERADICATE-B
- Risk calculator update
- Conclusions

Flow of ERADICATE-B

- **2688 Taiwanese chronic hepatitis B patients followed for a mean of 14.7 years; cirrhosis excluded by USG**



Tseng, Kao et al. Gastroenterology 2012

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ERADICATE-B Study: risk factors for higher HCC risk

Male gender

Older age

Higher ALT

Higher HBV DNA

Higher HBsAg

Genotype C

	Patients, n	Patient-years of follow-up	HCC, n	Annual incidence rate (per 100,000 patient-years)	Crude HR (95% CI)	*P* value
Sex						
Female	1054	15,440.3	37	239.6	1.0	
Male	1634	23,986.8	154	642.0	2.7 (1.9–3.8)	<.001
Age, *y*						
28–39	1407	21,236.5	62	292.0	1.0	
40–49	763	11,152.4	54	484.2	1.7 (1.2–2.5)	.004
50–59	369	5164.7	43	832.6	3.0 (2.1–4.5)	<.001
≥60	149	1873.5	32	1708.0	6.9 (4.5–10.6)	<.001
Serum ALT level, *U/L*						
<20	1051	16,611.0	27	162.5	1.0	<.001
20–39	854	11,908.6	49	411.5	2.8 (1.8–4.5)	
≥40	783	10,907.6	115	1054.3	7.2 (4.7–511.0)	<.001
HBeAg status						
Negative	2165	31,588.6	127	402.0	1.0	
Positive	523	7838.6	64	816.5	2.0 (1.5–2.7)	<.001
Serum HBV DNA level, *IU/mL*						
<200	438	6454.6	12	185.9	1.0	
200–1999	649	9780.3	17	173.8	0.9 (0.4–1.9)	.824
2000–19,999	555	8141.4	30	368.5	2.0 (1.0–3.9)	.044
20,000–199,999	292	4223.6	32	757.6	4.1 (2.1–8.0)	<.001
≥200,000	754	10,827.1	100	923.6	5.1 (2.–9.2)	<.001
Serum HBsAg level, *IU/mL*						
<10	129	1735.8	3	172.8	1.0	
10–99	268	3916.0	8	204.3	1.1 (0.3–4.2)	.881
100–999	703	10,269.6	43	418.7	2.3 (0.7–7.3)	.171
1000–9999	1215	18,077.3	108	597.4	3.2 (1.0–10.0)	.048
≥10,000	373	5428.5	29	534.2	2.9 (0.9–9.5)	.080
HBV genotype[a]						
B	1308	19,154.7	93	485.5	1.0	
C	312	4327.1	69	1594.6	3.4 (2.5–4.6)	<.001

Tseng, Kao. Gastroenterology 2012

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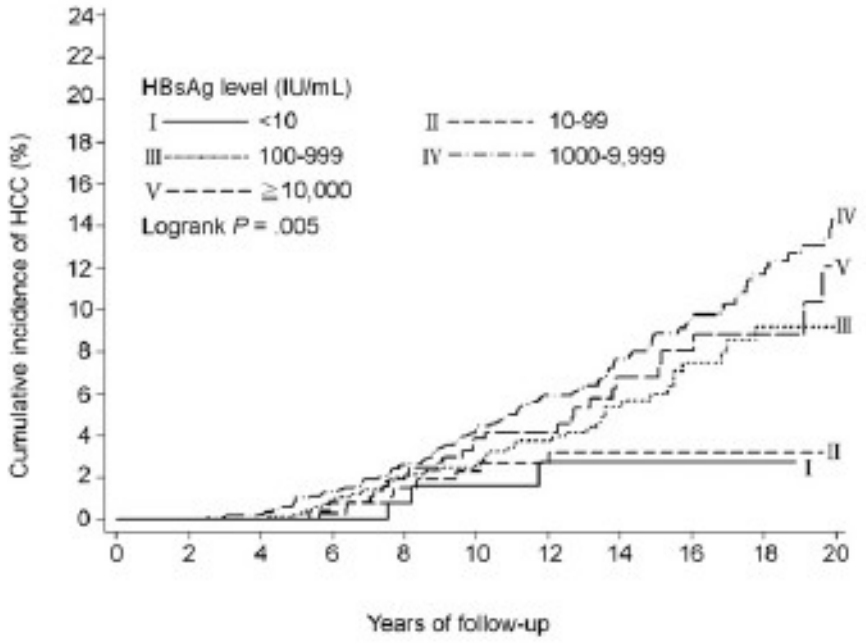
ERADICATE-B: HCC according to baseline HBsAg level

- In overall assessment, HBsAg level was not a significant risk factor for HCC
- However, in patients with lower HBV DNA levels, HBsAg level was a significant factor for HCC risk

Clinical utility of HBsAg level in patients with low HBV DNA



Number at risk											
Serum HBsAg level at baseline (IU/mL)											
<10	129	129	129	129	126	113	85	56	21	9	7
10-99	268	268	268	265	262	248	192	128	76	54	37
100-999	703	703	703	697	684	631	484	353	220	135	92
1000-9999	1215	1215	1212	1198	1175	1080	868	603	400	281	196
≥10000	373	373	373	372	363	329	263	184	119	74	50

Tseng, Kao. Gastroenterology 2012

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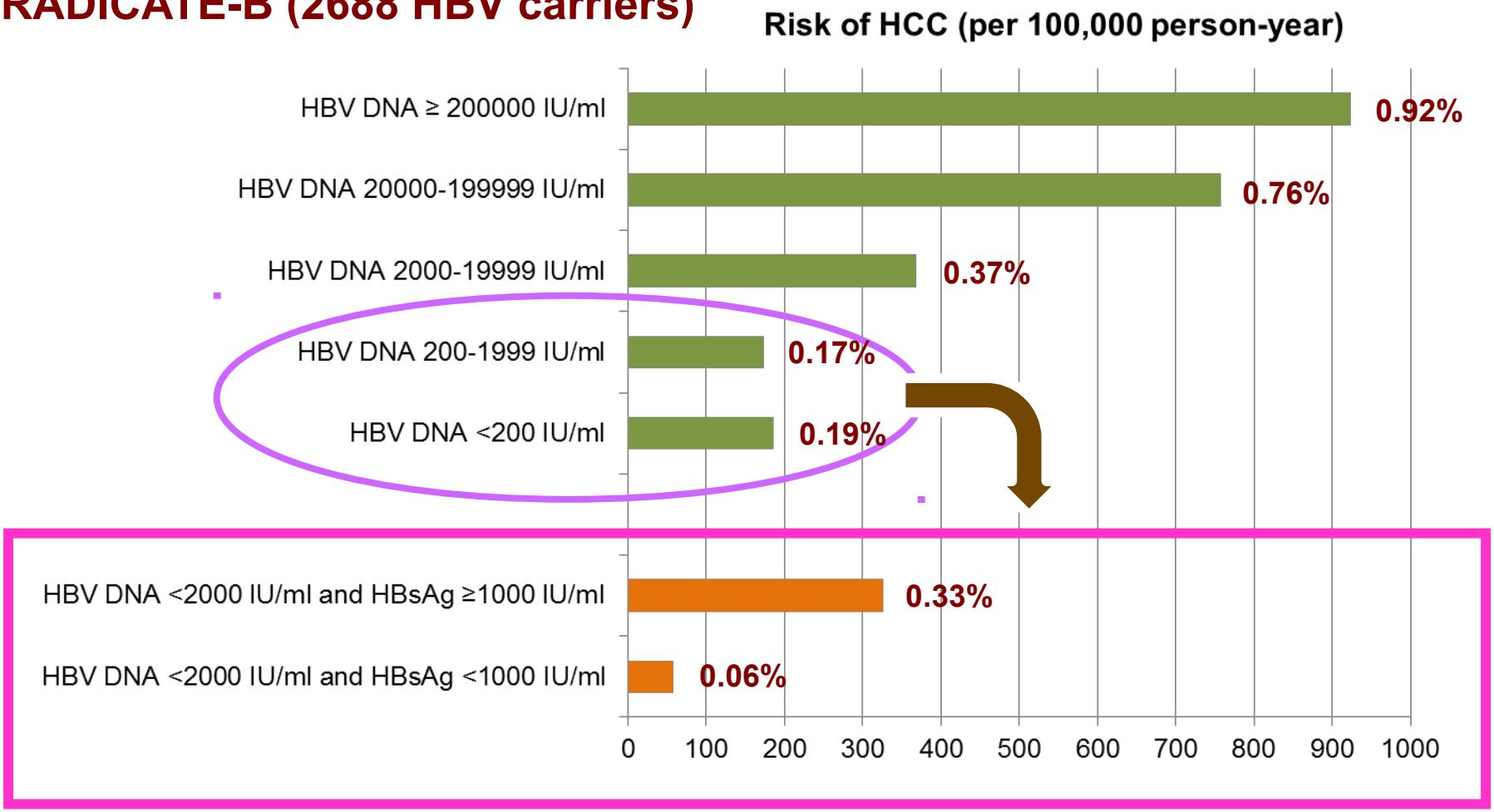
HBsAg level is an important risk factor in patients with low HBV DNA level (<2000 IU/mL)

ERADICATE-B (2688 HBV carriers)



*Start antiviral therapy at annual HCC risk of 0.3%

Tseng, Kao. Gastroenterology 2012; Chan HL. Gastroenterology 2012

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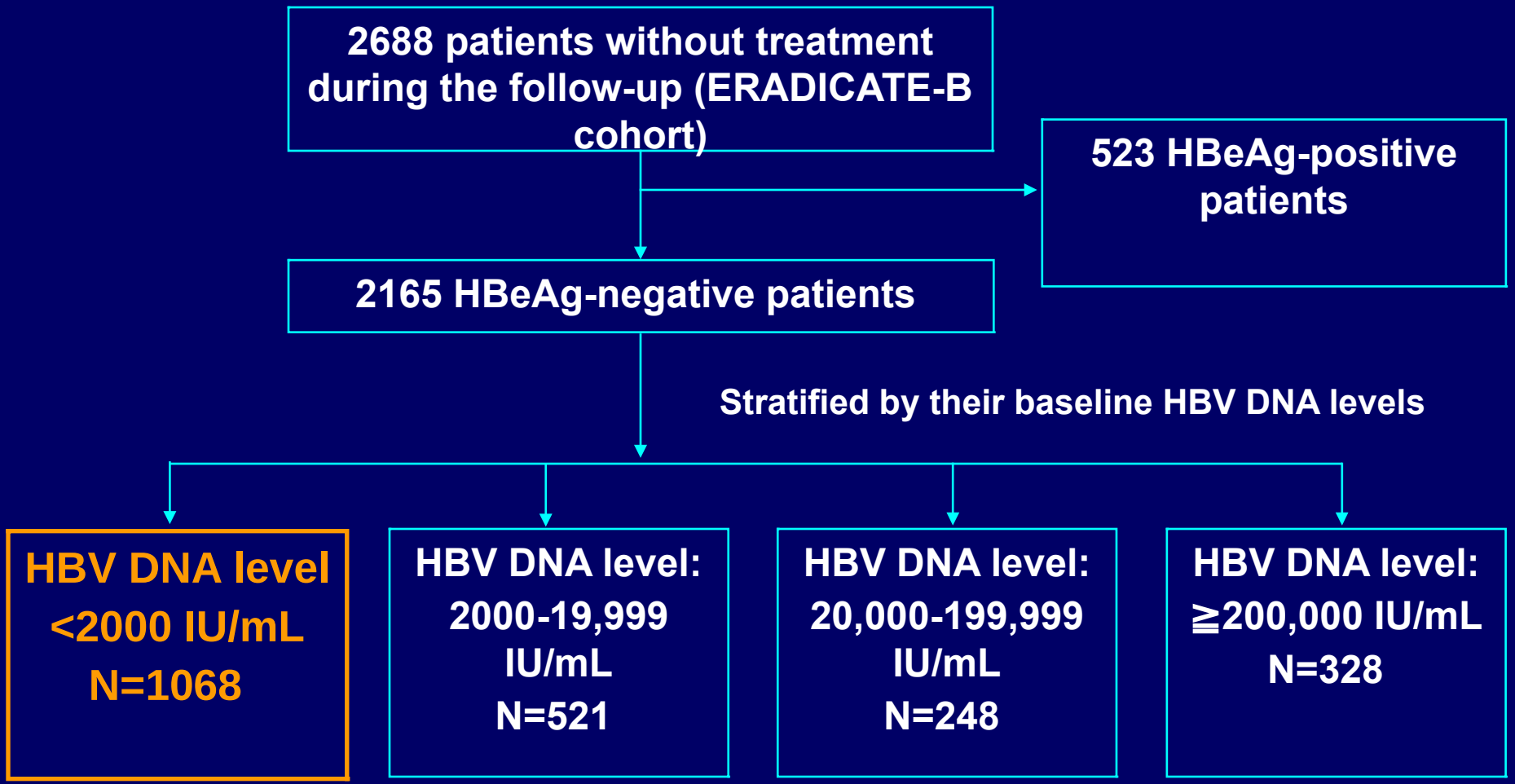
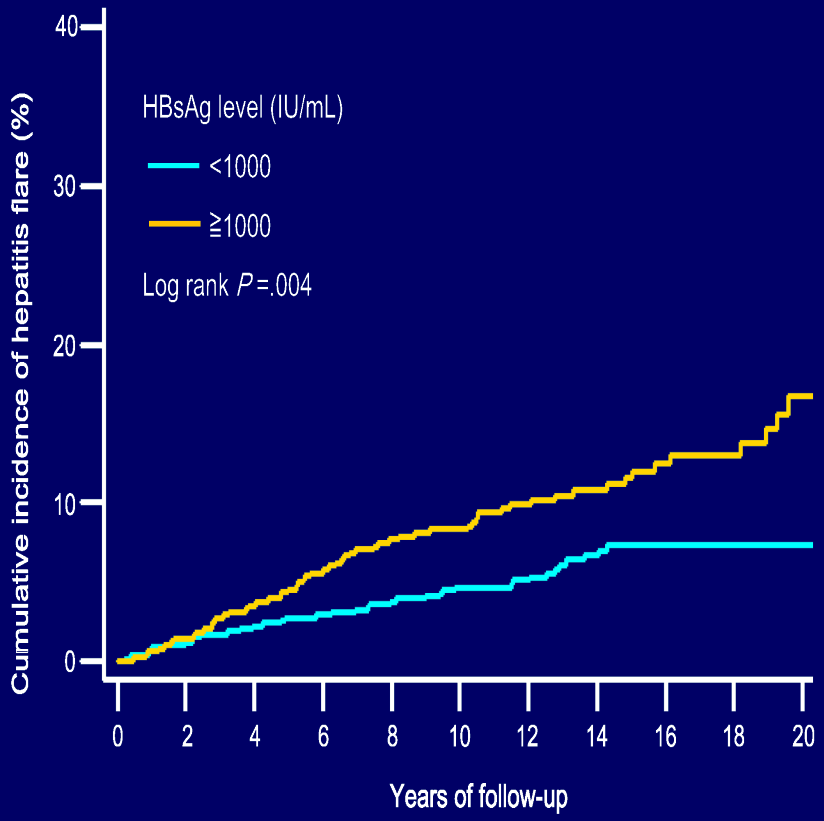
ERADICATE-B subcohort:
Low Viremia (LV) cohort

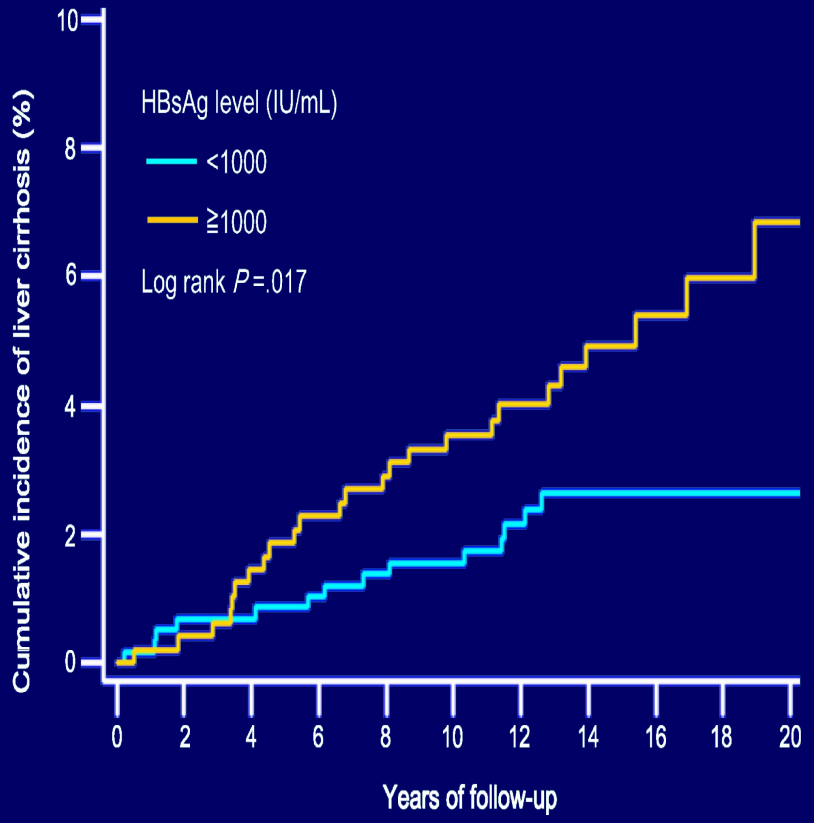


Tseng and Kao et al. Hepatology 2013.

HBsAg level > 1000 IU/mL predicts hepatitis flare and cirrhosis



Hepatitis f are



Cirrhosis

Tseng and Kao et al. Hepatology 2013.

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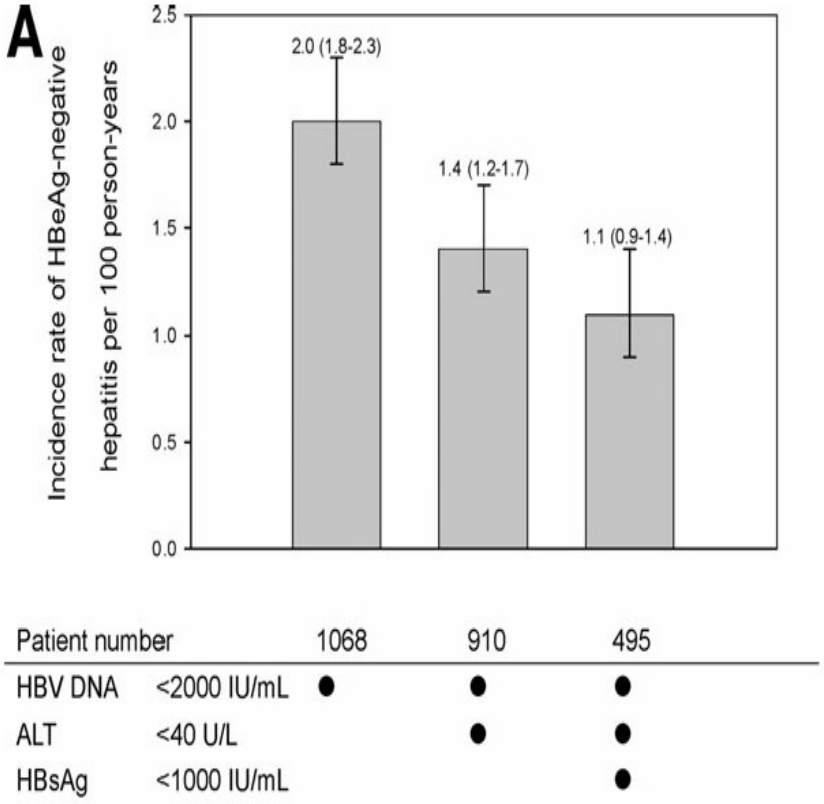
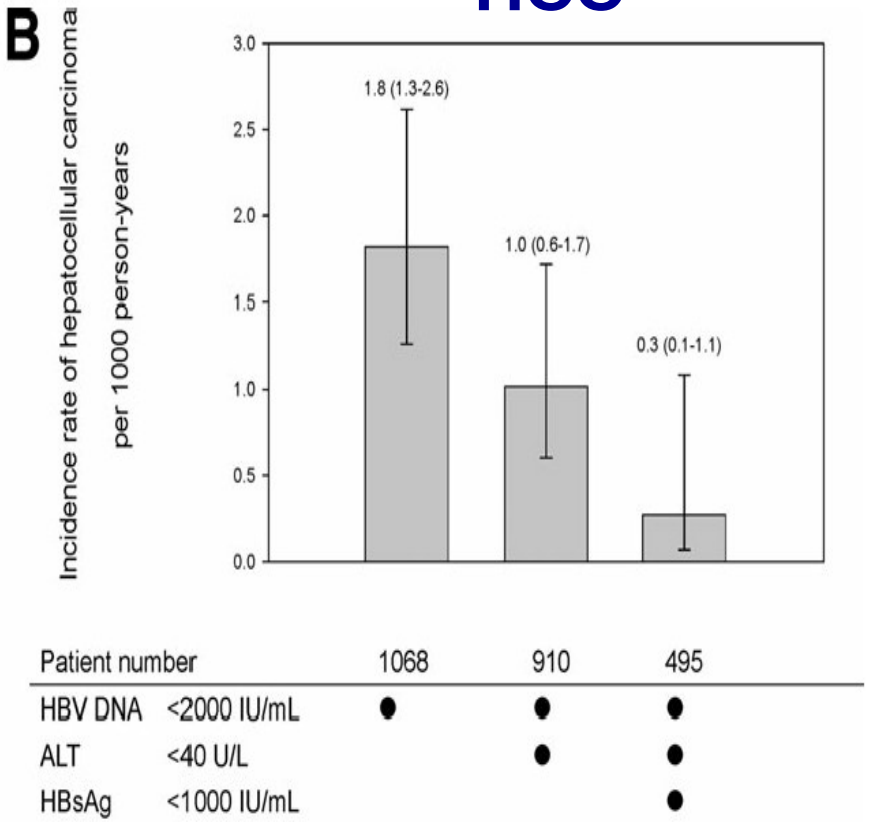
Incidence rates of ENH and HCC in different clinical settings of 1,068 patients with HBV DNA level <2,000 IU/mL

ENH



HCC



Tseng and Kao et al. Hepatology 2013.

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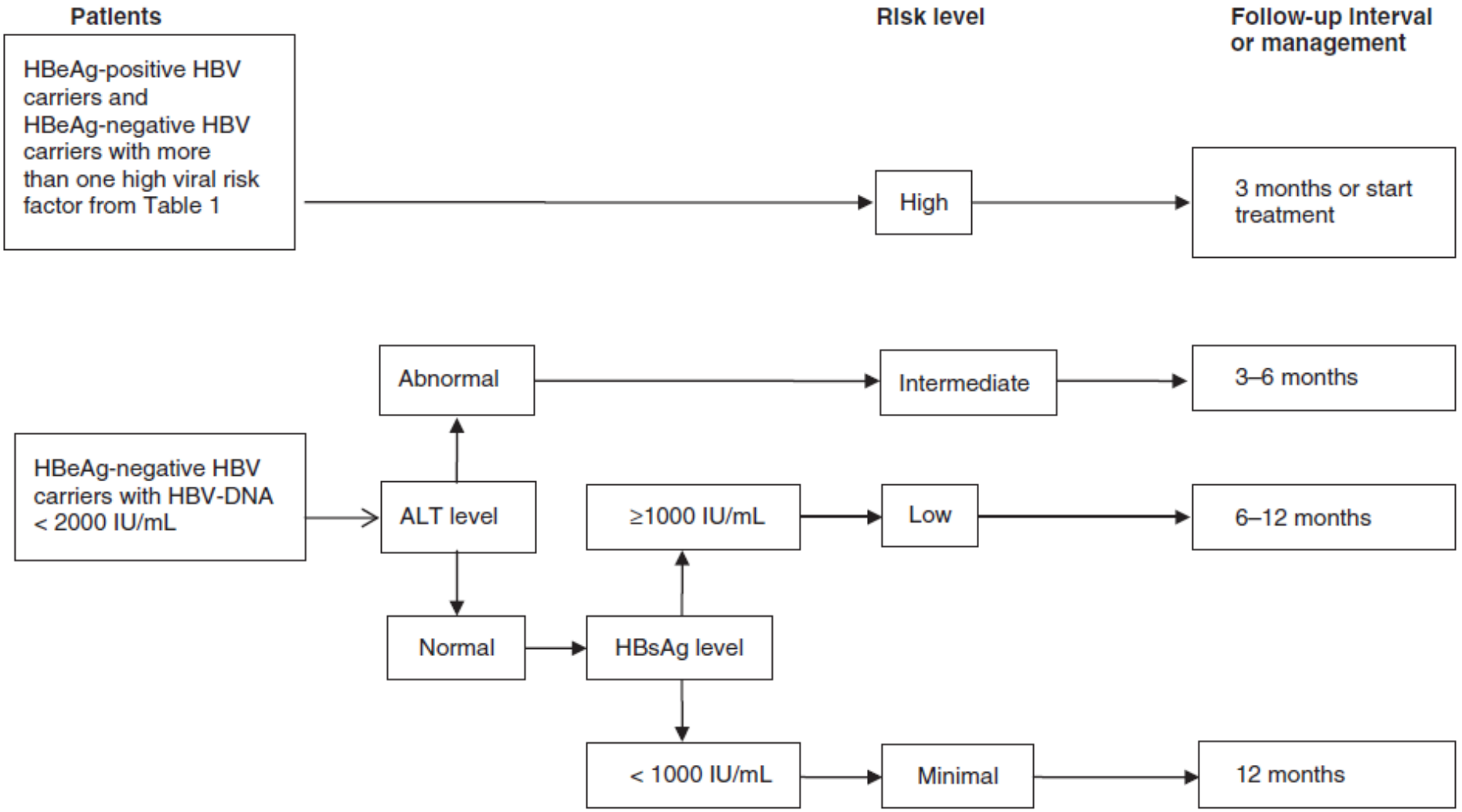
Algorithm to categorize disease progression in Asian HBV carriers



Modified from Tseng et al. *Hepatology* 2013

Lin & Kao. J Gastroenterol Hepatol 2012

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Outline

- HBV natural history cohorts
  - REVEAL-HBV
  - SEARCH-B
  - ERADICATE-B
- Risk calculator update
- Conclusions

REACH-B risk score

Development
Community-based REVEAL-HBV cohort

23820 cohort members recruited in Taiwan

4155 HBsAg seropositive

3851 tested serum HBV DNA on enrollment sample (REVEAL-HBV cohort)

3653 anti-HCV-seronegative subjects

3584 free of liver cirrhosis at study entry (131 developed HCC during follow-up)

Risk scores and predicted HCC risk for external validation

Validation
Hospital-based composite international cohort

CUHK cohort

426 patients (46 HCC cases)

Yonsei U cohort

259 patients (25 HCC cases)

UHK cohort

820 patients (40 HCC cases)

1505 CHB patients for validation (111 developed HCC during follow-up)

* All subjects were free of antiviral therapy during follow-up

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*Start antiviral therapy at annual HCC risk of 0.3%

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Can incorporation of HBsAg levels improve risk model calculations?

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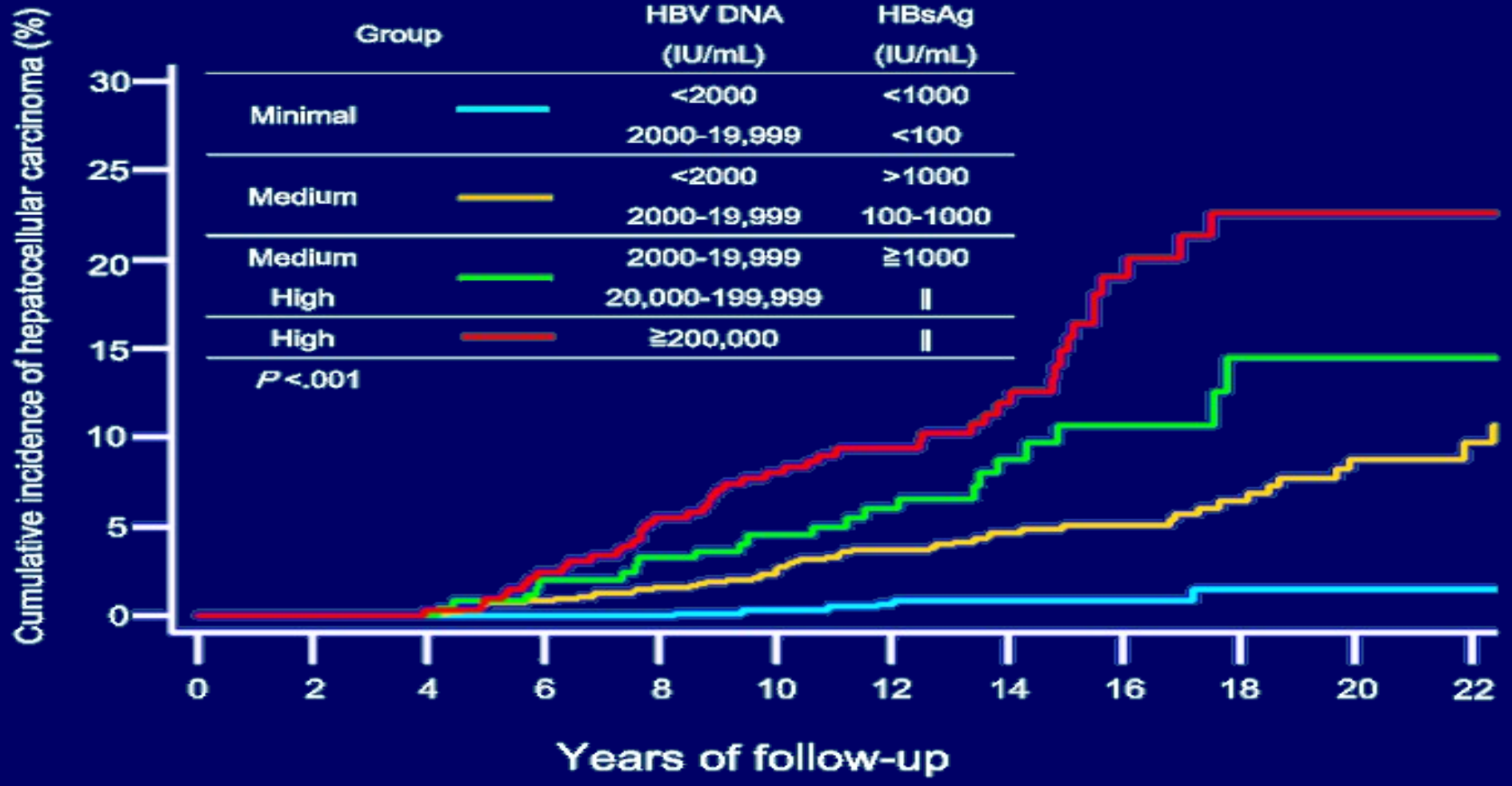
Reclassification of HCC risk in 2165 HBeAg(-) patients



Tseng and Kao, et al. JID 2013.

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Ongoing works on HCC risk calculator

Development
Community-based REVEAL-HBV cohort

3584 HBsAg-seropositive, anti-HCV-seronegative, free of liver cirrhosis at study entry (208 developed HCC during follow-up)

Model derivation

Two model / score:

- REACH-B + qHBsAg (REACH-B IIa)
- REACH-B + qHBsAg – HBV DNA level (REACH-B IIb)

Model validation

Validation
Hospital-based composite international cohort

CUHK cohort

426 patients (46 HCC cases)

ERADICATE-B cohort

2688 patients (191 HCC cases)

3114 CHB patients for validation (237 developed HCC during follow-up)

* All subjects were free of antiviral therapy during follow-up

Yang and Kao et al. Unpublished data.

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Comparison of various versions of REACH-B models/scores

	REACH-B	REACH-B IIa	REACH-B IIb
Risk parameters	Basic predictors+ HBV DNA	Basic predictors+ HBV DNA+ qHBsAg	Basic predictors+ qHBsAg
Discriminatory capability	Worst	Best	Good
Cost	Fairly expensive	Priciest	Cheapest
Potential usage	Should be replaced by new version tools	Used by hepatologists for management of CHB patients	First-line risk prediction tool for GP; community surveys; countries with limited resources

Yang and Kao et al. Unpublished data.

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MAJOR ARTICLE

Predicting Hepatitis B Virus (HBV) Surface Antigen Seroclearance in HBV e Antigen–Negative Patients With Chronic Hepatitis B: External Validation of a Scoring System

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Outline

- HBV natural history cohorts
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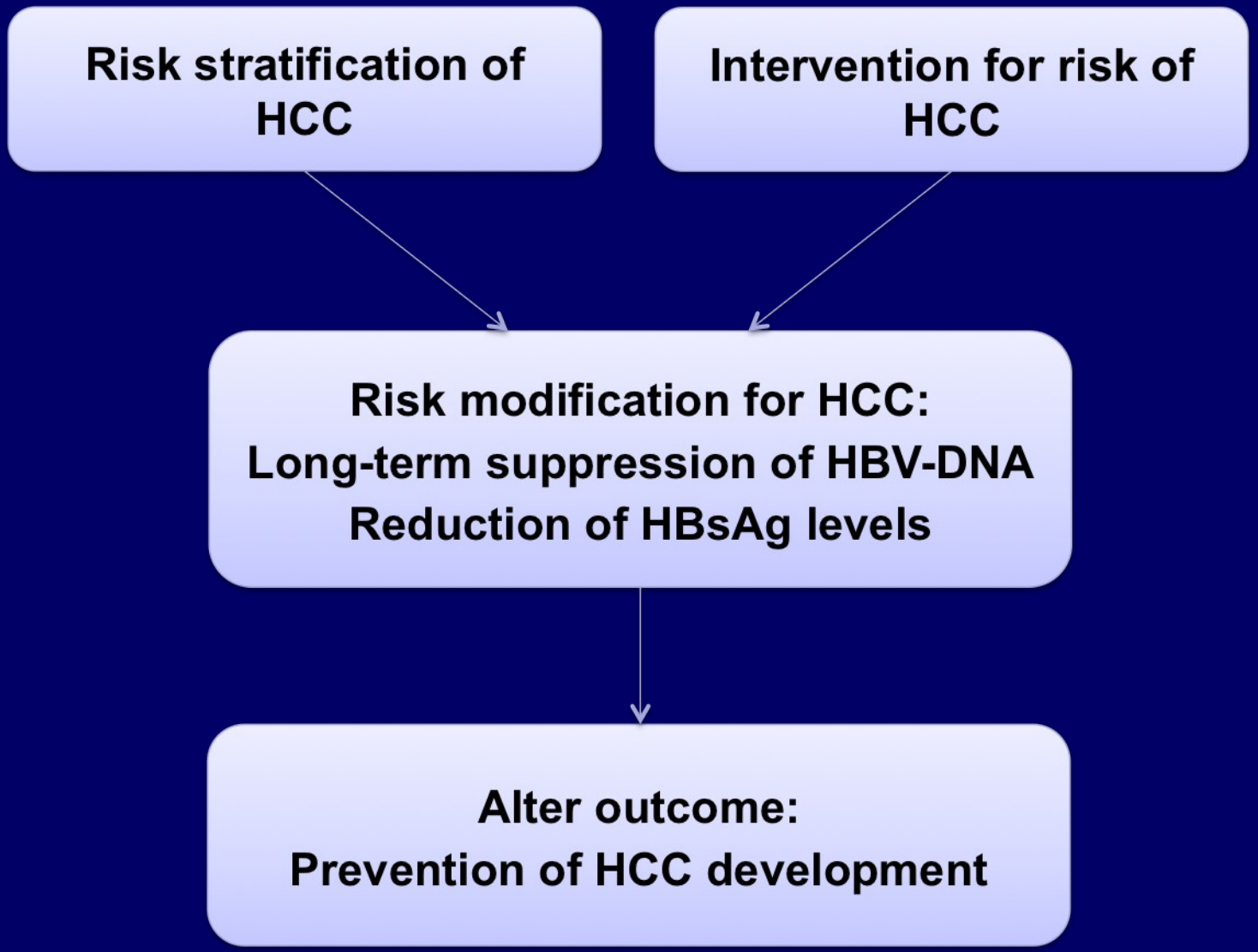
- Conclusions

Assessment and modification of risk factors for HCC



Lin & Kao. J Gastroenterol Hepatol 2012

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Conclusions:

What have we learned from HBV clinical cohorts?

- CHB is a complex disease with various clinical outcomes
- HBV natural history cohorts help resolve HBV factors affecting liver disease remission or progression
- Integrating qHBsAg levels into risk calculators can aid classification of patients whose disease will or will not progress
- Risk modification by antiviral treatment is mandatory and feasible

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