Interaction between cytochrome P450 1A2 genetic polymorphism and cigarette smoking on the risk of hepatocellular carcinoma : a case-control study in Japan

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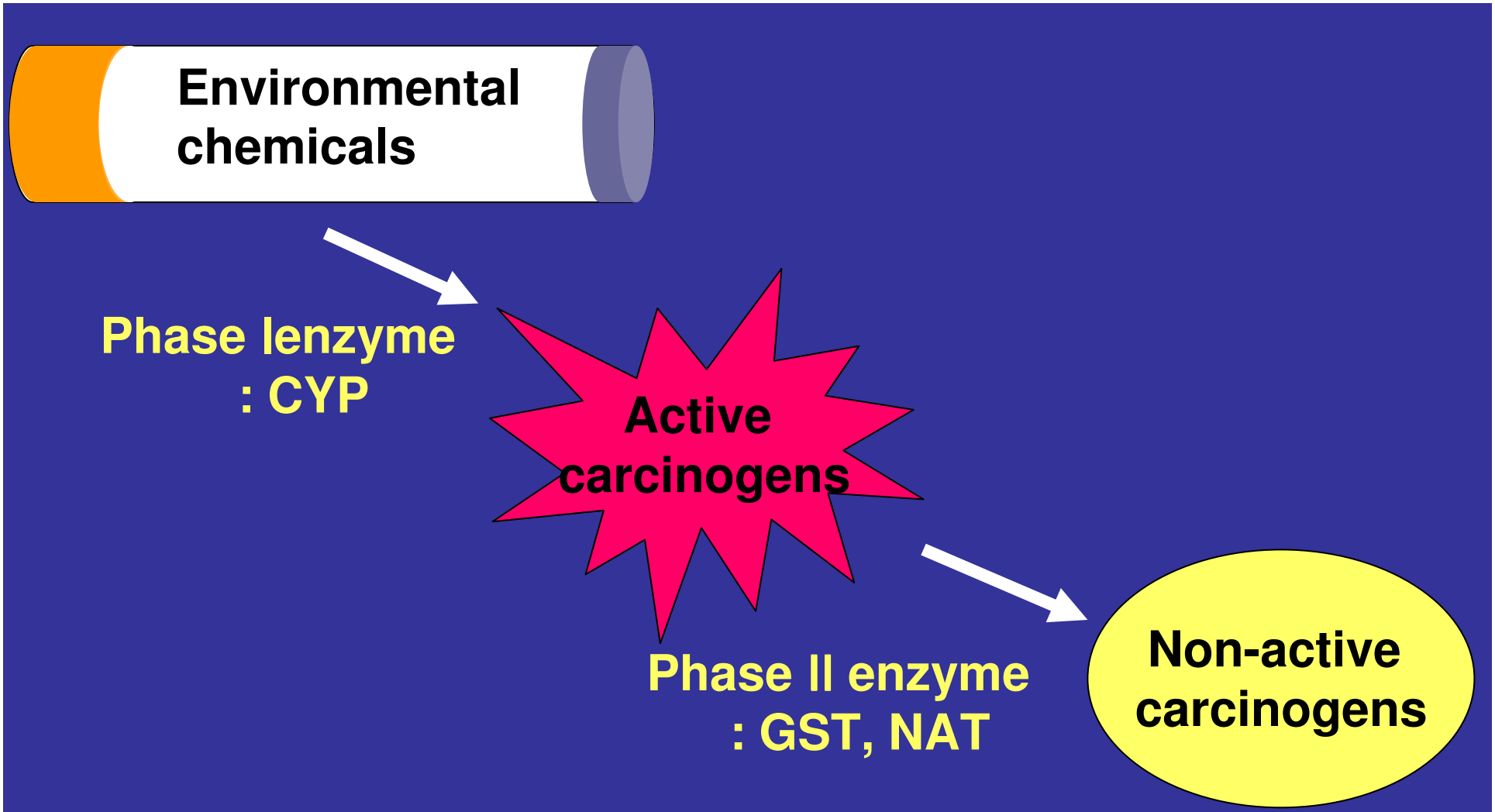
<Background>

The major causative factor of hepatocellular carcinoma (HCC) is chronic infection with hepatitis C virus and hepatitis B virus.

Cigarette smoking also has lately been recognized as a risk factor for HCC.



Mounting epidemiologic evidence suggests that genetic polymorphisms of drug metabolizing enzymes such as cytochrome P450 (CYP), glutathione S-transferase (GST) and N-acetyltransferase (NAT) may be involved in smoking-related hepatocarcinogenesis.

<Objective>

To examine whether genetic polymorphisms of *CYP1A1, CYP1A2, CYP2A6, CYP2E1, GSTM1* and *NAT2,* all of which represent typical candidate genes in the development of smoking-related cancers, are related to the risk of HCC with any interaction with cigarette smoking.

< Materials and Methods>

Case group

209 cases with HCC, who were admitted or outpatients of 2 main hospitals in Saga City (Saga Medical School Hospital and Saga Prefectural Hospital) between April 2001 and March 2004.

Control group 1

275 hospital controls, who were first time visitors at the general outpatient clinic of Saga Medical School Hospital between May 2001 and April 2003.

Control group 2

381 patients with chronic liver disease (CLD) without HCC, who were out- or inpatients of the two hospitals between September 2001 and March 2004.

Interview

Research nurses interviewed study subjects using a questionnaire on lifestyle factors (drinking & smoking)

Hepatitis virus markers

Plasma HBsAg and HCVAb

Genotyping

CYP1A1 (PCR-RFLP with *Msp*I, 3'-flanking region)
CYP1A2 (PCR-RFLP with *Dde*I, G-2964A)
CYP2A6 (PCR-RFLP with *Acc*II/*Eco81*I, deletion)
CYP2E1 (PCR-RFLP with *Rsa*I, C-1019T)
NAT2 (PCR-RFLP with *Asp718*/*Taq*I/*Bam*HI, C481T/G590A/G857A)
GSTM1 (PCR, deletion)

Statistical analysis

Unconditional logistic regression models to estimate adjusted odds ratios and their 95% confidence intervals

Characteristics of HCC cases, hospital controls (control group 1) and CLD patients (control group 2)

	HCC cases	Hospital controls	P value[a]	CLD patients	P value[b]
Number	209	275		381	
Mean age (year)	67.0	60.6	< 0.01	60.4	< 0.01
Male (%)	67%	65%	0.64	54%	< 0.01
Current smoker (%)	33%	25%	0.06	23%	< 0.01
Heavy-drinking history[c] (%)	23%	8%	< 0.01	10%	< 0.01
HBsAg-positive (%)	9%	2%	< 0.01	9%	0.97
HCVAb-positive (%)	86%	8%	< 0.01	86%	0.95

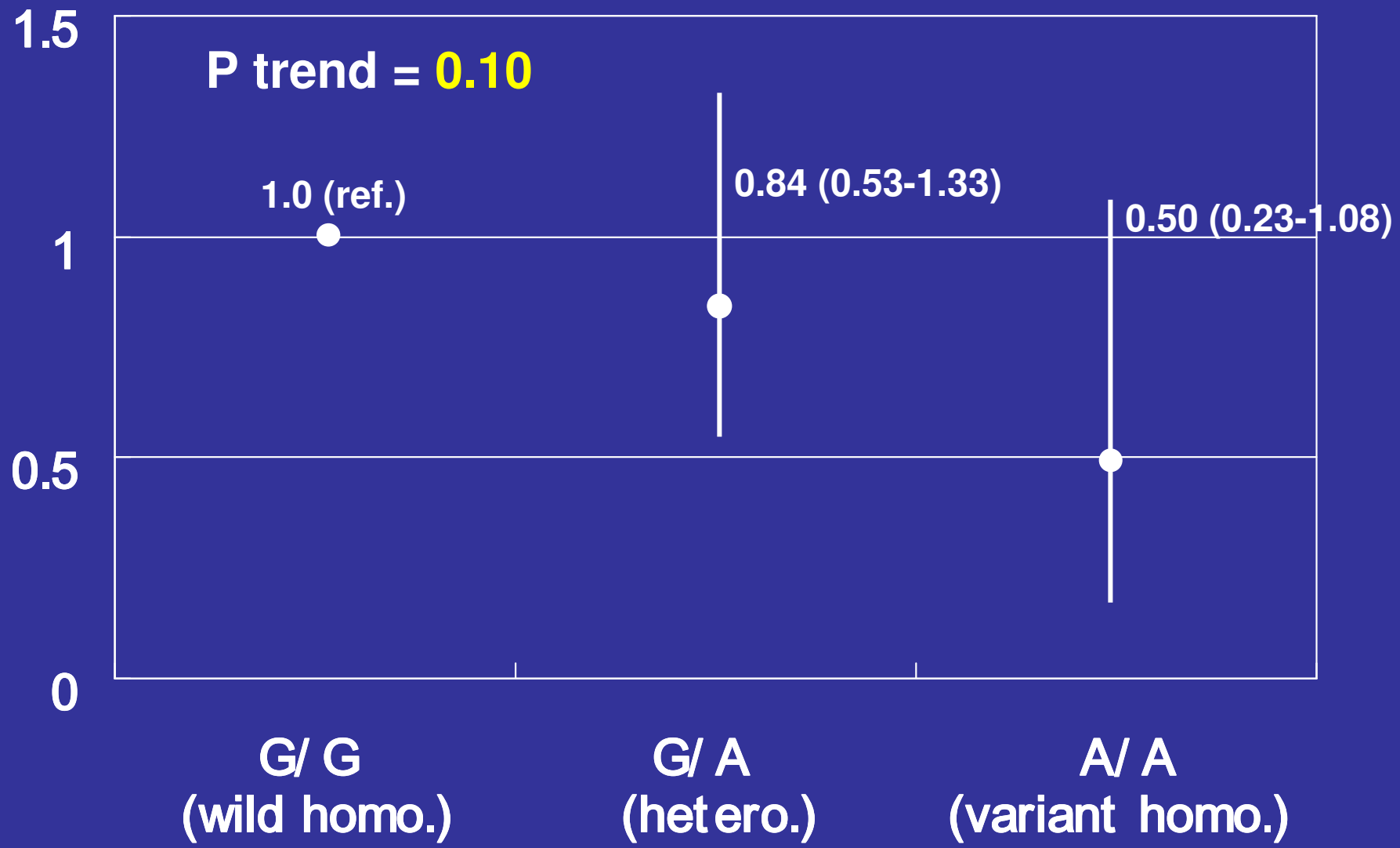
[a] P values for HCC cases vs. hospital controls.

[b] P values for HCC cases vs. CLD patients.

[c] Having drunk ≧69 g of alcohol per day for ≧10 years

Adjusted odds ratios* and 95% confidence intervals of HCC for *CYP1A2* G-2964A genotype

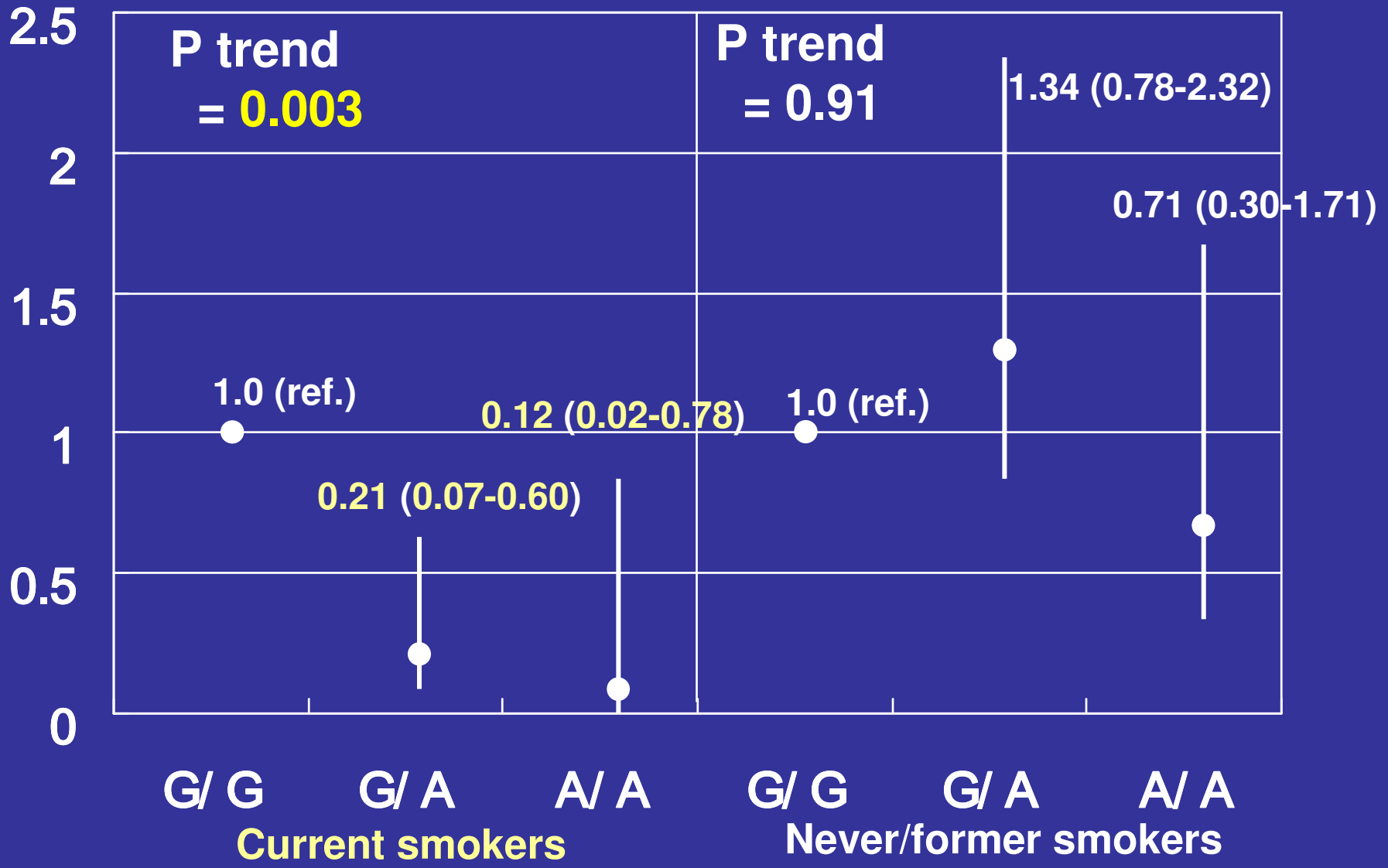
209 HCC cases vs. 381 CLD patients (control group 2)



*Adjusted for sex, age, smoking, drinking, HBsAg and HCVAb

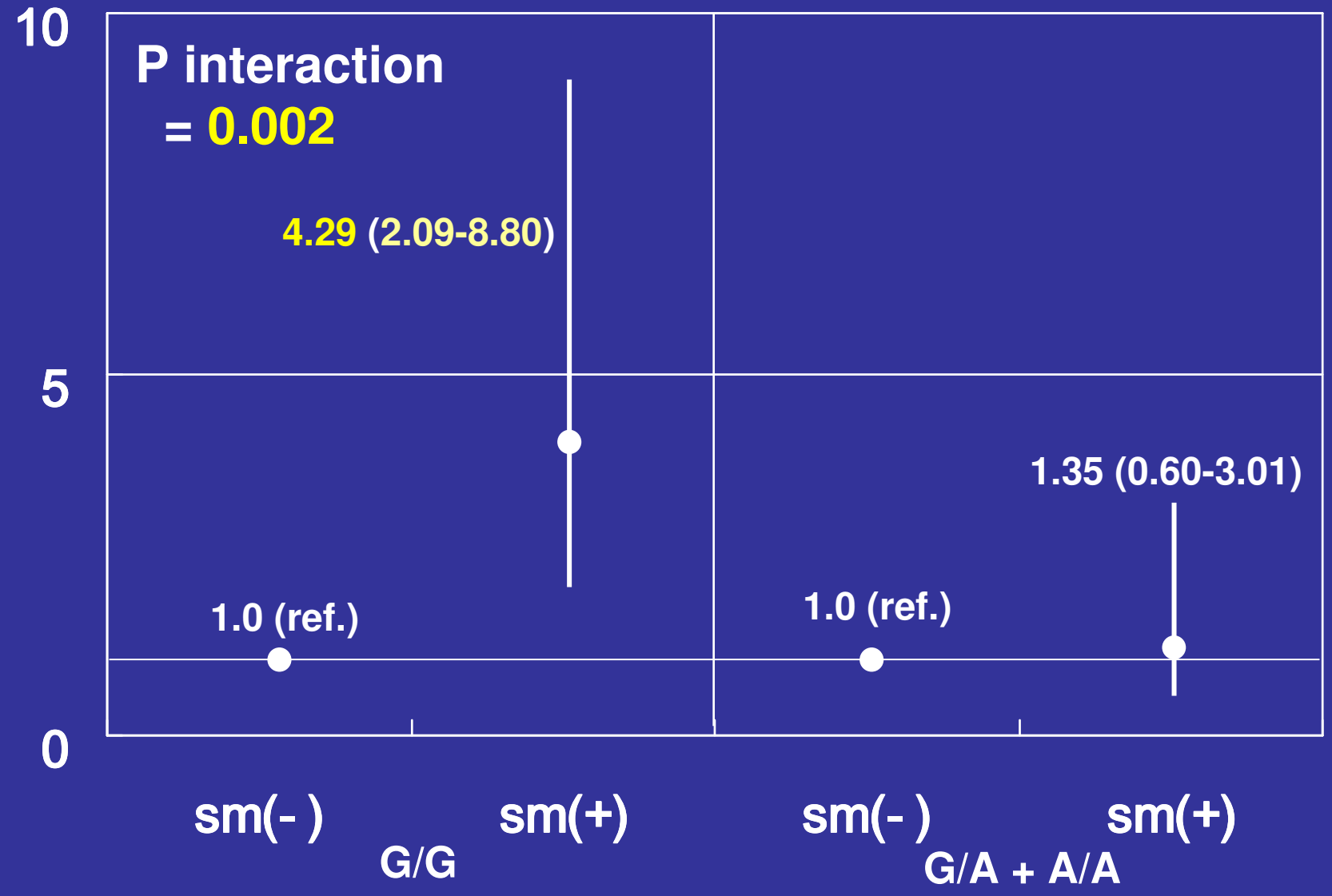
Adjusted odds ratios and 95% confidence intervals of HCC for *CYP1A2* G-2964A genotype by smoking status

209 HCC cases vs. 381 CLD patients (control group 2)



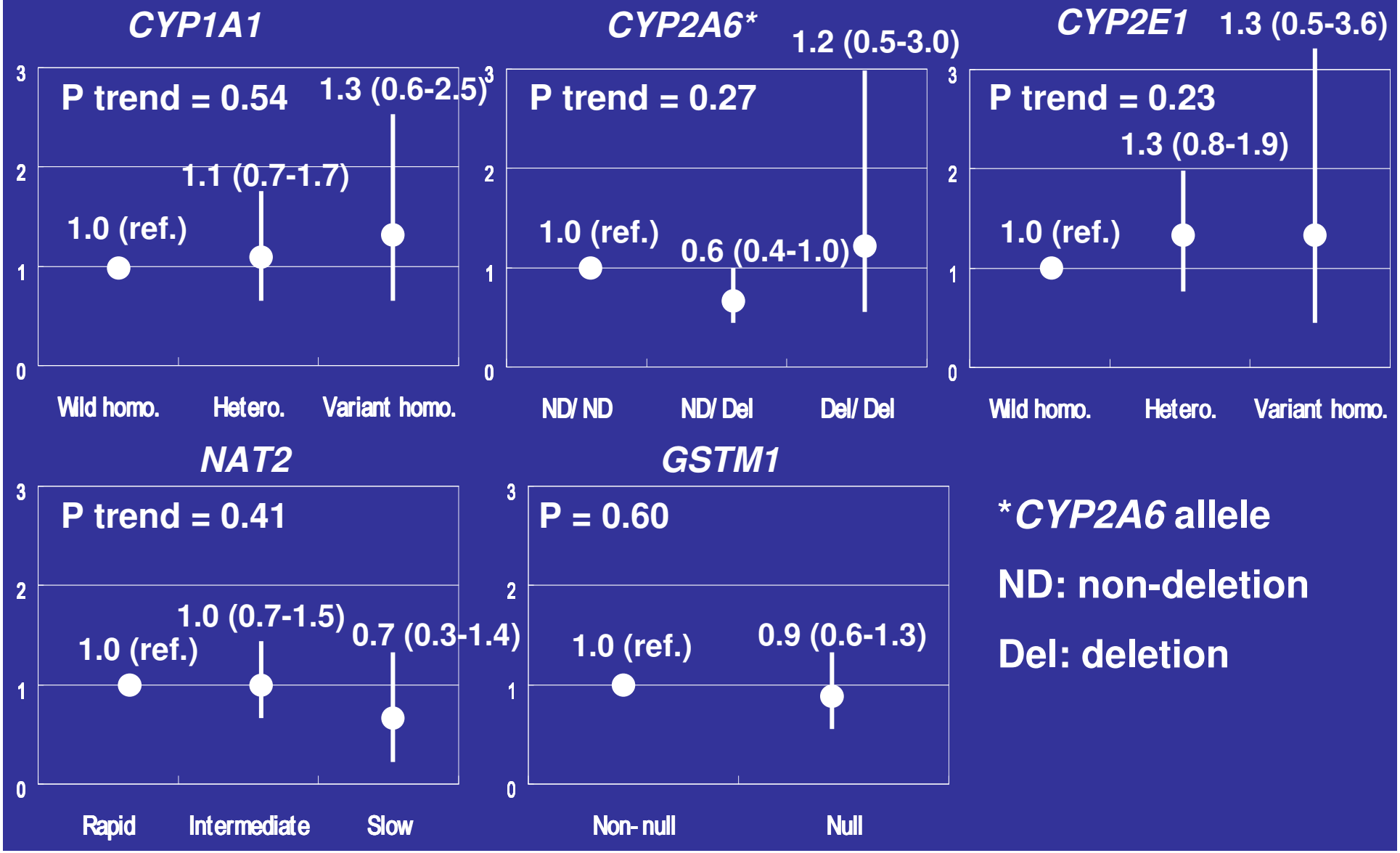
Adjusted odds ratios and 95% confidence intervals of HCC for current smoking (sm) by *CYP1A2* G-2964A genotype

209 HCC cases vs. 381 CLD patients (control group 2)



Adjusted odds ratios and 95% confidence intervals of HCC for *CYP1A1, CYP2A6, CYP2E1, NAT2 & GSTM1 genotypes*

209 HCC cases vs. 381 CLD patients (control group 2)



***CYP2A6 allele**

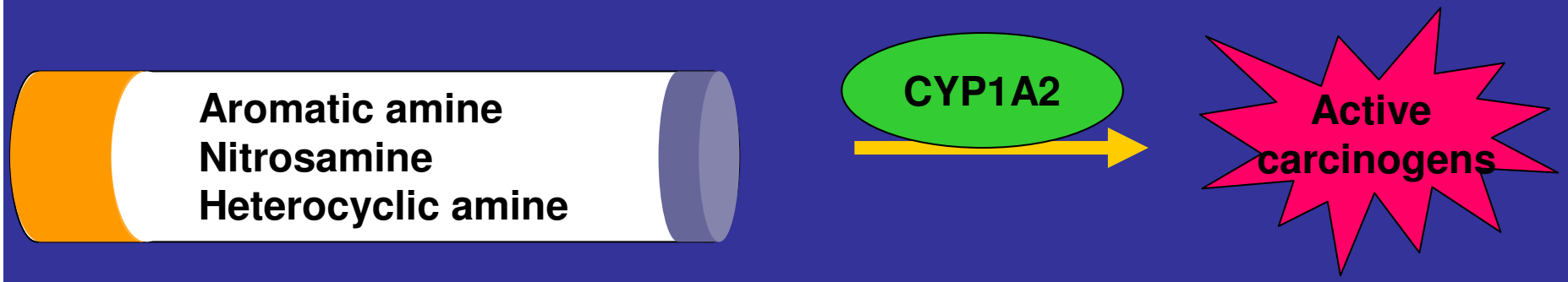
ND: non-deletion

Del: deletion

<Discussion>

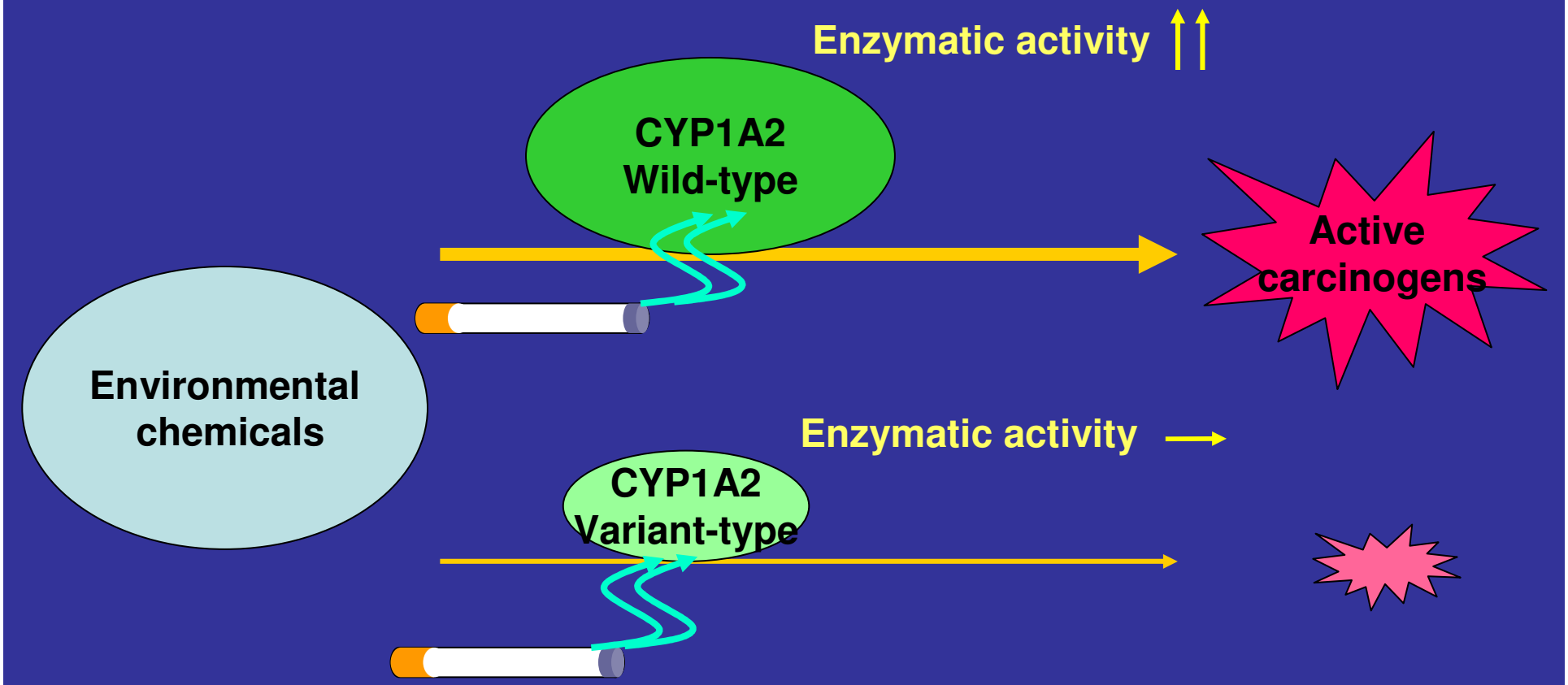
CYP1A2 is associated with the metabolic activation of environmental chemicals such as aromatic amines, tobacco-specific nitrosamines, and heterocyclic amines.

⇒ *CYP1A2* polymorphism has been suspected to have an influence on carcinogenesis.



Nakajima et al. observed that the wild-type allele (-2964G) , but not variant allele (-2964A), of *CYP1A2* was associated with increased enzymatic activity by smoking.

Nakajima et al. : *J. Biochem,* 1999.



Chen et al. demonstrated that homozygous carriers of the major haplotype (-3860G/-3113G /5347C) of *CYP1A2* were associated with increased HCC susceptibility in heavy smokers (odds ratio 2.14; 95% confidence interval 1.21-3.80).

Chen et al. : *Pharmacogenetics and Genomics*, 2006

In this study, the comparison between HCC cases and hospital controls (control group 1) did not show any significant association with the genetic polymorphisms including the *CYP1A2* polymorphism.

This may be due to the low positivity of HBV and HCV infection among hospital controls; statistical adjustment for hepatitis virus infection made relevant odds ratios very unstable.

<Conclusion>

The *CYP1A2* G-2964A polymorphism was associated with HCC risk among current smokers suffering from CLD, and it modified the risk associated with cigarette smoking among CLD patients.

Tobacco constituents metabolized by CYP1A2 may play an important role in hepatocarcinogenesis.