

# Synergistic effect of obesity and alcohol on the risk of hepatocellular carcinoma in men: a prospective cohort study

Rohit Loomba<sup>1, 2</sup>, Hwai-I Yang<sup>3</sup>, Jun Su<sup>4</sup>, David Brenner<sup>1</sup>, Uchenna Iloeje<sup>4</sup>, and Chien-Jen Chen<sup>3,5</sup>  
Division of Gastroenterology<sup>1</sup>, and Epidemiology<sup>2</sup>, University of California at San Diego, La Jolla, CA  
Genomics Research Center, Academia Sinica, Taipei, Taiwan  
Research and Development, Bristol-Myers Squibb Company, Wallingford, Connecticut, USA.  
Graduate Institute of Epidemiology, College of Public Health, National Taiwan University, Taipei, Taiwan



## Introduction

Body mass index (BMI) and alcohol use are independent risk factors for development of hepatocellular carcinoma (HCC). There are no prospective data whether obesity and alcohol are additive or synergistic in increasing the risk of incident HCC.

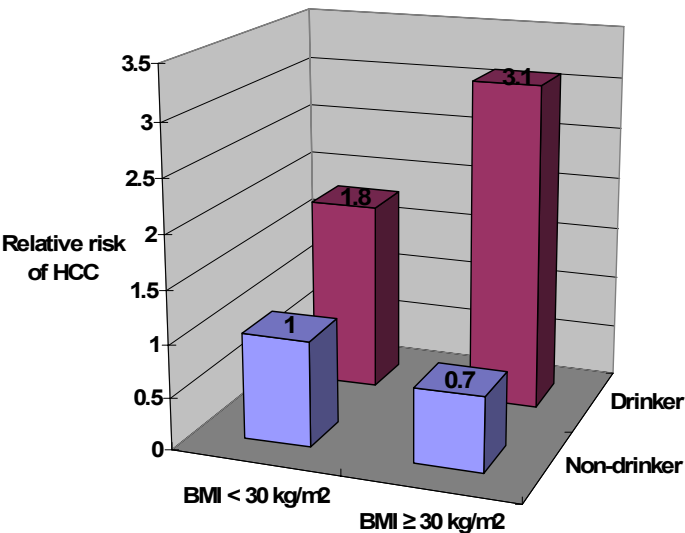
## Objectives

To examine whether obesity and alcohol are additive or synergistic in increasing the risk of incident HCC in HBsAg-positive Taiwanese men.

## Methods

A prospective study of 2260 HBsAg-Positive Taiwanese men who were followed for 14 years for future development of HCC Derived from REVEAL-HBV cohort. Mean ( $\pm$ SD) age and BMI were 46 ( $\pm$ 10) years and 24 ( $\pm$ 3) kg/m<sup>2</sup>. A fifth of participants reported alcohol use. Incident HCC cases were identified via linkage to national cancer registry. Multivariate adjusted hazard ratio (HR) & 95% CI were estimated using Cox-proportional hazards models. BMI was measured by a trained nurse At baseline visit and was categorized into Normal (<23 kg/m<sup>2</sup>), overweight (23 to <25 kg/m<sup>2</sup>), Obese (25 to <30 kg/m<sup>2</sup>), and extreme obese ( $\geq$ 30 kg/m<sup>2</sup>), based on the WHO guidelines. Alcohol use was Ascertained at baseline visit with a questionnaire as previously described. Alcohol drinkers were defined as having alcohol consumption at least 4 days per week for at least 1 year.

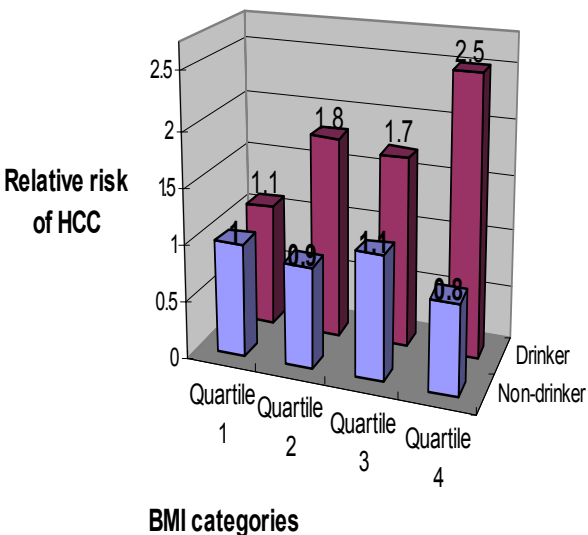
## Joint effect between obesity and alcohol with incident HCC



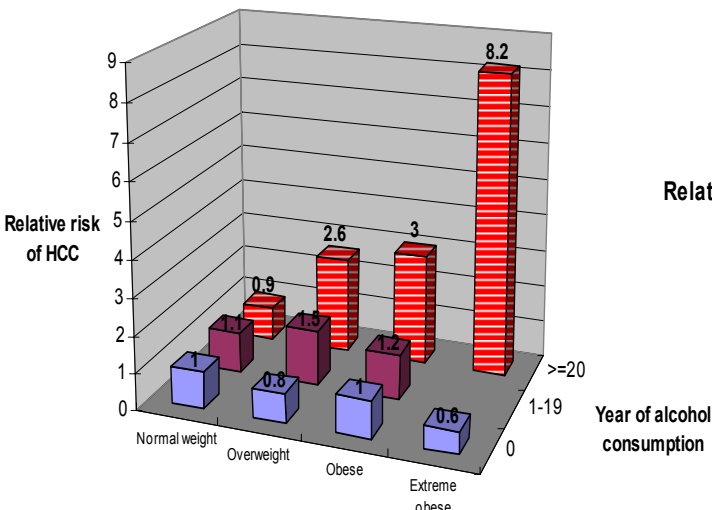
## Un-adjusted and multivariable-adjusted risk of incident HCC in HBsAg-positive men

| Variable                        | No. of participants | Person-years of follow-up | No. of HCC cases | Incidence rate per 100000 person-years | Crude HR (95% CI)   | P-value | Adjusted-HR (95% CI) | P-value |
|---------------------------------|---------------------|---------------------------|------------------|----------------------------------------|---------------------|---------|----------------------|---------|
| Age in 1-year increments        |                     |                           |                  |                                        | 1.07 (1.05-1.09)    | < 0.001 | 1.08 (1.06-1.10)     | <0.001  |
| BMI in 1kg/m2 increments        |                     |                           |                  |                                        | 1.02 (0.97-1.08)    | 0.39    | 1.00 (0.93-1.06)     | 0.9     |
| Smokers                         | 1214                | 13703.7                   | 72               | 525.4                                  | 1.02 (0.72-1.42)    | 0.93    | 0.96 (0.68-1.36)     | 0.81    |
| Alcohol users                   | 447                 | 4928.1                    | 42               | 852.3                                  | 1.91 (1.33-2.75)    | <0.001  | 1.54 (1.04-2.29)     | 0.031   |
| HBsAg +                         | 363                 | 6194.8                    | 57               | 920.1                                  | 4.07 (2.89-5.73)    | <0.001  | 2.83 (1.85-4.35)     | <0.001  |
| Elevated ALT $\geq$ 45 U/L      | 172                 | 2309.9                    | 27               | 1168.9                                 | 3.30 (2.17-5.03)    | <0.001  | 1.08 (0.67-1.72)     | 0.76    |
| HBV DNA $\geq$ 10,000 copies/ml | 681                 | 10702.9                   | 93               | 868.9                                  | 5.50 (3.82-7.92)    | <0.001  | 3.51 (2.23-5.51)     | <0.001  |
| Liver cirrhosis                 | 62                  | 509.1                     | 30               | 5892.8                                 | 16.64 (11.06-25.03) | <0.001  | 9.82 (6.22-15.50)    | <0.001  |
| Alcohol*BMI interaction         |                     |                           |                  |                                        | 1.12 (1.01-1.125)   | 0.029   | 1.06 (0.95-1.18)     | 0.29    |

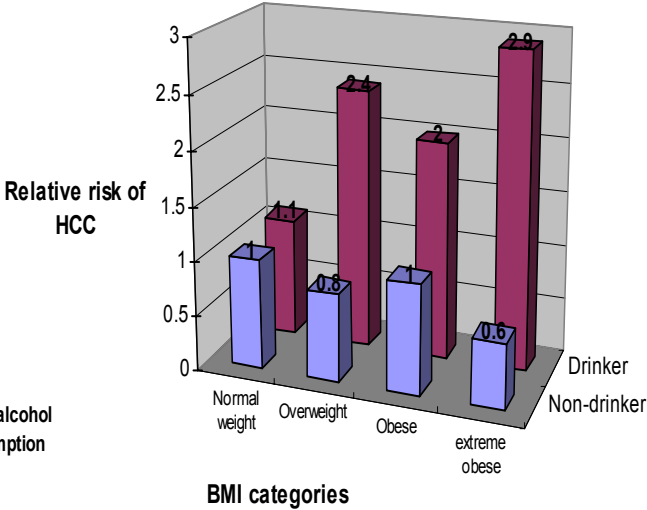
## Joint effect between WHO categories and duration of alcohol use with incident HCC



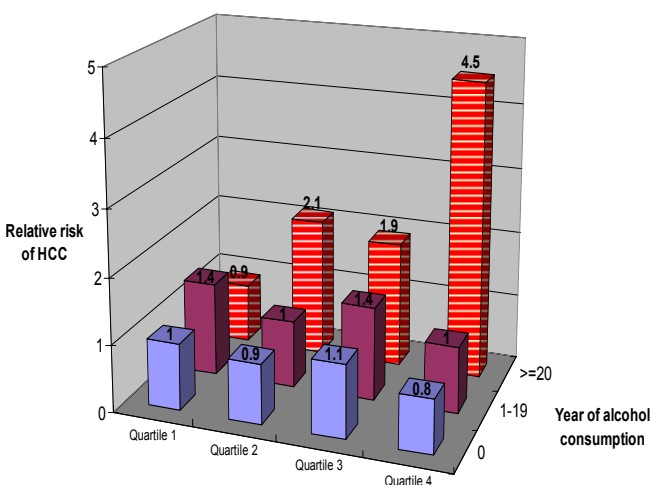
## Joint effect between BMI quartiles and alcohol use with incident HCC



## Joint effect between WHO BMI categories and alcohol use with incident HCC



## Joint effect between BMI quartiles and duration of alcohol use with incident HCC



## Results

Relative risk estimate due to interaction, attributable proportion due to interaction and synergy index were 1.59, 0.52, and 4.40, respectively, all suggestive of a multiplicative interaction between alcohol use and extreme obesity.

## Conclusions

Obesity and alcohol synergistically increase the risk of incident HCC in HBsAg-positive men. Lifestyle interventions such as weight loss in obese and reduction in alcohol consumption may be utilized to reduce the rising burden of HCC worldwide.