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# Association of processed food, synergistic effect of alcohol and HBV with Hepatocellular Carcinoma in a high incidence region of India

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ABSTRACT

*Background:* Dietary factors, tobacco, and alcohol use have been identified as important factors of rising various cancer incidence in several northeastern states of India. However, little is known about the factors associated with hepatocellular carcinoma (HCC) in this region. The aim of the paper was to identify the factors associated with HCC in the northeast region.

*Methods:* A case-control study was conducted in Arunachal Pradesh and Sikkim, two northeastern states of India, including 104 histologically-confirmed cases of HCC and same number (104) of age and sex matched control enrolled. Logistic regression analysis was performed to identify the factors associated with HCC.

*Results:* A statistically significant association was demonstrated between HCC and alcohol consumption, consumption of *'Sai-mod'* (OR 2.77, CI 1.57–4.87) a homemade alcohol beverage, and with HBV (OR 7.97, CI 3.36–18.94). Positive synergism index (S = 3.04) was observed between HBV and alcohol consumption to risk of HCC. Higher intake of processed meat (OR 2.56, CI 1.09–6.03) and processed fish (OR 2.24, CI 1.02–4.95) were found associated with increased risk of HCC; and decreased risk of HCC with fresh fish, fruits, and milk.

*Conclusions:* Strong relationship between different dietary factors, alcohol beverage with HCC suggests that control on dietary and drinking habit will be an important strategy to combat HCC in this region. Risk factors identified in this study will help to plan more effectively targeted risk reduction strategies and programs in this region.

## 1. Introduction

Liver cancer is the sixth most commonly diagnosed cancer with 7,82,000 new cases diagnosed in 2012 and third cancer related cause of deaths worldwide [1]. Hepatocellular Carcinoma (HCC), one of the most common type of liver cancer, in many regions of the world [2,3]. HCC is mainly associated with chronic Hepatitis-B Virus (HBV) and Hepatitis-C Virus (HCV) infections [3,4]. Several studies have also documented obesity, type 2 diabetes, tobacco smoking, and alcohol drinking as major risk factors for HCC in developed countries [5–7].

Several observational studies have shown close association with dietary factors with different cancer. A healthy diet can reduce the incidence rate of some types of cancers and poor diet will increase the risk [8]. Meat, especially red meat and processed meat consumption were shown to be associated with increased risk for different types of cancer [9–14]. Several studies have also documented significant association of socio-demographic factors, high intake of red and processed meat with increased risk of HCC [15–18]. However, intake of milk and yoghurt, white meats, eggs [19], vegetable [20], and fresh fruits [20,21] showed protective effect. Fish intake was also observed inversely associated with HCC [19]. Fish is a rich source of omega-3 fatty acids, and also contain relatively high amounts of vitamin D and selenium, which may protect from HCC or various cancer [16,19,22].

Developing countries like India, which have pockets of high incidence of HBV infections, HCC is emerging as one of the fastest spreading cancer compared to any other. The global surveillance of cancer (survival 1995–2009) documented only 4% of liver cancer patients survive for five years in India as compared to other part of the

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world (10%–20%) [23]. According to Population Based Cancer Registry (PBCR), 2012–14, Sikkim and Arunachal Pradesh (two northeastern states of India) reported the highest incidence of liver cancer among all cancers in the country. The northeast region of India is the habitat of diverse ethnic groups with different customs, food habits, use of red meat, and traditional processing of meat, drinking of different types of homemade liquor, smoking and use of smokeless tobacco with or without betel nut chewing. Though the incidence rate of HCC is being increasingly recognized in the state of Sikkim and Arunachal Pradesh, yet little is known about the risk factors associated with HCC in this region. The specific objective of this paper is to explore the dietary factors associated with HCC in the northeast region, among large geographically and culturally heterogeneous ethnic population of India.

## 2. Materials and methods

This population based case-control study was carried out by Regional Medical Research Centre (RMRC), Indian Council of Medical Research (ICMR), North East Region, India in collaboration with two PBCR, located at Sir Thodup Namgyal Memorial Hospital (STNM), Gangtok, Sikkim, and General Hospital, Naharlagun, Arunachal Pradesh. The study was carried out from April 2014 to August 2016. A total of 104 HCC diagnosed cases based on clinical and laboratory parameters of both sexes with same number of apparently health controls (matched for age and sex) living in Sikkim and Arunachal Pradesh were enrolled in the study. Cases were pathologically and/or cytologically confirmed HCC subjects of both sexes (male and female) with serum alpha-fetoprotein level greater than 400 ng/ml combined with at least one positive image on angiography, sonography, liver scan, and/or computed tomography scan were included. Patients diagnosed with stomach, colon, lung, pancreatic, breast or rectal cancer within the proceeding 5 years of HCC diagnosis; too old or too debilitated to be interviewed elaborately; and who refused to participate in the study were excluded from the study. Control subjects were selected from general population of Sikkim and Arunachal Pradesh. Clinically healthy, and non-malignant individuals from same neighbourhood of cases with age ( ± 5 years) and sex matched were included in control subjects. None of the controls had consanguinity with the cases. Moreover, patient of inherited metabolic diseases such as hemochromatosis, diabetes mellitus etc., and those who were non-resident of Sikkim and Arunachal Pradesh were not included in control subject. Sources of data collection for the cases includes Govt. Hospital, and other private laboratory and nursing homes of Sikkim and Arunachal Pradesh.

After obtaining written informed consent, trained social investigators collected the data from the eligible subjects by face-to-face interview using a pre-coded, closed ended questionnaire. The sociodemographic characteristics included participants' age, sex, educational status, occupational status and location of residence. The questionnaire included ranges of information including sociodemographic characteristics of participants, history of alcohol drinking habits, type of alcoholic beverages, dietary habits. Alcohol drinking habits were categorized into three categories, viz., non-drinker, former drinker, and current drinker. Subjects who were reported that they were regularly drink alcoholic beverage during index year were defined as current drinker, those who reported that they had stopped drinking the year before the index year or in the former were defined as former drinker, and those who reported that they never drank before were defined as non-drinker or abstainers. Diets and the dietary history of patients and controls were recorded based on 6 months of recall. Food frequency questions that contain details of dietary practices were included in the questionnaire. The frequency of consumption was classified as never eaten, occasionally, once a week, 2–4 times a week, and more than 4 times a week. Intake of red meat is defined as consumption of fresh pork, beef, mutton; intake of processed meat/fish defined as consumption of smoked meat/fish, sun dried meat/fish, salted and dried meat/fish

### 2.1. Statistical methods

Descriptive statistics was performed to describe different characteristics disaggregated by HCC status. Univariate and multiple logistic regression was performed to assess the factors associated with HCC status. First univariate logistic regression was performed to calculate the crude odds ratios (OR) and its corresponding 95% confidence interval (CI). Then multiple logistic regression analysis was performed to calculate adjusted odds ratio (Adj. OR) and corresponding 95% CI for determining independent associations between the factors and HCC status after adjusting for potential factors. Only variables that were found to be significantly associated with HCC status in univariate analysis at 5% level of significance were included in multiple regression model. All statistical analysis were two-sided *p*-values less than 0.05 were considered to denote statistical significance. All the statistical analyses were done using SPSS version 17. The interaction between alcohol intake and Hepatitis-B virus infection was calculated by fitting additive models, and synergy index 'S' proposed by Rothman [24] was calculated as $S = (OR_{AB} - 1)/(OR_A + OR_B - 2)$, in which $OR_{AB}$ denotes the odds ratio for joint exposure, $OR_A$ the odds ratio for exposure to one single factor, and $OR_B$ the odds ratio for exposure to another single factor. A value of S is 1 interpreted as indicative of additivity, and value > 1 interpreted as indicative of super additivity and synergism [25].

This study was approved by institutional ethical committee of Regional Medical Research Centre (Indian Council of Medical Research, New Delhi) North East Region, Assam, India

## 3. Results

Table 1 shows the distribution of cases and controls of HCC with respect to socio-demographic variables and other selected variables. The mean age at interview was 54.7 years among cases and 55.6 in controls. A higher proportion of cases were illiterate (73.1%), cultivator & unskilled worker (57.7%), reported from rural areas (83.6%), current drinker (40.4%). In the univariate logistic regression analysis, factors found to be significantly associated with HCC cases were illiterate (OR 2.57, CI 1.13–5.86), former drinker (OR 2.03, CI 1.02–4.04) and current drinker (OR 2.31 CI 1.17–4.59). Additional univariate logistic regression analysis was performed to find out the association of different alcohol beverage with HCC. Locally produce or homemade alcohol [locally known as *'sai-mod'*] was found significantly associated with increased risk of HCC (OR: 2.77, CI 1.57–4.88). In multiple logistic regression analysis, after adjusting age, sex, location of residence and controlling for all the significant factors in the univariate analysis, current drinker (OR 2.07, CI 0.97–4.42) and illiterate (OR 2.81, CI 0.99–7.95) were found associated with increased likelihood of HCC though statistically non-significant. Table 2 shows the joint effect of alcohol consumption and HBV. The estimated synergism index (S) was significantly greater than 1, indicating a joint effect of HBV and alcohol consumption. This indicated that alcohol consumption, in addition to its own effect, may magnify the effect of HBV on HCC.

Association of HCC by intake of non-vegetarian items are shown in Table 3. Factors found to be significantly associated with HCC cases in univariate analysis were frequent consumption of red meat, processed meat, and processed fish. A significant inverse trend was observed for intake of fresh fish in univariate analysis. In multiple regression analysis after adjusting for age and sex; consumption of: processed meat 4 & more times (OR 2.56, CI 1.09–6.03), processed fish 4 & more times (OR 2.24, CI 1.02–4.95) were found to be significantly associated with increased risk, and fish intake was statistically significantly inversely associated with HCC risk. Though statistically non-significant, consumption of red meat 4 & more times weekly (OR 2.07, CI 0.97–4.45) shows increased risk of HCC.

We have also examined the association of HCC by intake of beverage and fruits. The findings of univariate and multiple logistic