

Genetic and environmental determinants of risk of cholangiocarcinoma via

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Background

Cholangiocarcinoma is uncommon in the western countries but is increasing recent years. However the aetiology has been elucidated only for a limited portion of cases. Northeast Thailand has an exceptionally high incidence of liver cancer of up to 87.5 (male) and 37.2 (female) per 100,000 (world population adjusted incidence rate). Most of these cases have been attributed to cholangiocarcinoma. Infection with *Opisthorchis viverrini* (OV) is associated with cholangiocarcinoma. The prevalence of OV infection in Nakorn Phanom province was between ~30 and ~70% with substantial variation between villages, but less than 10% of the inhabitants develop cholangiocarcinoma. Animal experiments suggest that OV infection alone does not cause cholangiocarcinoma, and thus other environmental and genetic factors may play a role in causation. We hypothesized that genetic background may be a contributing factor in the occurrence of the cholangiocarcinoma. Previously we conducted a population-based case-control study in Nakorn Phanom in which sex, age and place of residence were matched individually (Int J Cancer 117: 854-860, 117: 1066, 2005). Polymorphisms of GSTM1 and GSTT1 alone were not associated with risk for cholangiocarcinoma while an elevated level of antibodies against OV was the strongest risk indicator (odds ratio = 27.09 (95% confidence interval CI: 6.30 116.57). Compared with subjects who had a normal antibody range and the wild type GSTM1 gene, those who had elevated antibodies had higher odds ratios of 10.34 (95% CI: 1.31 81.63) for wild type GSTM1 and 18.00 (95% CI: 3.33 97.40) for the null variant thereof, respectively. Past and current regular drinkers of alcohol had higher risk (odds ratio = 5.39 [95% CI: 1.11 26.06] and 4.82 [95% CI: 1.29 18.06], respectively). In the present work, we conducted the hospital-based case-control study in another endemic area of northeast Thailand, Ubon Ratchathani, and compared these effects in both areas. In addition we examined the association between polymorphism of ALDH2 gene and the risk of cholangiocarcinoma.

Materials and Methods

All cases with cholangiocarcinoma were identified in Ubon Ratchathani cancer center hospital. Diagnosis was based on abdominal ultrasonography in the hospital, with serological supportive evidence including a raised CA 19-9 and a normal level of alpha fetoprotein, although the latter was not obligatory. Each case was matched by sex, age (within 5 years) and place of residence (amphur, district) to a control candidate who was selected from the people that visited the hospital as health check. The polymorphism of the GSTM1 and GSTT1 genes was determined according to the procedure of Abdel-Rahman and colleagues using multiplex PCR¹⁵ with slight modification as described in the previous paper.

Results and Discussion

In Ubon Ratchatani, genetic polymorphism of GSTM1 or GSTT1 alone did not correlate with risk for cholangiocarcinoma, which is consistent with the data in Nakorn Phanom. Odds ratios for null variants of GSTM1 and GSTT1 genes were 0.95 (CI: 0.50-1.81) and 1.19 (CI: 0.67-2.12), respectively. Also elevated serum anti-OV

antibody was significantly associated to increased risk; odds ratio=23.00 (CI: 3.11-170.30). The relationship of alcohol use and smoking were also analyzed. Regular drinkers have slightly increased risk; odds ratio=1.48 (CI: 0.40-5.48). Regular smoker have increased risk; odds ratio=2.46 (CI: 0.76-7.91). ALDH2 variants had a protected risk; odds ratio=0.44 (CI: 0.19-1.02). Relations between the selected variables, gene polymorphism and risk of cholangiocarcinoma will be presented and discussed.