Polymorphisms of DNA repari-related genes and risk for cholangiocarcinoma in northease Thailand

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Background and Purpose

The incidence of cholangiocarcinoma in northeast Thailand is higher than that in other countries in Asia. Infection with the liver fluke, *Opisthorchis viverrini*, is an important factor in northeast Thailand where approximately one-third of the population is infected. This is related to the life style of the people in this area to enjoy eating raw fish. But not all people infected with liver fluke have cholangiocarcinoma. Animal experiments suggested that the liver fluke infection alone does not cause cholangiocarcinoma, but combined application of nitrosamine do cause the disease. We think other environmental and genetic factors may play a role in causing cholangiocarcinoma. We conducted case-control study in Ubon Ratchathani, northeast Thailand, and we analyzed the relationship between the polymorphisms of DNA repair-related genes (HOGG1, XRCC1, PARP1) and the risks of cholangiocarcinoma.

Material and Method

All cases with cholangiocarcinoma were identified at Ubon Ratchathaini cancer center hospital. Diagnosis was based on abdominal ultrasonography by a single radiologist at the hospital with serological supportive evidence including a raised CA 19-9 and a normal level of α-fetoprotein, although the latter was not obligatory. To each case, a control individual was selected being matched by sex, age (within 5 years) and place of residence. These control individuals were selected from those who visited Ubon Ratchathani cancer center hospital for health check. Total 115 matched pairs were analyzed in this study.

We extracted DNA from the blood and analyzed human 8-oxoguanine DNA glycosylase (HOGG1), X-ray repair cross-complementing group 1 (XRCC1) and poly (ADP-ribose) polymerase-1 (PARP-1) polymorphisms.

HOGG1 protein is a DNA glycosylase that is involved in excision repair of 8-hydroxy-2'deoxyguanine (8-OH-dG) from oxidatively-damaged DNA. 8-OH-dG is a major form of oxidative DNA damage. HOGG1-Ser and HOGG1-Cys proteins were produced due to genetic polymorphism at codon 326 in human cells. Activity in the repair of 8-deoxyguanine was greater in HOGG1-Ser protein than in HOGG1-Cys protein in the complementation assay of an *E. coli* mutant defective in repair of 8-deoxyguanine.

XRCC1 gene encodes a protein 633 amino acids. XRCC1 protein serves to orchestrate base excision repair via its role as a central scaffold protein. XRCC1 contains two functional regions, each sharing a BRCT domain. Poly (ADP-ribose) polymerase interacts with BRCT domain at the NH_2 terminus. DNA ligase III interacts with BRCT domain at the COOH terminus. XRCC1 Arg399Gln is located in BRCT domain at the NH_2 terminus.

PARP-1 is present in eukaryotic cells and is thought to be important for base excision repair after DNA damage. PAPR-1 is composed of DNA-binging domain, the automodiffication domain, and C-terminal catalytic domain. PARP-1 Val762Ala is located in C-terminal catalytic domain.

Result and Discussion

Although we were not able to find significant association between polymorphisms of *HOGG1 codon 326* or

PARP-1 codon 762 and the risk for cholangiocarcinmoma, we found the significant association between *XRCC1 codon 399* polymorphism (OR=0.55 CI=0.31~0.97 *P*=0.04) and the risk for cholangiocarcinoma; Individuals with putative risk gene for *XRCC1* (Arg/Gln or Gln/Gln) was at decreased risk of cholangiocarcinoma. The obtained data will be presented and the significance will be discussed.