泌尿道上皮癌與砷暴露、抽菸、第二相反應酵素和 DNA 修補系統酵素基因多形性之相關研究

A study on the association between urothelial carcinoma and arsenic exposure, cigarette smoking and genetic polymorphisms of phase II reaction enzyme and DNA repair system enzyme

中文摘要

泌尿道上皮癌大多發生於膀胱，其主要危險因子爲抽菸，過去研究發現，台灣西南沿海嘉義、台南地區及東北角蘭陽盆地的地下水中含有高濃度砷，且當地居民罹患膀胱癌之風險較高，另外研究指出第二相反應酵素、DNA 修補系統酵素之基因多形性可能會改變酵素的作用及個人的代謝與修補能力，進而影響對癌症的易感受性。故本研究欲探討泌尿道上皮癌與砷暴露、抽菸、第二相反應酵素（GSTO1-1、SULT1A1）與 DNA 修補系統酵素（hOGG1、XPD）基因多形性之相關性。本研究係病例對照研究，病例組爲奇美與嘉義基督教醫院，20 歲以上經病理診斷爲移形上皮細胞癌之膀胱癌、腎盂癌及輸尿管癌的病患，共 300 人；對照組爲 233 名來自相同醫院之老人健檢或是泌尿科病患，以頻率匹配的方式選取，匹配的條件爲性別與年齡（±5 歲）。利用結構式問卷及標準化訪視流程收集研究對象之基本人口學及相關危險因子之暴露史，並計算飲用水中位值砷濃度和累積砷暴露量；將已萃取之 DNA 利用聚合酵素連鎖反應、限制酵素片段長度多形性來進行基因型之分析。研究結果顯示飲用水中位值砷濃度與罹患泌尿道上皮細胞癌危險性具有劑量效應，在調整年齡、性別後飲用水中位值砷濃度>50 μg/L 者，其危險對比值爲 3.2（95%CI: 2.0-5.0）；而抽菸者仍有兩倍左右的危險性；GSTO1-1 基因型爲 C/C 者罹患泌尿道上皮癌的危險性較高 OR 值爲 1.8（95%CI: 1.2-2.7），SULT1A1 帶 A 對偶基者，罹患泌尿道上皮癌的危險較低 OR=0.4（95%CI: 0.3-0.8），均達統計上之顯著意義，hOGG1 與 XPD 有變異者，雖有較高之危險性但均未達統計顯著水準，具砷暴露且曾抽菸者其罹癌的風險爲八倍左右。本研究分析基因與環境暴露（砷或抽菸）共同作用，發現有砷暴露（飲用水中位值砷濃度>50 μg/L）且帶有 3 種以上危險性基因型者（危險性基因型是 GSTO1-1 基因型爲 C/C、SULT1A1 基因型爲 G/G、hOGG1 爲帶 G 對偶基及 XPD 基因型爲 A/C），其罹癌的風險性較未具砷暴露且代謝系統酵素只含一種以下危險性基因型者的 67 倍，此一情形亦發現在吸菸且具有三種以上危險性基因型者有較高的罹癌風險，其 OR 值爲 8.4，均達統計顯著水準。

英文摘要

Urothelial carcinoma (UC) mostly occurs in the bladder and its major risk factor is cigarette smoking. A significant association between ingested arsenic and bladder

cancer has been reported among residents in an arseniasis-endemic area in southwestern and northeastern Taiwan. Previous studies showed that genetic polymorphisms of DNA repair system enzyme and phase II reaction enzyme may alter function of these enzymes. Furthermore, individual susceptible to cancer risk may be different among various capacities to repair damaged DNA and metabolize environmental xenobiotics. The specific aim of the study is to investigate the association between UC and arsenic exposure, cigarette smoking and genetic polymorphisms of phase II reaction enzyme (GSTO1-1, SULT1A1) and DNA repair system enzyme (hOGG1, XPD). A total of 300 pathologically confirmed UC patients and 233 controls were recruited from Chia-yi Christian Hospital and Chi Mei Hospital. Controls were matched to the cases by age (±5 years) and sex. All cases and controls were interviewed during hospital admission by well-trained interviewers using standardized structured questionnaires of demographic variables and other traditional risk factors for UC. Indices of arsenic exposure including median arsenic concentration in drinking well water and cumulative arsenic concentration were calculated. Genetic polymorphisms of studied markers were genotyped with a PCR-RFLP assay. A significant dose-response relationship between risk of UC and indices of arsenic exposure was observed after adjustment for age and sex. Subjects who drank well water with median concentration of arsenic greater than 50μg/L had a 3.2-folds risk (95%CI: 2.0–5.0) of UC compared with referent group with arsenic lower than 50μg/L. Cigarette smokers had two-folds risk for development of UC. For study subjects who with GSTO1-1 C/C genotype had 1.8-folds risk of UC compared to other genotypes for the marker. When study subjects with SULT1A1 genotype of A allele, we observed a statistically significant reduced risk of UC (OR=0.4; 95%CI: 0.3–0.8). However, study subjects with variant types of hOGG1 and XPD did not show a significantly increased risk of UC. The UC risk of cigarette smokers with arsenic exposure had eight times risk for development UC than nonsmokers without arsenic exposure. The joint effect between gene and environment factors (arsenic and cigarette smoking) was also examined. The results showed that subjects who had arsenic exposure and carried more than three dangerous genotypes (dangerous genotype means GSTO1-1 is C/C, SULT1A1 is G/G, hOGG1 is C/G or G/G and XPD is A/C) of these markers have sixty seven times risk for development of UC than those who did not have arsenic exposure and also carried less than one dangerous genotype of metabolic system enzyme. The same association also found in the subjects who were smokers and carried more than three dangerous genotypes showing an odds ratio of 8.4 for risk of UC.