抽菸與 CYP2E1、GSTA1 及 GSTP1 基因多形性對泌尿道上皮癌發病危險性之交互作用研究

Joint effect on risk of urothelial carcinoma between cigarette smoking and genetic polymorphisms of CYP2E1、GSTA1 and GSTP1

中文摘要

全世界每年估計約有 330,000 例泌尿道上皮癌的新發病例，泌尿道上皮癌從 2001 年到 2005 年台灣地區年齡標準化發生率之趨勢來看，雖然發生率有稍減趨勢，但其發生率仍位居男性的第八位，女性的第十三位。泌尿道上皮癌的致癌因子包括年齡、性別、遺傳、基因、抽菸等，其中抽菸被認爲是最重要的致癌因子。致癌物質的產生與癌症相關的基因發生突變或是缺陷有關，代謝酵素活性的高低影響個體對環境汙染物的代謝能力，和個體對癌症的感受性，本研究的目的爲探討台灣族群 CYP2E1、GSTA1 及 GSTP1 之基因多形性與抽菸的交互作用對泌尿道上皮癌發生的影響。

本研究爲以醫院爲基礎的病例對照研究，病例組自 1998 年開始收集來自奇美醫院、2002 年開始收集來自嘉義基督教醫院、2004 年開始收集來自新光醫院泌尿外科的門診或住院病人，經病理診斷爲泌尿道上皮癌之膀胱癌、腎盂癌及輸尿管癌的病患，總人數爲 540 人。對照組爲與病例組個案經頻率匹配的方式選取，匹配的條件爲年齡（± 2.5 歲）與性別，收集來自嘉義基督教醫院與奇美醫院泌尿科門診之病患，需未曾罹患任何部位之良性或惡性腫瘤如腎臟或尿道結石、尿道狹窄，總人數爲 540 人。利用結構式問卷收集研究對象之基本人口學及相關危險因子之暴露史，以聚合酶連鎖反應（polymerase chain reaction, PCR）增幅 DNA 片段，再用限制片段長度多形性（restriction fragment length polymorphism, RFLP）方法進行基因多形性的判定，之後以多變項邏輯式迴歸（multiple logistic regression）進行各危險因子、基因多形性與罹患膀胱癌的多變項分析。

研究結果顯示在調整年齡、性別等因子後有抽菸習慣者與有喝酒習慣者罹患泌尿道上皮癌危險對比值分別爲爲 1.5 與 2.1，均達統計上顯著。在調整年齡、性別、抽菸、喝酒等危險因子後研究對象 CYP2E1 帶有 c1c1 基因型者罹患泌尿道上皮癌的危險性較高，危險對比值爲 1.2（95%CI: 0.9-1.5）。GSTA1 頻率基因分佈與危險對比值分析結果顯示以帶有 CT+CC 基因者當成參考族群，發現基因型爲 CC 者，調整年齡、性別、抽菸、喝酒之危險對比值爲 1.2（95%CI: 0.9-1.7）。GSTP1 頻率基因分佈與危險對比值分析結果顯示帶有 GG 基因型者罹患泌尿道上皮癌的危險對比值爲 1.4（95%CI: 0.6-3.4）；將帶有 AA 與 AG 基因者當成參考族群，發現基因型爲 GG 者，調整年齡、性別、抽菸、喝酒之危險對比值爲 1.5（95%CI: 0.6-3.6）。CYP2E1、GSTA1 及 GSTP1 基因多形性與抽菸之交互作用於調整年齡、

性別、喝酒結果爲未抽菸者且三者危險基因型數目爲 1 個者罹患泌尿道上皮癌的危險對比值爲 2.1（95%CI: 1.0-4.6），未抽菸且三者危險基因型數目爲 2 個含以上者罹患泌尿道上皮癌的危險對比值爲 1.4（95%CI: 0.8-2.7）；曾抽菸且三者危險基因型數目爲 1 個者罹患泌尿道上皮癌的危險對比值爲 1.8（95%CI: 1.0-3.6），曾抽菸且三者危險基因型數目爲 2 個含以上者罹患泌尿道上皮癌的危險對比值爲 2.5（95%CI: 1.3-5.0）皆達統計上顯著水準。當同時擁有抽菸喝酒兩項習慣者，罹患泌尿道上皮癌的危險性遠高於只擁有其中一項習慣者，由此可見菸酒對於泌尿道上皮癌症的協同作用值得未來進一步探討。

英文摘要

Background: Urothelial carcinoma (UC) mostly occurs in the bladder and its major risk factor is cigarette smoking. Although cigarette smoking is considered a major risk factor for bladder carcinoma, little is known about the interaction between metabolic genes such as Cytochrome P450 2E1、glutathione-S-transferase A1 (GSTA1), glutathione-S-transferase P1 (GSTP1) and tobacco smoking in this process. CYP2E1,GSTA1andGSTP1 catalyze the activation of some environmental procarcinogens present in tobacco smoke (i.e. nitrosoamines and heterocyclic amines). We conducted a hospital based case–control study to evaluate the potential association between genetic polymorphisms of CYP2E1,GSTA1and GSTP1 and urothelial carcinoma risk in Taiwan population.

Methods: A total of 540 pathologically confirmed UC patients and 540 controls were recruited from Chi Mei Hospital, Chia-yi Christian Hospital, Taipei Medic University Hospital and Shin Kong Wu Ho_Su Memorial Hospital. Controls were matched to the cases by age (±2.5 years) and sex. All cases and controls were interviewed during hospital admission by well-trained interviewers using standardized structured questionnaires including demographic variables and other traditional risk factors for UC. Genetic polymorphisms of studied markers were genotyped using a PCR-RFLP assay. Odds ratios (ORs) and 95% confidence interval (CI), obtained from unconditional multiple logistic regression, were used to measure the strength of the association between risk factors and risk of UC.

Results: Cigarette smokers and alcohol drinkers respectively had 1.5-folds and 2.1-folds risk for development of UC after adjusting for age, and sex. For study subjects who with CYP2E1 c1/c1 genotype had 1.2-folds risk of UC compared with other genotypes of the marker. For subjects who with GSTA1 CC genotype had 1.2-folds risk of UC compared with other genotypes(CT+TT) of the marker. When study subjects with GSTP1 GG genotype, had 1.2-folds risk of UC. We combined effects of GSTA1 and GSTP1 polymorphisms and used GSTA1 CC and GSTP1 GG as the risk genotypes, a significantly increased risk of UC was associated with the

subjects who carried more than two risk genotypes (adjusted OR=3.4, 95% CI: 1.0-11.0). When the combined effects of CYP2E1 and GSTA1 polymorphisms and used CYP2E1 c1/c1 and GSTA1 CC as the risk genotypes, a significantly increased risk of UC was associated with the subjects who carried more than two risk genotypes (adjusted OR=1.7, 95% CI: 1.0-2.7). The joint effect with gene and cigarette smoking was also examined. The results showed that subjects who had cigarette smoking and carried two risk genotypes of CYP2E1 and GSTA1 have 2.7-folds risk for development of UC than those who did not have cigarette smoking and also carried less than one risk genotype. Also found that subjects who had cigarette smoking and carried more than two risk genotypes of CYP2E1,GSTA1 and GSTP1 have a significantly increased risk (adjusted OR=2.5, 95% CI: 1.3-5.0) than those who did not have cigarette smoking and also carried less than one risk genotype.
Conclusion: In summary, CYP2E1,GSTA1 and GSTP1 polymorphisms were associated with UC risk. The joint effect with gene,cigarette smoking and drinking need further studied.