# 上皮生長因子接受器-1, -2 基因多形性與泌尿道上皮癌之相關研究

# Association study on genetic polymorphisms of epidermal growth factor receptor-1, -2 and urothelial carcinoma


## 中文摘要

泌尿道上皮癌中以膀胱癌的發生爲最多，在過去的研究發現抽菸爲最重要的危險因子，當患者罹患膀胱癌時通常爲表淺型的腫瘤，若發展成肌肉侵犯性的腫瘤後會有比較差的預後情形。上皮生長因子接受器（epidermal grouth factor receptor, EGFR）家族與腫瘤細胞的增生及進展有很大的相關，其中又以 EGFR 和 HER2 的表現與癌症之間最爲相關，因此探討泌尿道上皮癌患者 EGFR 及 HER2 的基因多形性，是否與泌尿道上皮癌及其臨床病理學特徵有關。

本研究採病例對照研究，其中有 325 位爲泌尿道上皮癌之膀胱癌、腎盂癌及輸尿管癌的患者，及 328 位經頻率匹配年齡（±2.5 歲）、性別之健康對照。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?連鎖反應（polymerase chain reaction, PCR）增幅 DNA 片段，再利用限制片段長度多形性（restriction fragment length polymorphism, RFLP）方法進行基因判定，之後以多變項邏輯式迴歸（multiple logistic regression）進行泌尿道上皮癌與各危險因子之多變項分析。

研究結果顯示在調整其它危險因子後，抽菸仍有 2.0 倍的危險性；EGFR R497K 帶有 G/G 基因型者比其他基因型者有較高的罹患泌尿道上皮癌的危險性 OR=1.7（95%CI: 1.1-2.5），而 EGFR A2073T 基因型爲 T/T 者比其他基因型者有較高的罹患泌尿道上皮癌的危險性 OR=1.7（95%CI: 1.1-2.5），均達統計上顯著意義。其中 EGFR R497K 與 A2073T 之間有連鎖不平衡的存在（D’ =0.821, R2=0.64），497R-2073T 的單型者罹患泌尿道上皮癌的危險性爲 497K-2073A 單型者的 1.4 倍（95%CI: 1.1-1.7）。從 EGFR 基因多形性的合併結果顯示，在不考慮 HER2 基因型的分析中，當帶有 3 個 EGFR 危險性基因型者，罹患泌尿道上皮癌的危險性爲最高（OR=3.1, 95%CI: 1.6-6.2）。而基因與抽菸的協同作用中發現，曾抽菸且帶有 3 個危險性基因型數目者罹患泌尿道上皮癌的危險性高達 13.9 倍（95%CI: 2.8-68.1），若依抽菸年數分層，則抽菸年數≧40 年且帶有 2 個以上危險性基因型數目者罹患泌尿道上皮癌的危險性高達 4.3 倍（95%CI: 1.8-10.6）。此外，在臨床病理學特徵的分析中，當病例組中級別 G3 與 G1 相較下，帶有大於 2 個危險性基因型者則有 8.1 倍的危險性（p=0.05），達邊緣性統計上顯著。

根據上述的結果認爲，泌尿道上皮癌與 EGFR R497K 及 A2073T 基因多形性之間有顯著相關，且當腫瘤分化程度愈差則與 EGFR 及 HER2 的危險基因型數目愈多有關，因此 EGFR 及 HER2 也許可作爲泌尿道上皮癌及其預後的腫瘤標記。


## 英文摘要

Background: Urothelial carcinoma (UC) mostly occurs in the bladder and its major risk factor is cigarette smoking. The surrival and recurrence of bladder cancer is dependent on the stage and grade of the initial tumor. For patients who affected with nonmuscle-invasive tumor will have better prognosis than those with muscle-invasive tumor. Epidermal growth factor receptor (EGFR) family plays a critical role in signal transduction pathway for cell proliferation, differentiation, prognosis and survival. Previous studies showed that expression of EGFR and HER2 is most significantly association with malignant tumors. Therefore, the specific aim of the study is to investigate the associated between UC and genetic polymorphisms of EGFR and HER2.

Methods: A total of 325 pathologically confirmed UC patients and 328 controls were recruited from Chi Mei Hospital and Chia-yi Christian 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 had two-folds risk for development of UC after adjustment for age, sex, educational level, and alcohol intake. For study subjects who with EGFR 497RR genotype had 1.7-folds risk of UC compared with other genotypes of the marker. When study subjects with EGFR 2073TT genotype, we observed a statistically significant increased risk of UC (adjusted OR=1.7, 95%CI: 1.1–2.5). Since EGFR R497K locus was in linkage disequilibrium with the A2073T locus (D'=0.821, R2=0.64), a significant increased risk of UC was observed among study subjects with the haplotype EGFR 497K-2073A (adjusted OR=1.4, 95%CI: 1.1-1.7). When the combined effects of these three EGFR polymorphisms and used (CA)n≧20, 497RR and 2073TT as the risk genotypes, a significantly increased risk of UC was associated with the subjects who carried three risk genotypes (adjusted OR=3.1, 95% CI: 1.6-6.2). The joint effect between gene and cigarette smoking was also examined. The results showed that subjects who had cigarette smoking and carried three risk genotypes of EGFR have 13.9-folds risk for development of UC than those who did not have cigarette smoking and also carried less than one risk genotype of EGFR. The OR for study subjects who had smoking duration≧40 years and carried more than two risk genotypes of EGFR were 4.3-folds risk. Moreover, the subjects carried more than three risk genotypes of EGFR and HER2 have borderline increased risk of G3 initial tumor than those with less than two risk genotypes of EGFR and HER2

(adjusted OR=8.1, p=0.0508).
Conclusion: In summary, EGFR R497K and A2073T polymorphisms were associated with UC risk. The tumor differentiation grade progressed with the increasing numbers of EGFR and HER2 risk genotypes.