



The effect of cigarette smoking and DNA methyltransferase genes polymorphisms on urothelial carcinoma risk in Taiwan

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Introduction

Previous studies suggested that global DNA methylation is involved in breast, lung, and colon carcinogenesis. However, only a few studies showed the interaction of DNA methyltransferase genes (DNMTs) genotypes and cigarette smoking on urothelial carcinoma (UC) risk.

Aims

We constructed a hospital-based case-control study to elucidate the interaction of DNMTs polymorphisms and cigarette smoking on UC carcinogenesis.

Material and Methods

Total 159 and 308 matched cases and controls were respectively recruited at the Department of Urology and Family Medicine, China Medical University Hospital in Taiwan. All subjects had completed questionnaire information and collected blood samples for the identification of enzyme gene polymorphisms. Genotyping of DNMT1 exon 4 His97Arg, DNMT1 exon 19 Pro463Pro, and DNMT3B -579G>T was performed by a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. Multivariate logistic regression models were used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) to determine the interactions of gene polymorphisms and cigarette smoking on the risk of UC after adjustment for other risk factors.

Conclusions

Ever smokers and people carrying DNMT1 His97Arg homozygous variant genotype respectively contributed to increase UC risk. A trend analysis indicated that people simultaneously having smoking habit and with DNMT1 His97Arg homozygous variant genotype have high UC risk. There is not the significant interaction of DNMT gene polymorphisms and cigarette smoking on UC risk.

Table 1. Sociodemographic characteristics, and cigarette smoking habits of 159 UC patients and 308 matched controls.

	UC patients (n = 159)	Controls (n = 308)	OR ^a (95% CI)
Age (years)	66.35 ± 0.89	65.25 ± 0.59	
Male (%)	83 (52.20)	164 (53.25)	
Educational level (%) ^b			
Elementary school	85 (53.46)	76 (24.68)	1.00*
Junior high school	52 (32.70)	136 (44.16)	0.35 (0.23-0.54)
College or above	22 (13.84)	96 (31.17)	0.18 (0.11-0.31)
Cigarette smoking habits			
Non-smoker	101 (63.52)	229 (74.35)	1.00
Former smoker	39 (24.53)	43 (13.96)	2.94 (1.72-5.02)
Current smoker	19 (11.95)	36 (11.69)	1.68 (0.88-3.19)
Ever smokers	58 (36.48)	79 (25.65)	2.41 (1.48-3.91)
Duration of cigarette smoking (years)	13.44 ± 1.54	8.78 ± 0.94	1.02 (1.01-1.04)
0	101 (63.92)	229 (74.59)	1.00 [†]
< 35	23 (14.56)	38 (12.38)	2.01 (1.03-3.92)
≥ 35	34 (21.52)	40 (13.03)	2.64 (1.42-4.89)
Missing	1	1	-
Amount of cigarette smoking (pack/day)	0.35 ± 0.04	0.23 ± 0.03	1.95 (1.27-2.99)
0	101 (63.52)	229 (74.35)	1.00*
< 1	25 (15.72)	40 (12.99)	1.96 (1.03-3.73)
≥ 1	33 (20.75)	39 (12.66)	2.79 (1.50-5.21)
Missing	0	0	-
Cumulative cigarette smoking (pack-years)	12.97 ± 1.69	8.01 ± 1.05	1.02 (1.01-1.03)
0	101 (63.52)	229 (74.59)	1.00*
< 30	24 (15.19)	40 (13.03)	1.92 (1.01-3.66)
≥ 30	33 (20.89)	38 (12.38)	2.81 (1.50-5.25)
Missing	1	1	-

^a OR values were adjusted for age and gender.

[†] trend $p < 0.05$

Table 2. The information of DNMT1 and DNMT3B gene polymorphisms of 159 UC patients and 308 matched controls.

	UC patients	Controls	OR (95% CI)
Number	159	308	
DNMT1 exon17 I311V (rs2228611 A>G)			
AA	23 (14.47)	38 (12.34)	1.00
AG	59 (37.11)	115 (37.34)	0.85 (0.46-1.55)
GG	77 (48.43)	155 (50.32)	0.81 (0.45-1.46)
AG+GG (vs. AA)	136 (85.53)	270 (87.66)	0.83 (0.47-1.45)
GG (vs. AA+AG)	82 (51.57)	153 (49.68)	0.92 (0.63-1.35)
p value for Hardy-Weinberg equilibrium = 0.03 (G freq: 0.69)			
DNMT1 exon4 His97Arg (rs16999593 C>T)			
CC	6 (3.77)	17 (5.52)	1.00
CT	47 (29.56)	116 (37.66)	1.15 (0.43-3.11)
TT	106 (66.67)	175 (56.82)	1.71 (0.65-4.47)
CT+TT (vs. CC)	153 (96.23)	291 (94.48)	1.49 (0.57-3.86)
TT (vs. CC+CT)	53 (33.33)	133 (43.18)	1.51 (1.01-2.25)
p value for Hardy-Weinberg equilibrium = 0.70 (T freq: 0.76)			
DNMT3B -579G>T (rs1569686)			
GG	0 (0)	4 (1.30)	
GT	22 (13.84)	40 (12.99)	
TT (vs. GG+GT)	137 (86.16)	264 (85.71)	1.06 (0.61-1.84)
p value for Hardy-Weinberg equilibrium = 0.09 (T freq: 0.92)			

^a OR values were adjusted for age and gender.

Table 3. The association between cigarette smoking habit, duration or amount or cumulative cigarette smoking and OR of UC stratified by DNMT-related gene polymorphisms

	Non-Smokers (n=330)		Ever Smokers (n=137)	
	Case/Control	Adjusted OR ^a (95% CI)	Case/Control	Adjusted OR ^a (95% CI)
DNMT1 exon17 I311V (rs2228611 A>G)				
AG+GG	84/201	1.00*	52/69	2.19 (1.23-3.90)
AA	17/28	1.52 (0.77-3.03)	6/10	1.70 (0.54-5.36)
DNMT1 exon4 His97Arg (rs16999593 C>T)				
CC+CT	33/102	1.00*	20/31	2.48 (1.12-5.49)
TT	68/127	1.64 (0.98-2.74)	38/48	2.86 (1.42-5.76)
DNMT3B -579G>T (rs1569686)				
GG+GT	11/31	1.00*	11/13	3.15 (0.97-10.22)
TT	90/198	1.52 (0.71-3.25)	47/66	2.87 (1.16-7.10)

^aMultivariate adjusted OR were adjusted for age, gender, and educational level. * p trend < 0.05 .