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Scientific paper

ASSOCIATION BETWEEN GLUTATHIONE S-TRANSFERASE OMEGA 1 *A140D* POLYMORPHISM IN THE TURKISH POPULATION AND SUSCEPTIBILITY TO NON-SMALL CELL LUNG CANCER

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Recent years have seen a growing evidence of ethnic differences in the frequency of glutathione S-transferase omega 1 (*GSTO1*) *A140D* gene polymorphism, which is associated with various cancers such as breast and liver. Until now however, no association has been investigated between the *GSTO1 A140D* polymorphism and lung cancer. The aim of our study was to see if there was one in the Turkish population. To do that, we identified *GSTO1 A140D* polymorphism in 214 unrelated healthy individuals and 172 patients with non-small cell lung cancer (NSCLC) using the polymerase chain reaction - restriction fragment length polymorphism (PCR-RFLP) method. The frequencies of A/A (wild type), A/D (heterozygous mutant), and D/D (homozygous mutant) *GSTO1 A140D* genotypes in healthy subjects were 48 %, 41 %, and 11 %, respectively. In NSCLC patients they were 48 %, 45 %, and 7 %, respectively. We found no significant association between the *GSTO1 A140D* gene polymorphism and NSCLC or its histological subtypes, namely squamous cell carcinoma or adenocarcinoma. Furthermore, this polymorphism did not correlate with smoking. Our study is the first to show that the frequency of *GSTO1 A140D* gene polymorphism in the Turkish population is similar to other Caucasian populations and that this polymorphism is not associated with susceptibility to NSCLC.

KEY WORDS: *Caucasian, ethnic differences, gene polymorphism, NSCLC*

Glutathione S-transferases (GSTs) is a superfamily of enzymes that play a key role in the protection of cells against numerous xenobiotics (including carcinogens) and oxidative stress (1). Human cytosolic GSTs are divided into several classes according to their genetic and biochemical properties such as GST alpha, GST mu, GST theta, GST pi, and GST omega (2). Glutathione S-transferase omega 1 (GSTO1) is expressed in a wide range of human tissues, including the lungs (3, 4). It also plays a role in apoptosis (5, 6) and is a potential reservoir of intracellular glutathione

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(GSH), which protects against cellular oxidative stress (4, 5, 7).

The protective role against cell toxicity can be weakened if enzyme activity is reduced, but the findings related to the *GSTO1* gene polymorphism *Ala140Asp/A140D* are still inconclusive; Tanaka-Kagawa et al. (8) have shown that it significantly reduces thiol transferase activity whereas Whitbread et al. (9) and Board and Anders (10) could not find any significant reduction in the enzyme activity resulting from aspartic acid substitution.

The frequency of *GSTO1 A140D* seems to vary between races (9, 11-18), but only a few studies investigated this frequency in Caucasians (9, 14, 17, 18). In the single study of *GSTO1 A140D* that included the Turkish population, Takeshita et al. (17) observed that its distribution differed from Caucasian populations, and was more similar to African, Eastern Asian, and Brazilian populations. However, this finding is challenged by a great variety in the distribution of the same gene polymorphism even within one population (19-22).

Recent studies have established an association between the *GSTO1 A140D* gene polymorphism and increased risk of breast, hepatocellular, bile duct, and urothelial cancer and acute lymphoblastic leukaemia in children (13, 23-25). In addition, several reports suggest that it may be associated with lung cancer in smokers (26-28). As about 80 % of the lung cancer patients are non-small cell lung cancer (NSCLC) (29) and cigarette smoke has an important impact on the development of its subtypes such as adenocarcinoma (AC) and squamous cell carcinoma (SCC) (30, 31), it would be important to know if there were any association between this gene polymorphism and the risk of NSCLC. However, to our knowledge, no data is available in this regard. The aim of our study was therefore to establish the frequency of the *GSTO1 A140D* polymorphism in the Turkish population and see whether this polymorphism was associated with susceptibility to NSCLC and its histological subtypes.

SUBJECTS AND METHODS

The study population consisted of 214 healthy controls and 172 patients with a histological diagnosis of the primary stage III or IV NSCLC, who were receiving platinum-based chemotherapy, as described elsewhere (32, 33). All subjects were genotyped for the *GSTO1 A140D* polymorphism, as determined by the polymorphic analysis of genomic DNA isolated from whole blood using the Promega Corporation (Madison, WI, USA) DNA purification kit and stored at -20 °C until use. *GSTO1 A140D* (rs4925) was determined with polymerase chain reaction - restriction fragment length polymorphism (PCR-RFLP) method described by Marahatta et al. (13). Repeated quality control analysis of randomly chosen 10 % of the samples confirmed a 100 % match.

All subjects were native Turkish Caucasians. Most were from the central Turkey, but also from other Turkish regions to represent the whole country. Healthy unrelated controls were selected from the general population. The exclusion criteria were pregnancy and present or previous history of malignancy. All subjects gave written informed consent, and completed a questionnaire with information on their sex, smoking, occupation, and health history. The study was approved by a local ethics committee.

Statistical analysis

Statistical analysis was performed using the SPSS 15.0 software (SPSS Inc., Chicago, IL, USA). We used Student's *t*-test to see if the two groups differred in age and smoking (using pack-years as the measure). To establish differences in the distribution of genotype/allele frequencies between the groups we used the chi-square test and Fisher's exact test where necessary. The chi-square test was also used to see whether the frequency of the *GSTO1 A140D* polymorphism in either group fitted the Hardy-Weinberg equilibrium model. Multivariate logistic regression (34) was used to calculate the odds ratios (OR) and 95 % confidence intervals between the genotypes and lung cancer, adjusted for smoking status, sex, and age. *P* values less than 0.05 were assumed to be significant.

RESULTS AND DISCUSSION

Allele frequencies and genotype distribution of the *GSTO1 A140D* polymorphism in our study significantly differ from those of African, Brazilian, and Eastern Asian populations and are similar to other Caucasian populations (Table 1). In addition, our results are in contrast with the findings for the Turkish population reported by Takeshita et al. (17), whose genotype distribution and allele frequencies are similar to those

of African, Brazilian, and Eastern Asian populations. This is rather unexpected because polymorphism frequencies of xenobiotic metabolising enzyme genes studied in the Turkish population so far, namely CYP, mEH, and GST, are generally similar to other Caucasian populations (20-22, 35). At this stage, we can only speculate about the reasons why our findings differ, as both studies used the same methods, and sample sizes were similar. However, Takeshita et al. (17) have not included important demographic information on their Turkish native-borns such as age, sex, race, and exclusion criteria with respect to the health status. The only information they have provided is that their population included native-borns of the

Table 1 *Allele frequencies and genotype distribution of the* GSTO1 A140D *polymorphism in different populations*

Population	n	Allele frequency		Genotype / *n* (%)			Reference
		A140	D140	A/A	A/D	D/D	
German	280	0.680	0.320	126 (46)	129 (46)	25 (9)	14
Italian	116	0.698	0.302	50 (43)	62 (53)	4 (3)	18
White American	735	0.655	0.345	319 (44)	315 (43)	93 (13)	12
White American	220	0.666	0.334	96 (44)	101 (46)	23 (11)	15
European Australian	100	0.665	0.335	45 (45)	43 (43)	12 (12)	8
Chinese	215	0.853	0.137*	158 (73)	55 (26)	2 (1)	16
Chinese	100	0.835	0.165*	71 (71)	25 (25)	4 (4)	8
Thai	98	0.870	0.130*	74 (76)	23 (23)	1 (1)	13
African	62	0.919	0.081*	52 (84)	10 (16)	0 (0)	8
Japanese	102	0.892	0.108*	81 (79)	20 (20)	1 (1)	17
Mongol	243	0.872	0.128*	183 (75)	58 (24)	2 (1)	17
Ovambo (Namibia)	163	0.960	0.040*	150 (92)	13 (8)	0 (0)	17
Brazilian	173	0.899	0.101*	146 (84)	19 (11)	8 (5)	11
Turkish	194	0.915	0.085*	162 (83)	31 (16)	1 (1)	17
Turkish	214	0.689	0.311	104 (48)	87 (41)	23 (11)	This study

** Significantly different when compared to this study (P<0.05).*

Table 2 *Characteristics of the study population*

	NSCLC patients (*n*=172)	Healthy controls (*n*=214)
Age / years		
Mean	56	49
Range	26 to 75	24 to 76
Gender / n *(%)*		
Male	156 (91)	118 (55)
Female	16 (9)	96 (45)
Smoking status / n *(%)*		
Never	15 (9)	87 (41)
Former	55 (32)	43 (20)
Current	102 (59)	84 (39)
Pack-years, mean*	56	15
Genotypes / n *(%)*		
A/A	48 (82)	48 (104)
A/D	45 (77)	41 (87)
D/D	7 (13)	11 (23)
NSCLC stage / n *(%)*		
III	77 (45)	
IV	95 (55)	
Tumor histology / n *(%)*		
SCC	65 (38)	
AC	59 (34)	
UNSCLC	48 (28)	

**Among ever smokers*

Table 3 *Combined effects of polymorphisms and smoking on NSCLC risk*

***GSTO1* genotype**	**Smoking**	**Control / *n***	**Case / *n***	**OR (95 % CI)***	***P***
A/A	Never	45	8	1	
A/A	Ever	59	74	3.58 (1.39 to 9.21)	0.008
A/D + D/D	Never	42	7	1.01 (0.32 to 3.14)	0.987
A/D + D/D	Ever	68	83	5.63 (2.15 to 14.74)	0.000
A/D + D/D	Never	42	7	1	
A/D + D/D	Ever	68	83	5.54 (1.96 to 15.67)	0.001
A/A	Ever	59	74	1	
A/D + D/D	Ever	68	83	1.04 (0.61 to 1.76)	0.884

**OR (odds ratio) and (95 % CI) confidence interval were calculated by multivariate logistic regression and adjusted for age and gender*

city of Adana in Turkey, whose data they received from a German physician.

Characteristics of the study population are presented in Table 2. As a group, NSCLC patients were older and had more smokers than controls ($P<0.05$). In addition, they smoked much more than controls ($P<0.05$). However, we did not find significant differences in the frequency of *GSTO1 A/A* (wild type), *A/D* (heterozygous mutant), and *D/D* (homozygous mutant) genotypes between NSCLC patients and controls, and they remained in the Hardy-Weinberg equilibrium ($P=0.456$ *vs*. $P=0.379$, respectively). No significant difference was also observed between men and women (data not shown).

We also looked into the distribution of *GSTO1* genotypes by histological subtypes in NSCLC patients but saw no statistically significant difference between controls and NSCLC or histological subtypes (data not shown). Using multivariate logistic regression (MLR) analysis adjusted for age, sex, and smoking, we established that *GSTO1* genotypes presented no risk for overall NSCLC or a particular histological subtype. Likewise, Granja et al. (11) and Marahatta et al. (13) did not find any association between this gene polymorphism and thyroid and colorectal cancers, respectively. Findings are still inconclusive and controversial, as some authors established an increased risk of breast, hepatocellular, bile duct and urothelial cancers, and acute lymphoblastic leukaemia in childhood in *GSTO1 A140D* mutant allele carries (13, 23-25) while more recent studies on breast cancer report no such association (36, 37).

Using MLR, we also established that smoking did not influence the relationship between *GSTO1 A140D* and the risk of NSCLC (Table 3). However, smoking alone, independent of the genotype, significantly increased the risk of NSCLC (Table 2). Likewise, Olsen et al. (23) could not detect any interaction between cigarette smoking and *GSTO1 A140D* in breast cancer, nor could Ada et al. (33) and Schneider et al. (38) establish an association between cigarette smoking and other *GST* polymorphisms in lung cancer, including NSCLC.

Our study may be limited by the sample size, especially in the analysis of the association between the polymorphism and cancer risk in the histological subtypes. However, this is the first report showing that the frequency of the *GSTO1 A140D* gene polymorphism in the Turkish population is similar to other Caucasian populations and that this polymorphism is not associated with susceptibility to NSCLC. Further research with a larger sample size is needed to verify this finding.

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Sažetak

POVEZANOST POLIMORFIZMA *A140D* GENA GLUTATION S-TRANSFERAZE OMEGA 1 I OSJETLJIVOSTI NA RAK PLUĆA NE-MALIH STANICA U TURSKOG STANOVNIŠTVA

Posljednjih godina sve više rezultata ispitivanja upozorava na rasne razlike u učestalosti polimorfizma *A140D* gena glutation S-transferaze omega 1 (*GSTO1*) koji je povezan s više oblika karcinoma, poput raka dojke i jetara. Dosada međutim nije ispitana povezanost *GSTO1 A140D* i raka pluća. Mi smo u ovom ispitivanju pokušali utvrditi postoji li takva povezanost u turskog stanovništva. Izdvojili smo 214 zdravih ispitanika koji nisu bili u rodu te 172 bolesnika s rakom pluća ne-malih stranica, u kojih je polimorfizam *GSTO1 A140D* utvrđen pomoću lančane reakcije polimerazom - cijepanjem restrikcijskim enzimima (PCR/RFLP). Učestalost *GSTO1 A140D* genotipova - divljeg tipa (A/A), heterozigotnog mutanta (A/D) odnosno homozigotnog mutanta (D/D) - u zdravih ispitanika iznosila je 48 %, 41 %, odnosno 11 %, a u bolesnika s rakom pluća ne-malih stanica 48 %, 45 % odnosno 7 %. Rezultati ispitivanja nisu pokazali značajne povezanosti između genskog polimorfizma *GSTO1 A140D* i raka pluća ne-malih stanica odnosno njegovih histoloških podtipova raka pločastih stanica ili adenokarcinoma. Također nisu pokazali povezanost između ovog polimorfizma i pušenja. Međutim, ovo je prvo ispitivanje koje je potvrdilo da učestalost *GSTO1 A140D* u turske populacije odgovara učestalosti pripadnika bijele (kavkaske) rase te da nije povezan s osjetljivosti na rak pluća ne-malih stanica.

KLJUČNE RIJEČI: *adenokarcinom, bijela rasa, genski polimorfizam, rak pločastih stanica, rasne razlike*

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