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# Tumor necrosis factor-alpha gene promoter -308 and -238 polymorphisms in patients with lung cancer as a second primary tumor

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**Background:** Lung cancer is the most common second primary cancer. We investigated whether the TNF- $\alpha$ -308 and TNF- $\alpha$ -238 polymorphisms were associated with the susceptibility and severity of lung cancer as the second primary cancer (LC2).

**Material/Methods:** This study included 104 patients from the group LC2. The control subjects included 2 groups. The first control group (LC1) comprised 201 unrelated patients with lung cancer as a first primary cancer. The second control group (HC) comprised 230 healthy blood donors, matched for sex and age to the study group.

**Results:** The frequencies of the TNF- $\alpha$ -238 polymorphism GG genotype and the G allele were higher in the LC2 group than in the LC1 group, but the differences did not reach significance ( $p=0.054$  and  $p=0.057$ , respectively). Similar differences were found in the TNF- $\alpha$ -238 polymorphism GG genotype and G allele between the LC2 group and the HC group ( $p=0.054$  and  $p=0.057$ , respectively). In terms of the different types of lung cancer, patients with a second primary NSCLC (non-small cell lung cancer) more frequently had TNF- $\alpha$ -238 polymorphism GG genotypes and G alleles than patients with a first primary NSCLC (the differences approached statistical significance:  $p=0.060$ ,  $p=0.064$ , respectively). All (100%) patients of group LC2 ( $n=104$ ) had the GG genotype and the G allele. GG genotype was exclusive and no A allele was found in group LC2.

**Conclusions:** TNF- $\alpha$ -238 polymorphism GG genotype and the G allele could have a promotional effect on the development of NSCLC in the group of patients with LC2.

**Key words:** second primary tumor • lung cancer • TNF- $\alpha$  polymorphism • molecular epidemiology • carcinogenesis

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## Background

A second primary tumor (SPT) or secondary malignancy refers to the occurrence of a new cancer that follows a previously treated malignant neoplasm, but it is not considered a metastasis of the initial neoplasm [1]. The frequency of SPTs, on average, ranges from 2% to 10%. Second or multiple primary cancers represent 16% of all new primary cancers in cancer survivors in the United States [2]. SPTs result in increased morbidity and mortality [3]. Overall, patients who survive certain types of cancer are at increased risk of a second primary cancer [4]. Considering “all cancers”, after a first cancer diagnosis, males have a 9.7% chance of developing a SPT within 10 years (about 1 in 10), and women have a 7.7% chance (about 1 in 13) [5]. The most common second primary cancers were found in lung, breast, colon, head and neck, uterine cervix, skin, and prostate [5,6]. A male predominance was observed for each of the 4 major cancer types to which both sexes are susceptible (lung, colon, head and neck, and melanoma). The 10-year cumulative risk of a lung SPT was 1.6% for males, and 0.7% for females.

Environmental exposure and genetic factors play a role in the pathogenesis and natural history of a second cancer, as in the first cancer. A number of genetic factors (e.g., normal genetic variations in the genome) will interact with environmental and/or occupational factors to modulate lung cancer susceptibility, survival, and therapy [7]. The chance of developing a second cancer depends on a number of factors, including the original type of cancer, age at diagnosis, sex, types of therapy received, effects of using therapeutic interventions, lifestyle choices, tobacco use, environmental exposures, genetic predisposition, the theory of a common clonal origin, and the “screening effect” [6,8].

A second primary lung cancer after the complete resection of a primary lung cancer developed in 2.2% of patients during a 19-year follow-up period in a Korean population [9]. The overall 5-year survival rate from the time of detecting the second primary lung cancer was 47.8%, and the 5-year survival rate of patients who underwent resection of the SPT was 77.0%. Surgical resection was shown to be feasible and effective in the management of a second primary lung cancer. Long-term surveillance for 5 years or more is essential for early detection, and it will increase the chance of resection of a second primary lung cancer.

Several genes may contribute to inter-individual variations in DNA repair capacity and cancer susceptibility. Thus, polymorphisms of genes involved in the major nucleotide excision repair pathway are of particular interest [10].

Tumor necrosis factor-alpha (TNF- $\alpha$ ) is an important factor in cancer development and spread [11]. It was shown that blood

levels of TNF- $\alpha$  were elevated in patients with solid tumors [12]. Therefore, it is reasonable to hypothesize that the expression level of TNF- $\alpha$  may be involved in cancer pathogenesis. Single-nucleotide polymorphisms within the TNF- $\alpha$  gene promoter region have been reported to be associated with susceptibility to various types of cancers [13]. Several cytokine promoter polymorphisms, including TNF- $\alpha$ -308 and TNF- $\alpha$ -238, were associated with altered protein levels and/or rates of transcription [14]. Among the polymorphisms associated with an elevated production of TNF- $\alpha$  were G/A transitions at positions -308 and -238 [15]; these polymorphisms have been the subject of many molecular epidemiological studies that investigated their significance in carcinogenesis [12,16,17].

The association between some TNF- $\alpha$  promoter polymorphisms and the risk of lung cancer remains controversial. Ethnic differences may play a role in conflicting results. The first lung cancer study that focused on the TNF- $\alpha$ -308 and TNF- $\alpha$ -238 polymorphisms investigated 202 Chinese patients with non-small cell lung cancer (NSCLC). They found that the -308 G/A and the -238 G/A polymorphisms in the TNF- $\alpha$  promoter region were significantly associated with lung cancer susceptibility [11]. Moreover, these 2 polymorphisms were shown to be related to the severity of disease. The -308A allele positively correlated with lung cancer development and progression; conversely, the -238A allele had a protective impact on the development of lung cancer.

In the present study, we investigated whether the TNF- $\alpha$ -308 and TNF- $\alpha$ -238 polymorphisms were associated with the susceptibility and severity of lung cancer as a SPT in a sample of Croatian patients.

## Material and Methods

### Subjects

This study included 104 patients with lung cancer (70 males and 34 females; mean age 68.25, range 50–85 years) as second primary malignancies (group LC2). Among these patients, 98 had NSCLC and 6 had SCLC. In addition, prior to the detection of lung cancer, 7 patients had previously had 2 malignant tumors, including cancers in the bladder and larynx, larynx and prostate, breast and thyroid, larynx and oral cavity, stomach and breast, lung and kidney, and skin and skin. There were 2 control groups. The first control group (LC1) comprised 201 unrelated patients with lung cancer (174 with NSCLC and 27 with SCLC). The second control group (HC) comprised 230 healthy blood donors, from the Clinical Hospital Blood Donor Registry, Rijeka, matched for sex and age to the study group. All tested groups were from the Croatian population living in Primorsko-Goranska County.

**Table 1.** Average ages at the time of diagnosis and the length of the DFI (years).

	Male (years)	Female (years)	p value	Both sexes (years)	p value
FPT-synchronous	64.77 $\pm$ 11.10	81.67	0.163	65.83 $\pm$ 11.53	
FPT-metachronous	59.51 $\pm$ 10.24	56.00 $\pm$ 11.18	0.136	58.19 $\pm$ 10.68	0.011
FPT-all	60.64 $\pm$ 10.58	56.75 $\pm$ 11.86	0.094	59.37 $\pm$ 11.11	
Lung cancer	67.39 $\pm$ 9.74	69.67 $\pm$ 7.48	0.237	68.25 $\pm$ 9.16	
DFI- metachronous	8.34 $\pm$ 6.89	13.42 $\pm$ 10.55	0.005	10.28 $\pm$ 8.78	0.706
DFI-all	6.73 $\pm$ 7.05	13.52 $\pm$ 10.90	<0.001	9.18 $\pm$ 9.13	

DFI – disease free interval between the first primary tumor and detection of lung cancer; FPT – first primary tumor.

In the study group (LC2), 7 patients had 3 different primary tumors and all other patients (n=97) had 2 primary malignant tumors. Of the 104 patients, 70 (67.3%) were male and 34 (32.7%) were female (ratio, 2.1:1). The average ages at the time of tumor diagnosis and the length of the disease-free interval between treatment of the first primary tumor and the detection of lung cancer are presented in Table 1.

The anatomical locations of primary tumors were in the larynx in 22 patients (21.1%); skin in 14 patients (13.4%); breast in 13 patients (12.5%); uterus in 12 patients (11.5%); oral cavity, prostate, and bladder in 8 patients (7.7%); colon and pharynx in 5 patients (4.8%); kidney in 3 patients (2.8%); and lung, parotid, penis, small bowel, liver, and stomach in 1 patient (1.0%). Among skin tumors, there were 8 melanomas, 3 squamous carcinomas, and 2 basal cell carcinomas.

Among the 7 patients (6.7%) with 3 primary tumors, the secondary malignancy locations were equally represented among the patients: 1 patient each had a tumor in the larynx, skin (basalioma), breast, oral cavity, prostate, kidney, and thyroid.

When classified according to sex, the most frequent sites for primary tumors in males were the larynx (n=21; 30.0%), skin (n=13; 18.6%), and prostate (n=9; 12.9%). In females, the leading primary tumor sites were the breast (n=14; 41.2%) and uterus (n=12; 35.3%).

Among all patients, 85 (81.8%) were smokers and 19 (18.2%) were non-smokers. The proportion of male smokers was significantly higher than females (male: female ratio, 4.5: 1; p<0.001).

Among patients with lung cancer, 49 (47.1%) had squamous carcinomas and 27 (26.0%) had adenocarcinomas. At the time of diagnosis, 34 patients (32.7%) were in tumor-node-metastasis (TNM) stages I and II, and 70 patients (67.3%) were in TNM stages III and IV.

Multiple tumors in a patient were classified as either synchronous or metachronous, based on Moertel's definition: synchronous tumors occurring within 6 months of detecting the first primary tumor, and metachronous tumors occurring more than 6 months after detecting the first primary tumor [18]. Both synchronous and metachronous tumors were included in this survey. There were 17 (15.3%) synchronous and 94 (84.7%) metachronous tumors.

This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

For each of patient, we prospectively collected data on the tumor site, patient age at diagnosis, sex, smoking status, stage of lung cancer, and histological differentiation. Time elapsed between the appearance of primary and secondary tumors, therapies for primary tumors, and some data about the LC1 group were collected retrospectively.

#### TNF-alpha polymorphism analyses

Genomic DNA was extracted from the peripheral blood lymphocytes according to standard protocols. The analysis of TNF- $\alpha$  gene polymorphisms was performed by polymerase chain reaction/restriction fragment length polymorphism (PCR-RFLP) analysis under conditions described by Shih et al. [11].

#### Statistical analysis

The mean values were compared between different groups of data with the t test. Allele and genotype frequencies were estimated by gene counting. Group differences in patient genotype and allele distributions were analyzed for statistical significance with the  $\chi^2$  test or Fisher's exact test, as appropriate. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to evaluate the effects of different genotypes/alleles. A p value <0.05 was considered statistically significant.

**Table 2.** Distribution of TNF- $\alpha$ -308 and TNF- $\alpha$ -238 polymorphism genotypes for patients with lung cancer as a second primary tumor (study group).

Second tumor type	TNF- $\alpha$ (308 G/A) polymorphism genotypes			Total	TNF- $\alpha$ (238 G/A) polymorphism genotypes			Total
	GG (%)	GA (%)	AA (%)		GG (%)	GA (%)	AA (%)	
Adenocarcinoma	16 (59.3)	10 (37.0)	1 (3.7)	27	27 (100.0)	0 (0.0)	0 (0.0)	27
Squamous carcinoma	33 (67.4)	13 (26.5)	3 (6.1)	49	49 (100.0)	0 (0.0)	0 (0.0)	49
Carcinoid	1 (50.0)	0 (0.0)	1 (50.0)	2	2 (100.0)	0 (0.0)	0 (0.0)	2
Unclassified NSCLC	13 (76.5)	4 (23.5)	0 (0.0)	17	17 (100.0)	0 (0.0)	0 (0.0)	17
Large cell carcinoma	1 (33.3)	2 (66.7)	0 (0.0)	3	3 (100.0)	0 (0.0)	0 (0.0)	3
SCLC	5 (83.3)	1 (16.7)	0 (0.0)	6	6 (100.0)	0 (0.0)	0 (0.0)	6
Total	69 (61.6)	30 (28.4)	5 (10.0)	104	104 (100.0)	0 (0.0)	0 (0.0)	104

NSCLC – non-small cell lung cancer; SCLC – small cell lung cancer.

## Results

The distributions of TNF- $\alpha$ -308 and TNF- $\alpha$ -238 polymorphism genotypes are presented in Table 2 for different histological types of lung cancer. We did not find any association between the particular genotypes and the length of the disease-free interval. Furthermore, we did not find an association between the genotypes and different clinical stages of lung cancer according to the TNM classification.

The distributions of TNF- $\alpha$ -308 and TNF- $\alpha$ -238 polymorphism genotypes and alleles among LC1 and LC2 group patients are presented in Tables 3 and 4. The HC group was a healthy population. There was no statistically significant difference in the distributions of the TNF- $\alpha$ -308 polymorphism genotype and alleles between the LC1 and LC2 groups or between the LC2 and HC groups. The frequencies of the TNF- $\alpha$ -238 polymorphism GG genotype and the G allele were higher in the LC2 group relative to the LC1 group, but the differences did not reach significance ( $p=0.054$  and  $p=0.057$ , respectively). Similar differences were found in the TNF- $\alpha$ -238 polymorphism GG genotype and G allele between the LC2 group and the HC group ( $p=0.054$  and  $p=0.057$ , respectively). In terms of the different types of lung cancer, patients with a second primary NSCLC more frequently had TNF- $\alpha$ -238 polymorphism GG genotypes and G alleles relative to patients with a first primary NSCLC (the differences approached statistical significance:  $p=0.060$ ,  $p=0.064$ , respectively). However, patients with a second primary SCLC and those with a first primary SCLC were not significantly different in the distributions of TNF- $\alpha$ -238 polymorphism GG genotypes or G alleles.

All (100%) patients of group LC2 ( $n=104$ ) had the GG genotype (homozygous GG) and the G allele.

## Discussion

We investigated the relationship between TNF- $\alpha$ -308 and TNF- $\alpha$ -238 promoter polymorphisms and the susceptibility to lung cancer as a SPT. The results revealed that the TNF- $\alpha$ -238 polymorphism had a possible impact on the incidence of lung cancer and the incidence of NSCLC as a group LC2. We found that 100% of patients of a group LC2 had the TNF- $\alpha$ -238 polymorphism GG genotype and the G allele. This frequency was nearly significantly different from that observed in the 2 control groups (LC1 and HC). In patients of group LC2 that had an NSCLC, a trend was observed that did not reach statistical significance. The patients with SCLC in group LC2 (only 6) also had 100% frequency of the GG genotype and the G allele, but this was not significantly different from the frequency observed in patients with SCLC in group LC1.

This study is the first to show that 100% of patients in group LC2 had the TNF- $\alpha$ -238 polymorphism GG genotype and the G allele. This result provided evidence that the TNF- $\alpha$ -238 GG genotype was associated with a greater possibility of developing LC2. Thus, this polymorphism could have a promotional effect on lung cancer and the development of NSCLC in the group of patients with LC2. In this study, the mean disease-free period in females was 13.52 years; this was significantly longer ( $p<0.001$ ) than the mean disease-free period in males (6.73 years). We speculate that this finding may have been due

**Table 3.** Distribution of TNF- $\alpha$  308 polymorphism genotypes and alleles among patients with lung cancer (LC2).

Characteristics	Genotypes			Total	Alleles	
	GG (%)	GA (%)	AA (%)		G (%)	A (%)
LC1	150 (74.6)	42 (20.9)	9 (4.5)	201	342 (85.1)	60 (14.9)
LC2	69 (66.3)	30 (28.9)	5 (4.8)	104	168 (80.8)	40 (19.2)
p-value; OR (95% CI)	0.129; 1.49 (0.89–2.50)				0.174; 1.357 (0.87–2.11)	
HC	171 (74)	53 (23)	6 (3)	230	395 (85.9)	65 (14.1)
p-value; OR (95% CI)	0.133; 1.47 (0.89–2.43)				0.095; 1.45 (0.94–2.23)	
Tumor type						
LC1 NSCLC	128 (73.6)	38 (21.8)	8 (4.6)	174	294 (84.5)	54 (15.5)
LC2 NSCLC	64 (65.3)	29 (29.6)	5 (5.1)	98	157 (80.1)	39 (19.9)
p-value; OR (95% CI)	0.152; 1.478 (0.87–2.52)				0.194; 1.352 (0.86–2.13)	
LC1 SCLC	22 (81.5)	4 (14.8)	1 (3.7)	27	48 (88.9)	6 (11.1)
LC2 SCLC	5 (83.3)	1 (16.7)	0 (0.0)	6	11 (91.7)	1 (8.3)
p-value; OR (95% CI)	0.915; 0.880 (0.08–9.29)				0.778; 0.727 (0.08–6.67)	

LC1 – first primary carcinoma; LC2 – second primary carcinoma; HC – controls; NSCLC – non-small cell lung cancer; SCLC – small cell lung cancer; OR (95% CI) – odds ratio (95% confidence interval).

**Table 4.** Distribution of TNF- $\alpha$  238 polymorphism genotypes and alleles among patients with lung cancer (LC2).

Characteristics	Genotypes			Total	Alleles	
	GG (%)	GA (%)	AA (%)		G (%)	A (%)
LC1	187 (93.0)	14 (7.0)	0 (0.0)	201	388 (96.5)	14 (3.5)
LC2	104 (100.0)	0 (0.0)	0 (0.0)	104	208 (100.0)	0 (0.0)
p-value; OR (95% CI)	0.054; 0.062 (0.00–1.05)				0.057; 0.064 (0.00-1.08)	
HC	214 (93.0)	16 (7.0)	0 (0.0)	230	444 (96.5)	16 (3.5)
p-value; OR (95% CI)	0.054;0.062 (0.004–1.05)				0.057; 0.06 (0.003-1.082)	
Tumor type						
LC1 NSCLC	162 (93.1)	12 (6.9)	0 (0.0)	174	336 (96.5)	12 (3.5)
LC2 NSCLC	98 (100.0)	0 (0.0)	0 (0.0)	98	196 (100.0)	0 (0.0)
p-value; OR (95% CI)	0.060; 0.066 (0.00–1.13)				0.064; 0.068 (0.00-1.24)	
LC1 SCLC	25 (92.6)	2 (7.4)	0 (0.0)	27	52 (96.3)	2 (3.7)
LC2 SCLC	6 (100.0)	0 (0.0)	0 (0.0)	6	12 (100.0)	0 (0.0)
p-value; OR (95% CI)	0.880; 0.785 (0.03–18.42)				0.912; 0.840 (0.04-18.62)	

LC1 – first primary carcinoma; LC2 – second primary carcinoma; HC – controls; NSCLC – non-small cell lung cancer; SCLC – small cell lung cancer; OR (95% CI) – odds ratio (95% confidence interval).

to the fact that most of the young women had breast cancer and uterine cancer as a first cancer and that there were fewer smokers among females than among males; both factors may have influenced our results that suggested a genetic predisposition to lung cancer.

Our results are inconsistent with those of a meta-analysis from 2011 that included 34 679 patients with cancer and found no significant association between the TNF- $\alpha$ -238 polymorphism

and the risk for cancer (including lung cancer) [19]. However, because lung cancer is affected by inflammatory cytokines, our results are consistent with those from an interesting study in an Italian population (163 cases), which included 66 patients with severe rheumatoid arthritis. They found that the TNF- $\alpha$ -238 GG homozygosity was present in 100% of cases. Thus, TNF- $\alpha$ -238 GG homozygosity appeared to be associated with severe rheumatoid arthritis [20]. Also, Shih et al. [11] found that the GG genotype of TNF- $\alpha$ -238 tended to be associated with advanced lung cancer.

Lung cancer is a multi-factorial disease; it results from complex interactions between environmental and genetic factors. It is possible that variants at some *loci* may confer a modest risk of cancer. However, some environmental factors may predominate in the development of lung cancer, like living habits and exposure to carcinogens. Without considering these factors, it may not be possible to determine the role of TNF- $\alpha$ -308 and TNF- $\alpha$ -238 polymorphisms in lung cancer development. Some short nucleotide polymorphisms of cytokines may exert complex and interacting functions with each other, which may alter the effects of TNF- $\alpha$ -308 and TNF- $\alpha$ -238 polymorphisms in the pathogenesis of lung cancer. Therefore, other polymorphisms should be taken into account to ascertain the true effects of cancer risk factors. Also, some polymorphisms might have different effects on different lung cancer subtypes.

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## Conclusions

TNF- $\alpha$ -238 polymorphism GG genotype and the G allele could have a promotional effect on the development of NSCLC as a second primary tumor. Our findings should be validated in larger, prospective studies or multicenter, case-control studies. Also, studies with patients with different ethnic backgrounds would allow further exploration of the genetic pathogenesis of second primary lung cancers.

## Conflict of interest

The authors have no conflicts of interest to declare in relation to this article.