Asian Jr. of Microbiol. Biotech. Env. Sc. Vol. 22 (4) : 2020 : 662-669

ISSN-0972-3005

SEARCH FOR A POSSIBLE ASSOCIATION BETWEEN THE GENETIC POLYMORPHISM CYP1A1 MSPI, AND LUNG CANCER IN AN ALGERIAN POPULATION

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(Received 15 September, 2020; accepted 10 October, 2020)

***Key words** : Lung cancer,* CYP1A1*, Polymorphism, Tobacco smoking*

Abstract – It is widely known that lung carcinoma is an environment-related sickness that develops as a consequence of exposure to mutagenic sellers, especially those present in tobacco. The CYP1A1 gene codifies the phase I enzyme aryl hydrocarbon hydroxylase (AHH) belonging to the cytochrome P450 machine that plays a pivotal role in the bio-activation of tobacco procarcinogens. Greater enzymatic activity is associated with the CYP1A1 ml polymorphism (T6235C transition) and has been described as a genetic susceptibility factor for lung cancer. This case-control study was carried out to verify if this association holds in a study population of 80 lung cancer patients and 85 controls from Eastern Algeria. Genetic polymorphisms were determined by Restriction Fragment Length Polymorphism (RFLP) assay. The frequencies of the genotypes CYP1A1 m1 in both groups were investigated to get odds ratios and 95 % confidence intervals. The TC Genotype and C allele were significantly higher in patients compared to healthy controls with [OR = 0.547 (0.235- 1.241), p = 0.130], and [OR = 0.536 (0.245 - 1.135), p = 0.083] respectively. However, these two factors were not found to be significantly associated with the risk of lung cancer. After stratification of the population according to tobacco consumption, non-smokers were at higher risk compared with smokers [OR = 0.086 (0.007 - 0.550), p = 0.003]. Our findings support the conclusion that CYP1A1m1 polymorphism does not seem to be associated with susceptibility to lung cancer in Eastern Algeria.

INTRODUCTION

Lung cancer is a common malignant tumor that is characterized by high morbidity, poor prognosis and is a leading cause of death in both men and women *(Cabral et al*., 2010), with over one million deaths worldwide annually (Ren *et al.*, 2013).

In Algeria 2856 cases of new lung cancer were diagnosed in men (Hamdi-Cherif *et al*., 2014); The evidence that *tobacco smoking* causes *lung cancer* is unequivocal, although only a small percentage of smokers during their lifetime develop the malignant disease (Ren *et al.*, 2013). Inherited genetic predisposition to disease has become a subject of intense research (Ren *et al.*, 2013), and studies suggest that an individual's genetic background affects the risk of developing lung cancer. Possible cancer susceptibility genes have been studied among oncogenes, tumor suppressor genes, DNA repair genes, and genes encoding phase I and phase II

enzymes.

Environmental Chemical Pollutants (ECPs) are increasingly present in our living environment as a result of the development of the modern industry and urbanization. Many ECPs are widely spread and difficult to be degraded in the environment. Among the ECPs polycyclic aromatic hydrocarbons are the most studied pollutants, and have been found in cigarette smoke and polluted indoor and outdoor air, and shown to be associated with the risk of many diseases including cancer (Shi *et al*., 2008). Most of these products are hydrophobic and the host organism needs the P450 enzyme battery to eliminate them (Jacquet *et al*., 1996). Both biological and biochemical evidence indicates that genetic polymorphisms of CYP1A1 can influence the balance between metabolic activation and detoxication of some toxicants, such as benzo(a) pyrene (Shi *et al*., 2008).

CYP1A1 gene is located in chromosome 15q22-q24 and in addition to the lung, it is also expressed in the liver, gastrointestinal tract, brain, lymphocytes, and macrophages. The m1 polymorphism, involving a *Msp*I restriction site, is a T6235C transition in the 3'-noncoding region of the gene, 250 bp downstream from the polyadenylation site (Mota *et al*., 2010). Expression of the CYP1A1 gene is upregulated by certain foreign chemicals, including PAHs, but the extent to which PAHs induce CYP1A1 varies considerably in human populations, this may explain the variability of the genetic predisposition to this kind of epithelial cancer. As first discovered in human lymphocytes, some individuals display very high inducibility. Kellerman and colleagues have shown that this phenotype is more frequent in lung cancer patients than in healthy individuals (Kellermann *et al*., 1973).

Elevated CYP1A1 inducibility is associated with pulmonary PAH-related DNA adduction and high lung cancer risk. Both CYP1A1 expression and the formation of these PAH-DNA adducts in human lung tissue are highly variable, possibly due to different exposure to environmental factors and genetic polymorphisms affecting the *CYP1A1* gene locus (Ezzeldin *et al*., 2017). It is important to mention that our population, to the best of our knowledge, has not been the object of any molecular study concerning this polymorphism for lung cancer till now.

This case-control study was performed to confirm or invalidate the hypothesis that there is a correlation between the presence of CYP1A1 m1 allele and lung cancer risk.

METHODS

Study population

This case-control study consisted of 80 patients with lung cancer and 85 cancer-free controls. The cases with histologically confirmed primary lung cancer were recruited from 2013 to 2016 in the governmental University Hospital Benbadis Constantine CHUC. They came from ten territorial units in Eastern Algeria, healthy controls were enrolled from the general population of the same geographical region.

Ethic statement

Written informed consent was obtained from all the subjects of the study. A standard questionnaire was used to document the socio-demographical characteristics, lifestyle, occupational exposure, smoking, histological subtype.

Molecular analysis

Blood collection and DNA extraction

Five to eight milliliters of whole blood was collected in vacutainers containing ethylenediamine tetra acetic acid (EDTA) for DNA extraction using a standard protocol of salt extraction procedure.

CYP1A1 m1 genotyping

Genotyping for the CYP1A1 m1 gene (rs4646903) was carried out using Polymerase Chain Reaction (PCR) based restriction fragment length polymorphism (RFLP). The primer sequences were primer forward 5' - TAG GAG TCT TGT CTC ATG CCT - 3', and primer reverse 5'- CAG TGA AGA GGT GTA GCC GCT- 3'. The PCR amplification was carried out in 50 µL reaction mixture containing 1 µL of DNA, 1X reaction buffer, 1,5 mM of $MgCl_2$, 200 µM of dNTPs, 0.2 µM of each primer, and 1 U *Taq* DNA polymerase. The samples were amplified using thermal cycle with an initial denaturation at 94 °C for 5 minutes followed by 30 cycles with denaturation at 94 °C for 30 seconds, annealing at 62 °C for 60 seconds and primer extension at 72 °C for 60 seconds, followed by a final extension step at 72 °C for 5 minutes.

Statistical analyses

The data were analyzed using the SPSS 26.0 program. Logistic regression analyses were done to

investigate the association of the independent variables. The results were considered to be significant at p values less than 0.05. Odds ratios and 95 % confidence interval were calculated to assess the relationship between CYP1A1 m1 and the risk of lung cancer.

RESULTS

General characteristic features of the study population

The general characteristic features of lung cancer patients (n = 80) and healthy controls (n=85) included in this study are given in Table 1. In the present study, there were 80 cases of lung cancer in the patient group (55 cases of lung adenocarcinoma, 22 cases of lung squamous cell carcinoma, 2 cases of small cell lung cancer, and 1 case of large cell lung cancer). The patient group comprised 68 males and 12 females with a mean age of 58.74 years; the control group comprised 85 healthy adults recruited over the same period as the patients; there were 80 males and 5 females with a mean age of 60.50 years. Lung cancer was predominant among men. There was no significant difference between the groups in terms of age and gender (p> 0.05).

Molecular analysis of CYP1A1 m1

The PCR products were analyzed in a 1 % agarose gel with BET and visualized using a UV transilluminator. For RFLP assay, digestion was carried out overnight at 37 °C, in a total volume of 15 μL of PCR product and 1U *Msp*I. In the presence of the 6235 C polymorphism, the enzyme *Msp*I digested the 340 bp PCR product in two bands of 200 bp and 140 bp. The wild type 6235C form corresponds to the absence of the restriction site (Figure 1)

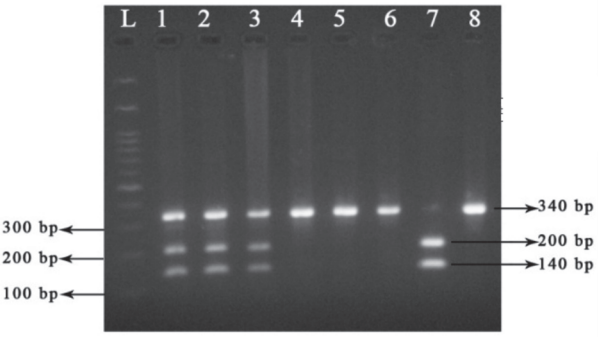

Fig. 1. Agarose gel electrophoresis of PR-RFLP patterns of CYP1A1 m1

Statistical analyses

All data were analyzed using the SPSS 26.0 program. Odds ratios with the corresponding confidence interval (95 % CI) were calculated to assess the relationship between CYP1A1 m1 and the risk of lung cancer. ORs are also performed to determine the risk of lung cancer associated with CYP1A1 m1 stratified with smoking status. The univariate logistic regression analysis was performed to assess associations with age, gender, smoking, and CYP1A1 m1 polymorphisms between the cases and controls. The results were considered to be significant at p values less than 0.05.
Univariate logistic regression

Table 1. General characteristics of the study population

Variables	Patients n=80 (%)	Controls n=85 (%)	p value
Gender			
Male	68 (85)	80 (94.1)	0.054
Female	12 (15)	5 (5.9)	
Age			
<60 years	18 (22.5)	10 (11.8)	0.066
≥ 60 years	62 (77.5)	75 (88.2)	
Histology			
Adenocarcinoma	55 (68.8)		
Squamous cell Carcinoma	22 (27.5)		
SCLC	2 (2.5)		
Others	1 (1.3)		
Smoking			
Smokers	66 (82.5)	51(60)	0.001*
Non smokers	14 (17.5)	34 (40)	

*p<0,05 SCLC : Small Cell Lung Cancer

Logistic regression analysis was performed by taking some risk factors like age, gender, smoking status, and CYP1A1 m1 polymorphism. We observed that smoking and CYP1A1 m1 polymorphism were the strongest predicting factors; other variables did not have any impact as reflected by a lack of significance (Table 2).

Genotyping distribution of CYP1A1 m1

The homozygous major TT, heterozygous TC, and homozygous minor CC genotype frequencies of the CYP1A1 m1 gene in healthy controls were 71 %, 14%, and 0% respectively, whereas the same in patients were 58 %, 21%, and 1.25 % respectively (Table 3). The TC Genotype was not significantly different between patients and controls groups [OR = 0.547 (0.235-1.241), p = 0.130]. The C allele was also not significantly higher in patients compared to healthy controls [OR = 0.536 (0.245-1.135), p = 0.083].

Risk of lung cancer associated with CYP1A1 m1 stratified by smoking exposure

Patients who were non-smokers and having a CYP1A1 m1 TC were significantly higher risk compared to the controls [OR= 0.086 (0.007-0.550), p=0.003] while patients who were smokers and having TC genotype were not at risk compared to the control group [OR= 1.076 (0.404-2.835), p=0.99]. The C allele also presented the same situation (with a significant difference among non-smokers and no difference among smokers) (Table 4).

Histology

The predominant genotypes for every pathological subtype are indicated in Table 5.

Table 2. Logistic regression for different variables in lung cancer

Variables	OR	(95 % CI)	p value
Age	0.891	0.483 to 1.643	0.712
Sex	0.354	0.119 to 1.056	0.063
Smoking	3.596	1.694 to 7.636	<0.001***
CYP1A1 m1	2.121	1.021 to 4.406	0.044*

* p<0,05; ** p < 0.01; *** p < 0.001

Table 3. Genotype and allelic distribution of the CYP1A1 m1 gene polymorphisms in lung cancer patients and healthy controls

Genotype	Patients (n = 80)	Controls (n=85)	OR	(95 % CI)	p value
TT	58 (72.5%)	71 (83.52%)	Ref.		
TC	21 (26.25 %)	14 (16.47%)	0.547	0.235 to 1.241	0.130
CC	1 (1.25 %)	0 (0 %)	-	-	0.454
Allele T	137 (85.62)	156 (91.76)	Ref		
Allele C	23 (14.38)	14 (8.24)	0.536	0.245 to 1.135	0.083

OR = Odds Ratio; CI = Confidence Interval.

Table 4. Risk of lung cancer associated with CYP1A1 m1 stratified with smoking status

	CYP1A1 m1	Cases/controls	OR	(95 % CI)	p value
Smokers	TT	49/39	Ref		
	TC	14/12	1,076	0.404 to 2.835	0.999
	CC	1/0	-	-	0,999
	Allele T	112/90	Ref		
	Allele C	16/12	0.934	0.382 to 2.227	0.999
Non-smokers	TT	9/32	Ref		
	TC	7/2	0.086	0.007 to 0.550	0.003*
	CC	0/0	-	-	0,999
	Allele T	25/66	Ref		
	Allele C	7/2	0.111	0.011 to 0.635	0,004*

* p< 0.05

DISCUSSION

Genetic polymorphisms of detoxification enzymes may regulate an individual's predisposition to cancer including lung cancer. Besides this, environmental and lifestyle also contribute to the predisposition of lung cancer (Peddireddy *et al*., 2016).

The distribution of lung cancer histological subtypes doesn't differ according to the sex: adenocarcinoma was the most frequently encountered subtype both in women and men. In contrast, in a similar study concerning European lung cancer patients, the distribution of lung cancer histological types differed according to the sex: 70% of the women patients had adenocarcinoma, while a more homogeneous distribution of the various histological types was seen among the male patients (Jacquet *et al*., 1996).

Our finding is consistent with the results of Yoon *et al.* (2008) and Yang *et al.* (2007)which propose that adenocarcinoma was the predominant histological type of lung cancer among patients. In contrast to our results, squamous cell carcinoma was the predominant subtype according to the findings of Sobti *et al*. (2004).

All carcinogens are lipophilic and tend to be converted into water-soluble hydrophilic compound, and can be easily removed from the body through the excretory system. This conversion or detoxification of carcinogens is achieved by the addition of one atom of oxygen to the carcinogenic compound, brought about by the superfamily of cytochrome p 450 phase I enzymes. This process of detoxification leads to the formation of reactive intermediates, whenever they are not neutralized form DNA adducts (Sreelekha *et al*., 2001).

In the present study, genotype frequencies of the *Msp*I polymorphism, indicated that the heterozygous genotype TC was present in 26.25% of cancer patients and in 16.47 % of controls [OR = 0.547(0.235-1.241) p= 0.130], whereas the homozygous mutant genotype CC was present in 1.25 % of the cancer patients and in 0 % of controls, The frequency of the C allele was different in the two tested populations; 14.38 % in the cancer patients, 8.24 % in the healthy population; the C allele was also not significantly higher in patients compared to the control group [OR = 0.536 (0.245-1.135), p = 0.083], and thus, by lack of significance p>0.05, our study has indicated that TC genotype was not associated with susceptibility to lung cancer, which was consistent with the results of Quiñones *et al.* (2001).

Similar results were found by Houlston (2000) in a study including 2058 cases and 2765 controls of different ethnic populations suggesting that there was no evidence of lung cancer risk associated with the variant (*Msp*I) of *CYP1A1*. In another study, no significant association was found between lung cancer and combined variant alleles of *CYP1A1 Msp*1 genotype (Sobti *et al*., 2004).

Hung *et al*. (2003) have also observed a slight and not statistically significant increase in risk with the CYP1A1 *Msp*I polymorphism and suggest that the *Msp*I polymorphism alone does not seem to have any effect on the risk of lung cancer. Another study has found no influence of the CYP1A1 *Msp*I genotype on PAH inducibility value distributions in a Caucasian population (Jacquet *et al*., 1996).

Honma *et al*. (2009) reported that CYP1A1 m1 gene polymorphisms have no influence on the risk of lung cancer in a Brazilian population. Jacquet *et al*. (1996) corroborate our findings and indicate that CYP1A1 m1 is not linked with a higher risk of developing lung cancer. Also, Huang *et al.* (2013) found no significant association between the genetic polymorphisms of CYP1A1 and the risk of lung cancer in Chinese Han ethnic populations from Central South China. Results of López-Cima *et al*. (2012) suggest that CYP1A1 *Msp* I is not associated with lung cancer risk in a population of Caucasians from Northern Spain. The results of another study established by Wright *et al*. (2010) confirm that CYP1A1 polymorphisms are a minor risk factor for Non Small Cell Lung Cancer (NSCLC) in

Table 5. Genotypic distribution of CYP1A1 m1 stratified by histological subtype

Genotype	Adenocarcinoma (%)	Squamous cell carcinoma (%)	SCLC (%)	Large cell lung carcinoma(%)
TT	36	19	2	1
TC	18	3	0	0
CC	1	0	0	0

SCLC: Small-Cell Lung Carcinoma.

Caucasians. Our results are consistent with the results obtained from Caucasians, Portuguese, and Spanish populations (Mota *et al*., 2010; Alexandrie *et al.*, 2004 and San Jose *et al.* 2010).

In contrast to our findings Ji *et al.* (2012) have provided comprehensive and clear evidence that CYP1A1 *Msp*I polymorphisms are an important modifying factor in determining susceptibility to lung cancer. In another study, Xu *et al.* (1996) have suggested that individuals who have the *MspI* variant *CYP1A1* gene are at a higher risk for lung cancer.

Hussein *et al.* (2014) have demonstrated an association between genetic polymorphisms in the CYP1A1 locus and elevated risk of lung cancer among Egyptians. Moreover, a meta-analysis conducted by Zhan *et al.* (2011) reported a significant association between these polymorphisms and lung cancer risk in Asians and Caucasians. Studies on Indian populations have shown a similar association between CYP1A1 variants and the risk of lung cancer (Sobti *et al*., 2003). Also, many other studies on Chinese (Song *et al*., 2001), South Indian (Sreeja *et al*., 2005), and Kashmiri (Shaffi *et al*., 2009) populations showed the prevalence of the CYP1A1 homozygous mutant genotype among lung cancer patients compared to controls.

The study of Girdhar *et al.* (2016) *et al.* demonstrated that the CYP1A1 m1 polymorphism is an important factor contributing to increased susceptibility to pathological development of lung cancer in a Northern Indian population. In another meta-analysis, Li *et al.* have confirmed the association of CYP1A1 m1 with the risk of lung cancer Li *et al.* (2014). Liu *et al.* (2016) discovered that *Msp*I polymorphism is correlated with susceptibility to lung cancer. The results of the study made by Peddireddy *et al.* (2016) are in parallel with the observations made in different populations worldwide, and the mutated genotype of CYP1A1 may play an important role in the etiology of lung cancer in the population of Andhra Pradesh state.

Probably the major reason for different results was due to the low penetrance of the *CYP1A1* gene in Caucasians and another non-Chinese ethnicity due to the absence or rarity of the CYP1A1 polymorphisms in their population (Shi *et al*., 2008).

CONCLUSION

In conclusion, there is no association between CYP1A1 m1 polymorphism and susceptibility to lung cancer in Eastern Algeria, for future studies, strict selection of patients, well-matched controls and larger sample sizes will be required; also, this polymorphism is not the only factor to be taken into account when examining the genetic susceptibility to this type of cancer. Also, gene-gene and gene-environment interactions should be considered to clarify the genetic etiology of this disease.

More information is needed to understand the regulation of CYP enzymes in humans. The studies should include the effect of dietary compounds on the expression of CYP enzymes, and the expression profile of CYP enzymes in the tissues that are targets for chemical toxicity or carcinogenesis. Without this information, the role of CYP genetic polymorphism in the biological consequences may not be accurately assessed.

ACKNOWLEDGMENTS

We would like to extend our gratitude to all members who voluntarily participated in the study, especially patients and controls, Yasmina Dadsi, Khadidja Boudaoud, and Aicha Djemaa for their participation. We are grateful to Nouredine Abadi the director of the Laboratory of Biology and Molecular Genetics, Constantine 3 University, for providing the necessary infrastructure to carry out this study; Special thanks are offered also to Mohamed Amine Benhammoud the Human Resources Director of the Hospital University Abdelhamid Benbadis Constantine.

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