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# Role of the functional polymorphism -163A>C of *CYP1A2* gene and cigarette smoking in the development of coronary heart disease in the Tunisian population

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Cytochrome P450 1A2 (CYP1A2) enzyme plays an important role in the homeostasis of the cardiovascular system through the metabolism of endogenous molecules such as arachidonic acids which have cardioprotective effects and exogenous molecules like tobacco chemicals that have atherogenic effects. The objective of this study was to evaluate the association between the functional polymorphism CYP1A2 -163A>C (rs762551) and coronary heart disease (CHD) in the Tunisian population and to determine whether the C allele confer a lower risk of CHD among smokers. We investigated a total of 400 controls and 379 coronary heart disease patients including 261 subjects with myocardial infarction (MI) and 118 with angina to validate this association. The results did not show any significant association between CYP1A2 -163A>C polymorphism and CHD or MI. However, the homozygous genotype CC of the single nucleotide polymorphism (SNP) -163A>C was found to be significantly associated with angina (OR = 2.13; 95% CI: 1.20-3.77; $p = 0.01$). We also, found that smokers carrying CC genotype have an increased risk of angina (OR = 3.82; 95% CI: 1.55-9.39; $p = 0.004$) in comparison to those carrying AA genotype. Our findings suggests that the CC genotype of CYP1A2 -163A>C polymorphism was associated with angina in the Tunisian population and this risk increased significantly among smokers with CC genotype.

**Key words:** cytochrome P450 1A2, coronary artery disease, cigarette smoking, genetic polymorphism, arachidonic acid.

## INTRODUCTION

Cytochrome P450 1A2 (CYP1A2) is one of the major cytochromes (CYPs) in the human liver (~13-15%), where it is constitutively expressed and is inducible (Zhou *et al*., 2009a). CYP1A2 mediates the oxidative metabolism of exogenous as well as endogenous molecules. This enzyme plays an important role in maintaining the homeostasis of the cardiovascular system, because it catalyses the formation and/or metabolism of several endogenous molecules (such as arachidonic acid) that are known to affect several cardiovascular functions (Elbekai & El-Kadi, 2006). Indeed, the oxidation of arachidonic acid leads to the formation of epoxyeicosatrienoic acids (EETs) (Zordoky & El-Kadi, 2010) that have been reported to regulate the fibrinolysis and coagulation process (Node *et al*., 2001) and to induce vasodilation (Zhang *et al*., 2001). Similarly, EETs increase endothelial cells growth and angiogenesis in the vascular bed (Wang *et al*., 2005) and they have antithrombotic (Node *et al*., 2001), anti-apoptotic (Chen *et al*., 2001) and anti-inflammatory properties (Campbell, 2000). EETs also protect against ischemia-reperfusion injury (Seubert *et al*., 2004).

Furthermore, CYP1A2 metabolizes a variety of exogenous compounds including caffeine (Hamdy *et al*., 2003) and a number of procarcinogens which are present in the main stream of tobacco smoke (IARC, 2004).

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Caffeine, which is present in different variety of beverages including coffee and tea, is catalyzed in approximately 95% by CYP1A2 through an initial $N^3$-demethylation, which results in the formation of 1,7 dimethylxanthine, i.e., paraxanthine (Hallström *et al*., 2010). Caffeine and paraxanthine was implicated in harmful cardiovascular effects (Riksen *et al*., 2009). Indeed, experimental studies have consistently shown that these compounds acutely raises blood pressure, circulating levels of (nor)epinephrine, serum cholesterol and homocysteine (Benowitz *et al*., 1995; Jee *et al*., 2001). Furthermore, caffeine induce arterial stiffness, impairs endothelium dependent vasodilation and ischemic and pharmacological preconditioning (Papamichael *et al*., 2005; Kloner, 2006).

Metabolic activation of procarcinogens (i.e., polycyclic aromatic hydrocarbons – PAHs, aromatic and heterocyclic amines – HAs) (Pavanello *et al*., 2007) by CYP1A2 enzyme leads to the formation of reactive metabolites that can bind to DNA to give adducts that have the potential to cause mutations and eventually lead to cancer (Pavanello *et al*., 2005). High CYP1A2 activity was therefore suggested as a susceptibility factor for cancer of the lung (Bartsch *et al*., 2000; Pavanello *et al*., 2007), as well as bladder (Landi *et al*., 1999) and colorectal cancer (Sachse *et al*., 2003; Moonen *et al*., 2005) where exposure to these compounds has been implicated in the etiology of the disease.

Metabolic activation of PAHs (like Benzo[*a*]Pyrene (B[*a*]P)) by CYP1A2 has also been implicated in the atherosclerotic plaque formation, which is one of the major causes of coronary heart disease (CHD) (Yan *et al*., 2000). Considerable experimental evidence suggests that B[*a*]P accelerates smooth muscle proliferation and promotes atherosclerosis in animals ranging from chickens to rats (Izzotti *et al*., 1995). In addition, B[*a*]P-related DNA adducts have been detected in atherosclerotic arteries (Izzotti *et al*., 1995; Zhang *et al*., 1998; Yan *et al*., 2000).

Several studies have indicated the presence of wide interindividual and ethnic differences in CYP1A2 activity (Aklillu *et al*., 2003). This CYP1A2 activity variation can be related to the exposition to environmental chemicals (which induce high CYP1A2 expression) or can be due to the occurrence of polymorphisms in the *CYP1A2* gene (Sachse *et al*., 2003). It has been suggested that approximately 35 to 75% of the interindividual variability in CYP1A2 activity is due to genetic factors (Rasmussen *et al*., 2002). Among CYP1A2 polymorphisms, two single nucleotide polymorphisms: -3858G>A in 5′-flanking region and -163A>C in intron 1 at position -163 have been related to change in CYP1A2 enzyme activity (Fujihara *et al*., 2007). The C allele of the SNP CYP1A2 -163A>C (rs 762551) has been reported to cause decreased enzyme activity in smokers (Sachse *et al*., 2003) which could lead to a reduction of PAHs and HAs metabolism and reduce the deleterious effect of their metabolites on the development of cancer and cardiovascular diseases. On the other hand, low inductibility C allele [CYP1A2-163C (CYP1A2*1F)] reduces the production of EETs and therefore reduces their cardiovascular protective effect and may constitute a risk factor for coronary heart disease.

CYP1A2-163C allele also decreased caffeine metabolism leading to the prolonged presence of caffeine in the circulation among the 'slow' metabolizers (C allele carriers) and thus increasing the risk of cardiovascular disease. In a case-control study, subjects with slow CYP1A2 metabolizers were at increased risk of myocardial infarction with increasing coffee consumption (Cornelis *et al*., 2006).

Little is known about the influence of CYP1A2 -163A>C polymorphism on CHD. To our knowledge, only one study reported on the effect of this SNP on myocardial infarction (MI) (Cornelis *et al*., 2004); however several studies have investigated the association between CYP1A2 -163A>C polymorphism and smoking related cancer [like lung cancer – B'chir *et al*. (2009) and colorectal cancer – Moonen *et al*. (2005)]. The purpose of this work was to determine, by a case-control study, the effect of the functional polymorphism CYP1A2 -163A>C on the development of CHD including MI and angina in the Tunisian population and to verify whether smoking habit modifies the risk.

## MATERIALS AND METHODS

### *Studied populations*

A total of 779 unrelated subjects were recruited into this study, including 379 patients with coronary heart disease (CHD) and 400 healthy controls. The study subjects were Tunisian; they were recruited from academic hospitals in the center of Tunisia between January 2007 and June 2009.

Cases were diagnosed by cardiologists in the cardiology services. Among the patients with CHD, 261 had experienced a MI and 118 had experienced an angina. Criteria for the diagnosis of MI were chest pain lasting > 30 min, elevated cardiac enzymes, and

electrocardiogram (ECG) changes suggestive of MI. The diagnosis of angina was made when there was a reminiscent chest pain and signs of myocardial ischemia on the ECG during the stress test.

The controls were recruited among volunteer blood donors and individuals admitted in hospital for routine clinical check-ups and health examinations. They were unharmed from any form of cardiovascular disease. Their habits and family histories were also investigated.

*Data collection*

Trained interviewers administered a questionnaire consisting of closed ended questions regarding smoking, sociodemographic characteristics, socioeconomic status, use of medication, and medical history including personal history of diabetes, hypertension dyslipidemia, and family history of CHD.

Participants were considered to have hypertension if they had elevated blood pressure (> 140/90 mmHg) on three separate occasions or if they were treated with antihypertensive medication. They were diabetic if they were taking antidiabetic medication or insulin therapies. They were defined as having dyslipidemia if they were taking lipid lowering drugs or had dyslipidemic serum level values. Body mass index (BMI) was obtained from the ratio of weight (kg) to height squared ($m^2$). All study participants were classified as either smokers or non-smokers. Informed consent was obtained from all participants and this study was carried out in accordance with the guidelines approved by the Ethical Committee of Farhat Hached Hospital in Sousse.

*Genotyping*

Genomic DNA was isolated from a sample of 10 ml of blood through a phenol chloroform extraction method. The samples were analyzed for genetic polymorphism (-163A>C) (rs 762551) in the intron 1 of the human CYP1A2 gene by polymerase chain reaction (PCR) followed by restriction fragment length polymorphism analysis (RFLP). The fragment containing the SNP -163A>C was amplified using the following primers: (forward) 5′-CAACCCTGCCAA TCTCAAGCAC-3′ and (reverse) 5′-AGAAGCTCT GTGGCCGAGAAGG-3′ (Eurofins MWG Operon, Ebersberg, Germany). The samples were amplified in a Thermolyne Amplitron II Series 1091 thermocycler (Barnstead Thermolyne Corporation, USA). The amplification was performed in a 50 µl volume containing 50 ng DNA, 2 ng $\mu l^{-1}$ of each primer, 2.5 mM MgCl2, 0.25 mM dNTP, and 1 U of Taq DNA polymerase with the buffer provided by the manufacturer (Promega, USA). PCR conditions included an initial denaturation step at 94°C for 5 min followed by 36 cycles of 94°C for 30 s, 66°C for 30 s and 72°C for 30 s. The final step was performed at 72°C for 10 min. The PCR products were then digested by *Apa*I restriction enzyme (provided by Promega manufacturer, USA) at 37°C for 2 hrs, separated by electrophoresis in a 2% agarose gel for 40 min and stained with ethidium bromide. The substitution A→C creates a restriction site for the *Apa*I (recognition sequence GGGCCC). The C allele would be digested into two fragments (714 and 205 bp), while the A allele would not be digested (919 bp).

*Statistical analysis*

Statistical analysis of the data was performed by using the SPSS 9.0 (SPSS Inc, Chicago, USA). Quantitative variables were expressed as mean ± standard deviation (SD) and qualitative variables were expressed in percent of the respective population.

Differences between cases and controls were compared by either Student's t-test for continuous variables and by chi-square test for qualitative data. The chi-square test was also used to estimate the contributions of the polymorphism to the development of CHD including MI, and angina. Risk of CHD, MI and angina associated with genotype was estimated by calculating the odds ratio (OR) and 95% confidence intervals (CI) using unconditional logistic regression, with the wild type as reference. Potential confounders, such as age, sex, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), cigarette smoking, smoking dose, and biochemical measurements were also included in the logistic regression models with stepwise selection. The statistical significance was defined as $p < 0.05$ and two-tailed $p$ values were reported.

## RESULTS

The relevant characteristics of the study subjects are shown in Table 1. The average age was significantly different between the two groups ($p < 0.001$); cases were older than the controls. Predominance of male subjects was observed in both groups. The frequencies of classical risk factors for CHD, such as hypertension, diabetes, BMI and smoking were significantly higher in CHD patients than in the control subjects. The lipid constants showed that high density li-

TABLE 1. Epidemiological characteristics of the studied population. Values are expressed as mean values (standard deviation, SD) for continuous variables and percentage for categorical variable. BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein

| Epidemiological characteristics | Cases (n = 379) | Controls (n = 400) | *p*-value |
|---|---|---|---|
| Gender (male/female) | 279/100 | 274/126 | 0.110 |
| Age (years) (SD) | 60.6 (10.5) | 52.2 (13.9) | < 0.001 |
| BMI (kg $m^{-2}$) (SD) | 27.1 (4.1) | 26.0 (4.3) | 0.002 |
| SBP (mm Hg) (SD) | 130.0 (20.1) | 122.0 (13.0) | < 0.001 |
| DBP (mm Hg) (SD) | 76.0 (12.0) | 72.0 (9.0) | < 0.001 |
| Hypertension (%) | 39.9 | 6.2 | < 0.001 |
| Diabetes (%) | 42.6 | 8.0 | < 0.001 |
| Cholesterol (mmol $l^{-1}$) (SD) | 4.3 (1.5) | 4.2 (1.2) | 0.701 |
| HDL Cholesterol (mmol $l^{-1}$) (SD) | 1.1 (0.5) | 1.3 (0.5) | < 0.001 |
| LDL Cholesterol (mmol $l^{-1}$) (SD) | 2.5 (1.3) | 2.2 (0.9) | < 0.001 |
| Triglycerides (mmol $l^{-1}$) (SD) | 1.6 (1.1) | 1.5 (1.0) | 0.382 |
| Smoking dose (Pack years) (SD) | 32.3 (27.2) | 19.9 (17.8) | < 0.001 |
| Smoking (%) | 55.2 | 40.8 | < 0.001 |

poprotein (HDL) and low density lipoprotein (LDL) values were significantly different between patients and controls whereas cholesterol and triglycerides were not different.

The CYP1A2 -163A>C genotypes was determined by PCR/*Apa*I digestion as shown in Figure 1. The non-digested band of 919 bp represented the wild type AA genotype, the presence of 714 and 205 bp bands indicated the mutant homozygote (CC) and the presence of all three bands (919, 714 and 205 bp) indicated heterozygosity (AC).

Testing for Hardy-Weinberg equilibrium showed that the genotype frequencies of CYP1A2 -163A>C polymorphism (rs 762551) did not deviate significantly from the frequencies expected under random mating conditions for those with CHD ($p = 0.1$) and those without CHD ($p = 0.5$).

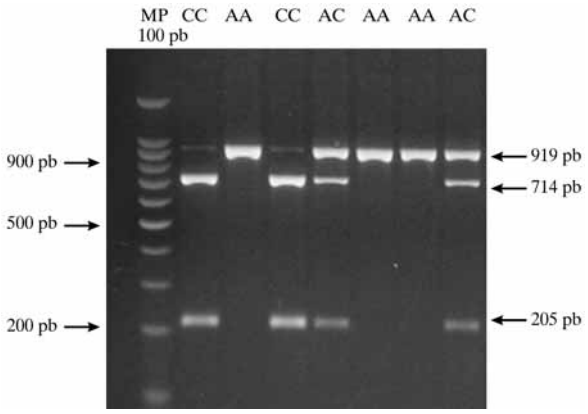


FIG. 1. Digestion profile of CYP1A2 -163A>C PCR product on a 2% agarose gel.

The distribution of the alleles and genotypes for the patients and healthy subjects is shown in Table 2. Genotype and allele frequencies did not differ significantly between patients (CHD and MI) and controls. However the CC genotype was more frequent in angina subjects (26.3%) compared to controls (16.7%).

There was no significant association between CYP1A2 -163A>C polymorphism and the presence of CHD or MI. The risk of CHD or MI was not significant even after adjusting for potential confounders (Table 2). However, we found that CYP1A2 -163A>C was significantly associated with angina ($p = 0.03$). Patients carrying the CC genotype had an increased risk of developing angina (OR = 2.13; 95% CI: 1.20-3.77; $p = 0.01$) compared to those carrying the AA genotype. The significantly higher angina risk of CC genotype was further enhanced after adjustment for common cardiovascular risk factors, including age, BMI, SBP, DBP, cholesterol, triglycerides, and smoking (OR = 3.29; 95% CI: 1.45-7.48; $p = 0.004$).

Because smoking was considerably associated with an increased risk for CHD (OR = 1.83; 95% CI: 1.38-2.44; $p < 0.001$) (data not shown) and is also a strong inducer of CYP1A2, we performed analyses separately for smokers and non-smokers. Table 3 shows the odds ratio for cases and controls considering CYP1A2 polymorphism and the smoking habit. For non-smokers the risk of developing CHD, MI or an-

TABLE 2. Frequency of genotypes of CYP1A2 -163A>C polymorphism in controls and patients with coronary heart disease (CHD), myocardial infarction (MI) and angina

| CYP1A2 -163A>C genotype | Control (%) (n = 400) | CHD (n = 379) | MI (n = 261) | Angina (n = 118) |
|---|---|---|---|---|
| AA | 147 (36.8) | 133 (35.1) | 101 (38.7) | 32 (27.1) |
| AC | 186 (46.5) | 171 (45.1) | 116 (44.4) | 55 (46.6) |
| CC | 67 (16.7) | 75 (19.8) | 44 (16.9) | 31 (26.3) |
| C allele frequency | 0.40 | 0.42 | 0.39 | 0.50 |
| $p$ ($\chi^2$) | | 0.54 | 0.86 | 0.03 |
| 95% CI | | | | |
| AA | | 1.00 | 1.00 | 1.00 |
| AC | | 1.02 (0.74-1.39) | 0.91 (0.64-1.28) | 1.36 (0.84-2.21) |
| CC | | 1.24 (0.83-1.85) | 0.96 (0.61-1.51) | 2.13 (1.20-3.77) |
| 95% CI* | | | | |
| AA | | 1.00 | 1.00 | 1.00 |
| AC | | 1.03 (0.67-1.58) | 1.00 (0.63-1.58) | 1.18 (0.57-2.46) |
| CC | | 1.27 (0.73-2.21) | 0.84 (0.44-1.60) | 3.29 (1.45-7.48) |

*adjusted for age, BMI , SBP, DBP, Cholesterol, Triglyceride and Smoking

TABLE 3. Association beween CYP1A2 -163A>C genotypes and risk of coronary heart disease, myocardial infarction and angina considering cigarette smoking status

| CYP1A2 -163A>C genotype | Control | CHD | MI | Angina |
|---|---|---|---|---|
| | | *n (%)* | | |
| *Non smokers* | | | | |
| AA | 76 (33.3) | 55 (32.9) | 34 (36.1) | 21 (28.8) |
| AC | 110 (48.2) | 82 (49.1) | 45 (47.9) | 37 (50.7) |
| CC | 42 (18.5) | 30 (18.0) | 15 (16.0) | 15 (20.5) |
| $p$ ($\chi^2$) | | 0.99 | 0.82 | 0.76 |
| 95% CI | | | | |
| AA | | 1.00 | 1.00 | 1.00 |
| AC | | 1.03 (0.66-1.62) | 0.91 (0.54-1.56) | 1.22 (0.66-2.24) |
| CC | | 0.99 (0.55-1.77) | 0.80 (0.39-1.63) | 1.29 (0.60-2.77) |
| 95% CI* | | | | |
| AA | | 1.00 | 1.00 | 1.00 |
| AC | | 0.86 (0.45-1.64) | 0.77 (0.38-1.56) | 1.13 (0.40-3.20) |
| CC | | 0.81 (0.35-1.85) | 0.53 (0.19-1.48) | 1.58 (0.48-5.21) |
| *Smokers* | | | | |
| AA | 63 (40.1) | 76 (36.9) | 65 (40.1) | 11 (25.0) |
| AC | 70 (44.6) | 87 (42.2) | 70 (43.2) | 17 (38.6) |
| CC | 24 (15.3) | 43 (20.9) | 27 (16.7) | 16 (36.4) |
| $p$ ($\chi^2$) | | 0.39 | 0.94 | 0.006 |
| 95% CI | | | | |
| AA | | 1.00 | 1.00 | 1.00 |
| AC | | 1.03 (0.65-1.63) | 0.97 (0.60-1.57) | 1.39 (0.60-3.19) |
| CC | | 1.49 (0.81-2.71) | 1.09 (0.57-2.09) | 3.82 (1.55-9.39) |
| 95% CI* | | | | |
| AA | | 1.00 | 1.00 | 1.00 |
| AC | | 1.16 (0.64-2.12) | 1.30 (0.60-2.12) | 1.30 (0.39-4.37) |
| CC | | 1.83 (0.82-4.09) | 1.12 (0.46-2.70) | 7.99 (2.24-28.43) |

*adjusted for age, BMI, SBP, DBP, cholesterol and triglycerides

gina was not significant for AC and CC genotypes. Furthermore, the interaction between CYP1A2 polymorphism and CHD or MI was not statistically significant among smokers. However, smoking history and carrying CC genotype was associated with 3.82-fold risk for angina (OR = 3.82; 95% CI: 1.55-9.39; $p = 0.004$), when compared to those carrying the AA genotype. After multivariate regression, the odds ratio (ORs) for angina considerably increased, it was nearly twice the non adjusted ORs (OR = 7.99; 95% CI: 2.24-28.43; $p = 0.001$) in smoking patients.

## DISCUSSION

In the present study, the prevalence of the SNP -163A>C of the CYP1A2 gene, located in intron 1 has been investigated as well as its relationship with CHD, MI and angina risk in the Tunisian population.

The frequency of the CYP1A2 -163A>C polymorphism (rs 762551) was not very different among ethnic groups. For the Tunisian population studied, the C allele frequency in controls was 40%; it was similar to that reported for Ethiopian (40%) (Aklillu *et al*., 2003) and Japanese (37%) (Soyama *et al*., 2005) but lower than that reported for Ovambos (54%), Koreans (68%) and Mongolians (79%) (Fujihara *et al*., 2007). The frequency of that allele was not different between Caucasians (32%) (Sachse *et al*., 1999; Cornelis *et al*., 2004), Egyptians (32%) (Hamdy *et al*., 2003) and Swedish (29%) (Nordmark *et al*., 2002).

CYP1A2 enzyme could play an important role in the cardiovascular homeostasis through, at least, two metabolic pathways: (i) CYP1A2 metabolizes arachidonic acids to epoxyeicosatrienoic acids (EETs) which are known to have cardiovascular protective effects (Gross *et al*., 2005; Zordoky & El-Kadi, 2010) (ii) this enzyme, activates tobacco mutagens involved in carcinogenesis, atherogenesis, and teratogenesis (Miller & Ramos, 2001). In addition, CYP1A2 enzyme and its mRNA were detected in endothelial cell suggesting that this enzyme would intervene in the endothelial function (Minamiyama *et al*., 1999). The interindividual variation in CYP1A2 activity suggests the presence of genetic polymorphisms that control its enzymatic activity. The exploration of the effects of these polymorphisms would allow us to better understand the interindividual variations of the CYP1A2 activity.

To the best of our knowledge, this case-control study is the second one to explore the interactive effect of CYP1A2 polymorphisms especially CYP1A2 -163A>C (rs 762551) on cardiovascular disease. Until now, the relation between CYP1A2 -163A>C polymorphism and MI in the Costa Rican population was investigated (Cornelis *et al*., 2004). These authors found that individuals homozygous for the low inducibility CYP1A2-163C allele (CYP1A2*1F) were at increased risk for MI (OR = 1.55; 95% CI: 1.10-2.18), which was not affected by the level of smoking (Cornelis *et al*., 2004). Another study conducted by the same author revealed that smokers with the slow metabolizer genotype CC may still have an increased risk of MI with increasing coffee consumption (Cornelis *et al*., 2006).

In our study, in contrast, we failed to observe an association with the SNP -163A>C for overall risk of CHD and for risk of MI. The smoking status did not appear to alter the effect of the genotype on these pathologies. However, in subgroup of angina, the slow metabolizers subjects (CC homozygous) seem to be at higher risk for angina; this risk is increased after adjustment for potential confounders. This result suggests that the low inducibility of CYP1A2 may lead to low EETs formation and thus increasing risk of CHD. Indeed, CYP1A2 was involved in the oxidation of endogenous compounds like arachidonic acids generating EETs (Zhou *et al*., 2009b; Zordoky & El-Kadi, 2010). EETs have been proposed to have protective cardiovascular effects as well these metabolites have been reported to possess vasodilating (Zhang *et al*., 2001), anti-inflammatory (Campbell *et al*., 2000), fibrinolytic (Node *et al*., 2001), anti-apoptotic (Chen *et al*., 2001), and potential anti-fibrotic effects (Levick *et al*., 2007).

When angina group was stratified in two subgroups (smokers and non smokers), we found that smokers carrying the low inducible CC genotype experienced a high risk for angina which increased after adjusting for potential cardiovascular risk factors when compared to AA homozygous smokers.

Increasing risk of angina through the diminution of EETs production in CC homozygous subjects seems to be accentuated by the proinflammatory and proxidative effect of tobacco compounds such as PAHs, aromatic amines and nitrosamines. In fact, epoxidation of PAHs via epoxyde hydrolase and its oxidation via aldo-keto reductase (AKR) pathways lead respectively to the formation of mutagen DNA adducts and PAH o-quinones. PAH o-quinones are both cyto- and genotoxic through the formation of reactive oxygen species (ROS) (Palackal *et al*., 2001).

In summary, this study is the first to report CYP1A2 -163A>C polymorphism (rs 762551) in relation to the CHD risk for the Tunisian population. Our results showed that the susceptible effect of the CYP1A2 -163A>C polymorphism on CHD among the Tunisians was mainly limited to angina. Indeed this polymorphism increased susceptibility for developing angina but not MI in the Tunisian population. This result allows us to ask whether these two diseases have the same physiopathology. However, due to the small sample size in the subgroup of angina, further studies incorporating a larger sample size and/or another ethnic population are needed to confirm the genetic role of CYP1A2 in the development of angina.

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