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ORIGINAL RESEARCH ARTICLE

CYP1A1 Ile462Val Polymorphism as a Risk Factor in Cervical Cancer Development in the Polish Population

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Abstract
Background and objective There are inconsistent data of the cytochrome *P450 1A1* (*CYP1A1*) Ile462Val (rs1048943) single nuclear polymorphism (SNP) as a genetic susceptibility factor for cervical cancer in various populations. Moreover, little is known about the interaction of this SNP with other risk factors, including contraceptive use, postmenopausal status, parity, and tobacco smoking.
Methods Polymerase chain reaction-restriction fragment length polymorphism was used to study the prevalence of the *CYP1A1* Ile462Val SNP in women with cervical cancer ($n = 456$) and controls ($n = 495$).
Results Logistic regression analysis adjusting for age, parity, oral contraceptive use, tobacco smoking, and menopausal status demonstrated that that the *CYP1A1* Ile/Val polymorphism was not associated with an increased risk of cervical cancer in all patients. The adjusted odds ratio (OR) for patients with the Ile/Val genotype vs. Ile/Ile genotype was 1.539 (95 % confidence interval [CI] 0.932–2.541, $p = 0.091$). However, an increase in cervical cancer risk was seen among patients with a positive history of tobacco smoking and parity. The adjusted OR for positive history of tobacco smoking with the Ile/Val vs. Ile/Ile genotypes was 2.978 (95 % CI 1.382–6.418, $p = 0.0052$). The adjusted OR for parity with the Ile/Val vs. Ile/Ile genotype was 1.739 (95 % CI 1.006–3.009, $p = 0.0472$).
Conclusion Our genetic study suggests that the *CYP1A1* Ile462Val SNP may be a risk factor for cervical cancer among patients with a positive history of tobacco smoking and parity.

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1 Introduction

Cervical cancer is the third most common type of cancer in women worldwide [1]. This cancer develops slowly; starting from a precancerous dysplasia designated cervical intraepithelial neoplasia (CIN) that may further develop to invasive cervical carcinoma [2, 3]. Almost all cervical cancers are caused by the human papilloma virus (HPV), which is considered the primary etiologic factor of this cancer [3, 4]. Some oncogenic HPV oncoproteins, including E6 and E7, cause a defect in the host's innate and adaptive immunity and change the apoptotic pathway, leading to immortalization of normal cervical epithelial cells [2, 4]. Apart from HPV, multiparity, oral contraceptive use, tobacco smoking, and environmental insults have been recognized as secondary risk factors [5].

Cytochrome P450 1A1 (CYP1A1) belongs to the CYP1 family and is involved in the metabolism of endogenous molecules and xenobiotics [6]. The actions of CYP1A1 include aryl hydrocarbon hydroxylase activity, which is the first step in the metabolism of tobacco polycyclic aromatic hydrocarbons, leading to their carcinogenic activation [7].

CYP1A1 also participates in the metabolism of estrogen [8]. Therefore, the activity of CYP1A1 may influence cells via at least two distinct pathways, i.e., smoking and estrogen, on cervical carcinogenesis [5].

Two single nucleotide polymorphisms (SNPs) in the *CYP1A1* gene have been studied as risk factors of cervical carcinogenesis: T3801C (rs4646903) and A2455G (rs1048943) [9]. The T3801C SNP is located in the 3′ untranslated region and A2455G corresponds to the substitution Ile462Val in exon 7. These two SNPs have been suggested as being in linkage disequilibrium (LD) in Caucasian populations [9]. The role of both of these SNPs in *CYP1A1* as risk factors in cervical cancer development in different ethnicities is still disputable [10–13]. Moreover, little is known about the interaction of these SNPs with the other known risk factors of cervical cancer. We evaluated the *CYP1A1* Ile462Val genotype and allele frequencies in patients with cervical cancer ($n = 456$) and controls ($n = 495$) in the Polish population, stratified based on contraceptive use, postmenopausal status, parity, and tobacco smoking.

2 Patients and Methods

2.1 Patients and Controls

The patients included 456 women with histologically determined cervical carcinoma according to the International Federation of Gynecology and Obstetrics. All women were enrolled between April 2007 and December 2012 at the Department of Radiotherapy, Greater Poland Cancer Center in Poznan, Poland (Table 1). The control group included 285 unrelated healthy female volunteers who were matched by age to the patients. The controls were enrolled during medical examination at the University Hospital, Clinic of Gynecological Surgery at Poznan University of Medical Science (Table 1). Data about parity, oral contraceptive use, tobacco smoking, and menopausal status were obtained during the clinical interview. Patients and controls were Caucasian, enrolled from the Wielkopolska (Greater Poland) area of Poland. Patients and controls provided written informed consent. The study was approved by the Local Ethical Committee of Poznan University of Medical Sciences.

Table 1 Clinical and demographic characteristics of patients and controls

Characteristic	Patients ($n = 456$)	Controls ($n = 495$)
Mean age[a] (years) ± SD	52.4 ± 9.8	51.9 ± 10.2
Tumor stage, *n* (%)		
IA	61 (13.4)	
IB	63 (13.8)	
IIA	59 (12.9)	
IIB	55 (12.1)	
IIIA	148 (32.5)	
IIIB	53 (11.6)	
IVA	9 (2.0)	
IVB	8 (1.7)	
Histologic grade, *n* (%)		
G1	87 (19.1)	
G2	145 (31.8)	
G3	98 (21.5)	
Gx	126 (27.6)	
Histologic type, *n* (%)		
Squamous cell carcinoma	384 (84.2)	
Adenocarcinoma	56 (12.3)	
Other	16 (3.5)	
Parity , *n* (%)		
Never	51 (11.2)	56 (11.31)
Ever	405 (88.8)	439 (88.6)
Oral contraceptive pill use, *n* (%)		
Never	248 (54.4)	278 (56.2)
Ever	208 (45.6)	217 (43.8)
Tobacco smoking, *n* (%)		
Never	295 (64.7)	331 (66.9)
Ever	161 (35.3)	164 (33.1)
Menopausal status, *n* (%)		
Premenopausal	159 (34.9)	190 (38.4)
Postmenopausal	297 (65.1)	305 (61.6)
HPV genotypes[b], *n* (%)		
16 and 18	311 (68.2)	
16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68	352 (77.2)	

[a] Age at first diagnosis

[b] HPV genotypes were determined by Cobas® HPV Test Roche Molecular Systems, Inc. (Alameda, CA, USA)

HPV human papilloma virus, *SD* standard deviation

2.2 Genotyping

DNA was obtained from peripheral leukocytes employing a salting-out procedure. Identification of the *CYP1A1* Ile462Val (rs1048943) polymorphic variant was performed by polymerase chain reaction-restriction fragment length polymorphism. The *CYP1A1* Ile462Val DNA fragment was amplified employing the primers 5′ ACCCATCTG AGTTCCTACC 3′ and 5′ TCCACCTTCACGCCCAGT 3′. The PCR-amplified fragments of *CYP1A1* that were 199 bp in length were isolated and digested with endonuclease HpyCH4III (5′ ACNGT 3′) from the New England BioLabs (Ipswich, USA). The *CYP1A1* Val allele was cleaved into 116-bp and 83-bp fragments, whereas the *CYP1A1* Ile

allele remained uncut. Presence of the *CYP1A1* Ile462Val polymorphism was verified by commercial sequencing analysis of 10 % randomly selected samples.

2.3 Statistical Analysis

The differences in genotypic and allelic distribution between patients and controls and their genotype deviation from the Hardy–Weinberg (HW) equilibrium were evaluated by the Chi-squared test. Moreover, the odds ratio (OR) and 95 % confidence intervals (95 % CI) were calculated. Unconditional logistic regression analysis was used to adjust for the effect of confounders such as age, parity, oral contraceptive use, tobacco smoking, and menopausal status. A p-value of <0.05 was considered statistically significant.

3 Results

3.1 Distribution of the *CYP1A1* Ile462Val Polymorphism in Women with Cervical Cancer

Prevalence of the *CYP1A1* Ile462Val genotypes did not display significant differences from the HW equilibrium between patients and controls. The distribution and adjusted analyses of the *CYP1A1* Ile462Val genotypes in cases and controls are presented in Table 2. The *CYP1A1* Ile/Val heterozygous genotype frequency was 1.5-fold greater in women with cervical cancer compared with controls and was 0.09 and 0.06, respectively. There were no individuals, either patients or controls, with the homozygous *CYP1A1* Val/Val genotype. The *CYP1A1* Val allele frequency was slightly increased in patients as compared with controls and was 0.04 and 0.03, respectively. Logistic regression analysis demonstrated that the *CYP1A1* Ile/Val polymorphism was not associated with an increased risk of cervical cancer. The adjusted OR for patients with the Ile/Val genotype vs. Ile/Ile genotype was 1.539 (95 % CI 0.932–2.541, $p = 0.091$). However, stratification of the patients based on the histologic type of cancer also did not show a contribution of the *CYP1A1* Ile/Val polymorphism with squamous cell carcinoma, adenocarcinoma, or with tumor stage and histologic grade (data not shown).

3.2 Stratified Analyses Between the *CYP1A1* Ile462Val Polymorphism and Cervical Cancer Risks

The age-adjusted assessment of the *CYP1A1* Ile462Val polymorphism and cervical cancer risk stratified by parity, oral contraceptive use, tobacco smoking, and menopausal status are listed in Table 3 and Fig. 1. An increase in cervical cancer risk was seen among patients with a positive history of tobacco smoking and parity. In patients with a positive history of tobacco smoking, the adjusted OR for the Ile/Val vs. Ile/Ile genotype was 2.978 (95 % CI 1.382–6.418, $p = 0.0052$). The adjusted OR for parity in patients with the Ile/Val vs. Ile/Ile genotype was 1.739 (95 % CI 1.006–3.009, $p = 0.0472$). However, no significant association was seen between *CYP1A1* Ile462Val and patients with a positive history of oral contraceptive use and menopausal women (Table 3; Fig. 1). Moreover, we did not find an association between *CYP1A1* Ile462Val and tumor stage, histologic grade, and type (Table 4; Fig. 2).

4 Discussion

The *CYP1A1* Ile462Val polymorphism has been shown to be a risk factor for many types of cancer and hematopoietic malignancies [14–21]. To date, the *CYP1A1* Ile462Val SNP has been shown to be a risk factor in the development of pharyngeal, prostate, lung, oral, ovary, bladder, and colorectal cancers [14–20]. In addition to these findings, the CYP1A1 Ile462Val SNP has been suggested to be a low-penetrant risk factor for acute leukemia [21]. There are also studies suggesting that the *CYP1A1* Ile462Val SNP may be a risk factor for cervical cancer development [11, 12]. However, we did not observe, in our study, the

Table 2 Association of the *CYP1A1* Ile462Val (rs1048943) polymorphism with cervical cancer

Genotype	Patients (frequency)	Controls (frequency)	OR (95 % CI)	p-Value[a]	Adjusted OR (95 % CI)[b]	p-Value[a]
Ile/Ile	415 (0.91)	466 (0.94)	Referent	–	Referent	
Ile/Val	41 (0.09)	29 (0.06)	1.588 (0.9689–2.416)	0.0646	1.539 (0.932–2.541)	0.091
Val/Val	0 (0.00)	0 (0.00)				
MAF	0.04	0.03				

[a] Chi-square analysis

[b] ORs were adjusted by age, parity, oral contraceptive use, tobacco smoking, and menopausal status

CI confidence interval, *OR* odds ratio

Table 3 Stratified analyses between the distribution of *CYP1A1* Ile462Val genotypes and cervical cancer risks: pregnancy, oral contraceptive use, tobacco smoking, and menopausal status

High-risk exposure	Patients		Controls		Adjusted OR (95 % CI)[a]	*p*-Value[b]
Genotype	Ile/Ile	Ile /Val	Ile/Ile	Ile /Val		
Parity						
Ever	370	35	416	23	**1.739 (1.006–3.009)**	**0.0472**
Never	45	6	50	6	1.596 (0.441–5.773)	0.4709
Oral contraceptive use						
Ever	187	21	205	12	1.923 (0.918–4,030)	0.0821
Never	228	20	261	17	1.370 (0.697–2.692)	0.3597
Smoking						
Ever	134	27	154	10	**2.978 (1.382–6.418)**	**0.0052**
Never	281	14	312	19	1.338 (0.575–3.113)	0.4983
Menopausal status						
Premenopausal	149	10	178	12	0.939 (0.391–2.257)	0.8885
Postmenopausal	266	31	288	17	1.857 (0.997–3.460)	0.0507

[a] (Ile /Val vs. Ile/Ile)

[b] Chi square analysis

All *p*-values were adjusted by age. Significant results are highlighted in bold font

CI confidence interval, *OR* odds ratio

CYP1A1 Ile462Val polymorphism to be a risk factor of cervical cancer in our patient group. Our results are similar to those of Gutman et al. [10], who did not find an increased risk for cervical cancer in the Jewish Israeli population. Moreover, there was no significant association between the *CYP1A1* Ile462Val SNP and cervical cancer in the Japanese population [13]. In contrast, the study conducted by Taskiran et al. [11] in the Turkish population demonstrated the CYP1A1 Val gene variant as a significant risk factor of CIN 1 and 2 and for cervical adenocarcinoma and squamous cell carcinoma. Joseph et al. [12] observed a significant contribution of the *CYP1A1* Ile462Val SNP to cervical cancer, when adjusted for HPV status in Indian populations. Moreover, the *CYP1A1* Ile462Val polymorphism has been inconsistently shown to be a risk factor of cervical cancer in the Chinese population [22–27]. In addition to these findings, two recently conducted meta-analyses have indicated that the Val gene variant may be a risk factor in cervical cancer development in Caucasian but not Asian populations [28, 29].

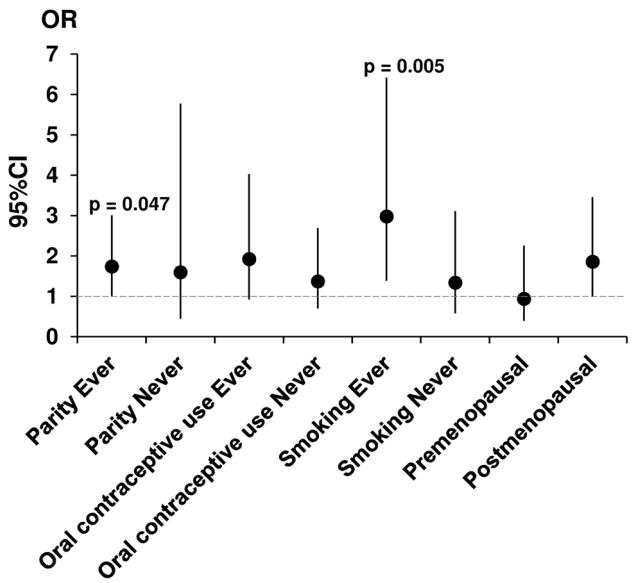

Fig. 1 Adjusted odds ratio (OR) plot for genotyping frequencies of the *CYP1A1* Ile462Val polymorphism for patients stratified based on parity, oral contraceptive use, tobacco smoking, and menopausal status. Each OR value is represented by the corresponding *black dot* with arms representing 95 % confidence intervals (95 % CI)

The use of tobacco has been recognized as a factor that can increase the risk of numerous carcinomas, including lung, larynx, mouth, esophagus, kidneys, urinary tract, cervix, and others [30]. In our study, we found that the *CYP1A1* Ile462Val SNP increased the risk of cervical cancer in women with a positive history of tobacco smoking. Gutman et al. [10] demonstrated that tobacco smoking is an independent risk factor for cervical cancer. The human CYP1A1 enzyme is present in many epithelial tissues and conducts oxidative reactions involved in the bioactivation of tobacco's aromatic hydrocarbons, aromatic amines, and nitrosamines to carcinogens [7, 31]. These substances interact with DNA leading to the formation of DNA adducts, which make the carrier prone to carcinogenesis [7, 31]. It has been demonstrated that tobacco consumers bearing the *CYP1A1* 462Val variant possess more polycyclic aromatic hydrocarbon-DNA adducts in

Table 4 Stratified analyses between the distribution of *CYP1A1* Ile462Val genotypes and clinical characteristics: stage, histologic grade, and type

Genotype	Ile/Ile	Ile/Val	OR (95 % CI)[a]	*p*-Value[b]
Controls	466	29		
Patients				
Clinical stage				
IA	55	6	1.753 (0.697–4.410)	0.2275
IB	57	6	1.691 (0.673–4.250)	0.2584
IIA	53	6	1.819 (0.722–4.583)	0.1982
IIB	49	6	1.968 (0.779–4.973)	0.1455
IIIA	139	9	1.040 (0.481–2.251)	0.9200
IIIB	48	5	1.674 (0.619–4.526)	0.3051
IVA	7	2	4.591 (0.912–23.107)	0.1006[c]
IVB	7	1	2.296 (0.273–19.300)	0.3907[c]
Histologic grade				
G1	80	7	1.406 (0.596–3.319)	0.4347
G2	133	12	1.450 (0.720–2.920)	0.2958
G3	91	7	1.236 (0.525–2.908)	0.6267
Histologic type				
Squamous cell carcinoma	353	31	1.407 (0.832–2.379)	0.2003
Adenocarcinoma	48	6	2.009 (0.794–5.081)	0.1336

ORs for patients with histologic grade Gx and unknown histologic type of cervical cancer were not calculated

[a] (Ile/Val vs. Ile/Ile)

[b] Chi square analysis

[c] Fisher exact test

CI confidence interval, *OR* odds ratio

white blood cells as compared with smokers without that variant [32]. Although the *CYP1A1* Ile462Val substitution situated in the heme-binding region of the enzyme did not change the enzyme's activity in vitro, this substitution is accompanied by a twofold increase in microsomal enzyme activity [33, 34]. The *CYP1A1* Ile462Val SNP has been proposed to be in complete LD with the *CYP1A1* T3801C (rs4646903) polymorphism, which experimentally exhibited up-regulation of enzymatic activity [9].

Moreover, we found a borderline risk for cervical cancer in women with the Ile462Val SNP that had a positive history of parity, which is in agreement with other studies demonstrating parity as a risk factor for cervical cancer [35]. It has been suggested that high parity might increase the risk of cervical carcinoma owing to the many years of transformation of the exocervical zone, leading this area to become more susceptible to direct exposure to HPV and carcinogens [35].

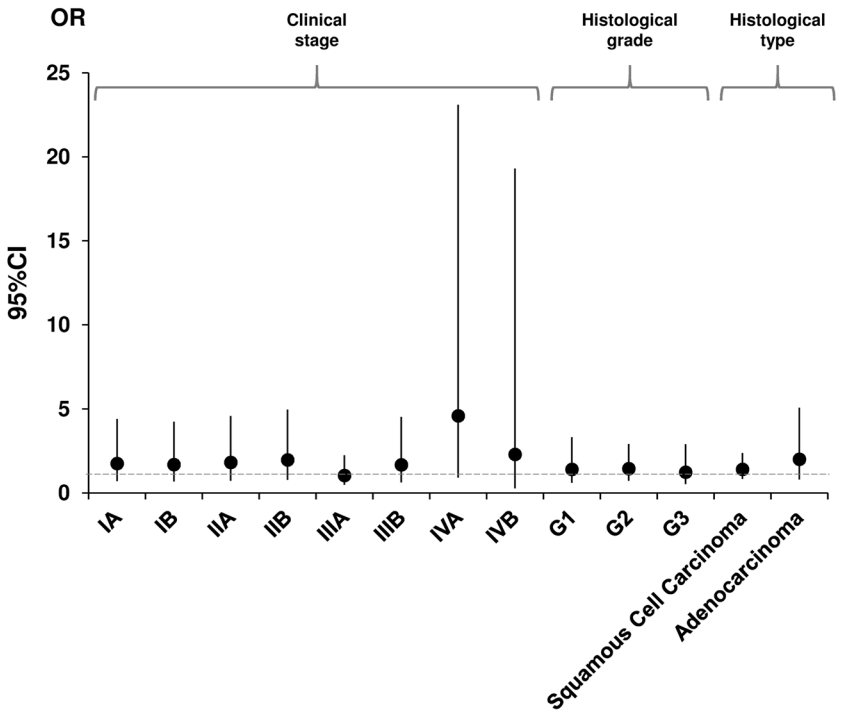

Fig. 2 Adjusted odds ratio (OR) plot for genotyping frequencies of the *CYP1A1* Ile462Val polymorphism for patients with cervical cancer stratified based on clinical characteristics: stage, histologic grade, and type. Each OR value is represented by the corresponding *black dot* with arms representing 95 % confidence intervals (95 % CI). ORs for patients with histologic grade Gx and unknown histological type of cervical cancer were not calculated

Our genetic evaluation is the first to demonstrate that the *CYP1A1* Ile462Val polymorphism can be a risk factor for cervical cancer in women with a positive history of tobacco smoking and parity, therefore this study should be replicated in other independent cohorts.

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