Ginekol Pol. 2011, 82, 925-932

PRACE POGLĄDOWE
ginekologia

Importance of CYP1A1 polymorphism and its transcriptional regulation in ovarian and endometrial cancer

Znaczenie polimorfizmu CYP1A1 i regulacji jego transkrypcji w podatności na raka jajnika i *endometrium*

Mrozikiewicz Przemysław M.[1,2], Grześkowiak Edmund[1], Seremak-Mrozikiewicz Agnieszka[3], Bogacz Anna[1,2], Barlik Magdalena[3], Semczuk Andrzej[4], Bartkowiak-Wieczorek Joanna[1,2], Drews Krzysztof[3]

[1] Laboratory of Experimental Pharmacogenetics, Department of Clinical Pharmacy and Biopharmacy, Poznan University of Medical Sciences, Poznan, Poland
[2] Department of Pharmacology and Experimental Biology, Institute of Natural Fibers and Medicinal Plants, Poznan, Poland
[3] Department of Perinatology and Gynecology, Poznan University of Medical Sciences, Poznan, Poland
[4] Department of Gynaecological Surgery, Lublin School of Medicine, Lublin, Poland

Abstract

Human cytochrome P450 1A1 is one of the most important enzymes participating in human carcinogenesis because it metabolites several procarcinogens to active carcinogenic metabolites. Additionally, enzymes of CYP450 family play an important role in estrogenes catabolization (17-β-estradiol and estron) to intermediate products (2-, 4-hydroxyestradiol and 2-, 4-hydroxyestrone) including CYP1A1 that catalyses hydroxylation to 2-hydroxyestrogens in the endometrium. Derivates of these compounds (4-hydroxyestrogens) are carcinogenic and could induce DNA damage leading to tumour transformation. The presence of CYP1A1 enzyme in genital tract tissues could induce chemical carcinogenesis initiating cancer development.

Recent studies also confirmed the role of CYP1A1 in the development of ovarian and endometrial cancer in humans. The presence of mutated CYP1A1 polymorphic variants influencing the CYP1A1 activity could be responsible for different interindividual susceptibility to genital cancers in women.

Key words: **cytochrome P450** / **CYP1A1** / **polymorphism** / / **ovarian** / **cancer** / **endometrial cancer** / **procarcinogens** /

Corresponding author:
Przemysław M. Mrozikiewicz
Laboratory of Experimental Pharmacogenetics,
Department of Clinical Pharmacy and Biopharmacy,
Poznan University of Medical Sciences, Poznan, Poland
St. Maria Magdalena str. 14
60-861 Poznan, Poland
e-mail: pmm@post.pl

Otrzymano: **15.08.2011**
Zaakceptowano do druku: **14.11.2011**

Ginekol Pol. 2011, 82, 925-932

Streszczenie

Ludzki cytochrom CYP4501A1 jest jednym z najważniejszych enzymów uczestniczących w procesie kancerogenezy, ponieważ metabolizuje wiele pro-kancerogenów do ich aktywnych kancerogennych metabolitów.
Dodatkowo, enzymy z rodziny CYP450 odgrywają ważną rolę w katabolizmie estrogenów (17-β-estradiol i estron) do produktów pośrednich (2-, 4-hydroksyestradiol oraz 2-, 4-hydroksyestron) uwzględniając CYP1A1, który katalizuje hydroksylację do 2-hydroksyestrogenu w endometrium. Pochodne tych związków (4-hydroksyestrogeny) są kancerogenne i mogą indukować uszkodzenia DNA prowadząc do transformacji nowotworowej komórki. Obecność enzymu CYP1A1 w tkankach narządów płciowych może indukować chemiczną kancerogenezę inicjując rozwój nowotworu.
Najnowsze badania potwierdziły rolę CYP1A1 w rozwoju raka jajnika i endometrium. Obecność zmutowanych wariantów polimorficznych genu CYP1A1 wpływających na aktywność CYP1A1 może być związana ze zróżnicowaniem osobniczym w podatności na nowotwory narządów płciowych u kobiet.

Słowa kluczowe: **cytochrom P450** / **CYP1A1** / **polimorfizm** / / **rak jajnika** / **rak *endometrium*** / **prokancerogeny** /

Introduction

Ovarian and endometrial cancers are serious medical and social problems of women with not fully explained etiology. Many risk factors for ovarian and endometrial cancers were already recognised (childless, obesity, consumption of animal fat, exposition to asbestos and talc for ovarian cancer; hyperestrogenism, late menopause, obesity, diabetes mellitus and hypertension for endometrial cancer) [1,2]. Besides the above-mentioned, in recent years the genetic background was shown to be involved in the etiology of these cancers [3]. The genes such as protooncogenes (*AKT2, Ki-Ras*), tumor suppressor genes (*TP53, BRCA1, BRCA2*) and mismatch repair genes (*MSH2, MLH1*) were indicated to be involved in the pathogenesis of ovarian cancer [4,5]. The question remains what is the role of polymorphic genes that modulate individual susceptibility to cancerogenesis.

The activity of carcinogen metabolizing-enzymes in the etiology of urogenital cancers is still unclear but preliminary reports indicate modulating role of themin urogenital carcinogenesis. Recently however, high levels of transcripts of dioxin-induced gene (*CYP1A1*) were found in endometriotic tissues [6]. The presence of CYP1A1 enzyme in genital tract tissues could induce chemical carcinogenesis initiating cancer development. It was assumed that presence of mutated *CYP1A1* variants could be responsible for different interindividual susceptibility to genital tract cancers.

Number of studies had proven that there is an independent effect of polymorphic variants of *CYP450* genes on the activity and the level of endogenous steroid hormones and the risk of cancer. Allelic variants of cytochrome P450, among them the *CYP1A1* gene, are associated with a high risk of hormone-dependent cancers [1,2,7]. Moreover, the metabolism of numerous carcinogens by the cytochrome P450 enzymes including CYP1A1 can also lead to different types of cancer. Because of the importance of investigations connected with ovarian and endometrial cancer etiology the goal of this manuscript is to briefly summarize the significance of *CYP1A1* genetic polymorphism in ovarian and endometrial cancers [8,9].

CYP1A1 – etiological considerations in urogenital cancers

The cytochrome P450 (CYP) superfamily is a large and diverse group of enzymes (hemoproteins) that participate in phase I metabolism reactions. These monooxygenases are capable of catalyzing metabolism of various xenobiotic chemicals including drugs, procarcinogens as well as endobiotic chemicals including fatty acids, steroids, eicosanoids, retinoids and prostaglandins [10-12]. Human cytochrome *P450* is a gene family consisting of 57 protein-coding genes and 58 pseudogenes classified into 18 families and 43 subfamilies based upon similarities in amino acid sequences [13,14]. The CYP enzymes are present in almost all human tissues, but they are most active in liver and suprarenal glands. In humans, the complex of cytochrome P450 contains more than 15 different enzymes which all play a role in drugs and procarcinogens metabolism as well as steroid hormones biochemical transformation.

The cytochrome P450 family was particularly well studied with regard to genetic polymorphisms and activity of enzymes. In recent years also its connection with development of different disorders was widely discussed. The best studied cytochromes are CYP2D6, CYP2C9, CYP2C19 and CYP1A1 [12,15].

Human cytochrome P450 1A1 (named CYP1A1, see http://www.imm.ki.se/ CYPalleles/cyp1A1.htm) is one of the most important enzymes in human carcinogenesis because it metabolites several procarcinogens to active carcinogenic metabolites. CYP1A1 oxygenates polycyclic aromatic hydrocarbons (PAHs), including many procarcinogenes (e.g. benzo[a]pyrene) to their final water-soluble derivatives with carcinogenic activity. Dioxins are strong CYP1A1 inducers, and the most common of them is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Dioxins bind to an intracellular aryl hydrocarbon receptor (AhR) that induces mRNA transcription followed by activation of xenobiotic-metabolizing enzymes known as CYP1A1, CYP1A2 and CYP1B1 [16,17].

Cytochrome CYP1A1 is involved in the I phase of biotransformation, and substrates for CYP1A1 enzyme are not only PAHs and dioxins but also drugs, hormones and other chemical compounds (Table I) [18].

The subfamily of CYP1A (including CYP1A1 and CYP1A2) contains conservative enzymes with 80% of homology between different species such as mice, rats, monkeys, and humans [20]. CYP1A1 is widely expressed first of all in lung, breast, lymphocytes and in placenta during pregnancy. This enzyme is also inducible in endothelial and epithelium cells of skin and intestinal cells, such as in embryonic cells. In recent years, several authors paid the attention to possible significance of expression alteration of *CYP1A1* in women with ovarian and endometrial cancers.

In addition, it was indicated that CYP enzymes play an important role in catabolization of estrogenes (17-β-estradiol and estron) to intermediate products (2- or 4-hydroxyestradiol and 2- or 4-hydroxyestrone) [21, 22]. CYP1A1 catalyses 2-hydroxylation to 2-hydroxyestrogens in the endometrium. Derives of 2-hydroxyestrogens (4-hydroxyestrogens) are carcinogenic and could induce DNA damage [23]. Recent approaches demonstrate that selective estrogen receptor modulators (SERMs) like tamoxifen, raloxifene probably increase the risk of endometrial cancer by enhancing the local estrogen biosynthesis and directing estrogen metabolism towards the formation of genotoxic and hormonally active estrogen metabolites with association of estrogen metabolizing enzymes - CYP1A1, CYP1B1, COMT, NQO1, and SF-1 [24].

CYP1A1 and its genetic polymorphism

The human *CYP1A1* gene coding CYP1A1 protein is located on chromosome 15 (15q24.1, 7 exons, 512 residues). The *CYP1A1* has been cloned and amino-acid sequence of CYP1A1 enzyme has been fully characterized. Several *CYP1A1* polymorphisms have been previously described in humans.

Two different nomenclature systems for the *CYP1A1* alleles that could lead to the potential confusion have been developed. The authors of both nomenclature systems have agreed in July 2000 that the nomenclature system given on the homepage [http://www.cypalleles.ki.se/cyp1a1.htm] should be the recommended one [25]. (Table II).

In the human for *CYP1A1* gene, four base substitutions were recognised. Mutation *m2* (*CYP1A1*2C*) exchanges isoleucine 462 to valine, the neighbouring *m4* exchanges threonine 461 to asparagine [26]. Mutations *m1* (*CYP1A1*2A*) and *m3* (*CYP1A1*3*) are located in the 3'-flanking region, while *m3* has been detected only in Africans [27]. Functional consequences of *m1* and *m2,* compared to wild-type (*CYP1A1*1*), have been presented as an increase in catalytic activity and a higher extent of inducibility [28].

An attractive interest of *CYP1A1* molecular alterations has been strongly linked to differences in the distribution of genetic polymorphisms in different ethnic populations worldwide [29]. For instance, Inoue and co-workers have studied 39 Japanese and 45 Caucasian samples assessing the prevalence of *CYP1A1* and *CYP1B1* polymorphisms. They reported that distributions of the *CYP1A1*2A* and *CYP1A1*2C* alleles were found more common in the Japanese population compared to the Caucasians. Interestingly, *CYP1A1*4* polymorphism has been not detected in the Japanese group. In conclusion they suggested that ethnic-related differences in the occurrence of genetic polymorphisms may determine the different susceptibilities in individuals towards environmental procarcinogens [30]. In Japan, the frequency of

Table I. *CYP1A1* substrates [19].

Substances connected with carcinogenesis
▪ Alkaloids (nicotine) ▪ Aromatic amines (3-methoxy-4-aminoazobenzene, 6-aminochrysene) ▪ Heterocyclic, aromatic amines (2-acetylaminofluorence, 2-amino-1-methyl-6-phenylimidazo [4,5-b]pyridine) ▪ Mycotoxins (aflatoxine B1, ochratoxin A) ▪ Polycyclic aromatic hydrocarbons (benzo[a]pyrene, 7,8-dihydroxybenzo[a]pyrene, 7,12-dimethylbenz[a]antracene (DMBA)) ▪ Tobacco-specific nitrosamines (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone)
Hormones
▪ 17-beta estradiol ▪ Estrone ▪ Testosterone ▪ Pregnenolone ▪ Progesterone
Drugs*
▪ Antineoplastic (tamoxifen, dacarbazine, flutamide, toremifene) ▪ Anestetic (benzoic acid ester, ropivacaine) ▪ Analgesic, anti-inflammatory (diclofenac, phenacetin, aminopyrine) ▪ Antidiabetic (troglitazone) ▪ Anticoagulant (warfarin) ▪ Axiolytic, sedative, hypnotic (clomethiazole, abecarnil) ▪ Cardiovascular (amidarone, carvedilol, nicardipine, propranolol, pranidipine) ▪ Dopaminergic (lisuride, terguride) ▪ Histamine H1 receptor anatgonist (cinnarizine, flunarizine) ▪ HMG-CoA reductase inhibitor (fluvastin) ▪ Others (chlorzoxazone, caffeine)
Other substrates
▪ Akyloxycoumarins (3'-cyano-7-ethoxycoumarin) ▪ Flavonoids (galangin, genistein, hesperetin, kaempferide)

* not clinically significant

*CYP1A1*2A* and *CYP1A1*2C* alleles was higher in the subjects with lung cancer [31]. This observation was not confirmed in Europe, however the frequency of *CYP1A1* point mutations is different in the various populations from small number of Caucasians to higher frequency in the Far East [28,32,33].

In recent years, many investigation of *CYP1A1* polymorphism in various ethnic groups were performed. The different mutations frequency of *CYP1A1* in the different races was shown. In Caucasians, the highest frequency of **2A* allele was found in the USA (13.4%) and Norway (11.5%), and they observed no presence of **4* allele [33,34]. The higher frequency of **4* allele was shown in Turkish healthy population – 5.7%. In this group, alleles of **2A* and **2C* occurred with 18.1% and 8.9% frequency, respectively [35]. Contrarily, the highest frequency of **2A* and **2C* alleles was found in Japan [36, 37].

Table II. *CYP1A1* alleles nomenclature and functional consequences [http://www.cypalleles.ki.se/cyp1a1.htm].

CYP1A1 allele	Previous name	Nucleotide change	Amino acid exchange/other effect
Frequent			
*CYP1A1*1*	*Wild-type*	-	
*CYP1A1*2A*	*m1*	3798T>C (*MspI*)	
*CYP1A1*2B*		2454A>G; 3798T>C (*MspI*)	Ile462Val
*CYP1A1*2C*	*m2*	2454A>G	Ile462Val
*CYP1A1*3*	*m3*	3204T>C	
*CYP1A1*4*	*m4*	2452C>A	Thr461Asn
Occasionally reported			
*CYP1A1*5*		2460C>A	Arg464Ser
*CYP1A1*6*		1635G>T	Met331Ile
*CYP1A1*7*		2345_2346insT	426Frameshift
*CYP1A1*8*		2413T>A	Ile448Asn
*CYP1A1*9*		2460C>T	Arg464Cys
*CYP1A1*10*		2499C>T	Arg477Trp
*CYP1A1*11*		2545C>G	Pro492Arg

The *CYP1A1**3 allele was only represented in the Afro-American population in the USA and not detected in any other population [29,38]. These investigations showed that in healthy populations the polymorphism of *CYP1A1* has a great population variability. Thus the obtained results of mutated alleles of *CYP1A1* have to be compared with the same healthy population.

In Polish population (Wielkopolska region) alleles of **2A*, **2C*, *4 occurred with 6.6%, 2.2% and 2.0% frequency, respectively. The *CYP1A1*3* was not detected [39]. Butykiewicz et al. and Motykiewicz et al. investigated the healthy population in Silesian region (South West part of Poland) mutation *CYP1A1* and found 2-fold higher frequency of **2C* allele than in the general population [40,41].

***CYP1A1* polymorphisms and ovarian cancer**

Recently, the hypothesis that *CYP1A1* polymorphism is a susceptibility carcinogenic factor in genital tract tissue, was discussed for ovarian cancer. Recent studies have also shown a correlation between these polymorphisms and a different response to the same therapy and the related toxicity among ovarian cancer patients [42]. Aktas et al. have shown that presence of **2C* allele predicts higher occurrence of ovarian cancer [43]. Goodman et al. presented a case-control study, performed between 1993 and 1994 in Hawaii, of ovarian cancer and polymorphisms in genes involved in catecholestrogen formation and metabolism. The study involved 129 epithelial ovarian cancer cases and 144 controls. They found no association between the *CYP1A1*2A* (*MspI*) polymorphism and ovarian cancer, however they revealed a positive statistical interaction between tobacco smoking and the *CYP1A1*2A* polymorphism on the risk of ovarian cancer [44].

In the study made by Delort et al. patients with ovarian cancer were genotyped for eleven polymorphisms in seven genes (including *CYP1A1* polymorphism) involved in estrogen and xenobiotic metabolism. The studied mutations increased ovarian cancer risk, but the results were not statistically significant [45].

Terry et al. examined the association between two polymorphic variants of *CYP1A1*2A/C* (*MspI* and *Ile/Val*) and ovarian cancer risk. The study involved 445 ovarian cancer cases and 472 general population controls. There was no increased risk for ovarian cancer associated with either the *MspI* or *Ile/Val* polymorphism. Elevated risk for ovarian cancer was found in patients with *Ile/Val* genotype who consumed more than median levels of caffeine [46].

Heubner et al. investigated the impact of the *CYP1A1*2C* (*Ile462Val*) polymorphism on the ovarian cancer risk and the disease progression. They observed a significant association between the presence of the *462Ile* allele with ovarian cancer. Besides that fact the study revealed statistically significant association between the *462Val* allele and platinum resistance, which was defined as a time interval <6 months to disease progression after administration of a platinum-based primary chemotherapy [47].

Some opposite results to the above mentioned data were presented by Holt et al. They carried out a case control study of 310 epithelial ovarian cancer cases and 585 controls. Patients were genotyped among others for *CYP1A1*2A*, **2C*, **3* and **4* polymorphisms. No association of ovarian cancer risk was observed with any of these polymorphisms [7].

Moreover, there are only few researches concerning the role of *CYP1A1* alleles in female genital cancers in Polish population. One of these performed by Seremak-Mrozikiewicz et al. showed higher frequency of heterozygotic genotype containing mutation *m4* (*CYP1A1*1/*4*) in ovarian cancer group (5.1% versus 1.9% controls). The Authors concluded that the higher frequency of mutated *CYP1A1*4* allele connected with lower frequency of *CYP1A1*2A* and *CYP1A1*2B* in endometrial and ovarian cancer groups indicates that differences in the metabolic activity of CYP1A1 could play a significant role in the pathogenesis of genital tract cancers [8].

Table III. Studies assessing the *CYP1A1* genetic polymorphisms in women with ovarian cancer.

Authors	Investigated genetic variants	Number of all patients cases/controls (population); ethnicity	[a]OR	p	Reference
Aktas et al., 2002	CYP1A1*2C (*Ile462Val*)	117/202 (Caucasian, Turkey)	6.07	>0.005	43
Delort et al., 2008	CYP1A1*2C (*Ile462Val*)	51/996 (Caucasian, France)	0.91	ns	45
Goodman et al., 2001	CYP1A1*2A (*MspI*) CYP1A1*2C (*Ile462Val*)	129/144 (Hawaii; mixed ethnicity)	1.4 0,91	ns ns	44
Gulyaeva et al., 2008	CYP1A1*2A (*m1*)	96/178 (Caucasian, Novosibirsk region, Russia)	1.44	ns	53
Heubner et al., 2010	CYP1A1*2C (*Ile462Val*)	(Caucasian, Germany)	2.6	0.001	47
Holt et al., 2007	CYP1A1*2A (*m1*)	White 277/449 Black 100/100	0.8 0.9	ns ns	7
	CYP1A1*3 (*m3*)	White 277/448 Black 33/126	- 0.6	 ns	
	CYP1A1*4 (*m4*)	White 277/447 Black 33/126 (African-American and Caucasian from Atlanta, Seattle and Detroit metropolitan areas, USA; mixed ethnicity)	1.4 -	ns	
[b]Mikhailova et al., 2006	CYP1A1*2A (*m1*)	168/172 (Caucasian, Novosibirsk region, Russia)	0.87	ns	48
Seremak-Mrozikiewicz et al., 2005	CYP1A1*4 (*m4*)	39/212 (Caucasian, Poland)	2.8	ns	8
Sugawara et al., 2003	CYP1A1*2C (*Ile462Val*) CYP1A1*2A (*MspI*)	46/31 (Oriental population, Japan)	1.16 1.33	ns ns	1
Terry et al., 2003	CYP1A1*2A (*MspI*) CYP1A1*2C (*Ile462Val*)	438/465 440/471 (USA; ethnicity not defined)	1.14 1.15	ns ns	46

[a]OR is the relative risk for patients with genotype conforming at least one mutation vs. those with wild-type genotype.

[b]Women groups with ovarian and endometrial cancer were analyzed together in this study.

Table IV. Studies assessing the *CYP1A1* genetic polymorphisms in women with endometrial cancer.

Authors	Investigated genetic variants	Number of all patients cases/controls (population); ethnicity	[a]OR	p	Reference
Doherty et al., 2005	CYP1A1*2A (*m1*) CYP1A1*2C (*m2*)	371/420 (Caucasian and African-American, USA; mixed ethnicity)	0.64 0.54	ns ns	2
Esinler et al., 2006	CYP1A1*2C (*Ile462Val*)	94/202 (Caucasian, Turkey)	2.54	<0.01	9
Esteller et al., 1997	CYP1A1*4 (*m4*)	80/60 (Caucasian, Spain)	6.36	0.0004	50
Gulyaeva et al., 2008	CYP1A1*2A (*m1*)	154/178 (Caucasian, Novosibirsk region, Russia)	0.97	ns	53
Hirata et al., 2008	CYP1A1*2A (*m1*) CYP1A1*2C (*m2*) CYP1A1*4 (*m4*)	150/165 (USA; ethnicity not defined)	0.42 0.99 1.5	0.0003 ns ns	23
McGrath et al., 2007	CYP1A1*2A (*MspI*) CYP1A1*4 (*Thr461Asn*) CYP1A1*2C (*Ile462Val*)	406/1008 392/975 409/975 (USA; mixed ethnicity)	1.19 0.78 0.86	ns ns ns	52
Rebbeck et al., 2006	CYP1A1*2C	450/1231 (Philadelphia metropolitan area, USA; mixed ethnicity)	1.68	ns	54
Seremak-Mrozikiewicz et al., 2005	CYP1A1*4 (*m4*)	71/212 (Caucasian, Poland)	3.1	ns	8
Sugawara et al., 2003	CYP1A1*2C (*Ile462Val*) CYP1A1*2A (*MspI*)	38/31 (Oriental population, Japan)	1.70 0.88	ns ns	1

[a]OR is the relative risk for patients with genotype conforming at least one mutation vs. those with wild-type genotype.

In the study performed by Mikhailova et al., the Authors assessed frequency of allelic variants of *CYP1A1*, *CYP1A2*, *CYP19* and *SULT1A1* genes and their association with the risk of ovarian and endometrial cancers. This investigation involved Caucasian population from Novosibirsk region (Russia). The Authors studied the following polymorphisms: *CYP1A1*2A* (T264C), *CYP1A2*1F* (C734A), CYP19 (*Arg264Cys*) and *SULT1A*2* (*Arg213His*). In this study there was no positive correlation of *CYP1A1* polymorphism and elevated risk of cancers [48].

The findings of these studies about *CYP1A1* polymorphism in women with ovarian cancer were listed in Table III. Based on the results presented in this table, we concluded that *CYP1A1*4* carriers were at higher risk of ovarian cancer. A moderate increase in risk of this cancer was noted among carriers of *CYP1A1*2A/C*.

***CYP1A1* polymorphisms and endometrial cancer**

There is limited number of studies worldwide assessing the frequency distribution of genetic polymorphisms in women with endometrial cancer, but some genetic researches were connected with this problem [1,8,49,50]. In the first report of Esteller and co-investigators, DNA isolated from 80 unrelated Caucasian women diagnosed with endometrial cancer was analyzed to examine two polymorphisms in the *CYP1A1* as potential molecular markers of uterine tumour. A statistically significant association was reported between endometrial cancer and both polymorphism studied (p=0.02; the OR and CI were 3.67 for both polymorphisms, respectively). No significant differences were found in the distribution of gene polymorphisms and histological type of the neoplasms [50].

In Japan, Sugawara et al. have studied two *CYP1A1* polymorphisms (*MspI* at non-coding 3'-flanking region and another at exon 7) in 159 female genital tract malignancies, including thirty-eight endometrial cancer (EC) women. The OR (1.7) of *Ile/Val* (*CYP1A1*2C*) polymorphism was higher in endometrial cancer group than those in the cervical cancer (OR=1.18) and ovarian cancer (OR=1.16) groups. Moreover, the *Val/Val* genotype was reported more frequently in endometrial cancer group compared to the control subjects. However, there was no significant association between gene polymorphisms and pathological features of gynaecological malignancies [1].

Sergentanis et al. performed a meta-analysis in order to examine the influence of three polymorphisms of *CYP1A1*2A* (*MspI*), **2C* (*Ile462Val*) and **4* (*Thr461Asp*) on endometrial cancer risk in Caucasian population. The Authors observed no association between these three analysed polymorphisms and endometrial cancer risk [51].

In the study by McGrath et al., three polymorphisms of *CYP1A1*2A* (*MspI*), **4* (*Thr461Asp*) and **2C* (*Ile462Val*) were evaluated as potential risk factors of endometrial cancer and their modification by cigarette smoking among 456 women with uterine neoplasms and 1134 matched controls. They observed no statistically significant associations between these polymorphisms and endometrial cancer risk or any significant effect modification by cigarette-smoking [52].

In our study we analysed 71 Polish women with endometrial cancer in order to elucidate the possible role of *CYP1A1* alleles in the pathogenesis of this malignancy. We have noticed the overrepresentation of *CYP1A1*4* allele in both, endometrial and ovarian cancer groups if compared to the controls (*CYP1A1*4* 2.8% vs. 0.9% in endometrial cancer group and *CYP1A1*4* 2.5% vs. 0,9% in ovarian cancer group, p=ns, OR=3.0 in endometrial cancer group and OR=2.9 in ovarian cancer group). The presence of *CYP1A1*1/*4* genotype was also higher in the endometrial cancer group compared to the controls (5.6% vs. 1.9%). In our controls, we have found frequencies of *CYP1A1* alleles similar to other Caucasians [8]. Our results were similar to the results obtained in other investigations. It is possible that the presence of **4* allele in subjects with these cancers could play an important role in the pathogenesis of their cancers. The summary of the above-mentioned researches was listed in Table IV.

Gulyaeva et al. studied the frequency of *CYP1A1*, *CYP1A2*, *CYP1B1*, *CYP19* and *SULT1A1* allelic variants in a female population of the Novosibirsk district and their association with the elevated risk of breast, ovarian, and endometrial cancers. The Authors revealed significant differences (OR=2.34, p=0.0002) in the allele distributions for *CYP1A1*2A* polymorphism between patients with breast cancer (118 patients) and controls (180 women). There were no statistically significant differences in genotype and allele distributions for *CYP1A1* polymorphisms in patients with ovarian cancer (96 patients) and endometrial cancer (154 patients). Moreover, differences in the allele and genotype distributions for *CYP1A2*1F* polymorphism in patients with breast cancer and ovarian cancer (OR=0.26, p=0.0000005 and OR=0.34, p=0.00000002) were observed. There were no significant differences for this polymorphism in women with EC [53].

In study performed by Hirata et al. 150 cases of endometrial cancer and 165 healthy controls were assessed to evaluate the genotype frequencies of 13 different polymorphisms of the *CYP1A1 (*2A*, **2C*, **3*, **4*), *CYP1A2*1F*, *CYP1B1* codon 432, *COMT* codon 158, *CYP17*, *SULT1A1* (*Arg213His*, 14A/G, 85C/T in the 3' flanking region), *SULT1E1*-64G>A promoter region, and *SHBG* genes. The decreased frequency of TC+CC genotypes of the *CYP1A1*2A* polymorphism was observed in EC patients in comparison to controls (OR=0.42). The T-A haplotype of *CYP1A1*2A* and *CYP1A1*2C* polymorphisms were increased in the study group [23].

McGrath et al. examined the associations between *CYP1A1* polymorphisms and endometrial cancer risk and the modification of these associations by cigarette smoking. The Authors studied **2B* (*MspI*), **4* and **2C* (*Ile462Val*) polymorphism among 456 women with endometrial cancer and 1134 healthy controls. There were no statistically significant associations between these polymorphisms and endometrial cancer risk or significant effect modification by cigarette smoking [52].

A case-control study involving 502 patients with endometrial cancer and 1326 healthy controls was undertaken by Rebbeck et al. The Authors genotyped the following genes: *COMT*, *CYP1A1*, *CYP1A2*, *CYP1B1*, *CYP3A4*, *PGR*, *SULT1A1*, *SULT1E1* and *UGT1A1*. The results revealed the association between the risk of endometrial cancer and *CYP1A1*2C* (OR=1.68), *SULT1A1*3* (OR=0.51) and the G/A variant in the promoter of *SULT1E1* (OR=1.45) [54].

Esinler et al. observed that patients with *Ile/Val* (*CYP1A1*2C*) genotype had a 5-fold higher risk of developing endometrial hyperplasia than those with Ile/Ile. In patients with endometrial hyperplasia a higher frequency of *Val* containing genotype (*Ile/*

Val and *Val/Val*) was found. In the endometrial cancer group the *CYP1A1 Ile/Val* allele was also more frequent (OR=2.54). The Authors concluded that variant alleles of the *CYP1A1* might be associated with endometrial cancer and endometrial hyperplasia risk [9].

In the study performed by Doherty et al., the Authors investigated the genotype frequency of genes correlated with endometrial cancer (*CYP1A1*2A*, *CYP1A1*2C*, *CYP1A1*4*. The study involved 371 endometrial cancer cases and 420 controls. Carrying at least one *CYP1A1 m1* or *m2* polymorphism allele was associated with a decreased risk of endometrial cancer (OR 0.64 and 0.54, respectively) [2].

In summary, the findings of studies presented at Table IV suggest that the *CYP1A1*2A* allele may decrease the risk of endometrial cancer; however, the *CYP1A1*4* allele may increase a relative risk of development of this cancer. No association of endometrial cancer risk was observed with any of the other examined polymorphisms.

***CYP1A1* gene polymorphisms and non-urogenital cancers**

In molecular-epidemiological studies functional consequences of **2A* and **2C* of *CYP1A1* have been discussed to be a risk factor for lung cancer development, but not for bladder cancer [26, 31, 36, 55]. There is also evidence that *CYP1A1* polymorphism is closely associated with lung cancer occurrence [37,56]. However, the role of *CYP2D6* was analyzed in recent studies and it was also suggest that *CYP2D6* is a risk factor for lung cancer development, suggestion not confirmed in other investigations [32, 57]. *CYP2D6* polymorphism was also connected with liver and bronchial cancers [58]. In most cases the functional significance of these polymorphisms has not been confirmed. These genetic polymorphisms most likely play a role in susceptibility to diseases related to exposure to toxic compounds and could have direct influence on the ovarian and endometrial tissues. Some authors also suggested the overrepresentation of one of *CYP1A1* mutations in the investigated groups of patients with cancer. In molecular-epidemiological studies, **2A* and **2C* alleles were identified to place their carrier at increased risk for lung cancer. High benzo[a]pyrene diol-epoxide DNA-adducts levels in blood cells occur in coke oven workers who are carriers of the **2A* allele [39, 59].

CYP1A1 and AhR – interaction important for carcinogenesis

The activity of CYP1A1 enzyme that generates a variety of genotoxic metabolites damaging DNA and potentially promoting cancer development, may be also determined by aryl hydrocarbon receptor [46,60,61]. It was shown that long-term exposure to carcinogens is connected with an increased risk for human malignancies, such as breast and prostate cancer [62,63]. Hence, both CYP1A1 enzyme activity and action of the aryl hydrocarbon receptor are claimed to play an important role in the carcinogenesis induced by many environmental xenobiotics.

AhR is a transcription factor that regulates the expression of genes, such as *CYP1A1*, *CYP1A2* and *CYP1B1* involved in the activation and detoxification of carcinogens [61]. AhR belongs to the class of basic-helix-loop-helix (bHLH)-Per-Arnt-Sim (PAS) proteins that is expressed mainly in human tissues such as liver, placenta, pancreas, lung and heart. AhR ligands are PAHs, for example benzo[a]pyrene and 7,12-dimethylbenz[a]anthracene (DMBA), dioxins (2,3,7,8-tetrachlorodibenzo-*p*-dioxin – TCDD) as well as polychlorinated biphenyls, some dietary compounds (indole-3-carbinol) and several endogenous compounds [64,65]. In the absence of a ligand, AhR is maintained in the cytoplasm in complex with chaperon proteins, such as Hsp90, ARA (known as XAP2 or AIP) and p23. After ligand binding, AhR detaches from the chaperon proteins and translocates to the nucleus, where it dimerizes with the AhR nuclear translocator (ARNT). The AhR/ARNT heterodimer binds to the xenobiotic response elements (XRE) of *CYP* genes regulating its expression [66]. Furthermore, ligand-activated AhR induces a novel PAS protein called AhR repressor that can inhibit AhR by dimerization with ARNT and binding to XRE repressing transcription [65,67]. An addition, endogenous AhR was shown to be able to induce cancer formation independent of the presence of exogenous ligand by its pro-proliferative and tumour-promoting properties [62,68]. Moreover, the findings of studies demonstrate overexpression of the AhR in the breast and prostate cancers, suggesting that this receptor can be an important target for the development of new drugs in the treatment of breast and endometrial cancers [62,69]. This is a new trend that completes knowledge about ovarian and endometrial cancer because not only *CYP1A1* polymorphism, but also action of aryl hydrocarbon receptor on the *CYP1A1* activity can have significant importance in determining cancer risk. Moreover, it is suggested that the interactions between *CYP1A1* polymorphism and substrates of this enzyme may increase a risk of tumour development.

Conclusion

In general, the CYP1A1 enzyme that metabolizes numerous procarcinogens, plays an important role in cancer formation. Several studies reported that *CYP1A1* polymorphism could be connected with risk of appearance of different types of cancer, for example endometrial and ovarian malignancies. It results from the presence of polymorphic alleles of *CYP1A1* that alter activity of this enzyme. Such interindividual differences in CYP1A1 activity may have influence on individual susceptibility to cancer risk. Our analysis presented in this work showed an increased risk of ovarian and endometrial cancers among carriers of *CYP1A1*4* allele and decreased risk of endometrial cancer for carriers with *CYP1A1*2A* allele. No association for these discussed cancers was observed in case of other examined polymorphisms.

Further studies are needed in order to determine the functional consequences of genetic variants of CYP1A1 enzyme and importance of its transcriptional regulation in the development of carcinogenesis. Moreover, additional knowledge about genetic risk factors for cancer progresses including *CYP1A1* polymorphism allows to determine the association between the distribution of specific CYP variant alleles and risk of appearance of tumours including also ethnic differences.

Acknowledgments

This work was supported by the Polish Ministry of Science and Higher Education, Grant No N405 676940.

References

1. Sugawara T, Nomura E, Sagawa T, [et al.]. CYP1A1 polymorphism and risk of gynecological malignancy in Japan. *Int J Gynecol Cancer.* 2003, 13, 785-790.
2. Doherty J, Weiss N, Freeman R, [et al.]. Genetic factors in catechol estrogen metabolism in relation to the risk of endometrial cancer. Cancer Epidemiol Biomarkers Prev. *2005, 14, 357-366.*
3. Lynch H, Casey M, Lynch J, [et al.]. Genetics and ovarian carcinoma. *Semin Oncol.* 1998, 25, 265-280.
4. Auersperg N, Edeson M, Mok S, [et al.]. The biology of ovarian cancer. *Semin Oncol.* 1998, 25, 281-304.
5. Daly M, Obrams G. Epidemiology and risk assessment for ovarian cancer. *Semin Oncol*. 1998, 25, 255-264.
6. Bulun S, Zeitoun K, Kilic G. Expression of dioxin-related transactivating factors and target genes in human eutopic endometrial and endometriotic tissues. *Am J Obstet Gynecol.* 2000, 182, 767-775.
7. Holt S, Rossing M, Malone K, [et al.]. Ovarian cancer risk and polymorphisms involved in estrogen catabolism. *Cancer Epidemiol Biomarkers Prev.* 2007, 16, 481-489.
8. Seremak-Mrozikiewicz A, Drews K, Semczuk A, [et al.]. CYP1A1 alleles in female genital cancers in the Polish population. *Eur J Obstet Gynecol Reprod Biol.* 2005, 118, 246-250.
9. Esinler I, Aktas D, Alikasifoglu M, [et al.]. CYP1A1 gene polymorphism and risk of endometrial hyperplasia and endometrial carcinoma. *Int J Gynecol Cancer.* 2006, 16, 1407-1411.
10. Nebert D, Gonzales F. P450 genes: Structure, evolution, and regulation. *Annu Rev Biochem.* 1987, 56, 945-993.
11. Nerbert D, Dalton T. The role of cytochrome P450 enzymes in endogenous signaling pathways and environmental carcinogenesis. *Nat Rev Cancer.* 2006, 6, 947-960.
12. Tsuchiya Y, Nakajima M, Yokoi T. Cytochrome P450-mediated metabolism of estrogens and its regulation in human. *Cancer Lett.* 2005, 28, 115-124.
13. Pavek P, Dvorak Z. Xenobiotic-induced transcriptional regulation of xenobiotic metabolizing enzymes of the cytochrome P450 superfamily in human extrahepatic tissues. *Curr Drug Metab*. 2008, 9, 129-143.
14. Jorge-Nebert L, Jiang Z, Chakraborty R, [et al.]. Analysis of human CYP1A1 and CYP1A2 genes and their shared bidirectional promoter in eight world populations. *Hum Mutat.* 2010, 31, 27–40.
15. Monostory K, Dvorak Z. Steroid regulation of drug-metabolizing cytochromes P450. *Curr Drug Metab.* 2011, 12, 154-172.
16. Whitlock J. Induction of cytochrome P4501A1. *Annu Rev Pharmacol Toxicol.* 1999, 39, 103-125.
17. Young C, Lo Y, Tsai Y, [et al.]. CYP1A1 gene polymorphisms as a risk factor for pterygium. *Mol Vis.* 2010,16, 1054-1058.
18. Guengerich F, Shimada T. Oxidation of toxic and carcinogenic chemicals by human P450 enzymes. *Chem Res Toxicol.* 1991, 4, 391-407.
19. Rendic S. Summary of information on human CYP enzymes: human p450 metabolism data. *Drug Metab Rev.* 2002, 34, 83-448.
20. Zuber R, Anzenbacherová E, Anzenbacher P. Cytochromes P450 and experimental models of drug metabolism. *J Cell Mol Med.* 2002, 6, 189-198.
21. Zhu B, Conney A. Functional role of estrogen metabolism in target cells: review and perspectives. *Carcinogenesis.* 1998, 19, 1-27.
22. Lee A, Cai M, Thomas P, [et al.]. Characterization of the oxidative metabolites of 17beta-estradiol and estrone formed by 15 selectively expressed human cytochrome p450 isoforms. *Endocrinology.* 2003, 144, 3382-3398.
23. Hirata H, Hinoda Y, Okayama N, [et al.]. CYP1A1, SULT1A1, and SULT1E1 polymorphisms are risk factors for endometrial cancer susceptibility. *Cancer.* 2008, 112, 1964-1973.
24. Williams-Brown M, Salih S, Xu X, [et al.]. The effect of tamoxifen and raloxifene on estrogen metabolism and endometrial cancer risk. *J Steroid Biochem Mol Biol.* 2011, 126, 78-86.
25. Ingelman-Sundberg M, Oscarson M, Daly A, [et al.]. Human cytochrome P-450 (CYP) genes: a web page for the nomenclature of alleles. *Cancer Epidemiol Biomarkers Prev.* 2001, 10, 1307-1308.
26. Cascorbi I, Brockmoeller J, Roots I. A C4887A polymorphism in exon 7 of human CYP1A1: population frequency, mutation linkages, and impact on lung cancer susceptibility. *Cancer Res.* 1996, 56, 4965-4969.
27. Crofts F, Cosma G, Currie D, [et al.]. A novel CYP1A1 gene polymorphism in African-Americans. *Carcinogenesis.* 1993, 14, 1729-1731.
28. Dracoulis N, Cascorbi I, Brockmoeller J, [et al.]. Polymorphism in the human CYP 1A1 gene as susceptibility factors for lung cancer: exon-7 mutation (4889 A to G), and a T to C mutation in the 3'- flanking region. *Clin Investig.* 1994, 72, 240-248.
29. Taioli E, Crofts F, Trachman J, [et al.]. A specific African-American CYP1A1 polymorphism is associated with adenocarcinoma if the lung. *Cancer Res.* 1995, 55, 472-473.
30. Inoue K, Asao T, Shimada T. Ethnic-related differences in the frequency distribution of genetic polymorphisms in the CYP1A1 and CYP1B1 genes in Japanese and Caucasian populations. *Xenobiotica.* 2000, 30, 285-295.
31. Kawajiri K, Nakachi K, Imai K, [et al.]. Identification of genetically high risk individuals to lung cancer by DNA polymorphism of cytochrome P4501A1 gene. *FEBS Lett.* 1990, 263, 131-133.
32. Hirvonen A, Husgafvel-Pursiainen K, Anttila S, [et al.]. Metabolic cytochrome P450 genotypes and assessment of individual susceptibility to lung cancer. *Pharmacogenetics.* 1992, 2, 259-263.
33. Tefre T, Ryberg D, Haugen A, [et al]. Human CYP1A1 (cytochrome P(1)450) gene: lack of association between the MspJ restriction fragment length polymorphism and incidence of lung cancer in a Norwegian population. *Pharmacogenetics.* 1991, 1, 20-25.
34. Shields P, Bowman E, Harrington A, [et al]. Polycyclic aromatic hydrocarbon-DNA adducts in human lung and cancer susceptibility genes. *Cancer Res.* 1993, 53, 3486-3492.
35. Aynaciouglu A, Cascorbi I, Mrozikiewicz P, Roots J. High frequency of CYP 1A1 mutations in a Turkisch population. *Arch Toxicol.* 1998, 72, 215-218.
36. Nakachi K, Imai K, Hayashi S, [et al.]. Genetic susceptibility to squamous cell carcinoma of the lung in relation to cigarette smoking dose. *Cancer Res.* 1991, 51, 5177-5180.
37. Hayashi S, Watanabe J, Nakachi K, Kawajiri K. Genetic linkage of lung cancer-associated Msp I polymorphism with amino acid replacement in the heme binding region of the human cytochrome P4501A1 gene. *J Biochem.* 1991,110, 407-411.
38. Kesley K, Spitz M, Zuo Z, Wiencke J. Polymorphism in the gluthathione S-transferase class mu and theta genes interact and increase susceptibility to lung cancer in minority populations (Texas, Unite States). *Cancer Cause Control.* 1997, 8, 554-559.
39. Mrozikiewicz P, Cascorbi I, Brockmoeller J, Roots J. CYP1A1 mutations 4887A, 4889G, 5639C, and 6235C in the Polish population and their allelic linkage, determined by peptide nucleic acid-mediated PCR clamping. *Pharmacogenetics.* 1997, 7, 303-307.
40. Butykiewicz D, Grzybowska E, Hemminki K, [et al.]. Modulation of DNA adduct levels in human mononuclear white blood cells and granulocytes by CYP1A1, CYP2D6 and GSTM1 genetic polymorphisms. *Mutat Res.* 1998, 415, 97-108.
41. Motykiewicz G, Michalska J, Pendzich J, [et al.]. A molecular epidemiology study in women from Upper Silesia, Poland. *Toxicol Lett.* 1998, 96, 195-202.
42. Vella N, Aiello M, Russo A, [et al.]. Genetic profiling and ovarian cancer therapy (Review). *Mol Med Report.* 2011, 4, 771-777.
43. Aktas D, Guney I, Alikasifoglu M, [et al.]. CYP1A1 gene polymorphism and risk of epithelial ovarian neoplasm. *Gynecol Oncol.* 2002, 86, 124-128.
44. Goodman M, McDuffie K, Kolonel L, [et al.]. Case-control study of ovarian cancer and polymorphisms in genes involved in catecholestrogen formation and metabolism.*Cancer Epidemiol Biomarkers Prev.* 2001, 10, 209-216.
45. Delort L, Chalabi N, Satih S, [et al]. Association between genetic polymorphisms and ovarian cancer risk. *Anticancer Res.* 2008, 28, 3079-3081.
46. Terry K, Titus-Ernstoff L, Garner E, [et al.]. Interaction between CYP1A1 polymorphic variants and dietary exposures influencing ovarian cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2003, 12, 187-190.
47. Heubner M, Wimberger P, Riemann K, [et al.]. The CYP1A1 Ile462Val polymorphism and platinum resistance of epithelial ovarian neoplasms. *Oncol Res.* 2010, 18, 343-347.
48. Mikhailova O, Gulyaeva L, Prudnikov A, [et al.]. Estrogen-metabolizing gene polymorphisms in the assessment of female hormone-dependent cancer risk. *Pharmacogenomics J.* 2006, 6, 189-193.
49. Seremak-Mrozikiewicz A, Drews K, Semczuk A, [et al.]. Polymorphism of CYP1A1 gene susceptibility for uro-genital cancers, The Proceedings of the Sixth Congress of the European Association for Clinical Pharmacology and Therapeutics, Istanbul, Turkey 2003, 174.
50. Esteller M, Garcia A, Martinez-Palones J, [et al.]. Germ line polymorphisms in cytochrome-P4501A1 (C4887 CYP1A1) and methylenetetrahydrofolate reductase (MTHFR) genes and endometrial cancer susceptibility. *Carcinogenesis.* 1997, 18, 2307-2311.
51. Sergentanis T, Economopoulos K, Choussein S, Vlahos N. Cytochrome P450 1A1 gene polymorphisms and endometrial cancer risk: a meta-analysis. *Int J Gynecol Cancer.* 2011, 21, 323-331.
52. McGrath M, Hankinson S, De Vivo I. Cytochrome P450 1A1, cigarette smoking, and risk of endometrial cancer (United States). Cancer Causes Control. 2007, 18, 1123-1130.
53. Gulyaeva L, Mikhailova O, Pustylnyak V, [et al.]. Comparative analysis of SNP in estrogen-metabolizing enzymes for ovarian, endometrial, and breast cancers in Novosibirsk, Russia. *Adv Exp Med Biol.* 2008, 617, 359-366.
54. Rebbeck T, Troxel A, Wang Y, [et al.]. Estrogen sulfation genes, hormone replacement therapy, and endometrial cancer risk. *J Natl Cancer Inst.* 2006, 98, 1311-1320.
55. Brockmoeller J, Cascorbi I, Kerb R, Roots J. Combined analysis of inherited polymorphisms in arylamine N-acetyltransferase 2, glutathione S-transferase M1 and T1, microsomal epoxide hydrolase and cytochrome P450 enzymes as modulators of bladder cancer risk. *Cancer Res.* 1996, 56, 3915-3925.
56. London S, Daly A, Fairbrother K, [et al.]. Lung cancer risk in African-Americans in relation to race-specific CYP1A1 polymorphism. *Cancer Res.* 1995, 55, 6035-6037.
57. London S, Daly A, Leathart J, [et al.]. Genetic polymorphism of CYP2D6 and lung cancer risk in African-Americans ans Caucasians in Los Angeles County. *Carcinogenesis.* 1997, 18, 1203-1214.
58. Roots I, Drakoulis N, Ploch M, [et al.]. Debrisoquine hydroxylation phenotype, acetylation phenotype, and ABO blood groups as genetic host factors if lung cancer risk. *Klin Wochenschr.* 1998, 66, 87-97.
59. Mrozikiewicz P, Landt O, Cascorbi I, Roots J. Peptide nucleic acid-mediated polymerase chain reaction clamping allows allelic allocation of CYP 1A1 mutations. *Anal Biochem.* 1997, 250, 256-257.
60. Nebert D, Dalton T, Okey A, Gonzales F. Role of aryl hydrocarbon receptor-mediated induction of the CYP1 enzymes in environmental toxicity and cancer. *J Biol Chem.* 2004, 279, 23847–23850.
61. Sienkiewicz P, Ciolino H, Leslie B, [et al.]. A novel synthetic analogue of a constituent of isodon excisus inhibits transcription of CYP1A1, -1A2 and -1B1 by preventing activation of the aryl hydrocarbon receptor. *Carcinogenesis.* 2007, 28, 1052–1057.
62. Schlezinger J, Liu D, Farago M, [et al.]. A role for the aryl hydrocarbon receptor in mammary gland tumorigenesis. *Biol Chem.* 2006, 387, 1175-1187.
63. Koutros S, Berndt S, Sinha R, [et al.]. Xenobiotic metabolizing gene variants, dietary heterocyclic amine intake, and risk of prostate cancer. *Cancer Res.* 2009, 69, 1877-1884.
64. Nguyen L, Bradfield C. The search for endogenous activators of the aryl hydrocarbon receptor. *Chem Res Toxicol.* 2008, 21, 102-116.
65. Pelkonen O, Turpeinen M, Hakkola J, [et al.]. Inhibition and induction of human cytochrome P450 enzymes: current status. *Arch Toxicol.* 2008, 82, 667-715.
66. Hankinson O. The role of the aryl hydrocarbon receptor nuclear translocator protein in aryl hydrocarbon receptor action. *Trends Endocrinol Metab.* 1994, 5, 240-244.
67. Mimura J, Ema M, Sogawa K, Fujii-Kuriyana Y. Identification of a novel mechanism of regulation of Ah (dioxin) receptor function. *Genes Dev.* 1999, 13, 20-25.
68. Yang X, Solomon S, Fraser L, [et al.]. Constitutive regulation of CYP1B1 by the aryl hydrocarbon receptor (AhR) in pre-malignant and malignant mammary tissue. *J Cell Biochem.* 2008, 104, 402-417.
69. Gluschnaider U, Hidas G, Cojocaru G, [et al.]. Beta-TrCP inhibition reduces prostate cancer cell growth via upregulation of the aryl hydrocarbon receptor. *PLoS One.* 2010, 5, e9060.