CYP3A5 POLYMORPHISM AND THE RISK OF CANCER: A METAANALYSIS

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Abstract

The two important genes of CYP450 are CYP3A4 and CYP3A5 that play a central role in drugs and hormones metabolisms that have a role in the etiology of cancers. Single nucleotide polymorphism (SNP) in these genes may increase the risk of developing cancers. Numerous functional SNPs of the CYP3A5 gene have been connected in cancer risk, but individually published investigation have exposed questionable consequences. The aim of the current investigation and meta-analysis was to examine the link between polymorphism CYP3A5*3 6986 A>G [rs776746] under the heterozygous model and an association with increased risk of cancer. Following the inclusion criteria, eight studies were incorporated and 42 studies were excluded in this metaanalysis. The numbers of cancer cases and healthy controls were 4959 and 5176, respectively. The heterogenecity model was significant in subgroup analysis of Chinese, Indian, Japanese and Asian population suffered in TB, CML, and breast cancers [OR: 0.50, 95 %CI: 0.30-0.81, P<0.01; OR= 1.57, 95 %CI: 1.00-2.47, P<0.05; OR=0.69; 95%CI=0.51-0.93; P<0.01; OR=0.61; 95%CI=0.42-0.89; P<0.01]. The overall statistics under heterozygous model [Fig: 2; OR=0.9187; 95%CI=0.82-1.02; P<0.1289] showed that polymorphism, CYP3A5*3 6986 A>G [rs776746] is not associated with cancer risk.

Keywords: CYP3A5, cancer risk, polymorphism, meta-analysis

Introduction

Drug efficacy can be effected by the genetic differences of individuals or populations. Therefore, pharmacogenetics variations is considered as an important aspect in the diseases treatments and situation with personalized medication. In the view of such conditions, the efficacy and toxicity of the drugs can be enhanced in a person by focusing on the

phase I and phase II drug metabolism genes e.g. cytochrome P450 family [Desta et al., 2004: Hoskin., 2009].

There are four genes in the CYP3A family. These genes are CYP3A4, CYP3A5, CYP3A7, and CYP3A43 that are well-known phase-I metabolism-related genes. These genes were traced in the 231-kb area of chromosome 7q21.1 [Goetz et al., 2001]. It is estimated that about 755 of the metabolic reaction are carried by CYP enzymes [Rae et al., 2012]. A huge number of investigations were carried out to find the consequence of genetic variation of CYP3A4 and CYP3A5. The CYP3A4 and CYP3A5 genes are most commonly involved in drug related reactions and activation of some drugs etc. [Regan et al., 2012]. Studies reported that CYP3A4 and CYP3A5 accounts for 36% of activity of all CYP3A genes. The expression level of these genes is 30% occurring in liver and intestine [brooks et al., 2013: Mani et al., 1993: Iusuf et al., 2011].

CYP3A5 expression associated with an intron 3 variation in liver. The CYP3A5*3 (CYP3A5 6986A>G) variant codes a different spliced mRNA with a premature terminator codon. More over wild type CYP3A5*1 mRNA is more stable than CYP3A5*3 mRNA which is more unstable and quickly degraded [Kuehl et al., 2001].

Earlier studies reported that, depending on the ethnicity the CYP enzymes indicated polymorphism across persons, with deficiencies going on in 1 to 30% of populations [Hesselink et al., 2003]..

Material and methods

Literature search

In the present analysis Case control study Papers before March 2014 were selected through Google advance search, PubMed, yahoo search, web of sciences. Papers were searched using the terms variants, polymorphisms, SNP or cancer risk and cyp3A5, polymorphism in cyp3A5 and enzyme superfamily p450 3A.

Inclusion and exclusion criteria

The criteria adopted for inclusion of the study papers were: (1) cyp3a5 polymorphism in population with cases and controls studies only (2) Confirmed cancer patients (3) case-control studies having sufficient genotypes of the required data. Exclusion criteria adopted in this meta-analysis were: (1) studies without cases or controls (2) incomplete in data, (4) editorial articles letters, reviews and meta-analysis.

Data extraction

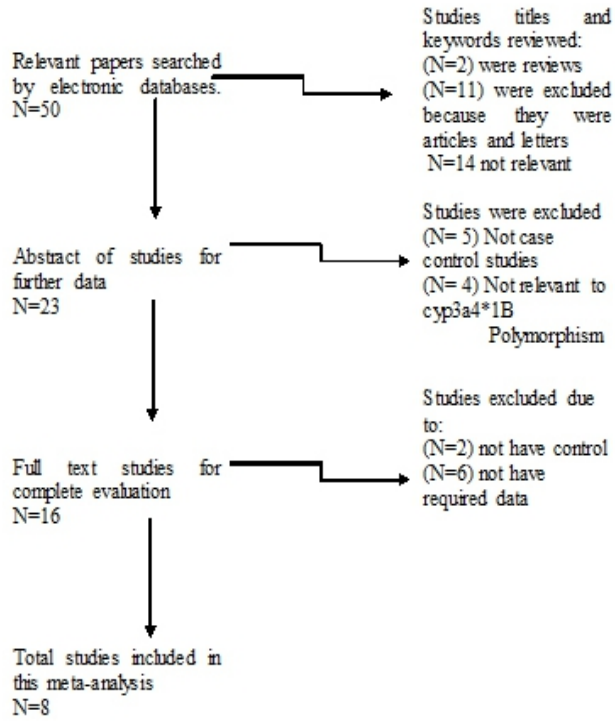
Data from the included papers extracted with the following characteristics: the first author name, year of publication, country, ethnicity, number of cases, and number of controls, genotype frequencies i.e. AA, AG,

and GG. Data were extracted separately from Chinese, Caucasian, African Americans, Indians, Japanese, United Kingdom, Finnish and Asian.

Statistical analysis

CYP3A5*1B (A>G) polymorphism and cancer risk was planned by odds ratios (ORs) with 95 %CI and was examined. All analyses were measured using Comprehensive Meta-Analysis Version 2.0 (14 North Dean Street, Englewood, NJ 07631, USA) and online OR calculators.

Fig.1 A flow chart of eight case–control studies in meta-analysis



Results

In the present study an attempt was made to know find the association between polymorphism CYP3A5*3 6986 A>G [rs776746] under the heterozygous model to know whether it is associated with increased risk of cancer or not. Following the inclusion criteria, eight studies were incorporated and 42 studies were excluded in this metaanalysis. The flow chart of study selection is shown in Fig. 1. The numbers of cancer cases and healthy controls were 4959 and 5176, respectively for evaluating the association between CYP3A5*3 6986 A>G [rs776746] polymorphism and

cancer risk. The publication years of included studies ranged from 2009 to 2012. Overall, two of these studies were conducted in Indian populations and one in each of African American, Chinese, Japanese, UK, Finnish and Asian populations. There were two breast cancer studies, three prostate cancer studies, one on each of leukemia, CML colorectal and TB.

Association between CYP3A5*3 6986 A>G [rs776746] polymorphism and cancer risk summary is given in the Table 1. Genotypic data and frequency of A allele and G allele is given. Heterozygous model with OR, LCI, UCI, P value determined for each study. The heterogenecity model was significant [table: 1] in Chinese, Indian, Japanese and Asian population suffered in TB, CML, and breast cancers [OR: 0.50, 95 %CI: 0.30-0.81, P<0.01; OR= 1.57, 95 %CI: 1.00-2.47, P<0.05; OR=0.69; 95%CI=0.51-0.93; P<0.01; OR=0.61; 95%CI=0.42-0.89; P<0.01]

The overall statistics under heterozygous model [Fig: 2; OR=0.9187; 95%CI=0.82-1.02; P<0.1289] showed that polymorphism, CYP3A5*3 6986 A>G [rs776746] is not associated with cancer risk. Cumulative statistics of the studies included in the current meta-analysis given in the Fig: 1 suggest that GG vs. AG is not associated in the cancer risk [95%CI=0.82-1.02; p< 0.1289]

Publication biases with Begger's funnel plot were achieved to weigh the publication biases of involved studies. No evidence of obvious unevenness was found under heterozygous model [Fig: 3]

CYP3A5*3 6986 A>G [rs776746]			CASES							CONTROL							RARE ALLELE VS HETEROZYGOUS [GG VS AG]				
AUTHOR NAME	population	Disorder /cancer type	AA	AG	GG	NO.	AG+GG	A allele	G allele	AA	AG	GG	NO.	AG+GG	A allele	G allele	OR	LCI	UCI	P value
Feng et al., 2012 [15]	Chinese	TB	27	78	47	152	125	0.43	0.57	17	60	73	150	133	0.31	0.69	0.50	0.30	0.81	0.01
Rao et al., 2011 [17]	Indian	Leukemia	12	84	48	144	132	0.38	0.63	124	71	46	241	117	0.66	0.34	0.88	0.53	1.47	0.63
Sailaja et al., 2010 [21]	Indian	CML	33	115	117	265	232	0.34	0.66	124	71	46	241	117	0.66	0.34	1.57	1.00	2.47	0.05
Shimada et al., 2009 [18]	Japanese	breast	33	160	210	403	370	0.28	0.72	20	132	251	403	383	0.21	0.79	0.69	0.51	0.93	0.01
Surekha et al., 2009 [22]	Asian	breast	25	132	92	249	224	0.37	0.63	28	103	118	249	221	0.32	0.21	0.61	0.42	0.89	0.01
Marikku et al., 2008 [20]	Finnish	prostate	9	117	628	754	745	0.09	0.91	3	95	628	726	723	0.07	0.93	0.90	0.67	1.19	0.46
Bethke et al., 2007 [19]	UK	colorectal	12	320	2225	2557	2545	0.07	0.93	16	363	2312	2691	2675	0.07	0.93	1.09	0.93	1.28	0.29
Plummer et al., 2003 a [16]	Caucasian	prostate	337	57	3	397	60	0.92	0.08	359	75	3	437	78	0.91	0.09	1.32	0.26	6.76	0.74
Plummer et al., 2003 b [16]	African American	prostate	6	18	14	38	32	0.39	0.61	5	16	17	38	33	0.34	0.66	0.37	0.28	1.94	0.53

Table 1 **CYP3A5*3 6986 A>G** polymorphism and risk of disease. meta-analysis andcharacteristics of included studies

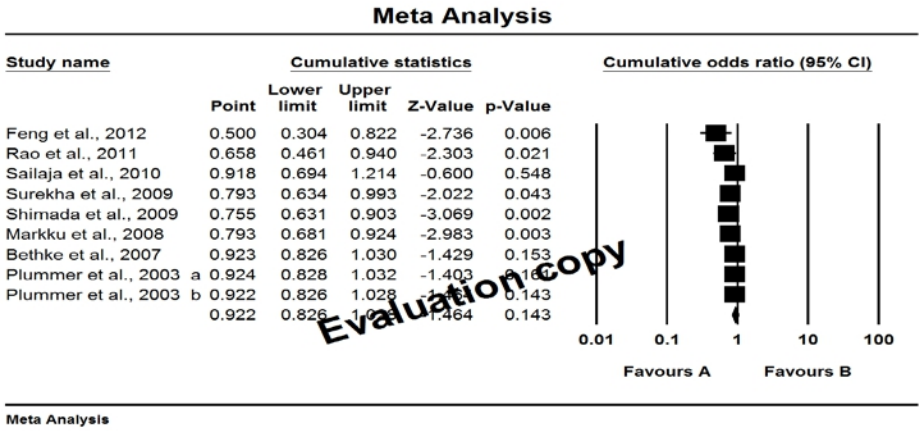


Fig 1 CYP3A5 polymorphism meta-analysis and cancer risk under model GG VS AG [Rare allele vs Heterozygous]

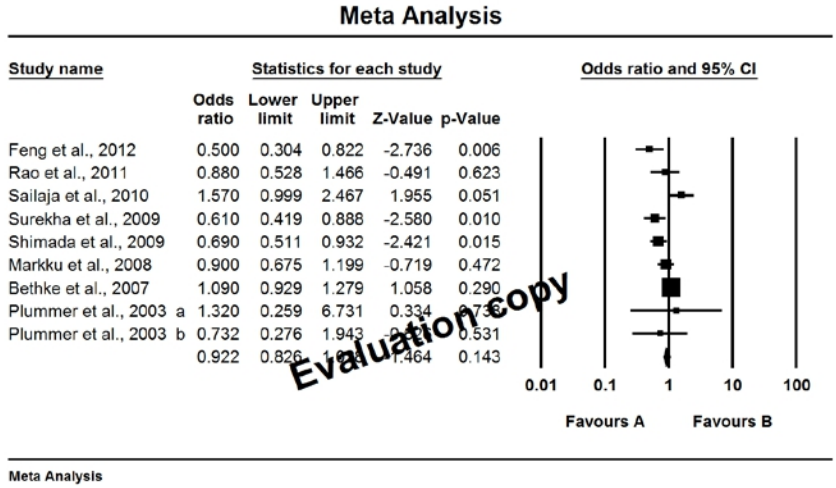


Fig 2. CYP3A5 polymorphism meta-analysis statistics for each study

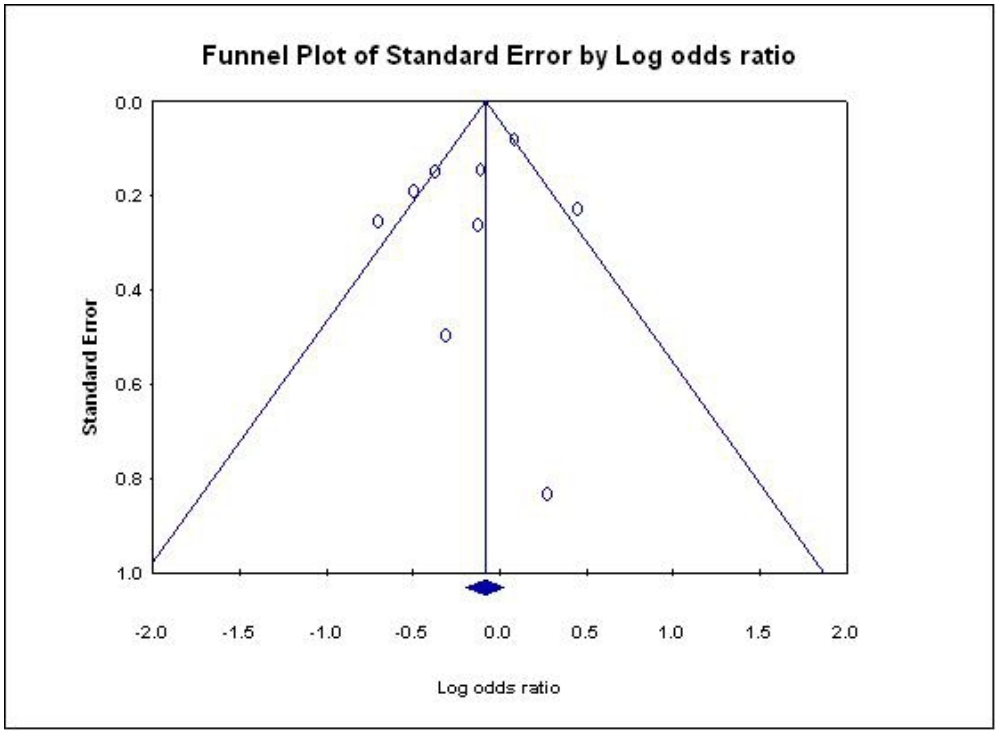


Fig 3. Begger's funnel plot for CYP3A5 polymorphism in meta-analysis

Discussion

RNA splicing and enzymatic activity is affected by a polymorphism in the intronic region of CYP3A5 gene (CYP3A5*3; SNP rs776746) playing a defensive role for TB in china [Coto et al., 2007].

Numerous racial groups display dissimilar occurrences of CYP450 allelic alternates, possibly due to prehistoric voyages of geologically divergent and remote anthropological clusters, shared with the effects of selective features, such as diet or illness [Lee et al., 2003]**.** Drug toxicity and response depends on the activity of inducers, dietary factors, and genetic factors that result of Inter-individual inconsistency in the catabolism of CYP3A substrates. The data available today showed that the activity of CYP3A5 gene is different in different ethnic groups is due to the polymorphisms in this genethat play a key role in drug clearance and response [Makeeva et al., 2008]**.** CYP3A5*1 is the single CYP3A5 variant that yields full-length CYP3A5 messenger RNA and showed the expression of CYP3A5 whereas the other collective CYP3A5 genetic variation in Caucasians, CYP3A5*3 6986 A>G [rs776746], expresses an abnormally spliced mRNA with a premature stop codon. Marked interethnic differences have been reported for the CYP3A5*3 allelic variant [Roy et al., 2005].

In the current metaanalysis no significant association was found between the single nucleotide polymorphism CYP3A5*3 and the risk of developing cancer in a rare allele vs heterozygous model (Fig: 2; OR=0.9187; 95%CI=0.82-1.02; P<0.1289) a previous study conducted on the Japanese population reported no significant association between CYP3A5*3 and the risk of developing breast cancer in a case control study conducted on Japanese Brazilians and non-Japanese Brazilians [Shimada et al., 2009]. The product of CYP3A5 also play an indirect role of inactivation of testosterone. That is the reason that CYP3A5*1 play protective activity of prostate cancer [Vaarala et al., 2008].

A 3/3 homozygous genotype and substantial raise CYP3A5*3 allele frequency in CML population was detected which showed that the loss of CYP3A5 expression linked with altered allele might be accountable for the buildup of endogenous steroids or xenobiotics in various tissue which might bring genotoxicity that consult the threat for disease vulnerability [21Bethke et al., 2007]. Further, previous studies also reported the same frequencies of CYP3A5*3 variant in together the leukemia and controls [Liu et al., 2002: Balanco et al., 2002: Aplenc et al., 2003: Bajpai et al., 2010] failed to detect significant relationship between CYP3A5 SNP and illness of severe CML patients, but the appearance of CYP3A5 in serious CML patients was strictly linked with the therapeutic result and diagnosis [Shen et al., 2008]. An earlier study published about the prevalence colorectal cancer in Bulgarian population showed no significant association between CYP3A5*3 6986 A>G [rs776746] variations and incidence this cancer [Petrova et al., 2007]. Similarly no significant association was found between the Finnish population and CYP3A5*1 or *3 variants, and risk of prostate cancer [Markku et al., 2008].

Our metaanalysis has several limitations. The studies included in this analysis and Cases and controls are also not too much. Further detailed information is needed to find the association between CYP3A5*3 SNP rs776746 and cancers risk and our result might be limited.

In conclusion no significant association was found between CYP3A5*3 SNP rs776746 and the risk of developing different types of cancers.

Acknowledgment

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Reference:

Aplenc R, Glatfelter W, Han P. CYP3A genotypes and treatment response in paediatric acute lymphoblastic leukemia. Br J Haematol. 2003;pp 122, 240-4

Bajpai P, Tripathi AK, Agrawal D. Genetic polymorphism of CYP3A5 in Indian chronic myeloid leukemia patients. Mol Cell Biochem. 2010; pp 336, 49-54

Bethke L, Webb E, Sellick G, Rudd M, Penegar S, Withey L et al. Polymorphisms in the cytochrome P450 genes CYP1A2, CYP1B1, CYP3A4, CYP3A5, CYP11A1, CYP17A1, CYP19A1 and colorectal cancer risk. BMC Cancer. 2007 Jul 5; pp 7:123.

Blanco JG, Edick MJ, Hancock ML. Genetic polymorphisms in CYP3A5, CYP3A4 and NQO1 in children who developed therapy-related myeloid malignancies. Pharmacogenetics. 2002; pp 12, 605-11.

Brooks JD, Teraoka SN, Malone KE. WECARE Study Collaborative Group, Bernstein JL, Figueiredo JC. Variants in tamoxifen metabolizing genes: a case-control study of contralateral breast cancer risk in the WECARE study. Int J Mol Epidemiol Genet. 2013;4(1): pp 35–48.

Coto E, Tavira B. Mar Frequencies of poor metabolizers of cytochromeetal. Functional polymorphisms in the CYP3A4, CYP3A5, and CYP21A2 genes=in the risk for hypertension in pregnancy. Biochem Biophys Res Commun. 2010; pp 397: 576-9.

Desta Z, Ward BA, Soukhova NV, Flockhart DA. Comprehensive evaluation of tamoxifen sequential biotransformation by the human cytochrome P450 system in vitro: prominent roles for CYP3A and CYP2D6. J Pharmacol Exp Ther. 2004; pp 310(3):1062–1075.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomized trials. Lancet. 2005; pp 365(9472):1687–1717.

Feng WX, Fang Liu, Yi Gu, Wei-Wei J, Lin S, Jing X, et al. Functional polymorphisms inCYP2C19 & CYP3A5 genes associated with decreased susceptibility for paediatric tuberculosis. Indian J Med Res 135, May 2012; pp 642-649.

Goetz MP, Schaid DJ, Wickerham DL, et al. Evaluation of CYP2D6 and efficacy of tamoxifen and raloxifene in women treated for breast cancer chemoprevention: results from the NSABP P1 and P2 clinical trials. Clin Cancer Res. 2011; pp 17(21):6944–6951.

Hesselink DA, van Schaik RH, van der Heiden IP. Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus. Clin Pharmacol Ther. 2003; pp 74(3):245–254.

Hoskins JM, Carey LA, McLeod HL. CYP2D6 and tamoxifen: DNA matters in breast cancer. Nat Rev Cancer. 2009; pp 9(8):576–586.
Iusuf D, Teunissen SF, Wagenaar E, Rosing H, Beijnen JH, Schinkel AP-glycoprotein (ABCB1) transports the primary active tamoxifemetabolites endoxifen and 4-hydroxytamoxifen, and restricts their brapenetration. J Pharmacol Exp Ther. 2011; pp 337(3):710–717.
Kuehl P, Zhang J, Lin Y, Lamba J, Assem M, Schuetz J et al. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. Nat Genet 2001; pp 27:383–91.
Lee, S.J., Usmani, K.A., Chanas, B., Ghanayem, B., Xi T., Hodgson, E et al. Genetic findings and functional studies of human CYP3A5 single nucleotide polymorphisms in different ethnic groups. Pharmacogenetics. 2003; pp 13, 461–472.
Liu TC, Lin SF, Chen TP. Polymorphism analysis of CYP3A5 in myeloid leukemia. Oncol Rep. 2002; pp 9, 327-9.
Makeeva O., Stepanov V., Puzyrev V., Goldstein D.B., Grossman, I. Global pharmacogenetics: genetic substructure of Eurasian populations and its effect on variants of drug-metabolizing enzymes. Pharmacogenomics. 2008; pp 847–868.
Mani C, Gelboin HV, Park SS, Pearce R, Parkinson A. Kupfer Metabolism of the antimammary cancer antiestrogenic agent tamoxifen.Cytochrome P-450-catalyzed N-demethylation and 4 hydroxylatioDrug Metab Dispos. 1993; pp 21(4):645–656.
Markku V, Mattila H, Ohtonen P, Tammela TL, Paavonen TK, Schleutker J. The interaction of CYP3A5 polymorphisms along the androgen metabolism pathway in prostate cancer. Int J Cancer. 2008 Jun 1;pp 122 (11):2511-6. Doi: 10.1002/ijc.23425.
Petrova DT, Yaramovb N, Toshevb S. Genotyping of CYP3A5 polymorphisms among Bulgarian patients with sporadic colorectal cancer and controls. Onkologie. 2007; pp 30, 559-63.
Plummer SJ, David VC, Pamela LP, Anthony PC, Graham C and John SW. Prostate Cancer Genotypes, Haplotypes, and Risk of CYP3A5 and CYP3A4. Cancer Epidemiol Biomarkers Prev; 2003; pp 12:928-932.
Rae JM, Drury S, Hayes DF. ATAC trialists. CYP2D6 and UGT2B7 genotype and risk of recurrence in tamoxifen-treated breast cancer patients. J Natl Cancer Inst. 2012; pp 104(6):452–460.
Rao NG. Manjula K. Sailaja D, Surekha D, Raghunadharao, Senthil R et al. Association of CYP3A5*3 polymorphism with development of acute leukemia. Indian Journal of Human Genetics. 2011; pp (17) 3

Regan MM, Leyland-Jones B, Bouzyk M. Breast International Group (BIG) 1-98 Collaborative Group. CYP2D6 genotype and tamoxifen response in postmenopausal women with endocrine responsive breast cancer: the breast international group 1-98 trial. J Natl Cancer Inst. 2012; pp 104(6):441–451.

Roy, JN., Lajoie J., Zijenah LS., Barama A., Poirier C., Ward B.J et al. CYP3A5 genetic polymorphisms in different ethnic populations. Drug Metab. Dispos. 2005; pp 33, 884–887.

Sailaja, K, D Surekha, D Nageswara Rao, D Raghunadha Rao, S Vishnupriya. Analysis of CYP3A5*3 and CYP3A5*6 Gene Polymorphisms in Indian Chronic Myeloid Leukemia Patients. *Asian Pacific J Cancer Prev.* 2010; pp 11, 781-784

Shen LJ, Chen FY, Wang T. Polymorphisms of CYP3A5 gene in acute leukemia patients and their role in chemotherapy and prognosis. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2008; pp 16, 26-30.

Shimada N, Motoki I, Yoshio K, Shiro Y, Hiroshi O, Ritsu K et al. Genetic polymorphisms in estrogen metabolism and breast cancer risk in case–control studies in Japanese, Japanese Brazilians and non-Japanese Brazilians. Journal of Human Genetics. 2009; pp 54, 209–215

Surekha D, Sailaja K, Nageswara RD, Padma T, Raghunadharao D and Vishnupriya S. Association of CYP3A5*3 and CYP3A5*6 Polymorphisms with Breast Cancer Risk. Biotechnology and Pharmacy. 2009; pp 3 (2) Europe PubMed center.

Vaarala M H., Mattila H., Ohtonen P., Tammela T L., Paavonen TK., Schleutker J. The interaction of CYP3A5 polymorphisms along the androgen metabolism pathway in prostate cancer. Int. J. Cancer. 2008; pp 122, 2511–2516.