Original Article

Association of CYP1A1 M2 (A2455G) Polymorphism with Susceptibility to Breast Cancer in Mazandaran Province, Northern Iran: A Case–control Study

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Abstract

Background: Breast cancer is one of the most frequent women malignancies in the world. The cytochrome P450 1A1 (*CYP1A1*) is a key enzyme in xenobiotics metabolism. Moreover, CYP1A1 plays a critical role in the etiology of breast cancer by involving in 2-hydroxylation of estrogen. Therefore, single-nucleotide polymorphisms (SNPs) of its coding gene have been verified to be important in cancer susceptibility. The aim of the study was to evaluate the association of *CYP1A1* M2 (A2455G) includes rs1048943 of this SNP polymorphism with the risk of breast cancer in Mazandaran province. **Methods:** Ninety-six breast cancer patients with known clinicopathological characters and 110 healthy women as control were genotyped for *CYP1A1* M2 polymorphisms by the restriction fragment length polymorphism technique. **Results:** The analysis of *CYP1A1* gene (polymorphism M2) showed that the frequency of homozygous wild genotypes (AA), heterozygous (AG), and mutant genotype (GG) in the patient group, respectively, 78%, 22%, and 0%, and also the frequency of genotypes AA, AG, and GG in healthy included 82%, 16%, and 2%, respectively. Statistical analysis by Logistic regression model at $P < 0.05$ showed no significant correlation between polymorphisms in *CYP*1A1M2 and breast cancer risk (odds ratio = 0.84, confidence interval = 0.33–2.17). **Conclusions:** The results indicated that the M2 allelic genotypes were significantly associated neither with breast cancer risk nor with clinicopathological characteristics in Mazandaran province.

Keywords: *Breast neoplasms, cytochrome P-450, Iran, polymorphism, restriction fragment length*

Introduction

Breast cancer is one of the main causes of cancer death among women. In 2012, it was responsible for the deaths of 522,000 women worldwide.[1] The results of the 10-year national cancer registry of Iran show that the breast cancer was the most common type of cancer in Iranian females, accounting for 24.6% of all cancers.[2] Much work on risk factor determination as well as risk factor evaluation on breast cancer has been carried out worldwide. Existing studies have demonstrated that more than 80 genetic variants or single nucleotide polymorphisms (SNPs) are associated with breast cancer risk.[3-6] On the other hand, a growing body of literature has shown that racial-ethnic identity is responsible for breast cancer risk and outcome.[7]

There are racial disparities in Iranian population. The largest of the population of Iran consists of Persians and Kurds, with smaller communities including Gilakis, Mazandaranis, Lurs, Tats, Talysh, and Baloch.[8] The Mazandarani population number is around three million people that are currently one of the main ethnic groups residing in the northern parts of Iran.[9] Mazandaran province is one of the major agricultural areas in Iran. Therefore, pesticides have widely been overused in this province. Following that the entering pesticides into the environment are the reasons for which the rate of cancer is increasing in this province. Despite the fact that these prevalence and modifiable risk factors related to breast cancer have been evaluated in Mazandaran province, no one to the best of our knowledge assessed genetic factors among Mazandarani breast cancer patients.[10,11]

CYP1A1, an enzyme of the cytochrome P450 superfamily, plays an important role in the metabolism of numerous endobiotics and xenobiotics. They profoundly

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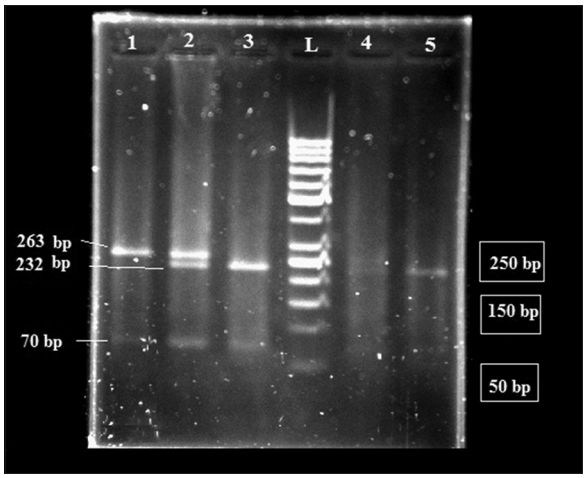

Figure 1: Gel electrophoresis of *CYP1A1*(M2) polymerase chain reaction products after digestion by *NcoI* enzyme. L shows the 50 bp DNA marker, No. 1 is mutant type of *CYP1A1*(M2) polymorphism (GG) (263 and 70 bp), No. 2 and 4 are the heterogeneous type of *CYP1A1*(M2) polymorphism (AG) (263, 232, 70and 31 bp), and No. 3 and 5 are the wild-type (AA) (232, 70and 31 bp) in different study groups

expresses in nonhepatic cells such as breast tissue. The *CYP1A1* gene, located in chromosome 15q22–q24, is 5987-bp long and encodes a 512 amino acid protein. It is a polymorphic gene required in metabolism of steroids and various potentially genotoxic chemicals.[12] Four SNPs in *CYP1A1* gene including M1 (a nucleotide change at T3801 in the 3'-flanking region), M2 (A2455G at exon 7), M3 (T3205C in the 3'-flanking region), and M4 (C2453A at exon 7) are assumed to be associated with breast cancer.[13,14] To date, these SNPs have not been evaluated in Mazandarani population. Hence, in the present case–control study, M2 polymorphism of *CYP1A1* was studied for its association with breast cancer in Mazandarani population.

Methods

Cases and controls

This case–control study was performed on 96 patients and 110 healthy donors, both groups were matched based on gender, age, and ethnicity. The mean age of patient and healthy individuals was 48.21 ± 8.2 years, and 46.27 ± 6.1 years, respectively. Patient samples were confirmed by oncologist and collected at referenced hospitals in Mazandaran province from September 2012 to December 2014. Demographic and clinicopathological data of patients were extracted from their records in hospitals. Cases with unclear properties were excluded from the study. The study was approved by the Ethics Committee of Sari University of Agricultural Sciences and Natural Resources (SANRU) based on the Declaration of Helsinki and its later amendments or comparable ethical standards. Patients were informed by a physician, and the protocol was explained to the participants, who gave their consent before inclusion.

DNA extraction

Five ml of peripheral blood was collected in ethylenediaminetetraacetic acid-containing tubes from both patients and control group, and DNA was extracted from blood lymphocytes by proteinase-K/SDS digestion and phenol-chloroform extraction as described elsewhere.[15] DNA concentration and purity of each sample were measured by ultraviolet spectrophotometer, and its purity was checked through agarose gel electrophoresis, then extraction was routinely stored at −20°C.

CYP1A1 (NcoI) genotyping (*CYP1A1 m2*)

An isoleucine 462 valine (rs1048943) substitution in exon7, which results in a loss of *NcoI* restriction site at the heme binding region, was determined by polymerase chain reaction (PCR) and restriction fragment length polymorphism. A 333 bp fragments containing T/C allele was amplified using forward: 5′-GAAAGGCTGGGTCCACCCTCT-3′ and reverse: 5′-CCAGGAAGAGAAAGACCTCCCAGCGGGCCA-3′primers. PCR amplification was performed in a 25 µl reaction containing 1X PCR buffer, 100 ng genomic DNA, 1.5 mM $MgCl_2$, 0.3 mM each forward and reverse primers, 0.2 µM dNTPs, and 2.5 U *taq* DNA polymerase (10 u/µl). The cycling conditions including an initial denaturation at 94°C for 3 min, 31 cycles of denaturation at 94°C for 40 s, annealing at 65°C for 30 s, extension at 72°C for 40 s, and a final extension at 72°C for 7 min. Products were analyzed by electrophoresis at 1.5% agarose gel and visualized by ethidium bromide staining. The amplified fragment (333 bp) was digested by 1 U *Nco*I restriction enzyme (ThermoFisher, USA) at 37°C for 2 h and analyzed on 2.5% agarose gel [Figure 1]. Wild-type DNA is cut by enzyme *NcoI* resulting in fragments 232 and 30 bp. The DNA carrying the variant is not cut resulting in 263 bp band.

Statistical analysis

All of the data were analyzed by SAS 9.1 statistics software (The SAS Institute, NC, USA). $P < 0.05$ was considered as statistical significance. The genotype and allele frequency of *CYP1A1* M2 genotype were tested for Hardy–Weinberg equilibrium for both patient and control group using Chi-square test. Odds ratio (OR), confidence intervals (CIs), and *P* value were calculated to estimate the association between risk of breast cancer or clinicopathological data and genotypes, using unconditional logistic regression. The OR was adjusted for potential confounding factor including age.

Results

Demographic and clinicopathological data of patients

The study performed on 96 patients and 110 control with known demographic and clinicopathological data which are shown in Table 1. The Student's *t*-test showed

no significant difference between two groups (patients and control) in some demographic data such as smoking and menopause ($P > 0.05$). Despite the importance role of family history in disease occurrence, only nine patients (10%) had a positive history.

The *CYP1A1* genotype distribution

Analysis of the results of polymorphism M2 showed that the frequency of wild homozygous (AA), heterozygous (AG) and homozygous mutant (GG) for polymorphism M2 in the patient group, was, respectively, 78%, 22%, and 0%in the control group, respectively, 82%, 16%, and 2%. The frequency of allele A and G were 89% and 11% in patients group, and 90% and 10% in control group. The Chi-square test showed that there is no association between genotypes in healthy and patients group ($P = 0.31$). The logistic regression model yielded no significant correlation between M2 polymorphism and breast cancer risk (OR = 0.74, CI = 0.33–2.17 and $P = 0.72$) [Table 2].

Table 1: The demographic and clinicopathological characteristics of patients

Clinicopathological variables	Number of the patient (%)
Age	
≤45	42 (45.6)
>45	50 (54.4)
Menopause status	
Positive	38 (42)
Negative	53 (58)
Grade	
I	3 (5)
II	53 (60)
III	31 (35)
TNM staging	
I-II	38 (45)
III-IV	47 (55)
Family history	
Positive	9 (10)
Negative	76 (90)
Smoking	
Positive	6 (7)
Negative	80 (93)
Cancer type	
Ductal carcinoma	77 (83)
Lobular carcinoma	15 (16)

TNM=Tumor/node/metastasis

Association between *CYP1A1* M2 polymorphism and known clinicopathological variables

The association between different genotypes of *CYP1A1* gene and clinicopathological features is listed in Table 3. Results showed that there is no significant association between the mutant genotypes and these characteristics including age at diagnosis ($P = 0.56$), type of cancer ($P = 0.69$), menopause ($P = 0.20$), grade ($P = 0.72$), stage ($P = 0.65$), smoking ($P = 0.95$), and family history ($P = 0.90$).

Discussion

In the present molecular epidemiological study, we attempted to find the association between *CYP1A1* M2 polymorphism and the risk of breast cancer and clinicopathological features in Mazandaran Province, Iranian population. Our results showed the mean age of females with breast cancer was 48.2 years. This finding is agreement with previous surveys by Sadjadi *et al*. in 2009 and Harirchi and *et al*. in 2011.[16,17] Their results revealed that the mean age of breast cancer on the Iranian population is between 47 and 49 years. Furthermore, in a meta-analysis study, in which 52 studies with 332,999 breast cancer patients were included, the average age of Iranian patients estimated 48.59 years.[18] The major of the epidemiological finding confirmed that mean age of breast cancer in Iranian population is one decade lower than Western countries.[19,20] Moreover, pathological features showed that most of the cases were diagnosed with an advanced stage (Stage III and IV) (55%). Our experiments were in lined with previous findings by Harirchi *et al*.[21] Apparently, the leading cause of this issue is lack of systematic screening programs for early detection of breast cancer in developing country including Iran.

Cancer investigations have been progressing toward the toxicogenomics studies examining the dynamic interactions between a specific individual genotype and different carcinogenic, teratogenic, and other xenobiotics. Cytochrome P450 superfamily is the major part of PhaseI biotransformation of xenobiotics. *CYP1A1* is a member of this family expressed in extrahepatic organs, especially in breast tissues.[22,23] The *CYP1A1* Ile/Val polymorphism (M2) is a result of an A/G change in exon 7, causing the amino acid exchange (462 Ile/Val) in the heme-binding region of the

Table 2: Distribution of *CYP*1A1 gene polymorphisms and breast cancer risk - as mentioned, compare the distribution by chi test

Polymorphism	Genotype	Number of subjects (%)		Nonadjusted[a]		Adjusted[b]		CI
		Case	Control	*P*	OR	*P*	OR	
M2	AA	75 (78)	91 (82)	-	1	-	1	-
	AG	21 (22)	17 (16)	0.53	0.74	0.72	0.84	0.33-2.17
	GG	0 (0)	2 (2)	0.98	>999.999	0.98	>999.999	<0.001->999.999
	AG + GG	21 (0)	19 (17)	0.41	0.80	0.83	0.906	0.35-2.28

[a]Logistic regression model, nonadjusted, [b]Logistic regression model, adjusted for diagnostic age. OR=Odds ratio, CI=Confidence interval

Table 3: Relationship between *CYP1A1* (M2) polymorphism and known clinicopathological variables

Clinicopathological variables	Genotype (%)		Adjusted[a]		
	AA	AG + GG	*P*	OR	CI
Age					
≤ 45	35 (83)	7 (17)	-	1	-
>45	35 (70)	15 (30)	0.56	0.66	0.16-2.25
Menopause					
Negative	31 (82)	7 (18)	-	1	-
Positive	33 (62)	20 (37)	0.20	4.89	0.42-5.71
Grade					
I-II	40 (71)	17 (29)	-	1	-
III	23 (75)	8 (25)	0.72	1.31	0.28-6.06
TNM staging					
I-II	27 (72)	11 (28)	-	1	-
III-IV	36 (77)	11 (23)	0.65	1.39	0.32-5.93
Family history					
Negative	53 (70)	23 (30)	-	1	-
Positive	6 (67)	3 (33)	0.90	1.16	0.10-13.48
Smoking					
Negative	56 (70)	24 (30)	-	1	-
Positive	6 (100)	0 (0)	0.95	>0.001	<0.001-> 999.999
Cancer type					
Ductal carcinoma (IDC)	65 (84)	12 (16)	-	1	-
Lobular carcinoma (ILC)	10 (67)	5 (33)	0.69	0.72	0.23-5.98

[a]Logistic regression model adjusted for diagnostic age. IDC=Invasive ductal carcinoma, ILC=Invasive lobular carcinoma, OR=Odds ratio, CI=Confidence interval

protein. The Val allele variant demonstrates an approximately 2-fold higher catalytic enzyme activity than Ile form.[24] Many studies have shown the association between *CYP1A1* M2 polymorphism and risk of lung cancer,[25] ovarian cancer,[26] colorectal cancer,[27] esophageal cancer,[28] and cervical cancer.[29] Statistical analysis by logistic regression model showed no statistical relationship between M2 genotype and breast cancer risk ($P = 0.72$ and OR = 0.84). Our results are in line with some previous reports in different population like Indian,[30] Danish,[31] and American,[32] and different Iranian ethnic like Gilaki[33] and Fars.[34] Their finding revealed that there is no correlation between polymorphism M2 of *CYP1A1* gene and breast cancer risk. Contrary to our results, some reports pointed out that there is a positive association between this polymorphism and risk of breast cancer.[14,35,36] Noticeably, Sergentanis and Economopoulos conducted a meta-analysis on Caucasian, Chinese, and African populations, as well as on premenopausal and postmenopausal women to examine the correlation of *CYP1A1* M2 polymorphism with breast cancer. The results demonstrated mutant genotype (GG) elevate risk of breast cancer and their results suggested that this polymorphism would be a good marker for prediction of breast cancer in these populations.[37] On the other hands, some lectures showed that GG genotype is associated with a trend of reduced breast cancer risk.[38,39] Furthermore, there was no significant association between clinicopathological features such as age, histological type, grade, and stage of tumors with M2 genotype. There are numerous conflicting epidemiological studies addressing correlations between the polymorphism and breast cancer development. The answer of these disagreements is in interaction between difference intrinsic and extrinsic factors. Intrinsic factors such as genetic variation and extrinsic factors are included ethnic difference, diet, geographical variation, and environmental exposures. The difference in genomic structure in ethnic groups can play a significant role on the rate of incidence and mortality among various cancers in populations. Therefore, a complex investigation in different ethnic groups is needed to achieve a validation answer for the association of genomic variation and breast cancer risk.

Conclusions

In summary, the results of present study suggest that CYP1A1 M2 polymorphism alone does not play a critical role in the breast cancer risk in Mazandaran province. Further studies, which take larger group from different ethnics, will need to clarify this issue.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, *et al.* Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.
2. Jazayeri SB, Saadat S, Ramezani R, Kaviani A. Incidence of primary breast cancer in Iran: Ten-year national cancer registry data report. Cancer Epidemiol 2015;39:519-27.
3. Easton DF, Pooley KA, Dunning AM, Pharoah PD, Thompson D, Ballinger DG, *et al.* Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 2007;447:1087-93.
4. Garcia-Closas M, Couch FJ, Lindstrom S, Michailidou K, Schmidt MK, Brook MN, *et al.* Genome-wide association studies identify four ER negative-specific breast cancer risk loci. Nat Genet 2013;45:392-8, 398e1-2.
5. Ghoussaini M, Fletcher O, Michailidou K, Turnbull C, Schmidt MK, Dicks E, *et al.* Genome-wide association analysis identifies three new breast cancer susceptibility loci. Nat Genet 2012;44:312-8.
6. Michailidou K, Hall P, Gonzalez-Neira A, Ghoussaini M, Dennis J, Milne RL, *et al.* Large-scale genotyping identifies 41 new loci associated with breast cancer risk. Nat Genet 2013;45:353-61, 361e1-2.
7. Davis MB, Newman LA. Breast cancer disparities: How can we leverage genomics to improve outcomes? Surg Oncol Clin N Am 2018;27:217-34.
8. Abrahamian E. A History of Modern Iran. New York: Cambridge University Press; 2008.
9. Nasidze I, Quinque D, Rahmani M, Alemohamad SA, Stoneking M. Concomitant replacement of language and mtDNA in South Caspian populations of Iran. Curr Biol 2006;16:668-73.
10. Naghibi SA, Shojaizadeh D, Montazeri A, Yazdani Cherati J. Epidemiology of breast cancer in mazandaran province, 2009-2010. J Mazandaran Univ Med Sci 2013;23:112-9.
11. Naieni KH, Ardalan A, Mahmoodi M, Motevalian A, Yahyapoor Y, Yazdizadeh B, *et al.* Risk factors of breast cancer in North of Iran: A case-control in mazandaran province. Asian Pac J Cancer Prev 2007;8:395-8.
12. Zhou SF, Liu JP, Chowbay B. Polymorphism of human cytochrome P450 enzymes and its clinical impact. Drug Metab Rev 2009;41:89-295.
13. Crofts F, Taioli E, Trachman J, Cosma GN, Currie D, Toniolo P, *et al.* Functional significance of different human CYP1A1 genotypes. Carcinogenesis 1994;15:2961-3.
14. Akhtar S, Mahjabeen I, Akram Z, Kayani MA. CYP1A1 and GSTP1 gene variations in breast cancer: A systematic review and case-control study. Fam Cancer 2016;15:201-14.
15. Sambrook J, Fritsch E, Maniatis T. Molecular Cloning: A Laboratory Manual. Vol. 9. New York: Cold Spring Harbor Laboratory Press; 1989. p. 14-9.9.
16. Sadjadi A, Nouraie M, Ghorbani A, Alimohammadian M, Malekzadeh R. Epidemiology of breast cancer in the islamic republic of Iran: First results from a population-based cancer registry. East Mediterr Health J 2009;15:1426-31.
17. Harirchi I, Kolahdoozan S, Karbakhsh M, Chegini N, Mohseni SM, Montazeri A, *et al.* Twenty years of breast cancer in Iran: Downstaging without a formal screening program. Ann Oncol 2011;22:93-7.
18. Yekta Kooshali M, Esmaeilpour-Bandboni M, Sharemi S, Alipour Z. Survival rate and average age of the patients with breast cancer in Iran: Systematic review and meta-analysis. J Babol Univ Med Sci 2016;18:29-40.
19. Harirchi I, Karbakhsh M, Kashefi A, Momtahen AJ. Breast cancer in Iran: Results of a multi-center study. Asian Pac J Cancer Prev 2004;5:24-7.
20. Taghavi A, Fazeli Z, Vahedi M, Baghestani AR, Pourhoseingholi A, Barzegar F, *et al.* Increased trend of breast cancer mortality in Iran. Asian Pac J Cancer Prev 2012;13:367-70.
21. Harirchi I, Ghaemmaghami F, Karbakhsh M, Moghimi R, Mazaherie H. Patient delay in women presenting with advanced breast cancer: An Iranian study. Public Health 2005;119:885-91.
22. Bozina N, Bradamante V, Lovrić M. Genetic polymorphism of metabolic enzymes P450 (CYP) as a susceptibility factor for drug response, toxicity, and cancer risk. Arh Hig Rada Toksikol 2009;60:217-42.
23. Schmidt CW. Toxicogenomics: An emerging discipline. Environ Health Perspect 2002;110:A750-5.
24. Moysich KB, Shields PG, Freudenheim JL, Schisterman EF, Vena JE, Kostyniak P, *et al.* Polychlorinated biphenyls, cytochrome P4501A1 polymorphism, and postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev 1999;8:41-4.
25. Zhan P, Wang Q, Qian Q, Wei SZ, Yu LK. CYP1A1 mspI and exon7 gene polymorphisms and lung cancer risk: An updated meta-analysis and review. J Exp Clin Cancer Res 2011;30:99.
26. Aktas D, Guney I, Alikasifoglu M, Yüce K, Tuncbilek E, Ayhan A, *et al.* CYP1A1 gene polymorphism and risk of epithelial ovarian neoplasm. Gynecol Oncol 2002;86:124-8.
27. Zheng Y, Wang JJ, Sun L, Li HL. Association between CYP1A1 polymorphism and colorectal cancer risk: A meta-analysis. Mol Biol Rep 2012;39:3533-40.
28. Zhuo WL, Zhang YS, Wang Y, Zhuo XL, Zhu B, Cai L, *et al.* Association studies of CYP1A1 and GSTM1 polymorphisms with esophageal cancer risk: Evidence-based meta-analyses. Arch Med Res 2009;40:169-79.
29. Sergentanis TN, Economopoulos KP, Choussein S, Vlahos NF. Cytochrome P450 1A1 (CYP1A1) gene polymorphisms and cervical cancer risk: A meta-analysis. Mol Biol Rep 2012;39:6647-54.
30. Singh V, Rastogi N, Sinha A, Kumar A, Mathur N, Singh MP, *et al.* A study on the association of cytochrome-P450 1A1 polymorphism and breast cancer risk in North Indian women. Breast Cancer Res Treat 2007;101:73-81.
31. Ghisari M, Long M, Røge DM, Olsen J, Bonefeld-Jørgensen EC. Polymorphism in xenobiotic and estrogen metabolizing genes, exposure to perfluorinated compounds and subsequent breast cancer risk: A nested case-control study in the danish national birth cohort. Environ Res 2017;154:325-33.
32. Li Y, Millikan RC, Bell DA, Cui L, Tse CK, Newman B, *et al.* Cigarette smoking, cytochrome P4501A1 polymorphisms, and breast cancer among African-American and white women. Breast Cancer Res 2004;6:R460-73.
33. Balkhi S, Mashayekhi F. CYP1A1 gene polymorphism and breast cancer. Ann Mil Health Sci Res 2017;15:1-4.
34. Farzaneh F, Noghabaei G, Barouti E, Pouresmaili F, Jamshidi J, Fazeli A, *et al.* Analysis of CYP17, CYP19 and CYP1A1 gene polymorphisms in Iranian women with breast cancer. Asian Pac J Cancer Prev 2016;17:23-6.
35. Miyoshi Y, Takahashi Y, Egawa C, Noguchi S. Breast cancer risk

associated with CYP1A1 genetic polymorphisms in Japanese women. Breast J 2002;8:209-15.
36. Surekha D, Sailaja K, Rao DN, Padma T, Raghunadharao D, Vishnupriya S, *et al.* Association of CYP1A1 * 2 polymorphisms with breast cancer risk: A case control study. Indian J Med Sci 2009;63:13-20.
37. Sergentanis TN, Economopoulos KP. Four polymorphisms in cytochrome P450 1A1 (CYP1A1) gene and breast cancer risk: A meta-analysis. Breast Cancer Res Treat 2010;122:459-69.
38. Chen C, Huang Y, Li Y, Mao Y, Xie Y. Cytochrome P450 1A1 (CYP1A1) T3801C and A2455G polymorphisms in breast cancer risk: A meta-analysis. J Hum Genet 2007;52:423-35.
39. García-Martínez A, Gamboa-Loira B, Tejero ME, Sierra-Santoyo A, Cebrián ME, López-Carrillo L, *et al.* CYP1A1, CYP1B1, GSTM1 and GSTT1 genetic variants and breast cancer risk in mexican women. Salud Publica Mex 2017;59:540-7.