RESEARCH ARTICLE

No Association of Cytochrome P450-1B1 Gene Polymorphisms with Risk of Breast Cancer: an Egyptian Study

Mona H Ibrahim[1], Reham A Rashed[2], Naglaa M Hassan[2], Nevin M Al-azhary[3,2]*, Asmaa I Salama[4], Marwa N Mostafa[5]

Abstract

It is thought that population characteristics of breast cancer may be due to a variation in the frequency of different alleles of genes such as *CYP1B1*. We aimed to determine the association of *CYP1B1* polymorphisms in 200 breast cancer cases and 40 controls by PCR-RFLP. Frequencies were assessed with clinical and risk factors in Egyptian patients. The genotype LV and the Leu allele frequencies for patients and controls were 42.9% and 50%, and 52.9% and 53.3%, respectively), with no significant differences observed (P values = 0.8 and 0.6, respectively). There was also no significant association between genotypes and any risk factors for cases (P>0.05) except laterality and metastasis of the tumor (P values=0.006 and 0.06, respectively). The *CYP1B1* polymorphism Val432Leu was not associated with breast cancer in Egypt, but may provide clues for future studies into early detection of the disease.

Keywords: Breast cancer - *CYP1B1* - gene polymorphism - disease association - Egypt

Asian Pac J Cancer Prev, **17 (6)**, 2861-2866

Introduction

Breast cancer remains a major cause of morbidity and mortality in women worldwide (Islamian et al., 2015). Risk of breast cancer is increased by a positive family history of the disease, particularly having one or more affected first-degree relatives, inherited mutations (genetic alterations) in BRCA1 and BRCA2, the best-studied breast cancer susceptibility genes, accounting for about 5-10% of all female breast cancers, an estimated 5-20% of male breast cancers and 15-20% of familial breast cancers. However, these mutations are very rare in the general population (much less than 1%). Scientists now believe that most familial breast cancer is due to the interaction between lifestyle factors and more common variations in the genetic code that confer a small increase in breast cancer risk, although the usefulness of this information to distinguish high-risk women is still under investigation (Sergentanis et al., 2012).

The incidence of breast cancer is rising sharply in many developing countries. Today, more than half of all cases have been diagnosed in developing countries (Shulman et al., 2010; Ajtkhozhina et al., 2011).

Increasing age is the most important risk factor for breast cancer; other factors that contribute to the high incidence of breast cancer include family health history, unsuitable living conditions, atmospheric contamination with high pollution emissions, chronic stress, conditions related to breastfeeding (either unilateral or breastfeeding less than 3 months or over 2 years) (Toleutay et al., 2013; Beysebayev et al., 2015), major inheritance susceptibility (Colditz et al., 2012) and germ-line mutation of many genes (Mavaddat et al., 2011).

Predisposition to cancer is influenced by the genotype for enzymes involved in the activation, inhibition and detoxification of plentiful carcinogenic agents. Polymorphisms of these genes, such as *CYP1B1*, which are involved in estrogen and xenobiotic metabolism, may be an important risk factor of developing breast cancer (Reding et al., 2012). *CYP1B1* is involved in hormonal carcinogenesis by its ability to degrade the metabolism of estradiol to 2- and 4-hydroxyestradiols. Although 2-hydroxyestradiol has little or no carcinogenic activity, 4-hydroxyestradiol (4-OHE2) and estrogen have both been shown to be potent carcinogens in animal models and humans as well as having estrogenic activity (Cavalieri et al., 1997). Besides, the 4-OHE2 catechol metabolite has been found in large quantities of breast cancer tissue (Gehan et al., 2013).

The *CYP1B1* gene is located on chromosome 2p21-p22 and contains three exons, one a noncoding exon, and two introns. The entire coding sequence of the gene,

*[1]Department of Clinical and Chemical Pathology, National Research Center, [2]Department of Clinical Pathology, [4]Department of Pathology, [5]Department of Medical Oncology, National Cancer Institute, Cairo University, Cairo, Egypt, [3]Biochemistry and Molecular Medicine Department, College of Medicine, Taibah University, Al-Madinah Al-Munawwarah, Saudi Arabia *For correspondence: nevin_elazhary@hotmail.com*

however, is contained in exons 2 and 3; exon 3 encodes the heme-binding region of the enzyme. There are two common polymorphisms of *CYP1B1*, in exon 2 (codon 119, Ala→Ser) and exon 3 (codon 432, Val→Leu) (Sassi et al., 2013).

Sequence variations of *CYP1B1* might be related to an increased incidence of breast cancer in some populations. Also, the activity of the enzyme was found to be higher in breast cancer than in its close normal tissue, so it is thought that this enzyme may be employed in the breast cancer pathogenesis (Reding et al., 2012).

Aim of the work: The aim of the present work is to investigate the frequency and possible association of The *CYP1B1* Val432Leu polymorphism and the risk of breast cancer in 200 newly diagnosed Egyptian breast cancer patients compared with 40 benign breast condition (age- and sex-matched) individuals as the control group then assess them with respect to patients' demographics, clinical characteristics and major risk factors (such as estrogen, progesterone receptors level and CA15.3) to detect any possible association with the prognosis and outcome.

Materials and Methods

Study design: This study is a retrospective study.

Patients: This study was carried out on 200 newly diagnosed breast cancer patients who were presented to the Adult Medical Oncology Department, National Cancer Institute (NCI), Cairo University in the period between August 2013 and September 2014, with 40 age- and sex-matched benign breast condition individuals as the control group. Their ages ranged from 20 to 78 years, and a structured questionnaire was used to elicit detailed information about the demographic factors, menstrual history and family history of cancer for each patient.

A written informed consent was approved by the Institutional Review Board (IRB) Ethical Committee of the NCI, which follows the rules of Helsinki IRB, and was obtained from each patient before starting the data collection. For the sake of each patient's privacy, they were assigned code numbers.

Methods: Collection and preservation of the sample:

A 10 ml peripheral blood sample was collected from each participant in EDTA tubes then treated and preserved as cell pellets kept at-20˚C.

Genetic polymorphism analysis: The total genomic DNA was extracted from preserved cell pellets using Pure Link Genomic DNA Kits Cat NO K1820-01, following the standard procedures according to the manufacturer's instructions.

Genetic analysis of *CYP1B1* was identified by polymerase chain reaction amplification and restriction fragment length polymorphism analysis (PCR-RFLP).

According to the sequence of the human *CYP1B1* gene, that was searched through the Gene Bank from the National Center for Biotechnology Information (NCBI). The primer sequence of the desired gene was as follows: 5'TCACTTGCTTTTCTCTCTCC-3' as a forward primer and 5'-AATTTCAGCTTGCCTCTTG-3' as a reverse primer to amplify a 650-bp fragment of exon 3.

The genomic DNAs of patients and controls were used as templates, and each PCR was performed in a GeneAmp PCR System using the Bio Rad system.

The PCR was conducted with a total volume of 50 ul as follows: 2 ul forward primer FR, 2 ul reverse primer RP, 5 ul DNA sample, 16 ul D.W and 25 ul Master Mix. The PCR was performed with 35 cycles of the following temperature condition: 94°C for 1 minute, followed by denaturation at 94°C for 30 seconds, annealing at 60°C for 30 seconds and extension at 72°C for 40 seconds, with a final extension at 72°C for 7 minutes. Each PCR product was subjected to ECO571 (New England Biolabs) restriction enzyme digestion prior to electrophoresis. The DNA fragments were then separated using agarose gel. The allele types were determined as follows: two fragments of 310- and 340-bp for the Leu allele and a single 650-bp fragment for the Val allele.

Statistical methods: Data management and analysis were performed using the Statistical Package for the Social Sciences (SPSS) program version 16. Data were summarized with mean, SD and frequency. A T test was used for analysis of two quantitative data. The chi-square test was used for the analysis of the qualitative data. A one-way ANOVA test was used for analysis of more than two quantitative data followed by a post hoc test for detection of significance.

Results

The mean ages for cases and controls were 51.23± 14.07 and 40.75±13.70,respectively). According to the PCR electrophoresis, allele analysis revealed LL, VV and LV genotypes. The fragments were as follows: The genotype (LL) produced two fragments of 310- and 340-bp, the heterozygous genotype (LV) produced three fragments of 310-, 340- and 650-bp and the homozygous genotype (VV) produced only one fragment of 650-bp. Figure 1

The genotype and allele frequencies for both patients and controls are listed in Table 1.

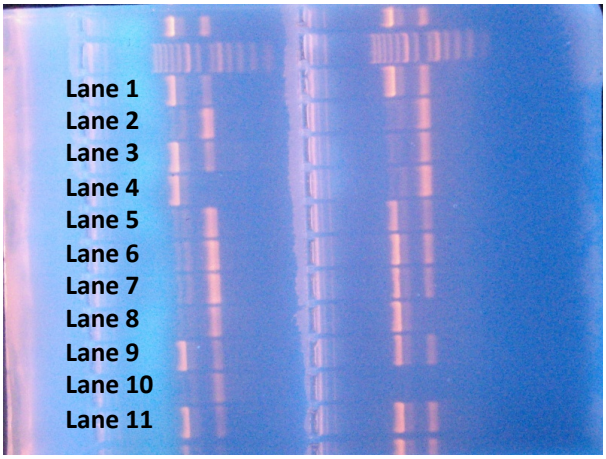

Figure 1. Lane 1, 3, 9, 11 heterozygous for leu allele L / V(310bp+340bp+650bp) Lane 2, 5, 6, 7, 8, 10 homozygous for leu allel L / L (310bp+340bp) Lane 4 homozygous for val allele V / V (650bp)

Table 1. Genotype and Allele Distribution in Breast Cancer Cases and Controls

Group	Cases number	Genotype						Alleles		Allele frequency	
		LV		LL		VV		Leu allele		Val allele	
		(%)	N	(%)	N	(%)	N	%	N	%	N
Patients	200	-42.9	84	-32.7	64	-24.5	48	-52.9	148	-47.1	132
Controls	40	-50	20	-30	12	-20	8	-53.3	32	-46.7	28
p-value							0.8			0.6	
Odds ratio							--			0.981	
95 % C.I.							---			0.445-2.162	

Table 2. Frequency Distribution of Demographic Data of Patients Included in the Study

Variables	N	%
Pathology:		
Invasive duct	182	91
Others	18	9
Genotype:		
LV	84	42.9
LL	64	32.7
VV	48	24.5
Laterality:		
Right	114	57
Left	86	43
Menopause:		
Pre-menopause	86	43
Post-menopause	114	57
Grade:		
2	184	92
3	16	8
Estrogen receptor:		
Negative	30	15
Positive	170	85
Progesterone receptor:		
Negative	40	20
Positive	160	80
Her2neu:		
Negative	152	76
Positive	48	24
Herceptin:		
Negative	80	60.6
Positive	52	39.4
Metastasis:		
Negative	128	81
Positive	30	19

The LV genotype was detected in 84 (42.9%) patients, the LL genotype was detected in 64 (32.7%) patients and the VV genotype was detected in 48 (24.5%) patients. In the control group, the genotype distribution was 20 (50%), 12 (30%) and 8 (20%) for LV, LL and VV genotypes, respectively.

There was no statistically significant difference observed in the genotype distribution between cases and controls (P value=0.8).

In regards to the allelic frequency of *CYP1B1*, the Leu allele was 52.9% for breast cancer patients and 53.3% for controls. The Val allele was 47.1% in the breast cancer cases and 46.7% for controls. There was no statistically significant difference in the distribution of alleles between patients and controls (p-value=0.6).

Tables 2 and 3 summarize the frequency distribution of the demographic data of the patients and its relation to the genotype. Stratification of the patients according to pathology of specimen with duct invasion, laterality (right or left), menopausal status (pre-menopause or post-menopause), genotype (LV, LL, VV) grading and tumor size, major risk factors such as estrogen, progesterone receptors, her2neu, Herceptin and finally metastasis.

In regards to the demographic data in relation to the genotype distribution of the patients, only the laterality of the tumor and metastasis showed a statistically significant difference (p values=0.006 and 0.06, respectively).

The lack of statistically significant associations with other breast cancer risk factors may be attributable to the small sample size of this sub-study.

Table 4 compares the frequency distribution of the different genotypes among postmenopausal and premenopausal patients and controls, showing the following frequencies of LV (38.2%, 33.3%), LL (32.7%, 33.3%) and VV (29.1%, 33.3%) for postmenopausal patients and controls. And LV (48.8%, 57.1%), LL (32.6%, 28.6%) and VV (18.6%, 14.3%) in regards to the premenopausal status showed no statistically significant difference between patients and controls (p value=0.9 for both statuses).

Table 5 summarizes the association between the major risk factors' mean and standard deviation in regards to CA15.3, age, positive nodes and total nodes, with different genotypes showing no statistical difference (p values=0.9, 0.1, 0.20 and 0.10, respectively).

Discussion

Breast cancer is an important public health problem in developing countries. In Africa, this burden is due to lack of knowledge and basic infrastructure for diagnosis, treatment and prevention (Akarolo-Anthony et al., 2010; Sylla and Wild, 2012). The increased incidence rate in Africa is because of the aging and growth of the population as well as the increased prevalence of risk factors associated with economic transition, including smoking, obesity, physical inactivity and reproductive behaviors (Parkin et al., 2010; Jemal et al., 2012).

A greater proportion of breast cancers occur among premenopausal women in Africa as compared to Westernized countries, reflecting unique risk factors and resulting in high associated disability and years of life lost (Soerjomataram et al., 2012).

Despite breast cancer becoming more common, it

Table 3. Genotype Distribution and Frequency of CYP1B1 According to Demographic Characteristics of Patients

Variables	LV genotype		LL genotype		VV genotype		P-value
	N	%	N	%	N	%	
Pathology:							
Invasive duct	76	90.5	62	96.9	40	83.3	0.2
Others	8	9.5	2	3.1	8	16.7	
Laterality:							
Right	62	73.8	24	63.1	24	50	0.006*
Left	22	26.2	14	36.8	24	50	
Grade:							
2	82	97.6	56	87.5	42	87.5	0.2
3	2	2.4	8	12.5	6	12.5	
Tumor size:							
2	50	59.5	52	81.2	32	66.7	0.3
3	32	38.1	12	18.8	16	33.3	
4	2	2.4	0	0	0	0	
Estrogen receptor:							
Negative	14	16.7	4	6.2	10	20.8	0.3
Positive	70	83.3	60	93.8	38	79.2	
Progesterone receptor:							
Negative	14	16.7	14	21.9	10	20.8	0.8
Positive	70	83.3	50	78.1	38	79.2	
Her2neu:							
Negative	62	73.8	52	81.2	36	75	0.7
Positive	22	26.2	12	18.8	12	25	
Herceptin:							
Negative	34	65.4	26	68.4	12	50	0.6
Positive	18	34.6	12	31.6	12	50	
Metastasis:							
Negative	46	69.7	46	92	34	89.5	0.06*
Positive	20	30.3	4	8	4	10.5	
Menopause:							
Pre-menopause	42	50	28	43.8	16	33.3	0.4
Post-menopause	42	50	36	56.2	32	66.7	

*Significant

Table 4. Comparison between Postmenopausal and Premenopausal Status of Patients in Regards to Genotype Distribution

Postmenopausal	Patients		Controls		P-value	Odds ratio	95 % C.I.
	N	%	N	%			
Genotype:							
LV	42	38.2	4	33.3	0.9	--	--
LL	36	32.7	4	33.3			
VV	32	29.1	4	33.3			
Premenopausal							
Genotype:							
LV	42	48.8	16	57.1	0.9	--	--
LL	28	32.6	8	28.6			
VV	16	18.6	4	14.3			

*Odds ratios could not be determined due to missing values in some cells.

Table 5. Association of Important Risk Factors to Genotype

Variables	LV		LL		VV		P-value
	Mean	SD	Mean	SD	Mean	SD	
CA153	28.58	25.07	27.7	24.8	25.62	26.08	0.9
Age	47.79	12.77	53.06	15.51	54.13	13.94	0.1
Positive node	5.36	6.95	1.94	3.28	3.6	4.01	0.2
Total node	12.68	8.53	13.6	10.02	19.8	8.72	0.1

*Significant $P < 0.05$

has a poor prognosis, and it is a disease with distinctive phenotypic and genotypic characterization in different ethnic/population groups may be due to variation in the frequency of different polymorphic alleles of genes such as (*CYP1B1*), and yet little is known about modifiable risk factors. Therefore, a focus is needed on identifying risk factors that may be amenable to intervention and that could lead to earlier access to care and improved survival.

Cytochrome P450 1B1 (*CYP1B1*), the predominant member of the CYP1 family, is a key enzyme in the production of potentially carcinogenic estrogen metabolites and the activation of environmental carcinogens. It is expressed in normal breast tissue as well as in breast cancer (Bailey et al., 1998).

Due to the important role of *CYP1B1* in mammary estrogen/carcinogen metabolism, this study examined the *CYP1B1* gene polymorphism to evaluate its possible role in the risk of breast cancer among Egyptian women.

Previous studies revealed an association between *CYP1B1* gene polymorphism and breast or lung cancer incidence (Watanabe et al., 2000). They stated that the inter-individual differences in activation of pro-carcinogens or metabolism of estrogen originating from genetic polymorphisms of the human *CYP1B1* gene may contribute to the susceptibility to human cancers. However, no sufficient data were obtained about the pathogenic role of this gene polymorphism in breast cancer tendency in the Egyptian population.

Reports from other investigations performed in postmenopausal Swedish women, with special emphasis on long-term menopausal hormone users, showed controversial results, specifically in a large population-based case-control study conducted by (Rylander-Rudqvist et al., 2003). In summary, their results strongly indicated that the studied *CYP1B1* gene polymorphisms do not influence overall breast cancer risk overall but may modify the risk after long-term menopausal hormone use.

We found no differences in the frequencies between genotype of patients and controls included in the study (P value=0.8). In regards to the allelic frequency of CYP1B, the Leu allele was 52.9% for patients and 53.3% for controls. The Val allele was 47.1% in patients and 46.7% for controls. There was no statistically significant difference in the distribution of alleles between patients and controls (P=0.6).

In our matched case-control study, we focused on the *CYP1B1*P450 polymorphism and its relation to several risk factors in breast cancer patients. No statistically significant difference was found between any of the risk factors and breast cancer. This is in accordance with a population-based case-control study conducted in Shanghai (Wen et al., 2005) to assess the association of breast cancer risk with *CYP1B1* and COMT polymorphisms. They found that neither the frequency of the *CYP1B1*and COMT alleles nor the estimated frequencies of *CYP1B1* haplotypes were significantly different between cases and controls. No overall associations of breast cancer risk were found with any of the cytochrome P450 1B1 and catechol-O-methyl-transferase genetic polymorphisms and breast cancer risk in Chinese women.

In our study, we observed that women who carried the VV genotype in *CYP1B1* were less likely to have estrogen receptor-positive breast cancer than those who carried the LL genotype. This result is not consistent with the finding of the previously mentioned study (Wen et al., 2005), but neither study showed any statistical significance (p values=0.3 and 0.33, respectively). However, their study showed that the women who carried one copy of the variant allele in *CYP1B1* codons 48 (P value=0.033) or 119 (P value=0.012) were less likely to have ER-positive breast cancer than those who were homozygous for the corresponding wild-type alleles. The relation between ER and the *CYP1B1* codon 432 and the COMT was not significant, nor was the relation between PR and the *CYP1B1* and COMT genotypes.

Estrogen unopposed by progestin is a major contributing factor in endometrial carcinogenesis. *CYP1B1* is responsible for the 4-hydroxylation of estrogen, may be important in endometrial cancer etiology as *CYP1B1* is an estrogen eliminator and may also form potentially genotoxic estrogen metabolites. So, in another two studies carried out by (Rylander et al., 2003; Rylander-Rudqvist et al., 2004), they investigated the *CYP1B1* genotype in association with endometrial cancer risk in the same population. They similarly found no evidence for an overall association between the *CYP1B1* genotype and endometrial cancer risk among Swedish postmenopausal women, nor was there any clear indication of gene-environment interaction.

In support of our study, (Bailey et al., 1998) in two previous studies examined the *CYP1B1* gene to determine whether genetic differences could account for inter-individual differences in breast cancer risk. They focused on exon 3, as it encodes the catalytically important heme-binding domain of the enzyme, and discovered three polymorphisms: m1, m2 and m3. To determine whether the polymorphic *CYP1B1* alleles hold implications as potential breast cancer risk factors, they compared the *CYP1B1* genotypes in 164 Caucasian and 59 African American breast cancer cases with those in age-, race-, and frequency-matched controls. Odds ratio calculations failed to show any significant association between any of the genotypes and breast cancer. Because *CYP1B1* is known to be involved in mammary estrogen metabolism, they investigated whether the estrogen receptor status is influenced by the *CYP1B1* genotypes. Caucasian patients with the m1 Val/Val genotype have a significantly higher percentage of estrogen receptor-positive (P=0.02) and progesterone receptor-positive breast cancers (P=0.003). There was no correlation with the m2 genotypes. These data suggested that the *CYP1B1* polymorphisms in exon 3 are not associated with increased breast cancer risk, but that the m1 polymorphism may be functionally important for steroid receptor expression in breast cancer of Caucasian patients. In Caucasians and African Americans breast cancer with CYPIA1, GSTM1 and GSTT1 polymorphisms are functionally important (Bailey et al., 1998).

The data obtained from the present study were also supported by (Lee et al., 2003), who performed a case-control study to assess the potential influence of CYP19 Arg (264) Cys and *CYP1B1* Leu (432) Val polymorphisms on breast cancer risk in a series of Korean breast cancer patients and controls. The results suggested that the CYP19 Arg (264) Cys polymorphism modifies breast cancer risk (OR=1.5, 95% CI=1.1-2.2), especially in association with alcohol consumption (P for interaction=0.04), whereas the *CYP1B1* Leu (432) Val polymorphism appeared to play no role in their study.

This contradicted the results obtained from (Jiao et al., 2010), who found in a recent study by using an allele-specific polymerase chain reaction method and direct DNA sequencing that the presence or absence of the two *CYP1B1* polymorphisms investigated, genotype and allele frequencies analyzed in breast cancer cases (n=152) and healthy age-matched controls (n=156),

suggested that certain polymorphisms in the *CYP1B1* gene might increase risk for breast cancer among the Han Chinese population, perhaps because they influence the efficiency of *CYP1B1* bio-transformation of estrogens or pro-carcinogens into DNA-reactive electrophiles that may act as cancer-initiating agents.

Another set of contradicting results was obtained by (Michael et al., 2009), who found that heterozygosity for the *CYP1B1* M1 genotype (*CYP1B1* M1 [Val/Leu]) was associated with a significant 59% increased risk of breast cancer, while homozygosity for the genotype (*CYP1B1* M1 [Leu/Leu]) conferred a non-significant 51% increased risk of breast cancer. They also stated that in premenopausal women, harboring at least one *CYP1B1* (Leu) allele conferred a significant two-fold increased risk for breast cancer (OR=2.04, 95% CI 1.10-3.78) with no significant association observed in postmenopausal women (OR=1.08, 95% CI 0.57-2.04). Their results suggested that the codon 432 polymorphism of the *CYP1B1* gene was associated with increased risk of breast cancer and is particularly involved in breast cancer risk in premenopausal women of African descent.

In conclusion: In our study, we found that the *CYP1B1* polymorphism was not associated with enhanced risk of breast cancer among Egyptian women. However, it may be found to be a susceptible gene for risk of breast cancer if done in other patients from different ethnic populations, providing important clues for future studies and early detection of breast cancer.

References

Ajtkhozhina, N, Nigmatova V, Khanseitova A, et al (2011). Polymorphic markers of some genes associated with multiple sclerosis in the population of Kazakhstan. *Russ J Genet*, **47**, 749-53.

Akarolo-Anthony S, Ogundiran T, Adebamowo C (2010). Emerging breast cancer epidemic: evidence from Africa. *Breast Cancer Res*, **12**, 8.

Bailey LR, Roodi N, Dupont W, et al (1998). Association of cytochrome-P450-1B1-*CYP1B1*-polymorphism-with-steroid-receptor-status in breast cancer. *Cancer Res*, **58,** 5038-41.

Bailey LR, Roodi N, Verrier C, et al (1998). Breast cancer and CYPIA1, GSTM1, and GSTT1 polymorphisms: evidence of a lack of association in Caucasians and African Americans. *Cancer Rese*, **58**, 65-70.

Beysebayev E, Tulebayev K, Meymanalyev T (2015). Breast cancer diagnosis by mammography in Kazakhstan-staging results of breast cancer with double reading. *Asian Pac J Cancer Prev*, **16**, 31-34.

Cavalieri E, Stack D, Devanesan P, et al. (1997). Molecular origin of cancer: Catechol estrogen-3,4-quinones as endogenous tumor initiators. *Proc Natl Acad Sci USA*. **94**, 10937-42.

Colditz G, Kaphingst K, Hankinson S, et al (2012). Family history and risk of breast cancer: nurses' health study. *Breast Cancer Res Treat*. **133**, 1097-104.

Gehan M, Azza A, Amel G (2013). Assessment of factors that hinder early detection of breast cancer among females at Cairo University Hospital. *World Appl Sci J*, **23**, 99-108.

Islamian J, Hatamian M, Rashidi M (2015). Nanoparticles promise new methods to boost oncology outcomes in breast cancer. *Asian Pac J Cancer Prev*, **16**, 1683-86.

Jemal A, Bray F, Forman D, et al (2012). Cancer burden in Africa and opportunities for prevention. *Cancer*, **118**, 4372-84.

Jiao H, Liu C, Guo W, et al (2010). Association of *CYP1B1* polymorphisms with breast cancer: a case-control study in the Han Population in Ningxia Hui Autonomous Region, P. R. China. *Biomark Insights*, **21**.

Lee K, Abel J, Ko Y, et al (2003). Genetic polymorphisms of cytochrome P450 19 and 1B1, alcohol use, and breast cancer risk in Korean women. *Br J Cancer*, **88**, 675-8.

Mavaddat N, Barrowdale, D, Andrulis I, et al (2011). Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the consortium of investigators of modifiers of BRCA1/2 (CIMBA). *Cancer Epidemiol Biomarkers Prev*, **21**, 134-47.

Michael N, Clareann H, Seymour J, et al (2009). Cytochrome P450 1B1 Val432Leu polymorphism and breast cancer risk in Nigerian women: a case control study. *Infectious Agents And Cancer*, **4**, 12.

Parkin D, Nambooze S, Wabwire-Mangen F, et al (2010). Changing cancer incidence in Kampala, Uganda, 1991-2006. *Int J Cancer*, **126**, 1187-95.

Reding K, Chen C, Lowe K, et al (2012). Estrogen-related genes and their contribution to racial differences in breast cancer risk. *Cancer Causes Control*, **23**, 671-81.

Rylander-Rudqvist T, Wedren S, Granath F, et al (2003). Cytochrome P450 1B1 gene polymorphisms and postmenopausal breast cancer risk. *Carcinogenesis*, **24**, 1533-9.

Rylander-Rudqvist T, Wedren S, Jonasdottir G, et al 2004). Cytochrome P450 1B1 gene polymorphisms and postmenopausal endometrial cancer risk. *Cancer Epidemiol Biomarkers*, **13**, 1515-20.

Sassi A, Popielarski M, Synowiec E, et al (2013). BLM and RAD51 Genes Polymorphism and Susceptibility to Breast Cancer. *Pathol Oncol Res*, **19**, 451-59.

Sergentanis T, Economopoulos K, Choussein S, et al (2012). Cytochrome P450 1A1 (*CYP1A1*) gene polymorphisms and cervical cancer risk: a meta-analysis. *Molecular Biol Reports*, **39**, 6647-54.

Shulman L, Willett L, Sievers A, et al (2010). Breast cancer in developing countries: opportunities for improved survival. *J Oncol*, **2010**, 1-6.

Soerjomataram I, Lortet-Tieulent J, Parkin D, et al (2012). Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. *Lancet*, **380**, 1840-50.

Sylla B, Wild C (2012). A million africans a year dying from cancer by 2030: What can cancer research and control offer to the continent? *Int J Cancer*, **130**, 245-50.

Toleutay U, Reznik, V, Kalmatayeva Z, et al (2013). Risk factors of breast cancer in Kyzylorda oblast of Kazakhstan: a case-control study. *Asian Pac J Cancer Prev*, **14**, 5961-64.

Watanabe J, Shimada T, Gillam E, et al (2000). Association of *CYP1B1* genetic polymorphism with incidence to breast and lung cancer. *Pharmacogenetics*, **10**, 25-33.

Wen W, Cai Q, Shu X, et al (2005). Cytochrome P450 1B1 and catechol-o-methyltransferase genetic polymorphisms and breast cancer risk in chinese women: results from the shanghai breast cancer study and a meta-analysis. *Cancer Epidemiol Biomarkers Prev*, **14**, 329-35.