AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Estrogen Receptor a (Esr1) Polymorphism and Breast Cancer

Ritu Yadav[*1], Preeti Chauhan[1], Vivek Kaushal[2], Minakshi Vashist[1]
1. Department of Genetics, M.D. University, Rohtak-124001
2. Department of Radiology, Pt. B.D. Sharma University of Health Science, Rohtak.

ABSTRACT

Estrogen receptor alpha (ESR1) belong to the nuclear receptor family of ligand-inducible transcription factors. It involves in both proliferation of breast cancer cells as well as in carcinogenesis. Many studies on polymorphisms suggested its correlation with various aspects of breast cancer. The most studied Polymorphisms are SNPs and microsatellites lying within intron one of estrogen receptor alpha (ESR1) gene. A possible linkage of ER gene found in families of breast cancer patients, suggested that either the ER gene itself or an adjacent gene may be a risk of breast cancer. These alleles have also been found to be associated with traditional risk factors of breast cancer including age, family history, menstrual cycle, menopausal status, anthropometric measurements (height, weight etc.) and pregnancy history. Estrogen receptor alpha (ER-α) status also plays a role in decisions making for endocrine therapy. This review focuses on association of estrogen receptors α (ESR1) polymorphism with the breast cancer risk. By understanding the frequency of occurrence of ER α polymorphism and associated risk factors may elucidate the breast cancer screening, prevention, and treatments strategies in future.

Keywords: Estrogen receptor α, breast cancer, SNP, Hormonal status.

*Corresponding Author Email: ritugenetics@gmail.com
Received 06 January 2015, Accepted 13 January 2015

INTRODUCTION

Please cite this article as: Yadav R *et al.*, Estrogen Receptor a (Esr1) Polymorphism and Breast Cancer. American Journal of PharmTech Research 2015.

Estrogens are a family of related molecules that stimulate the development and maintenance of female secondary sexual characters. The natural estrogens produced by women are steroid molecules and are derived from four rings of carbon atoms. The most prevalent forms of human estrogen are estradiol and estrone. Both are produced and secreted by the ovaries, although estrone is also made in the adrenal glands and other organs. During each menstrual cycle, estrogen normally triggers the proliferation of cells that form the inner lining of the milk glands in the breast. If pregnancy does not occur, estrogen levels fall at the end of each monthly menstrual cycle. In the absence of high estrogen levels, the milk gland cells that have proliferated every month will deteriorate and die, followed by a similar cycle of cell proliferation and cell death the following month. For the average woman, hundreds of cycles of breast cell division and cell death repeated from puberty to menopause. How do these estrogen-induced cycles of breast cell proliferation increase the risk of developing cancer is still unknown but it is certain that estrogen is instrumental in at least a subset of breast cancers (Nyante, 2009)[1]. Estrogens act on target tissues by binding to parts of cells called estrogen receptors. An estrogen receptor is a protein molecule found inside those cells that are targets for estrogen action. Estrogen receptors contain a specific site to which only estrogens can bind. The target tissues affected by estrogen molecules that contain estrogen receptors. Therefore, when estrogen molecules circulate in the bloodstream and move throughout the body, they exert effects only on cells that contain estrogen receptors (Simpson, *et al.,* 2005)[2]. In the absence of estrogen molecules, receptors are inactive and have no influence on DNA. But when an estrogen molecule enters a cell and passes into the nucleus, the estrogen binds to its receptor, causing the shape of the receptor to change. This estrogen-receptor complex then binds to specific DNA sites, called estrogen response elements, which are located near genes that are controlled by estrogen. After it has become attached to estrogen response elements in DNA, this estrogen-receptor complex binds to coactivator proteins so that nearby genes become active. The active genes produce messenger RNA, which guide the synthesis of specific proteins. These proteins can then influence cell behavior in different ways. The estrogen receptor (ER) exists in two forms known as ERα and ERβ. Both the estrogen receptors (ERs) functionally act as transcription factors to initiate target gene expression (Heldring, *et al.,* 2007)[3]. Estradiol is considered to be the more biologically potent estrogen because it has the strongest binding affinity for ER-alpha and ER-beta; estrone's binding affinity is approximately 60% for ERα and 40% for ERβ (Gruber, *et al.,* 2002)[4]. Biological and epidemiological evidence suggests that the estrogen receptor is a major factor in breast tumor formation and survival. Estrogen receptor expression has been considered to be present in two thirds of the total breast cancer cases

but many studies suggested its incidence closer to 80% (Nadji, *et al.*, 2005)[5]. Atypical ductal hyperplasia and lobular carcinoma in situ both express the estrogen receptor at higher levels than that of normal breast. Approximately 60-70% of ductal carcinoma in situ is ER-positive. Currently, a clinical role has been established for ERα. The primary focus of ERα in breast cancer is for predicting the response to hormonal treatment. Patients with breast cancers expressing ERα are approximately seven to eight times more likely to benefit from endocrine therapy than ERα negative patients. For the initial three to five years after primary diagnosis, ERα positive patients generally have a better outcome than ERα-negative patients. Several studies have suggested that there is need of elaborated studies on the other aspects of ERα gene, which may facilitate the understanding of nature of the disease.

Esr 1 Polymorphism

Each individual is unique, though comparison of the genomes of any two individuals shows only ~0.1% difference. Genetic polymorphism is the occurrence of two or more alleles of a gene at one locus, each with particular frequency in the same population. Gene polymorphism promotes diversity within a population which often persists over many generations. The Sources of polymorphism include SNPs, sequence repeats, insertions, deletions and recombination. These alterations arise somatically at a high rate in cancer cells as well as in germ cells, which can be transmitted as constitutional variants to next generations. Single nucleotide polymorphisms (SNPs) explain 95% of all variant DNA sites (Meyer, *et al.*, 2004)[6]. According to data obtained from the dbSNP there are 14,110,048 registered SNPs in the database which can be compared with the approximately 3.2 billion bases in the human haploid genome (Sherry, *et al.*, 1999)[7]. The sequence alterations occurring in the genome have no or little effect on cell function. The repetitive DNA sequences (e.g. microsatellites) are also susceptible to alterations. Other changes occur in coding or regulatory sequences and may alter gene function or expression and confer a selective advantage or disadvantage to the cell.

Single nucleotide polymorphism (SNP):

It involves the variation at a single nucleotide that occurs in at least one percent of a population (Risch, *et al.*, 2000)[8]. SNPs basically arise from mutation but there are several factors which keeps them in the population viz. founder effect, genetic drift and natural selection. There may be natural variations in a gene in which DNA sequence have no adverse effects on the individual and occur with fairly high frequency in the general population. On the other hand, there are certain variations in the DNA sequences which can affect human health and are prone to develop diseases and respond to pathogens, chemicals, drugs, and other agents. These polymorphisms are much larger in

size and involve long stretches of DNA. Although the effect of a SNP on a gene may not be large, yet even subtle effects can influence susceptibility to particular diseases. When the combination of two or more SNPs occurs in a population more or less frequently than is expected by chance, they are considered to be in linkage disequilibrium (LD). Haplotypes are the SNPs which are located close together on the same chromosome, that are less likely to be disrupted by meiotic crossing-over and that are thus inherited together. Certain regions in the genome are protected against such recombination and are referred to as Haplotype blocks. Therefore a number of SNPs (tagging SNPs) may capture most of the genetic diversity across that specific region (Johnson, *et al.*, 2001)[9]. SNPs can be divided into silent, harmless, harmful, and latent SNPs (Greenhut, *et al.*, 2008)[10]. Silent SNPs are variants in non-coding or coding regions and are thought to be nonfunctional. However, silent SNPs may indirectly change the transcription, structure and stability of the mRNA, transcript splicing and the kinetics of translation, and thereby the amount of protein, its structure and function. Moreover, silent SNPs may not be functional, rather as markers, i.e. in LD with the functional SNP. The harmless SNPs are located in coding or regulatory regions, but mostly have a subtle impact on genetic and cellular function, whereas the harmful SNPs are responsible for the increased risk of diseases. Previous studies have reported that common ER α polymorphisms are associated with cardiovascular disease risk, coronary artery disease, modify the effect of estrogen on HDL cholesterol level, changes in bone mineral density, vertebral fractures and many other diseases (Kobayashi, *et al.*, 2002; Shearman, *et al.*, 2003)[11,12]. As far as breast cancer is concern, there are several known polymorphisms in both exons and introns of the ESR1 gene, some of which alter the function of the receptor (Hall, *et al.*, 2001)[13]. Some of the known single nucleotide variants are c454-397T>C PvuII (rs2234693) and c454-351A>G XbaI (rs9340799) polymorphism in intron 1, 397 and 351base pair upstream of the exon 2 respectively, exon1/codon10 (TCT-TCC), exon4/codon325 (CCC-CCG), exon8/594 (ACG-ACA), +2464 C/T (rs3020314), -4576 A/C (rs1514348), ESR1- 104062C>T (rs851982), SNP rs3798577(T/C) (located at 3'UTR) and other SNPs -104062 C/T, SNPs, rs3020407, and rs3020401 (Andersen, *et al.*, 1994; Hsiao, *et al.*, 2004; Gallicchio, *et al.*, 2006; Siddig, *et al.*, 2008; Mavaddat, *et al.*, 2009; Anghel, *et al.*, 2006; Madeira, *et al.*, 2014)[14-20].

Microsatellites:

These are the tandem repeats of mono-, di-, tri- or tetra-nucleotide units or more that form clusters <10 to >100 base pairs in length. These sequences pose problems in the DNA replication machinery, and polymerase slippage that can result in unrepaired deletions or duplications of single or multiple repeat units. This occurs in germ cells, and over time it may results in a high

level of variability in number of repeats in the population. This variability may give rise to apparently non Mendelian inheritance within a generation when considering allelic associations in a particular population. The length of these repetitive fragments affects transcription of genes and hence the protein levels and can also influence the coding sequences to alter protein function (Lundin, *et al.,* 2007; Sand, *et al.,* 2002)[21,22]. The microsatellites vary in size; specific repeat lengths are more common than others and may have a different effect on the gene compared with both longer and shorter repeat sizes (Lundin, *et al.,* 2007)[21]. Microsatellites are good markers for studies of genetic linkage because they have high heterozygosity as compare to SNPs. They are highly mutable markers with often 15 or more alleles in any given population. Many researchers studied (GT)n dinucleotide repeat polymorphism (in promoter region located at 6.6 kb upstream of transcription start site) and -1174(TA)n tandem repeats (in promoter region) to find the association with breast cancer (Sand, *et al.,* 2002; Boyapati, *et al.,* 2004; Iobagiu, *et al.,* 2006; Anghel, *et al.,* 2006; Tsezou, *et al.,* 2008)[22-24,19,25]. These variants have been implicated in gene expression by the influence on transcription by affecting the secondary structure of DNA.

Esr1 Polymorphisms And Breast Cancer Susceptibility

There have been several association studies of ESR1 polymorphisms and breast cancer, but results have been somewhat inconsistent. Hill, *et al.,* (1989)[26] reported the association of c454-397T>C PvuII polymorphism in ESR1 gene with ER expression in 188 breast cancer patients. Most of the studies have been found increased risk of disease for XbaI and PvuII polymorphism while others have reported that XbaI not PvuII polymorphism was associated with breast cancer risk (Andersen *et al.,* 1994; Shin *et al.,* 2002) [14,27]. In some studies polymorphism was used as marker for breast cancer risk among the patients having repeated abortions (Berkowitz, *et al.,* 1994)[29]. Breast cancer incidence varies in different parts of the world. The fact that a breast cancer risk increases when moving from a low risk to a high risk area indicates that genetic variants differ between different ethnic groups (Ziegler, *et al.,* 1993)[30]. A number of studies have been published relating ESR1 polymorphism with breast cancer. Many studies have been documented significant association between ESR1 polymorphism and breast cancer while other studies did not found such relationship (Cai, *et al.,* 2003; Wedren, *et al.,* 2004; Franzel, *et al.,* 2005; 2006; Gail, *et al.,* 2008)[28,31-33]. A Korean population based study reported the decrease in breast cancer risk with XbaI SNP G in comparison with women without G allele (AA) (Wedren, *et al.,* 2004; Gail, *et al.,* 2008)[31,33]. They found G allele protective and A allele as a risk in c454-351A>G XbaI polymorphism and no association was found in breast cancer risk with c454-397T>C PvuII polymorphism, similar to many other studies (Andersen, *et al.,* 1994; Shin, *et al.,* 2002; Cai, *et al.,*

2003; Gail, *et al.*, 2008) [14,27,28,33]. According to a Caucasian population based study on 393 breast cancer patients and 790 controls, the relation between breast cancer and A allele (AA, AG) as compared to GG allele was found (Gail, *et al.*, 2008)[33]. They also reported no association between breast cancer and PvuII polymorphism (Yaich, *et al.*, 1992)[34]. In contrast Saad, *et al.*, (2008)[35] found PvuII polymorphism associated with risk of breast cancer however they found no association of XbaI polymorphism with risk of breast cancer in 40 patients. Certain studies have also found that both PvuII and XbaI polymorphism were associated with elevated risk of breast cancer (Onland-Moret, *et al.*, 2005; Shen, *et al.*, 2006; Jakimiuk, *et al.*, 2007; Javed, *et al.*, 2011)[36-39]. In addition some studies have found no effect at all for either of these polymorphisms (Yaich, *et al.*, 1992; Shin, *et al.*, 2003; Li, *et al.*, 2012; Alsheyab, *et al.*, 2012)[34,27,40,41]. Hsiao, *et al.*, (2004)[15] examined ESR1 exon1/codon10 (TCT-TCC), exon4/codon325 (CCC-CCG) and exon8/594 (ACG-ACA) to find the correlation with breast cancer risk and concluded that frequency of allele 1 in codon 10 & 325 was less in breast cancer cases as compared to controls. SNPs in codon 594 were found lower in breast cancer patients only having family than those without family history. Many studies have examined the association of $(GT)_n$ dinucleotide repeats and -1174(TA)n tandem repeats with breast cancer risks (Cai, *et al.*, 2003; Boyapati, *et al.*, 2004; Iobagiu, *et al.*, 2006; Tsezou, *et al.*, 2008)[28,23-25]. They observed (GT)n dinucleotide as highly polymorphic and significantly associated with risk of breast cancer. Patients having $(GT)_{17}$ or$(GT)_{18}$ alleles have been associated with decrease risk of breast cancer (Cai, *et al.*, 2003)[42]. However Boyapati, et al. (2005)[23] observed increased risk of death among participants carrying one $(GT)_{18}$ allele but when linked with PP allele of PvuII polymorphism, reduces the risk of breast cancer (Cai, *et al.*, 2003)[42]. Another dinucleotide (TA) tandem repeats have been identified with no significant difference in frequency as well as genotype distribution (SS, SL, LL) among cases and controls in univariate analysis (Wedren, *et al.*, 2004; Tsezou, *et al.*, 2008; Zheng, *et al.*, 2012)[31,25,43]. Whereas Anghel, *et al.*, (2006)[19] combined the (TA)n repeats with two other variables i.e. (CAG)n & (CA)n repeats and found out that longer CAG(≥28), shorter TA(<23) & CA(<23) repeats may acts as a possible genetic profile associated with breast cancer. On the other hand Iobagiu, *et al.*, (2006)[24] suggested a combined genotype profile of short (CA)n-long(TA)n-short (CAG)n could together contribute to breast cancer risk. These findings favor the polygenic model of breast cancer with gene-gene interactions; the combined effects of multiple low-risk polymorphisms confer a significant genetic predisposition. In addition some studies have also suggested possible linkage disequilibrium between (TA)n tandem repeats and other polymorphisms (PvuII, XbaI) in intron1 (Becherni, *et al.*, 2000)[44].

Genotypic/allelic and Haplotype frequencies:

Genotype frequency in a population is the number of individuals with a given genotype divided by the total number of individuals in the population. Genotypic frequencies are the indication of the genotypes which are the most or least prevalent in the population. Allele frequency is the percentage of all alleles at a given locus in a population gene pool represented by a particular allele (King, *et al.*, 2006)[45]. In population genetics genotype and allele frequencies are used to depict the amount of genetic diversity at the individual, population, and species level. Upon investigating the genotype distribution of associated SNPs in ESR1 gene and prevalence of their haplotypes have been shown to play a pivotal role in determining the frequency of sporadic breast cancer screening, in most of the studies (Franzel, *et al.*, 2005; Shen, et al. 2006; Jakimiuk, *et al.*, 2007; Javed, *et al.*, 2011)[32,37-39]. These studies have found that TT, TC genotype of PvuII SNP and AA, AG genotype of XbaI SNP was significantly associated with breast cancer in comparison with CC and GG genotype respectively. The prevalence of heterozygous genotype TC, GA has been found in population affected with breast cancer than in control groups (Javed, *et al.*, 2011; Araujo, *et al.*, 2011; Ramalhinho, *et al.*, 2013; Madeira, *et al.*, 2014)[39,46,47,20]. Whereas in some case control studies presence of AA genotype of XbaI SNP appears to be more prevalent in breast cancer affected population (Shin, *et al.*, 2003; Shen, *et al.*, 2006; Jakimiuk, *et al.*, 2007)[27,37,38] (Table 1). Further, some studies have focused on examining haplotypes to identify patterns of genetic variation that are associated with health and disease states. Haplotype is a set of single-nucleotide polymorphisms on a single chromatid of a chromosome pair that are associated statistically. It is thought that these associations, and the identification of a few alleles of a Haplotype sequence, can unambiguously identify all other polymorphic sites in its region. Such information is very valuable for investigating the genetics of diseases; a Haplotype is a group of genes within an organism that was inherited together from a single parent. These groups of genes inherited together because of genetic linkage, or the phenomenon by which genes that are close to each other on the same chromosome are often inherited together. Haplotype prevalence was examined on combining the PvuII and XbaI SNPs by different studies to show the effect on increased breast cancer risk. The information on distribution of ESR1 PvuII and XbaI genotype frequency and their haplotypes is compiled in Table1. The Haplotype distribution varies among different ethnic groups. The Asian population showed an increased frequency of Px Haplotype and a reduced frequency of PX Haplotype with respect to Caucasian population of European ancestry. While in African population px Haplotype was found at a lower frequency (Van, *et al.*, 2003)[48]. The divergences in haplotypes distribution are found among several studies. The Haplotype Px was detected in very low

frequency (<24%) in most of the studies (Onland-Moret, *et al.*, 2005; Araújo, *et al.*, 2011; Ramalihnho, *et al.*, 2013)[36, 46, 47]. Commonly pX Haplotype was not found or found at a very lower frequency in several populations. This frequency distribution might results from disequilibrium which is not complete and may be due to recombination or multiple mutations which have occurred at these two polymorphic sites. Multiple demographic and genetic events like natural selection, mutation, random drift, or gene flow, may contribute to create substantial levels of linkage disequilibrium in any given population. Thus, the inconsistency of haplotypes frequencies throughout different populations may be explained to some extent by the differential patterns of linkage disequilibrium in those populations (Goldstein, *et al.*, 2001)[50].

Table 1: Previous studies on relation of breast cancer with PvuII & XbaI SNPs, their genotypic distribution and prevalence of their haplotypes in ESR1 gene.

S.No	Reference (Country)	No. of patients	Gene polymorphism studied associated with breast cancer risk	Genotype distribution (%)		Associated Haplotype(%)		
				PvuII Polymorphism	XbaI Polymorphism	PvuII SNP PP(CC) Pp(CT) pp(TT)	XbaI SNP XX(GG) Xx(GA) xx(AA)	PX px Px pX
1	Yaich et al.1992 (Tennessee)	257	PvuII, XbaI	No association	No association	-	-	-
2	Andersen et al. 1994 (Norway)	360	PvuII, XbaI	No association	A allele as risk & G as protective	-	-	-
3	Shin et al. 2003 (South Korea)	205	PvuII, XbaI	No association	A allele as risk & G as protective	17.4 45.3 37.3	5.5 29.8 64.7	35.4 32.8 31.8 -
4	Cai et al. 2003 (China)	1069	PvuII, XbaI	T allele associated	A allele weakly associated	12.9 48.3 38.8	3.4 46.5 50.1	38 28.2 22 10.6
5	Wedren et al. 2004 (Sweden)	1556	PvuII, XbaI	No association	No association	-	-	-
6	Franzel et al. 2005 (Netherland)	620	PvuII, XbaI	T allele associated	A allele associated	-	-	-
7	Boyapati et al. 2005 (China)	1,069	PvuII, XbaI	No association	No association	-	-	-
8	Onland-Moret et al. 2005(Dutch)	3,77	PvuII, XbaI	Associated with risk	No association	18.3 39.8 23.6	14.6 34.5 32.4	17.3 47.4 24.4 10.9
9	Vandervord et al. 2006 (African American and white- American)	220	PvuII, XbaI	No association	No association	-	-	-
10	Shen et al. 2006	282	PvuII, XbaI	Associated with	Associated with non	15.7	7.6	4.1 37.4

	(China)			non significantly elevated risk	significantly elevated risk	45.3 39	31.5 60	←58.5→
11	Wang et al. 2007 (Caucasian)	393	PvuII, XbaI	No association	G allele as protective	-	-	-
12	Surekha et al. 2007 (India)	500	PvuII,	Associated with risk	_	35.3 37.3 27.3	-	-
13	Jakimiuk A et al. 2007 (Poland)	64 (postmen opausal women)	PvuII, XbaI	Associated with risk	Associated with risk	17.2 50 32.8	6.2 34.4 59.4	-
14	Hu et al. 2007 (China)	114	PvuII, XbaI	Associated with risk in premenopausal women	Associated with non significantly elevated risk in premenopausal women	14.2 51.3 34.5	2.7 30.1 67.2	-
15	Ladd et al. 2008 (Caucasian)	3,893	PvuII, XbaI	No association	No association	-	-	-
16	Abir A Saad et al. 2008 (Egypt)	40	PvuII, XbaI	Associated with risk	No association	-	-	-
17	Javed et al.2011 (Pakistan)	200	PvuII, XbaI	Strongly correlated with risk of breast cancer	Strongly correlated with risk of breast cancer	18.6 43.3 38.1	12.4 48.5 39.2	12.3 34.02 - - -
18	Sakoda et al. 2011 (China)	614	PvuII, XbaI	No association	No association	-	-	-
19	Araujo et al. 2011 (Brazil)	419 Random women	PvuII, XbaI	-	-	16.3 59.6 24.1	14.8 79.2 6	37.1 38.2 7.8 16.7
20	Alsheyab et al. 2012 (Jordan)	100	PvuII, XbaI	No association	No association	-	-	-
21	Li et al.2012(China)	1742	PvuII, XbaI	No association	No association	-	-	-
22	Ramalhinho et al. 2013 (Portuguese)	107	PvuII, XbaI	No association	A allele as risk & G as protective	17.8 56.1 26.2	23.4 43.9 32.7	54.2 13.1 19.6 13.1

23	Chatopadhyay et al. 2014 (India)	360	PvuII	T allele associated with elevated risk	-	10.8 45.6 43.6	-	-
24	Madeira et al. 2014 (Brazil)	164	PvuII, XbaI	Associated with risk	A allele as risk & G as protective	9 77 9	19 73 8	-

Breast Cancer Risk Factors in Relation with ESR1 Polymorphism

Epidemiologic research has identified several characteristics that are risk factors for breast cancer. The association between genetic polymorphism in ESR1 gene and risk of breast cancer has been the subject of increasing interest now days. As the breast cancer incidence varies in different parts of the world. The fact that a woman's breast cancer risk increases within one or two generations when moving from a low risk to a high-risk area indicates that not only genetic factors but also the environment affects breast cancer risk (Ziegler, *et al.,* 1993; Lichtenstein, *et al.,* 2000)[30,51]. The presence of a risk factor can often be associated with increased risk of breast cancer, while absence of certain risk factors might be associated with the decreased risk. Certain risk factors are discussed below:

Family History:

The risk of breast cancer increases if women have a family history of breast cancer. Although this risk is influenced by the number of women (and men) with breast cancer in her extended family of blood relatives the most importantly whether one or more first-degree relatives (mother, sister, daughter) are affected. McGuire, *et al.*, (1975)[52] validated breast cancer in relatives and reported that 78% validation was possible in first degree relatives and 54% in second degree relatives. A collaborative reanalysis of data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without breast cancer has estimated the risks associated with varying degrees of breast cancer history among first-degree relatives compared with women reporting no such family history of breast cancer (Azimi, *et al.,* 2009)[53]. Women with one, two, and three or more affected first-degree relatives had relative risks of 1.80 (99%CI: 1.69-1.91), 2.93 (99% CI: 2.36-3.64) and 3.90 (99% CI: 2.03-7.49), respectively. The findings were similar for women reporting mothers or sisters with breast cancer. A previous U.S. study found significantly high frequency of allele1 (CCC-CCG) in case subjects with a family history of breast cancer than in those without such a history (Roody, *et al.,* 1995)[54]. According to a meta-analysis, the relative risk of breast cancer for one or more Second degree relatives (grandmother, aunt, niece) diagnosed with the disease was lower, at 1.5 (95% CI: 1.4-1.6) (Pharoah, *et al.*, 1997)[55]. In a population based study of Australian women with breast cancer diagnosed before the age of 40, no evidences of association of family history with breast cancer has been observed (Southey, *et al.,* 1998)[56]. The association between breast cancer risk of ESR1, PvuII pp or Pp and XbaI Xx or xx genotypes seemed to be stronger among women with a family history of breast cancer than among women with no family history of breast cancer (Shen, *et al.,* 2006)[37]. Further studies are needed to validate these results focusing on ESR1 polymorphism by using large cohort.

Reproductive and menstrual history:

Most of the established breast cancer risk factors are related with menstrual and reproductive events of women's life. Polymorphism in ESR1 gene in combination with reproductive factors may alter the risk of breast cancer. It is suggested by many studies that polymorphism may exerts its effect differently at different points of women's life (Modugno, *et al.*, 2005)[57].

Age at menarche and menopause:

Menarche, the time of commencement of menstrual cycles, is characterized by monthly fluctuations in hormone levels, ovulation and cellular proliferation in the breast. Epidemiological studies of breast cancer have shown that women who had their first menstrual period at an age less than 12 years have a slightly higher risk of breast cancer (10% to 25%) than women who had their first menstrual period later (i.e. ≥12 years) (Kelsey, *et al.*, 1993; Bernstein, *et al.*,2002; Colditz, *et al.*, 2005)[58-60] . Early menarche prolongs a woman's exposure to estrogens and other female hormones (Key, *et al.*, 1988; Bernstein, *et al.*, 2002)[61,59]. Studies also have shown that women with an early age at menarche might have higher levels of estrogens for several years after menarche than women with later menarche. The involvement of polymorphism in increasing the rate of breast cancer was studied by many researchers. In particular the role of ESR1 PvuII and XbaI SNPs was reported in some studies (Stavrou, *et al.*, 2002; Jakimiuk, *et al.*, 2007)[62,38]. The menarche occurred six months later in girls with the AA genotype of the -351 A→G polymorphism than in girls with AG or GG genotypes and TT homozygote of the 397T→C polymorphism than in TC and CC genotype carriers. XbaI XX homozygote and homozygous for the PX haplotype found to have a delay in the age of menarche. The effect of PvuII polymorphism was not statistically significant. It may reflect the strong linkage disequilibrium with XbaI and the PX Haplotype which shows the strongest association with the age of menarche (Stavrou, *et al.*, 2002; Jakimiuk, *et al.*, 2007) [62,38]. Modugno, *et al.*, (2005)[57] noted later age at first menses (13 years) associated with -401 C/C, T/C genotype. The frequency of allele1 of codon 325 was also found significantly higher in cancer patients with age at menarche <=12 years old in comparison with age at menarche >12 years old (Azimi, *et al.*, 2009)[53]. In contrast some studies did not report any association between polymorphism and age of patient at menarche (Ramalhinho, *et al.*, 2013)[47]. Many epidemiological studies have suggested that longer exposure to estrogen might be a risk for breast cancer. During menopause, involution occurs in the breast which is characterized by decreased cell proliferation and an eventual reduction in the proportion of epithelial cells. Postmenopausal women have a 15– to 50% lower risk of breast cancer than premenopausal women of the same age (Lancet, 1997; Colditz, *et al.*, 2005)[63,60]. Many studies documented ESR1

genotype association with risk of breast cancer by age and menopausal status (Cai, *et al.*, 2003)[28]. The PvuII polymorphism is reported to have association with increased breast cancer risk in all levels defined by age and menopausal status. On the other hand XbaI polymorphism is confined to older or postmenopausal women (Zuppan, *et al.*, 1989; Cai, *et al.*, 2003)[64,28]. In some studies breast cancer patients with a pp genotype were significantly younger than women with PP or Pp genotype at the time of cancer diagnosis (Parl, *et al.*, 1989; Cai, *et al.*, 2003)[65,28]. Chattopadhyay, *et al.*, (2014)[66] observed the presence association of T allele of PvuII SNP with post menopausal status of women. Some studies have found out the increased PP genotype frequency of PvuII SNP in women with premenopausal status as compare to post menopausal women in fact some researchers correlated this with early onset of menopause to decrease the breast cancer risk (Weel, *et al.*, 1999; Surekha, *et al.*, 2007)[67,68]. A strong correlation between PvuII or XbaI polymorphism and menopause with breast cancer was observed in some studies. The premenopausal women carriers of pp and xx genotypes of XbaI and PvuII SNPs were found with increased risk of breast cancer (Hu, *et al.*, 2007)[69]. On the other hand some studies reported the association of A & T alleles of both polymorphisms with postmenopausal status of patients (Weel, *et al.*, 1999; Cai, *et al.*, 2003; Kok, *et al.*, 2005; Gail, *et al.*, 2008)[67,28,70,71]. In addition to these, some studies found no relation between ESR1 polymorphism and breast cancer risk among younger or elder women (Southey, *et al.*, 1998; Gonzaleze *et al.*, 2008)[56,72]. Cai, *et al*,. (2003) proposed significant association of GTn polymorphism with years of menstrual cycle, which supports the hypothesis, that breast cancer risk is associated with longer estrogen exposure.

Parity:

On average, parous women have about a 30% lower risk of breast cancer than nulliparous women (Ewertz, *et al.*, 1990; Kelsey, *et al.*, 1993; Colditz, *et al.*, 2005)[73,58,60]. For parous women, breast cancer risk decreases with the number of children and increases with the age at first full-term pregnancy, and both associations appear to be independent of the effect of breastfeeding (Ewertz, *et al.*, 1990; Kelsey, *et al.*, 1993; Lancet, 2002)[73,58,74]. For women who have their first child at older ages (ie after 29 years) breast cancer risk is about 40% higher than for women who have their first child early (before 25 years) irrespective of their number of children and duration of breastfeeding. This means that for some who have their first child at older ages (after 29 years) women, in particular women with only one child and who did not breastfeed; breast cancer risk is higher than for nulliparous women. Shin, *et al.*, (2003)[27] observed elevated breast cancer risk among nulliparous women or had first full term pregnancy at the late age, although this association was not statistically significant.

Breastfeeding:

Breastfeeding is associated with a decreased risk of breast cancer. Several biologic mechanisms have been pointed out that could account for the postulated protective effects of lactation. Russo, *et al.,* (1994)[75] indicates that lactation, as well as pregnancy increases the proportion of differentiated cells in the breast and, using animal models, they have demonstrated that differentiation of the cells of the mammary gland, prior to exposure to a carcinogen, protects from malignant transformation (Russo, *et al.,* 1982)[76]. Lowered estrogen levels have been observed following full-term birth and lactation. Decreased levels of serum prolactin have also been reported, but prolactin may have both some mitogen and differentiating influences on breast cells (Vonderhaar, *et al.,* 1998)[77]. The women who breastfed for at least three years have about an extra 10–20% reduction in risk compared with women who did not breastfeed. In contrast some researchers found no association of breast feeding and risk of cancer (Javed, *et al.,* 2011)[39]. There is further need to study the effect of breast feeding on risk of breast cancer in relation with ESR1 polymorphism.

Lifestyle:

A number of personal behaviors and exposures have been implicated as risk factors for breast cancer. These include habitual activities, such as diet, drinking alcoholic beverages, smoking and physical activity, as well as personal characteristics, such as body size, which are also influenced by lifestyle. Even though some women having high risk lifestyle factors however they may not develop breast cancer. This could be explained by the fact that genetic factors modify the effect of lifestyle on breast cancer risk (Lichtenstein, *et al.,* 2000)[51]. Dietary risk factors include alcohol and related beverage consumption. Daily alcohol consumption of 3 to 4 drinks has been associated with an approximately 30% higher risk than with non-consumption (Hamajima, *et al.,* 2002)[78]. The risk increases to almost 50% with consumption of more than 4 drinks. Many studied proposed interaction between PvuII, XbaI polymorphism and breast cancer risk including smoking, alcohol consumption, etc. (Madigan, *et al.,* 2000; Shin, *et al.,* 2003)[79, 27]. Some studies found strong relation between alcohol consumption and XbaI genotypes (Shin, *et al.,* 2003)[27]. The effect of smoking on breast cancer risk may be difficult to evaluate, since it may be confounded by alcohol (Hamajima, *et al.,* 2002; Jernström, *et al.,* 2005)[78,80]. Smoking has been associated with an increased risk in premenopausal women in some studies (Jernström, et al, 2005)[80]. Anthropometric factors are associated with estrogens levels and thus breast cancer risk. In postmenopausal women the majority of estrogen is produced through peripheral aromatization from androgens in fat tissue. The estrogen production is proportional to the amount of body fat (McTiernan, *et al,* 2003)[81]. Overweight women have a higher body mass index (BMI), i.e. weight/length2 (kg/m2), and may

therefore at higher postmenopausal breast cancer risk (Boyapati, *et al*, 2004)[23]. In premenopausal women estrogens are mainly produced in the ovaries and not in the fat tissue, and in this subgroup of women obesity is actually protective (Weiderpass, *et al*, 2004)[82]. Breast volume has also been associated with an increased risk of premenopausal breast cancer in lean women (Kusano *et al*, 2006). The association between BMI and ESR1 polymorphism is the well studied, particularly in intron 1 SNPs.Cai, *et al.*, (2003)[28] investigated association of these breast cancer risk factors with PvuII genotypes and found no evidences of such interactions. In an Indian study overweight and obese patients were found at elevated risk of breast cancer, proposed explanation was that fatty breast tissue absorb and accumulate the end products of xenobiotics and xenoestrogens. Distribution of adipose tissue is mediated by activation of ER through endocrine and paracrine effects. Hence estrogen exposure increases the breast cancer incidence (Surekha, *et al.*, 2007)[68]. The P allele and PP genotype frequencies of PvuII SNP tended to increase with increase in BMI, whereas Pp genotype frequency was elevated only in obese patients. The reverse was observed in case of pp genotype. Deng, *et al.*, (2000)[83] found c.454-397C → T TT to be associated with higher BMI and against a tendency to gain weight with age, which were previously shown to be associated with an increased risk for breast cancer. However no association was observed between BMI and a Haplotype constructed by the c.454-351A → G SNP and the c.975C → G SNP. Madigan, *et al.*, (2000)[79] found high estrogen level in women having high BMI, despite this they did not observed any effect of BMI in association between breast cancer risk and (GT)n polymorphism. In addition there are some studies which found no evidences of association between ESR1 polymorphism risk factors like BMI, smoking and alcohol consumption (Gallicchio, *et al.*, 2006)[84].

Clinical Relevance

It is estimated that approximately 20% of drug therapies are influenced by genetic polymorphisms in drug metabolizing genes(Ingelman-Sundberg, 2004)[85]. Pharmacogenomics refers to the study of different genes that determine drug behavior, whereas Pharmacogenetics refers to the study of inherited differences in drug metabolism and response (National Center for Biotechnology Information). Some researchers refer to the study of selected genes or polymorphisms to genetics and genomics referring to the whole genome-wide scans. An important example of Pharmacogenetics is the attempt to individualize treatment with the anti-estrogen tamoxifen (Goetz, *et al.*, 2008)[86]. ESR1 status plays a role in making decisions for endocrine therapy. The breast cancer patients with lower expression of ESR1 are not controlled by endocrine therapy resulting in greater tumor aggressiveness and poor prognosis (Giacinti, *et al.*, 2006)[87]. Many other

clinical studies suggested ESR1 (+) status correlates with improved prognosis, lower risk of relapse and better overall survival. Metastatic breast cancer with ER+ tumors is more likely to respond to endocrine therapy (McGuire, *et al.,* 1975)[52]. Response rate of estrogen receptor (ER) positive tumors to hormonal therapy has been reported in approximately 50% to 75%, while ER-negative tumors have a less than 10% chance of response in some studies (Wittliff, *et al.,* 1984)[88]. Estrogen receptor positive tumors patients have an improved overall prognosis and more likely to respond to antiestrogen therapy for advanced disease and significantly longer disease-free interval shown in many studies (McGuire, *et al.,* 1975; Knight, *et al.,* 1977; Gapinski, *et al.,* 1980)[52,89,90]. Although the role of estrogen receptors as prognostic and therapeutic tools has widespread acceptance in the management of breast cancer, approximately half of all ER (+) patients fail to respond to anti-estrogen therapy has been observed. Some researchers suggested the role of genetic polymorphism for such effects (Ingelman-Sundberg, *et al.,* 2004)[85]. Particular variant genotypes of ESR1 polymorphism might be associated with specific responses to the therapy. There is a need to study in detail, the effect of different ESR1 polymorphic genotypes in association with responses to different therapies so as to be used only for those patients who get benefited. In addition, Pharmacoepidemiology may also limit the number of adverse drug reactions, since patients with particular genotype who cannot respond to the drug administered may be offered with alternative treatment. Moreover, the development of new therapy panels in clinical trials would be more effective in the response evaluation in patients. Pharmacogenetics may therefore have a major impact, not only on the quality of life but also socioeconomic status of the patients.

CONCLUSION

A large number of studies have pointed out the role of ESR1 gene polymorphism in many aspects of breast cancer, but the functional impact of this polymorphism is not fully understood. Further functional analyses of ESR1 polymorphic variants are needed to investigate how polymorphism is involved in breast cancer development. This polymorphism may play a role in genetic susceptibility studies of breast cancer. After confirmation, these findings could have clinical importance in breast cancer management.

REFERENCES

1. Nyante SJ. Single Nucleotide Polymorphisms and the Etiology of Basal-like and Luminal A Breast Cancer: A Pathway-Based Approach [PhD thesis]. Chapel Hill: University of North Carolina; 2009.

2. Simpson PT, Reis-Filho JS, Theodora G, Lakhani, SR. Molecular evolution of breast cancer. The Journal of Pathology 2005; 248-54.
3. Heldring N, Pike A, Andersson S, Matthews J, Cheng G. Estrogen receptors: how do they signal and what are their targets. Physiological Reviews 2007; 87: 905–931.
4. Gruber CJ, Tschugguel W, Schneeberger C, Huber JC. Production and actions of estrogens. N Engl J Med 2002; 346(5): 340-52.
5. Nadji M, Gomez-Fernandez C, Ganjei-Azar P. Immunohistochemistry of estrogen and progesterone receptors reconsidered: Experience with 5,993 breast cancers. Am J Clin Pathol 2005; 123: 21-27.
6. Meyer UA. Pharmacogenetics – five decades of therapeutic lessons from genetic diversity. Nat Rev Genet 2004; 5: 669-76.
7. Sherry ST, Ward M, Sirotkin K. dbSNP-database for single nucleotide polymorphisms and other classes of minor genetic variation. Genome Res 1999; 9: 677-9.
8. Risch NJ. Searching for genetic determinants in the new millennium. Nature 2000; 405: 847-56.
9. Johnson GC, Esposito L, Barratt BJ, Smith AN, Heward J. Haplotype tagging for the identification of common disease genes. Nat Genet 2001; 29: 233-7.
10. Greenhut S, Kerrigan D, Kelly J, Hollen B. Understanding SNPs and cancer 2008.[database on the internet], http://nci.nih.gov/cancertopics/understandingcancer /geneticvariation.
11. Kobayashi N, Fujino T, Shirogane T. Estrogen receptor a polymorphism as a genetic marker for bone loss, vertebral fractures, and susceptibility to estrogen. Maturitas 2002; 41: 193- 201.
12. Shearman AM, Cupples LA, Demissie S. Association between estrogen receptor a gene variation and cardiovascular disease. JAMA 2003; 290: 2263-70.
13. Hall J, Couse J, Korach K. The multifaceted mechanisms of estradiol and estrogen receptor signaling. J Biol Chem 2001; 276: 36869-72.
14. Andersen TI, Heimd KR, Skrede M, Tveit K, Berg K, Borresen AL. Oestrogen receptor (ESR) polymorphisms and breast cancer susceptibility. Hum. Genet 1994; 94: 665-70.
15. Hsiao W, Young K, Lin S, Lin P. Estrogen receptor-α polymorphism in a Taiwanese clinical breast cancer population: a case–control study. Breast Cancer Res 2004; 6: 180-86.
16. Gallicchio L, Berndt SI, McSorley MA, Newschaffer CJ, Thuita LW. Polymorphisms in estrogen-metabolizing and estrogen receptor genes and the risk of developing breast cancer among a cohort of women with benign breast disease. BMC Cancer 2006; 6:173.

17. Siddig A, Mohamed AO, Awad S, Ahmed HH, Mohammed EZ, Abdu Af. Estrogen Receptor α Gene Polymorphism and Breast Cancer. Ann. N.Y. Acad. Sci. 2008; 1138: 95-107.
18. Mavaddat N, Dunning AM, Ponder BA, Easton DF, Pharoah PD. Common genetic variation in candidate genes and susceptibility to subtypes of breast cancer. Cancer Epidemiol Biomarkers Prev 2009; 18(1): 255-9.
19. Anghel A, Raica M, Marian C, Ursoniu S, Mitrasca O. Combined profile of the tandem repeats CAG, TA and CA of the androgen and estrogen receptor genes in breast cancer. J Cancer Res Clin Oncol 2006; 132: 727-33.
20. Madeira KP, Daltoe RD, Sirtoli GM, Carvalho AA, Azevedo Rangel LB, Silva IV. Estrogen receptor alpha (ERS1) SNPs c454-397T>C (PvuII) and c454-351A>G (XbaI) are risk biomarkers for breast cancer development. Mol Biol Rep 2014; 41: 5459-5466.
21. Lundin KB, Giwercman A, Dizeyi N, Giwercman YL. Functional in vitro characterisation of the androgen receptor GGN polymorphism. Mol Cell Endocrinol 2007; 264: 184-7.
22. Sand P, Luckhaus C, Schlurmann K, Gotz M, Deckert J. Untangling the human estrogen receptor gene structure. J Neural Transm 2002; 109: 567-83.
23. Boyapati SM, Shu XO, Gao YT, Dai Q, Yu H, Cheng JR. Correlation of blood sex steroid hormones with body size, body fat distribution, and other known risk factors for breast cancer in post-menopausal Chinese women. Cancer Causes Control 2004; 15: 305-11.
24. Iobagiu CC, Lambert M, Normand C. Microsatellite profile in hormonal receptor genes associated with breast cancer: Breast Cancer Res.Treat 2006; 1-7.
25. Tsezou A, Tzetis M, Gennatas C, Giannatou E, Pampanos A, Malamis G. Association of repeat polymorphisms in the estrogen receptors alpha, beta (ESR1, ESR2) and androgen receptor (AR) genes with the occurrence of breast cancer. The Breast 2008; 17:159-66.
26. Hill SM, Fuqua SA, Chamness GC, Greene GL, McGuire WL. Estrogen receptor expression in human breast cancer associated with an estrogen receptor gene restriction fragment length polymorphism. Cancer Res. 1989; 49: 145–148.
27. Shin A, Kim D, Nishio H. Estrogen receptor a polymorphism and breast cancer risk. Breast Cancer Res Treat 2003; 80: 127-31.
28. Cai Q, Shu XO, Jin F. Genetic polymorphisms in the estrogen receptor a gene and risk of breast cancer: results from the Shanghai Breast Cancer Study. Cancer Epidemiol Biomarkers Prev 2003; 12: 853-9.

29. Berkowitz GS, Stone JL, Lehrer SP. An estrogen receptor genetic polymorphism and the risk of primary and secondary recurrent spontaneous abortion. Am J Obstet Gynecol 1994; 171:1579-84.
30. Ziegler RG, Hoover RN, Pike MC, Hildesheim A, Nomura AM. Migration patterns and breast cancer risk in Asian-American women. J Natl Cancer Inst 1993; 85: 1819-27.
31. Wedren, S. Oestrogen receptor alpha gene haplotype and postmenopausal breast cancer risk: a case control study: Breast Cancer Res. 2004; 6(4): 437-49.
32. Franzel J, Van Duijnhoven, Irene D, Petra H, Mark R, Andre G. Polymorphisms in the estrogen receptor alpha gene and mammographic density. Cancer epidemiol biomarkers prev 2005; 14(11): 2655-60.
33. Gail S, Prins S, Kenneth S, Korach. The role of estrogens and estrogen receptors in normal prostate growth and disease. Steroids 2008; 73 (3): 233-2.
34. Yaich L, Dupont WD, Cavener DR, Parl FF. Analysis of the PvuII restriction fragment-length polymorphism and exon structure of the estrogen receptor gene in breast cancer and peripheral blood. Cancer Res 1992; 52: 77–83.
35. Saad AA, Moneim MA, TawabN. Association between Era gene polymorphism and the risk of breast cancer in agroup of Egyptian women. Bull. Alex. Fac. Med. 2008; 44: 4.
36. Onland-Moret NC, Roest H, Diederick M, Grobbee E, Petra H. The estrogen receptor a gene and breast cancer risk (The Netherlands). Cancer Causes and Control 2005; 16: 1195-1202.
37. Shen Y, Li DK, Zibao Zhang JW, Gao E. Joint Effects of the CYP1A1 MspI, ERα PvuII, and ERα XbaI Polymorphisms on the Risk of Breast Cancer: Results from a Population-Based Case-Control Study in Shanghai, China. Cancer Epidemiol Biomarkers 2006; 15: 342.
38. Jakimiuk AJ, Malgorzata N, Bogusiewicz M, Adamiak A, Skorupski P. Prevalence of estrogen receptor α PvuII and XbaI polymorphism in population of Polish postmenopausal women. Folia histochem cytobiol 2007; 45:331-38.
39. Javed Sadia, Muhammad Ali, Sobia Sadia, Muhammad AA. Combined effect of menopause age and genotype on occurrence of breast cancer risk in Pakistani population. Maturitas 2011; 69: 377-82.
40. Li Y, Liu F, Tan SQ, Wang Y, Li SW. Estrogen receptor-alpha gene PvuII (T/C) and XbaI (A/G) polymorphisms and endometriosis risk: a meta-analysis. j gene 2012; 7: 49.
41. Alsheyab F, Dannoun A, Awad D, Mosameh Y. Association between Estrogen Receptor alpha Polymorphisms and Breast Cancer Risk in Jordanian Women. Journal of Applied Biological Sciences 2012; 6(1): 13-20.

42. Cai Q, Gao YT, Wen W. Association of breast cancer risk with a GT dinucleotide repeat polymorphism upstream of the estrogen receptor-a gene. Cancer Res 2003; 63: 5727– 30.
43. Zheng Y, Huo D, Zhang J, Yoshimatsu TF, Niu Q. Microsatellites in the Estrogen Receptor (ESR1, ESR2) and Androgen Receptor (AR) Genes and Breast Cancer Risk in African American and Nigerian Women. PLos ONE 2012;7(7):40494.
44. Becherini L, Gennari L, Masi L. Evidence of a linkage disequilibrium between polymorphisms in the human estrogen receptor alpha gene and their relationship to bone mass variation in postmenopausal Italian women. Hum Mol Genet 2000; 9:2043-50.
45. King RC, Stansfield WR, Mullign PK. Dictionary of Genetics. 7th ed: Oxford University Press 2006;16-174. ISBN 978-0-321-79578-6.
46. Araújo LK, Rezende CL, Souza SL, Daltoé DR, Madeira PK, Herkenhoff LF. Prevalence of Estrogen Receptor Alpha PvuII (c454-397T>C) and XbaI (c454A>G) Polymorphisms in a Population of Brazilian Women. Braz. Arch. Biol. Technol. 2011; 54 (6): 1151-57.
47. Ramalhinho AC, Marques J, Breitenfeld L. Genetic polymorphims of estrogen receptor alpha 2397 PvuII (T>C) and 2351 XbaI (A>G) in a portuguese population:prevalence and relation with breast cancer susceptibility. Mol Biol Rep 2013; 40: 5093-03.
48. Van Meurs JB, Schuit SC, Weel AE, van der M. Association of 5' estrogen receptor alpha gene polymorphisms with bone mineral density, vertebral bone area and fracture risk," Hum Mol Genet 2003; 12: 1745–54.
49. Onland-Moret NC, van Gils CH, Roest M, Diederick E. The estrogen receptor a gene and breast cancer risk (The Netherlands). Cancer Causes and Control 2005; 16: 1195-1202.
50. Goldstein DB, Weale ME. Population genomics: linkage disequilibrium holds the key. Curr Biol 2001; 11: 576-9.
51. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000; 343(2):78-85.
52. McGuire WL, Carbone PP, Sears ME. Estrogen receptors in human breast cancer: an overview. New York Raven Press 1975; 1-8.
53. Azimi C, Abbasi S. Genetic polymorphisms in the estrogen receptor-α Gene codon 325(CCC}CCG) and risk of breast cancer among Iranian women: a case control study. Medical Journal of the Islamic Republic of Iran 2009; 23(2): 75-82.

54. Roodi N, Renee Bailey L, Kao WY, Verrier CS, Yee CJ. Estrogen Receptor Gene Analysis in Estrogen Receptor-Positive and Receptor-Negative Primary Breast Cancer. Journal of the National Cancer Institute 1995; 87(6):15.
55. Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA. Family history and the risk of breast cancer: a systematic review and meta-analysis. Int J Cancer 1997; 71:800-9.
56. Southey MC, Batten LE, McCredie MR, Giles GG, Dite G, Hopper JL et al. Estrogen receptor polymorphism at codon 325 and risk of breast cancer in women before age forty. J Natl Cancer Inst 1998; 90:532-36.
57. Modugno F, Zmuda JM, Potter D, Cai C, Ziv E, Cummings SR et al. Association of estrogen receptor alpha polymorphisms with breast cancer risk in older Caucasian women. Int J Cancer 2005; 116:984-91.
58. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. Epidemiol Rev 1993; 15:36-47.
59. Bernstein L. Epidemiology of endocrine-related risk factors for breast cancer. J Mammary Gland Biol Neoplasia 2002; 7: 3-15.
60. Colditz G, Baer H, Tamimi R. Epidemiology of Breast Cancer. New York: Oxford University Press, 2005.
61. Key TJ, Pike MC. The role of oestrogens and progestagens in the epidemiology and prevention of breast cancer. Eur J Cancer Clin Oncol 1988; 24: 29-43.
62. Stavrou I, Zois C, Ioannidis JP, Tsatsoulis A. Association of polymorphisms of the oestrogen receptor alpha gene with the age of menarche. Hum Reprod 2002; 17:1101–05.
63. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 Epidemiological studies of 52,705 women with breast cancer and 108,411 women without Breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 1997; 350: 1047-59.
64. Zuppan PJ. Polymorphisms at the estrogen receptor (ESR) locus and linkage relationships on chromosome 6q [abstract]. Cytogenet Cell Genet 1989; 51:1116.
65. Parl FF, Cavener DR, Dupont WD. Genomic DNA analysis of the estrogen receptor gene in breast cancer. Breast cancer Res Treat 1989; 14:57-64.
66. Chattopadhyay S, Siddiqui S, Akhtar MS, Najm MZ, Deo SVS, Shukla NK et al. Genetic polymorphisms of ESR1, ESR2, CYP17A1, and CYP19A1 and the risk of breast cancer: a case control study from North India. Tumor Biol 2014; 35:4517-27.

67. Weel AE, Uitterlinen AG, Westendorp IC. Estrogen receptor polymorphism predicts the onset of natural and surgical menopause. J Clin Endocrinol Metab 1999; 84:3146-50.
68. Surekha D, Vishnupriya S, Nageswara D, Sailaja K, Raghunadharao D. PvuII polymorphism of estrogen receptor –α gene in breast cancer. Indian journal of human genetics 2007; 13:3.
69. Hu Z, Song CG, Lu JS. A multigenic study on breast cancer risk associated with genetic polymorphisms of ER Alpha, COMT and CYP19 gene in BRCA1/BRCA2 negative Shangai women with early onset of breast cancer or affected relatives. J Cancer Res Clin Oncol 2007; 133:969-78.
70. Kok HS, Van Asselt KM, Van der Schouw YT, Peeters PH, Wijmenga C. Genetic studies to identify genes underlying menopausal age. Hum Reprod. 2005; 11:483-93.
71. Gail S, Prins S, Kenneth S, Korach. The role of estrogens and estrogen receptors in normal prostate growth and disease. Steroids 2008; 73(3): 233-44.
72. Gonzlaez-Zuloeta Ladd AM, Arias VA, Rivadeneira F, Siemes C, Hofman A, Stricker BH et al. Estrogen receptor alpha polymorphisms and postmenopausal breast cancer risk. Breast cancer Res Treat 2008; 107:415-19.
73. Ewertz M, Duffy SW, Adami HO. Age at first birth, parity and risk of breast cancer: a meta-analysis of 8 studies from the Nordic countries. Int J Cancer 1990; 46:597-603.
74. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. Lancet 2002; 360:187-95.
75. Russo J, Russo IH. Toward a physiological approach to breast cancer prevention. Cancer Epidemiol Biomarkers Prev 1994; 3: 353–64.
76. Russo J, Tay LK, Russo IH. Differentiation of the mammary gland and susceptibility to carcinogenesis. Breast Cancer Res Treat 1982; 2:5-73.
77. Vonderhaar BK. Prolactin: the forgotten hormone of human breast cancer. Pharmacol Ther 1998; 79:169-78.
78. Hamajima N, Hirose K, Tajima K. Alcohol, tobacco and breast cancer—collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br J Cancer 2002; 87:1234-45.
79. Madigan MP, Troisi R, Potischman N, Brogan D, Gammon MD, Malone KE et al. Characteristics of respondents and non-respondents from a case-control study of breast cancer in younger women. International Journal of Epidemiology 2000; 29: 793-98.

80. Jernström H, Sandberg T, Bågeman E , Borg Å, Olsson H. Insulin-like growth factor- 1 (IGF1) genotype predicts breast volume after pregnancy and hormonal contraception and is associated with circulating IGF-1 levels: implications for risk of earlyonset breast cancer in young women from hereditary breast cancer families. Br J Cancer 2005; 92(5):857-66.
81. McTiernan A, Rajan KB, Tworoger SS, Irwin M, Bernstein L, Baumgartner R et al. Adiposity and sex hormones in postmenopausal breast cancer survivors. J Clin Oncol 2003; 21:1961-6.
82. Weiderpass E, Braaten T, Magnusson C, Kumle M, Vainio H, Lund E et al. A prospective study of body size in different periods of life and risk of premenopausal breast cancer. Cancer Epidemiol Biomarkers Prev 2004; 13:1121-7.
83. Deng HW, Li J, Li JL, Dowd R, Davies KM, Johnson M et al. Association of estrogen receptor-alpha genotypes with body mass index in normal healthy postmenopausal Caucasian women. J Clin Endocrinol Metab 2000; 85:2748-51.
84. Gallicchio L, Berndt SI, McSorley MA, Newschaffer CJ, Thuita LW, Argani P et al. Polymorphisms in estrogen-metabolizing and estrogen receptor genes and the risk of developing breast cancer among a cohort of women with benign breast disease. BMC Cancer 2006, 6:173.
85. Ingelman-Sundberg M. Pharmacogenetics of cytochrome P450 and its applications in drug therapy: the past, present and future. Trends Pharmacol Sci 2004; 25:193-200.
86. Goetz MP, Kamal A, Ames MM. Tamoxifen pharmacogenomics: the role of CYP2D6 as a predictor of drug response. Clin Pharmacol Ther 2008; 83:160-6.
87. Giacinti L, Claudio P, Lopez M, Giordano A. Epigenetic information and estrogen receptor –α expression in breast cancer. Oncologist 2006; 11:1-8.
88. Wittliff JL. Steroid-hormone receptors in breast cancer. Cancer 1984; 53:630-43.
89. Knight WA, Livingston RB, Gregory EJ. Estrogen receptor as an independent prognostic factor for early recurrence in breast cancer. Cancer Res 1977; 37: 4669-71.
90. Gapinski PV, Donegan WL. Estrogen receptors and breast cancer: prognostic and therapeutic implications. Surgery 1980; 88(3): 386–93.