Chapter 2

Genetic Polymorphisms in Aromatase (CYP19) Gene and Cancer

Arjumand S. Warsy, Fatimah Basil Almukaynizi, Soad AlDaihan, Sophia Alam and Maha Daghastani

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.69208

Abstract

Estrogens play an important role in the development and progression of several types of cancers. The synthesis of estrogens occurs in almost all tissues of the body in addition to the gonads. The enzyme aromatase (CYP19A1) encoded by *CYP19A1* gene is involved in the synthesis of estrogens. Genetic variations in *CYP19A1* gene influence both the structure-function relationship of the enzyme and the rate of its synthesis. Extensive studies have reported different types of polymorphisms in the *CYP19A1* gene and have shown that the polymorphisms, depending on their location in the gene, have different effects on the function and activity of the gene product. Association studies have been conducted and have led to the realization that interpopulation differences are widespread. Not only do polymorphic forms exert different effects on the development of different cancers, due possibly to the influence of other genetic variations, environmental, metabolic, and epigenetic factors, but also are important as they lead to the interindividual differences seen during treatment of the cancer state. This chapter covers important aspects of the aromatase function, the *CYP19A1* gene structure, polymorphisms identified in the gene, different cancers and associated polymorphisms, and the role of the polymorphic forms in affecting the treatment strategies.

Keywords: aromatase, aromatase inhibitors, cancer, CYP19A1, estrogens, polymorphism

1. Introduction

By the late 1990s, several epidemiological and clinical studies had shown that estrogens play an important role in the development and progression of several types of cancers, in particular

breast, endometrial, prostrate, and colorectal cancer (CRC). A strong connection was shown to exist between initiation/promotion of cancer and excess of estrogens, as the latter increased mitotic activity. Initially, extensive studies linked the administration of exogenous hormones to the development of these cancers [1], and later it was shown that several estrogen-sensitive tissues act as intracrine organs, producing estrogens and hence elevating local hormone levels, which accelerated proliferation and growth of cancer cell [2].

There are four major naturally occurring estrogens, estrone (E1), estradiol (E2), estriol (E3), and estetrol (E4), which are produced only during pregnancy. Estradiol (E2) is an important estrogen, has the highest affinity to estrogen receptors, and is required for different physiological functions during all stages of life in both males and females [3]. Aromatase, due to its critical role in the synthesis of the different forms of estrogens from androgens [4], specifically estradiol from testosterone, estrone from androstenedione, and estriol from 16α-hydroxylated dehydroepiandrosterone, is incriminated as a major player in cancer biogenesis.

2. The enzyme "aromatase": a key player in estrogen synthesis

Aromatase (EC 1.14.14.1), also known as estrogen synthase, is the gene product of *CYP19A1* gene and is an important member of the cytochrome p450 superfamily, subfamily 19. It catalyzes a rate-limiting step during the aromatization of androgens to estrogens by three successive hydroxylations and eliminations of carbon at position 19 of the androgens (**Figure 1**) [5].

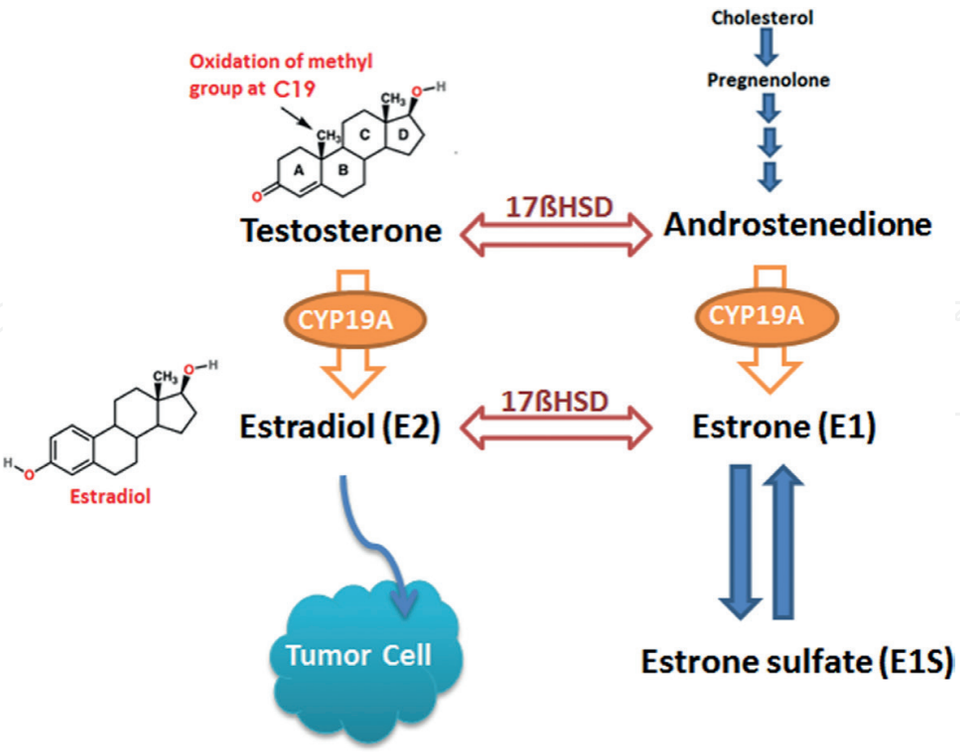

Figure 1. Role of aromatase in estrogen synthesis.

Several studies suggest that many tumors are dependent upon estrogens for their development and continued growth [6]. Blockage of any conversion in the pathway potentially leads to decreased estrogen production, but more specific suppression results from inhibition of the final step that is unique to estrogen biosynthesis, i.e., inhibition of aromatase. The key role of aromatase in estrogen biosynthesis has generated enormous interest in putative inhibitors of the enzyme and their use as therapy against endocrine-responsive tumors.

Initially, it was believed that the ovaries and placenta are the only site for the production of estrogens, which are involved in female reproductive functions. However, later studies conducted using many sophisticated and sensitive tests and equipment revealed that estrogens are also synthesized in the male gonadal tissues, i.e., the testis and epididymis, and in extragonadal tissues including liver, colon, prostate, brain, adrenal gland, skin, bone, hair follicles, adipose, and vascular tissues. This is due to the presence of aromatase, which is active in various tissues in both females and males, and hence estrogens are produced in gonads and in the extra-gonadal tissues [2, 7–9].

Aromatase is a dimer, a complex of two polypeptides; one is a specific cytochrome P450, which is the product of the *CYP19A1* gene. The other subunit is a flavoprotein, NADPH-cytochrome P450 reductase. This is ubiquitously present in most cells, and this wide distribution within the human body justifies its central role in different physiological processes [10].

2.1. Aromatase gene structure

The *CYP19A1* is located on chromosome 15 at q21.1 region and spans about 123 kb [11]. It has 10 exons and nine introns in all tissues where the coding region covers about 34 kb region, while the regulatory region is more than three times longer (approx. 95 kb) **(Figure 2)**. This is in the 5′ region of the gene and occurs as unique sequences, scattered upstream of the coding sequences. The regulatory region is unusually large and is composed of at least 10 tissue-specific promoters **(Figure 3)**. These promoters are used alternatively in different cell types. The regulation of each promoter depends on a distinct set of regulatory sequences in the DNA and specific transcription factors that bind to these sequences. The transcription factors bind the promoter, activating it and giving rise to splicing of an untranslated first exon onto this common junction immediately upstream of the translation start site in the coding region. The promoter region has the basic transcription elements, i.e., the TATA box, a CAAT box, and a GC box, and also contains different regulatory elements in different tissues [12].

This first exon (exon 1) occurs in multiple forms, which encode the 5′ untranslated region (UTR) of the *CYP19A* gene and are spliced out in a highly tissue-specific manner. Since the gene has multiple promoters, in each tissue the transcript is generated following tissue-specific splicing of alternative exons available for exon 1. For physiologic estrogen biosynthesis in the gonads, brain, vascular tissue, bone, adipose tissue, placenta, skin, and fetal liver, different partially tissue-specific promoters are used [13]. To date, nine different exon 1 subtypes have been reported, and each is expressed in a specific tissue as presented in **Table 1**. Exons 2–10 form the coding sequence of the gene and lie in a region, which is approximately 34 Kb in length. Exon 1, specific for the tissue, gets linked to exon 2 after splicing of the intervening sequences **(Figure 3)**. All transcripts have the same coding sequence generated from the sequences in exons 2–10 [12–14].

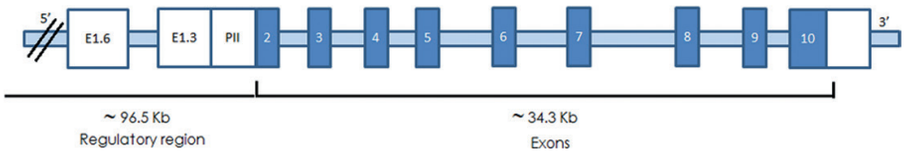

Figure 2. Structure of CYP19A gene.

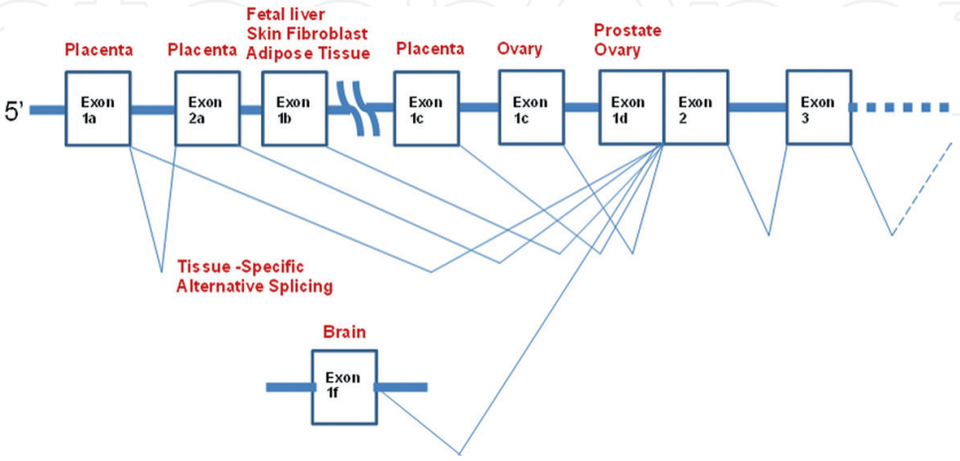

Figure 3. The 5′ gene region of the human *CYP19A1* gene. The 5′ untranslated region of the human aromatase gene is encoded by multiple exon 1. These are tissue specifically spliced and connected to exon 2 (modified from Ref. [4]). The lines linking exon 1 to exon 2 indicate that exon 1 is present as 5′ UTR in the tissue.

Exon 1 type	Expressed in (tissue)
I.1 (1a) and I.2 (1e)	—Placenta
I.3 (1c) and PII (1d)	—Ovary —Testis
I.4 (1b)	—Adipose tissue
I.5	—Fetal lung —Intestine
I.6	—Adipose —Bone tissues
I.7	—Adipose —Vascular endothelial tissues
1f	—Brain
II. I.3, I.7, and I.4	—Breast

Table 1. The multiple forms of exon 1 and the tissues in which each is expressed.

Investigations have shown the expression of aromatase gene in estrogen-dependent breast cancer (BC) tissues, endometrial carcinoma, and colorectal, gastric, liver, lung, ovarian, pancreatic, and prostatic cancers [2, 12]. The cell-specific expression of aromatase determines the presence or absence of aromatase activity in the tissue and hence the amount of available estrogens.

The transcriptional regulation of aromatase has been extensively investigated since the 1980s. Many mechanisms have been proposed to explain the underlying control of *CYP19A1* gene expression, in an attempt to elucidate the etiological role played by aromatase in cancer development and progression [15]. Several mechanisms at the transcriptional, posttranscriptional, and epigenetic levels have been unveiled. In addition to these mechanisms, extensive genetic variants of CYP19A1 gene have been identified that influence aromatase activity and may be regarded as prognostic factors for susceptibility to cancer development [16–18].

2.2. Genetic polymorphisms of the *CYP19A1* gene

The *CYP19A* gene seems to have acquired a number of variations in the coding, noncoding, and control sequences [17]. These variations result from different mutations, short tandem repeat (STR) polymorphisms, and single nucleotide polymorphisms (SNPs). The variations may influence expression of *CYP19A1* gene, activity of the enzyme, susceptibility to cancer development, and clinicopathological features of cancer, and some act as refractory and prognostic factors.

Frequencies at which the alleles occur in different populations differ considerably, and it is also shown that the differences in the plasma levels of several sex hormones may be due to the presence of different alleles, particularly in postmenopausal women. It is hypothesized that the genetic polymorphisms provide a probable explanation for differences in cancer risk among different ethnic groups. Hence, the presence of the different *CYP19A1* alleles may account partially for the racial differences in the frequency of the different types of cancer.

This section presents the polymorphisms identified in the *CYP19A1* gene and discusses their distribution in different populations, their association with different cancers, their influence on the development, prognosis, treatment strategies, and complications resulting from the treatment.

2.2.1. Short tandem repeat (STR) polymorphism

Short tandem repeats (STRs) were identified in the aromatase gene during the late 1990s, and some studies showed a higher incidence of cancers in individuals carrying different alleles of the *CYP19A1* gene. One of the most frequently reported STRs in *CYP19A1* is a tetranucleotide (TTTA) sequence, which occurs in different repeats ranging from 2 to 13.

Several studies conducted in different populations reported association between the tetranucleotide repeat sequence and cancer, while others failed to do so. Kristensen et al. [19] reported that a rare polymorphic A1 allele of *CYP19* repeat (TTTA)12 occurs at a significantly higher frequency in females suffering from breast cancer than controls (3.6 vs. 1.6%) and indicated that the carriers of the allele might have an increased risk of developing breast cancer (OR = 2.42; 95% CI = 1.03–5.80). Haiman et al. [20] showed that breast cancer cases had a statistically significant greater frequency of the (TTTA)10 repeat alleles (10 alleles; 2.3 vs. 0.7%; $p = 0.005$), but a nonsignificant increase in the frequency of the (TTTA)12 allele (12 alleles; 3.1 vs. 2.1%; $p = 0.11$). The 10 alleles were more frequent in patients with more advanced cancer disease, which were defined as four or more involved nodes or distant metastasis. A little later study on Japanese women reported similar results in breast cancer

(OR = 1.80; 95% CI = 0.97–3.36) risk [21]. Baxter et al. [22] also confirmed that breast cancer cases had a statistically significant positive association with the (TTTA)10 allele (1.5 vs. 0.2%; p = 0.028) and the (TTTA)8 allele (13.5 vs. 8.7%; p = 0.012), while the frequency of the (TTTA)12 allele was not statistically significant. A study by Miyoshi et al. [23] showed that the (TTTA)7 along with a trinucleotide deletion (−3bp) allele was increased significantly ($p < 0.05$) in breast cancer patients who were ER positive (OR = 1.72; 95% CI = 1.10–2.69), but not those who were ER negative. Among the Brazilian cancer patients, the (TTTA)10 allele associated positively with breast cancer development and the frequency of the allele was three times more compared to controls (p = 0.048) [24]. A study from China also showed a significantly higher frequency of (TTTA)10 allele in breast cancer cases (12.4%) than controls (8.2%) (p = 0.02) [25]. As presented in **Figure 4**, a recent study from Mexico showed significant differences in the repeat number in breast cancer patients compared to the normal controls.

Several studies were published from Russia, and it was shown by Artamonov et al. [26] that the allele (TTTA)8 was associated with BC (11.8 vs. 6.3%; p = 0.04). Risk of BC elevated if this allele was present with genotype A2/A2 of the tetranucleotide deletion (7.3 vs. 0%; p < 0.01). In Norwegian women [19], the association of breast cancer with the long allele (TTTA)12 was shown.

Kim et al. [28] reported that though there is no difference in the (TTTA)n genotype distribution between patients and controls, but there was a positive association between >(TTTA)10 and ER-negative tumors and between lower repeat polymorphism and ER-positive tumors (p = 0.019). A study on different ethnic groups (African-Americans, Japanese, Latinas, and non-Latina Whites) by Probst-Hensch et al. [29] reported contradictory results and showed no consistent association of (TTTA)n repeat polymorphism with breast cancer risk. This was in line with other studies from the USA [30] and Greece [31]. These studies show that the tetranucleotide polymorphism occurs in different populations, and the repeat variants show association with breast cancer in some and not others. Often, contradictory results are reported from the same population.

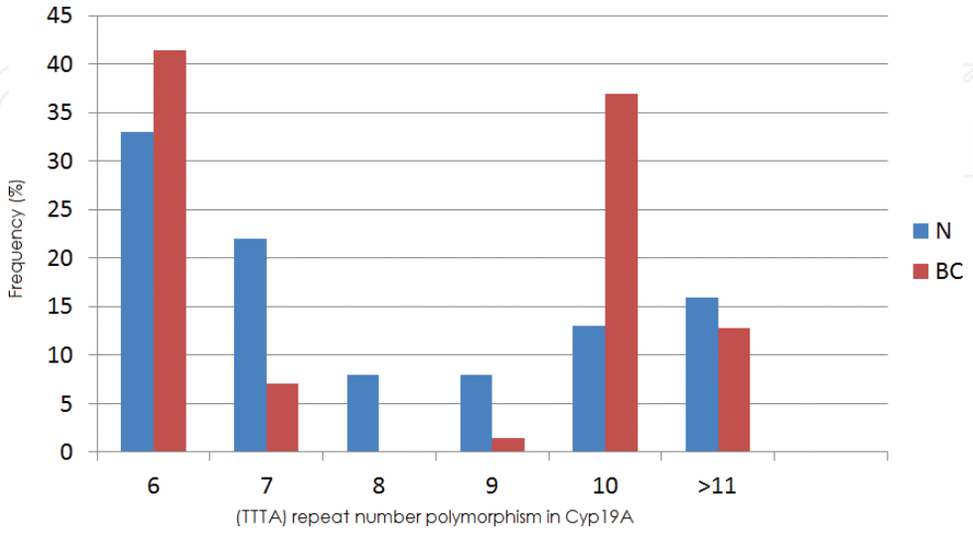

Figure 4. Frequency of TTTA repeat number polymorphism in breast cancer (BC) patients and normal (N) controls in a Mexican population (modified from Ref. [27]).

The (TTTA)n polymorphism has been reported to modify susceptibility to prostate cancer development in several studies in different populations. Most of the studies have shown that the longer alleles (TTTA)7 or more are associated with a higher risk of prostate cancer, and in some studies, it is shown that the association is also with cancer-specific survival [32, 33]. A study on the Japanese men reported that (TTTA)7 and (TTTA)8 alleles show association with the risk of prostate cancer [34]. It was also shown that when the patients were stratified according to the pathological grade or the clinical stage, there was no significant difference in the different genotypes. Tsuchiya et al. [35] regarded this polymorphism as a novel predictor of prostate cancer with bone metastasis. They showed that alleles longer than seven repeats (TTTA)7) were associated with worse cancer-specific survival. Tang et al. [36] further suggested that though these repeat polymorphism influence disease susceptibility, but the effect is modified by factors that alter hormone metabolism.

The (TTTA)n has also been investigated in endometrial cancer, and some studies have shown that the long alleles A6 and A7 occur at a higher frequency in the patients than the controls [37–39]. It was shown that the longer A6 and A7 alleles have higher intratumoral aromatase activity, thus predisposing to increased synthesis of estrogens and hence increasing the local estrogen concentration, which supports proliferation [40].

2.2.2. TCT insertion/deletion in intron 4

A TCT insertion/deletion (ins/del) polymorphism occurs in the intron 4 of the *CYP19A* gene, approximately 50 bp upstream to the (TTTA)n repeat. A few studies have linked breast cancer to the trinucleotide TCT deletion [31, 41]. In the British population, the TCT ins/del and a G-->T substitution in intron 4 were of rare occurrence (0.35 and 0.45, respectively), and both were in linkage disequilibrium with (TTTA)10 allele, which was reported to be linked to breast cancer susceptibility [41]. Similarly, in Korean breast cancer patients, 3-bp ins/del polymorphism showed a strong association with breast cancer risk [42], and other studies showed a stronger association with endometrial and prostate cancer risk [39, 43]. Coexisting (TTTA)n and 3-bp TCT deletion polymorphism show contradictory results in different studies [44, 45].

2.2.3. Single nucleotide polymorphisms

The presence of single nucleotide variations in the DNA sequence of *CYP19A1* gene was recognized in the earlier 1990s, and Ma et al. [46] reported 88 SNPs in 2005. To date several more SNPs have been identified, and several are of clinical interest, due to their predisposing or protective role in the development of cancer or other diseases. Some of these variations are rare, while others occur at a frequency of >1% and are polymorphic. Sourdaine et al. in 1994 [47] described several rare mutations in exons 3, 7, and 10 of the *CYP19A* gene in breast cancer patients. Kristensen et al. [48] reported a mutation in exon 10 (C > T) and showed that though the frequency of TT genotype was significantly higher in patients vs. controls ($p = 0.007$), particularly among those with stage III and IV diseases ($p = 0.004$) and with tumors larger than 5 cm ($p = 0.001$), it was a rare mutation. The T allele frequency was considerably higher in individuals who presented with more advanced disease and had larger (>5 cm) tumor size. The aromatase mRNA levels were high in the patient group and were associated with a switch to ovarian promoter from the one normally used, i.e., adipose promoter.

Single nucleotide polymorphism (SNP) association studies have been reported in several cancers and provide several interesting cues about the role of these variations. This section presents different types of cancer and the SNPs identified and studied.

3. CYP19A1 polymorphisms in different cancers

3.1. Variations in CYP19A1 gene and breast cancer

Breast cancer remains as the most frequently occurring cancer in all races and all ethnic groups (https://nccd.cdc.gov/uscs/toptencancers.aspx). Estrogens affect proliferation and growth of the cells in the breast. Thus, polymorphisms of the genes, which are involved in the estrogen biosynthesis and metabolism, have been regarded as factors affecting the risk of breast cancer. Research conducted since the early 1970s confirmed that the major risk and predisposing factor for breast cancer is increased exposure to estrogens and progesterone [49]. Obesity was also shown to be one of the factors since adipose tissues are an important source of endogenous estrogens [50]. Furthermore, local production of estrogens in the breast tissue was shown to play a major role in elevating hormone levels in the breast tissue, which in turn accelerates proliferation and growth of breast cells and subsequent progression to malignant transformation [51]. Genetic factors increase susceptibility to develop breast cancer, and in the 1990s, the identification of two breast cancer susceptibility genes, BRCA1 and BRCA2 [52], turned the attention of breast cancer research to the identification of possible genetic markers of breast cancer susceptibility. Extensive research has led to accumulation of knowledge about genetic variation in different genes, including the *CYP19A1* gene, due to its gene product, aromatase. **Table 2** summarizes some of the reports on SNPs in *CYP19A1* and shows that there are contradictions in different reports about the contribution of a SNP to breast cancer risk and there are population differences in the influence of the SNP on clinical presentation.

The rs10046 polymorphism is a C/T transition in the 3′ UTR of *CYP19A1* gene. It has been classified as a benign variant, which has recently been linked to aromatase deficiency (https://www.ncbi.nlm.nih.gov/clinvar/RCV000323501/). Recently, Farzaneh et al. [54] showed that there was a significant differences in allele and genotype frequencies for rs10046 in Iranian population with and without breast cancer (p-value = 0.01, OR (CI 95%) = 1.59 (1.1–2.3), p-value = 0.04, OR (CI 95%) = 1.7 (1.1–2.5), respectively). Zhang et al. [79] reported that among the ER+ Chinese women, the T allele of rs10046 was significantly associated with premenopausal breast cancer risk. Yoshimoto et al. [69] studied rs10046 polymorphism in Japanese women and reported that the C allele could be regarded as a risk predictor of breast cancer (p = 0.007). However, other studies on different populations failed to show any association. A study on Greenlandic Inuit women did not show any effect of rs10046 on the risk of breast cancer (%) [53]. Pineda et al. [72] showed that in a Spanish population the C allele may be linked to an increased risk of breast cancer. However, when they extended their findings to a meta-analysis, the association was lost. They concluded that it is possible that the effect of rs10046 is modified in the presence of other variants. Zins et al. [71], recently, showed that though rs10046 does not link to breast cancer risk, but the TT genotype affects the age of onset,

CYP19A1 SNP	Population/study location	Clinical implication	Reference
rs10046	Inuit women	Nonsignificant association with BC	[53]
rs10046	Iranian	Significant association with BC	[54]
rs762551 rs4646	Swedish	Predictive marker for early breast cancer events in AI-treated patients with ER-positive tumors	[8]
rs6493497	USA	Associated with decreased bone density with AI treatment	[10]
rs4646	China	AA is significantly associated with improved clinical outcome of hormone therapy; prolonged DFS	[55]
rs4646, rs10046, rs700518, rs749292 rs2289106, rs3759811, rs4775936	American	Significantly associated with decreases in triglycerides on letrozole treated	[12]
rs10046	Xinjiang Uigur women	TC genotype and an abortion can reduce the risk of the breast cancer	[56]
rs934635, rs60271534, rs700518	A meta-analysis	Treatment response	[57]
rs700518	Italy	Treatment response	[58]
rs4646, rs10046, rs936308	American	Were associated with bone AEs	[65]
rs4646	Chinese	Related to DFS in early breast cancer and that the prognosis index of the homozygous for the minor allele (AA) may depend on menopause status	[66]
rs700518, rs11856927	American ancestry, Hispanic Americans, and Mexico Whites	Significantly associated with increased breast cancer risk	[67]
rs4775936	UK	AI metabolism	[68]
rs10046	Japanese	Significant risk predictor	[69]
rs700519	India	Could be used as molecular markers to assess breast cancer	[70]
rs10046	Austrian population	Association with clinical characteristics	[71]
rs10046	Spain	Related to levels of circulating estradiol and to the estradiol/testosterone ratio	[72]
rs4646, rs1065779, rs1870050	Taiwan	Associated with poor survival of premenopausal women but does not affect survival of postmenopausal women	[73]
rs4646	American	May serve as a prognostic marker of the response to anastrozole in patients with MBC	[74]
rs10046, rs4646, rs2830, rs9926298, and rs9939609	China	Nonsignificant association with BC	[75]

CYP19A1 SNP	Population/study location	Clinical implication	Reference
rs700518, rs10459592, and rs4775936	Korea	Significantly associated with clinical efficacy	[76]
rs10046, rs4646, rs74929, rs727479	Italian	The aromatase enzyme function is not affected by polymorphisms of CYP19A1 gene in postmenopausal BC patients	[77]
rs4646, rs7167936	Swedish	Involved in both breast cancer risk and prognosis	[78]
Arg264Cys	Chinese	No association	[59]
Arg264Cys	Korean	Increased breast cancer risk	[60]
Arg264Cys	Chinese	No association	[61]
rs1008805	USA	G allele associates with breast cancer	[62]
rs2236722	Japanese	Trp more frequent in ER+	[63]
rs1870049, rs1004982, rs28566535, rs936306, rs11636639, rs767199, rs4775936, rs11575899, rs10046, rs4646	Chinese	No association	[64]

Table 2. Some of the SNP association studies reported in breast cancer.

where individuals carrying TT may develop breast cancer at an age younger than 50 years. It was also shown that the genotypes of rs10046 may influence the levels of estrogens and estrogen/testosterone ratio and also play a role in modulating the levels of other biochemical parameters [72].

The rs4646 polymorphism is an A/C transversion, located in the 3′ UTR of the *CYP19A1* gene. Some studies show it to be significantly associated with an increased risk of breast cancer. Among the Swedish breast cancer patients, rs4646 was strongly associated with the risk of breast cancer and the histological grade of the disease [78]. The A allele was associated with low histological grade and small tumor size ($p = 0.001$ and 0.015). Shao et al. [66] showed that AA is related to longer disease-free survival in Chinese breast cancer patient's population compared to the CC and CA genotype of the rs4646 genotype. Fasching et al. [80] showed that the rs4646 may influence disease-free intervals in breast cancer patients. They concluded that this variant may influence the prognosis of the disease but not through affecting estrogen levels.

Santa-Maria et al. [84] have recently reported that several SNPs influence the plasma lipid levels in patients treated with letrozole, where rs4646, rs10046, rs700518, rs749292, rs2289106, rs3759811, and rs4775936 decreased triglyceride levels and had a variable effect on the level of HDL-C.

A number of other SNPs have been investigated in breast cancer; some are associated with the risk of breast cancer, while others are not (**Table 2**). Some influence the clinical presentation of the disease, the prognosis, and the disease-free intervals, while still others modulate the effect of treatment and the associated complications.

3.2. Variations in CYP19A1 gene and endometrial cancer

Endometrial cancer (EC) is one of the most frequently encountered gynecologic malignancies, and a strong association is shown to exist between excess of estrogens and initiation and promotion of endometrial cancer [81]. As early as 1975, it became evident that estrogen may act as a carcinogen when unopposed by an adequate amount of progesterone. Many studies demonstrated higher risk of endometrial cancer in females on hormone replacement therapy [82]. Since exposure to endogenous estrogens was regarded as an important determinant of risk of endometrial cancer, several studies were initiated to identify genetic variants and the role they play as risk factor for the development of endometrial cancer. One of the earliest studies was reported from Russia and implicated genetic variants of *CYP19A1* in the etiology of endometrial cancer [38]. Mikhailova et al. [83] investigated the C --> T transition (Arg264Cys) in exon 7 of CYP19A1 gene but did not find any association. G/A and T/C polymorphisms of *CYP19A1* were investigated, but no significant association was identified ($p > 0.05$) [85]. Tao et al. [86] investigated several SNPs (rs1065779, rs700519, rs28566535, rs752760, and rs1870050) in *CYP19A1* gene. The results showed that the rs1870050 in the promoter region associates inversely, where the genotypes CC and AC had a 0.81 (95% CI = 0.68–0.97) and 0.58 (95% CI = 0.42–0.80), respectively. Gulyaeva et al. [87] showed that the CT genotype of R264C polymorphism increases the risk of endometrial cancer significantly with an OR = 3.73, $p = 0.0004$. Setiawan et al. [88] showed the association of the A allele of rs749292 and rs727479 with increased risk of endometrial cancer and a 10–20% increase in circulating estrogen levels in postmenopausal women. In another study, the A allele of rs4775936 was significantly associated (OR (per allele) = 1.22; 95% CI = 1.01–1.47; p(trend) = 0.04), while the T allele of rs10046 was marginally associated with increased risk of endometrial cancer (OR (per allele) = 1.20; 95% CI = 0.99–1.45; p(trend) = 0.06) [89]. Recently, Thompson et al. [18] reported the results of a genome-wide study and showed that rs727479 was associated most significantly with endometrial cancer and elevation in circulating estrogen (E2). Further studies are required in different populations to confirm the association of genetic variants of CYP19A1 with endometrial cancer.

3.3. Variations in CYP19A1 gene and prostate cancer

Prostate cancer is among the most frequently encountered non-cutaneous malignancy in men. Extensive research has been carried out to identify the etiology and pathological mechanisms, but the mechanism of prostate cancer development is not fully clear. Several factors have been implicated in its etiology including environmental, dietary, hormonal, lifestyle, and genetic factors. Studies have confirmed that estrogens may be closely involved in predisposing to or even causing cancer [90]. Aromatase is shown to be altered in patients with prostate cancer, and its expression is elevated almost 30 times in the cancer tissue compared to the normal tissue [91, 92]. The mechanisms by which estrogens induce carcinogenesis in prostate tissue have been hypothesized in several studies and involve genotoxicity, after chronic inflammation, epigenotoxicity, hyperprolactinemia, and prostatic ER-mediated changes. The genetic factors in the patient are gaining considerable interest, and genetic polymorphisms are being regarded as prognostic predictors of metastatic prostate cancer [93].

A few studies have reported the influence of *rs700519* on prostate cancer risk. This SNP is a C > T transition in exon 7 of *CYP19A1* gene and results in the substitution of Arg at position 264 by Cys. No association was reported among Bulgarians [94], African Americans [95], and Japanese [96]. However, a study on North Indian population showed that the variant Cys was associated with statistically significant increased risk of prostate cancer (OR = 2.28; 95% CI = 1.20–4.35; p = 0.012) [97]. Another report on Japanese showed that when prostate cancer patients were stratified according to clinical stage and pathologic grade of cancer, the CT and TT genotypes were associated significantly with high-grade carcinoma (OR = 2.59; 95% CI = 1.47–4.46; p = 0.048) [98]. A study on Caucasians showed that the C/T mutation was associated with prostate cancer risk, with only borderline significance after age and BMI adjustment. Interestingly, when the effect of the C/T mutation was evaluated with a mutation in androgen receptor (AR), the significance of the association with prostate cancer risk increased considerably [99]. Mononen et al. [100] explored the association between 18 variants and prostate cancer risk and identified a novel SNP, T201M. This SNP showed association with prostate cancer (odds ratio (OR) = 2.04; 95% confidence interval (95% CI) = 1.03–4.03; p = 0.04). Onsory et al. [97] showed that Cys allele in exon 7 of *CYP19A1* was also associated with statistically significant increased risk of prostate cancer (OR = 2.28; 95% CI = 1.20–4.35; p = 0.012). Other studies also showed that CYP19A1 polymorphisms may influence prostate cancer risk and survival by modifying promoter activity, with subsequent effects on the sex hormone milieu [101].

A study recently reported on two populations of African ancestry failed to show any association between rs60271534 and prostate cancer risk [17]. Another SNP 1531 C > T was investigated in the Turkish prostate cancer patients, but no significant association was observed [102]. Lévesque et al. [103] reported a study in which results obtained in Caucasians and Taiwanese were compared. It was shown that rs12900487, rs4441215, and rs2470152 in *CYP19A1* gene do not follow Hardy-Weinberg equilibrium and did not differ in their frequency between the patient and control group. Two other SNPs rs1870050 and rs2446404 significantly increased the risk of prostate cancer in the Caucasian population, while in the Taiwanese, only rs1870050 was associated significantly in the Caucasians but not in the Taiwanese [103].

The effect of two or more coexisting SNPs in influencing predisposition to prostate cancer is shown in several studies, thereby implying that the SNPs may behave synergistically or have antagonistic effect and thus bringing further heterogeneity to SNP action [96]. Cussenot et al. [32] reported that the long allele (>175 bp) of the TTTA repeat of *CYP19A1*, when existing with V432L polymorphism of *CYP1B1*, increases the risk of prostate cancer significantly. This effect was more obvious in the younger patients. Huang et al. [42] working on a Taiwanese population reported that the risk of developing prostate cancer increased significantly (from OR = 1.59; 95% CI = 1.04–2.44; p = 0.044), when TCT del/del genotype of *CYP19A1* coexists with (TTTA)7. The coexisting ins allele and (TTTA)12 also in the *CYP19A1* reduced the risk of developing prostate cancer. More recently, Kachakova et al. [94] have shown that the 7/8 genotype of (TTTA)n repeat polymorphism in *CYP19A1*, when coexisting with the C allele of rs1056837 in *CYP1B1*, predisposes to prostate cancer, while the 8/9 and the 7/12 genotypes of (TTTA)n of *CYP19A1* when existing with the C allele of *CYP1B1* associate with lower risk of prostate cancer and a reduced risk for aggressive disease.

Interestingly, it was shown that some of the SNPs in *CYP19A1* gene have a significant effect on the level of circulating steroid hormones including LH, testosterone, estradiol, SHBG, and

indices of insulin sensitivity. However, no association was reported between these polymorphisms and non-hormonal parameters including anthropometric parameters, blood pressure, lipids, hemoglobin, and prostate-specific antigen [104].

The plasma level of estrogens may also be altered by the presence of different SNPs in the *CYP19A1* gene. rs2470152, an intronic SNP, is significantly associated with the serum level of E2, while in individuals, the presence of rs2470152 results in the elevation of both E1 and E2 in men [105].

The presence of some SNPs also influences the effect of different nutritional and therapeutic agents used for protection from cancer. Sonoda et al. [106] report from Japan that the protective effect shown by isoflavones against prostate cancer is modified by the (TTTA) long repeat alleles and coexisting minor alleles of rs10046 in *CYP19A1*, even if the isoflavones are used at concentrations as high as 60 mg/day. On the other hand, homozygosity for the major allele of rs10046 in *CYP19A1* and also with coexisting short repeats of (TTTA) reduces the risk of prostate cancer development.

3.4. Variations in *CYP19A1* gene and colorectal cancer

It is well documented that estrogens play a role in the development and progression of colorectal cancer (CRC) [107–109]. The beneficial role played by estrogens in preventing CRC is obvious since males have a higher prevalence of CRC than premenopausal females, but the prevalence increases in menopausal females. Furthermore, females on hormone replacement therapy have a lower susceptibility to CRC [110]. However, it is shown that estrogens are locally produced in the colorectal tissue and result in a higher level of E2 and a lower level of E1. This imbalance in E2/E1 ratio may result in an increase in cell proliferation and concomitant decrease in apoptosis, thus increasing the risk of CRC [111–113]. Normally, in the colon, E2 is converted to E1 by 17β-HSD2 and 17β-HSD4. The E1 is antiproliferative, and the E2/E1 ratio keeps a check on the cell cycle. In colon cancer since this ratio is altered, proliferation is accelerated [111, 112]. A study on Chinese men showed that there were elevated E2 levels and the presence of CT/TT genotype of ESR2 receptor increased the risk of CRC to 2.3 (95% CI = 1.4–3.9), compared to those who had lower levels of E2 and the ESR2 genotype CC [114].

Polymorphisms are reported in *CYP19A1* gene, and some result in increased risk of CRC. Lin et al. [115] studied Caucasian patients of the European origin and genotyped the patients and controls for 13 different SNPs (rs4646, rs10046, rs2414096, rs727479, rs1008805, rs749292, rs93606, rs3751591, rs1004984, rs2445762, rs2446405, rs2740144, and rs32445765), distributed all over the *CYP19A1* gene. Only one SNP rs10046 showed a significant association with CRC risk. However, the significance was lost after correction for multiple comparisons. In a study from the USA, Slattery et al. [110] reported significant association of four SNPs (rs12591359, rs17523880, rs1961177, rs3751591) with increased risk of colon cancer and another four which increased the risk of rectal cancer [116]. However, after adjustment for multiple comparisons, only one SNP (rs12591359) showed significant association (OR = 1.44; 95% CI = 1.16–1.80). The AA genotype of this SNP was associated with an increased risk of cancer of the colon and decreased risk of the cancer of rectum. We genotyped Saudi CRC patients for six SNPs (rs4774585, rs936308, rs4775936, rs700518, rs28757184, and rs4646) in the *CYP19A1* gene but failed to see any association with CRC risk [117]. Lin et al. [116] studied haplotypes in the

CYP19A1 gene and identified one haplotype block, which associated with CRC, most likely reflecting association with the tagging SNP, rs1902584, in the block.

It has also been reported that aromatase also participates in metabolizing various compounds produced endogenously, including sex hormones, lipids, and other lipid derivatives. The rate of metabolism of these compounds depends on the amount and activity of the enzyme, which in turn may be altered by the alleles of the different SNPs. Metabolic end products produced may increase or decrease the risk of CRC and hence the interindividual differences in inherited metabolic susceptibility to CRC. Inflammatory response to different exogenous and endogenous factors may also have a role in CRC [110].

3.5. Variations in *CYP19A1* gene and ovarian cancer

Several clinical trials have provided evidence implicating hormone replacement therapy as a risk factor for development of ovarian cancer. However, the role played by estrogen in the etiology of ovarian cancer has yet to be unveiled. Polymorphisms in *CYP19A1* gene have been investigated in a few studies, to identify possible risk markers. Goodman et al. [118] conducted multiethnic (Japanese, Caucasian, Hawaiian, Filipino, and others) case-control study in Hawaii and investigated two SNPs (rs749292 and rs727479) in relation to ovarian cancer. They showed that the A allele of rs749292 was associated positively with ovarian cancer risk in a codominant model for all races combined, while the rs749479 did not show any association [118]. Both alleles increased the plasma estrogen levels by 10–20%. In an Australian population, no association was seen between rs10046 and ovarian cancer [119]. In a Polish population, several polymorphic loci were investigated, but no association was observed with any of the studied SNPs. More investigations are required to confirm association if any between the SNPs and ovarian cancer.

3.6. Variations in CYP19A1 gene and hepatocellular carcinoma

Worldwide, the prevalence of hepatocellular carcinoma (HCC) is high, classifying it as one of the most common malignancies. Studies have suggested that sex hormones, including androgen and estrogen, may be involved in HCC development and progression [120], pointing toward aromatase variants in HCC development. However, studies on *CYP19A1* polymorphism and the risk of HCC are few. Yuan et al. [121] failed to show any association between a non-synonymous SNP at codon 39 of the *CYP19A1* gene, which causes substitution of Trp by Arg and results in the synthesis of a nonfunctional aromatase. A positive association between A/C transversion and HCC risk was reported by Koh et al. [122]. This polymorphism occurs in the exon I.6 promoter of the *CYP19A1* gene and is located in a consensus sequence for a TFIID binding site. The C allele increases the expression of *CYP19A1* significantly, thereby increasing the synthesis of estrogens and androgens. Further studies are required to identify other risk markers for HCC in the *CYP19A1* gene.

3.7. Variations in *CYP19A1* gene and esophageal adenocarcinoma

Esophageal adenocarcinoma (EA) prevalence is on the rise in the young Western population. A strong gender bias is shown in epidemiological studies, with a sex ratio of 8:9.1. It is suggested that the estrogens may be a protecting factor in females, since estrogens have

been shown to stimulate apoptosis and decrease the growth of the esophageal squamous cells [123]. It also decreases the expression of Ki-67 while increasing E-cadherin expression [124]. However, not many studies have explored the role of SNPs in *CYP19A1* gene and the risk of EA development. Wu et al. [125] studied the role of rs2445762 of *CYP19A1* and showed that there was a significant association between this SNP and an early onset of EA (≤55 vs. >55 years), all $p < 0.05$ after adjusting for covariates and false discovery rate.

Recently, a study by Lagergren et al. [126] pooled 14 studies from three continents (Australia, Europe, and North America) and investigated the effect of 60 SNPs in *CYP19A1* gene as a risk factor for EA. However, no significant association was identified for any of the SNPs in any of the populations. Further studies are required in different populations to identify possible association between *CYP19A1* polymorphisms and EA risk.

3.8. Variations in *CYP19A1* gene and gastric cancer

Gastric cancer is the fourth most common cause of cancer-related death in the world [http://www.who.int/mediacentre/factsheets/fs297/en/]. Studies have suggested that long exposure to estrogens, of ovarian or exogenous origin, may provide a protection against development of cancer [127, 128]. This finding has led to the implication of estrogen receptor defects in the development of gastric cancer [129]. There are very few reports on the association between CYP19A1 gene polymorphism and gastric cancer risk. Freedman et al. [130] investigated 58 SNPs in six genes (*COMT*, *CYP1B1*, *CYP17A1*, *CYP19A1*, *HSD17B1*, and *SHBG*) which are involved in the biosynthesis of estrogen and androgen. None of the *CYP19A1* gene showed any association with gastric cancer risk. More recently, Cho et al. [131] conducted a population-based genetic association study, in which they investigated the role of genes for proteins involved in the steroid hormone biosynthesis pathways. Of the 108 SNPs investigated in five genes (*CYP19A1*, *HSD3B1*, *HSD17B2*, *CYP17A1*, *HSD17B1*), 10 SNPs in *CYP19A1* were significantly associated with the risk of gastric cancer. They concluded that *CYP19A1* may be an important player in elevating the risk of gastric cancer and could be considered as a genetic marker for gastric cancer susceptibility ($p < 0.05$). Since the association is unclear, further studies on *CYP19A1* gene polymorphism and the risk of gastric cancer, in different populations, are warranted and may help in the identification of possible genetic marker.

3.9. Variations in *CYP19A1* gene and testicular germ cell tumor

In young men, testicular germ cell tumor (TGCT) is reported to be the most common cancer. It is hypothesized that an imbalance in the in utero level of androgens and estrogens may be the major predisposing factor in influencing TGCT risk. Kristiansen et al. [132] conducted an investigation on Norwegian-Swedish case-parent trios and genotyped 105 SNPs in 20 genes whose gene products were involved in the sex hormone pathways. Three SNPs (rs2414099, rs8025374, and rs3751592) showed a statistically significant association with TGCT risk in the case-parent analysis. For each of the studied SNP, the T alleles were associated with an elevated risk of TGCT (OR = 1.30, 1.30, and 1.21, respectively). No differences were identified in allelic effect estimates when the parental inherited genetic variation was correlated with the TGCT risk in the offspring. Furthermore, no differences were observed between the

Norwegian and the Swedish populations for each of the studied SNP. It was concluded that aromatase may be a factor playing a role in the etiology of TGCT. However, this statement needs confirmation from further population-based studies.

4. Effect of SNPs on prognosis and survival of breast cancer patients

Some of the SNPs in CYP19A1 gene have been linked to disease prognosis and survival. It was shown that rs28566535, rs730154, and rs936306 are significantly associated with plasma levels of estrone as well as with breast cancer survival [133, 134]. Long et al. [135] showed an association between genetic polymorphisms of the CYP19A1 gene and breast cancer survival. Udler et al. [136] presented preliminary evidence suggesting that germline variation in genes involved in steroid hormone metabolism may alter breast cancer prognosis.

5. Effect of SNPs on hormonal parameters

Variations related to the effect of SNPs on biochemical and hormonal parameters are also reported in a few studies. Huhtaniemi et al. [104] did not find any associations between *CYP19A1* polymorphism and non-hormonal variables including anthropometric parameters, blood pressure, cognition sexual hemoglobin, blood lipids, and hemoglobin. Kidokoro et al. [137] showed that SNPs in *CYP19A* gene alter the levels of estrogens. Eriksson et al. [105] presented data showing that rs2470152 is clearly associated with serum E2 and E1 levels in men. Other investigations show the association between SNPs rs10046 and rs11575899 and endogenous estrogen levels [138, 139].

Estrogen levels are influenced by the presence of different genotypes of a SNP, as reported in some studies but not in others. Thompson et al. [18] showed in a comprehensive study that the SNP rs727479 was associated most strongly with circulating E2 concentrations in postmenopausal healthy controls and its effect was stronger in obese females. Cai et al. [140] showed that rs1902584 in block 1 was associated with estradiol only in overweight postmenopausal women.

6. Influence of SNPs in CYP19A1 gene on treatment with aromatase inhibitors

The treatment strategies have been extensively investigated in breast cancer, due to the high prevalence and associated morbidity and motility. There are a number of options for the treatment of the different types of cancer, and generally a multidisciplinary approach is preferred. The options are dependent on the type of cancer, patients' history, and the characteristics of the tumor. Some of the more common treatment strategies are surgery, radiotherapy, chemotherapy, and hormonal therapy. The two common antiestrogen therapies are tamoxifen and aromatase inhibitors. The former is used generally for the treatment of ER+ breast cancer in premenopausal women, while the latter is under investigation for treatment of premenopausal breast cancer

patients. In the postmenopausal women, the aromatase inhibitors (AIs) are reported to have a higher efficacy compared to tamoxifen in the postmenopausal group in relation to metastasis and prognosis in the presence of adjuvant treatment. However, ethnic differences and interindividual differences are frequently reported and are related to genetic variations.

As stated in the earlier part of this chapter, there are a significantly large number of SNPs in the CYP19A gene. Some of these have an influence on aromatase activity and hence influence the level of estrogens. Such mutations play a role in the effectiveness of the clinical efficacy related to treatment strategies.

Several studies have evaluated the effect of the genotype on the efficacy of the AI used for treatment of cancer. There are several contradictory reports, and the SNP may or may not associate with AI treatment complications. Those SNPs, which influence aromatase activity and are associated with elevated levels of estrogens, such as rs6493497 and rs7176005, seem to alter the effectiveness of AI [141]. On the other hand, it was shown that rs700518, rs10459592, and rs4775936 were significantly associated with higher clinical benefit rate with letrozole treatment [142]. Ferraldeschi et al. [68] investigated the effect of 56 SNPs on AI treatment and concluded that none of the variants independently were associated with improved AI efficacy and emphasized the significance of further studies on genetic biomarkers as prognostic factors in pharmacogenetic studies.

Table 3 lists a few SNPs and their influence on the outcome of AI treatment.

SNP	Effect on AI treatment	Reference
rs6493497	Almost 13-fold increase estradiol concentration in post-anastrozole. Alters effectiveness of AI treatment associated with decreased bone density in the exemestane-treated patients	[141]
rs7176005	Almost 11-fold increase estradiol concentration in post-anastrozole. Alters effectiveness of AI treatment	[141]
rs4646	Associated with poor response to the AI, letrozole ($p = 0.03$)	[134, 142]
rs700518	—GG genotype of rs700518 increases risk for significant loss of fat-free mass and increase in truncal fat with AI therapy —AA genotype of rs700518 is at risk for AI-associated bone loss	[142, 143]
rs700518	Significantly associated with higher clinical benefit rate with letrozole treatment	[142]
rs10459592		
rs4775936		
rs1062033	CC genotype in postmenopausal patients had lower spine and hip bone mineral density compared with the GG genotype. No correlation with AIs was established	[144]
rs60271534	Lower incidence of AI-associated arthralgia. But the effect was not definite as two different AIs were used	[145]
rs10046	Five-year disease-free survival was enhanced in premenopausal women on AI therapy	[146]
rs700519	Associated with lower aromatase activity, but no studies showed a significant correlation with AIs	[80]

AI, aromatase inhibitor.

Table 3. SNPs in CYP19A1 gene and their interaction with AI treatment.

7. Conclusions

Aromatase is an essential enzyme required for the synthesis of estrogens. The polymorphic forms of aromatase gene seem to contribute to the development of different forms of cancer, and several avenues await exploration. Population differences in the frequencies of different SNPs and the association with the different disease states need further detailed study. Association studies are required to confirm if there is a risk or protective effect of the SNP genotype. Studies on disease prognosis, in relation to the different genotypes of a SNP, are required. Finally, the influences of the SNP on treatment strategies are warranted. Individualized medicine is the dream of present-day clinicians. The role played by SNPs may contribute to achieve this dream.

Acknowledgements

We thankfully appreciate the support provided by the Central Laboratory during the preparation of this chapter.

Author details

Arjumand S. Warsy[1]*, Fatimah Basil Almukaynizi[2], Soad AlDaihan[3], Sophia Alam[4] and Maha Daghastani[5]

*Address all correspondence to: aswarsy@gmail.com

1 Central Laboratory, Center for Science and Medical Studies for Girls, King Saud University, Riyadh, Saudi Arabia

2 Central Laboratory and Prince Naif for Health Research Center, King Saud University, Riyadh, Saudi Arabia

3 Department of Biochemistry, College of Science, King Saud University, Riyadh, Saudi Arabia

4 Dr.Hassan Clinic, Phelps Hospital, Northwell, Health, Sleepy Hollow, NY, USA

5 Department of Zoology, College of Science, King Saud University, Riyadh, Saudi Arabia

References

[1] Watanabe S, Kobayashi Y. Exogenous hormones and human cancer. Japanese Journal of Clinical Oncology. 1993;**23**(1):1-13

[2] Sasano H, Harada N. Intratumoral aromatase in human breast, endometrial, and ovarian malignancies. Endocrine Reviews. 1998;**19**:593-607

[3] Nelson LR, Bulun SE. Estrogen production and action. Journal of the American Academy of Dermatology. 2001;**45**(3):S116-S124

[4] Harada N. Structure, regulation and polymorphisms of the Aromatase gene in Larionov A, eds. Resistance to Aromatase Inhibitors in Breast Cancer, Resistance to Targeted Anti-Cancer Therapeutics 8, Switzerland: Springer International Publishing Switzerland; 2015

[5] Simpson ER, Davis SR. Minireview: Aromatase and the regulation of estrogen biosynthesis-Some new perspectives. Endocrinology. 2001;**142**(11):4589-4594

[6] Henderson BE, Ross R, and Bernstein L. Estrogens as a cause of human cancer: The Richard and Hinda Rosenthal Foundation award lecture. Cancer Research. 1988;**48**:246-253

[7] Simpson E, Rubin G, Clyne C, Robertson K, O'Donnell L, Davis S, Jones M. Local estrogen biosynthesis in males and females endocrine-related. Cancer. 1999;**6**:131-137

[8] Sasano H, Uzuki M, Sawai T, Nagura H, Matsunaga G, Kashimoto O, Harada N. Aromatase in human bone tissue. Journal of Bone and Mineral Research. 1997;**12**:1416-1423

[9] Harada N, Sasano H, Murakami H, Ohkuma T, Nagura H, Takagi Y. Localized expression of aromatase in human vascular tissues. Circulation Research. 1999;**84**:1285-1291

[10] Simpson, ER, Clyne, C, Rubin, G, Boon, WC, Robertson, K, Britt, K, Speed, C, and Jones, M. Aromatase-A brief overview. Annual Reviews of Physical Chemistry. 2002;**64**:93-127

[11] Chen SA, Besman MJ, Sparkes RS, Zollman S, Klisak I, Mohandas T, Hall PF, Shively JE. Human aromatase: cDNA cloning, southern blot analysis, and assignment of the gene to chromosome 15. DNA. 1988;**7**:27-38

[12] Harada N, Utsumi T, Takagi Y. Tissue-specific expression of the human aromatase cytochrome P450 gene by alternative use of multiple exons 1 and promoters, and switching of tissue-specific exons 1 in carcinogenesis. Proceedings of the National Academy of Sciences of the United States of America. 1993;**90**:11312-11316

[13] Shozu M, Zhao Y, Bulun SE, Simpson ER. Multiple splicing events involved in regulation of human aromatase expression by a novel promoter, I.6. Endocrinology. 1998;**139**:1610-1607

[14] Simpson ER, Mahendroo MS, Means GD, Kilgore MW, Hinshelwood MM, Graham-Lorence S, et al. Aromatase cytochrome P450, the enzyme responsible for estrogen biosynthesis. Endocrine Reviews. 1994;**15**:342-355

[15] McPhaul MJ, Herbst MA, Matsumine H, Young M, Lephart ED. Diverse mechanisms of control of aromatase gene expression. Journal of Steroid Biochemistry and Molecular Biology. 1993;**44**(4-6):341-346

[16] Chen S, Itoh T, Wu K, Zhou D, Yang C. Transcriptional regulation of aromatase expression in human breast tissue. Journal of Steroid Biochemistry and Molecular Biology. 2002;**83**:93-99

[17] Brureau L, Moningo D, Emeville E, Ferdinand S, Punga A, Lufuma S,et al, Polymorphisms of estrogen metabolism-related genes and prostate cancer risk in two populations of African ancestry. PLoS One. 2016;**11**(4):e0153609

[18] Thompson DJ, O'Mara TA, Glubb DM, Painter JN, Cheng T, Folkerd E, et al, CYP19A1 fine-mapping and Mendelian randomization: Estradiol is causal for endometrial cancer. Endocrine-Related Cancer. 2016;**23**(2):77-91

[19] Kristensen VN, Andersen TI, Lindblom A, Erikstein B, Magnus P, Børresen-Dale AL. A rare CYP19 (aromatase) variant may increase the risk of breast cancer. Pharmacogenetics. 1998;**8**(1):43-48

[20] Haiman CA, Hankinson SE, Spiegelman D, De Vivo I, Colditz GA, Willett WC, et al. A tetranucleotide repeat polymorphism in CYP19 and breast cancer risk. International Journal of Cancer. 2000;**87**(2):204-210

[21] Miyoshi Y, Iwao K, Ikeda N, Egawa C, Noguchi S. Breast cancer risk associated with polymorphism in CYP19 in Japanese women. International Journal of Cancer. 2000;**89**(4):325-328

[22] Baxter SW, Choong DY, Eccles DM, Campbell IG. Polymorphic variation in CYP19 and the risk of breast cancer. Carcinogenesis. 2001;**22**(2):347-349

[23] Miyoshi Y, Ando A, Hasegawa S, Ishitobi M, Yamamura J, Irahara N, et al. Association of genetic polymorphisms in CYP19 and CYP1A1 with the oestrogen receptor-positive breast cancer risk. European Journal of Cancer. 2003;**39**(17):2531-2537

[24] Ribeiro FS, de Amorim LM, de Almeida Simão T, Mendonça GA, de Moura Gallo CV, Pinto LF. CYP19 (TTTA)n polymorphism and breast cancer risk in Brazilian women. Toxicology Letters. 2006;**164**(1):90-95

[25] Hu MB, Xie W, Xiong B, Han DF, Li Y, Feng MH, et al. Study on the relationship between polymorphisms of genes (CYP17, CYP19 and SULT1A1) and susceptibility to breast cancer in Chinese women. Zhonghua Liu Xing Bing Xue Za Zhi. 2006;**27**(4):351-355

[26] Artamonov VV, Liubchenko LN, Shabanov MA, Babenko OV, Nemtsova MV, Zaletaev DV. Association of polymorphism of genetic markers of CYP19 and CYP17 with sporadic breast cancer. Molecular Biology (Mosk). 2003;**37**(6):975-982

[27] Murillo-Ortiz B, Martínez-Garza S, Suárez García D, Castillo Valenzuela RD, García Regalado JF, Cano Velázquez G Association between telomere length and CYP19 TTTA repetition polymorphism in healthy and breast cancer-diagnosed women. Breast Cancer (Dove Med Press). 2017;**9**:21-27

[28] Kim JY, Lee CS, Kim HO, Jo YH, Lee J, Jung MH,et al. The association between genetic polymorphisms in CYP19 and breast cancer risk in Korean women. Oncology Reports. 2009;**22**(3):487-492

[29] Probst-Hensch NM, Ingles SA, Diep AT, Haile RW, Stanczyk FZ, Kolonel LN, et al. Aromatase and breast cancer susceptibility. Endocrine-Related Cancer. 1999;**6**(2):165-173

[30] Thyagarajan B, Brott M, Mink P, Folsom AR, Anderson KE, Oetting WS, et al. CYP1B1 and CYP19 gene polymorphisms and breast cancer incidence: No association in the ARIC study. Cancer Letters. 2004;**207**(2):183-189

[31] Dialyna I, Tzanakakis G, Dolapsakis G, Tsatsakis A. A tetranucleotide repeat polymorphism in the CYP19 gene and breast cancer susceptibility in a Greek population exposed and not exposed to pesticides. Toxicology Letters. 2004;**151**(1):267-271

[32] Cussenot O, Azzouzi AR, Nicolaiew N, Fromont G, Mangin P, Cormier L, et al. Combination of polymorphisms from genes related to estrogen metabolism and risk of prostate cancers: The hidden face of estrogens. Journal of Clinical Oncology. 2007;**25**(24):3596-3602

[33] dos Santos RM, de Jesus CM, Trindade Filho JC, Trindade JC, de Camargo JL, Rainho CA, et al. PSA and androgen-related gene (AR, CYP17, and CYP19) polymorphisms and the risk of adenocarcinoma at prostate biopsy. DNA and Cell Biology. 2008;**27**(9):497-503

[34] Suzuki K, Nakazato H, Matsui H, Koike H, Okugi H, Ohtake N, et al. Association of the genetic polymorphism of the CYP19 intron 4[TTTA]n repeat with familial prostate cancer risk in a Japanese population. Anticancer Research. 2003;**23**(6D):4941-4946

[35] Tsuchiya N, Wang L, Suzuki H, Segawa T, Fukuda H, Narita S, et al. Impact of IGF-I and CYP19 gene polymorphisms on the survival of patients with metastatic prostate cancer. Journal of Clinical Oncology. 2006;**24**(13):1982-1989

[36] Tang L, Yao S, Till C, Goodman PJ, Tangen CM, Wu Y, et al, Repeat polymorphisms in estrogen metabolism genes and prostate cancer risk: Results from the prostate cancer prevention trial. Carcinogenesis. 2011;**32**(10):1500-1506

[37] Bershteĭn LM, Imianitov EN, Suspitsyn EN, Grigor'ev MIu, Sokolov EP, Togo AV, et al. A polymorphism study of the CYP19 gene in endometrial cancer patients. Voprosy Onkologii. 2000;**46**(3):302-305

[38] Berstein LM, Imyanitov EN, Suspitsin EN, Grigoriev MY, Sokolov EP, Togo A, et al. CYP19 gene polymorphism in endometrial cancer patients. Journal of Cancer Research and Clinical Oncology. 2001;**127**(2):135-138

[39] Olson SH, Bandera EV, Orlow I. Variants in estrogen biosynthesis genes, sex steroid hormone levels, and endometrial cancer: A HuGE review. American Journal of Epidemiology. 2007;**165**(3):235-245

[40] Berstein LM, Imyanitov EN, Kovalevskij AJ, Maximov SJ, Vasilyev DA, Buslov KG, et al. CYP17 and CYP19 genetic polymorphisms in endometrial cancer: Association with intratumoral aromatase activity. Cancer Letters. 2004;**207**(2):191-196

[41] Healey CS, Dunning AM, Durocher F, Teare D, Pharoah PD, Luben RN, et al. Polymorphisms in the human aromatase cytochrome P450 gene (CYP19) and breast cancer risk. Carcinogenesis. 2000;**21**(2):189-193

[42] Huang YC, Chen M, Lin MW, Chung MY, Chang YH, Huang WJ, et al. CYP19 TCT trinucleotide Del/Del genotype is a susceptibility marker for prostate cancer in a Taiwanese population. Urology. 2007;**69**(5):996-1000

[43] Olson SH, Orlow I, Bayuga S, Sima C, Bandera EV, Pulick K, et al. Variants in hormone biosynthesis genes and risk of endometrial cancer. Cancer Causes & Control. 2008;**19**(9):955-963

[44] Paynter RA, Hankinson SE, Colditz GA, Kraft P, Hunter DJ, De Vivo I. CYP19 (aromatase) haplotypes and endometrial cancer risk. International Journal of Cancer. 2005;**116**(2):267-274

[45] Suspitsin EN, Grigoriev MY, Togo AV, Kuligina ES, Belogubova EV, Pozharisski KM, Distinct prevalence of the CYP19 Delta3(TTTA)(7) allele in premenopausal versus postmenopausal breast cancer patients, but not in control individuals. European Journal of Cancer. 2002;**38**(14):1911-1916

[46] Ma CX, Adjei AA, Salavaggione OE, Coronel J, Pelleymounter L, Wang L, et al. Human aromatase: Gene resequencing and functional genomics. Cancer Research. 2005;**65**(23):11071-11082

[47] Sourdaine P, Parker MG, Telford J, Miller WR. Analysis of the aromatase cytochrome P450 gene in human breast cancers. Journal of Molecular Endocrinology. 1994;**13**(3):331-337

[48] Kristensen VN, Harada N, Yoshimura N, Haraldsen E, Lonning PE, Erikstein B, et al. Genetic variants of CYP19 (aromatase) and breast cancer risk. Oncogene. 2000;**19**(10):1329-1333

[49] Feigelson HS, Henderson BE. Estrogens and breast cancer. Carcinogenesis. 1996;**17**(11): 2279-2284

[50] Siiteri PK. Adipose tissue as a source of hormones. American Journal of Clinical Nutrition. 1987;**45**(1 Suppl):277-282

[51] O'Neill JS, Miller WR. Aromatase activity in breast adipose tissue from women with benign and malignant breast diseases. British Journal of Cancer. 1987;**56**(5):601-604

[52] Castilla LH, Couch FJ, Erdos MR, Hoskins KF, Calzone K, Garber JE, et al. Mutations in the BRCA1 gene in families with early-onset breast and ovarian cancer. Nature Genetics. 1994;**8**(4):387-391

[53] Ghisari M, Eiberg H, Long M, Bonefeld-Jørgensen EC. Polymorphisms in phase I and phase II genes and breast cancer risk and relations to persistent organic pollutant exposure: A case-control study in Inuit women. Environmental Health. 2014;**13**(1):19

[54] 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 Pacific Journal of Cancer Prevention. 2016;**17**:(Spec No.):23-6

[55] Shao X, Cai J, Zheng Y, Wang J, Feng J, Huang Y, et al, S4646 polymorphism in CYP19A1 gene is associated with the efficacy of hormone therapy in early breast cancer. International Journal of Clinical and Experimental Pathology. 2015;**8**(5):5309-5317

[56] Yang L, Wang XY, Li YT, Wang HL, Wu T, Wang B, et al, CYP19 gene polymorphisms and the susceptibility to breast cancer in Xinjiang Uigur women. Genetics and Molecular Research. 2015;**14**(3):8473-8482

[57] Artigalás O, Vanni T, Hutz MH, Ashton-Prolla P, Schwartz IV.Influence of CYP19A1 polymorphisms on the treatment of breast cancer with aromatase inhibitors: A systematic review and meta-analysis. BMC Medicine. 2015;**13**:139

[58] Napoli N, Rastelli A, Ma C, Colleluori G, Vattikuti S, Armamento-Villareal R. Genetic polymorphism at Val80 (rs700518) of the CYP19A1 gene is associated with body composition changes in women on aromatase inhibitors for ER (+) breast cancer. Pharmacogenetics and Genomics. 2015;**25**(8):377-381

[59] Hu Z, Song CG, Lu JS, Luo JM, Shen ZZ, Huang W, et al. A multigenic study on breast cancer risk associated with genetic polymorphisms of ER Alpha, COMT and CYP19 gene in BRCA1/BRCA2 negative Shanghai women with early onset breast cancer or affected relatives. Journal of Cancer Research and Clinical Oncology. 2007;**133**(12):969-978

[60] Lee KM, Abel J, Ko Y, Harth V, Park WY, Seo JS, et al. Genetic polymorphisms of cytochrome P450 19 and 1B1, alcohol use, and breast cancer risk in Korean women. British Journal of Cancer. 2003;**88**(5):675-678

[61] Song CG, Hu Z, Yuan WT, Di GH, Shen ZZ, Huang W, et al. Effect of R264C polymorphism in CYP19A1 gene on BRCA1/2-negative hereditary breast cancer from Shanghai population of China. Zhonghua yi xue yi chuan xue za zhi= Zhonghua yixue yichuanxue zazhi= Chinese Journal of Medical Genetics. 2006;**23**(2):181-183

[62] Talbott KE, Gammon MD, Kibriya MG, Chen Y, Teitelbaum SL, Long CM, et al. A CYP19 (aromatase) polymorphism is associated with increased premenopausal breast cancer risk. Breast Cancer Research and Treatment. 2008;**111**(3):481-487

[63] Hamaguchi M, Nishio M, Toyama T, Sugiura H, Kondo N, Fujii Y, et al. Possible difference in frequencies of genetic polymorphisms of estrogen receptor alpha, estrogen metabolism and P53 genes between estrogen receptor-positive and -negative breast cancers. Japanese Journal of Clinical Oncology. 2008;**38**(11):734-742

[64] Chen C, Sakoda LC, Doherty JA, Loomis MM, Fish S, Ray RM, et al. Genetic variation in CYP19A1 and risk of breast cancer and fibrocystic breast conditions among women in Shanghai, China. Cancer Epidemiology Biomarkers Prevention. 2008;**17**(12): 3457-3466

[65] Leyland-Jones B, Gray KP, Abramovitz M, Bouzyk M, Young B, Long B, et al, CYP19A1 polymorphisms and clinical outcomes in postmenopausal women with hormone receptor-positive breast cancer in the BIG 1-98 trial. Breast Cancer Research and Treatment. 2015;**151**(2):373-384

[66] Shao X, Guo Y, Xu X, Zheng Y, Wang J, Chen Z, et al, The CYP19 RS4646 polymorphism IS related to the prognosis of stage I-II and operable stage III breast cancer. PLoS One. 2015;**10**(3):e0121535

[67] Boone SD, Baumgartner KB, Baumgartner RN, Connor AE, Pinkston CM, Rai SN, et al, Associations between CYP19A1 polymorphisms, Native American ancestry, and breast

cancer risk and mortality: The Breast Cancer Health Disparities Study. Cancer Causes & Control. 2014;**25**(11):1461-1471

[68] Ferraldeschi R, Arnedos M, Hadfield KD, A'Hern R, Drury S, Wardley A, et al, Polymorphisms of CYP19A1 and response to aromatase inhibitors in metastatic breast cancer patients. Breast Cancer Research and Treatment. 2012;**133**(3):1191-1198

[69] Yoshimoto N, Nishiyama T, Toyama T, Takahashi S, Shiraki N, Sugiura H, et al, Genetic and environmental predictors, endogenous hormones and growth factors, and risk of estrogen receptor-positive breast cancer in Japanese women. Cancer Science. 2011;**102**(11):2065-2072

[70] Chattopadhyay S, Siddiqui S, Akhtar MS, Najm MZ, Deo SV, 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. Tumour Biology. 2014;**35**(5):4517-4527

[71] Zins K, Mogg M, Schneeberger C, Abraham D, Schreiber M. Analysis of the rs10046 polymorphism of aromatase (CYP19) in premenopausal onset of human breast cancer. International Journal of Molecular Sciences. 2014;**15**(1):712-724

[72] Pineda B, García-Pérez MÁ, Cano A, Lluch A, Eroles P. Associations between aromatase CYP19 rs10046 polymorphism and breast cancer risk: From a case-control to a meta-analysis of 20,098 subjects. PLoS One. 2013;**8**(1):e53902

[73] Kuo SH, Yang SY, Lien HC, Lo C, Lin CH, Lu YS, et al, CYP19 genetic polymorphism haplotype AASA is associated with a poor prognosis in premenopausal women with lymph node-negative, hormone receptor-positive breast cancer. BioMed Research International. 2013;**2013**:562197

[74] Henry NL, Chan HP, Dantzer J, Goswami CP, Li L, Skaar TC, et al, Aromatase inhibitorinduced modulation of breast density: Clinical and genetic effects. British Journal of Cancer. 2013;**109**(9):2331-2339

[75] Liu L, Bai YX, Zhou JH, Sun XW, Sui H, Zhang WJ, et al, A polymorphism at the 3′-UTR region of the aromatase gene is associated with the efficacy of the aromatase inhibitor, anastrozole, in metastatic breast carcinoma. International Journal of Molecular Sciences. 2013;**14**(9):18973-18988

[76] Park IH, Lee YS, Lee KS, Kim SY, Hong SH, Jeong J, et al, Single nucleotide polymorphisms of CYP19A1 predict clinical outcomes and adverse events associated with letrozole in patients with metastatic breast cancer. Cancer Chemotherapy and Pharmacology. 2011;**68**(5):1263-1271

[77] Lunardi G, Piccioli P, Bruzzi P, Notaro R, Lastraioli S, Serra M, et al, Plasma estrone sulfate concentrations and genetic variation at the CYP19A1 locus in postmenopausal women with early breast cancer treated with letrozole. Breast Cancer Research and Treatment. 2013;**137**(1):167-174

[78] Darabi H, Czene K, Wedrén S, Li Y, Liu J, Hall P, et al. Genetic variation in the androgen estrogen conversion pathway in relation to breast cancer prognosticators. Breast Cancer Research and Treatment. 2011;**127**(2):503-509

[79] Zhang L, Gu L, Qian B, Hao X, Zhang W, Wei Q, et al. Association of genetic polymorphisms of ER-alpha and the estradiol-synthesizing enzyme genes CYP17 and CYP19 with breast cancer risk in Chinese women. Breast Cancer Research and Treatment. 2009;**114**(2):327-338

[80] Fasching PA, Loehberg CR, Strissel PL, Lux MP, Bani MR, Schrauder M,et al. Single nucleotide polymorphisms of the aromatase gene (CYP19A1), HER2/neu status, and prognosis in breast cancer patients. Breast Cancer Research and Treatment. 2008;**112**(1):89-98

[81] Ziel HK. Estrogen's role in endometrial cancer. Obstetrics and Gynecology. 1982 Oct;**60**(4):509-515

[82] Reich O, Regauer S, Tempfer C, Schneeberger C, Huber J. Polymorphism 1558 C > T in the aromatase gene (CYP19A1) in low-grade endometrial stromal sarcoma. European Journal of Gynaecological Oncology. 2011;**32**(6):626-627

[83] Mikhailova ON, Gulyaeva LF, Prudnikov AV, Gerasimov AV, Krasilnikov SE. 201. Estrogen-metabolizing gene polymorphisms in the assessment of female hormonedependent cancer risk. Pharmacogenomics Journal. 2006;**6**(3):189-193

[84] Santa-Maria CA, Blackford A, Nguyen AT, Skaar TC, Philips S, Oesterreich S, et al. Association of variants in candidate genes with lipid profiles in women with early breast cancer on adjuvant aromatase inhibitor therapy. Clinical Cancer Research. 2016;**22**(6):1395-1402

[85] Szyllo K, Smolarz B, Romanowicz-Makowska H, Lewy J, Kulig B. The T/C polymorphism of the CYP17 gene and G/A polymorphism of the CYP19 gene in endometrial cancer. Journal of Experimental & Clinical Cancer Research. 2006;**25**(3):411-416

[86] Tao MH, Cai Q, Zhang ZF, Xu WH, Kataoka N, Wen W, et al. Polymorphisms in the CYP19A1 (aromatase) gene and endometrial cancer risk in Chinese women. Cancer Epidemiology, Biomarkers & Prevention. 2007;**16**(5):943-949

[87] Gulyaeva LF, Mikhailova ON, PustyInyak VO, Kim IV, Gerasimov AV, Krasilnikov SE, et al. Comparative analysis of SNP in estrogen-metabolizing enzymes for ovarian, endometrial, and breast cancers in Novosibirsk, Russia. Advances in Experimental Medicine Biology. 2008;**617**:359-366

[88] Setiawan VW, Doherty JA, Shu XO, Akbari MR, Chen C, De Vivo I,et al. Two estrogen-related variants in CYP19A1 and endometrial cancer risk: A pooled analysis in the Epidemiology of Endometrial Cancer Consortium. Cancer Epidemiology, Biomarkers & Prevention. 2009; **18**(1):242-247

[89] Lundin E, Wirgin I, Lukanova A, Afanasyeva Y, Krogh V, Axelsson T, Selected polymorphisms in sex hormone-related genes, circulating sex hormones and risk of endometrial cancer. Cancer Epidemiology. 2012;**36**(5):445-452

[90] Barrett-Connor E, Garland C, McPhillips JB, Khaw KT, Wingard DL. A prospective, population based study of androstenedione, estrogens, and prostatic cancer. Cancer Research. 1990;**50**(1):169-173

[91] Ellem SJ, Schmitt JF, Pedersen JS, Frydenberg M, Risbridger GP. Local aromatase expression in human prostate is altered in malignancy. The Journal of Clinical Endocrinology and Metabolism. 2004;**89**:2431-2441

[92] Montgomery RB, Mostaghel EA, Vessella R, et al. Maintenance of intratumoral androgens in metastatic prostate cancer: A mechanism for castration-resistant tumor growth. Cancer Research 2008;**68**:4447-4454

[93] Nelles, JL Hu W, and Prins GS. Estrogen action and prostate cancer. Expert Review Endocrinology and Metabolism. 2011;**6**(3):437-451

[94] Kachakova D, Mitkova A, Popov E, Beltcheva O, Vlahova A, Dikov T, et al, Polymorphisms in androgen metabolism genes AR, CYP1B1, CYP19, and SRD5A2and prostate cancer risk and aggressiveness in Bulgarian patients. Turkish Journal of Medical Sciences. 2016;**46**(3):626-640

[95] Sarma AV, Dunn RL, Lange LA, Ray A, Wang Y, Lange EM, et al. Genetic polymorphisms in CYP17, CYP3A4, CYP19A1, SRD5A2, IGF-1, and IGFBP-3 and prostate cancer risk in African-American men: The Flint Men's Health Study. Prostate. 2008;**68**(3):296-305

[96] Fukatsu T, Hirokawa Y, Araki T, Hioki T, Murata T, Suzuki H, et al. Genetic polymorphisms of hormone-related genes and prostate cancer risk in the Japanese population. Anticancer Research. 2004;**24**(4):2431-2437

[97] Onsory K, Sobti RC, Al-Badran AI, Watanabe M, Shiraishi T, Krishan A, et al. Hormone receptor-related gene polymorphisms and prostate cancer risk in North Indian population. Molecular and Cellular Biochemistry. 2008;**314**(1-2):25-35

[98] Suzuki K, Nakazato H, Matsui H, Koike H, Okugi H, Kashiwagi B, et al. Genetic polymorphisms of estrogen receptor alpha, CYP19, catechol-O-methyltransferase are associated with familial prostate carcinoma risk in a Japanese population. Cancer. 2003;**98**(7):1411-1416

[99] Modugno F, Weissfeld JL, Trump DL, Zmuda JM, Shea P, Cauley JA, et al. Allelic variants of aromatase and the androgen and estrogen receptors: Toward a multigenic model of prostate cancer risk. Clinical Cancer Research. 2001;**7**(10):3092-3096

[100] Mononen N, Seppälä EH, Duggal P, Autio V, Ikonen T, Ellonen P, et al. Profiling genetic variation along the androgen biosynthesis and metabolism pathways implicates several single nucleotide polymorphisms and their combinations as prostate cancer risk factors. Cancer Research. 2006;**66**(2):743-747

[101] Kanda S, Tsuchiya N, Narita S, Inoue T, Huang M, Chiba S, et al. Effects of functional genetic polymorphisms in the CYP19A1 gene on prostate cancer risk and survival. International Journal of Cancer. 2015;**136**(1):74-82

[102] Ersekerci E, Sofikerim M, Taheri S, Demirtas A, Halis F. Genetic polymorphism in sex hormone metabolism and prostate cancer risk. Genetics and Molecular Research. 2015;**14**(3):7326-7334

[103] Lévesque É, Huang SP, Audet-Walsh É, Lacombe L, Bao BY, Fradet Y, et al, Molecular markers in key steroidogenic pathways, circulating steroid levels, and prostate cancer progression. Clinical Cancer Research. 2013;**19**(3):699-709

[104] Huhtaniemi IT, Pye SR, Holliday KL, Thomson W, O'Neill TW, Platt H, Payne D, et al. Effect of polymorphisms in selected genes involved in pituitary-testicular function on reproductive hormones and phenotype in aging men. Journal of Clinical Endocrinology and Metabolism. 2010;**95**(4):1898-1908

[105] Eriksson AL, Lorentzon M, Vandenput L, Labrie F, Lindersson M, Syvänen AC, et al. Genetic variations in sex steroid-related genes as predictors of serum estrogen levels in men. Journal of Clinical Endocrinology and Metabolism. 2009;**94**(3):1033-1041

[106] Sonoda T, Suzuki H, Mori M, Tsukamoto T, Yokomizo A, Naito S, et al. Polymorphisms in estrogen related genes may modify the protective effect of isoflavones against prostate cancer risk in Japanese men. European Journal of Cancer Prevention. 2010;**19**(2):131-137

[107] Nelson HD, Humphrey LL, Nygren P, et al. Postmenopausal hormone replacement therapy: Scientific review. JAMA 2002;**288**:872-881

[108] Nanda K, Bastian LA, Hasselblad V, Simel DL. Hormone replacement therapy and the risk of colorectal cancer: A meta-analysis. Obstetrics and Gynecology. 1999;**93**:880-888

[109] McMichael AJ, Potter JD. Reproduction, endogenous and exogenous sex hormones, and colon cancer: A review and hypothesis. Journal of the National Cancer Institute. 1980;**65**:1201-1207

[110] Slattery ML, Lundgreen A, Herrick JS, Kadlubar S, Caan BJ, Potter JD, and Roger K. Wolff Variation in the CYP19A1 gene and risk of colon and rectal cancer. Cancer Causes & Control. 2011;**22**(7):955-963

[111] English MA, Kane KF, Cruickshank N, Langman MJ, Stewart PM, Hewison M. Loss of estrogen inactivation in colonic cancer. Journal of Clinical Endocrinology and Metabolism. 1999;**84**:2080-2085

[112] English MA, Stewart PM, Hewison M. Estrogen metabolism and malignancy: Analysis of the expression and function of 17beta-hydroxysteroid dehydrogenases in colonic cancer. Molecular and Cellular Endocrinology. 2001;**171**:53-60

[113] Di Domenico M, Castoria G, Bilancio A, Migliaccio A, Auricchio F. Estradiol activation of human colon carcinoma-derived Caco-2 cell growth. Cancer Research. 1996;**56**:4516-4521

[114] Wu H, Xu L, Chen J, Hu J, Yu S, Hu G, et al. Association of estrogen receptor beta variants and serum levels of estradiol with risk of colorectal cancer: A case control study. BMC Cancer. 2012;**12**:276

[115] Lin J, Zee RY, Liu KY, Zhang SM, Lee IM, Manson JE, et al. Genetic variation in sex-steroid receptors and synthesizing enzymes and colorectal cancer risk in women. Cancer Causes & Control. 2010;**21**(6):897-908

[116] Lin JH, Manson JE, Kraft P, Cochrane BB, Gunter MJ, Chlebowski RT, et al, Estrogen and progesterone-related gene variants and colorectal cancer risk in women. BMC Medical Genetics. 2011;**12**:78

[117] Al-Mukaynizi FB, Alanazi M, Al-Daihan S, Parine NR, Almadi M, Aljebreen A, Azzam N, Alharbi O, Arafah M, Warsy A. CYP19A1 gene polymorphism and colorectal cancer etiology in Saudi population: Case-control study. OncoTargets and Therapy. 2017;**10**:1-9

[118] Goodman MT, Lurie G, Thompson PJ, McDuffie KE, Carney ME. Association of two common single-nucleotide polymorphisms in the CYP19A1 locus and ovarian cancer risk. Endocrine-Related Cancer. 2008;**15**(4):1055-1060

[119] Beesley J, Jordan SJ, Spurdle AB, Song H, Ramus SJ, Kjaer SK, et al. Association between single-nucleotide polymorphisms in hormone metabolism and DNA repair genes and epithelial ovarian cancer: Results from two Australian studies and an additional validation set. Cancer Epidemiology, Biomarkers & Prevention. 2007;**16**(12):2557-2565

[120] Di Maio M, Daniele B, Pignata S, Gallo C, De Maio E, Morabito A, et al. Is human hepatocellular carcinoma a hormone-responsive tumor? World Journal of Gastroenterology. 2008;**14**(11):1682-1689

[121] Yuan X, Zhou G, Zhai Y, Xie W, Cui Y, Cao J, et al. Lack of association between the functional polymorphisms in the estrogen-metabolizing genes and risk for hepatocellular carcinoma. Cancer Epidemiology, Biomarkers & Prevention. 2008;**17**(12):3621-3627

[122] Koh WP, Yuan JM, Wang R, Govindarajan S, Oppenheimer R, Zhang ZQ, et al. Aromatase (CYP19) promoter gene polymorphism and risk of nonviral hepatitis related hepatocellular carcinoma. Cancer. 2011;**117**(15):3383-3392

[123] Yang H, Sukocheva OA, Hussey DJ, Watson DI. Estrogen, male dominance and esophageal adenocarcinoma: Is there a link? World Journal of Gastroenterology. 2012;**18**(5):393-400

[124] Sukocheva OA, Wee C, Ansar A, Hussey DJ, Watson DI. Effect of estrogen on growth and apoptosis in esophageal adenocarcinoma cells. Diseases of the Esophagus. 2013;**26**(6):628-635

[125] Wu IC, Zhao Y, Zhai R, Liu G, Ter-Minassian M, Asomaning K, et al, Association between polymorphisms in cancer-related genes and early onset of esophageal adenocarcinoma. Neoplasia 2011;**13**:386-392

[126] Lagergren K, Ek WE, Levine D, Chow WH, Bernstein L, Casson AG, et al, Polymorphisms in genes of relevance for oestrogen and oxytocin pathways and risk of Barrett's oesophagus and oesophageal adenocarcinoma: A pooled analysis from the BEACON consortium. PLoS One. 2015;**10**(9):e0138738

[127] Camargo MC, Goto Y, Zabaleta J, Morgan DR, Correa P, Rabkin CS. Sex hormones, hormonal interventions, and gastric cancer risk: A meta-analysis. Cancer Epidemiology, Biomarkers & Prevention. 2012;**21**(1):20-38

[128] Lindblad M, Ye W, Rubio C, Lagergren J. Estrogen and risk of gastric cancer: A protective effect in a nationwide cohort study of patients with prostate cancer in Sweden. Cancer Epidemiology, Biomarkers & Prevention. 2004;**13**(12):2203-2207

[129] Wesołowska M, Pawlik P, Jagodziński PP. The clinicopathologic significance of estrogen receptors in human gastric carcinoma. Biomedicine & Pharmacotherapy. 2016;**83**:314-322

[130] Freedman ND, Ahn J, Hou L, Lissowska J, Zatonski W, Yeager M, et al. Polymorphisms in estrogen- and androgen-metabolizing genes and the risk of gastric cancer. Carcinogenesis. 2009;**30**(1):71-77

[131] Cho LY, Yang JJ, Ko KP, Ma SH, Shin A, Choi BY, et al, Genetic susceptibility factors on genes involved in the steroid hormone biosynthesis pathway and progesterone receptor for gastric cancer risk. PLoS One. 2012;**7**(10):e47603

[132] Kristiansen W, Andreassen KE, Karlsson R, Aschim EL, Bremnes RM, Dahl O, et al, Gene variations in sex hormone pathways and the risk of testicular germ cell tumour: A case-parent triad study in a Norwegian-Swedish population. Human Reproduction. 2012;**27**(5):1525-1535

[133] Huang CS, Kuo SH, Lien HC, Yang SY, You SL, Shen CY, et al. The CYP19 TTTA repeat polymorphism is related to the prognosis of premenopausal stage I-II and operable stage III breast cancers. The Oncologist. 2008;**13**(7):751-760

[134] Colomer R, Monzo M, Tusquets I, Rifa J, Baena JM, Barnadas A, et al. A single-nucleotide polymorphism in the aromatase gene is associated with the efficacy of the aromatase inhibitor letrozole in advanced breast carcinoma. Clinical Cancer Research. 2008;**14**(3):811-816

[135] Long JR, Kataoka N, Shu XO, Wen W, Gao YT, Cai Q, et al. Genetic polymorphisms of the CYP19A1 gene and breast cancer survival. Cancer Epidemiology, Biomarkers & Prevention. 2006;**15**(11):2115-2122

[136] Udler MS, Azzato EM, Healey CS, Ahmed S, Pooley KA, Greenberg D, et al. Common germline polymorphisms in COMT, CYP19A1, ESR1, PGR, SULT1E1 and STS and survival after a diagnosis of breast cancer. International Journal of Cancer. 2009;**125**(11):2687-2696

[137] Kidokoro K, Ino K, Hirose K, Kajiyama H, Hosono S, Suzuki T, et al. Association between CYP19A1 polymorphisms and sex hormones in postmenopausal Japanese women. Journal of Human Genetics. 2009;**54**(2):78-85

[138] Straume AH, Knappskog S, Lønning PE. Effect of CYP19 rs6493497 and rs7176005 haplotype status on in vivo aromatase transcription, plasma and tissue estrogen levels in postmenopausal women. Journal of Steroid Biochemistry and Molecular Biology. 2012;**128**(1-2):69-75

[139] Dunning AM, Dowsett M, Healey CS, Tee L, Luben RN, Folkerd E, et al. Polymorphisms associated with circulating sex hormone levels in postmenopausal women. Journal of the National Cancer Institute. 2004;**96**(12):936-945

[140] Cai H, Shu XO, Egan KM, Cai Q, Long JR, Gao YT, et al. Association of genetic polymorphisms in CYP19A1 and blood levels of sex hormones among postmenopausal Chinese women. Pharmacogenetics and Genomics. 2008;**18**(8):657-664

[141] Wang L, Ellsworth KA, Moon I, Pelleymounter LL, Eckloff BW, Martin YN, et al. Functional genetic polymorphisms in the aromatase gene CYP19 vary the response of breast cancer patients to neoadjuvant therapy with aromatase inhibitors. Cancer Research. 2010;**70**(1):319-328

[142] Garcia-Casado Z, Guerrero-Zotano A, Llombart-Cussac A, Calatrava A, Fernandez-Serra A, Ruiz-Simon A, et al. A polymorphism at the 3′-UTR region of the aromatase gene defines a subgroup of postmenopausal breast cancer patients with poor response to neoadjuvant letrozole. BMC Cancer 2010;**10**:36

[143] Napoli N, Rastelli A, Ma C, Colleluori G, Vattikuti S, Armamento-Villareal R. Genetic polymorphism at Val80 (rs700518) of the CYP19A1 gene is associated with body composition changes in women on aromatase inhibitors for ER (+) breast cancer. Pharmacogenet Genomics. 2015;**25**(8):377-388

[144] Napoli N, Rastelli A, Ma C, Yarramaneni J, Vattikutti S, Moskowitz G, et al. Genetic polymorphism at Val80 (rs700518) of the CYP19A1 gene is associated with aromatase inhibitor associated bone loss in women with ER + breast cancer. Bone. 2013;**55**(2):309-314

[145] Zarrabeitia MT, Hernandez JL, Valero C, A common polymorphism in the 5′-untranslated region of the aromatase gene influences bone mass and fracture risk. European Journal of Endocrinology. 2004;**150**:699-704

[146] Mao JJ, Su HI, Feng R, Association of functional polymorphisms in CYP19A1 with aromatase inhibitor associated arthralgia in breast cancer survivors. Breast Cancer Research 2011;**13**:R8