Chapter 7

Vitamin D, Its Receptor Gene Polymorphism and Breast Cancer

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Additional information is available at the end of the chapter

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Abstract

Vitamin D is synthesized within skin followed by the peripheral maturation in liver and kidneys. Vitamin D is most essential secosteroid produced its systemic functions via complex with steroid/thyroid nuclear receptor called vitamin D receptor (VDR). The binding of the vitamin D3 to VDR causes conformational changes that permit VDR-RXR heterodimer formation and VDR/ SRC-1 (transcriptional co-activator proteins) interactions. Functional expression and nuclear activation of VDR is necessary to produce its effects upon binding with vitamin D response element (VDRE) on target gene where it causes transcriptional activation resulting in the prevention of breast cancer by inhibiting proliferation, impeding differentiation and stimulating pro-apoptosis. Season, latitude, pigmentation of skin, aging, sunscreen use, obesity, and smoking all affect the production of vitamin D. In case of vitamin D deficiency or VDR gene polymorphisms, vitamin D responses are altered and probably are involved in the risk of breast cancer. Since many epidemiological, observational and interventional studies have been done to illustrate the role of vitamin D and its receptor gene polymorphism in breast cancer development but controversial findings have been observed. Therefore, the role of vitamin D and its receptor gene polymorphisms in development of breast cancer are still a matter of discussion.

Keywords: breast cancer, vitamin D, VDR, vitamin D receptor gene polymorphisms, VDR gene polymorphisms

1. Introduction

1.1. Breast cancer

Breast carcinoma is one of the most frequently diagnosed cancers among women worldwide with a high frequency reported in the West [1, 2]. This highest incidence of breast cancer in American whites and in most European countries reveal the long-standing high prevalence of reproductive factors associated with increased risk of breast cancer, including early menarche, late child bearing age, few pregnancies, hormone replacement therapy and increased mammography [3, 4]. In Israel, the increased incidence of breast cancer may reflect the disproportionately high prevalence of BRCA1 and BRCA2 mutations [5, 6].

Western lifestyle is another most important factor for Britain's high number of breast cancer cases fuelled by the women overeating, too much drinking and too little exercise doing in routine life. In addition, breastfeeding is also an important factor, which reduces the chance of developing breast cancer. Eastern women do not drink alcohol than women in the United Kingdom, and obesity ratio is much lower in Asian women than in western women, whereas breastfeeding rates are much higher in Asians (http://www.dailymail.co.uk/news/article-1301445/Western-lifestyle-blame-soaring-breast-cancer-rates.html). Affected women with breast cancer are usually young and often present with advanced disease [7]. According to a World Health Organization (WHO) estimate, around 25.2% people are diagnosed with breast cancer annually. The exact reason why a woman develops breast cancer is still unrevealed; though certain risk factors enhance a person's probability of getting breast cancer.

The factors that play a significant role in the aetiology of breast cancer include genetic [8, 9], hormonal [10, 11], environmental [12], lifestyle [13] and reproductive factors [14]. In addition, ovarian hormones (endogenous estrogen) are the key risk factors for the development of breast cancer and their progression among post-menopausal women [15, 16]. However, it is unclear that to what degree the effects of other risk factors may be mediated by their links with circulating free estradiol. Intake of vegetables and fruits are related with a substantial decrease of breast cancer risk [17, 18]. Vegetables are rich in antioxidants and certain phytochemicals may contribute to the reduced risk of breast cancer [19–21]. Plant-based diets are also high in fibres, which can decrease serum estrogen and could, in this way, contribute to reduced risk of breast cancer [22, 23]. In addition, increased consumption of fruit and vegetables are associated with lower rates of obesity, which is a crucial risk factor for post-menopausal breast cancer [24]. High energy intake, physical sluggishness, high body mass index (BMI) and weight put on are coupled to an increased breast [25] cancer risk. Low levels of HDL-C in breast cancer patients than in control subjects have also been documented [26]. But still, data from prospective studies are very limited (Moorman, 1998). Furthermore, consanguineous marriages are common in certain racial groups, which will increases the risk of breast cancer [27].

Among these contributing factors, vitamin D and its receptor gene polymorphisms may play a pivotal role in the development of mammary gland tumourigenesis [28].

1.2. Vitamin D and vitamin D receptor (VDR)

Vitamin D and VDR are the two most important participants playing a key role in vitamin D endocrine system in the prevention of breast cancer. Vitamin D is a sunshine vitamin, which is involved in a variety of actions and also reduces the risk of many cancers [29, 30].

VDR is a member of nuclear receptor (NR) superfamily and transcription regulating factor also called NR1I1 or nuclear receptor subfamily 1, group I and member 1. VDR is a high-affnity, low-capacity receptor having a molecular weight of about 48–55 kD. VDR is expressed in majority of human tissues. But some cells have decrease or no VDR expression including RBCs, mature cardiac and skeletal muscles and cerebellar Purkinje cells [31]. Its actions are preceded by the formation of heterodimer with retinoid X receptor (RXR), which causes the conformational changes in VDR and allow the binding of vitamin D3 at ligand binding domain (LBD). In addition, the heterodimer complex then binds with a specific sequence present in the DNA called vitamin D response element (VDRE). Genomic pathway involves the expression of genes in a tissue-specific manner [28].

1.2.1. VDR domains

VDR contain five functional domains (**Figure 1**) including:

1. A and B domains both are shortest domains contain 20 amino acids.
2. C domain (DNA binding domain or DBD) having two Zn fingers [32] motifs. Two alpha helices are found at the carboxy terminus of each Zn finger (namely helix A and B which constitutes DNA recognition and phosphate binding sites respectively).
3. Flexible hinge D domain is present in between C and E domains having the ability to change structural conformation after VDR ligand binding.
4. E domain (ligand binding domain or LBD) consists of 12 alpha helices along with 3 short beta strands, organized in a manner that it forms three dimensional hormone binding pockets of which vitamin D3 is attached.

Both N-ter and C-ter has activation function (called AF-2) in translation [33].

1.2.2. Vitamin D/VDR actions

1. **Genomic actions:** Vitamin D3 produces its pleiotropic effects by genomic and non-genomic actions. It mediates its genomic actions upon binding to intracellular nuclear transcription factor called VDR.
2. **Non-genomic actions:** Vitamin D also plays various non-genomic actions. Non-genomic actions are also called rapid actions, which are caused by the interaction of vitamin D with the membrane VDR to perform its biological effects through intracellular signalling pathways [35]. However, the contribution of non-genomic pathway in the development of anti-neoplastic effects on breast remains unclear.

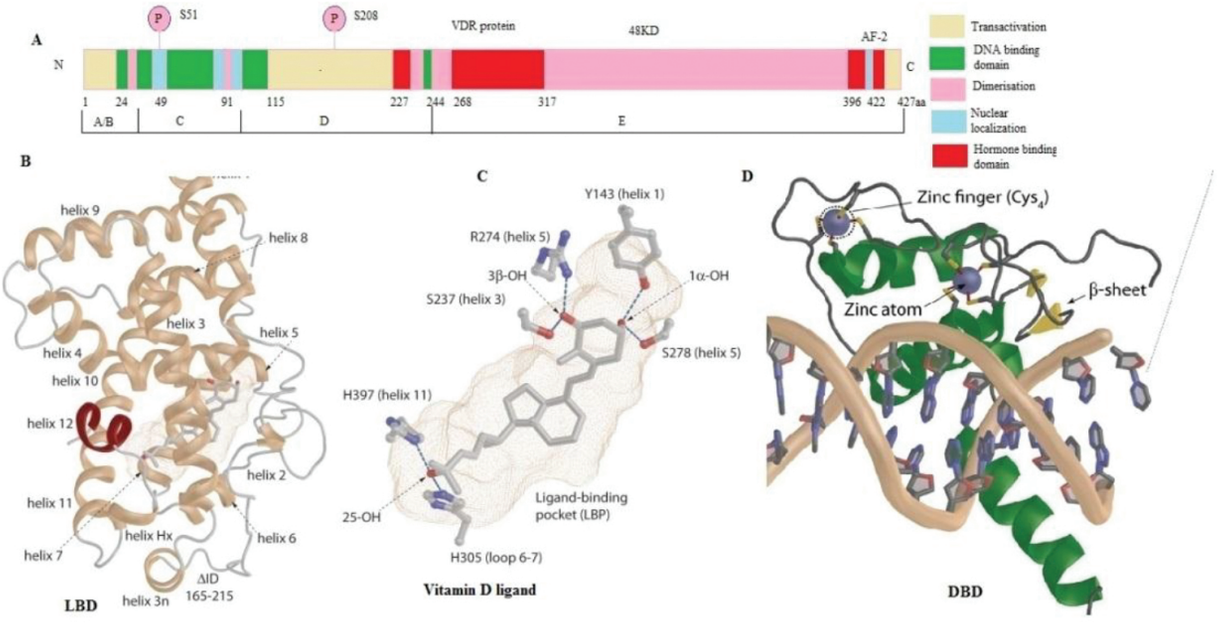

Figure 1. The crystal structure of VDR showing its functional domains [34]. (A) Schematic representation of VDR domains. (B) LBD of the VDR which contains 12 alpha helices. (C) The binding mode of Vitamin D in the hormone-binding pocket. (D) The DBD of the Vitamin D. The two zinc atoms are represented in blue in colour, whereas beta sheets are represented in yellow colour.

2. Bio-activation and metabolism of Vitamin D in normal breast

It is already known that vitamin D affects the breast cancer cell growth but limited information is available about its delivery, uptake and metabolism in mammary cells. Vitamin D is either derived from the gastrointestinal (GIT) absorption or synthesized within the skin under the exposure of UVB radiations, which then undergoes the 25-hydroxylation in liver in presence of 25-hydroxylase resulting in the production of 25(OH)D3. 25(OH)D3 is the precursor molecule for the synthesis of active Vitamin D3 (1,25(OH)2D3). It is a major circulating form of vitamin D, which is stored in adipose tissues. It is also an accurate biomarker of vitamin D, which determines the overall status of vitamin D in the body. However, the precursor does not readily binds to the VDR and must be converted into its active form, 1,25(OH)2D3, which has high binding affinity to VDR. The conversion of precursor vitamin D into its active metabolite occurs in the presence of 1-α-hydroxylases. Immunohistochemistry and *in situ* hybridization studies indicated strong expression of 1α-hydroxylase protein and mRNA in the distal convoluted tubule, the cortical and medullary part of the collecting ducts and the papillary epithelia. Lower expression was observed along the thick ascending limb of the loop of Henle and Bowman's capsule. Weaker and more variable expression of 1α-hydroxylase protein and mRNA was seen in proximal convoluted tubules, and no expression was observed in glomeruli or vascular structures [36]. Whereas lesser expression of 1α–hydroxylase was also observed in non–renal cells including keratinocytes, macrophages, prostatic epithelium, colonocytes [37, 38] and breast epithelium [39] to lesser extent. Kidneys and non-renal 1-α-hydroxylases are

encoded by the same gene mapped on the chromosome 12 [40]. However, the presence of this enzyme on non-renal tissues indicated that the non-renal tissues have the ability of vitamin D bio-activation, responsible to convert 25(OH)D3 into 1,25(OH)2D3. 1,25(OH)2D3 is virtually not detected in human serum under anephric conditions, which means that kidneys are the major source of 1,25(OH)2D3 in circulation. These observations emphasize that 1,25(OH)2D3 produced by the non-renal tissues is not released in the bloodstream. However, they act locally upon binding to VDR on the same tissues from where it is synthesized. Such local actions of vitamin D are likely included in proliferation, differentiation and apoptosis, which are discussed below in later sections.

2.1. Bio-activation pathways in breast cells

The above information supports the hypothesis that two distinct pathways may be involved in the bio-synthesis and bio-activation of vitamin D in breast such as 1,25(OH)2D3 and 25(OH)D3 (vitamin D precursor) pathways [41, 42].

2.1.1. Endocrine pathway

The endocrine pathway is involved with the circulation of 1,25(OH)2D3, which reaches the mammary tissues and produces anti-neoplastic effects through genomic pathway.

2.1.2. Autocrine/paracrine pathway

The other pathway is the autocrine/paracrine pathway involved with the 25(OH)D3, which reaches the mammary gland and converts into 1,25(OH)2D3 [43] in the presence of 1-α-hydroxylase to prevent breast cancer [41]. Most of the extra-renal tissues of the body have its own 1-α-hydroxylase enzyme needed for the production of active metabolite of vitamin D [37]. The circulating level of 25(OH)D3 seems to be the key regulator of tissue-specific synthesis of active vitamin D [37, 44]. The locally produced active vitamin D binds with VDRs of mammary epithelium in order to regulate the expression of more than 200 genes, which are involved in controlling cell proliferation, inhibit cell growth, stimulate cell differentiation, induce apoptosis and inhibit angiogenesis [45] and contribute in the prevention of breast tumourogenesis [46]. Moreover, mammary epithelial cells also contain 24-hydroxylase enzyme (CYP24), which converts active vitamin D into less active metabolites including 24,25-dihydrohydroxyvitamin D3 and 1,24,25-trihydroxyvitamin D3 [43]. For this reason, we can say that breast tissues contain all the elements of vitamin D signalling axis, which involve in the local synthesis as well as metabolism of vitamin D and its signal transduction through VDRs.

3. Vitamin D signalling in the prevention of breast cancer

3.1. VDR expression in breast

Several extra-renal epithelial cells of body express VDR, for example, epithelial cells of rat, mouse and human mammary glands. VDR expression is highest in breast tissues during

puberty, pregnancy and lactation in women [47]. In mice, the expression is highest in ductal epithelium when compared to terminal end-buds epithelium of mammary gland. In human, VDR-positive cells are found in basal and luminal layer of breast epithelium [39]. Cap cells and stromal compartments of breast are also rich in VDR [48–50]. The presence of VDR in different cells of breast highlights the complexity of vitamin D signalling in breast tissues.

3.2. Mechanism of vitamin D signalling in breast cancer prevention

Despite these consistent data, the exact mechanism of breast cancer prevention by vitamin D has yet to be discerned. Both 25(OH)D3 and 1,25(OH)2D3 exert its profound effects on normal VDR-positive breast epithelium such as hormone-stimulated growth inhibition, ductal elongation, ductal branching and induction of biomarkers involved in breast differentiation. The expression of VDR and 1-α-hydroxylase in mammary adipocytes also takes part in the prevention of cancer in whole tissue since adipocytes secrete diffusible signals in response to 25(OH)D3, which constrain morphogenesis of the nearby ductal tissues [48].

Furthermore, alteration in cellular energy metabolism, immune responses and other processes of vitamin D signalling in the prevention of breast cancer on non-tumourigenic breast epithelium is described below.

3.2.1. Anti-proliferation

Vitamin D causes cell-cycle arrest by direct or indirect involvement of growth factors and does not allow the cell to enter in the S phase from G1 phase [51]. It increases the expression of cyclin-dependent kinases (CDKs) inhibitors, including p21 and p27, and reduces the expression of CDK2, CDK4, cyclin D1, cyclin A1 and cyclin E1, which results in the arrest of cell-cycle progression [52, 53]. It is also involved in the downregulation of c-myc oncoprotein and inhibits the cell proliferation [54]. However, all these consequences describe that vitamin D hampers the cell proliferation by affecting the crucial controllers of cell-cycle progression. Furthermore, vitamin D also enhances the transcription factor CCAT enhancer-binding protein alpha (C/EBPα), which mediates the anti-proliferative effects of vitamin D observed in *in vitro* study on MCF-7 cells [55]. Tumour suppressor TCF-4 also hinder cell-cycle progression [56]. Beside these, vitamin D also causes the induction of BRCA 1 (breast cancer 1) gene, which is inversely associated with the cell proliferation, promotes tumour suppression and inhibits cell-cycle progression [57].

3.2.2. Growth arrest and pro-apoptosis

Vitamin D plays an important role in the induction of apoptosis in mammary tissues, since *in vitro* conditions, such as shrinkage of cell, condensation of chromatin network and fragmentation of DNA, have been observed in MCF-7 cells upon treatment with vitamin D [58]. The mechanism by which vitamin D induced apoptosis has not been fully understood. However, the most probable mechanism is the downregulation of anti-apoptotic protein, called Bcl2 (51). Vitamin D increases the tumour necrotic factor alpha (TNFα) with or without caspase 3 activation. In the caspase 3-independent mechanism, vitamin D-mediated induction of

apoptosis in MCF-7 cells is thought to be correlated with mitochondrial disruption, which causes the release of cytochrome C and formation of reactive oxygen species (ROS) resulting in the apoptosis [59]. Other mechanism of caspase-independent apoptosis induced by vitamin D-dependent Ca+ absorption is most likely associated with the increased activation of lysosomal proteases [60]. Finally, vitamin D also acts a pro-oxidant for breast cancer cells, which generally increase the redox potential [61] of carcinogenic cell, may be one of the most important underlying pro-aptototic mechanisms of vitamin D. The pro-oxidant action of vitamin D in MCF-7 cells could result from increased intra-cellular reactive oxygen species production during aerobic metabolism. Vitamin D inhibits the expression of one of the major constituents of the cellular defence system against ROS, like superoxide dismutase (SOD) [62]. This decrease could be one of the mechanisms underlying the pro-oxidant action of vitamin D. Indeed, it was previously reported that overexpression of SOD protects MCF-7 cells from being injured [63, 64] . Decrease in SOD levels would cause a shift in the balance between superoxides and hydrogen peroxide (H_2O_2). Increased levels of superoxides can, in turn, cause increased oxidative damage attributable to interaction with NO to form the highly toxic peroxynitrite [65] and to increased availability of free iron that supports hydroxyl radical formation through the Fenton reaction [66].

Changes in the redox state could translate into reversible oxidation of cysteines in major proteins that determine cell fate, such as protein kinases, protein tyrosine phosphatases and transcription factors (e.g. Sp1, activator protein-1, nuclear factor-κB and p53) [67–73]. The key components of the apoptotic process, such as mitochondrial permeability transition pores and increase caspases, are also subjected to redox regulation [74]. Oxidation of the cysteine in the active site of GAPDH may be considered a sensitive, easily accessible marker for these processes. It is noteworthy that the increase in the cellular redox potential was shown to abolish the DNA-binding ability of the transcription factors activator protein-1 and nuclear factor-κB [75] can cause apoptosis and prevent breast cancer. Notably, a recent study describes the relationship between p53 and VDR. Mutant P53 (mutp53) converts the Vitamin D pro-apoptotic activity into anti-apoptotic activity and attain oncogenic activity which demonstrate gain of function (GOF) [76].

3.2.3. Anti-angiogenesis

Vitamin D inhibits angiogenesis, which is another important feature for tumour growth and progression. It also has the ability to impede angiogenesis at very minute concentration [77] mediated through the downregulation of vascular endothelial growth factor (VEGF), tenascin-C, tumour growth factor α (TGF-α) and epidermal growth factor (EGF) [78, 79].

3.2.4. Anti-invasion or anti-metastasis

Vitamin D inhibits the invasion of tumour in nearby tissues but its deficiency promotes the growth of breast cancer cells in the bones of nude mice and alters the bone micro-environment [80]. This ability of vitamin D is supposed to be caused by the decrease expression of metalloproteinases (MMP-9) and serine proteinases (such as urokinase-type plasminogen activator and tissue-type plasminogen activator) along with the increased expression of their inhibitors

[81]. In addition, vitamin D also downregulates P-cadherin [82] and upregulates E-cadherin [83].

3.2.5. Anti-inflammation

Vitamin D reduces the expression of cyclooxygenase-2 (COX-2), which plays a crucial role in the synthesis of prostaglandin in many breast cancer cell lines in human. It increases the upregulation of 15-hydroxyprostaglandin dehydrogenase, an enzyme which is involved in catalysing the conversion of active prostaglandins into biologically inactive ketoderivatives [84]. Prostaglandins have been supposed to play a role in the breast cancer development and its progression [85]. Prostaglandins are secreted by the breast cancer cells or surrounding tissues promote tumour progression caused by cell proliferation, resistant to apoptosis, tumour invasion and angiogenesis [85]. An increased expression of COX-2 in breast cancer has been assumed to correlate with high-grade, large tumour size and poor prognosis [86].

3.2.6. Anti-estrogen

Vitamin D inhibits estrogen biosynthesis (steroidogenesis) and its biological actions [84]. Vitamin D suppresses the estrogen pathway by inhibiting the expression of gene which encodes aromatase (the enzyme which converts androgens to estrogen) [84]. Vitamin D also reduces the expression of estrogen receptor alpha (ERα-) [87]. The combined actions of vitamin D can decrease the estrogen and the receptor, which mediates their signalling in the prevention of breast cancer.

3.3. Vitamin D deficiency and breast cancer

The half-life of circulating vitamin D is approximately about 2–3 weeks which is a better indicator of blood vitamin D. Active vitamin D3 (1,25(OH)2D3) is locally synthesized from its precursor (25-(OH)D3) in almost all body cells because of the universal presence of 1α-hydroxylases in all cell type including breast [88]. So, the deficiency of 1-α hydroxylase may augment the deficiency of vitamin D and thereby associated with increased breast cancer risk and mortality [89].

Serum vitamin D concentrations and vitamin D supplementations are the independent predictors of breast cancer risk. Serum level of vitamin D of more than 50 ng/ml is associated with the 50% lower risk of breast cancer in women than serum values less than 30 ng/ml [90, 91]. In addition, breast cancer risk reduces in the pre-menopausal women who consume calcium and vitamin D orally [92]. Locally advanced breast cancer patients have more severe vitamin D deficiency than those with early-stage disease [93].

Deficiency of vitamin D is related with secondary hyperparathyroidism, which causes increased bone resorption, release of calcium from bones osteoclasts into the blood and may exacerbate osteoporosis with subsequent harsh effects on bone mineral density (BMD). In breast cancer patients, osteopenia and osteoporosis mostly occur because of early menopause and vitamin D deficiency, which is then augmented by chemotherapy and hormone replacement therapy [94]. Therefore, breast cancer patients are necessary to suffer a baseline metabolic

bone evaluation along with circulating vitamin D levels and bone mineral densitometry [94, 95].

Vitamin D deficiency is also associated with the recurrence, tumour size and death from breast cancer. It means that having enough amount of vitamin D may be able to keep a cancer from getting worse. In fact a recent meta-analysis concluded that high circulating level of vitamin D is weakly related with breast cancer incident; however, strong association was found with better breast cancer survival [89]. So, the maintenance of an optimal vitamin D status at the time of diagnosis and during 1-year follow-up period is necessary for improving survival of breast cancer patient.

There are four types of studies which illustrated whether exposure of ultraviolet B (UVB) radiations and low levels of vitamin D decrease the risk of breast cancer.

3.3.1. Geographical studies

In these studies, the geographical variation in the incidence or mortality of breast cancer is compared statistically with solar UVB radiations. The lower breast cancer incidence rate was found in the regions of high solar UVB radiations such as in Australia, China, France, Nordic countries, Spain and the United States [96].

3.3.2. Observational studies

Observational studies do comparison of vitamin D levels with the incidence of breast cancer among cases and controls. There are two categories of observational studies:

1. The studies in which vitamin D levels is measured near the time of breast cancer diagnosis are called case-control studies.
2. The studies in which vitamin D is measured at the time of women enrolment in studies prior to the breast cancer diagnosis are called nested case-control studies.

Only the case-control studies have reported that low levels of vitamin D are associated with breast cancer risk [97]. The reason why nested case-control studies have not reported the same results may be due to

1. breast cancer develops very rapidly, and
2. without supplementation, vitamin D levels tend to change little over time.

Observational studies have also documented that those females have higher vitamin D levels at the time of diagnosis live longer as compared to those with low vitamin D levels [46, 96]. In addition, the chances of mortality are higher in black women after diagnosis of breast cancer than in white women.

3.3.3. Laboratory studies

Laboratory studies have focused on the mechanisms of vitamin D in the contribution of reduced risk of breast and other cancer types. According to these studies, vitamin D allows

the cells to stay alive if they are the right type and present at the right place, or it helps the cells to commit suicide (apoptosis) if cells are not the right type or not present at the right place. Vitamin D also reduces the formation of blood vessels around tumours and decreases the ability of tumours to invade [98]. According to the randomized controlled trials, vitamin D reduced the risk of cancer, including breast cancer [99, 100].

4. Vitamin D receptor gene

The human VDR (hVDR) gene is located at long arm of chromosome 12 bands 13-14 (12q13-14) [101, 102]. The gene is 75 kb long and contains 11 exons [103]. This gene is divided into three regions: one coding region and two non-coding regions.

4.1. Non-coding regions

The 5′ promoter region of VDR lacks initiator (TATA and CAAT boxes) and is rich in GC content. It provides the putative site for binding of many transcription factors [103]. The promoter region is present at exon 1(1a, 1b, 1c, 1d, 1e, 1f). The promoter region facilitates the transcription activity of VDR target gene. The 3′ UTR contains poly (A) repeats, which is reported to be associated with the mRNA stability.

4.2. Coding region

Coding region comprises of exon 2–9. Exon 2, which have translation start codons, contains DNA-binding site, whereas exon 7, 8 and 9 have ligand (vitamin D) binding site [104].

5. Single nucleotide polymorphism (SNP)

Polymorphism is defined as the presence of two or more clearly different phenotypic variants of a particular DNA sequence in the same population of a species. The most common form of polymorphism is the single nucleotide polymorphism in which variation occurs at a single base pair usually present in approximately 1% of the population. These types of changes can be present in non-coding region of genes and in introns, which would not affect the translation of proteins, but these changes can affect the degree of gene expression and levels of proteins. The changes can also be present in coding regions of DNA or exons resulting in the formation of an altered protein sequence. Sometimes variation in exons do not cause the change in the structure of protein called synonymous polymorphisms.

These changes often produce or eliminate restriction sites for endonuclease to digest the DNA. As a result, fragments of DNA with a different length will be obtained which can be identified by gel electrophoresis. This process is called restriction fragment length polymorphisms (RFLPs). The produced fragments will be the undigested fragments, which is homozygous dominant, whereas the digested fragments are heterozygous and homozygous recessive.

Sometimes polymorphic alleles are linked with each other and within a population in non-random proportion is known as linkage disequilibrium (LD), [105] and the combination of alleles (blocks) or set of SNPs present on the same chromosome which tends to be inherited together is termed as haplotype. The size of these blocks is different ranging between 10 and 20 kb and could be important in determining the reason of genetic disorder.

6. SNPs in the VDR gene

The variation in the 5′-promoter region of VDR gene can change the sequence of mRNA as well as protein levels, whereas alteration in 3′ UTR sequence can disturb the stability of mRNA thereby affecting the efficacy of translated protein. Some SNPs have been existed in the VDR gene, including *Cdx*2 [106], *Fok*1 [107], *Bsm*1, *Taq*1, *EcoR*V [108], *Apa*1 [101] and *poly* (A) [109] microsatellite repeats.

6.1. *Cdx*2 SNP

The VDR *Cdx*2 (G-1739A) is the single nucleotide polymorphism, which was recognized by the sequence analysis of promoter region. It is an adenine to guanine (A to G) SNP situated at the promoter region of VDR gene at exon 1e. It was initially reported to be located at the 3731 bp upstream exon 1a of promoter region of VDR gene among Japanese women [106], but later identified to be located at 1739 kbp upstream of 1e exon just 2 kb away from the exon 1a among many ethnic population [110]. It is the binding region of *Cdx*2 protein, a most important intestine-specific caudal-related homeodomain protein, which increases the transcription of VDR. When A allele is present in *Cdx*2 promoter, the Cdx2 protein is bound more strongly as compared to when a G allele is present. The A allele stimulates the initiation of transcription, whereas G allele inhibits [106].

6.2. GATA SNP

GATA (A-1012G) is located at exon 1a in the core sequence of DNA called AGATAT [111]. It provides the binding of GATA protein and the binding site is present in A allele and absent in G allele. The mechanism of this polymorphism is not identified yet; however, this polymorphism alters the immune responses to cancer cells. A allele is responsible to reduce cytotoxic response to cancer cells. In addition, it is also an important element that if the transcription is begun in exon 1a or 1d. In presence of G allele, exon 1d comprises an alternate start codon which results in a formation of N-ter extended protein called VDRB1. G allele is most likely associated with the VDRB1 (long) protein, whereas A allele is related with the VDRA (short) protein.

6.3. *Fok*1 SNP

*Fok*1 polymorphism is also called start codon polymorphism (SCP). It is a thymine to cytosine (ATG to ACG) polymorphism located at the 10 bp upstream 5′ end of exon 2 on the DNA-

binding domain, which results in a formation of more active transcription factor that is three amino acids shorter [103, 112]. Those individuals who have ACG sequence in the start codon, the initiation of translation occurs at the second ATG site which results in a formation of three less amino acids at NH2 terminus containing 424 amino acids. If the initiation occurs at first ATG sequence, it produces full-length VDR protein containing 427 amino acids. In the presence of restriction site, alleles are designated as 'f', whereas its absence is designated as 'F' (active form) [113]. The restriction recognition site of *Fok*1 is 5′-GGATG*-3′; 3′-CCTAC*-5′ and enzyme cleaves 9/13 nucleotide downstream of the recognition site.

6.4. *Bsm*1-*Apa*1-*Taq*1 SNP

Most of the functional sequence variants identified near the 3′ region of VDR gene were *Bsm*1, *Apa*1 and *Taq*1 SNP. These SNPs are in linkage disequilibrium with each other and are located in the same haplotype block. Therefore, these SNPs may have the potential to influence the mRNA stability. The *Apa*1 and *Bsm*1 are located at intron 8, whereas *Taq*1 is located at exon 9 [114].

The presence of restriction enzyme site in these SNPs is designated as lower case letter such as b, a and t, whereas absence is designated as upper case letter including B, A, T. The restriction site for Bsm1 is 5′-GAATGCN*-3′, Apa1 is 5′-GGGCC*C-3′ and Taq1 is 5′-T*CGA-3′.

6.5. *Poly* (A) repeats

Poly (A) tail is a variable number of tandem repeats (VNTR) or short tandem repeats (STR) containing variable numbers of adenine nucleotide present at the 3′ UTR of VDR. *Poly* (A) is also linked with Bsm1, Apa1 and Taq1 polymorphisms and also involved in the mRNA stability of VDR. It varies in length and can be divided into two types:

1. The long (L) *Poly* (A) sequence in which 18–24 adenine nucleotide is present, and
2. The short (S) *Poly* (A) sequence in which 13–17 adenine nucleotide is present.

Because all four polymorphisms (*Bsm*1, *Apa*1, *Taq*1 and *Poly* (A)) are present in close proximity on the VDR gene, strong linkage disequilibrium exists among them. The two most common haplotypes are:

1. baTL haplotype in which *Bsm*1 and *Apa*1 restriction sites are present, whereas *Taq*1 site is absent along with the presence of long *Poly* (A) repeats.
2. BAtS haplotype *Bsm*1 and *Apa*1 restriction sites are absent, whereas *Taq*1 site is absent along with the presence of short *Poly* (A) repeats [115].

The baTL haplotype is reported to be associated with the increase incidence of breast cancer [116].

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7. VDR gene polymorphisms and breast cancer

VDR gene polymorphism is associated with the breast cancer risk [117–125] but insufficient data are available to find the relationship with breast cancer risk [126]. The studies have pointed out allelic variations in VDR gene, such as *Cdx*2, *Fok*1, *Bsm*1, *Taq*1, *Apa*1 and *Poly* A in different ethnic groups with breast cancer incidence with contradictory results [117, 118, 121, 126].

7.1. *Cdx*2 polymorphism and breast cancer

The contradictory observations were reported on the association of *Cdx*2 polymorphism and breast cancer susceptibility [125]. Recently, a meta-analysis has documented that *Cdx*2 polymorphism is linked with breast cancer susceptibility only in Africans [127]. However, no profound relations was observed between *Cdx*2 polymorphism and breast cancer risk among Pakistani population [126].

7.2. *Fok*1 polymorphism and breast cancer

*Fok*1 polymorphism contain large consensus sequence has no relationship with breast cancer incidence [116, 117]. But the association between *Fok*1 polymorphism and breast cancer was reported in several ethnic groups [113, 120], mainly in Caucasians [128, 129]. Nemenqani et al. [121] found that *Fok*1 polymorphism is associated with the ER and PR status of breast cancer and described that *Fok*1 polymorphism has a significant interaction with the ER status but not with PR status of breast cancer.

7.3. *Bsm*1 polymorphism and breast cancer

*Bsm*1 polymorphism is the most important functional VDR gene polymorphism, which is found to be associated with the risk of developing breast cancer [124]. However, it has also been documented that there is no relation between *Bsm*1 and breast cancer [119]. Rollison et al. [123] describe that *Bsm*1 is involved to alter the vitamin D intake and overall breast cancer risk. McCullough et al. [130] found that B allele of *Bsm*1 decreases breast cancer incidence by 20%.

7.4. *Taq*1 polymorphism and breast cancer

Many case-control studies suggested that *Taq*1 polymorphism is not associated with breast cancer risk [119–121]. But it has been reported that *Taq*1 is one of the functional polymorphisms which is linked with increased breast cancer incidence [131, 132]. A meta-analysis on large ethnic groups revealed that the *Taq*1 polymorphism increases the risk of breast cancer development in Caucasians; however, no profound association was observed among Asians [133].

7.5. Other polymorphisms and breast cancer

Positive association of poly A [118] or Apa1 [119] was found to be reported with breast cancer risk, showing a connection between polymorphism and likelihood of having a tumour.

8. Conclusion

This chapter concluded that women with breast cancer are more likely to have low vitamin D levels. Those women who do not get adequate vitamin D may be more likely to develop breast cancer later in life as compared to those who have higher vitamin D levels, who are less likely to develop breast cancer and less likely to die from breast cancer.

Because of the broad spectrum of vitamin D effects on mammary tissue, it is suggested to be a most important physiological growth regulator of mammary gland and could be a potential therapeutic agent. Additionally, due to the expression of VDR to a higher extent on breast epithelial cells, vitamin D signalling should also be monitored during breast cancer treatment. Since breast cancer is a complex disease which may or may not be associated with the decreased vitamin D levels or VDR polymorphisms. However, the functions and role of vitamin D and VDR cannot be neglected during breast cancer treatment.

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