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Review Article

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Role of Vitamin D Receptor Gene Polymorphism with Steroid Receptors in Breast Cancer: an Update

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Abstract: This review touches on new insights into the possible role of Vitamin D receptors genetic polymorphisms, and steroid receptors in the patients diagnosed with breast cancer. This is the most common cancer in women; further, it creates diverse illnesses among the diseased patients, and the prognosis is linked with the different subtypes present in the hormone receptors. Most of the review studies focus on the epidemiology of the disease. However, fewer studies are done on the genes polymorphism prognosis, which plays a more significant role in the prognosis and diagnosis of breast cancer, so by proper screening at the genetic level as early, can predict the disease in females which will help the clinicians in better management of the disease. Hence the burden of disease and its ill effects can be reduced in the patient care system. Thus the Vitamin D levels in the serum and the vitamin D receptors (VDR) transcriptionally controls its target genes in the cell proliferation, differentiation, and death pathways in a ligand-dependent manner, providing protection against cancer growth and progression. Also, there are strong relationships between VDR polymorphisms and steroid hormone (estrogen, progesterone, and androgen) receptors, which will help in the prognosis and diagnosis of breast cancer disease. We recommend early screening of these receptors using advanced molecular biology techniques like Real-time Polymerase chain reaction, Chemiluminescence, Western blotting which will help to detect the genotyping of these genes at the earlier stages and are non-invasive, patient-friendly, reliable, and accurate. Vitamin D receptor gene polymorphism and steroid receptors themselves can act as early predictive biomarkers for many studies that are to be warranted further in the different ethnic populations with large sample sizes.

Keywords- ***Breast cancer, steroid receptors, prognosis, Vitamin D Receptor (VDR), polymorphisms.***

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1. INTRODUCTION

Breast cancer is the most frequent cancer in women, accounting for more than one out of every ten new cancer diagnoses each year. It is also the second most common cancer among females [1,2]. Despite remarkable advancements in cancer therapy, the heterogeneity of breast cancer and the development of anticancer drug resistance remain key hurdles for effective treatment [3]. The majority of breast cancers are caused by the uncontrolled multiplication of epithelial cells in the mammary gland's ducts and lobules [4]. Having a first-degree relative with the disease, extremely thick breasts, past benign breast biopsy results, being on oral contraceptives, and having the first child at 30 years or older are all risk factors for breast cancer [5]. Furthermore, modifiable risk factors such as alcohol consumption and a high-fat diet contribute to the disease incidence [6]. The vitamin D receptor (VDR) is a mediator for the cellular effects of vitamin D and interacts with other cell signalling pathways that influences the cancer development. The biologically most active form of vitamin D is 1,25(OH)2D, which mainly exerts its anti-proliferative effects by binding to the vitamin D receptor (VDR) and acting in the complex as a transcriptional factor for a variety of genes, including those involved in cell differentiation and cell growth [7,8]. Higher vitamin D levels are thought to protect against a variety of malignancies, including breast cancer, through genomic effects controlled by the vitamin D receptor (VDR) [9]. There is mounting evidence that vitamin D is linked to a lower risk of breast cancer [10]. Apart from calcium homeostasis, vitamin D and its receptor (VDR) promote cell differentiation and suppress the proliferation of cells that have cancer-preventive capabilities [11]. The human VDR gene, which is located on chromosome 12q13-14, has about 470 single-nucleotide polymorphisms (SNPs). Fok1 (rs2228570), Bsm1 (rs1544410), Poly A (rs17878969), Apa1 (rs7975232), and Taq1 (rs7975232) are the most investigated SNPs [12]. Breast cancer risk is controlled by the prognosis of VDR gene polymorphism and steroid receptor status [13,14]. The polymorphism of the vitamin D receptor (VDR) is based on single nucleotide polymorphisms that might interfere with the activity of vitamin D which affects the prognosis of tumor [15]. This review touches on the role of Vitamin D receptor gene polymorphisms and steroid receptors status in prognosis and diagnosis of breast cancer as early biomarkers that can help clinicians to manage the disease better. Previously, many literature reviews on breast cancers touched on the epidemiology and prevalence, but no such study has been directly found which has been done on the plausible role of vitamin D receptor gene polymorphisms and on the steroid receptors status, if any are less and being done on single genes. For that, a comprehensive literature review has been done systematically to assemble all the latest material in all ethnic populations and prepare the same for the better management and prognosis of the disease. The aim and objective of this review are to offer a complete assessment of the role of VDR polymorphism and steroid receptor status in terms of modifying impacts on breast cancer risk, severity, progression rate, and disease prognosis, which will help the clinicians in improving the health index of patients.

2. METHODOLOGY

Using the National Library of Medicine's (NLM) PubMed, Medline and Scopus database search of previous years, we conducted an updated comprehensive evaluation of published research. Keywords including 'VDR gene polymorphisms,' 'Steroid receptors status,' and 'breast cancer' were utilized in the search. Articles on the role of VDR gene polymorphisms and steroid receptor status in relation to breast cancer risk and incidence were included in our analysis. Animal studies and research on breast cancer in men or teenagers were omitted from our investigation. The quality of the evidence for each part of the statement was rated as high (randomised controlled trial (RCT) evidence – level 1), moderate (intervention short of RCT or large observational studies – level 2), or low (case series, case reports, expert opinion – level 3). The clinical significance and weight of opinion favouring each statement were used to determine whether it was strong (S – recommendation) or weak (W – suggestion). Strong suggestions are clinically relevant best practices that will be applied to the majority of patients in the majority of circumstances. In contrast, weak statements should be examined by the clinician and will be applicable best practices only to specific patients or in certain circumstances.

3. Vitamin D receptors and breast cancer prognosis

Vitamin D interact with VDR in the breast epithelium in the same cell or in nearby cells in order to keep the cell differentiated and quiescent [16]. By studying case-control samples from breast cancer samples, Hemida et al., showed that the expression of VDR in breast cancer tissues was elevated, and an association exists with the expression of estrogen receptor alpha [17]. Heublein et al., and Huss et al., conducted retrospective studies which indicated that low VDR expression is a poor prognostic indicator for breast cancer[18,19]. Currently, the number of tumor node metastasis (TNM) is the most significant factor in determining how breast cancer patients will respond to treatment. However, individual differences reduces the accuracy of prediction. It is therefore imperative that breast cancer patients have a reliable biological indicator that can help predict their prognosis [20]. Despite the fact that vitamin D levels and VDR expression are associated with breast cancer prognosis [21,22], it seems that the expression of VDR is more reliable for considering the prognosis of breast cancer since vitamin D levels changes that are highly dependent on dietary exposure to sunlight. Furthermore, VDR protein expression has prognostic significance, but it has also been reported that expression of VDR mRNA has prognostic value in breast cancer [23,24]. Further studies are needed to elucidate the roles of expression and polymorphism of VDR mRNA in breast cancer.

4. Steroid receptor status concerning Breast cancer

Estrogen, Progesterone, and Androgen receptors (ER, PR, and AR), like VDR, are members of the nuclear receptor superfamily [25].

4.1 Estrogen Receptor

The estrogen Receptor (ER) is widely acknowledged as a significant predictor of the start of breast cancer in women. According to a survey done by the Department of Surgical Oncology and the Division of Molecular Medicine in India, 50.8 percent of patients were found to be ER-negative, whereas 49.2 percent were found to be ER-positive [26]. Surveillance, Epidemiology, and End Results (SEER) studies, on the other hand, showed that ER is negative in more than double the proportion of patients with breast cancer. It was discovered that 50.8 percent of breast cancer patients had negative ER, compared to 23.4 percent who had positive ER. The SEER reports also revealed that 24.8 percent of patients had Triple-

negative (TPN) tumors, compared to 15 percent of patients with TPN tumors, and that 76.4 percent of patients had a median age of 53 years. The study found that ER-negative increased among young women, with 63.5 percent of those under 50 years old, and dropped as women's ages grew [27]. In the primary tumor stage, ER staining was found in 74.2 percent of Whites, 13.7 percent of Blacks, 8.5 percent of Hispanics, 3.0 percent of Asians, and 0.6 percent of Others, respectively. It was discovered that patients with ER-positive rates ranging from 1% to 9% are more likely to get chemotherapy than patients with ER-positive rates greater than 10% who are treated with endocrine treatment. The presence of a positive estrogen receptor in women indicates an increased risk of breast and ovarian cancer. As a result, positive estrogen receptor cells boost surrounding cell proliferation, release paracrine hormones, and promote epithelial cell development[28]. Negative ER cells, on the other hand, aid mammary gland growth and restore the proliferation process. Positive estrogen receptor cells are identified in 20% of sporadic breast cancer cases, while negative estrogen receptor cells are seen in 70% to 80% of instances. When the size of the tumor grows large enough to reduce the estrogen effect on the patients, the ER-positive cells undergo metamorphosis and eventually perish. As a result, the negative estrogen receptor cell, like the positive estrogen receptor cell, undergoes neoplastic change as it grows older. As the tumor increases in size, positive estrogen receptors become differentiated, while negative estrogen receptors become stimulated by mitogenic signaling [29].

4.2 Progesterone Receptor

Progesterone receptors are members of the nuclear subfamily 3 (NR3C3) and belong to the protein group C. Positive progesterone receptors are malignant cells in the breast that are extremely sensitive to progesterone and have receptors that help hormones proliferate. Hormone therapy is used to inhibit estrogen receptors in those who have positive progesterone receptor cancer. Patients with negative progesterone receptor cancer, on the other hand, are not suggested to receive hormone therapy because it was ineffective for them [30]. When looking at the positive and bad aspects of progesterone receptors in India, it was discovered that they were present in 49.8% of patients suffering from breast cancer. There are 204 cases of lobular carcinoma and 50 cases of invasive lobular carcinoma. Invasive ductal carcinoma was found in 817 Indian women, and breast cancer was found in 16 of every 1087 Indian women. The Indians had a more significant percentage of progesterone receptors, which exhibited negative breast cancer proportions [31]. According to a survey conducted by the National Institutes of Health in the United States, 67.2 percent of women with breast cancer in the United States have positive progesterone receptors as well as positive estrogen receptors, while 19.0 percent of women with breast cancer have negative progesterone receptors and negative estrogen receptors. It was also shown that 12.2 percent of breast cancer patients had negative progesterone-receptors with positive estrogen-receptors, whereas 1.6 percent had positive progesterone-receptors with negative estrogen-receptors. It was also discovered that women with breast cancer who had positive progesterone-receptor and positive estrogen-receptor symptoms have a 30%-60% decreased likelihood of dying from the disease [32].

4.3 Androgen Receptor

The nuclear receptor known as the androgen receptor is strongly linked to the development of the prostate. It's a breast cancer expression that also recognizes luminal genes and the luminal-androgen receptor (LAR) subtype. The expression of numerous luminal genes is linked to positive androgen receptors, which are also linked to the HER2 pathway. Furthermore, when compared to positive androgen receptors, androgen receptors were negatively related with grade I/II vs III malignancies in high proportions [33,34].

5. *VDR polymorphism and Steroid receptor status concerning Breast Cancer prognosis.*

The steroid hormone receptor status has an impact on the link between vitamin D and breast cancer risk. Reduced 25(OH)D has been linked to an increased incidence of advanced breast cancer and, to a lesser extent, ER+ PR+ breast cancer, which has a better prognosis [35]. Due to its lack of relationship with numerous determinants or markers of breast cancer, such as tumour type, lymph node status, hormone receptors, Ki-67 expression, and p53 levels, the VDR polymorphism was previously not considered a predictive factor for breast cancer [36]. Hormone receptor status, Ki-67, triple-negative status, and tumour size are all linked to lower VDR expression, according to a recent study[37]. Because of the lack of conclusive research in this area, more research is needed**.** VDR expression varies greatly between different types of breast cancers, with studies reporting almost 90% expression in ER+ tumours compared to only 27% in basal/triple-negative tumours, implying an inverse association between VDR expression and cancer severity [38]. Abbas et al., found a link between the TaqI VDR polymorphism (containing at least one copy of the t allele) and ER-positive postmenopausal breast cancer [39]. A recent investigation found that FokI polymorphisms have a similar favorable effect on the development of ER+ cancer in Saudi women patients [14]. Premenopausal Chinese women with both the aa genotype of the ApaI polymorphism and the ER haplotype experienced a delayed onset of menarche. This finding is substantial as the age of menarche is a significant risk factor for breast cancer [40]. The steroid hormone receptor status is known to influence the relationship between vitamin D and breast cancer risk [41]. Various processes such as frequency identification of FFLL and FfLL genotypes against FokI and poly(adenylate) grouping, comparing tumor grade, lymph node involvement, and estrogen receptor (ER) status among cancer patients, and VDR genotype are some of the methods that aid in determining the levels, stages, and progression of cancer in patients. For example, adjusted odds ratios (OR) for age at sampling, HRT use, and menopausal state at diagnosis were observed to be 1.12 (0.62–2.04) in the identification of total tumor grade in tumor grade I, FFLL or FfLL. As a result, it can be concluded that the use of FokI, poly (adenylate) grouping, and other techniques aided in gaining a thorough understanding of the tumor grade present in breast cancer patients [42]. VDR polymorphisms, which include the bb genotype, are directly linked to the spread of breast cancer. The bb genotype, which was derived from VDR BsmI polymorphisms, was found to have four times the chance of developing metastases as the BB genotype [43]. Furthermore, the TT genotype derived from the VDR TaqI polymorphism is strongly linked to an elevated risk of 1.8 lymph node metastases. Females that have more of the haplotype baTL have a higher chance of acquiring metastatic illness, especially in Caucasian female communities [44]. As a result, VDR polymorphisms are connected to the development of breast cancer risks in individuals.

6. *Heterogeneity in VDR expression concerning Steroid receptors status*

The effects of vitamin D endocrine signaling on distinct cell types in mammary tissues are poorly understood. Breast cancer is a diverse illness that develops from a variety of mammary epithelial cell types [45]. The inner luminal layer and outer basal layer of myoepithelial cells make up the mammary epithelium. A recent genome-wide transcriptome research in human tissues found that CYP24A1 is expressed differently in luminal progenitor cells, suggesting that the vitamin D pathway may play a role in mammary cell lineage development [46]. In normal human breast tissues, major steroid receptors VDR, ER, and AR revealed differential expression between luminal and basal cell types. VDR expression, which is commonly coupled with ER and/or AR, was observed during particular stages of luminal cell differentiation and suppression during other stages, according to Santagata et al.[47]. In some cases of breast cancer, variations in VDR expression may lead to unresponsiveness or resistance to vitamin D supplementation. Additionally, epigenetic alterations in VDR and CYP24A1 have been linked to vitamin D resistance [48]. Individuals with malignancies that are positive for ER, VDR, and AR all have a better prognosis [49]. These findings highlight the need of assessing VDR polymorphisms and steroid receptor status in breast cancer samples at the same time [50,51].

7. CONCLUSIONS

VDR gene polymorphism is a highly effective indicator for predicting and assessing the beginning and progression of breast cancer when taken collectively. Further research on the link between VDR genetic polymorphisms and breast cancer incidence in patients who are classified based on their steroid receptor (ER, PR, and AR) status is required. This will allow researchers to explore the relationship between VDR and the molecular subtypes of breast cancer, which will aid in the development of more tailored therapies for patients. In this review article more has been added related to breast cancer, prognosis, and diagnosis which will help the clinicians to establish new treatment protocols in systematically managing the diseases. Further studies are needed for eradicating the diseases by targeting the gene at the protein level in the human body system, in order to improve the health index of our woman gender. Therapeutic approaches are needed for best treatment protocols and will curtain fewer surgical procedures.

8. AUTHOR'S CONTRIBUTION STATEMENT

Ashok Kumar Dogra, conceptualized, prepared the original draft, reviewed, edit the draft, and designed the study; Dr. Pranav Prakash curated data; Dr. Sanjay Gupta, discussed methodology; Dr. Meenu Gupta, review the draft; Dr. Archana Prakash, analyzed and revised the draft; Haamid Bashir, provided valuable inputs towards designing the manuscript. All authors approved, read, and approved the final version of the manuscript.

9. CONFLICT OF INTEREST

Conflict of interest declared none

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