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REVIEW PAPER

Environmental factors affecting the risk of breast cancer and the modulating role of vitamin D on this malignancy

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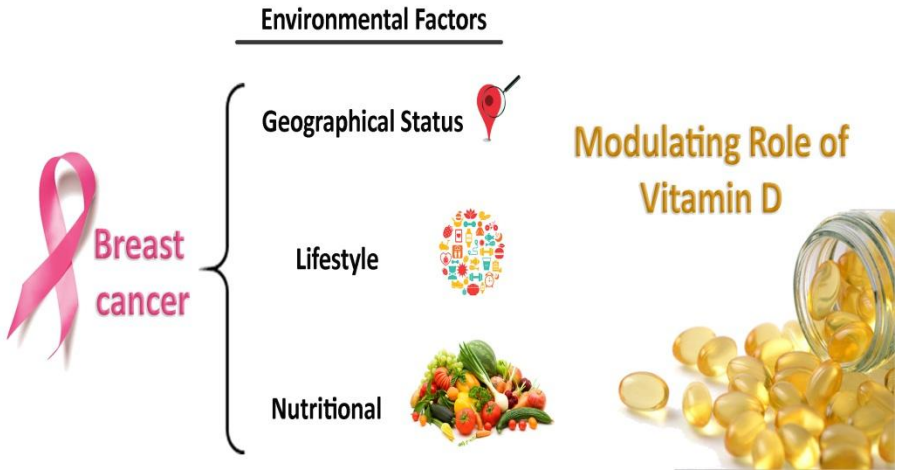
Highlights

- Breast cancer is the most common type of cancer in women worldwide.
- Several genetic and environmental factors alter the risk of breast cancer.
- Environmental factors affecting breast cancer include geographical status, lifestyle, and nutritional factors.
- Vitamin D could contribute to the pathophysiology of breast cancer by involving apoptosis, angiogenesis, and metastasis.

Graphical Abstract



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Abstract

Breast cancer is the most common type of cancer in women worldwide and is the second leading cause of cancer-related death in women after lung cancer. The disease is affected by factors such as the genetic structure of hormonal profiles and different lifestyles. Geographical status, living status, age of marriage, obesity, and nutritional factors are among the environmental factors predisposing to breast cancer. Among dietary supplements, the protective effect of vitamin D on breast cancer has been confirmed. The inverse relationship between sun exposure and breast cancer mortality has been proven. The direct link between decreased serum vitamin D and an increased risk of breast cancer has also been confirmed. In some breast cancer cells, the active form of vitamin D increases the expression of adhesion molecules, which prevents cancer from invasion and metastasis. In addition, this active form has anti-angiogenic activity and can inhibit cancer cell invasion. In this review, we narrate the environmental factors affecting the risk of breast cancer and the modulating role of vitamin D in this malignancy.

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1. Introduction

The term cancer is derived from the Greek word crab. The ancient Greek physician Hippocrates likened diffuse cancer to a crab. Although our understanding of the disease has improved since then, this explanation still seems appropriate. Cancer is a disease in which cells in the body grow uncontrollably due to defects in the natural regulatory mechanisms of cell growth and proliferation. An important feature of a cancerous gland is its ability to spread or metastasise in the body (Asgari, 2021; Ebadi et al., 2020; Dauda et al., 2020). In most types of cancer, solid glands commonly occur in certain parts of the body, in the skin, breast, lungs, intestines, or prostate gland. The disease may spread to other parts of the body through the blood and lymphatic system. As our understanding of cancer has increased over the past 20 years, lifestyle changes and effective screening programs, as well as new types of treatment, have led to advances in the prevention and treatment of cancer (Brown, 2019).

Breast cancer is a common disease, accounting for 10% of all cancers in both men and women, and is the second most common cancer after lung cancer. Breast cancer is the most common cancer among women, as it accounts for 22% of all cancers in women (Atoum and Alzoughool, 2017). In Iran, breast cancer is the most common among cancers diagnosed in women (Blasiak et al., 2020). This type of cancer in Iran with 16% of all cancers in women is the fifth leading cause of cancer death among Iranian women (Faramarzi et al., 2021). Breast cancer is a disease that originates in the malignant cells of the breast tissue and multiplies irregularly and increasingly and passes through the immune and defense systems without causing a defensive or aggressive reaction in the body's immune system. Breast cancer usually begins as a hard mass in the upper and outer part of the breast and may spread to the axillary lymph nodes and then spread throughout the body. The lymphatic system is one of the main ways in which breast cancer spreads (Cao et al., 2018). Geographical location, living status, age at marriage and obesity are among the environmental factors predisposing to breast cancer. Weight gain plays an important role in the risk of breast cancer. Gender also plays a major role in breast cancer. Also, breast cells in women are much higher than in men and the risk of occurrence in women is much higher than in men. Age is another risk factor for breast cancer, and older people are more likely to develop breast cancer (Gabr, 2017). Some gynecological issues such as the age of first menstruation, age of onset of menopause, age of first delivery, duration of breastfeeding, use of birth control pills, use of hormone replacement therapy also play a key role in increasing the risk of breast cancer (Welsh, 2018). Diet is another important factor in changing the risk of breast cancer. Vitamins, in particular vitamin D, play a key role in the pathophysiology of breast cancer (Ahmed et al., 2019; Zeidali et al., 2021).

Low vitamin D intake may increase the risk of breast cancer. Vitamin D is made into the skin through the conversion of 7-dehydrocholesterol following adequate exposure to the sun's ultraviolet rays. It exists in a limited number of foods such as milk and is found in fatty fish, vitamin D supplements, and fish liver oil (Crew et al., 2019). Vitamin D, received from all sources, is hydroxylated in the liver and converted to 25-hydroxyvitamin D. Calcifediol form is the preferred biomarker and preferred biomarker of vitamin D. Second hydroxylation is necessary for the synthesis of the active form of vitamin D, calcitriol, which is present in tissues containing the enzyme 1-alpha hydroxylase, such as the breast, kidney, colon, and prostate (Fathi et al., 2019). The active form of vitamin D increases cell differentiation, inhibits proliferation, and has the potential to alter cancer risk. Vitamin D receptor mediates the action of calcitriol and is a transcription factor in the nucleus that is present in most cells in the body, including cancer and normal breast cells, through which these cells can respond to 1,25(OH)2D (Sabernezhad, 2021). In this review, we narrate the environmental factors affecting the risk of breast cancer and the modulating role of vitamin D in this malignancy.

2. *Environmental factors*

2.1. *Overweight and obesity*

Weight gain plays an important role in the risk of breast cancer (Kazemian et al., 2019). Because fat cells release estrogen, women who gain 10-15 kg after adolescence have a higher risk of developing this type of

cancer. Weight gain after the age of 18 is associated with a significant increase in postmenopausal breast cancer. Obesity is associated with both an increased risk of developing breast cancer in postmenopausal women and an increased risk of breast cancer mortality. However, regular exercise can overcome this problem and reduce the risk of breast cancer (Zhou et al., 2020).

2.2. Gender and age

Gender is a major risk factor for breast cancer, as breast cells are much higher in women than men. But the main reason for the higher prevalence of breast cancer in women is that breast cells in women are more exposed to the growth-stimulating effects of estrogen and progesterone, which is an effective factor in increasing the rate of breast cancer in women than men (Falzone et al., 2020). Older people are more likely to develop breast cancer, which is why most cases of breast cancer have been reported in people over the age of 50. Studies show that breast cancer in women under 55 follows a sigmoid status. 6.6% of cases are diagnosed before the age of 40, 4.2% are diagnosed before the age of 35 and 1% are diagnosed before the age of 30. The average risk of breast cancer is 1 in 173 at age 40 and approximately 1 in 1,500 at age 30 (Zhou et al., 2020).

2.3. Gynecological issues

The age of first menstruation is one of the factors involved in the risk of breast cancer. Girls who have their first period before the age of 12 are at greater risk than those who have a later period because estrogen levels rise in the girls' blood after puberty. The longer a woman menstruates, the longer she is exposed to the hormone and the more likely she is to be associated with breast cancer (Welsh, 2017). The age of onset of menopause can also be another factor in breast cancer. Women whose menopause is older than the society average are at greater risk. The older menopause, the more breast tissue is exposed to these hormones and the risk of cancer increases. After menopause, estrogen levels are low, progesterone is absent, and breast cell division is very low. The age of the first delivery can also be involved in breast cancer. Women who give birth for the first time after the age of 30 are at higher risk than women who give birth at a younger age (Yolchiyeva et al., 2020). Breastfeeding time is another factor that plays a role in breast cancer risk. The risk of breast cancer in women decreases with increasing breastfeeding time. The risk was 28% lower in women who breastfed their children for 12 months than in those who breastfed for less than 6 months. This rate is 40% lower in women who have been breastfeeding for 13-24 months. The use of birth control pills also plays a role in the development of breast cancer. Contraceptive pills are known to be one of the most effective factors in breast cancer because the main components of birth control pills are estrogen and progesterone hormones and it has a direct effect on hormones and increases the risk of cancer (Zhou et al., 2020; Haghshenas and Ghanbari Malidarreh, 2021).

2.4. Diet and life style

Diet or lifestyle changes the risk of breast cancer. Studies show that a high-fat diet is associated with a higher rate of breast cancer than a low-fat diet. Consumption of vegetables has a high protective effect on breast cancer, but fruit, fiber, and meat consumption are ineffective (Hamzeie et al., 2021). In contrast, there is a positive association between alcohol consumption and breast cancer, which increases the risk of cancer. Reducing the intake of nutrients such as vitamin C, folate, and F3-carotene may increase the risk of alcohol dependence. The type of food and diet not only plays a role in causing breast cancer but also plays an important role in reducing complications, improving and preventing the progression of cancer after having this type of cancer. Taking vitamins can have a protective effect. Vitamins E, D, A, folic acid, and selenium also play a role in reducing the risk of cancer (Ahmed et al., 2019). Among these, vitamin D is one of the vitamins in the diet that has a protective role against the development and progression of breast cancer. Some risk factors involved in breast cancer are demonstrated in Fig. 1.

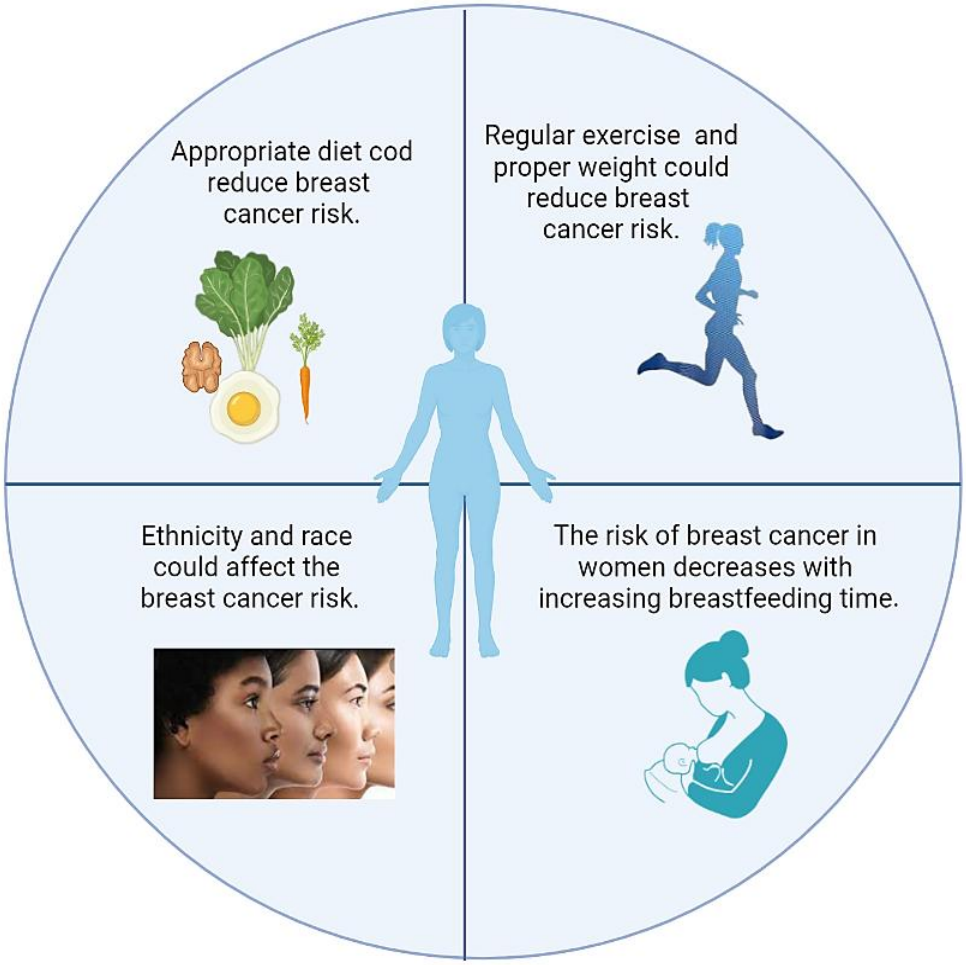

Fig. 1. Some environmental factors are involved in the alteration of breast cancer. As shown in the figure, diet, exercise, ethnicity, and breastfeeding time could alter the risk of breast cancer.

2.5. Vitamin D

Vitamin D is given to a group of fat-soluble hormone precursors (hormone precursors or prohormones usually have little hormonal activity themselves). The two major forms of vitamin D that are important in the human body are vitamin D2 or ergocalciferol and vitamin D3 or cholecalciferol. Plants naturally produce vitamin D2, and vitamin D3 is naturally produced by the body when the skin is exposed to ultraviolet light (especially UVB radiation) in the sun. Vitamin D2 and vitamin D3 are also commercially produced. Vitamin D, also called calciferol, helps bones grow and strengthen by controlling the balance of calcium and phosphorus. This vitamin helps bone metabolism by increasing the absorption of phosphorus and calcium from the intestines and decreasing excretion by the kidneys and also regulates the activity of genes involved in cell growth (Yolchiyeva et al., 2020).

The main source of this vitamin, except for plant sources such as grains and animals including fish and milk, is sunlight. So that staying in the sun for 10 to 20 minutes provides the human body's daily need for this vitamin. The deficiency of this vitamin also causes osteoporosis in old age. Vitamin D helps prevent diseases such as rickets in children, osteomalacia in adults, and osteoporosis in old age. This vitamin also helps a lot in the growth and strength of bones and cell growth. The daily requirement for this vitamin for each adult is 10 μg or a maximum of 2,000 units (IU) per day (Gabr, 2017).

Ultraviolet radiation to human skin causes a substance called dehydrocholesterol to be converted to vitamin D in the kidneys through various stages in the body. People with lighter skin than those with darker skin can meet their need for this vitamin in less time under the sun. The active form of vitamin D in the body, namely 1 and 25-dihydroxy vitamin D or calcitriol, is made from vitamin D2 or vitamin D3. To make this active form,

vitamin D2 and vitamin D3 are changed in the liver to produce 25-hydroxyvitamin D, which travels through the blood to the kidneys, where it changes again to 1 and 25-hydroxy (Crew et al., 2019; Kazemian et al., 2019).

2.6. The role of vitamin D in breast homeostasis

Breast epithelial cells produce 1 and 25-dihydroxyvitamin D from the circulation of 25-hydroxyvitamin D by the enzyme 1- alpha-hydroxylase, and this active form of vitamin D is used centrally. It does not enter the bloodstream and is used topically in the same breast tissue. 1,25-Dihydroxyvitamin D attach to the vitamin D receptor, which then forms a heterodimer with the retinoic acid receptor. This complex absorbs regulatory molecules and this combination retrieves molecules with common regulatory properties and binds to vitamin D response elements (VDRE) in the promoter region, and increases its transcriptional effects such as cell proliferation and apoptosis, and differentiation and autophagy. It should be noted that the signaling pathway of vitamin D in the breast is regulated by hormones such as parathormone and estrogen and factors such as calcium and insulin-like growth factor (Welsh, 2017).

The concentration of 25-hydroxyvitamin D is also a key factor in regulating the synthesis of 1 and 25-dihydroxyvitamin D in breast epithelial cells. Studies on the effect of vitamin D on breast cancer cells have shown that vitamin D consumption increases differentiation and apoptosis in these cells, an effect that is quite comparable to the antitumor activity of agents such as anthracyclines, taxanes, and tamoxifen (Miri et al., 2021).

2.7. Anti-cancer effects of vitamin D

2.7.1. Regulation of the cell cycle by vitamin D

The cell cycle consisted of 5 phases, which are: G0, G1, S, G2 and M. The formation of cyclin-dependent kinases (CDK) and cyclin complexes regulates the stages of phase passage. The results show that vitamin D compounds inhibit growth and differentiation by affecting the cell cycle in many cell systems (Cao et al., 2018). In most studies, it has been reported that vitamin D stops the cell from passing from the G0/1 phase to the S phase. To progress from stage G1 to S, type D cyclins form complexes with CDK4 or CDK6. These complexes are active kinases that specifically phosphorylate proteins of the retinoblastoma family. This phosphorylation leads to the inactivation of retinoblastoma, which eventually releases histone deacetylase and induces transcription of target genes.

Some type E cyclins bind to activated CDK2 and increase the rate of phosphorylation in retinoblastoma and other substrates. In the hypophosphorylated state, retinoblastoma releases factor E2F, which can activate transcription of many genes necessary for DNA replication, mitosis, and genes that control the passage of later phases of the cell cycle. A type-A cyclin also binds to CDK2 to phosphorylate new substrates during phase S. Cyclin-dependent kinase inhibitors, such as proteins INK4, P27, P21, and other proteins, regulate the formation of active cyclin-CDK complexes. Calcitriol and other steroids in the vitamin D family induce p21 expression in many cell types. The importance of P21 in the anti-proliferative action of vitamin D has been seen in prostate cancer cell lines. This induction is done through various mechanisms. The p21 promoter contains a VDRE, and gene transcriptional activation is mediated directly by binding to the VDR (Zhou et al., 2020).

2.7.2. Anti-inflammatory, anti-invasive and anti-metastatic effects

Prostaglandin is secreted from breast cancer cells or surrounding tissues and causes cancer cell proliferation and resistance to apoptosis and stimulates cancer cell invasion and metastasis as well as the expression of cyclooxygenase 2 (COX-2) which is involved in the synthesis of prostaglandin in breast cancer cells (Sabernezhad, 2021). In cancer tissue, vitamin D reduces the expression of COX-2. Vitamin D also increases the expression of 15-hydroxy prostaglandin dehydrogenase, which catalyzes the conversion of prostaglandins to inactive ketone compounds. Vitamin D can also inhibit the synthesis and biological function of estrogen. Decreased expression of aromatase enzyme also inhibits estrogen pathway (O'Brien et al., 2018). Two reduced regulatory mechanisms of 1 and 25-dihydroxyvitamin D through aromatase in breast cancer were reported as follows: 1) Direct inhibition of aromatase transcription; 2) An indirect effect due to decreased levels and activity

of Prostaglandin E2 (PGE2) which is a major stimulator of aromatase transcription in breast cancer. Some anticancer effects of vitamin D are illustrated in Fig. 2.

2.8. Effects of vitamin D on apoptosis

Apoptosis is the physiological mechanism of cell death. Induction of apoptosis by vitamin D plays a key role in stopping cell growth. In many cell types, vitamin D analogues alter the content of anti-apoptotic regulatory proteins in the BcL-2 family. Vitamin D affects the levels of proapoptotic proteins (Bax-bak) and anti-apoptotic proteins (BCL-2, BCL-xl) and shifts the balance of these proteins to apoptosis. The effects of the vitamin are applied in both genomic and non-genomic ways (Fathi et al., 2019).

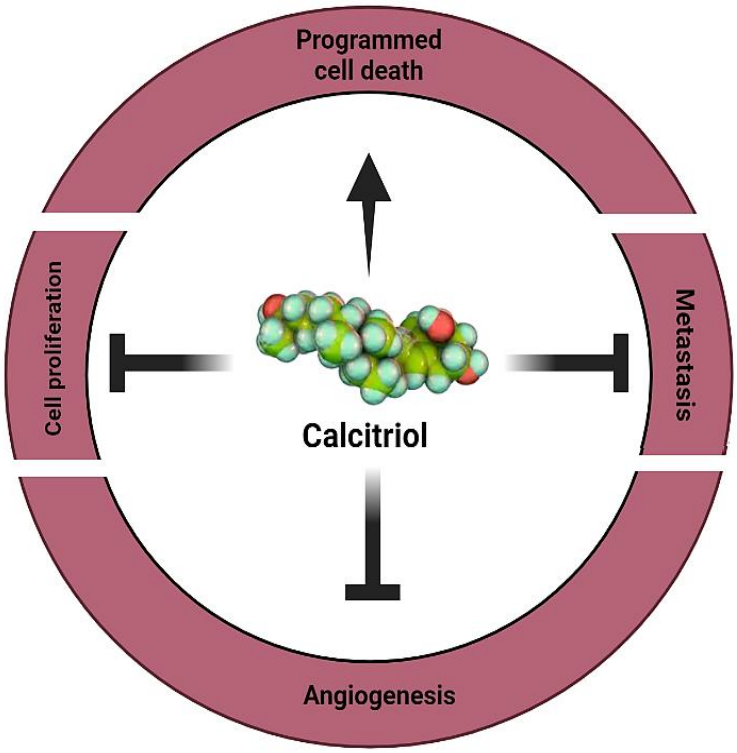

Fig. 2. Some anticancer effects of vitamin D. This vitamin could induce programmed cell death (apoptosis) and inhibit angiogenesis, cell proliferation, and metastasis.

2.9. Genomic effects of vitamin D

In general, the main function of 1,25-Dihydroxyvitamin D was generally accepted through the genomic pathway, which involves the binding of the hormone to the intracellular vitamin D receptor (VDR) with a molecular weight of 48-50 kDa. It is a large family of steroid receptors that is part of a functional structure. This structure is characterized by an N-terminal amino variable, a highly conserved DNA-binding domain (DBD) and a ligand-binding domain (LBD) is located in the carboxy C-terminal and is connected to the DBD. DBD mediates VDR binding to DNA and is involved in protein-protein interactions. While LBD binds to the ligand and acts to form receptor dimers and cofactors through the helical region, it has been identified as the active domain (AF-2). LBD contains the number of serine residues that are used as a key factor in VDR transcriptional regulation activity. As 1,25-Dihydroxyvitamin D is a small lipophilic molecule, it can easily penetrate the cell membrane and be released by the cell. In cells, 1,25-Dihydroxyvitamin D binds to VDR with a high affinity, which then stabilizes LBD agonist compounds. In agonist compounds, the VDR structure can perform some of the functions that lead to the opening of chromatin through the use of histone acetylase. The second type of active collaborator form is communication with the basic transcription apparatus and stimulates target genes through related proteins. In contrast, in the absence of VDR ligand, it interacts with co-repressor protein, which leads to the use of deacetylation of chromatin, resulting in suppresses gene transcription (Farokhian et al., 2021).

2.10. Non-genomic effects of vitamin D

Non-genomic pathways include regulation of calcium channel voltage valves, the opening of chloride channels, regulation of PKC activity, which eventually leads to the initiation of biological responses such as inhibition of cell proliferation and stimulation of cell differentiation. Recent studies have shown that variants of this rapid response through membrane receptors with properties binding to different ligands of VDR have been proposed as one of the specific membrane receptors 1,25-Dihydroxyvitamin D. Annexin II and ErP57 are thiol reductase proteins that are membrane receptors that mediate the non-genomic actions of vitamin D (Kazemian et al., 2019; Bakhshi et al., 2021).

2.11. Vitamin D receptor and breast cancer risk

The VDR gene was discovered in 1969, and since then the role of VDR in the endocrine system and the presence of its function in more than 30 tissues and organs of the body have been studied (Ebadi et al., 2020). To date, 60 different polymorphisms have been discovered in the VDR gene, located at different points in the VDR gene, including introns and exons, and in the downstream untranslated region (3'UTR). VDR is encoded by a large 75 kbp gene located on the long arm of chromosome 12 (12q12-14) and consists of 6 promoters and regulatory regions, 3 exons at the end of 5' which are non-coding and there are 8 coding regions in exon 9-2 at the end of '3. The domain related to exon 2-4 is responsible for interacting with the VDR elements (VDREs) in the target genes, and the domain encoded by exon 6-9 is responsible for binding the ligand to 1,25-dihydroxyvitamin D. Since the effect of vitamin D is exerted through the VDR receptor, and this receptor mediates the transmission of signals from the vitamin D cycle to the cell nucleus, it can affect the transcription of a number of genes, such as those involved in encoding insulin-like growth hormone-binding proteins. Therefore, it transmits the effect of insulin-like growth factors on cell growth (Negri et al., 2020).

VDR is an important mediator in the effect of vitamin D in the cell and other interactions with other intracellular signaling pathways that negatively affect cancer progression. Therefore, polymorphism in the VDR gene sequence can affect the structure of this receptor; it may also affect the influence of this receptor. Vitamin D receptor was first identified in breast cancer cells in 1979 as a member of the nuclear receptor family for steroid hormones and acts as a ligand-activated transcription factor and regulates the expression of some genes. In addition to its major role in maintaining extracellular calcium levels, VDR activation affects the expression of more than 200 genes involved in cell growth, differentiation, and apoptosis (Vaisi-Raygani and Asgari, 2021).

VDR gene polymorphisms may affect receptor affinity for vitamins, DNA binding, RNA transcription, and protein synthesis. The VDR gene has several polymorphisms. More than 25 polymorphisms of the VDR gene have been identified in the white population (Hassanpour, 2021). Only a few of these polymorphisms have been studied in relation to cancer, including polymorphisms in exon 2 of the VDR gene (rs10735810; FokI); intron 8 polymorphism (rs1544410; BsmI); intron 8 polymorphism (rs7975232; ApaI); polymorphism in exon 9 (rs731236; TaqI); the polymorphism is in the 3'UTR region of the VDR gene, which is a replicate sequence of poly (A) (Ahmed et al., 2019) and the other polymorphism is in exon 11 (rs739837; BglI). These polymorphisms could alter the function of the VDR gene and then breast cancer susceptibility.

3. Conclusion

Breast cancer is one of the most common cancers in women and can cause many problems in a person's life. There are several factors involved in increasing the risk of this cancer. These include weight gain and obesity, aging, gynecological issues, lifestyle, and nutrition. Vitamins especially vitamin D play an important role in the pathophysiology of breast cancer. In some breast cancer cells, the active form of vitamin D increases the expression of E-cadherin, which prevents cancer from invasion and metastasis. In addition, this active form has anti-angiogenic activity. Prostaglandin is secreted by cancer cells in the breast or surrounding tissues, causing the cancer cell to proliferate and become resistant to apoptosis, and it can also stimulate cancer cell invasion and metastasis. The expression of cyclooxygenase 2 (COX-2), which is involved in prostaglandin synthesis, also

increases in breast cancer cells. In cancer tissue, vitamin D reduces the expression of COX-2. Vitamin D also increases the expression of 15-hydroxy prostaglandin dehydrogenase, which catalyzes the conversion of prostaglandin to inactive ketone compounds. Vitamin D also exerts its anti-cancer activity by interfering with the function of the hormone estrogen. This vitamin can inhibit the synthesis and biological function of estrogen. Understanding the molecular mechanisms of vitamin D function in the pathophysiology of breast cancer will help improve the prevention and treatment of this disease.

References

Ahmed, J.H., Makonnen, E., Fotoohi, A., Yimer, G., Seifu, D., Assefa, M., Tigeneh, W., Aseffa, A., Howe, R., Aklillu, E., 2019. Vitamin D status and association of VDR genetic polymorphism to risk of breast cancer in Ethiopia. *Nutrients*, **11**(2), 289. https://doi.org/10.3390/nu11020289

Asgari, R., 2021. The role of ESR1 PvuII T/C variant in the female reproductive process: A review. *Cent. Asian J. Med. Pharm. Sci. Innov.*, **1**(1), 22-27. https://doi.org/10.22034/CAJMPSI.2021.01.04

Atoum, M., Alzoughool, F., 2017. Vitamin D and breast cancer: latest evidence and future steps. *Breast Cancer: Basic Clin. Res.*, **11**, 1178223417749816. https://doi.org/10.1177/1178223417749816

Bakhshi, B., Rostami-Ahmadvandi, H., Fanaei, H., 2021. Camelina, an adaptable oilseed crop for the warm and dried regions of Iran. *Cent. Asian J. Plant Sci. Innov.*, **1**(1), 39-45. https://doi.org/10.22034/CAJPSI.2021.01.05

Blasiak, J., Pawlowska, E., Chojnacki, J., Szczepanska, J., Fila, M., Chojnacki, C., 2020. Vitamin D in Triple-Negative and BRCA1-Deficient Breast Cancer—Implications for Pathogenesis and Therapy. *Int. J. Mol. Sci.*, **21**(10), 3670. https://doi.org/10.3390/ijms21103670

Brown, R.B., 2019. Vitamin D, cancer, and dysregulated phosphate metabolism. *Endocrine*, **65**(2), 238-243. https://doi.org/10.1007/s12020-019-01985-y

Cao, Y., Du, Y., Liu, F., Feng, Y., Cheng, S., Guan, S., Wang, Y., Li, X., Li, B., Jin, F., Lu, S., 2018. Vitamin D aggravates breast cancer by inducing immunosuppression in the tumor bearing mouse. *Immunotherapy*, **10**(7), 555-566. https://doi.org/10.2217/imt-2017-0131

Crew, K.D., Anderson, G.L., Hershman, D.L., Terry, M.B., Tehranifar, P., Lew, D.L., Yee, M., Brown, E.A., Kairouz, S.S., Kuwajerwala, N. and Bevers, T., 2019. Randomized double-blind placebo-controlled biomarker modulation study of vitamin D supplementation in premenopausal women at high risk for breast cancer (SWOG S0812). *Cancer Prev. Res.*, **12**(7), 481-490. https://doi.org/10.1158/1940-6207.CAPR-18-0444

Dauda, A.S., Abdulkadir, M.A., Opara, J.A., 2020. Urban health dynamics and population variables: a case study of environmental sanitation of Maiduguri metropolis in Nigeria. *Cent. Asian J. Environ. Sci. Technol. Innov.*, **1**(2), 93-100. https://doi.org/10.22034/CAJESTI.2020.02.04

Ebadi, A.G., Toughani, M., Najafi, A., Babaee, M., 2020. A brief overview on current environmental issues in Iran. *Cent. Asian J. Environ. Sci. Technol. Innov.*, **1**(1), 1-11. https://doi.org/10.22034/CAJESTI.2020.01.08

Falzone, L., Grimaldi, M., Celentano, E., Augustin, L.S., Libra, M., 2020. Identification of modulated MicroRNAs associated with breast cancer, diet, and physical activity. *Cancers*, **12**(9), 2555. https://doi.org/10.3390/cancers12092555

Faramarzi, A., Jahromi, M.G., Ashourzadeh, S., Jalilian, N., 2021. Metastatic and pathophysiological characteristics of breast cancer with emphasis on hereditary factors. *Cent. Asian J. Med. Pharm. Sci. Innov.*, **1**(3), 104-113. https://doi.org/10.22034/CAJMPSI.2021.03.01

Farokhian, S., Nejad, E.T., Nejad, G.M., 2021. Studying the Effect of Biofertilizers on the yield of *Sesamum indicum* Genotypes under Drought Stress. *Cent. Asian J. Plant Sci. Innov.*, **1**(1), 32-38. https://doi.org/10.22034/CAJPSI.2021.01.04

Fathi, N., Ahmadian, E., Shahi, S., Roshangar, L., Khan, H., Kouhsoltani, M., Dizaj, S.M., Sharifi, S., 2019. Role of vitamin D and vitamin D receptor (VDR) in oral cancer. *Biomed. Pharmacother*, **109**, 391-401. https://doi.org/10.1016/j.biopha.2018.10.102

Gabr, H.M., 2017. Vitamin D level in breast cancer premenopausal patients before and after adjuvant therapy. *Egypt. J. Rad. Sci. Applic.*, **30**(1), 85-93. https://doi.org/10.21608/ejrsa.2017.1210.1013

Haghshenas, H., Ghanbari Malidarreh, A., 2021. Response of yield and yield components of released rice cultivars from 1990-2010 to nitrogen rates. *Cent. Asian J. Plant Sci. Innov.*, **1**(1), 23-31. https://doi.org/10.22034/CAJPSI.2021.01.03

Hamzeie, M., Abdolmaleki, A., Zohre-Vand, F., Khazayel, S., 2021. Correlation of a well-known genetic variation in one carbon metabolism pathway with breast cancer susceptibility in Iranian population. *Cent. Asian J. Med. Pharm. Sci. Innov.*, **1**(4), 176-184. https://doi.org/10.22034/CAJMPSI.2021.04.02

Hassanpour, O., 2021. The study of A1298C variation in MTHFR gene as a molecular risk factor for male infertility in Iran. *Cent. Asian J. Med. Pharm. Sci. Innov.*, **1**(1), 15-21. https://doi.org/10.22034/CAJMPSI.2021.01.03

Kazemian, E., Amouzegar, A., Akbari, M.E., Moradi, N., Gharibzadeh, S., Jamshidi-Naeini, Y., Khademolmele, M., As'habi, A., Davoodi, S.H., 2019. Vitamin D receptor gene polymorphisms affecting changes in visceral fat, waist circumference and lipid profile in breast cancer survivors supplemented with vitamin D3. *Lipids Health Dis.*, **18**(1), 1-10. https://doi.org/10.1186/s12944-019-1100-x

Miri, A., Kiani, E., Habibi, S., Khafaei, M., 2021. Triple-negative breast cancer: biology, pathology, and treatment. *Cent. Asian J. Med. Pharm. Sci. Innov.*, **1**(2), 81-96. https://doi.org/10.22034/CAJMPSI.2021.02.05

Negri, M., Gentile, A., de Angelis, C., Montò, T., Patalano, R., Colao, A., Pivonello, R., Pivonello, C., 2020. Vitamin D-induced molecular mechanisms to potentiate cancer therapy and to reverse drug-resistance in cancer cells. *Nutrients*, **12**(6), 1798. https://doi.org/10.3390/nu12061798

O'Brien, K.M., Sandler, D.P., Xu, Z., Kinyamu, H.K., Taylor, J.A., Weinberg, C.R., 2018. Vitamin D, DNA methylation, and breast cancer. *Breast Cancer Res.*, **20**(1), 1-11. https://doi.org/10.1186/s13058-018-0994-y

Sabernezhad, M., 2021. Quantitative analysis of p53 substitution mutation and breast cancer; An informative study in Iranian population. *Cent. Asian J. Med. Pharm. Sci. Innov.*, **1**(1), 8-14. https://doi.org/10.22034/CAJMPSI.2021.01.02

Vaisi-Raygani, A., Asgari, R., 2021. Association of inflammation with female reproductive system disorders. *Cent. Asian J. Med. Pharm. Sci. Innov.*, **1**(2), 67-73. https://doi.org/10.22034/CAJMPSI.2021.02.03

Welsh, J., 2017. Function of the vitamin D endocrine system in mammary gland and breast cancer. *Mol. Cell. Endocrinol.*, **453**, 88-95. https://doi.org/10.1016/j.mce.2017.04.026

Welsh, J., 2018. Vitamin D and breast cancer: Past and present. *J. Steroid Biochem. Mol.*, **177**, 15-20. https://doi.org/10.1016/j.jsbmb.2017.07.025

Yolchiyeva, F., Hacjiyeva, S., Huseyinli, A.A., Hasanova, A., 2020. Ecological problems of water resources in Azerbaijan and their impact on human health. *Cent. Asian J. Environ. Sci. Technol. Innov.*, **1**(2), 71-76. https://doi.org/10.22034/CAJESTI.2020.02.01

Zeidali, E., Korrani, H.M., Alizadeh, Y., Kamari, F., 2021. Ethnopharmacological survey of medicinal plants in semi-arid rangeland in western Iran. *Cent. Asian J. Plant Sci. Innov.*, **1**(1), 46-55. https://doi.org/10.22034/CAJPSI.2021.01.06

Zhou, L., Chen, B., Sheng, L., Turner, A., 2020. The effect of vitamin D supplementation on the risk of breast cancer: a trial sequential meta-analysis. *Breast Cancer Res. Treat.*, **182**(1), 1-8. https://doi.org/10.1007/s10549-020-05669-4

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