© 2015
Scienceline Publication
www.science-line.com

ISSN: 2322-4789
Asian Journal of Medical and Pharmaceutical Researches
Asian J. Med. Pharm. Res. 5(4): 39-45, Dec 25, 2015

AJMPR

Different Levels of Vitamin D and Breast Cancer: A Review

Faezeh Modarresi-Ghazani[1], Mohammad Esmaeil Hejazi[2] and Veghar Hejazi[2]

[1]*Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*
[2]*Respiratory Diseases, Tuberculosis and Lung Disease Research Center, Department of Internal Medicine, Tabriz University of Medical Sciences, Tabriz, Islamic Republic of Iran*

ABSTRACT: In the last decade, there has been increasing evidence regarding the anti-proliferative effects of vitamin D. The purpose of present article was to review different aspects of vitamin D on breast cancer. We conducted a comprehensive search in electronic database including PubMed, Medline and Google Scholar for randomized clinical trials published in the last 5 years up to January 2016. A majority of the articles focused on the relationship between vitamin D and risk of breast cancer, and then on the vitamin D's effects on aromatase inhibitors side effects, vitamin D polymorphism and also breast cancer stage. The present literature was unable to prove any association between vitamin D and risk of developing breast cancer; however vitamin D polymorphism is involved in developing breast cancer. On the other hand, high serum level of vitamin D can decrease aromatase inhibitors' musculoskeletal effects. This can make vitamin D eligible as an adjuvant therapy to cancer treatment. It is highly recommended to treat vitamin D deficiency and provide the ideal serum level of vitamin D among patients with breast cancer who are receiving aromatase inhibitors.

Keywords: Vitamin D, Breast cancer, Aromatase inhibitors

REVIEW ARTICLE
PII: S2322-4789150008-5
Received 18 Nov. 2015
Accepted 19 Dec. 2015

INTRODUCTION

Cell proliferation is strictly regulated by checkpoints. Vitamin D can up regulate the cyclin dependent kinase inhibitor e.g. p21cip1 and p27kip1 and therefore arrest the cell-cycle at GI/S checkpoint (Di Rosa et al., 2013). Hypoxia and DNA-damage contribute to tumour growths (Valko et al., 2006) and vitamin D enhances anti-oxidant responses (Bao et al., 2008 and Peehl et al., 2004). In fact vitamin D is necessary for DNA damage repair and its deficiency leads to impaired DNA segments and development of malignancy (Bikle and Jiang, 2013). Insulin like Growth Factors (IGF) are mitogens and survival agents involved in pathogenesis of several malignancies(Yu and Rohan, 2000). Results from Microarray analysis indicate that vitamin D_3 is involved in regulation of IGFBP3, a modulator factor of IGF-1 in human prostate cancer cell line and breast cancer (BC) cell lines(Krishnan et al., 2004 and Swami et al., 2003). Vitamin D has anti-angiogenesis effects since it can down-regulate VEGF-1 and Glucose-transporters and prevent angiogenesis (Kovalenko et al., 2010). Vitamin D can modulate cancer-associated autophagy, inhibiting tumour formation (Bristol et al., 2012 and Hoyer-Hansen and Jaattela, 2008). Vitamin D can suppress tumour invasion and metastasis by inhibiting serine proteases and metalloproteases as well as up-regulation of E-catenin (Larriba et al., 2013). Vitamin D_3 also modulates COX-2 (Moreno et al., 2006 and Thill et al., 2010) and reduces IL-17 levels (Milovanovic et al., 2012). IL-17 lymphocytes can turn into T-reg cells and contribute to cancer-development (Maruyama et al., 2010). On the other hand vitamin D_3 has pro-apoptotic effects through up-regulating the pro-apoptotic protein BAK and increasing the release of pro-apoptotic factors including BAG-I from the nucleus (Di Rosa et al., 2013) .

Clinical observations indicate that a significant link exists between ultraviolet B radiation and many types of cancer (Grant, 2012 and 2013).

Vitamin D and breast cancer

Vitamin D plays an important role in developing mammary glands as Vitamin D Receptors (VDRs) are expressed in normal mammary glands. Data regarding this subject is obtained using VDR- knockout mice. Zinser et al. (2002) reported that vitamin D depletion in these mice causes an increased response to estrogen and progesterone, resulting in an increased cell growth. Furthermore mammary gland regression after weaning was delayed in VDR-knockout mice leading to reduced apoptosis in the cell (Zinser and Welsh, 2004).

On molecular point of view histological studies demonstrated that VDR protein is present in normal breast

tissue (Berger et al., 1988 andLopes et al., 2010). Expression of the vitamin D metabolism enzymes (CYP27B1 and CYP24A1) has discrepancies in different studies due to different methodologies. One study states that they are not detectable in all of the cases (Lopes et al., 2010). Studies demonstrate that vitamin D binding protein-derived Gc Macrophage Activating Factor (GcMAF) can activate macrophages and these macrophages can attack breast cancer cells and destroy them (Thyer et al., 2013). Studies also demonstrate that Fok1 polymorphism and breast cancer risk are associated (Wang et al., 2013). Vitamin D can reduce the invasiveness of breast tumour by inhibiting metalloproteinase MMP-9, induction of plasminogen-activator inhibitor and down-regulation of the plasminogen-activator (Hansen et al., 1994). Furthermore vitamin D can reduce an invasive promoter molecule called P-cadherin in breast cancer cells (Pendas-Franco et al., 2007).

Relationship between vitamin D and breast cancer risk

One of the largest clinical trials regarding this matter is the European Prospective Investigation into Cancer and Nutrition study. During this study, 7760 cases of invasive breast cancer cases, consisting of both pre and post-menopausal women, were followed up for 8.8 years. The purpose of the study was to see whether or not dietary intake of calcium and vitamin D has any effect on breast cancer risk. After comparing the highest and lowest quintile of vitamin D and calcium intake, no significant association was observed between vitamin D/calcium intake and breast cancer risk (Abbas et al., 2013).

Next large study was The Norwegian women and cancer study. This large cohort study included 41,811 women and investigated the effect of solar vitamin D effective UV radiation, together with calcium and vitamin D intake and risk of breast cancer. The mean follow up period was 8.5 years. Results indicated that there was no significant association between dietary vitamin D or vitamin D effective UV radiation with risk of developing breast cancer (Edvardsen et al., 2011).

Another large sampled study was conducted to see how source of vitamin D can affect the risk of breast cancer. This study was carried out in South western US among Hispanic and non-Hispanic white patients with matched controls. Interestingly results indicated that there was an inverse relationship between vitamin D supplementation and BC whereas dietary Vitamin D was positively associated with BC risk (Rollison et al., 2012).

Other clinical trials have yielded in different results. A case control study among five ethnic groups including White, African American, Native Hawaiian, Japanese and Latino, comprising 707 postmenopausal women with BC was conducted. The measured laboratory parameters included 25(OH) D3, 25(OH) D2and 25(OH) D. After the analysis of data, it was revealed that 25 (OH) D3 and 25 (OH) D levels were negatively associated with risk of BC, but only among white women and not in other races (Kim et al., 2014). Another case control study among 297 Pakistani women with was performed to evaluate the risk factors of developing BC. Among the potential factors involved in BC, use of vitamin D supplements was protective against BC risk comparing to non-users of vitamin D (Shamsi et al., 2013).

The last clinical trial is a case control study by Amir et al. Patients included 231 invasive BC cases and 856 controls. Serum level of 25(OH) D was used as the vitamin D marker. According to the results, 25 (OH) D levels was not a risk factor for cancer risk (Amir et al., 2012).

Vitamin D and aromatase inhibitor side effects

AIs are one of the main elements in anti-breast cancer regimen because most of the breast cancers are hormone dependent (Bulun et al., 2005). Common side effects of AIs include musculoskeletal symptoms (MSK) and bone loss. MSK symptoms are the most common side effect and the major reason for discontinuation of therapy by women taking AIs (Niravath, 2013). Several studies have been conducted to prove the potential benefits of vitamin D as a means to reduce MSK symptoms of AIs.

A study by Rastelli et al. (2011) was a double blinded placebo controlled clinical trial to investigate the effects of high dose vitamin D supplementation on MSK symptoms in women receiving anastrozole. Patients were categorized according to their baseline level of 25 (OH) D levels. Patients with 25(OH) D level of 20-29 ng/ml received 50,000 IU vitamin D/week for 8 weeks and then one capsule every month for 2 months or placebo. In the other group, patients with 25(OH) D level of 10-19ng/ml received the high dose vitamin D for 16 weeks and then every month for 2 months or placebo. Results indicated that supplementation with vitamin D every week was able to enhance MSK symptoms and bone loss in these patients (Rastelli et al., 2011).

Another placebo controlled randomized trial was conducted among post-menopausal women with increased risk of BC. Baseline vitamin D levels were measured for these patients. Results indicated that there was a non-

significant relationship between vitamin D and risk of MSK symptoms (Singh et al., 2012).

The association between vitamin D and MSK symptoms has also been investigated among Korean population. Purpose of this study was to evaluate the effect of vitamin D in prevention of MSK symptoms among post-menopausal women with BC. These women were randomly assigned to receive 0.5 µg calcitriol and 5 mg Alendronate. This combination of vitamin D and Alendronate was able to prevent bone loss which was a result of AIs (Rhee et al., 2013). On the other hand, results of another study reports that among postmenopausal women who are taking AI, MSK symptoms are more likely to be seen in patients whose vitamin D level are below 40 ng/ml, while this amount of vitamin D is less common among asymptomatic patients. Vitamin D level of below 40 ng/ml was also associated with developing tenosynovitis in these patients (Singer et al., 2014).

Vitamin D polymorphism and breast cancer

There are a few studies which have investigated the association of vitamin D genes' polymorphism and breast cancer. The Tromso study was conducted among 9528 patients whose DNA was genetically analyzed. The purpose of the study was to see if Single Nucleotide Polymorphism (SNP) is associated with risk of BC. Results indicated that the rs6013897 genotypes (which are located at the 24-hydroxylase gene) are significantly associated with BC (Jorde et al., 2012).

On the other hand, a study by Perna et al. (2013) was carried out to see whether or not genetic variations in vitamin D receptor genes are important in breast cancer. They assembled 498 patients with BC and followed them up for a mean of 5 years to observe breast cancer mortality. Interestingly results indicated that rs731236 allele was associated with an increased risk of breast cancer mortality (Perna et al., 2013).

Other aspects of vitamin D and breast cancer

Researchers are also interested in finding a link between vitamin D level and stage of BC. Several studies were conducted to see if any link exists between vitamin D and BC stage. The first one included 82 women with BC. A majority of women (72%) had vitamin D level below 30 ng/ml. Results indicated that vitamin D serum level was not associated with markers of differentiation (grade), apoptosis (Bcl2) or response to neo adjuvant chemotherapy but vitamin D deficient women had a more proliferative phenotype of breast cancer because lower serum vitamin D levels were related to higher tumor Ki67 as a marker of proliferation (Clark et al., 2014). On the other hand, Women's Healthy Eating and Living Study among 904 women indicated that 25(OH)D level had no significant relationship with BC stage (Jacobs et al., 2013).

During an interesting study by Qin et al. (2013) 36 healthy women were enrolled whose serum and nipple aspirate fluid were analyzed. These women were divided into 4 groups, group 1 received placebo, group 2 received 400 IU vitamin D_3, group 3 received 2000 IU vitamin D_3 and group 4 received 2000 IU vitamin D_3 plus 400 mg celecoxib. Analyses of samples indicated that group 3 had the lowest prostaglandins and the highest TGFβ2. Adding celecoxib had no beneficial effects (Qin et al., 2013).

DISCUSSION

Retrieved articles about vitamin D and risk of BC are inconclusive. The two large trials, the European Prospective Investigation into Cancer and Nutrition study (Abbas et al., 2013) and also The Norwegian Woman and Cancer Study (Edvardsen et al., 2011) could not prove any beneficial effect of vitamin D on BC risk. Both of the studies had reasonable sample size and the follow up period was long, however in both of these studies, the researchers' evaluated vitamin D and calcium by their dietary intake and not by their serum level. The dietary vitamin D might not have provided the desired vitamin D level.

The conflicting role of genetics can be greatly observed in the multiethnic cohort study which proves the reverse association of vitamin D serum level and risk of developing BC only among white women (Kim et al., 2014). This is clinically important and can be used as a guide for future studies since future clinical trials are better to be conducted among people with similar race.

The next considerable aspect of vitamin D would be its potential to ameliorate the side effects of AIs. AIs are now used as the first line therapy for treatment of postmenopausal ER+BC (Hiscox et al., 2009) but their use contributes to higher Bone Mineral Density (BMD) loss and bone fracture comparing to tamoxifen (Eastell et al., 2008). As stated before, MSK symptoms and bone loss is the major side effect so prevention and treatment of bone fractures is essential among these women. Supplementation of vitamin D together with calcium is strongly recommended. Of the reviewed articles, the first one supplemented 224 women with BC with either daily low dose vitamin D or weekly high dose vitamin D. Comparing the two groups, vitamin D level in weekly high dose group was significantly increased contrary to the low dose group

(Peppone et al., 2011). Furthermore according to another trial among 24 women with metastatic BC, use of 2-7 µg/day of oral Paricalcitol (an analogue of vitamin D) was safe to use (Lawrence, Akman, Melin, Case, & Schwartz, 2013). Additionally a review by Datta et al. (2013) stated that a range of 200-1000 IU/day of vitamin D and 500-1500 mg of calcium is harmless to maintain bone mineral density.

In the case of vitamin D and AI side effect, the major clinical trials reviewed in this article have concluded that higher vitamin D level was successful in decreasing AI side effects and highlight the role of vitamin D as an adjuvant therapy for women. As stated before, genetics and polymorphism are important factors affecting vitamin D's role. The study of Jorde et al. (2013) revealed that polymorphism in 24-hydroxylase gene is associated with BC. This was later confirmed by Perna et al. (2013) proving that vitamin D receptor genes can affect developing BC.

There is still little information about the possible link between vitamin D and BC recurrence. There is only one study on the subject in which 3085 women with BC and 512 controls were enrolled. Results indicated no relationship between 25(OH) D level and BC recurrence (Jacobs et al., 2011).

Table1. A summary of studies about the effects of vitamin D on risk of developing breast cancer up to January2016

Subjects	Follow up period	Supplementation	Results
7760 invasive BC cases	8.8 years	-	No effect of vit D and calcium intake on BC risk
41811 healthy women	8.5 years	-	No effect of vit D & calcium intake and UV radiation on BC risk
1,527 non-hispantic whites and 791 hispanic BC cases	-	-	vitamin D supplement use was inversely associated with BC
707 women with BC	-	-	Reverse association between vit D and risk of BC only among white women
297 cases with BC	-	-	Useful effect of vit D supplementation on BC risk factors
231 invasive BC and 856 controls	-	-	No useful effect of vit D level on BC risk factors

BC: Breast cancer; Vit D: Vitamin D; UV: Ultraviolet.
The – means that these studies did not have follow up periods.

Table 2. A summary of studies about the effects of vitamin D on aromatase inhibitor side effects up to January 2016

Subjects	Follow up period	Supplementation	Results
60 women with breast cancer and MSK symptoms	6 months	Group A received 50,000 IU capsules weekly for 8 weeks then monthly for 4 months or placebo. Group B (10-19 ng/ml) received either HDD for 16 weeks and then monthly for 2 months, or placebo.	Weekly high dose vitamin D improves MSK symptoms and could have a positive effect on bone health
416 postmenopausal women aged 40-70 years, who are at increased risk of BC	-	-	Only a small and a non-significant effect of baseline vitamin D levels were seen on the risk of MSK symptoms.
98 Korean postmenopausal women early BC	6 months	5-mg of alendronate and 0.5-µg of calcitriol or placebo	A combination of 5-mg alendronate and 0.5-µg calcitriol is effective in preventing bone loss due to AI in Korean postmenopausal women with early breast cancer.
52 patients with MSK symptoms	6 months	--	Vit D deficiency leads to the AI-associated MSK pain syndrome and in particular to the development of tendonitis

MSK: musculoskeletal; IU: International Unit; AI: Aromatase Inhibitor.

CONCLUSION

According to the reviewed articles the relationship between vitamin D and risk of developing BC is still inconclusive and the major trials about this aspect decline the link. In order to certainly point out a role for vitamin D and BC risk, measuring vitamin D serum level is necessary to be carried out. Future clinical trials need to be conducted among similar races to eliminate the role of genetics. Fortunately the association between vitamin D and AI side effects is almost promising. In most of the reviewed articles, vitamin D deficiency among the participants was

quiet high and vitamin D was able to reduce MSK symptoms and BMD loss, therefore it is strongly recommended to the physicians to start treating vitamin D deficiency among BC patients. A dose of 200-1000 IU/day of vitamin D has been shown to be safe among these patients. Other aspects of vitamin D and BC are yet to be determined and there is no certain evidence to consider a clinically important role for vitamin D status to determine breast cancer stage or the effect of vitamin D polymorphism on breast cancer.

Competing interests

There is no conflict of interest in present review article.

REFERENCES

Abbas S, Linseisen J, Rohrmann S, Chang-Claude J, Peeters PH, Engel P et al. (2013). Dietary intake of vitamin D and calcium and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition. Nutr. Cancer, 65(2): 178-187.

Amir E, Cecchini RS, Ganz PA, Costantino JP, Beddows S, Hood N et al. (2012). 25-Hydroxy vitamin-D, obesity, and associated variables as predictors of breast cancer risk and tamoxifen benefit in NSABP-P1. Breast Cancer. Res. Treat., 133(3): 1077-1088.

Bao BY, Ting HJ, Hsu JW and Lee YF (2008). Protective role of 1 alpha, 25-dihydroxyvitamin D3 against oxidative stress in nonmalignant human prostate epithelial cells. Int J Cancer, 122(12): 2699-2706.

Berger U, Wilson P, McClelland RA, Colston K, Haussler MR, Pike JW and Coombes RC (1988). Immunocytochemical detection of 1, 25-dihydroxyvitamin D receptors in normal human tissues. J. Clin. Endocrinol. Metab., 67(3): 607-613.

Bikle DD and Jiang Y (2013). The protective role of vitamin d signaling in non-melanoma skin cancer. Cancers (Basel), 5(4): 1426-1438.

Bristol ML, Di X Beckman MJ, Wilson EN, Henderson SC, Maiti A and Gewirtz DA (2012). Dual functions of autophagy in the response of breast tumor cells to radiation: cytoprotective autophagy with radiation alone and cytotoxic autophagy in radiosensitization by vitamin D 3. Autophagy, 8(5): 739-753.

Bulun SE, Lin Z, Imir G, Amin S, Demura M, Yilmaz B and Deb S (2005). Regulation of aromatase expression in estrogen-responsive breast and uterine disease: from bench to treatment. Pharmacol. Rev, 57(3): 359-383.

Clark AS, Chen J, Kapoor S, Friedman C, Mies C, Esserman L and DeMichele A (2014). Pretreatment vitamin D level and response to neoadjuvant chemotherapy in women with breast cancer on the I-SPY trial (CALGB 150007/150015/ACRIN6657). Cancer Med., 3(3): 693-701.

Datta M and Schwartz GG (2013).Calcium and vitamin D supplementation and loss of bone mineral density in women undergoing breast cancer therapy. Crit. Rev. Oncol. Hematol, 88(3): 613-624

Di Rosa M, Malaguarnera M, Zanghi, A, Passaniti A and Malaguarnera L (2013).Vitamin D3 insufficiency and colorectal cancer. Crit. Rev. Oncol. Hematol., 88(3): 594-612.

Eastell R, Adams JE, Coleman RE, Howell A, Hannon R. A, Cuzick J and Clack G (2008). Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. J. Clin. Oncol., 26(7): 1051-1057.

Edvardsen K, Veierod MB, Brustad M, Braaten T, Engelsen O and Lund E (2011). Vitamin D-effective solar UV radiation, dietary vitamin D and breast cancer risk. Int. J. Cancer, 128(6): 1425-1433.

Grant WB (2012). Ecological studies of the UVB-vitamin D-cancer hypothesis. Anticancer Res., 32(1): 223-236.

Grant WB (2013). Update on evidence that support a role of solar ultraviolet-B irradiance in reducing cancer risk. Anticancer Agents Med. Chem., 13(1): 140-146.

Hansen CM, Frandsen TL, Brunner N and Binderup L (1994). 1 alpha, 25-Dihydroxyvitamin D3 inhibits the invasive potential of human breast cancer cells in vitro. Clin. Exp. Metastasis, 12(3): 195-202.

Hiscox S, Davies EL and Barrett-Lee P (2009). Aromatase inhibitors in breast cancer. Maturitas, 63(4): 275-279.

Hoyer-Hansen M and Jaattela M (2008). Autophagy: an emerging target for cancer therapy. Autophagy, 4(5): 574-580.

Jacobs ET, Thomson CA, Flatt SW, Al-Delaimy WK, Hibler EA, Jones LA and Pierce JP (2011).Vitamin D and breast cancer recurrence in the Women's Healthy Eating and Living (WHEL) Study. Am. J. Clin. Nutr., 93(1): 108-117.

Jacobs ET, Thomson CA, Flatt SW, Newman VA, Rock CL and Pierce JP (2013). Correlates of 25-hydroxyvitamin D and breast cancer stage in the Women's Healthy Eating and Living Study. Nutr. Cancer, 65(2): 188-194.

Jorde R, Schirmer H, Wilsgaard T, Joakimsen R. M, Mathiesen E. B, Njolstad I and Grimnes G (2012). Polymorphisms related to the serum 25-hydroxyvitamin D level and risk of myocardial infarction, diabetes, cancer and mortality. The Tromso Study. PLoS One, 7(5): 37295.

Kim Y, Franke AA, Shvetsov YB, Wilkens LR, Cooney RV, Lurie G and Goodman MT (2014). Plasma 25-hydroxyvitamin D3 is associated with decreased risk of postmenopausal breast cancer in whites: a nested case-control study in the multiethnic cohort study. BMC Cancer, pp. 14- 29.

Kovalenko PL, Zhang Z, Cui M, Clinton SK and Fleet JC (2010). 1,25dihydroxyvitamin D-mediated orchestration of anticancer, transcript-level effects in the immortalized, non-transformed prostate epithelial cell line, RWPE1. BMC Genomics, 11- 26.

Krishnan AV, Shinghal R, Raghavachari N, Brooks JD, Peehl DM and Feldman D (2004). Analysis of vitamin D-regulated gene expression in LNCaP human prostate cancer cells using cDNA microarrays. Prostate, 59(3): 243-251.

Larriba MJ, Gonzalez-Sancho JM, Barbachano A, Niell N, Ferrer-Mayorga G and Munoz A (2013). Vitamin D Is a Multilevel Repressor of Wnt/b-Catenin Signaling in Cancer Cells. Cancers (Basel), 5(4): 1242-1260.

Lawrence JA, Akman SA, Melin SA, Case LD and Schwartz GG (2013). Oral paricalcitol (19-nor-1,25-dihydroxyvitamin D2) in women receiving chemotherapy for metastatic breast cancer: a feasibility trial. Cancer Biol. Ther., 14(6): 476-480.

Lopes N, Sousa B, Martins D, Gomes M, Vieira D, Veronese LA and Schmitt F (2010). Alterations in Vitamin D signalling and metabolic pathways in breast cancer progression: a study of VDR, CYP27B1 and CYP24A1 expression in benign and malignant breast lesions. BMC Cancer, pp. 10-483.

Maruyama T, Kono K, Mizukami Y, Kawaguchi Y, Mimura K, Watanabe M and Fujii H (2010). Distribution of Th17 cells and FoxP3 (+) regulatory T cells in tumor-infiltrating lymphocytes, tumor-draining lymph nodes and peripheral blood lymphocytes in patients with gastric cancer. Cancer Sci., 101(9): 1947-1954.

Milovanovic M, Pesic G, Nikolic V, Jevtovic-Stoimenov T, Vasic K, Jovic Z and Pesic S (2012). Vitamin D deficiency is associated with increased IL-17 and TNFalpha levels in patients with chronic heart failure. Arq Bras. Cardiol., 98(3): 259-265.

Moreno J, Krishnan AV, Peehl DM and Feldman D (2006). Mechanisms of vitamin D-mediated growth inhibition in prostate cancer cells: inhibition of the prostaglandin pathway. Anticancer Res., 26(4a): 2525-2530.

Niravath P (2013). Aromatase inhibitor-induced arthralgia: a review. Ann. Oncol., 24(6), 1443-1449.

Peehl DM, Shinghal R, Nonn L, Seto E, Krishnan AV, Brooks JD and Feldman D (2004). Molecular activity of 1,25-dihydroxyvitamin D3 in primary cultures of human prostatic epithelial cells revealed by cDNA microarray analysis. J. Steroid Biochem. Mol. Biol., 92(3): 131-141.

Pendas-Franco N, Gonzalez-Sancho J. M, Suarez Y, Aguilera O, Steinmeyer A, Gamallo C, Munoz A (2007). Vitamin D regulates the phenotype of human breast cancer cells. Differentiation, 75(3): 193-207.

Peppone LJ, Huston AJ, Reid ME, Rosier RN, Zakharia Y, Trump DL and Morrow GR (2011). The effect of various vitamin D supplementation regimens in breast cancer patients. Breast Cancer Res. Treat., 127(1): 171-177.

Perna L, Butterbach K, Haug U, Schottker B, Muller H, Arndt V and Brenner H (2013). Vitamin D receptor genotype rs731236 (Taq1) and breast cancer prognosis. Cancer Epidemiol. Biomarkers Prev., 22(3): 437-442.

Qin W, Smith C, Jensen M, Holick MF and Sauter ER (2013). Vitamin D favorably alters the cancer

promoting prostaglandin cascade. Anticancer Res., 33(9): 3861-3866.

Rastelli AL, Taylor ME, Gao F, Armamento-Villareal R, Jamalabadi-Majidi S, Napoli N and Ellis MJ (2011). Vitamin D and aromatase inhibitor-induced musculoskeletal symptoms (AIMSS): a phase II, double-blind, placbo-controlled, randomized trial. Breast Cancer Res. Treat., 129(1): 107-116.

Rhee Y, Song K, Park S, Park HS, Lim SK and Park BW (2013). Efficacy of a combined alendronate and calcitriol agent (Maxmarvil(R)) in Korean postmenopausal women with early breast cancer receiving aromatase inhibitor: a double-blind, randomized, placebo-controlled study. Endocr. J., 60(2): 167-172.

Rollison DE, Cole AL, Tung KH, Slattery ML, Baumgartner KB, Byers T and Giuliano AR (2012). Vitamin D intake, vitamin D receptor polymorphisms, and breast cancer risk among women living in the southwestern U.S. Breast Cancer Res. Treat., 132(2): 683-691

Shamsi U, Khan S, Usman S, Soomro S and Azam I (2013). A multicenter matched case control study of breast cancer risk factors among women in Karachi, Pakistan. Asian Pac J. Cancer Prev., 14(1): 183-188.

Singer O, Cigler T, Moore AB, Levine AB, Do HT and Mandl LA (2014). Hypovitaminosis D is a predictor of aromatase inhibitor musculoskeletal symptoms. Breast J., 20(2): 174-179.

Singh S, Cuzick J, Mesher D, Richmond B& Howell A (2012). Effect of baseline serum vitamin D levels on aromatase inhibitors induced musculoskeletal symptoms: results from the IBIS-II, chemoprevention study using anastrozole. Breast Cancer Res Treat, 132(2): 625-629.

Swami S, Raghavachari N, Muller UR, Bao YP and Feldman D (2003). Vitamin D growth inhibition of breast cancer cells: gene expression patterns assessed by cDNA microarray. Breast Cancer Res. Treat., 80(1): 49-62.

Thill M, Fischer D, Hoellen F, Kelling K, Dittmer C, Landt S and Becker S (2010). Prostaglandin metabolising enzymes and PGE2 are inversely correlated with vitamin D receptor and 25(OH) 2D3 in breast cancer. Anticancer Res., 30(5): 1673-1679.

Thyer L, Ward E, Smith R, Fiore MG, Magherini S, Branca JJ and Pacini S (2013). A novel role for a major component of the vitamin D axis: vitamin D binding protein-derived macrophage activating factor induces human breast cancer cell apoptosis through stimulation of macrophages. Nutrients, 5(7): 2577-2589.

Valko M, Rhodes CJ, Moncol J, Izakovic M and Mazur M (2006). Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem. Biol. Interact., 160(1): 1-40.

Wang J, He Q, Shao YG, Ji M and Bao W (2013). Associations between vitamin D receptor polymorphisms and breast cancer risk. Tumour. Biol., 34(6): 3823-3830.

Yu H and Rohan T (2000).Role of the insulin-like growth factor family in cancer development and progression. J Natl. Cancer Inst., 92(18): 1472-1489.

Zinser G M and Welsh J (2004). Accelerated mammary gland development during pregnancy and delayed postlactational involution in vitamin D3 receptor null mice. Mol. Endocrinol., 18(9): 2208-2223.