Different Levels of Vitamin D and Breast Cancer: A Review

Faezeh Modaresi-Ghazani¹, Mohammad Esmaeil Hejazi²,⁎ and Veghar Hejazi²

¹Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
²Respiratory 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 developing breast cancer; however vitamin D polymorphism is in 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

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 G1/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 D₃ 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 D₃ 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 D₃ 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 and Lopes 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 FokI 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 postmenopausal 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 D₃, group 3 received 2000 IU vitamin D₃ and group 4 received 2000 IU vitamin D₃ 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.
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).

**Table 1.** A summary of studies about the effects of vitamin D on risk of developing breast cancer up to January 2016

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

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Follow up period</th>
<th>Supplementation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>52 patients with MSK symptoms</td>
<td>6 months</td>
<td>--</td>
<td>Vit D deficiency leads to the AI-associated MSK pain syndrome and in particular to the development of tendonitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Follow up period</th>
<th>Supplementation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 women with breast cancer and MSK symptoms</td>
<td>6 months</td>
<td>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.</td>
<td>Weekly high dose vitamin D improves MSK symptoms and could have a positive effect on bone health</td>
</tr>
<tr>
<td>416 postmenopausal women aged 40-70 years, who are at increased risk of BC</td>
<td>-</td>
<td>-</td>
<td>Only a small and a non-significant effect of baseline vitamin D levels were seen on the risk of MSK symptoms.</td>
</tr>
<tr>
<td>98 Korean postmenopausal women early BC</td>
<td>6 months</td>
<td>5-mg of alendronate and 0.5-µg of calcitriol or placebo</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Follow up period</th>
<th>Supplementation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSK: musculoskeletal; IU: International Unit; AI: Aromatase Inhibitor.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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**


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


