REVIEW ARTICLE

The association between Vitamin D and health outcomes in women: A review on the related evidence

Nahid Ramezani Jolfaie[1], Mohammad Hossein Rouhani[1], Shokouh Onvani[1], Leila Azadbakht[1,2,3]

[1]Department of Community Nutrition, School of Nutrition and Food Sciences, Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, [2]Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, [3]Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

Background: Vitamin D has a wide range of physiological functions in skeletal and nonskeletal tissues which may play a role in many diseases. The aim of this study was to evaluate the recent evidence regarding the effects of Vitamin D on several health outcomes in women including breast cancer, ovarian and endometrial cancers, hypertension, and osteoporosis. **Materials and Methods:** We searched PubMed and Google Scholar databases through March 2016. We included the most current systematic reviews and meta-analyses assessing the associations of Vitamin D intake and/or serum 25-hydroxyvitamin D (25(OH)D) levels with the risk of incidence of breast cancer, ovarian and endometrial cancers, hypertension, and osteoporosis. **Results:** Many studies have represented that Vitamin D supplementation and high 25(OH)D levels can decrease the risk of breast cancer occurrence or mortality. However, there is no strong evidence to support the existence of a relationship between Vitamin D and ovarian or endometrial cancers. Furthermore, the results regarding the effects of Vitamin D on hypertension were inconsistent. Although observational studies have shown an association between Vitamin D and hypertension, there is no evidence regarding effectiveness of Vitamin D in lowering blood pressure in several clinical trials. On the other hand, the findings associating the impact of Vitamin D on osteoporosis were more definitive and most studies have represented that Vitamin D may have beneficial effects on osteoporosis. **Conclusion:** Although the adequate Vitamin D level can play a protective role in the incidence and development of breast cancer, hypertension, and osteoporosis, there is limited evidence regarding ovarian and endometrial cancers.

Key words: 1, 25- dihydroxyvitamin D, 25-hydroxyvitamin D, breast cancer, endometrial cancer, hypertension, osteoporosis, ovarian cancer, Vitamin D

How to cite this article: Jolfaie NR, Rouhani MH, Onvani S, Azadbakht L. The association between Vitamin D and health outcomes in women: A review on the related evidence. J Res Med Sci 2016;21:76.

INTRODUCTION

Vitamin D is considered a collection of fat-soluble steroids that found in two forms: Vitamin D_3 (cholecalciferol) from animal sources and Vitamin D_2 (ergocalciferol) from plant sources.[1,2] Although Vitamin D can be obtained from few dietary sources including oily fish (salmon), eggs, fortified dairy products, or pharmacologic supplementation, most Vitamin D requirements are provided from natural synthesis in the skin.[3,4] The 7-dehydrocholesterol in plasma membranes of the epidermis and dermis through sunlight exposure, ultraviolet B rays can be converted to Vitamin D_3.[4] Vitamin D from the skin and diet is activated during 25-hydroxylation in the liver, 25-hydroxyvitamin D (25(OH)D), and subsequent hydroxylation in the kidneys, 1,25-dihydroxyvitamin D (1,25(OH) 2D).[1,5] 25(OH)D, calcidiol, is the dominant metabolite of Vitamin D in the circulation that represented the Vitamin D status and 1,25(OH) 2D, calcitriol, is known as the biological active form of Vitamin D. The hormonal activity of calcitriol is exerted through binding to the nuclear Vitamin D receptor (VDR).[5-7]

Access this article online	
Quick Response Code:	Website: www.jmsjournal.net
	DOI: ****

Address for correspondence: Prof. Leila Azadbakht, Department of Community Nutrition, School of Nutrition and Food Sciences, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: azadbakht@hlth.mui.ac.ir

Received: 24-01-2016; **Revised:** 08-03-2016; **Accepted:** 25-05-2016

Normal serum 25(OH)D value is 20 ng/ml (50 nmol/L) which if be <20 ng/ml is classified into the deficiency category.[8] Low sun exposure, reduced dietary Vitamin D intake, and older age are the most common factors associated with Vitamin D deficiency.[9] The worldwide prevalence of Vitamin D deficiency is approximately 1 billion.[10] The rate of inadequate Vitamin D levels among younger and older postmenopausal women has been estimated to be about 50% globally.[11] The suboptimal levels of 25(OH)D below 30 ng/ml was also reported in more than 50% of postmenopausal women consuming osteoporosis medication.[3,12] Prevalence of Vitamin D insufficiency and marginal status is higher in female than male population.[13,14] As Vitamin D has important physiological functions through maintaining mineral homeostasis,[15] it has proposed that Vitamin D deficiency can lead to several musculoskeletal disorders including rickets and skeletal abnormalities in children, osteomalacia, osteopenia, osteoporosis, and incidence of fractures in adults.[16] In recent years, researchers found that VDRs were expressed in several tissues and cells and, therefore, had a wide range of biological functions. Therefore, many hypotheses arose that low Vitamin D values may be associated with various diseases such as cancers, infections, autoimmune diseases, diabetes mellitus, and cardiovascular diseases.[17-20] Recent attention has been focused on the Vitamin D effects on body health and the association between Vitamin D and diseases has been extensively investigated in several studies. In this article, we assessed the recent review studies in regarding the roles of Vitamin D in the several aspects of women health.

MATERIALS AND METHODS

A literature search was conducted to identify studies assessing the associations of Vitamin D intake and/or serum 25(OH)D levels with the risk of incident breast cancer, ovarian or endometrial cancers, hypertension, and osteoporosis. We searched the PubMed and Google Scholar databases through March 2016 for relevant reports. Search keywords included Vitamin D, 25(OH)D, 1, 25-dihydroxyvitamin D, breast cancer, ovarian cancer, endometrial cancer, hypertension, and osteoporosis. The unrelated literature was excluded after titles and abstracts screening. Then, the full text of remained papers was reviewed for those articles with relevant relationships. Finally, the most current systematic reviews and meta-analyses in this regards were selected.

RESULTS

Articles included in our study are shown in Figure 1. Details of included studies are reported in Table 1.

Vitamin D and breast cancer

Breast cancer is considered a common disease and a leading cause of mortality in women.[39] It has been estimated that

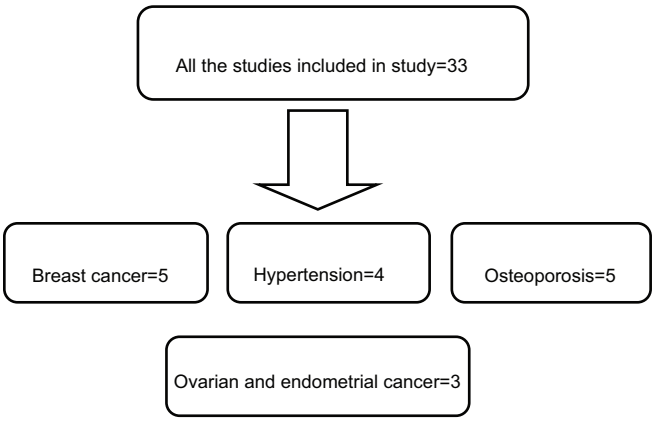

Figure 1: Flowchart of conducted studies in the field of Vitamin D

there are approximately 1.4 million new cases of breast cancer and over 450,000 mortality annually.[40] There are several well-established risk factors for breast cancer such as age, gender, density of breast tissue, parity, genetic, and alcohol use.[5,41] Vitamin D plays the important roles in the mammary gland through regulation of calcium transport during lactation, differentiation hormones, and milk protein production.[41] The complex of Vitamin D and VDRs in the normal breast epithelial cells can regulate transcription of more than sixty genes that are responsible for effects of antiproliferative, prodifferentiating, antimetastatic, and proapoptotic on cells.[21,41] It has been suggested that Vitamin D can lead to the decrease in benign epithelial proliferation disorders and subsequently the breast cancer risk through reduction of breast mammographic density and antiproliferation and prodifferentiation activities.[22] Although evidence from experimental and laboratory studies has generally shown an association between higher Vitamin D levels and lower breast cancer risk, the results of human researches are somewhat controversial.[42]

Stoll *et al*. reviewed the studies examining the association between breast cancer and Vitamin D from different sources (skin synthesis or food or supplementation). They suggested that elevated serum 25(OH)D levels through the sun exposure as well as dietary intake and an over 400 IU/day Vitamin D supplementation were associated with a reduced risk of breast cancer.[23]

Similar findings were also reported in a pooled analysis on the 11 epidemiological studies regarding the relationship between levels of serum 25(OH)D and breast cancer risk. It was observed that individuals in the highest quintile versus the lowest quintile of serum 25(OH)D had a reduction in risk of breast cancer (odds ratio [OR] = 0.63, 95% confidence interval [CI] = 0.47–0.80). On the other hand, this study reported that there was an approximately 10% reduction in risk of breast cancer followed by every 10 ng/ml increase in serum 25(OH)D concentration.[21]

Table 1: Studies examined association of Vitamin D and some of the health outcomes

Study	Type of study	Number/sex	Design and aim	Results
Bauer *et al*.[5]	Dose-response meta-analysis	9 prospective studies comprising 5206 cases and 6450 controls	Plasma Vitamin D levels, menopause, and risk of breast cancer	A step-wise inverse association was observed beyond a threshold of 27 ng/ml
Mohr *et al*.[21]	Pooled analysis	11 case-control studies	Serum 25(OH)D and prevention of breast cancer	A serum 25(OH)D level of 47 ng/ml was associated with a 50% lower risk of breast cancer
Chen *et al*.[22]	Meta-analysis	36 studies	Vitamin D, calcium, and the prevention of breast cancer	Circulating 25(OH)D was found to be associated with a 45%decrease in breast cancer
Stoll *et al*.[23]	Systematic review	37 studies	The relationship between breast cancer and Vitamin D	An increased 25(OH)D level seems associated with a decreased risk of breast cancer recurrence
Maalmi *et al*.[24]	Systematic review and meta-analysis	Five studies including 4413 breast cancer patients	Serum 25(OH)D levels and survival in breast cancer patients	Higher 25(OH)D levels (>75 nmol/L) were associated with significantly reduced mortality in patients with breast cancer
Ordóñez-Mena *et al*.[25]	Meta-analysis	-	Prediagnostic Vitamin D concentrations and cancer risks in older individuals	There was some evidence of increased breast cancer risk with higher 25(OH)D concentrations
Zeleniuch-Jacquotte *et al*.[26]	Nested case-control	Including 830 cases and 992 controls from 7 cohorts	Circulating 25(OH)D and risk of endometrial cancer	Results do not support a protective role of Vitamin D against endometrial cancer
Cook *et al*.[27]	Systematic literature review		Vitamin D and ovarian cancer	There is no evidence that Vitamin D exposures reduce the risk for ovarian cancer occurrence or mortality
Yin *et al*.[28]	Meta-analysis	10 studies	Circulating Vitamin D, and ovarian cancer risk	Nonsignificant inverse association of circulating 25(OH)D with ovarian cancer incidence was found
Liu *et al*.[29]	Review	-	The role of Vitamin D in blood pressure	Low Vitamin D concentrations appear to significantly associate with hypertension
Beveridge *et al*.[30]	Systematic review and meta-analysis	46 trials (4541 participants)	Effect of Vitamin D supplementation on blood pressure	Vitamin D supplementation is ineffective as an agent for lowering blood pressure
Tamez *et al*.[31]	Review	-	Vitamin D in blood pressure	Observational studies show inverse association between Vitamin D and blood pressure but trials have yielded inconclusive results
Kunutsor *et al*.[32]	Meta-analysis	8 cohort studies 283,537 participants	Vitamin D and risk of future hypertension	10 ng/ml increment in baseline 25(OH) D levels was related to 22% decrement in hypertension incident
Ke *et al*.[33]	Systematic review	Ten prospective studies (*n*=58,262)	Vitamin D status and hypertension	Younger females showed strong associations between high 25(OH)D levels and hypertension risk
Watanabe and Okazaki[34]	Review	-	Vitamin D deficiency and fracture	Vitamin D supplementation to Vitamin D deficient osteoporotics reduces the fracture incidence by both increasing bone mineral density and reducing falls
Liao *et al*.[35]	Systematic review	11 studies	Management of osteoporosis with calcitriol in elderly Chinese patients	Treatment with calcitriol can improve quality of life in patients with osteoporosis
Bischoff-Ferrari *et al*.[36]	Pooled analysis	31,022 persons (mean age, 76 years; 91% women) with 1111 incident hip fractures and 3770 nonvertebral fractures	Vitamin D dose requirements for fracture prevention	High-dose Vitamin D supplementation (≥800 IU daily) was favorable in the prevention of hip fracture and any nonvertebral fracture in persons 65 years of age or older
Reid *et al*.[37]	Systematic review and meta-analysis	23 studies	Vitamin D supplements on bone mineral density	Continuing widespread use of Vitamin D for osteoporosis prevention in community-dwelling adults without specific risk factors for Vitamin D deficiency seems to be inappropriate
Bischoff-Ferrari[38]	Review	-	Which Vitamin D oral supplement is best for postmenopausal women?	For fracture prevention a higher serum 25(OH)D threshold of 75 nmol/l (30 ng/ml) should be targeted

25(OH)D = 25-hydroxyvitamin D

Another meta-analysis by Maalmi *et al*. including five prospective cohort studies during a follow-up of 2.7–24 years has been conducted to evaluate the association between serum 25(OH)D levels and survival among patients with breast cancer. They observed that patients with high 25(OH)D levels had a significant reduced risk of overall mortality (hazard ratio [HR] =0.62, 95% CI = 0.49–0.78) and breast cancer-specific mortality (HR = 0.57, 95% CI = 0.38–0.84) compared to patients with low 25(OH)D levels. Furthermore, dose-response analyses demonstrated that the increase in 25(OH)D by 20 nmol/L leads to reduce in overall (HR = 0.82, 95% CI = 0.75–0.88) and breast cancer-specific (HR = 0.82, 95% CI = 0.71–0.93) mortality.[24] However, this significant association between Vitamin D and risk of breast cancer in pervious reviews has not been completely confirmed by other researches.

A meta-analysis by comparing the high and low total Vitamin D intake showed that there is a significant association between Vitamin D intake and breast cancer risk in cohort studies (relative risk [RR] =0.90, 95% CI = 0.83–0.98) but not in the case–control studies (RR = 0.95, 95% CI = 0.69–1.32). In addition, when subgroup analysis was conducted according to menopausal status, there was a significant association between Vitamin D intake and breast cancer risk in the premenopausal women (RR = 0.83, 95% CI = 0.73–0.95). On the other hand, no significant inverse relationship between circulating 25(OH)D levels and risk of breast cancer was observed in the both postmenopausal and premenopausal women.[22]

Furthermore, the findings of dose-response meta-analysis comprising 5206 cases of breast cancer and 6450 controls demonstrated that there was a marginal significant inverse association between circulating 25(OH)D and risk of breast cancer (RR/5 ng/ml = 0.99, 95% CI = 0.97–1.00). Moreover, this meta-analysis revealed that menopause status can be affected on association between plasma 25(OH)D and breast cancer risk. Although the inverse relationship between circulating 25(OH)D and risk of breast cancer was observed in the postmenopausal women (RR/5 ng/ml = 0.97, 95% CI = 0.93–1.00), there was no dose-response association among premenopausal women (RR/5 ng/ml = 1.01, 95% CI = 0.98–1.04). However, no reduction in risk of postmenopausal breast cancer per 5 ng/ml increase in 25(OH)D was observed above 35 ng/ml of 25(OH)D concentration.[5]

The results of cohorts participating in the CHANCES consortium showed that there was no association between lower 25(OH)D concentrations and increment of most cancers. However, there was some evidence of increased breast cancer risk with higher 25(OH)D concentrations.[25]

Vitamin D and ovarian or endometrial cancers

Ovarian and endometrial cancers are the most common gynecologic neoplasms among women.[26,43,44] Several risk factors have been recognized for these cancers such as old age, family history, high estrogen and low progesterone levels, nulliparity, and obesity.[26,45]

The VDRs have been detected in endometrial and ovarian cell lines which mediate the role of 1,25(OH)2D in these tissues.[27] Moreover, it has been suggested that 1,25(OH)2D can lead to inhibition of cell proliferation and induction of apoptosis in the ovarian cancer cells through down-regulation of telomerase activity.[46] Although these biological reasons suggest that Vitamin D may associate with the incidence and mortality of ovarian and endometrial cancers, the exact role of Vitamin D in the etiology of these cancers has remained controversial.[27,47] The results of the studies that conducted in this field are not consistent.

In a systematic review, the evidence related to association between ovarian cancer occurrence or mortality with Vitamin D levels was evaluated. Although there was a reductions in the incidence or mortality with increased latitude, sunlight, or dietary/supplement Vitamin D intake in the approximately half of the ecologic and case–control studies, the other half case–control and cohort studies reported no significant associations. This systematic review suggests that there is no strong evidence regarding whether the increased Vitamin D levels can reduce the risk of ovarian cancer incidence or mortality.[27]

In a nested case–control study, including 830 endometrial cancer cases from seven cohorts, no associations were observed between 25(OH)D concentration and endometrial cancers risk.[26] The results regarding the association between circulating 25(OH)D and endometrial cancer risk represented that there was a nonsignificant overall ORs associated with concentrations of <25 nmol/L (1.21, 95% CI = 0.75–1.98) and ≥75 nmol/L (0.98, 95% CI = 0.71–1.35) to compare with the reference category (50–75 nmol/L).[26] Indeed, these findings did not support the protective role of Vitamin D against the endometrial cancer.

In another meta-analysis including 883 cases of ovarian cancer, the association between 25(OH)D and the ovarian cancer risk was assessed. Although in the seven studies, a tentatively reduced risk of ovarian cancer incidence was observed, there was no significant inverse relationship in pooled analyses (RR = 0.83, 95% CI = 0.63–1.08, P = 0.166) for an increase levels of circulating 25(OH)D by 20 ng/ml.[28]

Vitamin D and hypertension

Hypertension is considered a prevalent disorder worldwide as well as among the Iranian population which imposes a

substantial burden on the health system. Old age, genetics, stressful lifestyle, obesity, etc., have been recognized as various risk factors contributing to hypertension.[48-50] Although Vitamin D deficiency is another influential factor regarding high blood pressure (BP), the role of serum Vitamin D levels on hypertension remained not clear.[48,51] Negative regulation of the renin gene, direct effects on vascular function through existence of 1α-hydroxylase enzyme in the endothelial and vascular smooth muscle cells, and playing an important role in calcium metabolism are several potential mechanisms associating the regulation of Vitamin D on BP which are not firmly established.[29,51,52] Indeed, it has been assumed that Vitamin D deficiency can promote the secondary hyperparathyroidism, increment the aldosterone secretion, and stimulate the renin-angiotensin system.[53]

Although a number of observational and epidemiologic researches have proposed that Vitamin D deficiency can be associated with hypertension, in some trials, there are no convincing results representing that Vitamin D supplementation has a protective role in hypertension.[2,30,48]

Liu *et al*.[29] reviewed the evidence associating the effects of Vitamin D on BP in postmenopausal women. They found a direct association between low Vitamin D status and hypertension in observational studies. However, findings from clinical trials were inconsistent. This review suggested that in hypertensive patients with Vitamin D deficiency, Vitamin D supplementation can be more effective.[29]

Similar findings were also reported in another review evaluating the association between Vitamin D and the risk of developing elevated BP. Although there were strong observational evidence representing the association between Vitamin D deficiency and hypertension, clinical trials have yielded inconclusive results.[31]

A meta-analysis of 46 trials which comprised 4541 subjects was conducted to assess whether Vitamin D supplementation can reduce BP. The results found no significant effect of Vitamin D supplementation on systolic (effect size = 0.0, 95% CI = −0.8–0.8 mmHg) or diastolic BP (effect size= −0.1, 95% CI = −0.6–0.5 mmHg). This survey suggested that Vitamin D was not an antihypertensive agent.[30]

Another systematic review and meta-analysis studied the evidence of prospective studies that investigated the associations of circulating 25(OH)D levels and dietary Vitamin D intake with the risk of hypertension. The results showed that there is a significant inverse relationship between baseline circulating 25(OH)D levels and risk of hypertension incident in seven studies measuring serum 25(OH)D levels (RR = 0.70, 95% CI = 0.58–0.86), but it is not significant in four studies examining the dietary Vitamin D intake (RR = 1.00, 95% CI = 0.95–1.05). Moreover, dose-response analysis indicated that per 10 ng/ml increment in circulating 25(OH)D levels, the hypertension risk was reduced by 12%.[32]

A systematic literature review and meta-analysis of all observational studies was conducted on data published up to early 2014 on Vitamin D status and risk of hypertension. There was no increment in hypertension risk in older ages with Vitamin D deficiency, but high level of Vitamin D showed significant association with risk of hypertension in younger females (RR = 0.36 [0.18–0.72], OR = 0.62 [0.44–0.87]).[33]

Vitamin D and osteoporosis

Osteoporosis is associated with abnormalities of mineral homeostasis that can result in progression of bone loss, impaired bone microarchitecture, and consequently greater risk of fragility and fracture.[54] Fractures, especially hip fractures, are common among postmenopausal women contributing to morbidity and mortality considerably.[55,56] It has also been reported that the rate of inadequate Vitamin D levels is high in postmenopausal women suggesting existence of a link between Vitamin D deficiency and osteoporosis.[9] There is evidence associating the existence of VDRs within the three major bone cell types including osteoblasts, osteocytes, and osteoclasts.[57] Vitamin D plays an important role in maintaining mineral homeostasis and subsequently bone mineralization. It regulates the serum calcium and phosphorus values by affecting their metabolism and absorption in bone, gut, and kidneys.[9,17,54] On the other hand, Vitamin D deficiency can also cause low bone mineral density via secondary hyperparathyroidism.[34] Moreover, it has been proposed that 1,25(OH)2D can stimulate the differentiation of osteoblasts and osteoclastogenesis.[35] Nonetheless, the results of observational studies and clinical trials examining the effects of Vitamin D supplementation on bone mineral density and fractures have been inconsistent. Furthermore, the controversy regarding the optimal concentrations of 25(OH)D for optimizing skeletal health has been yet remained.[36,37]

The review study summarizing the recent recommendations on Vitamin D by the International Osteoporosis Foundation (IOF), the Institute of Medicine, and the US Endocrine Society suggests that Vitamin D_3 or Vitamin D_2 supplements should be consumed at a dose of 800 IU/day among postmenopausal women for prevention of osteoporosis, falls, and fractures. According to the institute of medicine recommendation, a minimal serum 25(OH)D threshold of 20 ng/ml (50 nmol/L) is needed for prevention of Vitamin D deficiency. On the other hand, the IOF and the US Endocrine Society recommend for prevention of

falls and fracture, serum 25(OH)D levels should be higher threshold of 30 ng/ml (75 nmol/L).[38] Similarly, in another review is recommend that serum 25(OH)D level more than 30 ng/ml is suitable for bone health. Furthermore, it has suggested that Vitamin D supplementation in osteoporotic patients with Vitamin D deficiency can reduce the fractures incidence through increment of bone mineral density and reduction of falls.[34]

Based on the findings of a meta-analysis included 31,022 persons (91% women), high-dose Vitamin D supplementation (≥800 IU/day) resulted in favorable reduction of hip fracture risk (30%) and any nonvertebral fracture risk (14%) among subjects aged ≥65 years.[36]

The meta-analysis of 23 studies including 4082 participants (92% women) was conducted to assess whether Vitamin D supplementation can affect bone mineral density. This analysis did not show any beneficial effect from Vitamin D supplementation on bone density. However, among five sites including lumbar spine, femoral neck, total hip, trochanter, total body, or forearm, a small but significant increase in bone density at the femoral neck was only observed (mean difference = 0.8, 95% CI = 0.2–1.4).[37]

Another systematic review evaluated the results of six trials regarding calcitriol therapy alone and five trials on calcitriol therapy combined with other antiosteoporotic agents in elderly osteoporotic men and women. This study suggested that calcitriol can reduce bone turnover markers and improve bone mineral density and muscle strength in short-term treatment without side effects. However, it was observed that combination of calcitriol with various other therapeutic bone agents compared to calcitriol monotherapy can lead to more significant beneficial effects on fracture risk, bone pain, and bone mineral density in osteoporosis treatment.[35]

DISCUSSION

The overall results of the recent reviews suggest that Vitamin D supplementation and high 25(OH)D levels can be beneficial in decreased risk of breast cancer as a one of the most common cancers among women.[21,23,24] However, there is no strong evidence to support the existence of a relationship between Vitamin D and ovarian or endometrial cancers. Indeed, in numerous trials and observational studies have not been observed that Vitamin D exposures can reduce the risk of these cancers.[26,28,44] Furthermore, the results on the effects of Vitamin D on hypertension were inconsistent; a number of surveys especially observational studies have shown an association between Vitamin D and hypertension, but in some other trials, there is no evidence regarding effectiveness of Vitamin D as an agent for lowering BP. Moreover, the findings associating the impact of Vitamin D on osteoporosis were more definitive and most studies have represented that Vitamin D can have beneficial effects in osteoporosis. Moreover, it has been reported that Vitamin D along with therapeutic bone agents has a more considerable role in osteoporosis treatment.[35]

Many possible reasons may be responsible for different findings of various studies in this regards. There are many variables that can affect the Vitamin D status including solar radiation, latitude, dietary and biochemical factors, supplements use, weight, total body fat percentage, age, and month of blood sampling,[58-61] and the adjustment for these confounders may be different among studies causing various conclusions. For instance, if the seasonal variation in 25(OH)D concentrations is not taken into account, it can lead to misclassification of Vitamin D status.[60] In addition, the existence of other potential confounders such as publication bias, varying assessment methods, and measurement errors may potentially lead to biases and different results.[5] It has proposed that reduced estrogen can lead to decrease in Vitamin D activation and VDR expression. Therefore, menopause status can be another factor associating with Vitamin D status that many studies did not enable to adjust the effect of menopausal status on association between Vitamin D and risk of diseases.[29,62,63]

This review tries to summarize the result of most recent systematic review and meta-analysis regarding prevalent diseases among female population. However, there are some limitations in our studies. We included only most recent systematic review and meta-analysis studies in our article and it did not conduct systematically. Moreover, studies were assessed only qualitatively. Nevertheless, we focused only on women and review the most recent studies. Further researches need to be conducted to find the exact effect of Vitamin D, especially on endometrial and ovarian cancers.

CONCLUSION

Although findings from the many studies have been represented that adequate Vitamin D can play a protective role in the incidence and development of breast cancer, hypertension, and osteoporosis as well as sometimes in ovarian and endometrial cancers, these results have not yet been confirmed in the number of researches. Therefore, we cannot make definitive deductions yet and more well-designed clinical trials and cohort studies considering all potential confounder factors with long follow-up period are needed to determine definite protective effect of Vitamin D against these diseases and to find the optimal doses of Vitamin D intake.

Acknowledgments

This research was funded by the Isfahan University of Medical Sciences, Isfahan, Iran.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

AUTHORS' CONTRIBUTIONS

NRJ, MHR and LA contributed in the conception of the work. NRJ and MHR searched data bases and extracted data. MHR and LA analyzed data. SO revised the manuscript. NRJ, MHR, LA and SO wrote the manuscript. All authors approved the final version of the manuscript, and agreed for all aspects of the work.

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