Abstract

Increasing evidence points to the role of vitamin D (VD) supplementation in cancer management. A comprehensive search of online databases was undertaken for all research studies relating to VD supplementation in cancer survivorship published up to November 2017. Eighteen studies meeting the inclusion criteria were selected for this review, the majority of which involved supplementation in breast cancer. This review concludes that VD supplementation plays an important role in disease free survival (DFS) in a number of cancers, particularly breast. In other cancers, the role of VD supplementation is less clear, and more research is required. More research is also required to investigate the most effective dose and duration of VD supplementation to benefit cancer survivors.

Key words: cancer; vitamin D; breast; survival.

Key Phrases

- Vitamin D (VD) supplementation plays a beneficial role in disease free survival and quality of life of breast cancer survivors.

- Evidence suggests that achieving vitamin D levels greater than 40 ng/ml benefits musculoskeletal pain and bone loss in breast cancer patients

- The role of VD supplementation is less clear in other cancers.

- The length of time required for supplementation to be effective remains unclear, with periods ranging from 2 months to 10 years across studies.

- Oncology clinical nurse specialists and advanced nurse practitioners are ideally positioned to promote and educate breast cancer patients about VD supplementation.

Background

Cancer rates and costs of treatment continue to rise; it is therefore essential to develop alternative therapies to prevent cancer incidence and treat it in an efficient, yet affordable, manner (Moukayed and Grant, 2017). Growing evidence supports the link between cancer risk and VD deficiency, thus, supplementation could play a role in helping to prevent deficiency and potentially improve cancer incidence, prognosis and outcome (Feldman et al, 2014; Chowdhry et al, 2014).

Vitamin D (VD) is not a vitamin, rather it is the pre-cursor to *calcitriol* (1,25(OH)D3), a steroid hormone that mediates various actions in numerous body tissues (Feldman *et al,* 2014). Serum 25-hydroxyvitamin D (25(OH)D) is the main circulating form of VD, which has a long half-life and is relatively stable, thus, it is the most accurate indicator of VD status (Saw et al, 2014). (See Table 1).

Among the general population, approximately one-billion people worldwide have VD deficiency or insufficiency (Holick, 2011). In the UK, a 50% prevalence of vitamin D insufficiency and 16% deficiency is reported in winter and spring among the white population, with much higher rates of deficiency among South Asians (over 90% being insufficient or deficient in vitamin D) (Hyppönen and Power, 2007).

There appears to be no global consensus of the definition of VD status. The Institute of Medicine (IOM) committee define deficiency as concentrations of 25(OH)D at 20 ng/ml (Ross et al, 2011), compared to a 30 ng/ml cut-point by the Endocrine Society (Holick et al, 2011). However, it is important to note that the IOM definition relates to bone health and not cancer (Feldman et al., 2014), and oncology experts advise that neither of these recommendations can be applied to cancer patients (Wesa and Cassileth, 2017). Nonetheless, the National Comprehensive Cancer Network has

recommended that cancer patients should maintain a level above 30ng/ml for bone-related health (Gralow et al, 2013). More specifically, Grant (2018), in a review of epidemiological studies examining risk of cancer incidence, progression, and mortality, concludes that vitamin D_3 supplementation should aim to raise serum 25(OH)D concentrations to above 100-125 nmol/l (40-50 ng/ml).

VD supplement use plays a crucial role in cancer patients' lives as they are more likely to spend time indoors because of the adverse symptoms accompanying the disease and its treatment, such as cancer-related fatigue (Feldman et al, 2014). In 1980 Garland and Garland (1980) first proposed “the vitamin D hypothesis”, that is, the theory that VD protects against cancer. Their report suggested that mortality of people with colon cancer in the United States (US) were highest in places with the least sunlight and resulted from a lack of VD. Recent studies have begun to expand this theory further, highlighting the potential significance of supplementation in the prevention and management of cancer disease and progression (Teleni et al, 2013).

The latest recommendations from the IOM concerning dietary intake for VD in cancer remains unresolved due to the conflicting nature of the available evidence (Ross et al, 2011). The IOM recommend daily requirements of 600 International Units per day (IU/day) of VD for people under seventy-years of age and 800 IU/day for people aged seventy and over (Ross et al, 2011). Controversially, the Endocrine Society committee suggest doses up to 2,000 IU/day may be necessary for some individuals to maintain sufficient 25(OH)D concentrations, and people with a greater Body Mass Index (BMI) (>30 kg/m^2) require three times the value of those with healthy BMIs (Holick *et al,* 2011). In terms of guidance for practitioners on recommendations around vitamin D supplementation for cancer patients, the task Force Report published by the National Comprehensive Cancer Network has recommended that VD

is supplemented to maintain concentrations above 30ng/ml for bone-related health (Gralow et al, 2013).

Methodology

The aim of review was to summarise the evidence related to VD supplementation in cancer survivorship to guide nurses on the appropriate advice for patients with cancer. A systematic search of studies published from January 1st 2010 to November 20th 2017 pertaining to Vitamin D supplementation in cancer survivors was undertaken in the following databases: PubMed, EMBASE, CINAHL and Scopus. A combination of the following key words was used: “Cancer”, “Oncology”, “Survivor”, “Survivorship”, “Vitamin D” “Vit D”, “Ergocalciferol”, “Cholecalciferol” and “Hypovitaminosis D”. All records of the search (n=264) were imported into Endnote and, following removal of duplicates (n=49), titles and abstracts of all records were screened to determine if they met the following inclusion criteria: Studies including adults or children cancer survivors; studies including cancer patients undergoing treatment; patients taking VD supplementation with or without calcium. Studies investigating VD supplementation in healthy subjects (i.e., pre-cancer diagnosis) or in conjunction with other vitamin supplements or alternative therapies were excluded. Eighteen studies meeting the inclusion criteria were selected. Each study was critiqued to extract a set of relevant data based on a standardised framework for quantitative research (Polit and Beck, 2017) (See Table 2)

Findings

The eighteen studies reviewed were primarily based in the US and seven studies involved breast cancer (BCA) patients. Overall, the reported baseline 25(OH)D

concentrations ranged from 2 ng/ml to 81 ng/ml and a wide range of the patients were recorded as Vitamin D (VD) deficient (2.5% to 89.7%). No consensus on the definition of VD deficiency was evident in the reviewed studies.

In total, 7,214 patients were included in the reviewed studies (Figure 1). The majority of studies investigated the effects of *cholecalciferol* (VD3) rather than *ergocalciferol* (VD2). A meta-analysis of randomised control trials (RCTs) indicated that VD3 is more effective at elevating 25(OH)D concentrations than VD2 (Tripkovic et al, 2012), thus, the choice of supplementation appeared to be justified in these studies.

Vitamin D Supplementation and Breast Cancer

The majority of studies involving BCA were observational. The most recent observational study involving non-metastatic BCA demonstrated that VD supplementation significantly enhanced disease free-survival (DFS), but not overall survival (OS) (Zeichner et al, 2015) (See Table 1). Among the subjects receiving supplementation, 69.2% exhibited a 5-year DFS compared to 48.3% in the non-supplemented group (P=0.02). In the final multivariate model, VD supplementation, regardless of initial dose or level, correlated with significant improvement in DFS (P =0.026). The presence of lymphovascular invasion, larger tumours and a greater number of metastatic lymph nodes were correlated with worse DFS, with a trend toward improved DFS observed in supplemented patients. (95% Confidence Interval (CI), 0.41-1.06) (Zeichner et al, 2015). In this study, while no significance was observed between supplementation and OS, the authors suggested this could be due

a *ceiling effect* given the number of deaths that occurred in the patient population (n= 21) (Zeichner et al, 2015). Moreover, extraneous influencing factors such as Estrogen Receptor Positive (ER+), non-smoker, adjuvant radiation therapy and a lower BMI may have posed a threat to the internal validity of the observed effects on DFS. This points to many factors having an effect on overall survival among breast cancer survivors.

In contrast, an earlier study exploring the impact of high-dose supplementation on palliation and bone turnover in breast cancer patients with bone metastases reported that VD supplementation had a positive effect on pain (Amir et al, 2010). However, significant variations were noted in the number of pain sites between baseline and month four (P= 0.010), with the researchers concluding that adjuvant bisphosphonate therapy (known to improve DFS) may have influenced their findings (Amir et al, 2010). Supplementation had no significant impact on N-telopeptide, the urinary bone reabsorption marker. Mean 25(OH)D levels were deficient at baseline (<30 ng/ml) but were greater than 60 ng/ml by month four (P < 0.001), whereas serum parathyroid hormone (PTH) significantly decreased (P<0.001), confirming the researchers' hypothesis that VD supplementation would rectify secondary hyperparathyroidism (Amir et al, 2010).

Pain was also measured in two prospective observational studies evaluating the relationship between VD supplementation and musculoskeletal outcomes in BCA patients on aromatase inhibitor therapy (Khan et al, 2010; Prieto-Alhambra et al, 2011). The total dose of VD supplemented in the first study (Khan et al, 2010) was nearly four-times higher than the intervention used in the other study (Prieto-Alhambra et al, 2011); yet, both studies demonstrated an improvement in musculoskeletal symptoms in patients that achieved 25(OH)D concentrations greater than 40 ng/ml. Similar concentrations were achieved in a cross-sectional study (Peppone et al, 2011)

using a dose equivalent to that used in Khan et al (2010), with a more significant increase in 25(OH)D levels observed in patients treated with a high-dose intervention (P< 0.01).

Similar 25(OH)D levels achieved beneficial effects in a later study by Prieto-Alhambra et al (2012). In this study, reaching 25(OH)D concentrations greater than 40 ng/ml was associated with 1.7% less bone mineral density (BMD) loss in the lumbar spine region (LS) (P= 0.007 after multivariate adjustment). In the whole cohort, each 10 ng/ml increase in 25(OH)D concentrations was inversely correlated with a 0.5% reduction in bone loss at LS (P<0.001 after multivariate adjustment) (Prieto-Alhambra et al, 2012). After supplementation, VD increments also showed a 0.6% reduction in LS bone loss for every 10 ng/ml increase in 25(OH)D levels (95% CI 0.4-0.8%; P< 0.001). This finding further supports that of Peppone et al (2011), mentioned earlier, which suggested that patients with VD concentrations below 32 ng/ml experienced significantly lower LS-BMD levels when compared to patients with levels above this concentration (P=0.03) (Peppone et al, 2011).

Vitamin D Supplementation and Other Solid Tumour Malignancies

Twelve studies reviewed the effects of VD supplementation in other cancers (with some including breast cancer patients), including two systematic reviews (SRs) (Buttigliero et al, 2011; Teleni et al, 2013). In a study including a heterogeneous cancer patient group, suboptimal 25(OH)D levels were observed in 70% of the cohort (Vashi et al, 2010). After supplementation, prostate cancer subjects achieved the highest mean serum level overall (42.1 ng/ml). The greatest improvement, however, was seen in lung cancer patients who achieved a mean increase of 22.7 ng/ml (Vashi et al,

2010). The lowest increase was observed in colorectal cancer patients (13.2 ng/ml), potentially influenced by the severe gastrointestinal toxicity experienced by these patients (Vashi et al, 2010). Baseline 25(OH)D levels appeared to be a significant determinant for improvement, such that patients with lower 25(OH)D concentrations at baseline experienced greater improvement (P<0.001) (Vashi et al, 2010). However, linear regression analysis revealed that the 1 ng/ml decrease in baseline 25(OH)D with every 0.44 ng/ml increase in concentrations was not statistically significant (95% CI: 0.29-0.60 ng/ml) (Vashi et al, 2010). These findings suggest in practice, greater improvements will be seen in patients with low level of 25(OH)D at baseline.

Prostate cancer patients also showed great improvements in 25(OH)D levels in a more recent study undertaken to determine the safety and efficacy of a daily dose 4000 IU of VD on prostate-specific-antigen (PSA) levels and the rate of progression (Marshall et al, 2012). No significant changes were exhibited in PSA levels (P=0.27), rejecting the researchers' initial hypothesis. However, there was a significant improvement seen in the rate of progression as calculated by the number of positive biopsy cores at study completion relative to baseline. Over half of the cohort experienced a reduction in positive cores and no elevation in Gleason score[1] (Marshall et al, 2012). A significantly smaller percentage of men in the intervention group appeared to experience disease progression when compared to the control group (34% vs. 63%, respectively; P=0.05). Moreover, serum 25(OH)D levels significantly increased with supplementation (P<0.00001) with the mean values reaching 66 ng/ml (Marshall et al, 2012). Positive correlation was observed between lower baseline

[1] Gleason Score: A system of grading prostate cancer tissue based on how it looks under a microscope where a high Gleason score indicates that the cancer tissue is very different from normal and the tumour is more likely to spread.

25(OH)D concentrations and improvements in PTH levels which concurs with the previously mentioned study, suggesting that those with lower baselines respond better to VD supplementation (Vashi et al, 2010). This relationship of VD and PTH levels was further established in a recent observational study involving gastric cancer patients, which reported that patients with severe VD deficiency at baseline tended to have PTH levels in the range of hyperparathyroidism (greater than 70 pg/ml) (P=0.005) (Climent et al, 2017). After twelve months of supplementation, 38 patients achieved 25(OH)D levels above 30 ng/ml, 5 of whom, achieved concentrations greater than 100 ng/ml with no adverse effects (Climent et al, 2017). In tandem with this increase, serum intact PTH (iPTH) levels decreased in most patients and only eleven patients maintained levels higher than 70 ng/ml (28.9%) (Climent et al, 2017).

Another recent observational study also observed a link between severe VD deficiency (<10 ng/ml) and PTH levels in 33% of patients with gastro-entero-pancreatic neuroendocrine neoplasms (NENs), 30% of which also had high PTH levels (Massironi et al, 2017). A significant inverse relationship between 25(OH)D concentrations and DFS (P=0.01, rs= -0.22) was found and, contradictory to the findings of the BCA study mentioned earlier (Zeichner et al, 2015), positive correlation was exhibited between VD supplementation and OS (P=0.0016; P=0.0035 with multivariate adjustment) (Massironi et al, 2017). All supplemented patients achieved 25(OH)D concentrations between 20 and 40 ng/ml, prompting the researchers to conclude that VD supplementation can improve disease progression among patients with gastro-entero-pancreatic neuroendocrine neoplasms (NENs) , and deficient patients could have a more favourable clinical course if they received VD (Massironi *et al,* 2017). However, the study findings should be viewed with some caution, as a large number of patients

underwent curative surgery during the intervention phase which may have influenced the improved OS and DFS outcomes (Massironi et al, 2017).

In contrast, another recent observational study observed significant improvements in DFS (P= 0.035) but not in OS (P= 0.308) in oesophageal cancer patients (Wang et al, 2016). The study found significant improvements in various aspects of patients' quality of life (QOL) after supplementation which remained significant after adjustment for potential confounders. This included *physical functioning* (P= 0.004), *fatigue* (P= 0.03), and *eating habits* (P= 0.019). However, the effects of VD demonstrated in this study on QOL and DFS could not be validated relative to baseline 25(OH)D concentrations as they were not measured. Moreover, significant differences appeared to exist between the demographic characteristics of the population, such as age and smoking status (Wange et al, 2016). Both smoking and age influence BMI, and BMI alters the effects of supplement absorption, with greater outcomes seen in those with lower BMI's (Holick et al, 2011).

Another observational study involving colorectal cancer patients also found a positive association between VD and symptom related QOL (Lewis et al, 2016). However, unlike previously mentioned studies, no statistical significance was evident between VD and DFS or OS (Massironi et al, 2017). Similarly, a recent clinical trial concluded that VD with or without calcium, had no impact on the adjusted risk ratio for colorectal adenoma patients (P=0.99 and P=0.93 respectively; 95% CI) compared with non-supplemented subjects (Baron et al, 2015). This prompted the researchers to suggest that VD supplementation may have a weaker association with adenomas than it does in later stages of cancers. However, as highlighted earlier, lower doses of VD, such as that used by Baron et al (2015), have little impact on the clinical outcomes in cancer survival, thus, a higher-dose may have improved the results (Peppone et al,

2011). However, while higher doses of VD have to been reported as safe, Wesna and Cassileth (2017) caution that most trials have not reported on VD levels above 60 ng/mL and, therefore, the overall risk-benefit of high dose Vitamin D supplementation remains unclear.

A SR including a meta-analysis of three trials aimed to explore the effect of VD supplementation on enhancing PSA response in advanced prostate cancer patients (Buttigliero et al, 2011) and observed no significant improvement PSA response rate, mirroring the results of a previously mentioned study involving prostate cancer patients (Marshall et al, 2012). In contrast, a more recent SR (with no meta-analysis undertaken) assessed the efficacy of VD supplementation in raising the concentration of 25(OH)D (Teleni et al, 2013). Significant increases in 25(OH)D concentrations were associated with doses between 1,943 to 14,286 IU D_3/day and not supplementation below 1,000 IU D_3/day. A decrease in levels was noted in patients supplemented with 600 IU D_3/day, which ensued the researchers conclusion that standard-dose regimens may not be adequate in maintaining, much less correcting 25(OH)D levels in patients undergoing anti-cancer treatments (Khan et al, 2010; Teleni et al, 2013). The findings supported the use of high-dose supplementation to achieve improvements in BMD and musculoskeletal symptoms in BCA (Teleni et al, 2013).

Vitamin D supplementation and Hematologic Malignancy

Three studies reviewed VD supplementation in leukaemia patients. Two studies observed the effects of VD and calcium supplementation on BMD in paediatric acute lymphoblastic leukaemia (ALL) (Kaste et al, 2014; Demisroy et al, 2017) and the third involved chronic lymphocytic leukaemia (CLL) (Kubeczko et al, 2016).

In the earlier of the two ALL studies, no significant changes in mean lumbar spinal bone mineral density (LS-BMD) values or mean LS-BMD *Z-scores*[2] were observed between supplement and placebo groups (P=0.44 and P=0.86, respectively) (Kaste et al, 2014). Although values were of no statistical significance, individuals with Z-scores less than -2 at baseline who received supplementation, appeared to exhibit a greater increase in BMD than those in the placebo group (P=0.15). Moreover, no significant differences were recorded in median 25(OH)D levels between the two groups (24.0 ng/ml each; P=0.83) (Kaste et al, 2014).

In contrast, the second, more recent, study focusing on ALL reported significant decreases in BMD Z-scores for total body, total body less head and lumbar spine (1-4) (L1-L4) between first and second assessments of their supplemented group (P=0.005, 0.005 and P=0.025, respectively) (Demisroy et al, 2017). This study reported a significant increase in median 25(OH)D and calcium concentrations in the supplemented group (P=0.01 and P=0.024, respectively). The researchers clarified that decreases in BMD scores were expected to dramatically increase in the first two years of treatment and gradually increase thereafter and used *historical controls*[3] to compare the BMD Z-scores of supplemented patients with survivors who did not receive supplementation with VD during their treatment (Demisroy et al, 2017). Unlike the studies mentioned previously, this increase in 25(OH)D levels did not correlate with significant decreases in PTH levels (P>0.05).

[2] Z-scores: the number of standard deviations above or below the mean for the patient's age, sex and ethnicity

[3] Patients with the same condition who were treated in the past and are used to control bias on the outcome variable and avoid threats to the internal validity of the study (LoBiondo-Wood & Haber, 2014)

A correlational relationship between 25(OH)D concentration and PTH was, however, observed in all CLL subjects involved in a recent interventional study ($P<0.01$) (Kubeczko et al, 2016). All subjects attained mean 25(OH)D levels of 41 ± 7 ng/ml and normal PTH levels, including those who had secondary hyperparathyroidism.

The research undertaken with leukaemia patients is limited with conflicting findings. However, while more trials are needed, the evidence suggests benefits in the avoidance of vitamin D deficiency in this cohort of patients.

Discussion

The findings strongly suggest that VD supplementation does play a beneficial role in the clinical outcomes of cancer survivorship. This review has highlighted that VD supplementation plays an important role in DFS in a number of cancers, particularly breast. However, in other cancers, the role of VD is less clear, indicating that more research is required to determine whether the results of BCA studies are generalisable to all cancers.

Supplementation also appeared to play a beneficial role in QOL by reducing bone loss, improving musculoskeletal symptoms and restoring PTH levels. The optimal 25(OH)D concentration to achieve these beneficial outcomes was between 30 and 40 ng/ml, with current evidence suggesting that achieving levels greater than 40 ng/ml benefits musculoskeletal pain and bone loss in BCA patients, and concentrations 30 ng/ml and above aid in the restoration of PTH levels in the range of hyperparathyroidism. Future RCTs are needed to discern the most advantageous target concentrations, and the stage at which supplementation is most advantageous.

Several studies supplemented with doses that were 2-3 times greater than the recommendations made by the IOM and Endocrine Society, with a tolerable upper intake of 14,286 IU/day (Peppone et al, 2011). High-doses, when compared to low-doses of supplementation were associated with more positive outcomes. Doses considered “high” ranged from 1,000 to greater than 14,286 IU/day, and were predominantly given to patients with severe deficiency. However, the effects associated with these doses appeared to vary within and between cancer types. Further research is required to establish the optimal high-dose regimen that results in benefits for individual cancers and clinical outcomes. This knowledge could maximize known benefits and avoid both known (hypercalcemia) and potential unknown adverse effects.

It is important to determine the dose necessary to achieve 25(OH)D concentrations that result in reasonable benefit in individual cancers and assure these levels are maintained (Pludowski et al, 2018). Measuring 25(OH)D concentration is the most prudent approach to ensure that patients’ 25(OH)D levels are in the advantageous range (30 to 40 ng/mL). Few studies had values for 25(OH)D from initial diagnosis, thus, the samples used for analyses did not likely represent the true levels at diagnosis. For future studies, measurement of 25(OH)D concentrations prior to subject enrolment, and only including subjects with deficiency, should be a priority.

Another factor to consider when prescribing VD to patients is the risk of non-adherence (Touskova et al, 2016). Electronic monitoring devices (EMDs) may be beneficial when measuring adherence. This system utilises real-time measurement to record each time a patient opens their medication and stores the data for analysis (Williams et al, 2013). Some devices are capable of sending reminders to the patients, thereby enhancing compliance.

Both duration and frequency of supplementation must be considered alongside the patients' likeliness to adhere to the intervention. The period required for supplementation to be effective remains unclear, with included interventions ranging from 2 months to 10 years. In addition, the effectiveness of monthly compared to daily doses of supplementation needs to be investigated through extensive experimental research depending on dose requirements, 25(OH)D levels, cancer type and goal of treatment (i.e., Improved DFS, OS and/or QOL). Large RCTs are needed to monitor vitamin D levels and supplement adjustments to determine specific cancer-related dose requirements (Wesna and Cassileth, 2017). However, until more conclusive evidence is available, the aim should be to avoid vitamin D deficiency among cancer patients.

While long-term RCTs are not currently available to conclusively determine the therapeutic benefits of VD in cancer survivorship, available data is compelling enough to encourage supplementation in breast cancer survivorship to avoid deficiency and improve health. For breast cancer survivors taking aromatase inhibitors, higher doses of vitamin D may help decrease treatment-related side effects (Dowling et al, 2017; Wesna and Cassileth, 2017), and thereby has a positive effect on quality of life in survivorship.

Several RCTs are also currently ongoing and will extend current knowledge by investigating the protective effects of VD supplementation on other cancers, including melanoma (Saw et al, 2014; De Smedt et al, 2017).

Oncology clinical nurse specialists and advanced nurse practitioners are ideally positioned to promote and educate breast cancer patients about VD supplementation

from diagnosis through to survivorship (Meade et al, 2017; Dowling et al, 2017). Nurse-led care results in consistent communication between nurses and their patients and can improve their knowledge about their disease with the aim of reassuring them that they are receiving high-quality, evidence-based, patient-centred care. This can be achieved through the development of survivorship care-planning which encourages the continuity of care and the provision of consistent written and verbal information as required by the patient (Meade et al, 2017).

Education regarding the importance of VD supplementation also needs to be emphasised to general nursing staff and other healthcare professionals. The use of evidence-based information to support, as well as define, best practices ensures that care is based on current knowledge, patient preference and clinical expertise (Stevens, 2013). Nurses are powerful, influencing forces within the interdisciplinary team and inspire the future workforce to provide care based on the most recent available evidence (Stevens, 2013).

In conclusion, the safety and efficacy of VD supplementation in cancer survivorship has been demonstrated throughout the studies reviewed, as well as the easy availability of this multi-purpose supplement. This suggests that VD supplementation can, and should, be recommended in cancer survivorship, even while we await the data of future RCTs, with the aim being to avoid vitamin D deficiency among cancer patients.

Conflict of interest

None.

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