Review Article

Future Of Vitamin D In Cancer: Where Are We Today?

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ABSTRACT:
Vitamin D, an essential nutrient, is a precursor of a potent steroid hormone that regulates a broad spectrum of physiological processes. Vitamin D sufficiency is accessory with protection against malignancy in a number of tissues clinically, and a powerful body of evidence from animal and cell culture studies supports this protective role [22]. Numerous epidemiological, preclinical and cellular researches have revealed that vitamin D levels have an inverse relation with cancer mortality, while others have considered it a inherent risk factor [74]. There is increasing evidence linking the incidence and prognosis of certain cancers to low serum25 (OH) D3 levels. This article is a descriptive review of recent epidemiological findings regarding, serum 25-hydroxyvitamin D [25(OH)D] concentrations, vitamin D supplementation, and genetic variations in 25(OH)D concentration for incidence, progression, survival, and mortality rates of overall and breast, lung, colorectal, and Prostatic adenocarcinoma which include geographical ecological studies, observational studies associated with oral vitamin D intake and serum 25-Hydroxyl vitamin D [25(OH)D] concentrations, randomized Controlled trials (RCTs) of cholecalciferol supplementation, studies of genetic allele polymorphisms affecting 25(OH)D concentrations and mechanisms [75].Thus, all kinds of studies should be considered when assessing how vitamin D affects cancer. Therefore, using large observational claims, database, with real world unstructured treatment patterns, we qualitatively reviewed the epidemiological evidence within the oncology literature on the association between usage of vitamin D supplement and minimization of cancer risk with suggestions on how the evidence may be strengthened

Keywords— 25-Hydroxyl vitamin D, cancer, malignancy, epidemiology

I. INTRODUCTION

Cancer is a malignant disease characterized by rampant growth of body's cells which may escalate to other body parts. Vitamin D is a steroid hormone that has various physiologic effects in several tissue sand it is transformed through two hydroxylation reactions to its most active form (1,25-dihydroxyvitamin D) [85].The first observation of an inverse correlation between sunlight exposure and overall cancer incidence and mortality in North America was published almost 80 years ago. Thereafter, in 1980 and 1992, the initial epidemiological studies linking less sunlight subjection and high risk of colon and prostate cancers were proclaimed. Edward Gorham and colleagues carried out cohort and nested studies, including the first study that found an association of a serum vitamin D compound with reduced cancer risk [72].**William B. Grant** then meted out numerous ecologic studies that extended the vitamin D-cancer theory to other cancers [86].Several lines of population-based studies revealed an inverse correlation between serum 25-hydroxyvitamin D (25(OH)D) levels and soaring risk of gastric, colon, prostrate, breast, and other cancers. Moreover, there are strong evidences from several cell culture and animal studies to support the anti-tumorgenic effects of vitamin D[72].It is now becoming evident that deficiency of calciferol can contribute to the growth and progression of many forms of cancers, and thus maintenance of sufficient serum vitamin D levels might be beneficial for prevention and treatment of cancer.

II. DISCUSSION

Vitamin D has multiple anti-carcinogenic roles in cancer that are well-described at the molecular level and culminate in decreasing cancer cell proliferation and invasion potential and promoting apoptosis or cancer cell differentiation.

Vitamin D, Past, Present, Future

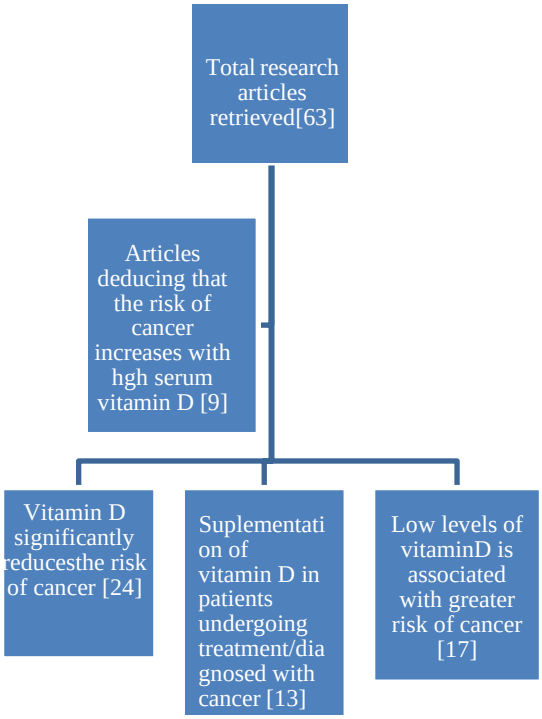
All In the last decade, abundance, as well as the allotment for vitamin D testing heightened substantially globally. The explosion of vitamin D utilization is result of many promising observational studies that have associated vitamin D concentration with health benefits in cardiovascular diseases, cancer, diabetes, fertility, and many others. The number of published papers on vitamin D, as well as diseases associated with its deficiency, upsurges daily [73]. Over the last 30 years, vitamin D metabolites have received, growing attention for their potential to prevent and/or retard cancer development. Laboratory studies have shown pleiotropic anti-cancer effects of the hormonal form of vitamin D, 1,25-dihydroxycholecalciferol (1,25(OH)2D), including control of cell differentiation, proliferation, and metastasis. Inter-relation between vitamin D and the innate history of cancer also have been detected in epidemiologic studies, which often anticipated the laboratory studies. Most sero-epidemiological studies have used measurements of the

pro- hormonal form of vitamin D, 25-hydroxyvitamin D (25- OHD), the accepted marker of an individual's vitamin D status.[11]

Vitamin D insufficiency has been categorized to be linked with an array of cancers, including breast cancer, colorectal cancer, multiple myeloma, and prostate cancer. Certain studies have shown vitamin D levels to have an inverse relation with cancer mortality, while others have considered it a potential risk factor. Elevated vitamin D concentrations are related with a 3- fold declined risk for pancreatic cancer (highest vs. lowest quintile, >26.2 vs. <12.8 mg/ml).[74]

Meta-analysis of prospective cohort studies suggest that vitamin D deficiency is associated with an increased risk of multiple types of cancer, including all cancers, colorectal cancer, bladder cancer, head and neck cancer, liver cancer and also death due to cancer. These associations have been explained by in vitro and in vivo effects of the active form of vitamin D (1,25 OH2 (dihydroxy) vitamin D), which promotes cellular differentiation, decreases cancer cell growth, stimulates cell death (apoptosis) and reduces angiogenesis.[1]

Despite the biological plausibility that vitamin D has an anticancer role, the literature on the relationship between cancer and 25(OH)D concentrations remains more controversial. The research findings evaluating the role of vitamin D as a possible preventive agent against cancer vary, and the optimal serum 25(OH)D concentration for cancer and other diseases prevention is still unknown. Overall, the results from a number of cell line experiments, mouse studies, ecological studies, observational studies and some clinical trials indicate that vitamin D has anticancer activity.[49]



Studies on serum vitamin D in Breast Cancer

Table I describes studies on serum vitamin D in patients with breast cancer. The studies are organized sequentially by the year of publication.

Imtiaz et al [65]carried out a case control study of Ninety breast cancer patients and equal number of age-matched healthy females for a period of 6 months to establish serum vitamin D levels in breast cancer patients and to evaluate its risk interconnection with grade and phase of the tumor. They notably found that the mean serum vitamin D level in the breast cancer patients was 9.3 ng/ml and in the control, group was 14.9 ng/ml (P value <0.001). Vitamin D deficiency was seen in 95.6% (86) breast cancer patients and in 77% (69) of the control group (P value <0.001). Among the breast cancer patients, the tumor characteristics did not show any significant associations with serum levels of vitamin D. Premenopausal breast cancer females had a mean serum vitamin D level of 10.5 ng/ml and postmenopausal females had a mean value of 13.5ng/ml (P value 0.015). Low BMD did not correlate significantly with vitamin D deficiency (P value 0.787).

Shaukat et al [52]performed a case control study which included 94 female patients (42 cases and 52 controls). They used the ELISA technique to study serum25-(OH) 2D levels in ng/ml and Vitamin D deficiency was considered at serum level less than 20ng/ml. They observed that Serum Vitamin D levels were significantly lower in cases (85.7%) than controls (55.8%) and the unadjusted and adjusted ORs for breast cancer in cases and controls showed a statistically significantly increased risk of breast cancer with low vitamin D concentration (p value0.003). They concluded that vitamin D deficiency was associated with risk of breast cancer.

O'Brien et al[71] studied the relationships between serum vitamin D, DNA methylation, and breast cancer using a case-cohort sample (1070 cases, 1277 in sub cohort) of non-Hispanic white women. They notably found that Of the CpGs in vitamin D-related genes, cg21201924 (RXRA) had the lowest p value for association with25 (OH)D ($p = 0.0004$). Twenty-two other candidates CpGs were associated with 25(OH)D ($p < 0.05$; RXRA, NADSYN1/DHCR7, GC, or CYP27B1). They also observed an interaction between

25(OH)D and methylation at cg21201924 in relation to breast cancer risk (ratio of hazard ratios = 1.22, 95% confidence interval 1.10–1.34; $p = 7 \times 10{-}5$), indicating a larger methylation-breast cancer hazard ratio in those with high serum 25(OH)D concentrations. Their findings suggested that 25(OH)D concentrations were associated with DNA methylation of CpGs in several vitamin D-related genes, with potential links to immune function-related genes and methylation of CpGs in vitamin D-

related genes may interact with 25(OH)D to affect the risk of breast cancer

Ismail et al [58] conducted a prospective study which included 50 Egyptian women with primary invasive, non-metastatic breast cancer. The serum level of 25(OH) D was measured by ELISA at diagnosis, before any cancer treatment. Vitamin D deficiency was defined as 25(OH) D<20 ng/ml. Patients were followed up for a median of 30 months (range: 18-48). They detected that the median level of 25(OH)D was 29.0 ng/mL (range: 10.0-55.0 ng/mL). Fifteen patients (30%) had vitamin D deficiency, which was positively associated with larger tumor size ($p < 0.001$), higher grade ($p = 0.014$), advanced stage ($p = 0.001$), lymph node positivity ($p = 0.012$), and HER2/Neu receptor expression ($p = 0.002$). It was also linked with worse overall survival (OS) and disease-free survival (DFS) ($p = 0.026$, and $p = 0.004$, respectively). On multivariate analysis, DFS was independently affected by vitamin D deficiency with an HR of 2.8 (95% CI: 1.6-7.0, $p = 0.022$) and advanced stage, i.e., stage II had worse survival compared to stage I with an HR of 4.8 (95%CI: 1.1-21.7, $p = 0.042$). They culminated that Vitamin D deficiency had a negative effect on overall and disease-free survival in breast cancer cases, being related to tumor size, stage, grade, nodal status and HER2/neu receptor expression.

They observed that 25OHD and 27HC levels were inversely correlated ($p = 7.0E{-}3$), Excluding two statistical outliers. Shamsi et al[49] examined the prevalence of vitamin D inadequacy and breast cancer in Pakistani women and observed that compared to patients with sufficient serum vitamin D (>30 ng/ml), women with serum vitamin D deficiency (<20ng/ml), had a higher risk of breast cancer (OR = 1.65, 95%CI: 1.10,2.50).

They also concluded that Women with history of vitamin D supplementation one year prior to enrollment, had significant protective effect against breast cancer (OR = 0.32, 95% CI: 0.24, 0.43). Their research implied that Serum vitamin D deficiency was associated with increased risk of breast cancer, while vitamin D supplementation was associated with decreased risk of breast cancer.

Going et al[70] measured27HC, 25-hydroxyvitamin D 25OHD), and 1,25(OH)2Din sera of 29 breast cancer patients before and after supplementation with low-dose (400 IU/day) or high-dose (10,000 IU/day) vitamin D in the interval between biopsy and surgery. They perceived a significant increase ($p = 4.3E{-}5$) in 25OHD and a decrease ($p = 1.7E{-}1$) in 27HC in high-dose versus low-dose vitamin D subjects.

Crew et al [59] reported that after a year of vitamin D3 20,000 IU/week in premenopausal women at high-risk of breast cancer, changes in mammographic density (MD) at 12 and 24 months were small and did not differ significantly between the active and placebo arms. Notably, compared to standard-dose vitamin D alone, the addition of vitamin D3 20,000 IU/week led to a significant increase in serum 25(OH)D, the main circulating form, and serum 1,25(OH)D, the activated form of vitamin D. There were also non-significant decreases in serum IGF-1 and IGFBP-3 at 12 months with vitamin D supplementation, which correlated with MD at 12 months. Cholecalciferol at a dose of 20,000 IU/week for a year was well-tolerated. Their studies suggested that there is insufficient evidence to support the use of vitamin D supplementation for breast cancer risk reduction among high-risk premenopausal women.

Table I: Studies on Serum Vitamin D in Breast cancer

First author, year, place (ref.)	Study design, Sample size	CANCER TYPE	AIM OF THE STUDY	RESULT OF THE STUDY	CONCLUSIONS
Noureen Shaukat, 2017, Pakistan (15)	A case control study. 42 cases and 52 controls	Breast	To determine the association between vitamin D deficiency and breast cancer.	They observed that Serum Vitamin D levels were significantly lower in cases (85.7%) than controls (55.8%) and the unadjusted and adjusted ORs for breast cancer in cases and controls showed a statistically significantly increased risk of breast cancer with low vitamin D concentration (p value0.003).	Vitamin D deficiency was associated with risk of breast cancer.
O'Brien, 2018, USA(64)	Cast control-cohort 1070 cases, 1277 in sub cohort.	Breast	To further investigate a possible link between vitamin D and DNA methylation.	An interaction was observed between 25(OH)D and methylation at cg21201924 in relation to breast cancer risk (ratio of hazard ratios = 1.22, 95% confidence interval 1.10–1.34; $p = 7 \times 10{-}5$), indicating a larger methylation-breast cancer hazard ratio in those with high serum 25(OH)D concentrations.	25(OH)D concentrations were associated with DNA methylation of CpGs in several vitamin D-related genes, with potential links to immune function-related genes. Methylation of CpGs in vitamin D-related genes may interact with 25(OH)D to affect the risk of breast cancer.

First author, year, place (ref.)	Study design, Sample size	CANCER TYPE	AIM OF THE STUDY	RESULT OF THE STUDY	CONCLUSIONS
Abeer Ismail, 2018, Egypt (35)	A prospective study, 50 women	Breast	To determine the frequency and prognostic significance of vitamin D deficiency in Egyptian women with breast cancer	The median level of 25(OH)D was 29.0 ng/mL (range: 10.0-55.0 ng/mL). Fifteen patients (30%) had vitamin D deficiency, which was positively associated with larger tumor size ($p < 0.001$), higher grade ($p = 0.014$), advanced stage ($p = 0.001$), lymph node positivity ($p = 0.012$), and HER2/Neu receptor expression ($p = 0.002$). It was also linked with worse overall survival (OS) and disease-free survival (DFS) ($p = 0.026$, and $p = 0.004$, respectively).	Vitamin D deficiency had a negative effect on overall and disease-free survival in our breast cancer cases, being related to tumor size, stage, grade, nodal status and HER2/neu receptor expression.
Catherine C. Going, 2020, USA (28)	A pilot breast cancer trial. 29 breast cancer patients.	Breast	To correlate if Vitamin D supplementation decreases serum 27-hydroxycholesterol.	A significant increase ($p=4.3E-5$) in 25OHD and a decrease ($p =1.7E-1$) in 27HC was observed in high-dose versus low-dose vitamin D subjects. Excluding two statistical outliers, 25OHD and 27HC levels were inversely correlated ($p = 7.0E-3$).	Vitamin D supplementation can decrease circulating 27HC of breast cancer patients, likely by CYP27A1 inhibition.

First author, year, place (ref.)	Study design, Sample size	CANCER TYPE	AIM OF THE STUDY	RESULT OF THE STUDY	CONCLUSIONS
Shamsi, 2020, Pakistan (105)	A multi-center case control study. 411 newly diagnosed,784 control.	Breast	To study the association of vitamin D with breast cancer among women in Karachi, Pakistan.	Compared to patients with sufficient serum vitamin D (>30 ng/ml), women with serum vitamin D deficiency (<20ng/ml), had a higher risk of breast cancer (OR = 1.65, 95%CI: 1.10,2.50). Women with history of vitamin D supplementation one year prior to enrollment, had significant protective effect against breast cancer (OR = 0.32, 95% CI: 0.24, 0.43).	Serum vitamin D deficiency was associated with increased risk of breast cancer, while vitamin D supplementation was associated with decreased risk of breast cancer.
Katherine D. Crew, 2020, USA (50)	Randomized Double-Blind Placebo Controlled Biomarker Modulation Study. 200 post-menopausal women.	Breast	To evaluate the effect of vitamin D supplementation on MD in premenopausal women at high risk for breast cancer, evaluate the effects of vitamin D 20,000 IU/week on blood-based biomarkers associated with breast cancer risk (IGF-1, IGFBP-3) and safety.	Comparing the active and placebo groups at 12 months, MD changes were small and did not significantly differ. Mean MD changes at 12 and 24 months were −0.3% and −1.2%, respectively, in the active arm and +1.5% and +1.6% with placebo ($p>0.05$), MD was positively correlated with serum IGF-1 and IGF-1/IGFBP-3 ($p<0.01$).	There is insufficient evidence to support the use of vitamin D supplementation for breast cancer risk reduction among high-risk premenopausal women.

Studies on serum vitamin D in Lung Cancer

Table II describes studies on serum vitamin D in patients with lung cancer. The studies are organized sequentially by the year of publication.

Hoffer et al [30]performed single arm open-label pharmacokinetic trial, where outpatients with advanced lung cancer consumed 20,000 IU vitamin D daily with the largest meal of the day for 2 weeks followed by 10,000 IU per day for another week. Plasma concentrations of 25-hydroxyvitamin D [25(OH)D], parathyroid hormone, calcium, vitamin C and C-reactive protein were analysed on code days 0, 14 and 21, and serum vitamin D binding protein (VDBP) concentrations on days 0 and 21. Of the 91 patients enrolled in the study, 85 % had hypovitaminosis D and 41 % had hypovitaminosis C e. Final plasma 25(OH)D concentrations were subnormal (<75 nmol/L) for 13 % of the patients

and sub-target (<120 nmol/L) for 44
% of them. In most cases, subnormal and sub-target These results suggest that a loading dose of 30,000 IU per day for 14 days would be safe and effective for patients who are obese or at risk of severe hypovitaminosis D. The preliminary nature of the study design, and the failure to achieve target 25(OH)D concentrations for a large proportion of the patients, do not allow any firm conclusion about the clinical effects of correcting hypovitaminosis D in this patient population. Nevertheless, no evidence was obtained that partial correction of hypovitaminosis D greatly improved mood, reduced distress or relieved cancer-related symptoms.

Feng et al [32]conducted meta-analysis based on 17 prospective cohort studies, with 138,858 participants with 4368 incident cases, this meta-analysis provides the most up-to-date epidemiological evidence supporting higher circulating 25- hydroxyvitamin D is helpful for lung cancer. They performed a dose–response analysis which revealed that increasing 10 nmol/L dose of circulating 25-hydroxyvitamin D was associated with an 8% reduction in the risk of lung cancer risk and a 7% reduction in the risk of lung cancer mortality. They deduced that their findings underscore the notion that higher vitamin D was significantly associated with lung cancer decrement.

Table II: Studies on Serum Vitamin D in Lung cancer

First author, year, place (ref.)	Study design, Sample size	CANCER TYPE	AIM OF THE STUDY	RESULT OF THE STUDY	CONCLUSIONS
L. John Hoffer, 2016, Canada (75)	A single arm open-label pharmacokinetic trial. 91 patients.	Lung	To assess appropriate vitamin D loading regimen for patients with advanced lung cancer.	The vitamin D load increased the average plasma 25(OH)D concentration to 116 ± 34 nmol/L (mean ± SD); the median concentration was 122 nmol/L (interquartile range103–134).	These results suggest that a loading dose of 30,000 IU per day for 14 days would be safe and effective for patients who are obese or at risk of severe hypovitaminosis D.
Qianqian Feng, 2017, China (38)	A dose–response meta-analysis of prospective cohort studies. 138,858 participants with 4368 incident cases.	Lung	To clarify and quantitatively assess the correlation between circulating 25-hydroxyvitamin D and lung cancer.	Higher circulating 25hydroxyvitamin D significantly decreased risk of lung cancer (relevant risk [RR]:0.84;95% confidence interval (CI): 0.74–0.95; P=.006.	The findings underscore the notion that higher vitamin D was significantly associated with lung cancer decrement.
Tadashi Akiba, 2018, Japan (30)	A Randomized, Double-Blind, Placebo-Controlled Trial. 155 patients.	Lung	To examine whether vitamin D supplementation can improve the prognosis of patients with non-small cell lung cancer.	The vitamin D group showed significantly better 5-year RFS (86% vs. 50%, P =0.04) and OS (91% vs. 48%, P = 0.02) than the placebo group. Relapse and death occurred in 40 (28%) and 24 (17%) patients, respectively.	In patients with NSCLC, vitamin D supplementation may improve survival of patients with early-stage lung adenocarcinoma with lower 25(OH)D levels.

Akiba et al [43]in a randomized, double-blind, placebo-controlled trial in patients with NSCLC found that, (1) vitamin D supplementation did not improve RFS and OS in the total study population, (2) patients with high 25(OH)D (20 ng/mL) before taking the supplement showed better OS than those with low 25(OH)D (<20 ng/mL), (3) In restricting the analysis to the subgroup with early-stage adenocarcinoma with low 25(OH)D, the vitamin D group showed significantly better 5-year RFS and OS than the placebo group, (4) Among the examined polymorphisms, 5-year RFS and OS were better in patients with DBP1 TT than in those with TG/GG genotypes, as well as in patients with CDX2 AA/AG than with GG genotypes, both of which remained significant even after adjustment by stage, adenocarcinoma, low 25(OH)D, and vitamin D supplementation. Through this they inferred that in patients with NSCLC, vitamin D supplementation

may improve survival of patients with early-stage lung adenocarcinoma with lower25(OH)D levels.

Studies on serum vitamin D in Colorectal and Prostate Cancer

Table III describes studies on serum vitamin D in patients with colorectal cancer (CRC) and prostate cancer. The studies are organized sequentially by the year of publication.

Wagner et al [18] executed a Double-blind randomized clinical trial which consisted of 66 subjects out of which, 63 completed the dosing protocol. They evaluated vitamin D metabolite levels and Ki67 labeling in surgical prostate tissue. Preventive measures, PTH, and prostate-specific antigen (PSA) were also evaluated. They noted that Prostate tissue and serum levels of vitamin D metabolites, including calcitriol, multiplied dose dependently (P < .03) and were substantially advanced in the 40 000-IU/d batch relative to each other dose group (P < .03). Prostate vitamin D metabolites corresponded productively with serum levels (P <.0001). Ki67 measures did not differ significantly among vitamin D dose groups. However, cross-sectional analysis indicated that the calcitriol level attained in prostate was inversely associated with Ki67 intensity and Ki67 (3+) percent positive nuclei in prostate cancer and benign tissue (*P* <.05). Safety measures did not change adversely with dosing. Compared with the 400-IU/d group, serum PTH and PSA were lower in the combined higher- dose groups at the end of the study (*P* <.02). they concluded that Oral vitamin D3 raised prostate calcitriol levels (level 1 evidence) and modestly lowered both PSA and PTH. Although Ki67 expression did not differ among dose groups, its levels correlated inversely with prostate calcitriol.

Baron et al [48] recruited patients with recently diagnosed adenomas and no known colorectal polyps remaining after complete colonoscopy. They randomly assigned 2259 participants to receive daily vitamin D3 (1000 IU), calcium as carbonate (1200 mg), both, or neither in a partial 2×2 factorial design. They notably discovered that participants who were randomly assigned to receive vitamin D had a mean net increase in serum 25-hydroxyvitamin D levels of 7.83 ng per milliliter, relative to participants given placebo. Overall, 43% of participants had one or more adenomas diagnosed during follow-up. The adjusted risk ratios for recurrent adenomas were 0.99 (95% confidence interval [CI], 0.89 to 1.09) with vitamin D versus no vitamin D, 0.95 (95% CI, 0.85 to 1.06) with calcium versus no calcium, and 0.93 (95% CI, 0.80 to 1.08) with both agents versus neither agent. They concluded that Daily supplementation with vitamin D3 (1000 IU), calcium (1200 mg), or both after removal of colorectal adenomas did not significantly reduce the risk of recurrent colorectal adenomas over a period of 3 to 5 years.

Santaland et al [19] performed a retrospective, cross-sectional, observational study to evaluate the relationship between prostate cancer and vitamin D levels and reduce the risk of the disease. They observed that the percentage of subjects with prostate cancer with vitamin D levels <75 nmol/L (1.6%) was significantly less than subjects with vitamin D levels ≥75 nmol/L (2.2%) (0.74; 95% CI = 0.58–0.93, p = 0.0103).

Wesselink et al[45] carried out a prospective cohort study which included 1733 colorectal cancer patients. They detected that After adjustment for other demographic and lifestyle factors 25(OH) D3 levels decreased 6.7 nmol/L (95 %CI -9.8; -3.8) more in patients receiving chemotherapy compared to patients who underwent surgery. They hypothesized that Vitamin D supplement use and treatment appear to be important determinants of 25(OH)D3 levels during the first six months after CRC diagnosis, although the difference in 25(OH)D3 levels was minor.

Table III: Studies on serum vitamin D in Colorectal and Prostate Cancer

First author, year, place (ref.)	Study design, Sample size	CANCER TYPE	AIM OF THE STUDY	RESULT OF THE STUDY	CONCLUSIONS
John A. Baron, 2015, USA(26)	A randomized, double-blind, placebo-controlled trial. 2813 participants	Colorectal	To study the comprehensive potential of higher intake and serum levels of vitamin D and calcium to reduce the risk of colorectal neoplasia.	The adjusted risk ratios for recurrent adenomas were 0.99 (95% confidence interval [CI], 0.89 to 1.09) with vitamin D versus no vitamin D, 0.95 (95% CI, 0.85 to 1.06) with calcium versus no calcium, and 0.93 (95% CI, 0.80 to 1.08) with both agents versus neither agent.	Daily supplementation with vitamin D3 (1000 IU), calcium (1200 mg), or both after removal of colorectal adenomas did not significantly reduce the risk of recurrent colorectal adenomas over a period of 3 to 5 years.
Marcus Stanaland, 2017, USA (27)	Retrospective, cross-sectional, observational study.	Prostrate	To evaluate the relationship between prostate cancer and vitamin D levels and reduce the risk of the disease.	The percentage of subjects with prostate cancer with vitamin D levels <75 nmol/L (1.6%) was significantly less than subjects with vitamin D levels ≥75 nmol/L (2.2%) (0.74; 95% CI = 0.58–0.93, p = 0.0103).	Among the documented risk factors for prostate cancer from the available data, age, military service, and race group were significantly associated with prostate cancer diagnosis.
E.Wesselink, 2020, Netherlands(47)	Prospective cohort study, 1733 CRC patients.	Colorectal	To investigate which clinical characteristics in conjunction with demographic and lifestyle factors, were associated with 25(OH)D3 levels at diagnosis and six months later.	After adjustment for other demographic and lifestyle factors 25(OH) D3 levels decreased 6.7 nmol/L (95 %CI -9.8; -3.8) more in patients receiving chemotherapy compared to patients who underwent surgery only.	Vitamin D supplement use and treatment appear to be important determinants of 25(OH)D3levels during the first six months after CRC diagnosis, although the difference in 25(OH)D3 levels was minor.

Studies on serum vitamin D in Multi-site Cancer.

Table IV describes studies on serum vitamin D in patients with other as well as multiple cancer sites. The studies are organized sequentially by the year of publication.

J-B Wang [13]performed a nested case–control study in the Lin Xian Nutrition Intervention Trials on participants developing incident liver cancer or dying from chronic liver disease over 22 years of follow-up. Standard serum 25(OH) vitamin D was analysed in 226 incident liver cancer cases, 282 incurable liver disease deaths and 1063 age-, sex- and trial-matched controls. The mean serum vitamin D level in controls was inadequate (20 nmol l–1). Compared with the lowest quartile, subjects in the fourth quartile had lower risk of chronic liver disease death (OR ¼ 0.34, 95% CI ¼ 0.21–0.55). Nonetheless, they interpreted that in a low vitamin D population, higher serum 25(OH) vitamin D concentrations were associated with significantly lower risk of chronic liver disease deaths, and among those with higher serum calcium, incident liver cancer.

Trude Eid Robsahm et al [11]investigated association of serum 25-hydroxyvitamin D (25-OHD) levels with cancer death, using repeated measurements of serum 25-OHD. Pre- diagnostic serum specimens were assorted in population health inspections in Norway (1973– 2004). individuals who thereafter developed cancer (1984– 2004) gave a second serum specimen at the time of cancer diagnosis. Reiterate samples existed from 37 colon cancers, 124 lymphomas, 193 lung cancers and 202 breast cancers. Serum 25-OHD was measured via competitive radioimmunoassay the median 25-OHD levels were 63.3 and 62.5 nmol/L, respectively. During follow-up, 313 cancer deaths occurred. Compared to low pre-diagnostic 25-OHD levels (<46 nmol/L), higher levels (≥46 nmol/L) had significantly lower HRs (39– 54%) of case fatality. Donors who had both samples at high (≥62 nmol/L) levels had 59% lower HR of case fatality, compared to those for whom both samples were at low levels (<46 nmol/L). Furthermore, versus a decline in serum 25-OHD (Median −22.4 nmol/L) from pre- diagnostic to diagnostic samples, a rise (median22.3 nmol/L) was associated with lower case fatality (HR 0.57, 95% CI 0.43−0.75). Their study demonstrates that 25-OHD levels <46 nmol/L, both several years prior to and at the time of cancer diagnosis, were associated with higher case fatality. They further deduced that lower hazards of case fatality in cases with rise in serum 25-OHD toward diagnosis, when the pre-diagnostic sample was collected ≥10 years prior to the diagnosis.

Fie Juhl Vojdeman et al [25] examined the association between serum levels of vitamin D and cancer incidence in the Capital Region of Denmark. The study population of 217,244 individuals had a median level of vitamin D of 46 nmol/L (IQR 27–67 nmol/L), a median age of 48.8 years (IQR 33.5–64.1 years), female predominance (65.3%), and a low comorbidity burden (Charlson Comorbidity Index of 0 in 79.5%) with pulmonary disease being the most frequent comorbidity. A total of 18,359 individuals were diagnosed with an incident cancer (8.5% of the population) during the follow-up period. Non-melanoma skin cancer (N = 5045) was the most frequent incident cancer followed by breast cancer (N = 2167), lung cancer (N = 1707), prostate cancer (N = 1470), and colon recto sigmoidal cancers (N = 1108) No associations were found between increments of 10 nmol/L vitamin D and incidence of breast, colorectal, urinary, ovary or corpus uteri cancer. However, higher levels of vitamin D were associated with higher incidence of non-melanoma (HR 1.09 [1.09–1.1]) and melanoma skin cancer (HR 1.1 [1.08–1.13]) as well as prostate (HR 1.05 [1.03–1.07]) and hematological cancers (HR 1.03 [1.01–1.06]), but with lower incidence of lung cancer (HR 0.95 [0.93– 0.97]). The median level of vitamin D differed depending on cancer type ranging from 47 nmol/L in individuals developing an incident lung or rectum cancer to 58 nmol/L in individuals developing a non-melanoma skin cancer. Their study concluded that vitamin D levels are not associated with the incidence of several major cancers such as breast, urinary and colon-recto sigmoidal cancers in a population from primary care in Denmark, but higher vitamin D levels are associated with a higher incidence of skin, prostate, hematological cancers, and non-Hodgkin lymphomas solely as well as a lower incidence of lung cancer. These results should be interpreted in the light of the representativeness of the cohort as well as the known limitation of registry studies in lack of information on potential confounding factors.

Acikgoz et al [9]carried out a nested case control to analyze the effect of serum 25- hydroxyvitamin D (25(OH)D) level on lung, breast, colorectal and prostate cancers in people aged 30+ years, they interpreted Serum 25(OH)D levels did not show a significant association with breast, colorectal and prostate cancers. There was an inverse association between 25(OH)D level and lung cancer risk, where the OR values for the first, second and third quartiles, compared with the fourth quartile (1.00), were 2.92 (CI: 0.82–10.35), 3.76 (CI: 1.14–12.37) and 3.55 (CI: 1.04– 12.08) respectively. Hence, they concluded that low 25(OH)D levels were associated with a greater than threefold increased risk of lung cancer;no

Table IV: Studies on serum vitamin D in Multi-site Cancer.

First author, year, place (ref.)	Study design, Sample size	CANCER TYPE	AIM OF THE STUDY	RESULT OF THE STUDY	CONCLUSIONS
J-B Wang, 2013, China (38)	A nested case–control study. 1063 subjects.	Multi-site cancer	To examine the association between serum 25(OH) vitamin D concentrations and subsequent risk of primary liver cancer incidence and chronic liver disease mortality	The median serum vitamin D level in controls was low (20 nmol l–1). Compared with the lowest quartile, subjects in the fourth quartile had lower risk of chronic liver disease death (OR¼0.34, 95% CI¼0.21–0.55).	In a low vitamin D population, higher serum 25(OH) vitamin D concentrations were associated with significantly lower risk of chronic liver disease deaths.
Trude Eid Robsahm, 2019, USA (3)	Prospective cohort studies. 556 cases.	Multi-site cancer	To investigate the association b/w Circulating 25-OHD and cancer mortality using repeated measurements of serum 25-OHD.	The median time between pre-diagnostic and diagnostic samples was 14.4 years. The median 25-OHD levels were 63.3 and 62.5 nmol/L, respectively. During follow-up, 313 cancer deaths occurred. Compared to low pre-diagnostic 25-OHD levels (<46 nmol/L), higher levels (≥46 nmol/L) had significantly lower HRs (39–54%) of case fatality.	The results suggest a causal relationship between vitamin D and cancer case fatality.

cancer.

First author, year, place (ref.)	Study design, Sample size	CANCER TYPE	AIM OF THE STUDY	RESULT OF THE STUDY	CONCLUSIONS
Fie JuhlVoideman, 2019, Denmark (34)	A population-based study. 217,244 individuals	Multi-site cancer	To examine the association between serum levels of vitamin D and cancer incidence.	No associations were found between increments of 10 nmol/L vitamin D and incidence of breast, colorectal, urinary, ovary or corpus uteri cancer. However, higher levels of vitamin D were associated with higher incidence of non-melanoma (HR 1.09 [1.09–1.1]) and melanoma skin cancer (HR 1.1 [1.08–1.13]) as well as prostate (HR 1.05 [1.03–1.07]) and haematological cancers (HR 1.03 [1.01–1.06]), but with lower incidence of lung cancer (HR 0.95 [0.93–0.97]).	Their study concluded that vitamin D levels are not associated with the incidence of several major cancers such as breast, urinary, and colon-recto sigmoidal cancers in a population from primary care in Denmark, but higher vitamin D levels are associated with a higher incidence of skin, prostate, haematological cancers, and non-Hodgkin lymphomas solely as well as a lower incidence of lung cancer.
Ayla Acikgoz, 2020, Turkey (46)	A nested case–control study. 606 persons (179 cases and 427 controls)	Multi-site cancer	To investigate prospectively the effect of serum 25 hydroxyvitamin D (25(OH)D) level on lung, breast, colorectal and prostate cancers in people aged 30+ years.	Serum 25(OH)D levels did not show a significant association with breast, colorectal and prostate cancers. There was an inverse association between 25(OH)D level and lung cancer risk, where the OR values for the first, second and third quartiles, compared with the fourth quartile (1.00), were 2.92 (CI: 0.82–10.35), 3.76 (CI: 1.14–12.37) and 3.55 (CI: 1.04– 12.08) respectively.	It was seen that low 25(OH)D levels were associated with a greater than threefold increased risk of lung cancer; no association was detected for breast, colorectal and prostate cancers

Association was detected for breast, colorectal

CONCLUSION: In our article we have comprehensively reviewed the prevalence of vitamin D in cancer. Most of the researches, case studies, randomized clinical trials were directed towards the significant reduction in risk of cancer through vitamin d supplementation, and other compelling effects of vitamin D in diagnosis of cancer. However, there are some possible restrictions of vitamin D based cancer therapy which should be considered to build better curative approaches. From a conceptual approach our review of observational studies should be considered with some exceptions as there were an array of analysis and clinical trials,

moreover, the studies were inquisitive and arbitrary, without confirmed results. Ideally, more unequivocal evidence of vitamin D on any cancer risk reduction should be obtained through large, population-based, longitudinal RCTs with adequate doses of vitamin D as

interventions. Unravelling such intricate networks involving cancer and vitamin D will contribute to the understanding of vitamin D in cancer and provide promising new opportunities for cancer management.

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