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ASSOCIATION OF VITAMIN D SERUM LEVELS AND OVARIAN CANCER : A SYSTEMATIC REVIEW

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ABSTRACT

Background: *Knowing the modifiable risk factors for prevention and improved prognosis is crucial, as the prognosis of ovarian cancer is poor and there are few population-level interventions for early identification and long-term therapeutic success. Research on cancer has shown a great deal of scientific interest in vitamin D since it may be one of these factors.*

Aims : *This systematic review is to review the association of vitamin D serum levels in patients with ovarian cancer*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed and SCIENCE DIRECT, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 329 articles, whereas the results of our search on SCIENCE DIRECT brought up 298 articles. The results of the search conducted for the last year of 2014 yielded a total 8 articles for PubMed and 12 articles for SCIENCE DIRECT. In the end, we compiled a total of 4 papers, 3 of which came from PubMed and 1 of which came from SCIENCE DIRECT. We included four research that met the criteria.*

Conclusion: *In summary, some of the studies showed vitamin D supplementation is not necessary to increase the survival rate of ovarian cancer in the absence of a vitamin D shortage. There are limited studies about the association of vitamin D and ovarian cancer.*

Keyword: *Vitamin D, ovarian cance*

INTRODUCTION

Because of its heterogeneity and typically delayed detection, ovarian cancer ranks among the worst malignancies that affect women. Debilitating side effects are a result of the current first-line treatments, which include intense chemotherapy and debulking surgery. Finding novel, efficient treatments with fewer side effects—adjuvant therapies—that might lower the dosages of chemotherapy that are required is therefore an unmet medical need. In addition to its anticancer properties, vitamin D is one of the primary regulators of blood calcium and phosphorus homeostasis. It inhibits the ability of cancer cells to proliferate and spread by inducing differentiation and death. Nevertheless, dosages that produce hypercalcemia are also beneficial against cancer.[1]

According to the International Agency for Research on Cancer, ovarian cancer (OC) will afflict 313,000 women and result in 207,000 deaths in 2020, making it the eighth most prevalent and seventh deadly kind of cancer in women. Because of its late diagnosis, which already greatly reduces the prospects of a treatment, OC is also known as the "silent killer." The 5-year survival rate for OCs is just 42% or 26% in stage III (51%) or stage IV (29%), depending on the stage at which they are identified.[1]

The fundamental function of vitamin D, a fat-soluble prohormone, is to preserve calcium homeostasis. Numerous epidemiological studies have demonstrated the critical role vitamin D plays in preventing cancer by controlling metabolism and cellular growth. According to research on the cellular mechanism of vitamin D in ovarian cancer, both genomic and nongenomic signal transduction pathways allow vitamin D to have antitumorigenic and protective effects. These findings suggest that vitamin D deficiency raises the risk of ovarian cancer and that vitamin supplements can be a useful tool in the fight against cancer. Consequently, this review describes the epidemiology, molecular mechanism and evidence linking vitamin D deficiency to ovarian cancer.[2]

With the greatest death rate among women, ovarian cancer is the sixth most common cause of cancer-related deaths. With a fewer than 40% five-year survival rate, it is frequently discovered at an advanced stage in the majority of patients. Over the past few decades, there has been no discernible advancement in the treatment of ovarian cancer through the use of platinum-based pharmacological regimens in conjunction with surgical debulking. Therefore, novel biomarkers for ovarian cancer are needed in order to facilitate early identification and prevention prior to the development of the illness.[3]

Research on vitamin D's ability to prevent cancer has attracted a lot of scientific attention. Sunlight exposure through the skin is the primary source of vitamin D in the body because it catalyzes the conversion of 7-dehydrocholesterol to vitamin D3 (cholecalciferol). Vitamin D2 (ergocalciferol) and vitamin D3 can also be obtained through diet through supplements, fortified foods (such milk, cereals), and natural sources (like fish and eggs). Next, the circulating form of vitamin D, 25-hydroxyvitamin D (25(OH)D: calcidiol, is created in the liver from vitamins D2 and D3. The hormonally active form, 1,25-dihydroxyvitamin D (1,25(OH)2D: calcitriol), is next created in the kidneys from these two forms. Overall, there is biologic plausibility for a relation between vitamin D and ovarian cancer, which is supported by experimental research, but the epidemiological evidence remains unclear.[4]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we review published literature contains the association of vitamin D serum levels and ovarian cancer cases. This is done to provide an explanation and improve the handling of treatment at the patient. As the main purpose of this paper, to show the relevance of the difficulties that have been identified as a whole.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used "vitamin D" and "ovarian cancer" as keywords.The search for studies to be included in the systematic review was carried out using the PubMed and SCIENCE DIRECT databases by inputting the words: *(("ovarian neoplasms"[MeSH Terms] OR ("ovarian"[All Fields] AND "neoplasms"[All Fields]) OR "ovarian neoplasms"[All Fields] OR ("ovarian"[All Fields] AND "cancer"[All Fields]) OR "ovarian cancer"[All Fields]) AND ("vitamin d"[MeSH Terms]*

OR "vitamin d"[All Fields] OR "ergocalciferols"[MeSH Terms] OR "ergocalciferols"[All Fields])) AND ((clinicaltrial[Filter]) AND (2014:2024[pdat])) used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

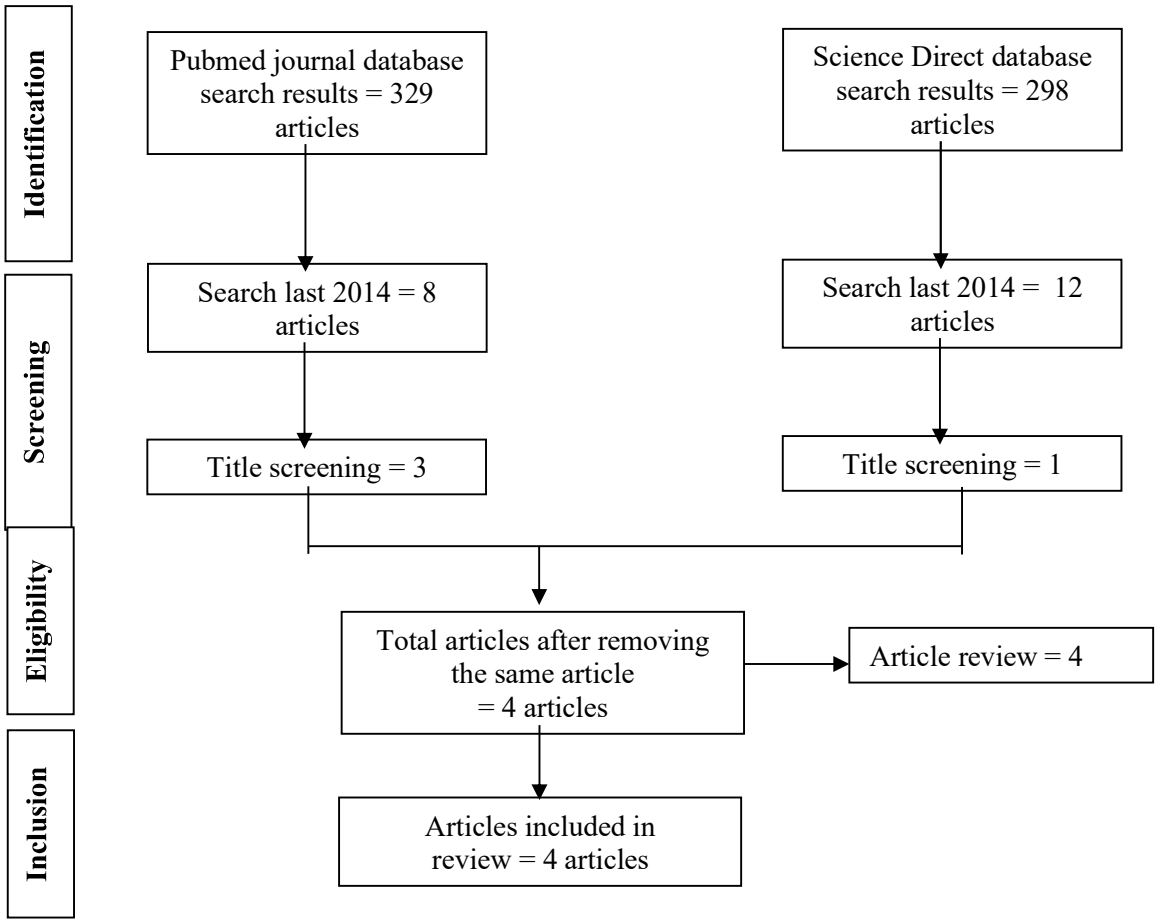

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 329 articles, whereas the results of our search on SCIENCE DIRECT brought up 298 articles. The results of the search conducted for the last year of 2014 yielded a total 8 articles for

PubMed and 12 articles for SCIENCE DIRECT. In the end, we compiled a total of 4 papers, 3 of which came from PubMed and 1 of which came from SCIENCE DIRECT. We included four research that met the criteria.

Webb, et al[4] (2015) showed that women with ovarian cancer who had greater serum 25(OH)D concentrations at diagnosis had longer survival times. This implies that the level of vitamin D upon diagnosis may be a separate predictor of prognosis, if verified by more research. Furthermore, raising vitamin D levels may increase the chances of ovarian cancer survival if the link is proven to be causative.

Ross, et al[5] (2024) showed that serum 25(OH)D concentration and survival specific to ovarian cancer are not correlated. Our findings imply that vitamin D supplementation is not necessary to increase the survival rate of ovarian cancer in the absence of a vitamin D shortage.

Table 1. The litelature include in this study

Author	Origin	Method	Sample	Result
Webb et al, 2015[4]	Australia	Case control study	1.631 patients	In all, 59% of the women passed away during the follow-up period, with ovarian cancer accounting for 95% of these fatalities. While tumor histology, stage or grade, or comorbidities were not significantly correlated with circulating 25(OH)D concentrations (mean: 44 nmol/L), they were with age, state of residency, season of blood collection, and body mass index. Longer survival was substantially correlated with higher 25(OH)D concentrations at diagnosis (adjusted HR: 0.93; 95% CI: 0.88, 0.99 per 10 nmol/L). However, no significant correlation was seen between 25(OH)D assessed after initial therapy or progression-free survival.
Ross et al, 2024[5]	Australia	Prospective cohort study	886 patients	Only 14% and 8% of participants had 25(OH)D concentrations < 50 nmol/L during and after main therapy, respectively. Mean 25(OH)D concentrations were lower during and after primary treatment (92 and 91 nmol/L, respectively). Throughout the five years of follow-up, there was no correlation found between 25(OH)D and the survival specific to ovarian cancer [HR 1.10 (95% CI: 0.76, 1.61) and 0.95 (0.54, 1.68) for the highest vs. lowest quintile during and after treatment, respectively].
Sajo et al, 2020[6]	Nigeria	Case control study	70 patients	The participants' average age was 50.6 ± 11.1 years. A statistically significant correlation was not seen (p = 0.09) between blood vitamin D insufficiency and EOC.

				However, after adjusting for potential confounders in a multivariable analysis, there was no statistically significant relationship found with EOC (adjusted odds ratio 0.99; 95% confidence interval 0.97–1.00; p = 0.06). Nevertheless, a 10 mmol/L change in circulating vitamin D levels was associated with EOC among the study participants (adjusted odds ratio 0.96; 95% confidence interval 0.93–0.99; p = 0.04). Furthermore, there was no proof that these confounders and changes in circulating 25(OH)D levels had an interaction impact on the risk of EOC.
Kolnsberg et al, 2019[7]	Germany	Cohort study	688 patients	Across all 688 samples, the average 25(OH)D level was 18.31±11.71 ng/ml. Individuals without a cancer had lower levels than those with benign illness. Between these two groups, there was no discernible difference, nevertheless. Using the Mann-Whitney test, the analysis of 25(OH)D levels in various carcinomas and endometriosis in connection to seasons revealed substantial results, particularly for breast, ovarian, and endometrial cancer. U-test: Endometrial cancer: U=11.00, z=−2.21, p=0.027, spring/summer U=1965.00, z=-4.86, p<0.001 for breast cancer, and U=5.00, z=-2.98, p=0.003 for ovarian cancer. Autumn/spring: ovarian cancer: U=4.00, z=−2.94, p=0.003, breast cancer: U=2294.50, z=−4.75, p<0.001. Summer/autumn: endometrial cancer: U=14.00, z=−2.41, p=0.016 Breast cancer: U=2933.00, z=-4.34, p<0.001 in the summer and winter. autumn/winter: breast cancer: U=3377.50, z=− 4.29, p<0.001

Sajo, et al[6] (2020) showed that regarding the association between the change in circulating 25(OH)D levels and the risk of EOC, there was no indication of an interaction effect between these factors. There was no statistically significant correlation found in the study between the risk of EOC and circulating levels of vitamin D. It may be possible to determine whether there is a real correlation between vitamin D and EOC with improved data on sun exposure in the future and food composition.

Kolnsberg, et al[7] (2020) showed that overall, cancer patients had lower 25(OH)D levels than cancer-free people, albeit not much lower. Regarding the effects of the seasons on patients with ovarian, endometrial, and breast cancer, noteworthy

findings were presented. Regarding menopausal status, nicotine, or grade in connection to 25(OH)D levels, no discernible impacts were seen.

DISCUSSION

Several recent studies reviewed the anticancer effects of different vitamins on selected female malignancies. Globally, ovarian cancer ranks ninth among women for cancer diagnoses; however, incidence rates differ by region, with North America and Europe having the highest rates and Africa and Asia having the lowest. The majority of ovarian cancers are aggressive in nature, meaning that by the time of diagnosis, the illness has migrated outside of the pelvis, greatly decreasing the likelihood of long-term therapeutic effectiveness. This results in a dismal prognosis. Controlling ovarian cancer requires prevention, but there aren't many recognized modifiable risk factors. Similarly, the only known characteristics that affect survival are of a clinical or biological origin; they include the cancer's grade, histology, age at diagnosis, and stage. As such, these factors cannot be changed.[8]

The fundamental function of vitamin D, a fat-soluble prohormone, is to preserve calcium homeostasis. Numerous epidemiological studies have demonstrated the critical role vitamin D plays in preventing cancer by controlling metabolism and cellular growth. According to research on the cellular mechanism of vitamin D in ovarian cancer, both genomic and nongenomic signal transduction pathways allow vitamin D to have antitumorigenic and protective effects. These findings suggest that vitamin D deficiency raises the risk of ovarian cancer and that vitamin supplements can be a useful tool in the fight against cancer. Thus, the epidemiology, molecular mechanism, and evidence relating vitamin D insufficiency to ovarian cancer are described in this study.[2]

Skin that has been exposed to sunlight or food sources produces vitamin D. The primary source of UVB light, or sunshine, is needed to produce sufficient amounts of vitamin D. In the epidermis, it has the ability to transform 7-dehydrocholesterol (7-DHC) into vitamin D3. Following this, vitamin D3 combines with albumin and vitamin D binding protein (DBP) to enter the bloodstream. Enough amounts of circulating hormone are ensured by maintaining equilibrium levels of both free and DBP-bound vitamin D. The active form of vitamin D3, known as 1,25(OH)2D3 (calcitriol), is produced by a group of enzymes that are mostly found in the kidney and liver.[9]

First, in the liver, vitamin D3 is transformed into 25(OH)D3, the primary metabolite of vitamin D found in blood and the most accurate measure of vitamin D status. Afterwards, a sequence of enzyme processes in the kidneys or other target organs convert 25(OH)D3 into 1,25(OH)2D3. Following its entry into target cells, 1,25(OH)2D3 interacts to the nucleus's vitamin D receptor (VDR), which controls cellular activity.[9]

The Garland brothers originally suggested that vitamin D levels and cancer rates could be associated in 1980 when they found that those who were deficient in the vitamin and lived in higher latitudes were more likely to develop malignant tumors. More proof that there is a significant inverse relationship between mean daily sun radiation levels and ovarian cancer mortality came from their following ecologic investigation. Compared to 1,25(OH)2D3, whose blood levels are presently the gold standard for assessing vitamin D status, 25(OH)2D3 has a longer half-life.[10]

The variety of current cell lines reflects the variability of OC. The cell lines derived from identical tumor types exhibit significant variation in their susceptibility to vitamin D and its derivatives. This might be brought about by variations in both their mutational landscape and the expression of the vitamin D system's constituent parts. Although VDR is found in the majority of cell lines that are known to exist, both its expression and that of CYP27B1 and CYP24A1 are quite variable.[1]

There is variability in the expression level of VDR between malignant and normal ovarian tissues. While some studies revealed that the VDR level was lower in tumors than in normal ovaries, others observed greater levels in ovarian tumors when compared to healthy tissue. While 1,25D3 or its analogs may raise protein levels in OC cell lines in a cell line-dependent manner, they have no effect on VDR mRNA levels. It's interesting to note that 1,25D3 or its analogs' anticancer effects are not predicted by how they affect CYP24A1 expression in various OC cell lines.[1]

To get a deeper understanding of how vitamin D affects the incidence of ovarian cancer, it will be crucial to conduct an exposure evaluation that includes all vitamin D sources over the etiologically relevant time. The impact of early life exposures on the risk of cancer in later life is becoming increasingly acknowledged. Future research using cohorts of children, adolescents, or young adults, or cohorts based on new births, will be instructive if vitamin D intake is more significant in ovarian cancer risk throughout early life. However, it will take several years before such data are accessible due to the lengthy induction period of ovarian and other malignancies and the resources needed to conduct such research. Indeed, the very small sample sizes of the 25(OH)D studies that we included in our evaluation reduced their power. Using validated regression models that predict 25(OH)D levels from self-reported lifestyle, environment, and personal characteristics that influence levels and that are more readily obtained in large studies is a suggested cost-effective way to obtain a measure of total vitamin D exposure from all sources.[8]

CONCLUSION

In summary, some of the studies showed vitamin D supplementation is not necessary to increase the survival rate of ovarian cancer in the absence of a vitamin D shortage. There are limited studies about the association of vitamin D and ovarian cancer.

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