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Circulating 25-Hydroxy Vitamin D Levels and Risk of Ovarian Cancer: An Updated Meta-analysis

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Abstract

A previous systematic review evaluating the hypothesis that serum vitamin D deficiency was associated with risk of ovarian cancer concluded a tentative association without statistical significance. The aim of this SR was to conduct an Updated Meta-analysis (UMA). Using citation discovery tools, additional articles were selected from cited lists based on 4 selected articles. Each Odds Ratio (OR) and its 95% Confidence Intervals (CI) from the selected cohorts were extracted by two methods such as highest versus lowest method and interval collapsing method (ICM). Random effect model was applied if I-squared value was over 50%. A publication bias was evaluated using Egger's test. Of 14 cohorts, the summary OR [and their 95% CI] (I-squared value) based on ICM was 1.14 [1.02-1.27] (82%). The summary OR estimated from 12 Caucasian cohorts kept the statistical significance. The P-value of Egger's test was 0.086. This UMA supported the lower level of serum vitamin D was associated with an increased risk of ovarian cancer. Additional follow-up studies are required due to potentially high I-squared value.

Keywords: Vitamin D; Ovary neoplasm; Risk factor; Systematic review; Meta-analysis

Abbreviations

25(OH)D: 25-Hydroxy vitamin D; CDT: Citation Discovery Tools; CI: Confidence Interval; EDS: the End Date for Search; HLM: the Highest versus Lowest Method; ICM: Interval Collapsing Method; logOR: logarithm Odds Ratio; NCC: Nested Case-Control study; OR : Odds Ratio; SElogOR: Standard Error of logarithm Odds Ratio; sOR: summary Odds Ratio; SR : Systematic Review; UMA: Updated Meta-Analysis

Introduction

Ovarian cancer is one of the major gynecologic cancers and is the fourth leading cause of cancer death among American women [1]. The incidence of ovarian cancer among Korean women has been rising over the past 20 years [2]. Risk factors of ovarian cancer include variables related to pregnancy and childbirth history [3], but extensive research is needed to pinpoint the exact cause.

Since Jiang *et al*., [4] reported in their 2004 study that 1,25(OH)D suppresses ovarian cancer cell proliferation and induces apoptosis, many studies have examined blood vitamin D level and risk of ovarian cancer [5,6]. However, a meta-analysis of these analytic epidemiologic studies could not establish statistical significance [7]. Thus, Theodoratou *et al*., [8] suggested that a concrete conclusion cannot be drawn.

In 2011, Yin *et al*., [7] reported a meta-analysis of four Nested Case-Control studies (NCCs) that had been published before early August 2010 [9-12]. Then, it is necessary to perform another meta-analysis for an update by extending the search period to late March 2019, which would be about 10 years of extension. This study aimed to perform an Updated Meta-Analysis (UMA) as an update in order to test the hypothesis that reduced serum 25(OH)D increases the risk for ovarian cancer.

Materials and Methods

Considering that the purpose of this study is to update an existing meta-analysis [7], it is necessary to add relevant literatures that were published after the End Date for Search (EDS) of the existing meta-analysis. Thus, a search list was created using the four studies [9-12] selected by Yin *et al*., [7] and the Citation Discovery Tools (CDT) of cited by provided by PubMed [13]. The EDS was set to end of March 2019, and the same inclusion criteria used by Yin *et al*., [7] in their systematic review were used. In other words, we selected analytic epidemiological studies that measured serum 25(OH)D level of participants and identified the risk of ovarian cancer.

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Table 1: Summary of the extracted information of 14 study groups.

Reference number	Study groups	Race	HLM		ICM	
			logOR	SElogOR	logOR	SElogOR
12	CLUE	C	0.15	0.02	0.14	0.02
12	CPS-II	C	-0.4	0.87	-0.4	0.87
11	FMC	C	0.59	0.35	0.48	0.16
12	MEC	C	0.48	0.39	0.49	0.37
18	New Delhi	A	1.1	0.51	1.1	0.51
17	NHANES	C	1.37	0.64	1.37	0.64
19	NHS	C	-0.24	0.12	-0.07	0.17
19	NHS-II	C	0.39	0.19	0.2	0.18
10	NSHDS	C	0.19	0.4	0.4	0.28
10	NYUWHS	C	-0.41	0.53	-0.27	0.38
12	PLOC	C	0.02	0	0.02	0
12	SWHS	A	0.22	0.43	0.22	0.43
9	WHS	C	0.13	0.59	-0.48	0.32

*HLM: Highest versus Lowest Method; ICM: Interval Collapsing Method; logOR: logarithm Odds Ratio; Race: A (Asian) C (Caucasian); SElogOR: Standard Error of logarithm Odds Ratio

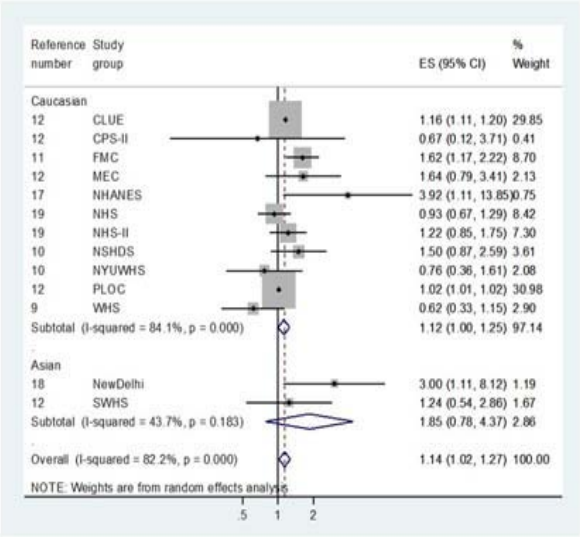

Figure 1: Forest plot for estimating the summary effect size (ES) by race using interval collapsing method.

After selecting the literatures based on the inclusion criteria above, the two following extraction methods were applied. First, the Highest versus Lowest Method (HLM) was used to identify information for the highest and lowest intervals in the serum 25(OH)D distribution, and Odds Ratio (OR) and 95% Confidence Interval (CI) were taken. Second, to address the limitation of the HLM, where only a part of the presented information is used, we used the Interval Collapsing Method (ICM), which utilizes information in all presented intervals [14,15]. In other words, if a study categorized serum 25(OH)D levels into three or more intervals, we used summary OR (sOR) and their 95% CI of the presented information.

If the OR and 95% CI were presented with the lowest serum 25(OH)D level as the reference, we used the inverse such that the highest serum level is used as the reference. This was to reflect the study hypothesis to investigate the risk of cancer according to a low serum level. The logarithm OR (logOR) and Standard Error of logOR (SElogOR) were computed from the extracted OR and 95% CI values.

Heterogeneity of studies was assessed with I-squared value (%). A random effect model was used when I-squared value was 50% or higher, while a fixed effect model was used when I-squared value was below 50% [16]. Subgroup analysis was performed for Caucasians and Asians. Publication bias was examined using funnel plot and Egger's test. Statistical significance was set at 0.05.

Results

We used the CDT in PubMed to identify 58 studies that cited the four studies selected by Yin *et al.*, [7] and the corresponding meta-analysis. From them, we selected three additional articles that satisfied the inclusion criteria [17-19]. All these studies were published after August 2010, but there were no relevant literatures published after 2014.

Among seven studies selected for meta-analysis [9-12,17-19], Mohapatra *et al.*, [18] was a case-control study, while the remaining six studies were NCCs. For the 14 study groups presented in seven studies, logOR and SElogOR values were computed using the two extraction methods (Table 1). Tworoger *et al.*, [9] and Prescott *et al.*, [19] reported duplicate study results regarding NHS and NHS-II cohorts, and we chose the information presented by Prescott *et al.*, [19], as they had a larger sample with more extensive information. Among 14 study groups, two involved Asian women (SWHS, New Delhi).

For the 14 study groups, sOR [95% CI] (I-squared value, %) using the HLM method was 1.11 [0.99-1.24] (81.5) (Table 2). However, with the ICM, sOR [95% CI] (I-squared value, %) was 1.14 [1.02-1.27] (82.2), which was statistically significant (Figure 1).

The study groups were divided into two subgroups, one including 12 cohorts of Caucasian women and the other including 2 studies of Asian women. When subgroup analysis was performed using data extracted with ICM, the results for Caucasian women were statistically significant, while that for Asian women were not (Table 2). Egger's test on 14 study groups showed that there was no publication bias (P=0.086) (Figure 2).

Discussion

Study results using the ICM showed that reduced serum 25(OH)

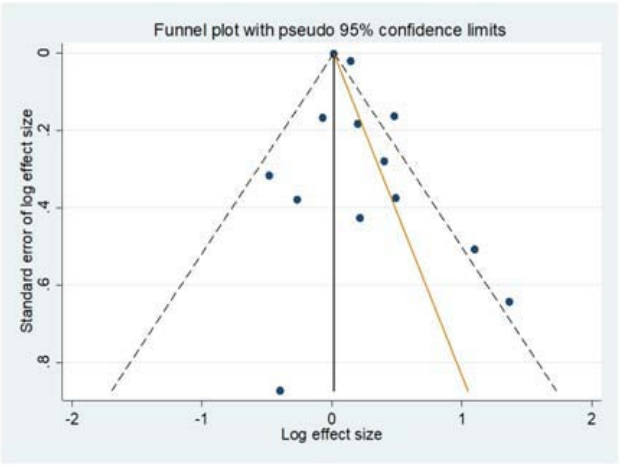

Figure 2: Funnel plot for 14 study groups (p-value of Egger's test=0.086).

Table 2: Summary odds ratio [95% confidence intervals] (I-squared value, %) of {number} selected cohorts by the extracting method.

	HLM	ICM
All {14}	1.11 [0.99-1.24] (81.5)	1.14 [1.02-1.27] (82.2)
Caucasian {12}	1.09 [0.97-1.22] (83.4)	1.12 [1.00-1.25] (84.1)
Asian {2}	1.85 [0.78-4.37] (43.7)	1.85 [0.78-4.37] (43.7)

*HLM: Highest versus Lowest Method; ICM: Interval Collapsing Method

D statically significantly increases the risk of ovarian cancer by 1.14 times [95% CI: 1.02-1.27]. As Yin *et al.*, [7] could not establish statistical significance using 10 cohorts and only mentioned a tentative association; this study is meaningful for identifying a statistically significant risk based on a meta-analysis of 14 study groups.

This study has two strengths. First, we were able to increase statistical power by using the ICM, which maximally utilizes the presented results for each study group [14]. As shown in Table 2, the sOR computed using the ICM was farther away from 1 compared to that computed using the HLM, and statistical significance was established. Second, it was able to effectively select relevant literatures published after August 2010 with minimal time and human resources by utilizing the CDT in PubMed [13]. Particularly, we were able to update additional follow-up results for the NHS and NHS-II cohorts using the cited by option [9,19]. This emphasizes the need to perform UMA for existing meta-analyses more frequently [13]. Additionally, if there are additional results for a specific cohort, UMA could be performed more easily and quickly by using the CDT on the cohort list selected in this study.

The major limitations of this study and suggestions are as follows. First, the level of heterogeneity of the 14 cohorts was very high, at 82.2%. If the effect of publication bias is low, as shown by the Egger's test, additional studies with a larger study population are needed. Muller *et al.*, [20] NCC comprising lung cancer patients from well-known cohorts worldwide is a good example. Second, the most recent year of publication for the selected literatures was 2013. Considering that we are in the year 2019 and there have been no relevant literatures since 2013, the follow-up period for cohorts should be extended in the future. Third, although statistically insignificant, the sOR for the two Asian women cohorts were high compared to that of Caucasian women. As ovarian cancer has genetic associations [21], additional studies are needed to substantiate racial differences in the risk of ovarian cancer from reduced serum vitamin D.

Conclusion

Despite above limitations, this UMA results serve as grounds to eliminate the argument that there is no association between reduced serum vitamin D level and risk for ovarian cancer. Furthermore, based on our findings, an elevation of serum vitamin D may be considered as a measure to prevent ovarian cancer.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019; 69: 7-34.
2. Jung KW, Won YJ, Kong HJ, Lee ES, The Community of Population-based Regional Cancer Registries. Cancer Statistics in Korea: Incidence, Mortality, Survivial, and Prevalence in 2016. Cancer Res Treat. 2019; 51: 417.
3. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. Cancer Biol Med. 2017; 14: 9-32.
4. Jiang F, Bao J, Li P, Nicosia SV, Bai W. Induction of ovarian cancer cell apoptosis by 1,25-dihydroxyvitamin D3 through the down-regulation of telomerase. J Biol Chem. 2004; 279: 53213-53221.
5. Cook LS, Neilson HK, Lorenzetti DL, Lee RC. A systematic literature review of vitamin D and ovarian cancer. Am J Obstet Gynecol. 2010; 203: 70.
6. Guo H, Guo J, Xie W, Yuan L, Sheng X. The role of vitamin D in ovarian cancer: epidemiology, molecular mechanism and prevention. J Ovarian Res. 2018; 11: 71.
7. Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H. Meta-analysis: Circulating vitamin D and ovarian cancer risk. Gynecol Oncol. 2011; 121: 369-375.
8. Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JP. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ. 2014; 348: g2035.
9. Tworoger SS, Lee IM, Buring JE, Rosner B, Hollis BW, Hankinson SE. Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of incident ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2007; 16: 783-788.
10. Arslan AA, Clendenen TV, Koenig KL, Hultdin J, Enquist K, Agren A, et al. Circulating vitamin d and risk of epithelial ovarian cancer. J Oncol. 2009; 2009: 672492.
11. Toriola AT, Surcel HM, Agborsangaya C, Grankvist K, Tuohimaa P, Toniolo P, et al. Serum 25-hydroxyvitamin D and the risk of ovarian cancer. Eur J Cancer. 2010; 46: 364-369.
12. Zheng W, Danforth KN, Tworoger SS, Goodman MT, Arslan AA, Patel AV, et al. Circulating 25-hydroxyvitamin D and risk of epithelial ovarian cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. Am J Epidemiol. 2010; 172: 70-80.
13. Bae JM, Kim EH. Citation Discovery Tools for Conducting Adaptive Meta-analyses to Update Systematic Reviews. J Prev Med Public Health. 2016; 49: 129-133.
14. Bae JM. Comparison of methods of extracting information for meta-analysis of observational studies in nutritional epidemiology. Epidemiol Health. 2016; 38: e2016003.
15. Bae JM. Reinterpretation of the results of a pooled analysis of dietary carotenoid intake and breast cancer risk by using the interval collapsing method. Epidemiol Health. 2016; 38: e2016024.
16. Shim SR, Shin IS, Bae JM. Intervention meta-analysis using STATA software. J Health Info Stat. 2016; 41: 123-134.
17. Bakhru A, Mallinger JB, Buckanovich RJ, Griggs JJ. Casting light on 25-hydroxyvitamin D deficiency in ovarian cancer: a study from the NHANES. Gynecol Oncol. 2010; 119: 314-318.
18. Mohapatra S, Saxena A, Gandhi G, Koner BC, Ray PC. Vitamin D and VDR gene polymorphism (*FokI*) in epithelial ovarian cancer in Indian population. J Ovarian Res. 2013; 6: 37.
19. Prescott J, Bertrand KA, Poole EM, Rosner BA, Tworoger SS. Surrogates of long-term vitamin d exposure and ovarian cancer risk in two prospective cohort studies. Cancers (Basel). 2013; 5: 1577-1600.
20. Muller DC, Hodge AM, Fanidi A, Albanes D, Mai XM, Shu XO, et al. No association between circulating concentrations of vitamin D and risk of lung cancer: an analysis in 20 prospective studies in the Lung Cancer Cohort Consortium (LC3). Ann Oncol. 2018; 29: 1468-1475.
21. Prat J. Ovarian carcinomas: five distinct diseases with different origins, genetic alterations, and clinicopathological features. Virchows Arch. 2012; 460: 237-249.