J Chin Med Assoc

ORIGINAL ARTICLE

Vitamin D in gynecological diseases

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Abstract

Background: Most reproductive system studies suggest the protective effects of vitamin D, but vitamin D deficiency and insufficiency are growing global health issues. The present study investigates the association between vitamin D deficiency/insufficiency and gynecologic diseases to identify illness risks at different serum vitamin D levels in Taiwan.

Methods: A total of 7699 female adults aged ≥20 years with results for both serum vitamin D and gynecologic-associated diseases were drawn from the Taiwan MJ cohort. We analyzed the correlation between serum vitamin D levels and results from reproductive system evaluations, including history of dysmenorrhea, results of Pap smear, high-risk human papillomavirus (HPV) infection of the cervix, mammography, and ultrasound of breast and pelvis.

Results: Over 80% of participants showed vitamin D deficiency/insufficiency. Participants with abnormal Pap smear results, high-risk HPV infection, and history of dysmenorrhea showed significantly lower levels of serum vitamin D ($p < 0.001$–0.05). Serum vitamin D deficiency was significantly associated with positive high-risk HPV infection of the cervix ($p < 0.05$) and dysmenorrhea ($p < 0.001$). After controlling for age as a confounding variable for each gynecologic disease, level of serum vitamin D was significantly associated with abnormal breast ultrasound (odds ratio = 0.724) and uterus ultrasound (odds ratio = 0.673 – 0.8), and dysmenorrhea (odds ratio = 0.829).

Conclusion: Associations were found between vitamin D deficiency and endometriosis, uterine myoma, dysmenorrhea, abnormal Pap smear results, and high-risk HPV infection of the cervix. Therefore, vitamin D supplements may present a cost-effective benefit for the prevention and treatment of gynecologic diseases, and thus reduction of healthcare expenditures.

Keywords: Breast mass; Cervical intraepithelial neoplasm (CIN); Endometriosis; Human papillomavirus (HPV); Vitamin D

1. INTRODUCTION

Vitamin D is a steroid and its role in the extraskeletal system has been widely studied. Previous studies have reported vitamin D impacting several physiologic systems with different clinical influences, such as cancer prevention and protection against degenerative disease.[1,2]

For women, vitamin D plays a role in reproductive function and severity of associated disease, including uterine myomas, endometriosis, Human papillomavirus (HPV) infection, and cervical intraepithelial neoplasm (CIN) of the uterus.[3–6] Sufficient serum vitamin D may help reduce risk of ovarian cancer.[7] Previous studies have found that sufficient serum vitamin D can reduce breast cancer incidence by 45%.[8] Vahedpoor et al. found that vitamin D supplements has effects on intraepithelial lesion of the uterine cervix regression.[9] Most findings showed vitamin D has protective effects against disease in women.

However, despite these advantages, vitamin D deficiency and insufficiency are growing global health issues with as prevalence as high as 94.6% and may be related to increased incidence of diabetes, cancer, and autoimmune disease.[10,11] In gynecology, vitamin D deficiency is a potential risk factor for female genital tract and breast malignancies.[12] Another study has shown lower serum vitamin D levels are associated with larger uterine myoma sizes and development of uterine myoma.[13] Özgü et al. found women with positive HPV infection have statistically lower serum vitamin D level compared healthy women.[6]

Average serum vitamin D levels may be influenced by food intake, sun exposure, and life quality. Serum 25-hydroxyvitamin D3 (Cholecalciferol) (25OHD) level is now generally considered to indicate short-term vitamin D status according to its clinical significance.[14] The World Health Organization (WHO) defines vitamin D insufficiency as a serum 25OHD level below 20 ng/mL (50 nmol/L).[15] Another study defined vitamin D insufficiency and deficiency respectively as serum 25OHD levels between 20 and 30 ng/mL (50–75 nmol/L) and below 20 ng/mL (50 nmol/L).[10] There is a lack of consensus on optimal levels of 25OHD.

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Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2021) 84: 1054-1059.

Received July 11, 2021; accepted August 10, 2021.

doi: 10.1097/JCMA.0000000000000607.

<zdoi: 10.1097/JCMA.0000000000000607>

The present study investigates the association between vitamin D deficiency/insufficiency and gynecologic diseases and to identify illness risks at different serum 25OHD levels in Taiwan.

2. METHODS

2.1. Data Collection

Data for this study were sourced from the Taiwan MJ cohort, an ongoing prospective cohort of health examinations conducted by the MJ Health Screening Centers in Taiwan.[16] These examinations cover more than 100 important biological indicators, including anthropometric measurements, blood tests, imaging tests, etc. Each participant completed a self-administered questionnaire to collect information of personal and family medical history, current health status, lifestyle, physical exercise, sleep habits, and dietary habits.[17]

The MJ Health Database only includes participants who provided informed consent. The study protocol was approved by the Institutional Review Board of the Tri-Service General Hospital, National Defense Medical Center (IRB No.: A202005137). Fig. 1 presents the participant selection process. Female participants aged ≥20 years with results for both serum vitamin D and gynecologic-associated diseases from June 1, 2018, to November 30, 2020, were drawn from the Taiwan MJ cohort.

The gynecologic-associated diseases included reports of dysmenorrhea from the questionnaire or positive results from various gynecologic examinations, including Pap smear, HPV test, mammography, or ultrasound of breast and pelvis. Pelvic ultrasound was performed on the uterus, endometriosis/endometrium, rectouterine pouch, ovaries, and adnexa.

Pap smears were performed by gynecologists and the reports were obtained from a single clinical laboratory in Taiwan using the Bethesda 2001 nomenclature.[18] Abnormal Pap smear findings included any kind of atypical, dysplastic, or more severe pathologic cells in the cervix, ranging from Atypical Squamous Cells of Undertermined Significance (ASCUS), CIN to carcinoma.

HPV test using a cervical swab was performed by gynecologists using the Cobas 4800 HPV Test (Roche Molecular Systems, Pleasanton, CA) for high-risk HPV detection. The Cobas 4800 HPV test concurrently detects the presence of any of 14 high-risk HPV types: HPV-16 and 18 separately, and 12 pooled HPV genotypes (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) as non-16/18 high-risk HPV type. Abnormal or positive HPV findings referred to presence of any type of high-risk HPV listed above. The presence of cervical HPV generally represents HPV infection.

Breast and pelvic ultrasonography examinations were performed and reported immediately as indicated by expert radiologists and gynecologists. Mammogram images were reviewed by two radiologists for confirmation of abnormalities. Data for ultrasound and mammography with abnormal findings may refer to any specific findings, such as calcification on mammography, uterine myomas in uterus ultrasound, or cysts in adnexal ultrasound. Data indicated some status or anatomical changes were excluded, such as dense breast comment or implantations found on mammography, implantations or fatty breasts in breast ultrasound, posthysterectomy/oophorectomy status, atrophic uterus or adnexa, intrauterine pregnancy, presence of intrauterine contraceptive device, or bicornuate uteri.

2.2. Serum Vitamin D Level

To separately analyze the association of target diseases between different vitamin D (25OHD) levels, we divided the serum vitamin D level results into 3 groups: deficiency (<20 ng/mL), insufficiency (20–30 ng/mL), and sufficiency (≥30 ng/mL). Serum vitamin D (25OHD) levels were measured using Abbott Architect i2000 (Abbott, Abbott Park, IL).

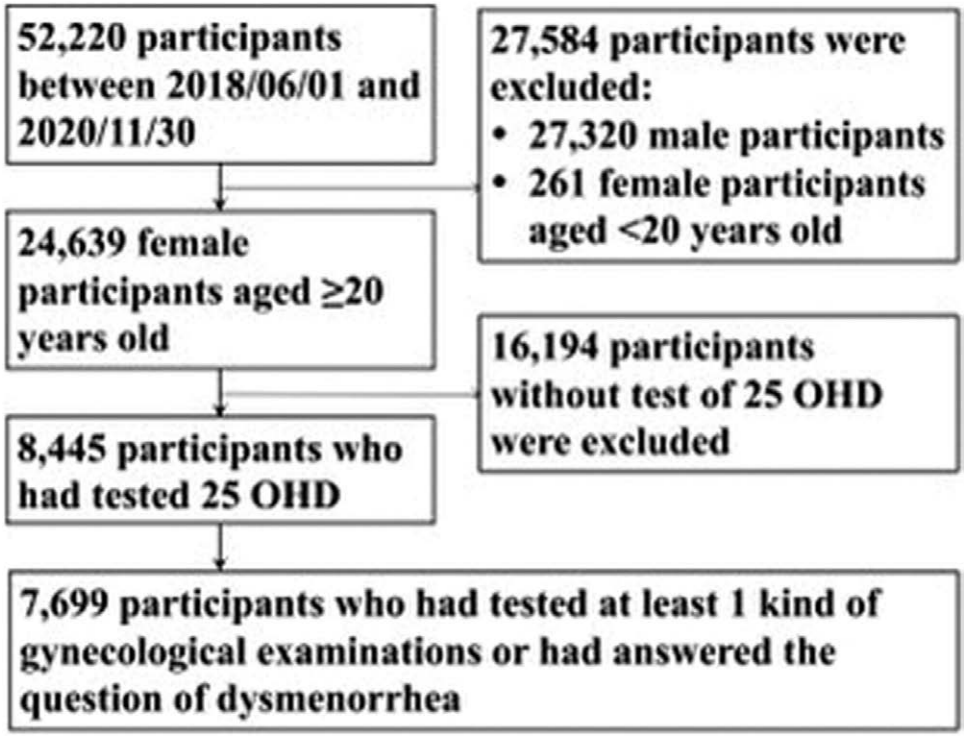

Fig. 1 Cohort selection process. 25OHD = 25-hydroxyvitamin D3

2.3. Statistical Analysis

We used independent t test and chi-square test to analyze differences in association between serum vitamin D and gynecologic diseases. We used logistic regression to control for age effects and compare the odds ratios of different levels of serum vitamin D. No logistic regression was performed for ultrasound of ovaries/adnexa and retrouterine pouch and level of vitamin D due to a lack of significance from the t-test and chi-square test. All statistical analyses were performed using Stata version 14.2 (Stata, College Station, TX).

3. RESULTS

Table 1 summarizes the participants' general characteristics. There were 52,220 participants in the Taiwan MJ cohort between June 1, 2018, and November 30, 2020, of which 8445 participants were women over 20-years-old with available serum vitamin D (25OHD) level results. Among these, 7699 participants had records of gynecological diseases.

The mean age of the 7699 cases is 44.48 years old. Half of participants are aged 30 to 49, and one-third is over 50. Over 80% of participants showed vitamin D deficiency (41.6%) or insufficiency (42.3%). Only 1240 cases (16.1%) showed serum vitamin D within the normal range.

Participants were not tested for every gynecologic disease, nor did they report on dysmenorrhea. Mammography results were excluded due to the sample size being insufficient to run statistical analysis. Abnormal results for Pap smear and HPV test were respectively 5.4% and 7.7%. Fifty-four percent of participants have showed abnormal breast ultrasound findings. About 59% participants reported a history of painful periods. About 35% had undergone gynecological ultrasound, with abnormal findings for uterus, endometrium/endometriosis, ovaries and adnexa, and rectouterine pouch, respectively, 41.5%, 2.6%, 6.3%, and 0.2%.

Table 2 shows the mean of serum vitamin D level between gynecologic examinations. Participants with abnormal Pap smear, positive HPV test, and history of dysmenorrhea showed significantly lower levels of serum vitamin D ($p < 0.001$–0.05). Serum vitamin D levels were slightly significant lower with abnormal findings for breast ultrasound and ultrasound suggesting endometriosis than in the control group ($p < 0.1$). Serum vitamin D level was found to have a significant difference between normal and abnormal uterus' ultrasound, with the abnormal group having higher level vitamin D levels (21.39 ± 8.05 vs 20.63 ± 7.80).

Table 3 shows the associations between gynecologic diseases and different levels of serum vitamin D. Serum vitamin D deficiency was significantly associated with positive HPV results (9.4% vs 6.7%–5.8%, $p < 0.05$). Dysmenorrhea was strongly correlated to serum vitamin D deficiency ($\chi^2 = 44.38$, $p < 0.001$), with the sufficient group reporting lower incidence (50.3%) compared with the deficient (62.7%) and insufficient (56.6%) groups.

We applied logistic regression and controlled the age as a confounding variable for each gynecologic disease. As shown in Table 4, the level of serum vitamin D was significantly associated with abnormal of breast ultrasound (odds ratio = 0.724), dysmenorrhea (odds ratio = 0.829), and ultrasound of uterus (odds ratio = 0.673–0.8). The odds ratio for the insufficiency and sufficiency groups was less than 1, and the deficiency group would more likely to be abnormal after controlling for age.

Table 1

Characteristics of study participants

Characteristics	N	Mean	SD
Age	7699	44.48	(12.70)
20–29	969	12.59%	
30–39	1970	25.59%	
40–49	2127	27.63%	
50–59	1617	21.00%	
60–69	766	9.95%	
70 above above	250	3.25%	
Total	7699	100.00%	
25OHD (ng/mL)	7699	22.08	(8.55)
Deficiency	3204	41.62%	
Insufficiency	3255	42.28%	
Sufficiency	1240	16.11%	
Total	7699	100.00%	
Pap smear			
Normal	4412	94.60%	
Abnormal	251	5.40%	
Total	4663	100.00%	
HPV			
Negative	1817	92.30%	
Positive	151	7.70%	
Total	1968	100.00%	
Breast utrasound			
Normal	430	46.00%	
Abnormal	505	54.00%	
Total	935	100.00%	
Dysmenorrhea			
No	2450	41.40%	
Yes	3467	58.60%	
Total	5917	100.00%	
Ultrasound of uterus			
Normal	1576	58.50%	
Abnormal	1116	41.50%	
Total	2692	100.00%	
Ultrasound of endometrium/endometriosis			
Normal	2618	97.40%	
Abnormal	70	2.60%	
Total	2688	100.00%	
Ultrasound of ovaries and adnexa			
Normal	2518	93.70%	
Abnormal	170	6.30%	
Total	2688	100.00%	
Ultrasound of rectouterine pouch			
Normal	2682	99.80%	
Abnormal	6	0.20%	
Total	2688	100.00%	

25OHD = 25-hydroxyvitamin D3; HPV = Human papillomavirus; N = case numbers.

4. DISCUSSION

CIN is a precancerous process that precedes cervical malignancy. HPV infection is a well-known risk factor for CIN and cancer.[19] Özgü et al. reported that women positive for HPV DNA found on the cervix and abnormal pap smear have significantly lower levels of serum vitamin D compared with women with negative HPV DNA.[6] Our study revealed similar findings and lower vitamin D levels correlated to higher incidence of abnormal pap smear results and HPV infection. Moreover, more serious vitamin D deficiencies increase the likelihood of positive for HPV detection and abnormal pap smear results, likely due to the anti-inflammation and immune regulation function of vitamin D. Vahedpoor et al. found that use of vitamin D supplements results in mild CIN regression because of some anti-inflammatory effects.[9] Another study found that vaginal vitamin D supplements had an antidysplastic effect on mild CIN but not on moderate CIN.[20] Future work may investigate use of vitamin D supplements for the prevention or treatment of CIN or HPV infection.

Table 2

Differences in serum vitamin D levels among gynecologic diseases

	N	Mean	SD	T test
Pap smear				1.983[a]
Normal	4412	22.88	(8.84)	
Abnormal	251	21.85	(8.29)	
Total	4663	22.82	(8.81)	
HPV				2.384[b]
Negative	1817	22.04	(8.21)	
Positive	151	20.49	(7.63)	
Total	1968	21.92	(8.17)	
Breast ultrasound				1.157
Normal	430	21.20	(7.94)	
Abnormal	505	20.60	(7.97)	
Total	935	20.87	(7.96)	
Dysmenorrhea				6.515[c]
No	2450	21.96	(8.21)	
Yes	3467	20.56	(8.05)	
Total	5917	21.14	(8.15)	
Ultrasound of uterus				-2.457[b]
Normal	1576	20.63	(7.80)	
Abnormal	1116	21.39	(8.05)	
Total	2692	20.94	(7.91)	
Ultrasound of endometrium/ endometriosis				1.641[d]
Normal	2618	20.97	(7.95)	
Abnormal	70	19.73	(6.23)	
Total	2688	20.94	(7.91)	
Ultrasound of ovaries and adnexa				-0.689
Normal	2518	20.91	(7.89)	
Abnormal	170	21.36	(8.14)	
Total	2688	20.94	(7.91)	
Ultrasound of rectouterine pouch				0.409
Normal	2682	20.94	(7.91)	
Abnormal	6	19.53	(8.44)	
Total	2688	20.94	(7.91)	

[a]$p < 0.05$.
[b]$p < 0.01$.
[c]$p < 0.001$.
[d]$p < 0.1$.
HPV = human papillomavirus.

Table 3

χ^2 test and contingency table of serum vitamin D and gynecologic diseases

	Deficiency		Insufficiency		Sufficiency		
	N	%	N	%	N	%	χ^2 tset
Pap smear							2.37
Normal	1675	94.0%	1911	94.9%	826	95.3%	
Abnormal	107	6.0%	103	5.1%	41	4.7%	
Total	1782	100.0%	2014	100.0%	867	100.0%	
HPV							6.11[a]
Negative	754	90.6%	772	93.3%	291	94.2%	
Positive	78	9.4%	55	6.7%	18	5.8%	
Total	832	100.0%	827	100.0%	309	100.0%	
Breast ultrasound							4.76
Normal	184	42.6%	195	50.1%	51	44.7%	
Abnormal	248	57.4%	194	49.9%	63	55.3%	
Total	432	100.0%	389	100.0%	114	100.0%	
Dysmenorrhea							44.38[b]
No	1021	37.3%	1045	43.4%	384	49.7%	
Yes	1714	62.7%	1364	56.6%	389	50.3%	
Total	2735	100.0%	2409	100.0%	773	100.0%	
Ultrasound of uterus							2.71
Normal	744	59.9%	639	58.1%	193	55.1%	
Abnormal	498	40.1%	461	41.9%	157	44.9%	
Total	1242	100.0%	1100	100.0%	350	100.0%	
Ultrasound of endometrium							2.29
Normal	1208	97.3%	1067	97.1%	343	98.6%	
Abnormal	33	2.7%	32	2.9%	5	1.4%	
Total	1241	100.0%	1099	100.0%	348	100.0%	
Ultrasound of ovaries and adnexa							1.49
Normal	1167	94.0%	1030	93.7%	321	92.2%	
Abnormal	74	6.0%	69	6.3%	27	7.8%	
Total	1241	100.0%	1099	100.0%	348	100.0%	
Ultrasound of rectouterine pouch							0.17
Normal	1238	99.8%	1097	99.8%	347	99.7%	
Abnormal	3	0.2%	2	0.2%	1	0.3%	
Total	1241	100.0%	1099	100.0%	348	100.0%	

[a]$p < 0.05$.
[b]$p < 0.001$.
HPV = Human papillomavirus; N = case numbers.

Most previous studies have found that breast cancer risk increases with lower vitamin D status,[21,22] while the relation to benign breast disease has been investigated less. Our results found the vitamin D deficiency group had more abnormal breast ultrasound results than the insufficient group, but no difference was found between the sufficient and deficiency group, although the breast examinations from our database did not distinguish between benign or malignant disease. This inconclusive result may be due to the small sample size used in our study. Alipour et al. found that lower serum vitamin D levels were associated with breast cancer and benign disease when compared with a control group, with risks increasing with vitamin deficiency severity, may support our findings.[23] Moreover, Shamsi et al. found vitamin D supplements protect against breast cancer.[24] Future work may require a larger sample size to identify the association.

For diseases related to the uterus and adnexa, our data seem to indicate that lower vitamin D levels are associated with more endometriosis or endometrial disease, but this finding is not supported after controlling for age as a confounding variable, possibly due to the small sample size for abnormal endometrium/ endometriosis ultrasound. No significant association was found between vitamin D level and adnexal lesions. For endometriosis/ endometrium ultrasound, the most common problem identified was endometriosis, defined as endometrial glands being found in locations beyond the endometrium, triggering a characteristic inflammatory and immune response.[25] Vitamin D may provide immunologic protection against endometriosis.[4] Harris et al. found a 24% risk reduction for endometriosis given sufficient vitamin D levels.[26]

Uterine myomas was the most common disease found through uterus ultrasound of our cohort. A positive relationship was initially observed between vitamin D levels and uterine myoma. However, after controlling for age as a confounding variable, vitamin D sufficiency is found to be associated with reduced abnormal finding uterus ultrasound findings. Uterine myomas is a common disease among women, and epidemiological and in vitro studies have found an association between increased myoma risk and low vitamin D levels, while vitamin D was also found to have an antifibroid effect.[13,27–30] Our finding supported this conclusion. Halder et al. showed in vivo that vitamin D may

Table 4

Logistic regression of gynecologic diseases and serum vitamin D

	B	SE	OR	95%CI
Pap smear				
Serum Vitamin D (Deficiency as reference group)				
Insufficiency	0.007	(0.145)	1.007	[0.758,1.339]
Sufficiency	0.090	(0.198)	1.094	[0.743,1.613]
Age	-0.033[a]	(0.006)	0.967	[0.956,0.978]
Constant	-1.359[a]	(0.255)		[-1.859,-0.860]
N	4663			
HPV				
Serum Vitamin D (Deficiency as reference group)				
Insufficiency	-0.282	(0.187)	0.754	[0.523,1.088]
Sufficiency	-0.319	(0.282)	0.727	[0.418,1.264]
Age	-0.021[b]	(0.009)	0.979	[0.963,0.996]
Constant	-1.449[a]	(0.351)		[-2.136,-0.761]
N	1968			
Breast ultrasound				
Serum Vitamin D (Deficiency as reference group)				
Insufficiency	-0.322[b]	(0.141)	0.724	[0.549,0.955]
Sufficiency	-0.154	(0.216)	0.858	[0.562,1.309]
Age	0.012	(0.007)	1.012	[0.999,1.025]
Constant	-0.163	(0.282)		[-0.715,0.389]
N	935			
Dysmenorrhea				
Serum Vitamin D (Deficiency as reference group)				
Insufficiency	-0.100	(0.059)	0.905	[0.806,1.016]
Sufficiency	-0.188[b]	(0.086)	0.829	[0.700,0.981]
Age	-0.043[a]	(0.003)	0.958	[0.953,0.963]
Constant	2.189[a]	(0.114)		[1.965,2.412]
N	5917			
	B	**SE**	**OR**	**95%CI**
Ultrasound of uterus				
Serum Vitamin D (Deficiency as reference group)				
Insufficiency	-0.224[b]	(0.091)	0.800	[0.669,0.956]
Sufficiency	-0.396[c]	(0.134)	0.673	[0.517,0.875]
Age	0.063[a]	(0.004)	1.065	[1.057,1.074]
Constant	-2.937[a]	(0.172)		[-3.274,-2.599]
N	2692			
Ultrasound of endometrium				
Serum Vitamin D (Deficiency as reference group)				
Insufficiency	0.020	(0.257)	1.020	[0.616,1.690]
Sufficiency	-0.774	(0.495)	0.461	[0.175,1.217]
Age	0.015	(0.011)	1.015	[0.994,1.036]
Constant	-4.206[a]	(0.471)		[-5.128,-3.284]
N	2688			

[a]$p < 0.001$
[b]$p < 0.05$
[c]$p < 0.01$.
CI = confidence interval; HPV = Human papillomavirus; N = case numbers; OR = odds ratio; SE = standard error.

have therapeutic effect for myoma.[31] Sufficient vitamin D levels can reduce the incidence of myoma by 32%.[13] This finding suggests vitamin D supplements can be considered for treatment. As part of its health promotion efforts, the MJ clinic encourages vitamin supplement to ensure sufficiency, and it is possible some participants were already taking vitamin D supplements in response to uterine myoma, but this information would not have been included in the questionnaire.

One of the most best-known symptoms of endometriosis and uterine myomas is dysmenorrhea, represented by pelvic pain with menstruation. In our study, lower vitamin D levels showed a significant correlation with dysmenorrhea, even after controlling for age as a confounding variable. Lasco et al. demonstrated that vitamin D supplements decrease the severity of dysmenorrhea and help women reduce the use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in a randomized double-blinded study.[32] Moreno et al. suggested that vitamin D regulates prostaglandin pathways by decreasing the level of proinflammatory cytokines.[33] Following the above descriptions, vitamin D supplements may present an alternative treatment for dysmenorrhea, especially for those with allergies to NSAIDs or a history of peptic ulcers.

The present observational study is subject to several limitations. First, it is difficult to control all confounding factors among participants, such as the food intake, sun exposure, and life quality, which could potentially impact serum vitamin D levels. Second, the abnormal imaging findings (ultrasound and mammography) from participants do not present a final diagnosis. We have discussed the diseases potentially indicated by these findings and linked to current published data. Finally, the relative small sample size hinders analysis of significance, and future studies may establish clearer relationships between vitamin D levels and disease incidence by including larger samples with finding-to-disease follow-up records.

In conclusion, our data revealed associations between lack of vitamin D and endometriosis, uterine myoma, dysmenorrhea, abnormal Pap smear results, and high-risk HPV infection of the cervix. In the future, vitamin D supplements thus may present a cost-effective benefit for the prevention and treatment of gynecologic diseases, and the reduction of healthcare expenditures.

ACKNOWLEDGMENTS

This study was supported by Tri-Service General Hospital grants TSGH-D109-106, TSGH-D110-136, TSGH-SS-D-109017, and TSGH-SS-D-110018.

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