Comparison of Serum 25-Hydroxyvitamin D Levels in Patients With Malignant and Benign Gynaecological Disease

LAURA KOLNSBERG[1], MARION RIFFELMANN[2] and MICHAEL FRIEDRICH[1]

[1]Department of Gynaecology and Obstetrics, Helios Hospital Krefeld, Krefeld, Germany;
[2]Institute of Laboratory Medicine, Helios Hospital Krefeld, Krefeld, Germany

Abstract. *Background/Aim: Many studies have shown an antiproliferative, anti-inflammatory, anti-angiogenetic, and apoptosis-inducing effect of Vitamin D. A vitamin D deficiency has been associated with an increased risk for different types of cancer. This study examined vitamin D 25(OH)D levels in gynaecological cancers in comparison with benign gynaecological diseases. Patients and Methods: Serum 25(OH)D levels in 688 gynaecological patients (488 with malignant, 200 with a benign gynaecological disease) were assayed between 2009 and 2015 using an electrochemi-luminescence immunoassay. Results: In total, the 25(OH)D levels in cancer patients were lower, but not significantly lower than those in cancer-free patients. Significant results were shown regarding seasonal effects for patients with breast-, endometrial and ovarian cancer. No significant effects occurred with regard to menopause status, nicotine, or grade in relation to 25(OH)D levels. Conclusion: 25(OH)D levels seem to influence gynaecological cancers.*

The incidence of breast cancer is 100/100,000 women in Germany per year, with the highest incidence seen between 45 and 75 years of age (1). The incidence increases each year because of early diagnosis *via* screening and thus, there is a shift to a higher frequency of early stage diseases (1). The cumulative lifetime risks amount to 13 percent for acquiring the disease and 5 percent for dying from the disease (2). As such, breast cancer is the most frequent cancer type in German women (3).

Vulvar cancer is a rare disease, 3% to 5% of all genital carcinomas are induced through vulvar cancer, with an incidence of 1.5-4 per 100,000 / women in Germany (2, 4). Endometrial cancer, with 11,370 new cases per year, is considered as the fourth most common malignant disease in German women (5). There are two major types of endometrial cancer, Type I, called endometroid adenocarcinoma and Type II, non-endometroid endometrial cancer. Type I is the most frequent with about 80% occurrence, and is associated with estrogen exposure (6). The 5-year overall survival rate of 82% is much higher than the 58% for Type II endometrial cancer (7).

Ovarian cancer is one of the sixth most frequent types of cancer in women, and has the highest mortality rate. The lifetime risk is about 1%. The peak age of disease is at 60 years of age (between 50 and 70 years). Three-quarters of the patients are diagnosed at an advanced stage III or IV (8).

Cervical cancer occurs in 9 out of 100,000 women per year with a peak occurrence at the age of 53 years (between 40 and 59 years of age). Cervical precancerous lesions are present a hundred times more frequently at the age of 34 years (9).

Vitamin D is a lipophilic steroid hormone, which is synthesized in the liver from cholesterol. 7-dehydrocholesterol is metabolized to provitamin D3 by UV-B in the skin and is converted to cholecalciferol (Vitamin D3) (10, 11). In the liver, cholecalciferol is transformed into 25-hydroxy-cholecalciferol (25-OH-D3, calcidiol) which is the best indicator of the vitamin D status in the blood (12). 25-OH-D3 is transported *via* vitamin D Binding protein (DBP) to the kidney for its hydroxylation to the active form, 1,25 dihydroxycholecalciferol (calcitriol) (12). This transformation is under the control of phosphate. Low phosphate stimulates formation of calcitriol and *vice versa*. Calcitriol supports the enteral resorption from calcium and phosphate (13).

CYP27b1 is also found in other tissues like breast, prostate and colorectal and produces 1,25(OH)2D3. This binds to the vitamin D receptor, influences gene expression and supports proliferation and differentiation of cells (14, 15). In addition, an anti-carcinogenic effect of high vitamin D levels has been discovered (16, 17).

Correspondence to: Laura Kolnsberg, Department of Gynaecology and Obstetrics, Helios Hospital Krefeld, Lutherplatz 40, 47805 Krefeld, Germany. Tel: +49 2151322201, Fax: +49 2151322220, e-mail: laura.kolnsberg@helios-kliniken.de

Patients and Methods

This study's cohort consisted of 688 patients who received medical treatment at the Department of the Helios hospital Krefeld, Germany, from 2009 to 2015. A total of 200 patients suffered from benign gynaecological disease and 488 had gynaecological cancers like endometrial, ovarian, vulvar, cervical and breast cancer. The patients were informed about the study and provided written consent for having blood samples taken and stored for scientific analysis. After written consent was obtained, an additional capillary blood sample was obtained and stored at the Institute of Hygiene and Laboratory Medicine at $-20˚C$ until further analysis. The following points were examined from the patients clinical and pathology records: disease, malignant or benign, season of blood draw pre or post menopause age at blood draw, nicotine abuse, grading.

The 25(OH)D levels were analysed at the Institute of Hygiene and Laboratory Medicine with an electrochemiluminescence immunoassay. To compare the 25(OH) levels, different testing methods were used, *e.g.* Mann-Whitney *U*-test, Kruskal-Wallies-test, Chi-square-tests and Spearman correlation. Differences with a *p*-value of less than 0.05 were defined as statistically significant. The statistical analysis was performed with IBM SPSS Statistics 22, IBM Corp. Released 2013. IBM SPSS Statistics for Macintosh, Version 22.0. (IBM Corp. Armonk, NY, USA).

Results

The 25(OH)D average level of all 688 samples was 18.31 ± 11.71 ng/ml. Patients with benign disease had higher levels (19.00 ± 12.50 ng/ml, median=17.20 ng/ml) than patients with a carcinoma (18.03 ± 11.37 ng/ml, median=14.91 ng/ml). However, there was no significant difference between these two groups (Mann-Whitney *U*-test: U=47389.50, z=–0.60, *p*=0.551).

Table I shows the different 25(OH)D levels for each group of patients. In the group of patients with benign disease, patients with endometriosis showed the highest 25(OH)D levels, while patients with complications during pregnancy had the lowest 25(OH)D levels. In the malignant group, patients with breast cancer had the highest levels and patients with cervical cancer had the lowest 25(OH)D levels.

Seasonal influence. 25(OH)D levels in patients from both groups were lowest in spring (benign: 14.27 ± 12.60 ng/ml, median=9.57 ng/ml; malignant: 14.42 ± 9.76 ng/ml, median=11.31 ng/ml). Highest levels were found in summer in patients with benign disease (23.73 ± 10.66 ng/ml; median=21.89 ng/ml) as well as in cancer patients (21.64 ± 11.20 ng/ml, median=21.10 ng/ml).

The significance of seasonal effects for both groups were calculated with the Mann-Whitney *U*-test. Significant differences in the levels of 25(OH)D in benign disease were revealed by comparing spring/summer, spring/autumn, winter/summer, spring/winter, and autumn/summer. Almost the same results were described in malignant disease, however, comparison of spring/winter and autumn/winter did not show a significant difference (Table II).

Table I. *25(OH)D levels in different benign gynaecological diseases and cancers.*

	Disease	MW±SD (ng/ml)	Median (ng/ml)
Benign (N=200)	Bleeding disorders	20.37±12.87	19.36
	Benign findings of the ovaries	19.41±12.40	17.04
	Postmenopausal bleeding	20.00±10.94	23.93
	Benign findings of the	17.29±12.22	15.14
	Endometriosis	27.05±16.85	23.64
	Pregnancy complications	16.59±10.02	15.44
Malignant (N=488)	Endometrial cancer	15.81±8.35	13.53
	Ovarian cancer	16.13±9.69	14.58
	Vulvar cancer	18.61±14.61	11.47
	Breast cancer	18.69±11.76	15.57
	Cervical cancer	13.59±6.63	10.55

Table II. *Examination of significant effects: 25(OH)D levels in benign and malignant diseases in relation to seasons.*

	25(OH)D-levels	Mann-Whitney *U*-test
Benign	Spring<Summer	U=565.00 z=–4.72, *p*<0.001
	Spring<Autumn	U=1148.50, z=–2.83, *p*=0.005
	Winter<Summer	U=563.500, z=–2.67, *p*=0.008
	Spring<Winter	U=635.00, z=–2.26, *p*=0.024
	Spring<Summer	U=1156.00, z=–2.50, *p*=0.012
	Winter/Autumn	U=1072.00, z=–0.47, *p*=0.636
Malignant	Spring<Summer	U=3604.50, z=–5.63, *p*<0.001
	Spring<Autumn	U=4573.00, z=–5.27, *p*<0.001
	Winter<Summer	U=4746.00, z=–4.65, *p*<0.001
	Spring/Winter	U=7586.50, z=–0.86, *p*=0.390
	Autumn/Summer	U=6241.50, z=–0.97, *p*=0.330
	Winter<Autumn	U=5964.50, z=–4.25, *p*<0.001

Table III. *Comparison of 25(OH)D-levels in different seasons.*

	25(OH)D-levels in quartiles: Comparison seasons	Mann-Whitney *U*-test
Benign	Spring <Summer	U=580.00, z=–4.78, *p*<0.001
	Spring<Autumn	U=1255.00, z=–2.34, *p*=0.019
	Winter<Summer	U=552.50, z=–2.90, *p*=0.004
	Spring<Winter	U=693.50, z=–1.84, *p*=0.066
	Autumn<Summer	U=1115.00, z=–2.847, *p*=0.004
	Winter/Autumn	U=1096.00, z=–0.31, *p*=0.756
Malignant	Spring<Summer	U=3803.00, z=–5.40, *p*<0.001
	Spring<Autumn	U=4976.50, z=–4.71, *p*<0.001
	Winter<Summer	U=4777.50, z=–4.74, *p*<0.001
	Spring/Winter	U=7845.00, z=–0.439, *p*=0.661
	Autumn/Summer	U=6186.50, z=–1.13, *p*=0.260
	Winter<Autumn	U=6169.00, z=–4.04, *p*<0.001

Table IV. *Comparison of 25(OH)D levels in gynaecological cancer and endometriosis in relation to seasons.*

25(OH)D-levels	Entity	Mann-Whitney *U*-test
Spring	Endometrial cancer	U=11.00, z=–2.21, *p*=0.027
<	Breast cancer	U=1965.00, z=–4.86, *p*<0.001
Summer	Ovarian cancer	U=5.00, z=–2.98, *p*=0.003
	Other entities	No significant differences *p*>0.604
Spring	Breast cancer	U=2294.50, z=–4.75, *p*<0.001
<	Ovarian cancer	U=4.00, z=–2.94, *p*=0.003
Autumn	Other entities	No significant differences *p*>0.139
Spring/Winter	Other entities	No significant differences *p*>0.127
Summer	Endometrial cancer	U=14.00, z=–2.41, *p*=0.016
>	Other entities	No significant differences *p*>0.102
Autumn		
Summer	Breast cancer	U=2933.00, z=–4.34, *p*<0.001
>	Other entities	No significant differences *p*>0.120
Winter		
Autumn	Breast cancer	U=3377.50, z=–4.29, *p*<0.001
>	Other entities	No significant differences *p*>0.103
Winter		

Table V. *Comparison of 25(OH)D levels in quartiles in gynaecological cancer and endometriosis in relation to seasons.*

25(OH)D levels-Quartiles	Entity	Mann-Whitney *U*-test
Spring	Endometrial cancer	U=9.00, z=–2.50, *p*=0.013
<	Breast cancer	U=2078.00, z=–4.66, *p*<0.001
Summer	Ovarian cancer	U=8.50, z=–2.76, *p*=0.006
	Other entities	No significant differences *p*>0.604
Spring	Breast cancer	U=2531.50, z=–4.20, *p*=0.000
<	Ovarian cancer	U=8.50, z=–2.59, *p*=0.010
Autumn	Other entities	No significant differences *p*>0.080
Spring/Winter	Other entities	No significant differences *p*>0.081
Summer/	Endometrial cancer	U=21.00 z=–1.96 *p*=0.050
Autumn	Other entities	No significant differences *p*>0.152
Summer	Breast cancer	U=2897.00, z=–4.58, *p*<0.001
>	Other entities	No significant differences *p*>0.129
Winter		
Autumn	Breast cancer	U=3486.50, z=–4.16, *p*<0.001
>	Other entities	No significant differences *p*>0.109
Winter		

The 25(OH)D levels were classified in quartiles: 1st quartile ≤9.59 ng/ml, 2nd quartile 9.60-15.49 ng/ml, 3nd, quartile 15.50-24.24 ng/ml, and 4th quartile ≥24.25 ng/ml.

The comparison of 25(OH)D levels in quartiles for the different seasons showed significant effects as per Table III. Mann-Whitney-*U*-test revealed significant differences for spring/summer, spring/autumn, winter/summer and autumn/summer in the benign group. In the cancer group significant effects were described for spring/summer, spring/autumn, winter/summer and winter/autumn (Table III).

The examination of 25(OH)D levels in the different carcinomas and endometriosis in relation to seasons indicated significant outcomes especially for breast, ovarian and endometrial cancer with the Mann-Whitney *U*-test: Spring/summer: Endometrial cancer: U=11.00, z=–2.21, *p*=0.027, Breast cancer: U=1965.00, z=–4.86, *p*<0.001, ovarian cancer: U=5.00, z=–2.98, *p*=0.003. Spring/autumn: breast cancer: U=2294.50, z=–4.75, *p*<0.001, ovarian cancer: U=4.00, z=–2.94, *p*=0.003. Summer/autumn: endometrial cancer: U=14.00, z=–2.41, *p*=0.016 summer/winter: breast cancer: U=2933.00, z=–4.34, *p*<0.001 autumn/winter: breast cancer: U=3377.50, z=–4.29, *p*<0.001 (Table IV).

With the use of the Mann-Whitney *U*-test significant differences in 25(OH)D levels in quartiles in relation to seasons and entities were examined. Especially patients with breast cancer showed significant associations (Table V).

Influence of menopause status. The 25(OH)D levels in pre- and post-menopausal patients did not show a significant association neither in the benign (U=3244.50, z=0.22, *p*=0.826) nor in the malignant group (U=17701.50, z=–0.45, *p*=0.964).

Same results applied to the examination of quartiles. No significant difference was found between pre- or post-menopausal patients (U=53001.50, z=–0,60, *p*=0.546) and differentiation of benign or malignant disease.

Regarding the different carcinomas and endometriosis, the Mann-Whitney *U*-test found no statistically significant association between 25(OH)D levels and menopause status (Endometriosis: U=2.00, z=–1.28, *p*=0.201, endometrial cancer: U=62.00, z=–0.29, *p*=0.775, breast cancer: U=9490.50, z=–0.16, *p*=0.877, ovarian cancer: U=51.00, z=–0.26, *p*=0.776, vulvar cancer: U=25.00, z=0.05, *p*=0.958, cervical cancer: U=59.50, z=–1.08, *p*=0.280). The examination of 25 (OH)D levels in quartiles in relation to menopause status for different carcinomas did not show a significant result (*p*>0.26) (Table VI).

Influence of age. Spearman correlation showed a significant association between 25(OH)D levels and age in the malignant group (r_s=–0.096, *p*=0.034) but not in the benign group (rs=0.013, *p*=0.854). After division into quartiles, a significant correlation to age was found in patients with gynaecological cancer r_s=–0.11, *p*=0.015). There was no statistically significant effect after classification by age, over and under 50 years.

Table VI. *Significance of 25(OH)D levels and 25(OH)D levels in quartiles in gynaecological cancers and endometriosis in relation to menopause status (Mann-Whitney U-test).*

Entity	25(OH)D-levels	25(OH)D-levels in quartiles
Endometriosis	U=2.00, z=−1.28, *p*=0.201	U=3.50, z=−1.06, *p*=0.290
Endometrial cancer	U=62.00, z=−0.29, *p*=0.775	U=57.00, z=−0.54, *p*=0.589
Breast cancer	U=9490.50, z=−0.16, *p*=0.877	U=9400.00 z=−0.28, *p*=0.779
Ovarian cancer	U=51.00, z=−0.26, *p*=0.776	U=46.00, z=−0.59, *p*=0.555
Vulvar cancer	U=25.00, z=0.05, *p*=0.958	U=23.00, z=−0.28, *p*=0.779
Cervical cancer	U=59.50, z=−1.08, *p*=0.280	U=60.00, z=−1.13, *p*=0.260

Especially breast cancer patients had a significant association with age (Spearman correlation r_s=−0.15, *p*=0.004). This result was also found after division into quartiles (Spearman correlation r_s=−0.16, *p*=0.002). Other entities did not show a correlation. Also, after classification of patients into over and under 50 years of age, no significant effects were found with the Mann-Whitney *U*-test (*p*>0.194).

Influence of nicotine abuse. There was no significant association between 25(OH)D levels and nicotine abuse either for patients in the malignant group (U=13917.00, z=−1.18, *p*=0.240) or for patients in the benign gynaecological disease group (U=3653.50, z=−0.66, *p*=0.240). Table VII shows the average standard deviation and median of 25(OH)D levels in both groups of nicotine consumption, yes or no.

The classification into quartiles did not reveal a difference, as no significant results were found in the Mann-Whitney *U*-test for benign disease (U=3738.00, z=−0.43, *p*=0.665) or cancer patients (U=14045.00, z=−1.08, *p*=0.279).

Examinations of each cancer group and of endometriosis did not reveal any significant association in relation to nicotine abuse (*p*>0.184, respectively; *p*>0.253).

Influence of grade. In this study, 488 patients had cancer, out of which 87 had a Grade 1 cancer [25(OH)D levels 17.39±10.51 ng/ml (median=14.83 ng/ml)]. The 25(OH)D levels in 236 patients with Grade 2 cancer were 18.98±12.32 ng/ml (median=15.86 ng/ml) and in 164 patients with Grade 3-cancer were 17.04±10.31 ng/ml (median=14.13 ng/ml). One patient had a Grade 4 cancer (10.08±0 ng/ml (median=14.91 ng/ml). Spearman correlation did not show a significant association between the grade of the cancer and 25(OH)D levels (r_s=−0.31, *p*=0.490). Also, following classification into quartiles no significant differences were observed (Spearman correlation: r_s=−0.035, *p*=0.442).

A significant association of different gynaecological cancer types with grading and 25(OH)D level was not observed. The classification into quartiles also showed no significant differences (Table VIII).

Table VII. *25(OH)D levels in patients with benign and malignant gynaecological diseases in relation to nicotine consumption.*

	Nicotine abuse	MW±SD (ng/ml)	Median (ng/ml)
Benign findings	Yes	20.46±13.86	17.32
	No	18.56±11.82	17.23
Malignant findings	Yes	17.36±12.30	13.91
	No	17.99±10.79	15.04

Table VIII. *Significance of 25(OH)D levels and 25(OH)D levels in quartiles in dependence of grade for different gynaecological cancers (Spearman Rho coefficient).*

Entity	25(OH)D levels	25(OH)D-levels in quartiles
Endometrial cancer	r_s=−0.14, *p*=0.420	r_s=−0.20, *p*=0.235
Breast cancer	r_s=−0.00, *p*=0.969	r_s=−0.01, *p*=0.856
Ovarian cancer	r_s=0.06, *p*=0.748	r_s=0.15, *p*=0.403
Vulvar cancer	r_s=−0.12, *p*=0.627	r_s=−0.04, *p*=0.868
Cervical cancer	r_s=−0.07, *p*=0.723	r_s=−0.02, *p*=0.924

Discussion

The aim of the study was to compare the 25(OH)D levels in patients with gynaecological cancers with those in patients with benign gynaecological disease. 25(OH)D is attracting attention because it seems to influence carcinoma and, also, internal ailment. Supplementation of 25(OH)D could reduce internal ailment, the incidence of carcinoma and improve outcomes (18, 19). The National Health and Nutrition Examination Survey defined a serum 25-hydroxyvitamin D concentration of ≤20 ng/ml (50 nmol/l) as a deficiency level (20). The Department of Nutritional Sciences, University of Toronto mentioned an optimal value of 30 ng/ml (75 nmol/l) (21).

Our study showed that the average level for all patients was 18.31±11.71 ng/ml, indicating a vitamin D deficiency.

The 25(OH)D levels in patients with a benign gynaecological disease were a slightly higher in comparison to patients with a gynaecological carcinoma. A Chinese study from 2015 to 2018 involving 4728 pregnant women found also a deficiency in vitamin D with levels ranging from 43.22±18.41 nmol/l in 2015, to 39.3±15.1 nmol/l in 2016 and 36.6±17.0 nmol/l in 2017 (22). Streb *et al*. have obtained similar results, 25(OH)D levels were lower in patients with breast cancer than in the healthy group (23). As expected, the highest 25(OH)D levels were found in the summer and the lowest in spring with significant effects in both groups. Same results were shown following classification into quartiles. Analysis of each gynaecological tumor and seasonal comparison resulted in significant associations especially for breast, endometrial, and ovarian cancer. Hintzpeter *et al*. have also shown seasonal changes in serum 25(OH)D levels. They observed the lowest levels in March and the highest levels in June (24). A study from Demark with 3092 individuals reported the same seasonal variations (25). Acevedo *et al*. have found higher vitamin levels in breast cancer patients in summer than in winter (26).

A comparison of 25(OH)D levels and menopause status showed higher levels for post-menopausal women, but there was no significant association with any of the different parameters like benign/ malignant group, quartiles or tumor classification. Same results have been described in a study by Shriazi *et al*. (27). Scott *et al*. have reported an association with higher breast cancer risk among post-menopausal women; this relation was not valid for pre-menopausal women (28). Our analysis regarding age and vitamin D levels demonstrated a significant correlation in the malignant group and after subdivision, especially for breast cancer patients. Shirazi *et al*. have also found a positive correlation between age and 25(OH)D levels (27). A study from Japan has shown significantly lower levels for women under 30 years of age (29). The reason could be that older individuals take more supplements than younger ones.

As in our study, Shirazi *et al*. did not show a significant relation between vitamin D status and smoking (27). This result applied to all our examined groups. Brot *et al*. have shown a different outcome in a study involving 510 perimenopausal women (50 percent smokers) with significantly reduced 25(OH)D levels (30). Cabaset *et al*., in a study with healthy pregnant women in their first trimester, found that former smokers had a smaller risk for low 25(OH)D levels (31).

We could not find a significant correlation between the grade of cancer and 25(OH)D levels. Imitaz *et al*. have obtained the same results indicating no significant association with the grade, state or hormone receptor status in a study of 90 breast cancer patients (32). In a case control study with ovarian cancer patients, Walentowicz-Sadlecka *et al*. have reported that a significant effect of the grade and 25(OH)D levels was missing as well (33). Another case control study with 78 breast cancer patients and 78 healthy women has reported a significant relationship between grade and 25(OH)D levels with lower levels in poorly differentiated tumors. They have also examined the relation between 25(OH)D levels and pre- and post-menopausal breast cancer patients. No statistically significant effects were observed (34).

Conclusion

An association was found between benign gynaecological disease and gynaecological cancers to vitamin D, although not all differences were significant. Additional studies are needed regarding the use vitamin D for prevention or therapy of cancers.

Conflicts of Interest

No conflicts of interest exist regarding this study.

Authors' Contributions

Study conception and design: Michael Friedrich; Acquisition of data: Laura Kolnsberg; Laboratory supply: Marion Riffelmann; Analysis and interpretation of data: Laura Kolnsberg; Drafting of manuscript: Laura Kolnsberg; Critical revision: Michael Friedrich.

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