SPANDIDOS PUBLICATIONS

Circulating 25-hydroxyvitamin D concentration in German cancer patients

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Abstract. The serum 25-hydroxyvitamin D [25(OH)D] concentration was measured in 20 patients with prostatic carcinoma, compared to 75 subjects with prostatic hyperplasia, in 24 male and 17 female patients with melanoma, in 26 female patients with breast cancer, 7 patients with ovarian carcinoma and 3 patients with cervix carcinoma among subjects followed in a German polyclinical centre. In >50% of these 174 subjects, 25(OH)D concentration was <20 μg/l. In most subject groups, a seasonal decrease of 25(OH)D concentration was observed during the winter period. An age-related decrease in such a concentration was also observed in subjects with prostatic hyperplasia examined in the late summer/early autumn period and in female cancer subjects, at the exclusion of patients with breast cancer. In the latter patients, however, a positive correlation prevailed between age and 25(OH)D concentration. Hence, it is proposed that an abnormally low serum 25(OH)D concentration represents a preferential risk factor, in middle-aged women, for breast cancer, as compared to other neoplasic manifestations in female subjects.

Introduction

Vitamin D deficiency is now recognized as a pandemic (1). It has been associated with increased risk of various diseases, including common cancers. Attention was indeed recently drawn to prospective studies of serum 25-hydroxyvitamin D concentration and cancer mortality, especially in the USA (2). Conflicting results were reported, however, concerning the association between 25-hydroxyvitamin D and either total cancer mortality or specific (e.g. colorectal) cancer mortality. Moreover, even when higher plasma 25-hydroxyvitamin D levels were found associated with a decrease incidence of cancer, as was indeed the case for colorectal cancer, the influence of 25-hydroxyvitamin D on the outcome of patients with established colorectal cancer remained unknown (3). In Germany, progression of malignant melanoma was already found to be associated with reduced 25-hydroxyvitamin D serum levels (4).

With this information in mind, the major aims of the present study were to measure the plasma concentration of 25-hydroxyvitamin D in 97 German cancer patients. The results collected in 20 patients with prostatic carcinoma were compared to those obtained in 75 subjects with prostatic hyperplasia. The cancer patients also included 24 male and 17 female patients with melanoma, 26 female subjects with breast cancer, 7 female subjects with ovarian cancer and 3 female patients with cervix carcinoma. In each case, the incidence of low serum 25-hydroxyvitamin D concentration, as well as the seasonal dependency and age relationship, were also investigated.

Materials and methods

The serum concentration of 25-hydroxyvitamin D [25(OH)D] was assayed with a radioimmunoassay (DiaSorin, Sillwater, MN, USA) as previously described (5). The gender, age and sampling month were recorded in all subjects. Whenever so required, individual measurements exceeding the upper limit of the individual 95% confidence interval were excluded from the further analysis of results. The statistical significance of differences between mean values was assessed by use of Student's t-test. All results are presented as mean values (± SEM) together with the number of individual determinations (n) or degree of freedom (df).

Results

Seasonal aspect in subjects with prostatic hyperplasia. In the subjects with prostatic hyperplasia <70 years old, the serum concentration of 25-OH was higher ($p<0.003$) in September and October (27.2±1.9 μg/l; n=20) than in the November to February period (20.3±1.1 μg/l; n=25). Such was no more the case, however, in the older subjects with prostatic hyperplasia (Table I). Thus, in the latter subjects the 25(OH)D serum concentration was virtually identical ($p>0.6$)

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Table I. Serum 25(OH)D concentration in 75 subjects with prostatic hyperplasia.

Age (years)	Months	25(OH)D (μg/l)
<70		
61.8±1.6 (20)	9-10	27.2±1.9 (20)
60.8±1.2 (25)	11-2	20.4±1.1 (25)
>70		
76.7±1.2 (14)	9-10	18.7±1.3 (14)
74.1±1.2 (16)	11-2	19.8±2.1 (16)

Table II. Serum 25(OH)D concentration in 19 subjects with prostatic carcinoma.

Age (years)	Months	25(OH)D (μg/l)
<70		
63.0±1.8 (5)	9-10	24.2±1.8 (6)
>70		
75.5±2.1 (6)	9-11	20.3±3.1 (6)
77.3±1.5 (8)	12-3	14.7±2.5 (8)

in September and October (18.7±1.3 μg/l; n=14) and in the November to February period (19.8±2.1 μg/l; n=16). These data also indicate that the 25(OH)D serum concentration decreased with age ($p<0.005$) in September and October, but no more so ($p>0.75$) in the November to February period. As a matter of fact, no significant correlation between 25(OH)D serum concentration and age ($r= -0.1426$; $p>0.1$) was observed when considering together all 75 subjects with prostate hyperplasia.

Comparison of subjects with prostatic carcinoma versus prostatic hyperplasia. In the 20 subjects with prostatic carcinoma, one individual value for plasma 25(OH)D (50.4 μg/l) was discarded because it largely exceeded the upper limit (41.8 μg/l) of the 95% confidence interval, i.e. the mean value plus ($t_{0.05}$.SD), for these 20 subjects.

In the winter period (December to March inclusive), the 25(OH)D serum concentration averaged in 8 elderly patients (77.3±1.5 years) with prostatic carcinoma 14.7±2.5 μg/l, as compared ($p>0.15$) to 19.8±2.1 μg/l in 16 subjects of comparable age (74.1±1.2 years; $p>0.1$) with prostatic hyperplasia. The latter subjects included 10 patients (75.6±1.7 years) who, like 7 subjects with prostatic carcinoma, displayed a serum 25(OH)D concentration <20.0 μg/l and averaging 14.9±1.4 μg/l, on one hand, and 6 patients of comparable ($p>0.09$) age (71.5±0.6 years) with a serum 25(OH)D concentration >20.0 μg/l averaging 28.0±2.9 μg/l, i.e. a value almost twice higher ($p<0.005$ or less) than that recorded either in the 8 aged subjects with prostatic carcinoma or the 10 aged subjects with prostatic hyperplasia and abnormally low plasma 25(OH)D concentration, on the other hand. A somewhat comparable situation prevailed in the 6 elderly patients with prostatic carcinoma examined during the late summer and early autumn (Table II). Of the 6 elderly patients (75.5±2.1 years) 3 again displayed a serum 25(OH)D concentration <20.0 μg/l, with an overall mean value of 20.3±3.1 μg/l (n=6), not significantly higher ($p>0.15$ or more) than that found either in elderly patients with prostatic carcinoma examined in the winter period or elderly patients with prostatic hyperplasia examined in September and October.

Last, in the 5 subjects with prostatic carcinoma below the age of 70 (63.0±1.8 years) and also examined in late summer and early autumn, the serum 25(OH)D concentration averaged 24.2±1.8 μg/l. Thus in subjects with either prostatic hyperplasia or carcinoma, the highest mean value was found in the patients below the age of 70 and examined in late summer and early fall. Pooling together the results collected in these two groups of subjects, the results recorded in late summer and autumn in the patients >70 years averaged 73.2±5.1% (n=20; $p<0.003$) of the corresponding mean values found in the same pathologic situation and at the same season(s) in the patients below the age of 70 (100.0±5.9%; n=25).

The mean values recorded in the patients with prostatic carcinoma averaged 88.9±8.1% (df=67; $p>0.2$) of the mean corresponding values found in subjects with prostatic hyperplasia belonging to the same age group and examined at the same time of the year.

Once again, no significant correlation between 25(OH)D concentration and age ($r= -0.1613$; $p>0.1$) was observed in the 19 subjects with prostatic carcinoma.

Melanoma patients. Forty-one patients with melanoma were also examined. They included 24 males and 17 females. Among the 24 male subjects, two relatively young subjects (33 and 54 years old) were discarded because they displayed abnormally high values for plasma 25(OH)D concentration (45.9 and 50.7 μg/l) exceeding the upper limit of the 95% confidence interval of these 24 subjects (i.e. 43.4 μg/l). The remaining 22 male subjects had a mean age of 57.2±2.8 years. The plasma 25(OH)D concentration averaged 13.0±1.6 μg/l (n=15) in the subjects examined during the winter and early spring period (December to April) as distinct ($p<0.02$) from 22.0±3.2 μg/l (n=7) in the subjects examined between May and October inclusive (Table III). In these 22 male subjects with melanoma, no significant correlation ($r= -0.1729$; $p>0.1$) was found between serum 25(OH)D concentration and age. Even when considering all 116 male subjects concerned by this study, covariance analysis, which avoids the possible interference of group difference(s), failed to detect any significant negative correlation between 25(OH)D concentration and age ($r= -0.482$; $p>0.1$).

The mean age of the 17 female subjects with melanoma (51.6±3.4 years) was not significantly different ($p>0.2$) from that of the 22 male subjects with melanoma considered above. In these female subjects, the mean plasma 25(OH)D concentration was again higher in the patients examined in the May to August period (27.1±2.8 μg/l; n=8) than in those examined in the December to April period (18.5±4.3 μg/l). Such a difference became statistically significant ($p<0.02$) when ignoring one 73-year-old female subject examined in February and displaying a plasma 25(OH)D concentration

a.

Serum 25(OH)D concentration in 39 subjects with

Sex	Months	Age (years)	25(OH)D (μg/l)
Male	5-10	51.9±4.7 (7)	22.0±3.2 (7)
	12-4	59.7±3.4 (15)	13.0±1.6 (15)
Female	5-8	46.5±5.5 (8)	27.1±2.8 (8)
	12-4	56.1±4.0 (9)	18.5±4.3 (9)

Table IV. Serum 25(OH)D concentration in 26 subjects with breast cancer.

Age (years)	25(OH)D (μg/l)	<20 μg/l
<56		
47.9±1.4 (13)	14.7±1.2 (13)	12/13[a]
≥56		
65.0±1.0 (13)	24.1±2.9 (13)	4/13

[a]The other patient displayed a 25(OH)D serum concentration of 20.0 μg/l at 52.

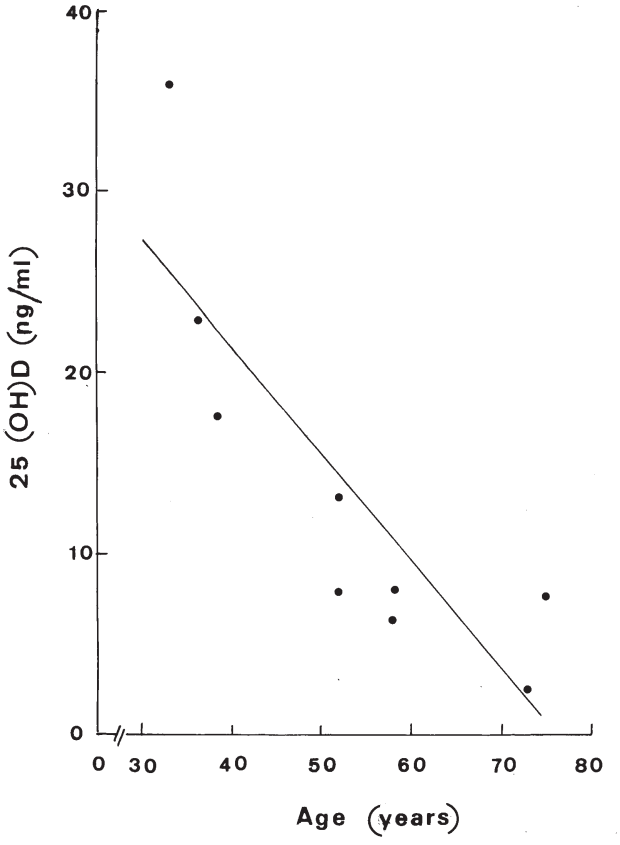

Figure 1. Inverse correlation between serum 25(OH)D concentration and age in 9 female patients with ovarian and cervix carcinoma.

(46.1 μg/l) well above the upper limit of 95% confidence interval (35.0 μg/l) for the other 8 subjects in this group, with a mean value of 15.0 ± 3.0 μg/l (n=8).

Thus, in both male and female subjects with melanoma, the plasma 25(OH)D concentration was lower in the winter than summer period. Pooling all available data (including the result collected in the above-mentioned 73-year-old lady), the measurements collected in the summer period averaged 156.9±13.7% (n=15; p<0.004) of the mean corresponding value recorded in subjects of the same gender examined in the winter period (100.0±11.4%; n=24). As documented in Table III, the mean age was not significantly different in the patients examined in the winter and summer period, whether in male (p>0.19) or female subjects (p>0.15).

Despite comparable mean age, the overall mean value for serum 25(OH)D concentration was higher (p<0.005) in the 17 female subjects with melanoma (22.5±2.8 μg/l) than in the 22 male subjects with melanoma (15.9±1.7 μg/l). In the 16 selected female subjects with melanoma, a significant negative correlation (r= -0.5309; p<0.04) was found between 25(OH)D concentration and age.

Ovarian and cervix carcinoma. Seven patients with ovarian carcinoma and 3 patients with cervix carcinoma were also examined. No less than 7 out of these 10 subjects displayed a plasma 25(OH)D concentration <20 μg/l with a mean value of 9.0±1.9 μg/l (n=7). One 71-year-old subject with ovarian carcinoma displayed a plasma 25(OH)D carcinoma (32.0 μg/l) twice higher than the upper limit of the 95% confidence interval (16.3 μg/l) derived from the measurements made in the six other older subjects in these groups (61.8±3.9 years; n=6). As illustrated in Fig. 1, when excluding the just mentioned abnormally high value, there was a highly significant negative correlation (r= -0.8439; n=9; p<0.006) between age and serum 25(OH)D concentration in the remaining 9 patients in these two groups. As expected, covariance analysis of the results recorded in the 16 selected female subjects with melanoma and 9 selected female subjects with either ovarian or cervix carcinoma confirmed the negative correlation (r= -0.6506; p<0.001) between serum 25(OH)D concentration and age.

Table V. Serum 25(OH)D concentration in 26 subjects with breast cancer.

Months	Age (years)	25(OH)D (μg/l)
5-10	55.4±3.6 (10)	24.4±3.3 (10)
12-3	57.1±2.2 (18)	16.2±1.8 (10)

Breast cancer. Twenty-six female patients with breast cancer were also examined. Sixteen of these patients displayed a serum 25(OH)D concentration <20 μg/l (Table IV). Once again, the serum 25(OH)D concentration was higher (p<0.03) in the May to October period than in the December to March period, despite comparable age (p>0.6) in these two periods (Table V).

Unexpectedly, in these 26 subjects, there was a significant positive correlation (r=0.4193; p<0.05) between age and

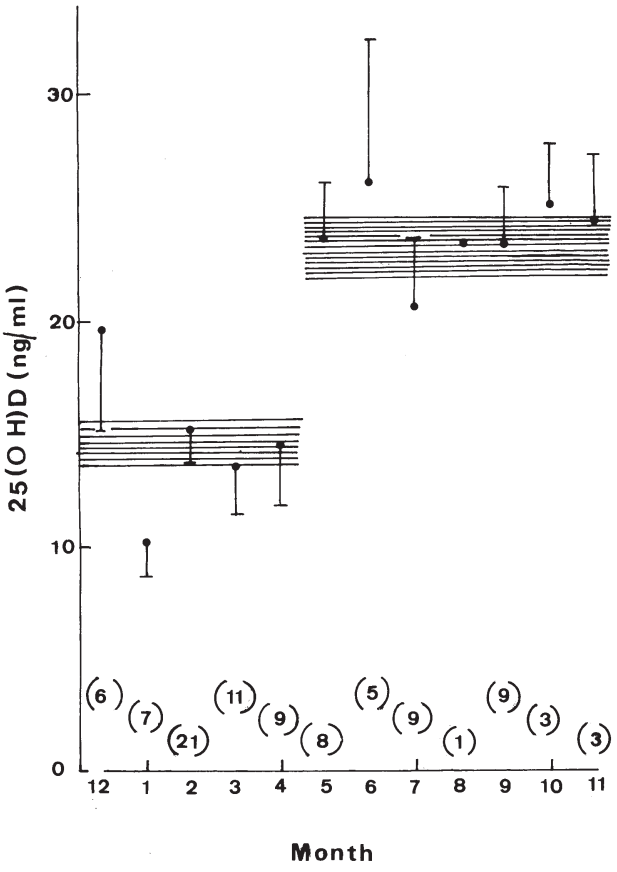

Figure 2. Serum 25(OH)D concentration in 92 cancer patients as a function of the sampling month from December (12) to November (11). Mean values (± SEM) refer to the number of individual observations indicated in parentheses at the bottom of the figure. The horizontal shaded area depicts the range (mean ± SEM) of all measurements made in the December to April and May to November periods.

serum 25(OH)D concentration. This was borne out by the fact that the latter concentration was higher ($p<0.01$) in the 13 subjects with an individual age above the mean value for the 26 patients with breast cancer (24.1±2.9 μg/l) than in the 13 subjects with an age below the same mean value (14.7±1.1 μg/l).

Yet, the overall mean age for these 26 female patients (56.1±1.9 years) did not differ significantly ($p>0.1$) from that of the other 25 female subjects considered in this study (51.3±2.8 years). Likewise, the mean 25(OH)D serum concentration in the 26 patients with breast cancer (19.3±2.0 μg/l) failed to differ significantly ($p>0.7$) from that recorded in the 25 other female subjects considered in this study (18.3±2.1 μg/l). Moreover, neither the age nor the 25(OH)D serum concentration differed significantly ($p>0.3$ or more) in the 11 breast cancer patients treated and apparently cured and the 15 breast cancer patients still affected by this disease.

Integrated data. In the 167 subjects here under consideration, the serum 25(OH)D concentration was higher ($p<0.001$) in the May to October period (23.4±1.0 μg/l; n=69) than in the November to April period (17.2±0.8 μg/l; n=98). Incidentally, in this case, such a concentration already reached in November a mean value (20.0±1.0; n=27) significantly lower (df=55; $p<0.03$) than that recorded in September (23.9±1.3; n=30), the latter value being virtually identical to that characterizing the overall May to October period.

A comparable situation prevailed when considering only the 92 cancer subjects, with mean monthly values <20 in the December to April period and >20 in the May to November period (Fig. 2). Thus, during the latter period the serum 25(OH)D concentration averaged 23.2±1.4 μg/l (n=38), as distinct ($p<0.001$) from only 14.6±1.0 μg/l (n=54) in the former period.

No gender difference was investigated in the 92 cancer subjects because their mean age was significantly higher ($p<0.001$) in male patients (64.5±2.1 years) than in female patients (53.9±1.7 years; n=51).

Last, a high incidence of serum 25(OH)D concentration <20 μg/l was recorded in all groups of subjects here under consideration. Such an incidence already amounted to 48.0% in the 75 male subjects with prostatic hyperplasia. It increased ($p<0.05$) to 59.7±4.3% in the 6 groups of cancer patients.

Discussion

The present study affords five major pieces of information. First, it reveals the high incidence of abnormally low values for serum 25(OH)D concentration, <20 μg/l, prevailing in German patients. Such a low concentration was found in ~50% of the 75 male subjects with prostatic hyperplasia, and the latter incidence was further increased in the 6 groups of cancer patients.

Second, it documents that, in most cases, the 25(OH)D serum concentration was higher in the late spring/summer/early fall period than in the rest of the year (Fig. 2). Such was the case, for instance, in the patients with prostatic carcinoma below the age of 70 years, in the male and female subjects with melanoma and in the patients with breast cancer.

Third, it indicates that, at least in certain groups, the serum 25(OH)D concentration decreased with increasing age (Fig. 1). This was most obvious in the female subjects, at the exclusion of those with breast cancer. It was also observed in the patients with prostatic hyperplasia examined in the late summer/early autumn period. It failed, however, to reach statistical significance when considering together all 116 male subjects concerned by this study. Whenever present, this age-related decrease in 25(OH)D concentration may well be attributable, in part at least, to the fact that the same light exposure increases such a concentration much more markedly in young than in aged subjects (6).

Fourth, the present results reveal a gender difference in patients with melanoma. Thus, despite comparable age, the mean value for 25(OH)D serum concentration was higher in 17 female subjects with melanoma than in 22 male subjects with melanoma.

Last, the most unexpected finding consisted in the positive correlation between age and 25(OH)D serum concentration found in female subjects with breast cancer. Such a finding contrasts with the mirror image found, as indicated above, in the other female cancer patients. Therefore, it suggests that an abnormally low serum 25(OH)D concentration represents a preferential risk, at least in female subjects under the mid-fifty age, for breast cancer as distinct from other neoplastic

. Such a proposal is consistent with both the inhibition of breast cancer cell proliferation by $1\alpha,25(OH)2D_3$ (7) and the protective effect of ultraviolet B irradiance on breast cancer risk (8).

Taken as a whole, the present study emphasizes the possible unfavourable role of vitamin D deficiency in the development of pathologic situations. In such a perspective, emphasis may be placed on the finding suggesting a link between vitamin D deficiency and the occurrence of breast cancer in middle-aged women. In our opinion, the latter finding duly merits move extensive investigations.

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