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# Association Between Prostate Cancer and 25-Hydroxyvitamin D2 Levels: National Health and Nutrition Examination Survey 2007−2008 Results

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**Purpose:** To report an association between prostate cancer and vitamin D levels among different races in a single population in the United States.

**Materials and Methods:** We investigated whether there was an association between vitamin D level and prostate cancer in different races in the United States. We used data collected from 1,363 men during the National Health and Nutrition Examination Survey 2007–2008. Multivariate logistic regression analysis was used to evaluate the independent associations between vitamin D levels (not only 25-hydroxyvitamin D [25(OH)D], but also 25(OH)D2 and D3) and prostate cancer. Association between vitamin D levels and prostate specific antigen level was also analyzed in non-Hispanic white males without prostate cancer.

**Results:** Older age was significantly associated with prostate cancer in all races ($p < 0.05$), whereas vitamin D ($p=0.024$), especially 25(OH)D2 ($p=0.027$) was significantly higher only in non-Hispanic white males. There was no difference in vitamin D levels between non-Hispanic white males with a prostate specific antigen concentration $>3$ ng/mL and $\leq 3$ ng/mL.

**Conclusions:** This study revealed a positive association between vitamin D, especially 25(OH)D2, and prostate cancer only in non-Hispanic white males. And vitamin D was not associated with prostate specific antigen level causing detection bias. **(Korean J Urol Oncol 2020;18:32-39)**

**Key Words:** Prostate cancer · Vitamin D · Age · Prostate specific antigen

## INTRODUCTION

Prostate cancer is the most common malignant cancer affecting adult males in the United States, but the etiological factors for prostate cancer are not completely understood. Vitamin D is a fat-soluble vitamin produced by exposure to sunlight or obtained from the diet. The biological functions of vitamin D include participation in bone metabolism and remodeling and antiproliferative and antiangiogenic effects.[1] Many studies have revealed that vitamin D has protective effects against the development of prostate cancer.[2-4] However, the results of a recent meta-analysis suggest that there is a positive association between higher levels of vitamin D and prostate cancer risk.[5]

Vitamin D levels are affected by skin pigmentation, which differs according to race. Levels of vitamin D are

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also determined by diet, which differs between and within Western and Asian populations. In the United States, the incidence rates of prostate cancer are 70% greater in African American compared with non-Hispanic white populations. African American populations have lower mean circulating 25-hydroxyvitamin D levels.[6]

We investigated whether there was association between vitamin D status, which was assessed using serum 25-hydroxyvitamin D (25(OH)D) concentrations, and prostate cancer in different races. We used data from the National Health and Nutrition Examination Survey (NHANES) 2007-2008 for the analysis.

## MATERIALS AND METHODS

### 1. Study Population

The NHANES is an ongoing cross-sectional observational study that collects health-related information using multistage probability sampling of the civilian, non-institutionalized United States population. The Institutional Review Board of the National Center for Health Statistics approved the protocol for the NHANES. Informed consent was obtained from all participants. We used data obtained from male participants (≥40 years of age), which was obtained during the 2007-2008 NHANES cycle.

NHANES datasets can be downloaded at NHANES website (https://wwwn.cdc.gov/nchs/nhanes). The questionnaires, data sets, and related documentation page lists all the survey cycles from the most recent to most historic. We used the current NHANES, also known as continuous NHANES, which refers to the 2-year cycles of data produced since 1999. Each cycle is divided into 5 sections labeled by collection method: demographics, dietary, examination, laboratory, and questionnaire. We could select specific variables to be included in our analysis by downloading specific files. All information regarding which files contain specific variables are listed on documentation files.

### 2. Measurement and Classification of Variables

Serum 25(OH)D metabolites were measured at a Centers for Disease Control laboratory using the Diasorin assay. The total serum 25(OH)D (nmol/L) concentration was calculated as the sum of 25(OH)D3 and 25(OH)D2, excluding the C3-epi-25(OH)D3 metabolite. Vitamin D data were collected as part of the NHANES in the southern United States during the winter months and in the northern United States during the summer months. Serum total cholesterol concentration was measured using an enzyme-based assay. In the men diagnosed with prostate cancer, all variables were measured after the diagnosis of prostate cancer. Since prostate specific antigen (PSA) varies with treatments, PSA was not evaluated in those with prostate cancer or prostatitis. Men who had prostate manipulation (e.g., prostate biopsy, surgery, or cystoscopy) within 1 month or rectal examination within 1 week were also excluded from PSA evaluation. The serum total PSA level was measured using the Hybritech method (Beckman Access, Fullerton, CA, USA).

Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared. Dietary calcium and vitamin D intake amounts were based on a single 24-hour dietary recall.

### 3. Subgroup Analysis

Each participant was assigned by race to one of 3 groups (i.e., non-Hispanic white, non-Hispanic black, and Others [e.g., Mexican American and Hispanic]). There were limited numbers of participants in the non-White race groups. Therefore, the vitamin D and PSA subgroups were confined to the non-Hispanic white group. The vitamin D intervals were taken from Tuohimaa et al.,[7] who described the U-shape of prostate cancer risk. The PSA cut point of 3.0 ng/mL was set using National Comprehensive Cancer Network guidelines[8] and subgroup analysis by PSA was done on only non-Hispanic white males without prostate cancer, and who have PSA results available.

### 4. Statistical Analysis

The results were reported as mean (standard deviation) values for continuous variables and as percentage values for categorical variables. For the univariate analysis, t-tests and analysis of variance were used to compare continuous variables. A multivariate logistic regression model was used to evaluate the association between prostate cancer and vitamin D level after adjusting for potential confounding factors that were related to an increased prostate cancer risk. We used multivariate models of logistic regression that included all risk factors that were revealed to be statistically significant by the univariate analysis and evaluated odds ratios

(ORs) by adjusting for potential confounders using a series of models. In the non-Hispanic white males without prostate cancer, multivariate logistic regression model was used to explain the relationship between PSA >3 ng/mL and other variables in the same way.

IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA) was used for the statistical analyses. All statistical tests were two-tailed, and a p-value <0.05 was considered to indicate a statistically significant result.

## RESULTS

The baseline characteristics of the study population are presented in Table 1. Among the 1,363 participants, 55.6% were non-Hispanic white. The percent who had a prostate cancer diagnosis in the non-Hispanic white group was 6.3% compared with 10.2% in the non-Hispanic black group. There were no differences in BMI between the 3 groups. The distribution in vitamin D level indicated that most of the non-Hispanic white males had adequate levels of vitamin D (i.e., ≥20 ng/mL [49.9 nmol/L], Institute of Medicine).[9] Consistent with previous study results, vitamin D levels were significantly lower in the non-Hispanic black group compared with the other races.[6] The groups with vitamin D levels <40 nmol/L had no prostate cancer compared with the groups with vitamin D levels ≥40 nmol/L (Table 2).

The results of the univariate and multivariate analyses indicated that non-Hispanic whites with a prostate cancer were significantly older and had higher 25(OH)D2 levels compared to those without a prostate cancer (Table 3). Older age was significantly associated with prostate cancer in the group of non-Hispanic blacks. However, 25(OH)D2 and 25(OH)D3 levels were not associated with prostate cancer (Table 4). Also, in the Others group, the results of univariate and multivariate analyses revealed that older age was significantly associated with prostate cancer (Table 5).

Among 710 non-Hispanic white males without prostate cancer, 688 men who have PSA results available were included in the subgroup analysis by PSA. The results of the univariate analysis indicated that the members of the non-Hispanic white group with a PSA level >3 ng/mL were significantly older and had lower body weights, lower calcium intakes, and higher 25(OH)D2 levels compared with those with PSA levels ≤3 ng/mL. However, age was the only statistically significant factor in the multivariate analysis (Table 6).

## DISCUSSION

The results of our analysis indicated that in non-Hispanic white males, higher vitamin D levels were significantly and independently associated with prostate cancer, even after adjustment for multiple potential confounding variables. To the best of our knowledge, this study of a United States

**Table 1.** Characteristics of the study population

| Characteristic | Race | | | p-value‡ |
|---|---|---|---|---|
| | White† (n=758) | Black† (n=256) | Others† (n=349) | |
| Age (yr) | 62.8±12.7 | 59.2±10.9 | 57.3±11.5 | <0.001 |
| Weight (kg) | 90.2±19.1 | 89.9±21.5 | 83.0±15.8 | <0.001 |
| Body mass index (kg/m$^2$) | 29.1±5.5 | 29.2±6.5 | 29.1±4.6 | 0.997 |
| Total cholesterol (mg/dL) | 190.4±41.4 | 198.2±41.3 | 205.1±42.0 | <0.001 |
| Calcium (mg/day)* | 954.8±568.3 | 737.8±471.7 | 903.6±570.9 | <0.001 |
| Vitamin D (25(OH)D2+25(OH)D3)* (μg/day) | 4.9±5.4 | 3.6±5.9 | 4.7±4.6 | 0.004 |
| 25(OH)D (nmol/L) | 71.3±20.7 | 44.5±18.4 | 58.3±17.6 | <0.001 |
| 25(OH)D2 (nmol/L) | 5.6±9.4 | 4.5±8.3 | 3.5±6.0 | 0.001 |
| 25(OH)D3 (nmol/L) | 65.7±21.2 | 40.0±17.7 | 54.8±17.2 | <0.001 |
| Prostate cancer | 48 (6.3) | 26 (10.2) | 5 (1.4) | <0.001 |

Values are presented as mean±standard deviation or number (%).
25(OH)D2: 25-hydroxyvitamin D2, 25(OH)D3: 25-hydroxyvitamin D3.
*Calcium and vitamin D indicate the amount taken by the diet. †These include those with prostate cancer and those without. ‡p-value calculated using analysis of variance.

**Table 2.** Characteristics of non-Hispanic white males by categories of vitamin D level

| Characteristic | Non-Hispanic White (n=758) | | | | | p-value† |
|---|---|---|---|---|---|---|
| | ≤19 (n=2) | 20-39 (n=34) | 40-59 (n=180) | 60-79 (n=308) | ≥80 (n=234) | |
| Age (yr) | 70.0±14.1 | 61.8±9.8 | 62.2±13.1 | 63.0±13.1 | 63.0±12.2 | 0.841 |
| Weight (kg) | 112.1±43.2 | 93.6±25.7 | 92.7±20.2 | 90.3±18.2 | 87.3±17.6 | 0.015 |
| Body mass index (kg/m$^2$) | 34.2±11.6 | 30.6±8.1 | 29.9±5.3 | 29.2±5.2 | 28.2±5.1 | 0.005 |
| Total cholesterol (mg/dL) | 176.5±5.0 | 193.3±49.2 | 187.8±43.0 | 190.0±40.1 | 192.5±41.0 | 0.779 |
| Calcium (mg/day)* | 670.5±430.6 | 912.2±668.2 | 873.9±479.4 | 962.1±560.6 | 1,015.9±620.3 | 0.130 |
| Vitamin D (25(OH)D2+25(OH)D3)* (μg/day) | 2.7±1.7 | 3.4±3.7 | 4.1±3.7 | 5.0±6.1 | 4.9±5.4 | 0.017 |
| 25(OH)D (nmol/L) | 1.5±0.0 | 1.6±0.4 | 3.8±5.9 | 5.8±9.0 | 7.2±12.0 | <0.001 |
| 25(OH)D2 (nmol/L) | 13.6±4.5 | 28.8±4.9 | 47.7±7.6 | 63.7±10.5 | 87.9±17.3 | <0.001 |
| 25(OH)D3 (nmol/L) | 0 (0) | 0 (0) | 10 (5.6) | 17 (5.5) | 21 (9.0) | 0.222 |

Values are presented as mean±standard deviation or number (%).
25(OH)D2: 25-hydroxyvitamin D2, 25(OH)D3: 25-hydroxyvitamin D3.
*Calcium and vitamin D indicate the amount taken by the diet. †p-value calculated using analysis of variance.

**Table 3.** Characteristics of non-Hispanic white males by prostate cancer history

| Characteristic | Never been diagnosed with prostate cancer (n=710) | Diagnosed with prostate cancer (n=48) | p-value† | p-value‡ | OR (95% CI) |
|---|---|---|---|---|---|
| Age (yr) | 62.0±12.6 | 74.4±6.8 | <0.001 | <0.001 | |
| Weight (kg) | 90.4±19.2 | 87.1±16.4 | 0.257 | | |
| Body mass index (kg/m$^2$) | 29.2±5.6 | 28.4±4.2 | 0.344 | | |
| Total cholesterol (mg/dL) | 190.7±41.5 | 184.9±39.2 | 0.345 | | |
| Calcium (mg/day)* | 955.9±571.6 | 938.0±522.9 | 0.833 | | |
| Vitamin D (25(OH)D2+25(OH)D3)* (μg/day) | 4.9±5.5 | 4.8±3.5 | 0.164 | | |
| 25(OH)D (nmol/L) | 70.8±20.5 | 78.2±22.1 | 0.015 | 0.024 | 1.017 (1.002-1.032)† |
| 25(OH)D2 (nmol/L) | 5.2±9.1 | 10.6±11.7 | 0.003 | 0.027 | 1.026 (1.003-1.050)† |
| 25(OH)D3 (nmol/L) | 65.5±21.0 | 67.7±24.2 | 0.497 | | |

Values are presented as mean±standard deviation.
25(OH)D2: 25-hydroxyvitamin D2, 25(OH)D3: 25-hydroxyvitamin D3.
*Calcium and vitamin D indicate the amount taken by the diet. †p-value calculated using t-test. ‡p-value calculated using logistic regression for multivariate analysis.

population is the first to compare differences in vitamin D levels with prostate cancer among different races.

There have been conflicting data in terms of the prostate cancer risk according to serum vitamin D levels. Our result that there was a significant positive association between 25(OH)D2 levels and prostate cancer in non-Hispanic white males is not consistent with the results of previous studies that found that higher vitamin D levels have a beneficial role.[2-4,10,11] However, several recent studies have found that elevated vitamin D levels increase the risk of prostate cancer.[5,12-14] The mechanisms that contribute to the association between greater 25(OH)D levels and prostate cancer development are unclear. However, we can speculate that at higher levels, 25(OH)D displaces $1,25(OH)_2D$ from vitamin D binding protein. Pettifor et al. and others have found that an increase in free $1,25(OH)_2D$ can result from displacement from vitamin D binding protein by higher 25(OH)D levels.[15-17] $1,25(OH)_2D$ inhibits cell proliferation, angiogenesis, and other metabolic activities. Therefore, the subsequently lower levels of $1,25(OH)_2D$ that result from 25(OH)D binding to vitamin D binding protein may promote prostate cancer development.

**Table 4.** Characteristics of non-Hispanic black males by prostate cancer history

| Characteristic | Never been diagnosed with prostate cancer (n=230) | Diagnosed with prostate cancer (n=26) | p-value† | p-value‡ |
|---|---|---|---|---|
| Age (yr) | 58.2±10.8 | 68.8±7.3 | <0.001 | <0.001 |
| Weight (kg) | 89.9±22.1 | 90.1±15.5 | 0.967 | |
| Body mass index (kg/m$^2$) | 29.1±6.7 | 30.0±5.5 | 0.504 | |
| Total cholesterol (mg/dL) | 198.4±41.7 | 196.2±38.8 | 0.796 | |
| Calcium (mg/day)* | 749.2±483.6 | 637.0±339.4 | 0.251 | |
| Vitamin D (25(OH)D2+25(OH)D3)* (μg/day) | 3.3±3.3 | 6.3±15.6 | 0.339 | |
| 25(OH)D (nmol/L) | 43.9±18.6 | 49.8±16.1 | 0.122 | |
| 25(OH)D2 (nmol/L) | 4.6±8.6 | 3.5±5.3 | 0.540 | |
| 25(OH)D3 (nmol/L) | 39.3±17.8 | 46.2±15.9 | 0.058 | |

Values are presented as mean±standard deviation.
25(OH)D2: 25-hydroxyvitamin D2, 25(OH)D3: 25-hydroxyvitamin D3.
*Calcium and vitamin D indicate the amount taken by the diet. †p-value calculated using t-test. ‡p-value calculated using logistic regression for multivariate analysis.

**Table 5.** Characteristics of the Others group (Mexican American and Hispanic) by prostate cancer history

| Characteristic | Never been diagnosed with prostate cancer (n=344) | Diagnosed with prostate cancer (n=5) | p-value† | p-value‡ |
|---|---|---|---|---|
| Age (yr) | 57.0±11.4 | 73.4±5.4 | 0.001 | 0.011 |
| Weight (kg) | 83.0±15.8 | 80.7±17.4 | 0.740 | |
| Body mass index (kg/m$^2$) | 29.1±4.6 | 29.2±4.2 | 0.956 | |
| Total cholesterol (mg/dL) | 205.6±41.8 | 176.4±51.7 | 0.124 | |
| Calcium (mg/day)* | 909.0±572.8 | 535.8±229.4 | 0.147 | |
| Vitamin D (25(OH)D2+25(OH)D3)* (μg/day) | 4.7±4.6 | 2.6±3.0 | 0.319 | |
| 25(OH)D (nmol/L) | 58.4±17.6 | 50.1±22.5 | 0.296 | |
| 25(OH)D2 (nmol/L) | 3.5±6.0 | 2.4±2.2 | 0.682 | |
| 25(OH)D3 (nmol/L) | 54.9±17.2 | 47.7±21.6 | 0.354 | |

Values are presented as mean±standard deviation.
25(OH)D2: 25-hydroxyvitamin D2, 25(OH)D3: 25-hydroxyvitamin D3.
*Calcium and vitamin D indicate the amount taken by the diet. †p-value calculated using t-test. ‡p-value calculated using logistic regression for multivariate analysis.

25(OH)D consists of 25(OH)D2 and 25(OH)D3, which are the 2 significant forms of vitamin D. 25(OH)D2 have the same effects on prostate cancer growth inhibition but with fewer hypercalcemia-related side effects. Therefore, many studies have exploited the efficacy of 25(OH)D2.[18-21] Some of the studies have analyzed total 25(OH)D without separating 25(OH)D2 and 25(OH)D3. Unlike previous studies, we analyzed 25(OH)D2 and 25(OH)D3 separately in this study. 25(OH)D2 (ergocalciferol) is a plant-based sterol found in fungi that occur on roughage. 25(OH)D3 (cholecalciferol) is animal-based sterol that can be obtained from vitamin supplements or from endogenous synthesis in the skin. Our study results indicated that only 25(OH)D2 level was significantly associated with prostate cancer in non-Hispanic white males. Normal and malignant prostate cells contain vitamin D receptor, which mediates the anti-proliferative action of 1,25 $(OH)_2D3$.[22,23] However, 1,25 $(OH)_2D3$ and 1,25$(OH)_2D2$ have similar dose-dependent inhibition effects on prostate cancer cells.[24] Therefore, we can infer that although both 25(OH)D2 and 25(OH)D3 are related to prostate cancer, the main risk factor is most likely to be 25(OH)D2 level because the differences in 25(OH)D3 are not statistically significant between those with and without prostate cancer. 25(OH)D2 and 25(OH)D3 levels have not been analyzed separately in most studies.[1,4,5,7,12] Therefore, 25(OH)D2 and 25(OH)D3 should be studied in-

**Table 6.** Characteristics of non-Hispanic white males without prostate cancer history[§] by prostate specific antigen (PSA) category

| Characteristic | PSA≤3 ng/mL (n=575) | PSA>3 ng/mL (n=113) | p-value[†] | p-value[‡] |
|---|---|---|---|---|
| Age (yr) | 60.0±12.5 | 71.2±8.1 | <0.001 | <0.001 |
| Weight (kg) | 91.3±19.5 | 85.5±17.4 | 0.003 | 0.347 |
| Body mass index (kg/m$^2$) | 29.3±5.6 | 28.5±5.1 | 0.160 | |
| Total cholesterol (mg/dL) | 191.1±41.1 | 193.0±44.2 | 0.647 | |
| Calcium (mg/day)* | 983.0±595.3 | 845.5±440.1 | 0.005 | 0.601 |
| Vitamin D (25(OH)D2+25(OH)D3)* (μg/day) | 5.0±5.3 | 4.8±6.6 | 0.695 | |
| 25(OH)D (nmol/L) | 4.9±9.0 | 6.9±9.7 | 0.046 | 0.396 |
| 25(OH)D2 (nmol/L) | 65.5±21.3 | 67.0±19.8 | 0.496 | |

Values are presented as mean±standard deviation.
25(OH)D2: 25-hydroxyvitamin D2, 25(OH)D3: 25-hydroxyvitamin D3.
*Calcium and vitamin D indicate the amount taken by the diet. [†]p-value calculated using t-test. [‡]p-value calculated using logistic regression for multivariate analysis. [§]Only non-Hispanic white males without prostate cancer history who have prostate specific antigen results available are included.

dividually, and future studies are warranted to further investigate the role of 25(OH)D2, which is just almost 10 percent of 25(OH)D3.

In Table 3, it seems that higher vitamin D levels in prostate cancer are due to the older age because the older age is the significantly associated with prostate cancer. However, because there were no significant differences in age between the vitamin D levels in Table 2, we could know that higher vitamin D level is not due to the older age.

In the NHANES study, PSA levels were not evaluated in men with prostate disorders, including prostate cancer; men with prostate cancer were excluded from the analysis of the relationship between vitamin D and PSA level. In our multivariate analysis, vitamin D was not associated with PSA level causing detection bias, similar to the research by Anic et al.,[25] which found that PSA concentration is not associated with serum 25(OH)D using NHANES 2001-2006 data.

Calcium and vitamin D intake are not associated with prostate cancer. Studies that examine the effects of vitamin D and calcium in different races, especially in Asian populations, are needed because few studies have been published.[26-29] The relationship between adiposity and prostate cancer risk has been extensively investigated but remains unclear. The results of some studies have not supported adiposity as a risk factor for prostate cancer, but a recent meta-analysis found that there is a positive association between BMI and prostate cancer risk.[30,31] However, the results of our study indicated that there was no association between BMI and prostate cancer for any race group.

This study had several limitations. First, because we used a cross-sectional study design, the presence of a causal relationship could not be evaluated. Second, the NHANES study excluded individuals with a prostate cancer from the evaluation of PSA. Therefore, a broad analysis of the relationship between PSA and vitamin D levels in prostate cancer patients could not be performed. Third, in the prostate cancer patients, all variables were measured after the prostate cancer diagnosis. However, we could not get the exact information about the interval between the prostate cancer diagnosis and the variables measurement, and the prostate cancer treatment and physical activity related to prostate cancer disease status might have affected vitamin D levels. Blood samples taken before a prostate cancer diagnosis should be used to examine the contributions of 25(OH)D2 and 25(OH)D3. Further analyses of the relationship between 25(OH)D2 and prostate cancer should be performed. Fourth, the vitamin D data were collected during the summer months in the northern latitudes and during the winter months in the southern latitudes for practical reasons. Seasonal variations in vitamin D levels could not be evaluated in this study. Fifth, positive association between 25(OH)D2 levels and prostate cancer was limited to non-Hispanic white males. Further studies with larger sample sizes in other races are required to validate our findings in non-Hispanic white males.

## CONCLUSIONS

To our knowledge, this study is the first to suggest an association between 25(OH)D2 levels and prostate cancer in non-Hispanic white males. This study revealed a positive association between vitamin D, especially 25(OH)D2, and prostate cancer, however, vitamin D was not associated with PSA level. Further studies should be performed to investigate the role of 25(OH)D2 in prostate cancer.

## CONFLICT OF INTEREST

The authors claim no conflicts of interest.

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