# Effect of serum 25-hydroxyvitamin D level on lung, breast, colorectal and prostate cancers: a nested case–control study

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## Abstract

**Background:** Published studies show that vitamin D deficiency is widespread and it has been suggested that it increases the risk of lung, breast, colorectal and prostate cancers.

**Aims:** To investigate prospectively the effect of serum 25-hydroxyvitamin D (25(OH)D) level on lung, breast, colorectal and prostate cancers in people aged 30+ years.

**Methods:** In this nested case–control study, the data and collected serum samples from a cohort study, the Balçova Heart Study, during 2007–09, were used. Additional data were collected using a questionnaire in the follow-up. We determined incident lung, breast, colorectal and prostate cancer cases during 2008 and 2013. Serum 25(OH)D levels of 606 persons (179 cases and 427 controls) from the Balçova Heart Study were measured. Odds ratio (OR) and 95% confidence interval (CI) were calculated using logistic regression analysis.

**Results:** Serum 25(OH)D levels did not show a significant association with breast, colorectal and prostate cancers. There was an inverse association between 25(OH)D level and lung cancer risk, where the OR values for the first, second and third quartiles, compared with the fourth quartile (1.00), were 2.92 (CI: 0.82–10.35), 3.76 (CI: 1.14–12.37) and 3.55 (CI: 1.04–12.08) respectively.

**Conclusion:** It was seen that low 25(OH)D levels were associated with a greater than threefold increased risk of lung cancer; no association was detected for breast, colorectal and prostate cancers. Cohort studies with larger populations are needed to better understand the effect of vitamin D level on cancer risk.

Keywords: cancer; vitamin D; 25-hydroxyvitamin D; nested case–control

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## Introduction

Breast cancer, colorectal cancer and lung cancer in women and lung cancer, prostate cancer and colorectal cancer in men are among the 5 most common cancer types. Among the various risk factors, micronutrients and vitamins are also studied. The active form of vitamin D, 1,25(OH)2D, has antineoplastic properties. In studies on human malignant cell lines, 1,25(OH)2D has been shown to decrease cell proliferation and increase cell differentiation (*1*).

The vitamin D deficiency rate is stated to be 40–100% among the elderly living in the United States of America (USA) and Europe (*2,3*). Evidence linking vitamin D deficiency with increased cancer risk and mortality has been found in studies conducted over the last 20–30 years (*2,4*). Although epidemiologic studies indicate that vitamin D levels are inversely associated with colorectal cancer (*5–12*), several studies found inconsistent results for this association (*13,14*). The findings of epidemiologic studies investigating the relationship between vitamin D and breast cancer have been inconsistent. Some nested case–control studies reported no association (*8,15–17*), whereas others reported inverse associations (*7,18–20*). Results suggesting that high vitamin D level increases prostate cancer risk were found in studies investigating the relationship between vitamin D and prostate cancer risk (*21–24*). In other studies, low vitamin D level was found to increase prostate cancer risk (*7,25*), although no significant association has also been reported (*26–28*). The number of studies investigating the relationship between vitamin D and lung cancer is limited. Cohort and nested case–control studies show no relationship between the vitamin D level and lung cancer risk (*29–31*), while some show that a low vitamin D level increases lung cancer risk (*7,32*).

The aim of this study was to investigate the effect of serum 25(OH)D levels on lung, breast, colorectal and prostate cancer prospectively in a population cohort.

## Methods

### *Study population*

The present study has a nested case–control design and was conducted in İzmir Province (38.25° N), located in the west of Turkey. The first active surveillance cancer registry in Turkey was established in Izmir. The Balcova Heart Study, a cohort study, was performed in collaboration with Dokuz Eylül University Medi-

cal School and the Municipality of Balcova District in İzmir. The baseline data collection for this study was carried out between October 2007 and May 2009. This cohort was originally set up to investigate risk factors and determine cardiovascular disease incidence. The participants comprise the largest population cohort study for chronic diseases in Turkey. In the Balçova Heart Study, questionnaires were completed and blood samples were taken from 12 915 individuals aged 30+ years; serum samples were stored under appropriate conditions (–80 °C) (33). In this study, 25(OH)D levels were measured using these serum samples. For each case and control, the 25(OH)D measurement was performed only once.

Using OpenEpi software, the sample size of the study, for OR 0.60 with 95% CI, 80% power and a case:control ratio of 1:2, was calculated as 254 cases and 508 controls, a total of 762 individuals.

The case group in this study consisted of individuals who were diagnosed with lung, breast, colorectal, prostate and ovarian cancer between 2008 and 2013. However, the ovarian cancer cases were not analysed as a separate group as only 6 cases were detected. The data for the people with cancer living in Balcova during the study period were obtained from Izmir Cancer Registry to determine the case group. In this surveillance system, quality control is carried out in line with International Association of Cancer Registries criteria (34). Among these cases, those included in the Balçova Heart Study cohort constituted the case group of the study. Those who had been diagnosed with cancer before the project were not included in the case group or the control group. Cancer cases diagnosed between 2008 and 2013 were found and included in the case list consisting of 288 individuals. However, 21 individuals were excluded since the period between diagnosis and blood sampling (0–3 months) was too short (10,11). The maximum time between sampling for 25(OH)D measurement and cancer reporting was 5 years and 3 months. For each cancer case (267), 2 individuals with no cancer diagnosis (534) were selected randomly from the cohort. Controls were frequency matched to cases in terms of age (±3 years), sex, neighbourhood and date of blood sampling (±10 days). None of the cancer cases nor the controls took a vitamin D supplement prior to blood sampling. The samples from 88 cases and 107 controls were insufficient to measure 25(OH)D levels. Frequency matching was rechecked after excluding these individuals. The laboratory analysis was carried out on samples from 179 cases and 427 controls, a total of 606 individuals. Other covariates addressed within the scope of the study were collected using an additional survey during face-to-face interviews.

Written approval for the study was obtained from the Non-Interventional Clinical Research Ethics Committee of Dokuz Eylül University (Decision No. 2012/01-24). Previously, the Balçova Heart Study Project had received approval from the Ethics Committee of Dokuz Eylül University (Decision No. 2007/337). Participants gave written consent regarding the use of serum samples in future studies within the scope of the project.

## Laboratory measurements

The best indicator of vitamin D status is serum 25(OH) D level due to its relatively long half-life (approximately 2–3 weeks) (2,3). Serum 25(OH)D level was measured using the radioimmunoassay method. Total serum vitamin D (D2 and D3) was examined using a Siemens Advia Centaur XP immunology analyser. Serum 25(OH)D measurement was performed in the Dokuz Eylül University Hospital Laboratory, which has international quality and accreditation certificates. During the serum 25(OH)D measurement, laboratory personnel were blinded. Blood samples were analysed in random sequence. Serum 25(OH)D levels were reported as ng/mL.

## Data analysis

Categorical variables were presented as numbers and percentages. Mean and standard deviation, median, first quartile (Q1), fourth quartile (Q4), minimum and maximum values of the 25(OH)D level were calculated for case and control groups. When comparing the 25(OH)D levels, the independent samples t-test was used under parametric conditions and the Mann–Whitney U test was used under non-parametric conditions. The chi-squared test for trend was used to determine the association between the case and control groups in terms of 25(OH)D quartiles. Other categorical variables were analysed using Pearson's chi-squared test.

Multinomial logistic regression analysis was used to obtain risk estimates according to serum 25(OH) D level quartiles. The variables were adjusted using cancer-specific risk factors for each cancer according to the Harvard Cancer Risk Index (35). Logistic regression analysis was done, adjusting for age, sex and body mass index (BMI) in the colorectal cancer group, plus smoking in the lung cancer group, and age and BMI in the breast and prostate cancer groups. In the control group, 25(OH)D quartiles were used as reference in grouping (1st quartile: ≤ 8.61 ng/mL, 2nd quartile: 8.62–13.67 ng/mL, 3rd quartile: 13.68–19.14 ng/mL, 4th quartile: ≥ 19.15 ng/mL). All cases ($n$ = 179), lung cancer cases ($n$ = 42) and colorectal cancer cases ($n$ = 22) were compared with all controls ($n$ = 427) in the study. For prostate cancer, only males ($n$ = 211) and for breast cancer only females ($n$ = 216) in the control group were included in the analysis.

After data analysis, using these cases and control numbers, post-hoc power calculations were made for each cancer and for all cases. The power was 95% for the lung cancer, 40% for the prostate cancer, 10% for the colorectal cancer, 4% for the breast cancer cases and 60% for all cases. $P$-value < 0.05 was accepted as the statistical significance level. Statistical analyses were performed using SPSS, version 15.0s.

**Table 1 Demographics and baseline characteristics at time of blood collection in cancer cases and controls, Izmir, 2008-2013**

| Characteristic | Cases (n = 179)[a] | Controls (n = 427) | Cancer type | | | |
|---|---|---|---|---|---|---|
| | | | Lung (n = 42) | Colorectal (n = 22) | Breast (n = 57) | Prostate (n = 52) |
| | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) |
| Age (years) | 60.5 (0.8) | 60.6 (0.5) | 64.4 (10.4) | 61.9 (12.3) | 56.0 (11.3) | 62.9 (6.8) |
| | No. (%) | No. (%) | No. (%) | No. (%) | No. (%) | No. (%) |
| ***Sex*** | | | | | | |
| Female | 89 (49.7) | 216 (50.6) | 14 (33.3) | 12 (54.5) | 57 (100.0) | – |
| Male | 90 (50.3) | 211 (49.4) | 28 (66.7) | 10 (45.5) | – | 52 (100.0) |
| ***Educational status*** | | | | | | |
| Illiterate | 13 (7.3) | 31 (7.3) | 5 (12.5) | 3 (13.6) | 5 (8.8) | – |
| Literate | 6 (3.4) | 28 (6.6) | 3 (7.5) | 1 (4.5) | – | 2 (3.8) |
| Primary | 83 (46.9) | 209 (49.3) | 18 (45.0) | 10 (45.5) | 28 (49.1) | 23 (44.2) |
| Secondary | 23 (13.0) | 45 (10.6) | 4 (10.0) | 3 (13.6) | 9 (15.8) | 7 (13.5) |
| High school | 33 (18.6) | 69 (16.3) | 8 (20.0) | 2 (9.1) | 11 (19.3) | 11 (21.2) |
| University | 19 (10.7) | 42 (9.9) | 2 (5.0) | 3 (13.6) | 4 (7.0) | 9 (17.3) |
| ***BMI (kg/m²)*** | | | | | | |
| < 25.00 | 37 (20.7) | 63 (14.8) | 12 (28.6) | 3 (13.6) | 11 (19.3) | 9 (17.3) |
| 25.00–29.99 | 81 (45.3) | 189 (44.4) | 19 (45.2) | 9 (40.9) | 20 (35.1) | 30 (57.7) |
| ≥ 30.00 | 61 (34.1) | 174 (40.8) | 11 (26.2) | 10 (45.5) | 26 (45.6) | 13 (25.0) |
| ***Smoking status*** | | | | | | |
| Current | 60 (33.9) | 110 (25.9) | 20 (50.0) | 7 (31.8) | 18 (31.6) | 14 (26.9) |
| Former | 55 (31.1) | 127 (30.0) | 14 (35.0) | 5 (22.7) | 11 (19.3) | 23 (44.2) |
| Never | 62 (35.0) | 187 (44.1) | 6 (15.0) | 10 (45.5) | 28 (49.1) | 15 (28.8) |
| ***Physical activity*** | | | | | | |
| Yes | 60 (72.3) | 201 (77.0) | 1 (50.0) | 9 (75.0) | 11 (32.4) | 27 (79.4) |
| No | 23 (27.7) | 60 (23.0) | 1 (50.0) | 3 (25.0) | 23 (67.6) | 7 (20.6) |
| ***Family history of cancer (lung, colorectal, breast, ovarian, prostate)*** | | | | | | |
| Yes | 27 (32.5) | 63 (24.1) | 1 (50.0) | 4 (33.3) | 12 (35.3) | 9 (26.5) |
| No | 56 (67.5) | 198 (75.9) | 1 (50.0) | 8 (66.7) | 22 (64.7) | 25 (73.5) |

[a]*Ovarian cancer included.*

## Results

The total number of all cancer cases was 179 and the total number of controls was 427. The mean age of all cases and controls was 60.5 years; 50.3% of cases and 49.4% of controls were male (Table 1). We found that 34.1% of cases and 40.8% of controls were obese (BMI ≥ 30.0 kg/m²). 33.9% of cases and 25.9% controls were smokers at the time of the study. Around a quarter of cases and controls were physically inactive (cases: 27.7%, controls: 23.0%). A family history of cancer was reported in 32.5% of cases and 24.1% of controls (Table 1).

The mean 25(OH)D level in cancer cases included in the study was 14.8 ng/mL (inter quartile range: 8.8–18.6 ng/mL) and the mean level in controls was 14.3 ng/mL (inter quartile range: 8.6–19.1 ng/mL). When all cancer cases were assessed together, no significant difference was found between cases and controls in terms of mean 25(OH)D level ($P > 0.05$). The mean 25(OH)D level in lung cancer cases was statistically significantly lower compared with the control group ($P < 0.05$). No significant difference was found between colorectal cancer cases and controls in terms of median 25(OH)D level ($P > 0.05$). Also, no significant difference was found between breast and prostate cancer cases and controls in terms of mean 25(OH)D level ($P > 0.05$) (Table 2).

Comparing the highest quartile of 25(OH)D level with the lower quartiles, the 25(OH)D level was not found to be associated with colorectal and breast cancer risk ($P > 0.05$). An inverse and significant relationship was found between the 25(OH)D level and lung cancer risk. When the 25(OH)D level was adjusted according to smoking, age, sex and BMI, risk increased in the first, second and third quartiles compared with the fourth quartile [2.92 (95% CI 0.82–10.35); 3.76 (95% CI 1.14–12.37); 3.55 (95% CI 1.04–12.08)] respectively. However, statistically significant risk increase was detected only in the second and third quartiles ($P < 0.05$) (Table 3).

In univariate analysis (chi-squared test for trend) prostate cancer risk increased as vitamin D level increased ($P < 0.05$, not shown in table). When the 25(OH)D level was adjusted according age and BMI in logistic regression analysis, prostate cancer risk decreased in first and second quartiles and increased in the third quartile compared

**Table 2 Serum levels of 25 (OH)D concentration among cancer and control groups, Izmir, 2008-2013**

| Group | No. | Serum level of 25 (OH)D (ng/mL) | | | | Effect size (Cohen's d) |
|---|---|---|---|---|---|---|
| | | Mean (SD) | Median (Q1, Q4)[a] | Min | Max | |
| ***All*** | | | | | | |
| Cases | 179 | 14.85 (8.51)[b] | 14.36 (8.80,18.68) | 4.20 | 77.06 | 0.07 |
| Controls | 427 | 14.31 (7.09) | 13.67 (8.61,19.14) | 4.20 | 38.48 | |
| ***Lung*** | | | | | | |
| Cases | 42 | 12.36(5.35) [b]* | 11.40 (8.00, 16.12) | 4.20 | 27.37 | 0.31 |
| Controls | 427 | 14.31 (7.09) | 13.67 (8.61,19.14) | 4.20 | 38.48 | |
| ***Colorectal*** | | | | | | |
| Cases | 22 | 13.56(6.25) | 12.78 (7.52, 18,55)[c] | 4.40 | 24.80 | 0.11 |
| Controls | 427 | 14.31 (7.09) | 13.67 (8.61,19.14) | 4.20 | 38.48 | |
| ***Breast*** | | | | | | |
| Cases | 57 | 14.48 (11.69)[b] | 11.73 (7.05, 18.62) | 4.20 | 77.06 | 0.19 |
| Controls | 216 | 12.71 (6.83) | 11.45 (6.67, 17.27) | 4.20 | 38.49 | |
| ***Prostate*** | | | | | | |
| Cases | 52 | 18.01 (6.73)[b] | 17.47 (14.25, 21.05) | 6.45 | 47.14 | 0.30 |
| Controls | 211 | 15.95 (7.01) | 14.78 (10.46, 20.54) | 4.20 | 36.26 | |

*SD = standard deviation.*

**P < 0.05*

*[a]Q1 = quartile 1, Q4 = quartile 4.*

*[b]Independent samples t-test.*

*[c]Mann–Whitney U test.*

with the fourth quartile. However, these results were not statistically significant ($P > 0.05$) (Table 3).

## Discussion

### All cancers

In light of the fact that vitamin D deficiency is common in Turkey, as in most parts of the world, this study examined the effect of serum 25(OH)D levels of individuals aged ≥ 30 years on lung, breast, colorectal and prostate cancer. When all cancer cases were examined together, no increase was observed in cancer risk for the lower quartiles compared with the highest quartile of the 25(OH)D level.

### Lung cancer

Mean 25(OH)D level of lung cancer cases was significantly lower compared with the control group. Similar results were found in a case–control study conducted in the Czech Republic (7), while no significant difference was found between cases and controls in a nested case–control study from Finland (*30*).

Compared with the highest quartile of the 25(OH)D level, cancer risk increased in the lower quartiles. Lung cancer risk significantly increased in the second quartile and third quartiles compared with the highest vitamin D quartile. However, the 95% confidence intervals in the results were very large due to there being only 4 cases in the reference group. Therefore, the results should be considered with these limitations in mind. The results of the meta-analyses published in 2015 support our findings, reporting that vitamin D level and lung cancer incidence were inversely associated (*36*).

In a cohort study conducted in Finland, no significant relationship was found for men in the lowest vitamin D level compared with the highest, whereas a high vitamin D level was significantly protective against lung cancer in women (*29*). In an ecological study comparing lung cancer incidence data and geographical location for 111 countries, it was shown that lung cancer incidence varied according to proximity to the equator. Lung cancer incidence was found to decrease in countries with higher UVB exposure. When adjusted for the effect of smoking, lung cancer incidence continued to decrease (*37*). Also, in nested case–control studies conducted in the USA and Finland, a relationship was found between vitamin D and lung cancer risk (*30,31*).

### Colorectal cancer

In meta-analyses performed in 2009 and 2011, it was seen that vitamin D level and colorectal cancer incidence were inversely associated (*13,38*). In a more recent meta-analysis published in 2017, it was found that a higher 25(OH) D level was associated with a lower risk for colorectal cancer; however, this advantage is gradually lost as levels increase beyond 50–60 ng/mL (*39*). In several nested case–control studies conducted between 2009 and 2012, the relationship between colorectal cancer and vitamin D level was not consistent (*6,8,10,11*).

In our study, there was no difference between mean level of 25(OH)D in the colorectal cancer and control groups. In 2 nested case–control studies conducted using the Nurses' Health Study and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, vitamin

**Table 3 Lung, colorectal, breast and prostate cancer risk according to serum 25-hydroxyvitamin D level quartiles, Izmir, 2008-2013**

| Group | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 |
|---|---|---|---|---|
| *Quartile values, ng/mL* | ≤ 8.61 | 8.62–13.67 | 13.68–19.14 | ≥ 19.15 |
| ***All cancers*** | | | | |
| No. cases/controls | 44/107 | 40/107 | 54/107 | 41/106 |
| OR (95% CI) | 1.06 (0.64–1.75) | 0.96 (0.57–1.61) | 1.30 (0.80–2.12) | 1.00 (ref) |
| OR (95% CI)[a] | 1.09 (0.64–1.87) | 1.01 (0.60–1.70) | 1.36 (0.83–2.24) | 1.00 (ref) |
| ***Lung*** | | | | |
| No. cases/controls | 11/107 | 15/107 | 12/107 | 4/106 |
| OR (95% CI) | 2.72 (0.84–8.82) | 3.71 (1.19–11.56) | 2.97 (0.92–9.50) | 1.00 (ref) |
| OR (95% CI)[b] | 2.92 (0.82–10.35) | 3.76 (1.14–12.37) | 3.55 (1.04–12.08) | 1.00 (ref) |
| ***Colorectal*** | | | | |
| No. cases/controls | 7/107 | 5/107 | 5/107 | 5/106 |
| OR (95% CI) | 1.38 (0.42–4.50) | 0.99 (0.27–3.52) | 0.99 (0.27–3.52) | 1.00 (ref) |
| OR (95% CI)[a] | 1.33 (0.384.70) | 1.01 (0.27–3.69) | 0.96 (0.26–3.53) | 1.00 (ref) |
| ***Breast*** | | | | |
| No. cases/controls | 22/75 | 10/52 | 12/48 | 13/41 |
| OR (95% CI) | 0.92 (0.42–2.02) | 0.60 (0.24–1.52) | 0.78 (0.32–1.91) | 1.00 (ref) |
| OR (95% CI)[c] | 0.93 (0.41–2.08) | 0.60 (0.23–1.55) | 0.79 (0.32–1.97) | 1.00 (ref) |
| ***Prostate*** | | | | |
| No. cases/controls | 3/32 | 8/55 | 22/59 | 19/65 |
| OR (95% CI) | 0.32 (0.08–1.16) | 0.49 (0.20–1.22) | 1.27 (0.62–2.58) | 1.00 (ref) |
| OR (95% CI)[c] | 0.35 (0.09–1.31) | 0.56 (0.22–1.41) | 1.35 (0.65–2.82) | 1.00 (ref) |

*OR = odds ratio; CI = confidence interval.*

[a]*Adjusted according to smoking, age, sex and body mass index (BMI).*

[b]*Adjusted according to age, sex and BMI.*

[c]*Adjusted according to age and BMI.*

D levels of cases were found to be lower compared with controls (*5*,*11*). In the nested case–control study from the European Prospective Investigation into Cancer and Nutrition cohort, a lower mean vitamin D level was significant in the colon cancer group, but not significant in rectum cancer group (*6*).

As a result of a pooled analysis using the Health Professionals Follow-up Study and the Nurses' Health Study performed in the USA, a significant relationship was found for colorectal cancer in higher levels compared with the lowest quintile (*5*). In a nested case–control study from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, colorectal cancer risk was significantly lower in the highest vitamin D quintile compared with the lowest quintile (*11*). In contrast, vitamin D level had no significant effect on colorectal cancer risk in a 2011 case–control study conducted in the USA (*13*) nor in a 2015 cross-sectional study conducted in South Korea (*14*). Similar results were obtained in our study, however, the sample size was too low to detect a small effect.

In studies which identified a relationship between vitamin D level and colorectal cancer, further studies on the biological effect of the vitamin D–colorectal cancer relationship and the genetics of vitamin D receptors are recommended as well as randomized clinical trials to evaluate whether supplementation can prevent colorectal cancer (*6*).

## Breast cancer

In epidemiological studies, it is suggested that maintaining vitamin D level in the normal range has a protective effect against breast cancer (*2*). In some reviews published between 2005 and 2013, it was noted that there is insufficient evidence to suggest that a high vitamin D level decreases risk of breast cancer, and studies to date have not been able to find adequate evidence (*2*,*4*). However, in meta-analyses performed between 2010 and 2013, vitamin D level and breast cancer were found to be inversely associated (*40*,*41*).

In our study, no significant difference was found between the breast cancer and control groups in terms of mean vitamin D level. The results of the Malmö Diet and Cancer Study (nested case–control study) support our findings (*15*). In a nested case–control study conducted in France (*20*), and in case–control studies conducted in Germany (*18*) and the Czech Republic (*7*), mean vitamin D values in breast cancer cases were found to be lower than in controls.

Although a lower breast cancer risk was seen in the lower quartiles compared with the highest 25(OH) D quartile in our study, this was not statistically

significant. The results of some other nested case–control studies also support our findings (*8,15–17*). In a nested case–control study in postmenopausal women, Green et al. found that breast cancer risk was 34% lower in the highest vitamin D quartile compared with the lowest (*42*). In another nested case–control study, it was determined that breast cancer risk was 48% lower in the highest vitamin D quartile (19). In the French E3N cohort, breast cancer risk was 27% lower in the highest vitamin D quintile compared with the lowest quintile (*20*).

### *Prostate cancer*

In studies conducted in recent years, new evidence has been obtained related to vitamin D and prostate cancer. It is noted that a low or high vitamin D level is a risk factor for prostate cancer, and vitamin D has a U-shaped effect on prostate cancer risk (*22,43,44*).

Mean vitamin D level in prostate cancer cases was not different from that of controls in our study. The vitamin D–prostate cancer relationship is still a controversial topic. There have been studies suggesting a higher vitamin D level for prostate cancer cases compared with controls (*21–24,26,28*) as well as studies suggesting the exact opposite, (*7,25*). It is noted in the current literature that experts need to be more careful in relation to vitamin D supplementation, since a high vitamin D level might increase prostate cancer risk (*43,44*).

In trend analysis, prostate cancer risk increased as vitamin D level increased. However, this relationship was not observed in the logistic regression analysis. In our study, the power was 40% for prostate cancer, which may be the reason for the lack of a significant association between vitamin D and prostate cancer. There have been case–control studies which found a trend with vitamin D levels (*23,24*). In a case–control study, Shui et al. found that when the lowest vitamin D level (14.4 ng/mL) was accepted as the reference, prostate cancer risk decreased by 13% in the second quartile, 21% in the third quartile and 14% in the fourth quartile, however this decrease was not statistically significant (*27*). In a nested case–control study, it was found that when the lowest vitamin D quintile was taken as the reference, aggressive prostate cancer risk was raised 1.12 times in the second quintile, 1.61 times in the third quintile, 1.42 times in the fourth quintile and 1.32 times in the fifth quintile (*21*). Our findings parallel the results from the meta-analysis of observational studies (3956 cases in 11 studies), showing no relationship between 25(OH)D level and risk of prostate cancer (*45*).

### *Strengths and limitations*

An important strength of this study is that it is a nested case–control study derived from a cohort study in order to evaluate the vitamin D-cancer relationship. However, the size of the cohort was rather small, which was a limitation, since it was planned in order to examine cardiovascular disease. Although it was sufficient when all cancer types are considered, it has a low power for the individual cancer types; this may be the reason for the lack of a statistically significant association between vitamin D and cancer, especially for colorectal cancer cases. Another limitation was that the 25(OH)D measurements were performed only once. Single measurements may not accurately reflect vitamin D status. However, it has been demonstrated that serum 25(OH)D concentration at a single point in time may be a useful biomarker of vitamin D status over a 5-year period (*46*). In our study, the maximum time between sampling for 25(OH)D measurement and cancer reporting was 5 years 3 months.

A recent systematic review comparing results of studies from Turkey and Europe found that 25(OH)D level was lower in the Turkish group compared with the Europeans (*3*). In our study, 81.1% of healthy controls had a vitamin D level suggesting deficiency (≤ 20 ng/mL). Although the mean 25(OH)D level in controls was lower, it was not significantly different from the cases. These low levels of vitamin D are reported in almost all population studies in Turkey, which makes it more difficult to demonstrate risk differences between groups in terms of vitamin D level.

The strengths of our study include the fact that the serum samples used to determine vitamin D level were taken before individuals were diagnosed with cancer and kept under appropriate conditions. This is the first nested case–control study investigating vitamin D and cancer relationship in Turkey. The fact that cancer cases were obtained from the Izmir Cancer Registry contributed to the certainty of cases. Vitamin D measurement was performed in a laboratory with international quality and accreditation certificates. The study was well powered (95%) to examine the lung cancer group, which showed a strong association between vitamin D and lung cancer.

## Conclusion

We found that a low vitamin D level was associated with an increased lung cancer risk. Vitamin D level and prostate cancer showed an inverse association although the relationship was not statistically significant and no relationship was found between vitamin D level and breast and colorectal cancer. Cohort studies with larger populations are required to better understand the relationship between vitamin D and cancer. Low levels of vitamin D in cases and controls might hinder the demonstration of differences in risk between groups in terms of vitamin D level. In addition, because of low vitamin D levels seen generally in the Turkish population, it is recommended to investigate the relationship between other diseases and vitamin D level.

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# Effet du taux de 25-hydroxyvitamine D sérique sur les cancers du poumon, du sein, du côlon et du rectum et de la prostate : une étude cas-témoin nichée dans une cohorte


## Résumé

**Contexte** : Les études publiées montrent que la carence en vitamine D est répandue et laissent penser qu'elle augmente le risque de cancers du poumon, du sein, du côlon et du rectum et de la prostate.

**Objectifs** : Examiner de manière prospective l'effet du taux de 25-hydroxyvitamine D sérique (25(OH)D) sur les cancers du poumon, du sein, du côlon et du rectum et de la prostate chez les personnes âgées de 30 ans et plus.

**Méthodes** : La présente étude cas-témoin nichée dans une cohorte a utilisé les données et les échantillons de sérum recueillis dans le cadre d'une étude de cohorte la « Balçova Heart Study », réalisée au cours de la période comprise entre 2007 et 2009. Des données supplémentaires ont été recueillies à l'aide d'un questionnaire lors du suivi. On a déterminé les cas incidents de cancer du poumon, du sein, du côlon et du rectum et de la prostate en 2008 et 2013. Les taux de 25(OH)D sérique de 606 personnes (179 cas et 427 témoins) obtenus lors de l'étude « Balçova Heart Study » ont été mesurés. Les odds ratio (OR) et les intervalles de confiance (IC) à 95 % ont été calculés à l'aide de l'analyse de régression logistique.

**Résultats** : Les taux de 25(OH)D sérique n'ont pas montré d'association significative avec les cancers du sein et de la prostate, ni avec le cancer colorectal. Il y avait une association inverse entre le niveau de 25(OH)D et le risque de cancer du poumon pour lequel les valeurs OR pour les premier, deuxième et troisième quartiles, par rapport au quatrième quartile (1,00), étaient de 2,92 (IC : 0,82-10,35), 3,76 (IC : 1,14-12,37) et 3,55 (IC : 1,04-12,08) respectivement.

**Conclusion** : Il a été constaté que de faibles taux de 25(OH)D étaient associés à un triplement au minimum du risque de cancer du poumon ; aucune association n'a été détectée pour les cancers du sein et de la prostate, ainsi que pour le cancer colorectal. Des études de cohorte avec des populations plus importantes s'avèrent nécessaires pour mieux comprendre l'effet du taux de vitamine D sur le risque de cancer.


# تأثير مستوى مصل 25–هيدروكسي فيتامين د على أمراض سرطان الرئة، والثدي، والقولون والمستقيم، والبروستاتا: دراسة متداخلة للحالات الإفرادية المقترنة بحالات ضابطة

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## الخلاصة

**الخلفية**: بيّنت الدراسات المنشورة انتشار نقص فيتامين د، وأشارت إلى أنه قد يكون أحد أسباب زيادة مخاطر التعرض للإصابة بأمراض سرطان الرئة، والثدي، والقولون والمستقيم، والبروستاتا.

**الأهداف**: هدفت الدراسة إلى تحري الأثر المتوقع لمستوى مصل 25–هيدروكسي فيتامين د على أمراض سرطان الرئة، والثدي، والقولون والمستقيم، والبروستاتا في الأشخاص الذين يبلغون من العمر 30 عاماً فأكثر.

**طرق البحث**: في هذه الدراسة المتداخلة للحالات الإفرادية المقترنة بحالات ضابطة، استُخدمت البيانات وعينات المصل المُجمَّعة من دراسة أترابية أُجريت في الفترة بين عامي 2007 و2009 عن أمراض القلب في منطقة بالكوفا. وجُمعت بيانات إضافية باستخدام استبيان في مرحلة المتابعة. وقد حُددت حالات الإصابة بأمراض سرطان الرئة، والثدي، والقولون والمستقيم، والبروستاتا في الفترة بين عامي 2008 و2013. وفي هذه الدراسة، خضع 606 أشخاص لقياس مستويات مصل 25–هيدروكسي فيتامين د (179 حالة إفرادية و247 حالة ضابطة). وحُسبت نسبة الأرجحية وفاصل ثقة قدره 95% باستخدام تحليل الانحدار اللوجستي.

**النتائج**: لم تثبت الدراسة وجود أي علاقة جوهرية بين مستوى مصل 25–هيدروكسي فيتامين د وبين أمراض سرطان الثدي، والقولون والمستقيم، والبروستاتا. ولكن، تبين وجود علاقة عكسية بين مستوى مصل 25–هيدروكسي فيتامين د ومخاطر الإصابة بسرطان الرئة؛ حيث أن قيم نسبة الأرجحية في الربعيات الأولى والثانية والثالثة مقارنة بالربعية الرابعة كانت 2.92 (بفاصل ثقة: 0.82–10.35)، و3.76 (بفاصل ثقة: 1.14–12.37) و3.55 (بفاصل ثقة: 1.04–12.08) على التوالي، على الرغم من أنها لم تكن أمراً جوهرياً بالنسبة للربعية الأولى.

**الاستنتاج**: اتضح ارتباط مستويات مصل 25–هيدروكسي فيتامين د المنخفضة بازدياد مخاطر الإصابة بسرطان الرئة بحوالي ثلاثة أضعاف؛ بينما لم تثبُت أي علاقة بين هذه المستويات وأمراض سرطان الثدي، والقولون والمستقيم، والبروستاتا، والمبيض. وهناك حاجة إلى إجراء مزيدٍ من الدراسات الأترابية التي تشمل عدداً أكبر من السكان، بحيث يمكن فهم أثر مستوى فيتامين د على مخاطر الإصابة بالسرطان بصورة أفضل.

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