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Serum 25-hydroxyvitamin D levels and risk of overall and site-specific cancers in Korean adults: results from two prospective cohort studies

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Abstract

Background The link between vitamin D and cancer remains inconclusive. In this study, we aimed to explore the relationship between circulating vitamin D levels and overall and site-specific cancers in Korean adults using data from two large prospective cohort studies.

Methods Baseline serum 25-hydroxyvitamin D [25(OH)D] levels were measured in a subset of participants from the Cardiovascular Disease Association Study (2005–2012) and the Health Examinees Study (2009–2013). We followed 46,514 adults aged ≥ 40 years who consented to linkage with national cancer registry data. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for cancer incidence according to quartiles of season-standardized 25(OH)D levels.

Results The median season-standardized 25(OH)D level was 45.6 nmol/L (interquartile range: 33.6–59.7 nmol/L). During the median follow-up of 10.6 years, 3,529 incident cancer cases were recorded. Compared with the first quartile, the upper quartiles of serum 25(OH)D were associated with a lower risk of overall cancer [HR (95% CI): 0.86 (0.77–0.95), 0.84 (0.75–0.93), and 0.80 (0.72–0.89), respectively; *P* for trend < 0.001]. For site-specific cancers, the HRs (95% CIs) for the comparison of extreme quartiles of serum 25(OH)D were 0.72 (0.52–0.99) for colorectal cancer, 0.32 (0.21–0.50) for liver cancer, and 0.75 (0.55–1.04) for lung cancer. Upon categorization of serum 25(OH)D levels based on absolute cut-off points, participants with levels ≥ 75 nmol/L had significantly lower risks of overall, liver, and lung cancers compared with those with levels < 30 nmol/L.

Conclusions These findings suggest that higher 25(OH)D levels are associated with a lower risk of overall and some site-specific cancers in the Korean population.

Clinical trial number Not applicable.

Keywords Vitamin D, 25-hydroxyvitamin D, Cancer incidence, Cancer registry data, Cohort study

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Background

Evidence on the role of vitamin D in skeletal health is well established, providing the basis for determining deficiency levels and intake requirements [1]. Vitamin D is primarily synthesized endogenously in the skin through exposure to sunlight (ultraviolet B, UVB) and is obtained, to a lesser extent, from dietary intake and supplements [2]. In the liver, vitamin D is metabolized to 25-hydroxyvitamin D [25(OH)D], the major circulating form of vitamin D, and is converted in the kidneys to 1,25-dihydroxyvitamin D, which regulates calcium and phosphate metabolism [2, 3]. Given the distribution of vitamin D receptors (VDRs) and vitamin D metabolic enzymes in extra-renal tissues unrelated to calcium homeostasis [4, 5], the extra-skeletal benefits of vitamin D have been investigated in various chronic diseases, including cancer [6].

Preclinical data have demonstrated the anticancer effects of vitamin D, postulating that the inhibition of tumor cell proliferation, induction of cell differentiation, and sensitization to apoptosis constitute the underlying protective mechanisms [7, 8]. Ecological studies have provided early evidence of inverse correlations between solar UVB exposure and the incidence or mortality of several cancer types, suggesting a potential role for vitamin D in cancer [9–12]. However, in epidemiological studies based on individual-level data, evidence on the role of vitamin D in cancer remains inconclusive. Results from prospective and case-control studies suggest a fairly consistent inverse association between 25(OH)D levels and the risk of colorectal cancer [13, 14], but not for overall cancer [15] or other site-specific cancers such as lung and breast cancer [16, 17]. Summary relative risks (RRs) from previous studies indicate a positive association between 25(OH)D levels and prostate cancer risk [18, 19]. Furthermore, results from prospective studies suggest that the association of 25(OH)D levels with total cancer incidence is weaker compared to that with cancer-related mortality [15]. Similar results were observed in a meta-analysis of randomized controlled trials (RCTs), where vitamin D supplementation significantly reduced total cancer mortality but had no significant effect on cancer incidence [20]. Factors other than vitamin D may have a greater influence on cancer incidence compared to cancer prognosis [7], warranting further research in this field.

Furthermore, studies on the relationship between 25(OH)D levels and the risk of overall [21, 22] and site-specific cancers [21, 23–25] among Asian populations are limited. Cancer has been the leading cause of death in the Republic of Korea since 1983, accounting for more than one in five deaths in 2022 [26]. A recent prospective cohort study reported a significant inverse association between serum 25(OH)D levels and cancer mortality, particularly for deaths due to gastrointestinal cancer [27]. Similarly, a retrospective study of Korean adults observed an inverse association between serum 25(OH)D levels and the risk of colorectal cancer [25]. However, to the best of our knowledge, no data exists on the association between 25(OH)D levels and the risk of overall and major cancers in the Korean population.

In this study, we aimed to investigate the association between serum 25(OH)D levels and the risk of overall and site-specific cancers in two large prospective cohort studies of Korean adults.

Methods

Study population

The Korean Genome and Epidemiology Study (KoGES) is a consortium project comprising three population-based cohorts and three gene-environment model studies conducted by the National Institute of Health at the Korea Disease Control and Prevention Agency (KDCA) [28]. KoGES aims to establish a health database and biobank to study risk factors of common diseases in Koreans, with the goal of reducing the burden of chronic diseases and improving quality of life. This analysis utilized two population-based cohorts from KoGES: the Cardiovascular Disease Association Study (CAVAS) and the Health Examinees (HEXA) study. CAVAS (2005–2012) enrolled 28,337 individuals aged ≥ 40 years from rural areas, while the HEXA study (2004–2013) enrolled 173,119 individuals aged ≥ 40 years from health examination centers in metropolitan and major cities. Baseline blood samples were collected and stored at − 150 °C until analysis. Follow-up surveys were conducted for CAVAS participants in six of the 11 counties and for HEXA participants in 18 of 38 centers. Additional biochemical analyses were conducted between 2018 and 2020 using frozen serum samples from a subset of participants at sites where follow-up survey had been initiated. In the HEXA study, biochemical analyses were limited to participants enrolled between 2009 and 2013 who had completed the first follow-up survey, due to the study's large scale and the need to focus on a manageable subset. In total, 21,265 CAVAS participants (98% of 21,714) and 27,998 HEXA participants (73% of 38,159) were included in the analysis, contributing additional biochemical data. Of these 49,263 participants, we excluded those with missing data on serum 25(OH)D levels ($n = 69$) or those not linked to the cancer registry data ($n = 15$). We further excluded participants with a history of cancer at baseline ($n = 1{,}828$) and those who died or were diagnosed with cancer during the first two years of follow-up ($n = 837$). Consequently, 46,514 participants were included in the present study. The KoGES was approved by the Institutional Review Boards (IRBs) of the KoGES group collaborators and the KDCA. All participants provided written

informed consent. This study was approved by the IRB of the KDCA (IRB No. 2022-07-07-C-A).

Measurement of serum 25(OH)D levels

Total serum 25(OH)D levels, including 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3, were measured using liquid chromatography-tandem mass spectrometry. For the CAVAS, serum samples were transported frozen and analyzed at Seoul Clinical Laboratories (Yongin, Korea) between 2018 and 2019 using the QTRAP 5500 mass spectrometer (AB SCIEX, Framingham, MA, USA). For the HEXA study, frozen samples were analyzed at Green Cross Laboratories (Yongin, Korea) between 2019 and 2020 using the Acquity UPLC Xevo-TQ (Waters, Milford, MA, USA). Quality control samples with known concentrations were included at regular intervals to monitor method performance. In internal quality control samples, the average coefficients of variation for 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 were each less than 5.0%. The accuracy of the analytical method was confirmed using Standard Reference Material 972a from the National Institute of Standards and Technology.

Ascertainment of cancer incidence

Cancer records were obtained from the Korea Central Cancer Registry using participants' resident registration numbers [28]. Cancer incidence was classified according to the International Classification of Diseases, 10th Revision. Classification of major cancer sites is shown in Supplementary Table 1. Information on vital status was obtained from the Cause of Death Statistics provided by Statistics Korea. Follow-up time was calculated as the interval from baseline to the date of first cancer diagnosis, death, or the end of the study period (December 31, 2020).

Assessment of covariates

Data on demographic and lifestyle factors, supplement use, medical history, and family history of cancer were collected via interviewer-administered questionnaires [28]. Smoking (pack-years) and alcohol drinking (g/day of ethanol) over the past year were calculated. Regular exercise was defined as hours per week spent on activities sufficient to induce sweating. Information on menopausal status and menopausal hormone therapy use was also obtained. Height and weight were measured by trained staff, and body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Diabetes was defined as a self-reported physician diagnosis or a fasting glucose level ≥ 126 mg/dL.

Statistical analyses

To account for seasonal variation in 25(OH)D levels in each cohort, we regressed 25(OH)D levels onto a sine and a cosine term of transformations of the month of blood draw [29]. A seasonally standardized 25(OH)D value for each participant was calculated by adding their residual from the regression to the intercept, representing the predicted annual mean concentration. Season-standardized 25(OH)D values were used for all analyses. Serum 25(OH)D levels were categorized into quartiles or guideline-suggested cut-offs [1]. Sex-specific quartiles were used for prostate and female breast cancer analyses. Cox proportional hazards models estimated adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between 25(OH)D levels and overall and site-specific cancer risk. The fully adjusted model was adjusted for age (years), sex, cohort study, education level, cigarette smoking (none, < 10, 10–< 20, 20–< 30, or ≥ 30 pack-years), alcohol drinking (none, < 5, 5–< 15, 15–< 30, or ≥ 30 g/day of ethanol), regular exercise (none, < 4.5, or ≥ 4.5 h/week), BMI (kg/m^2), diabetes, and family history of cancer. For thyroid and breast cancer analyses, menopausal status and hormone therapy use (premenopausal, postmenopausal/never use, or postmenopausal/ever use) was further adjusted. In breast cancer analysis, smoking (never- or ever-smokers) and alcohol drinking (none, < 5, or ≥ 5 g/day of ethanol) were categorized more broadly. The proportional hazards assumption was tested using time-dependent covariates and satisfied for all variables except for age in prostate cancer analysis; therefore, age-stratified Cox proportional hazards models were used for the analysis of prostate cancer (< 60 and ≥ 60 years). *P* values for trend were calculated by assigning the median value of each vitamin D category as a continuous variable.

Several subgroup analyses were performed to assess whether the observed associations were modified by other factors. First, the association between serum 25(OH)D levels (per 25 nmol/L) and overall cancer risk was stratified by subgroups, including age, sex, cohort study, smoking status, current alcohol drinking, regular exercise, BMI, and multivitamin use. Second, the association between serum 25(OH)D levels and overall and site-specific cancer risk was examined using sex- or cohort-specific quartiles. Lastly, subgroup analyses were conducted to evaluate the association between serum 25(OH)D levels and site-specific cancers, focusing on subgroups of interest, such as smoking status for lung cancer, age group for prostate cancer, and menopausal status for breast cancer. For liver cancer, the association between serum 25(OH)D levels and cancer risk was examined among participants without a history of liver disease (acute liver disease, fatty liver, chronic hepatitis, or liver cirrhosis), as assessed in 74% of participants. The statistical significance of the interaction was assessed using a likelihood ratio test, comparing models with and

without the interaction term between vitamin D levels and the subgroup variable.

A two-tailed *P*-value < 0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

The median (interquartile range) of serum 25(OH)D level was 45.6 (33.6–59.7) nmol/L (divide by 2.496 to obtain the value in ng/mL). Baseline characteristics according to the quartiles of serum 25(OH)D levels are presented in Table 1. Participants with higher serum 25(OH)D levels were more likely to be older, men, from the CAVAS cohort (recruited from rural areas), and supplement users, and less likely to have a family history of cancer. Participant' characteristics stratified by sex and cohort are shown in Supplementary Table 2.

During the median follow-up of 10.6 years (interquartile range: 9.4–12.8 years), 3,529 incident cancer cases were recorded. The risk of overall and site-specific cancers according to the quartiles of serum 25(OH)D levels is presented in Table 2. Compared with the first quartile, the HRs (95% CIs) for overall cancer risk in the second, third, and fourth quartiles were 0.86 (0.77–0.95), 0.84

Table 1 Characteristics of participants according to quartiles of serum 25(OH)D levels

	Serum 25(OH)D levels, nmol/L			
	Quartile1	**Quartile2**	**Quartile3**	**Quartile4**
	(*n* = 11,630)	**(*n* = 11,630)**	**(*n* = 11,626)**	**(*n* = 11,628)**
Serum 25(OH)D, nmol/L	26.8 (22.1–30.4)	39.7 (36.6–42.6)	52.0 (48.7–55.6)	70.6 (64.5–80.1)
Age, years	52.9 ± 8.5	54.8 ± 8.7	56.9 ± 9.0	59.2 ± 8.9
Sex				
Men	2064 (17.7)	3609 (31.0)	4832 (41.6)	6004 (51.6)
Women	9566 (82.3)	8021 (69.0)	6794 (58.4)	5624 (48.4)
Menopausal status/ hormone therapy				
Premenopausal	4192 (44.5)	2719 (34.7)	1581 (24.0)	798 (14.7)
Postmenopausal/never use	4059 (43.0)	4058 (51.9)	4017 (60.9)	3669 (67.3)
Postmenopausal/ever use	1182 (12.5)	1048 (13.4)	993 (15.1)	980 (18.0)
Cohort				
CAVAS	2450 (21.1)	4098 (35.2)	5969 (51.3)	7584 (65.2)
HEXA study	9180 (78.9)	7532 (64.8)	5657 (48.7)	4044 (34.8)
Education level				
Elementary school or below	2262 (19.6)	3082 (26.6)	4275 (36.9)	5197 (44.9)
Middle school	1728 (15.0)	1975 (17.1)	1899 (16.4)	2054 (17.7)
High school	4349 (37.7)	3959 (34.2)	3291 (28.4)	2823 (24.4)
College or above	3204 (27.8)	2551 (22.1)	2105 (18.2)	1510 (13.0)
Cigarette smoking, pack-years	3.0 ± 9.4	5.3 ± 12.6	7.7 ± 15.9	9.8 ± 17.4
Alcohol drinking, g/day of ethanol	3.6 ± 11.5	6.5 ± 29.9	8.8 ± 23.3	11.3 ± 26.1
Regular exercise, hours/week	2.3 ± 3.7	2.6 ± 4.1	2.6 ± 4.2	2.3 ± 4.1
Body mass index, kg/m^2	23.8 ± 3.1	24.3 ± 3.0	24.4 ± 3.0	24.2 ± 3.0
Multivitamin use				
No	9895 (85.4)	9696 (83.7)	9446 (81.7)	9133 (79.0)
Yes	1688 (14.6)	1892 (16.3)	2121 (18.3)	2432 (21.0)
Diabetes				
No	10,677 (91.9)	10,487 (90.2)	10,302 (88.7)	10,319 (88.9)
Yes	943 (8.1)	1137 (9.8)	1315 (11.3)	1294 (11.1)
Family history of cancer				
No	8129 (70.3)	8408 (72.7)	8496 (73.6)	8706 (75.4)
Yes	3427 (29.7)	3154 (27.3)	3048 (26.4)	2833 (24.6)
Season at blood draw				
Spring (March to May)	1530 (13.2)	1713 (14.7)	1225 (10.5)	1026 (8.8)
Summer (June to August)	4729 (40.7)	3977 (34.2)	4502 (38.7)	5010 (43.1)
Autumn (September to November)	3447 (29.6)	3014 (25.9)	2650 (22.8)	2221 (19.1)
Winter (December to February)	1924 (16.5)	2926 (25.2)	3249 (27.9)	3371 (29.0)

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CAVAS, Cardiovascular Disease Association Study; HEXA, Health Examinees

Data are presented as the median (interquartile range), mean ± SD, or n (%)

Table 2 Hazard ratios and 95% confidence intervals of overall and site-specific cancer risk according to quartiles of serum 25(OH)D levels

	Serum 25(OH)D levels[a], nmol/L				P for trend
	Quartile1	Quartile2	Quartile3	Quartile4	
Median	26.8	39.7	52.0	70.6	
No. of at risk	11,630	11,630	11,626	11,628	
Person-years	119,462	124,396	128,980	132,223	
All cancer					
No. of event	717	779	942	1,091	
HR (95% CI)[b]	Reference	0.86 (0.77–0.95)	0.84 (0.75–0.93)	0.79 (0.72–0.88)	< 0.001
HR (95% CI)[c]	Reference	0.86 (0.77–0.95)	0.84 (0.75–0.93)	0.80 (0.72–0.89)	< 0.001
Gastric cancer					
No. of event	80	102	141	175	
HR (95% CI)[b]	Reference	0.90 (0.67–1.21)	0.92 (0.69–1.22)	0.86 (0.64–1.15)	0.38
HR (95% CI)[c]	Reference	0.88 (0.66–1.19)	0.90 (0.67–1.20)	0.84 (0.62–1.13)	0.30
Colorectal cancer					
No. of event	72	83	123	127	
HR (95% CI)[b]	Reference	0.84 (0.61–1.15)	0.93 (0.68–1.26)	0.74 (0.54–1.01)	0.08
HR (95% CI)[c]	Reference	0.83 (0.60–1.14)	0.90 (0.66–1.23)	0.72 (0.52–0.99)	0.06
Liver cancer					
No. of event	49	48	68	55	
HR (95% CI)[b]	Reference	0.61 (0.41–0.92)	0.59 (0.40–0.88)	0.34 (0.22–0.52)	< 0.001
HR (95% CI)[c]	Reference	0.60 (0.40–0.90)	0.56 (0.38–0.83)	0.32 (0.21–0.50)	< 0.001
Lung cancer					
No. of event	64	89	128	158	
HR (95% CI)[b]	Reference	0.89 (0.65–1.24)	0.87 (0.63–1.19)	0.76 (0.55–1.04)	0.07
HR (95% CI)[c]	Reference	0.91 (0.66–1.26)	0.87 (0.64–1.20)	0.75 (0.55–1.04)	0.06
Thyroid cancer					
No. of event	115	119	90	84	
HR (95% CI)[b]	Reference	1.25 (0.96–1.62)	1.15 (0.86–1.53)	1.33 (0.98–1.80)	0.11
HR (95% CI)[d]	Reference	1.23 (0.95–1.60)	1.12 (0.84–1.50)	1.30 (0.96–1.77)	0.15
Prostate cancer					
Median	33.6	47.1	59.1	77.1	
Person-years	41,839	43,730	45,469	46,819	
No. of event/at risk	60/4,126	71/4,128	83/4,128	103/4,127	
HR (95% CI)[e]	Reference	1.05 (0.74–1.48)	1.11 (0.79–1.56)	1.20 (0.85–1.70)	0.25
HR (95% CI)[c]	Reference	1.07 (0.75–1.51)	1.15 (0.82–1.62)	1.31 (0.93–1.86)	0.10
Female breast cancer					
Median	24.6	36.0	47.7	65.7	
Person-years	76,834	80,547	83,742	86,081	
No. of event/at risk	89/7,500	78/7,503	70/7,505	53/7,497	
HR (95% CI)[f]	Reference	0.94 (0.69–1.28)	0.95 (0.69–1.31)	0.81 (0.57–1.17)	0.29
HR (95% CI)[d]	Reference	0.97 (0.72–1.32)	0.99 (0.72–1.38)	0.86 (0.60–1.24)	0.47

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; HR, hazard ratio; CI, confidence interval

[a]The median (interquartile range) of serum 25(OH)D levels in overall cohort, men, and women were 45.6 (33.6–59.7) nmol/L, 52.8 (41.1–66.5) nmol/L, and 41.5 (30.6–55.0) nmol/L, respectively

[b]The model was adjusted for age in years, sex, and cohort

[c]The model was further adjusted for educational level, cigarette smoking, alcohol drinking, regular exercise, body mass index, diabetes, and family history of cancer

[d]The model was further adjusted for educational level, cigarette smoking, alcohol drinking, regular exercise, body mass index, diabetes, and family history of cancer; and in women, menopausal status/hormone therapy

[e]The model was stratified by age group and adjusted for age in years and cohort

[f]The model was adjusted for age in years and cohort

(0.75–0.93), and 0.80 (0.72–0.89), respectively (*P* for trend < 0.001). Among site-specific cancers, a significant inverse association was observed between serum 25(OH)D levels and liver cancer risk. The HRs (95% CIs) for liver cancer risk in the upper quartiles were 0.60 (0.40–0.90), 0.56 (0.38–0.83), and 0.32 (0.21–0.50), respectively (*P* for trend < 0.001), compared with the first quartile. The risk of colorectal and lung cancers appeared to decline with increasing serum 25(OH)D quartiles. The HRs (95% CIs) comparing extreme quartiles were 0.72 (0.52–0.99) for colorectal cancer and 0.75 (0.55–1.04) for lung cancer (*P* for trend = 0.06 for each). When analyzing serum 25(OH)D levels using absolute cut-off points, participants with levels ≥ 75 nmol/L exhibited a 24% lower risk of overall cancer compared with those with levels < 30 nmol/L (Table 3). For site-specific cancers, significant inverse associations were observed for liver and lung cancers.

When serum 25(OH)D was analyzed as a continuous variable, the HR (95% CI) for overall cancer risk per 25 nmol/L increment was 0.93 (0.89–0.98). In subgroup analyses, significant interactions were observed between serum 25(OH)D levels and factors such as age, sex, cohort, and smoking status, in relation to overall cancer risk (Fig. 1). The inverse association between serum 25(OH)D levels and overall cancer risk was stronger among adults aged 40–59 years than those in adults aged ≥ 60 years. Further subgroup analyses were

Table 3 Hazard ratios and 95% confidence intervals of overall and site-specific cancer risk according to absolute cut-offs of serum 25(OH)D levels

	Serum 25(OH)D levels, nmol/L				P for trend
	< 30	30 to < 50	50 to < 75	≥ 75	
No. of at risk	8,382	18,976	14,900	4,256	
Person-years	85,425	203,437	167,528	48,671	
All cancer					
No. of event	510	1,306	1,289	424	
HR (95% CI)[a]	Reference	0.85 (0.77–0.94)	0.80 (0.72–0.90)	0.76 (0.66–0.88)	< 0.001
Gastric cancer					
No. of event	52	168	205	73	
HR (95% CI)[a]	Reference	0.93 (0.68–1.28)	0.96 (0.69–1.33)	0.91 (0.62–1.35)	0.82
Colorectal cancer					
No. of event	50	145	151	59	
HR (95% CI)[a]	Reference	0.86 (0.62–1.19)	0.77 (0.54–1.08)	0.82 (0.54–1.24)	0.32
Liver cancer					
No. of event	35	88	82	15	
HR (95% CI)[a]	Reference	0.61 (0.41–0.91)	0.42 (0.27–0.65)	0.19 (0.10–0.36)	< 0.001
Lung cancer					
No. of event	47	147	182	63	
HR (95% CI)[a]	Reference	0.82 (0.58–1.15)	0.76 (0.54–1.07)	0.63 (0.42–0.95)	0.03
Thyroid cancer					
No. of event	80	190	108	30	
HR (95% CI)[b]	Reference	1.29 (0.99–1.69)	1.23 (0.90–1.68)	1.52 (0.97–2.37)	0.12
Prostate cancer					
Person-years	13,158	61,580	75,805	27,313	
No. of event/at risk	19/1,318	95/5,921	148/6,890	55/2,380	
HR (95% CI)[c]	Reference	0.96 (0.58–1.57)	1.13 (0.69–1.85)	1.08 (0.62–1.86)	0.46
Female breast cancer					
Person-years	72,267	141,857	91,723	21,358	
No. of event/at risk	85/7,064	138/13,055	57/8,010	10/1,876	
HR (95% CI)[d]	Reference	1.01 (0.77–1.33)	0.81 (0.57–1.16)	0.68 (0.35–1.34)	0.13

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; HR, hazard ratio; CI, confidence interval

[a]The model was adjusted for age in years, sex, cohort, educational level, cigarette smoking, alcohol drinking, regular exercise, body mass index, diabetes, and family history of cancer

[b]The model was adjusted for age in years, sex, cohort, educational level, cigarette smoking, alcohol drinking, regular exercise, body mass index, diabetes, and family history of cancer; and in women, menopausal status/hormone therapy

[c]The model was stratified by age group and adjusted for age in years, cohort, educational level, cigarette smoking, alcohol drinking, regular exercise, body mass index, diabetes, and family history of cancer

[d]The model was adjusted for age in years, cohort, educational level, cigarette smoking, alcohol drinking, regular exercise, body mass index, diabetes, family history of cancer, and menopausal status/hormone therapy

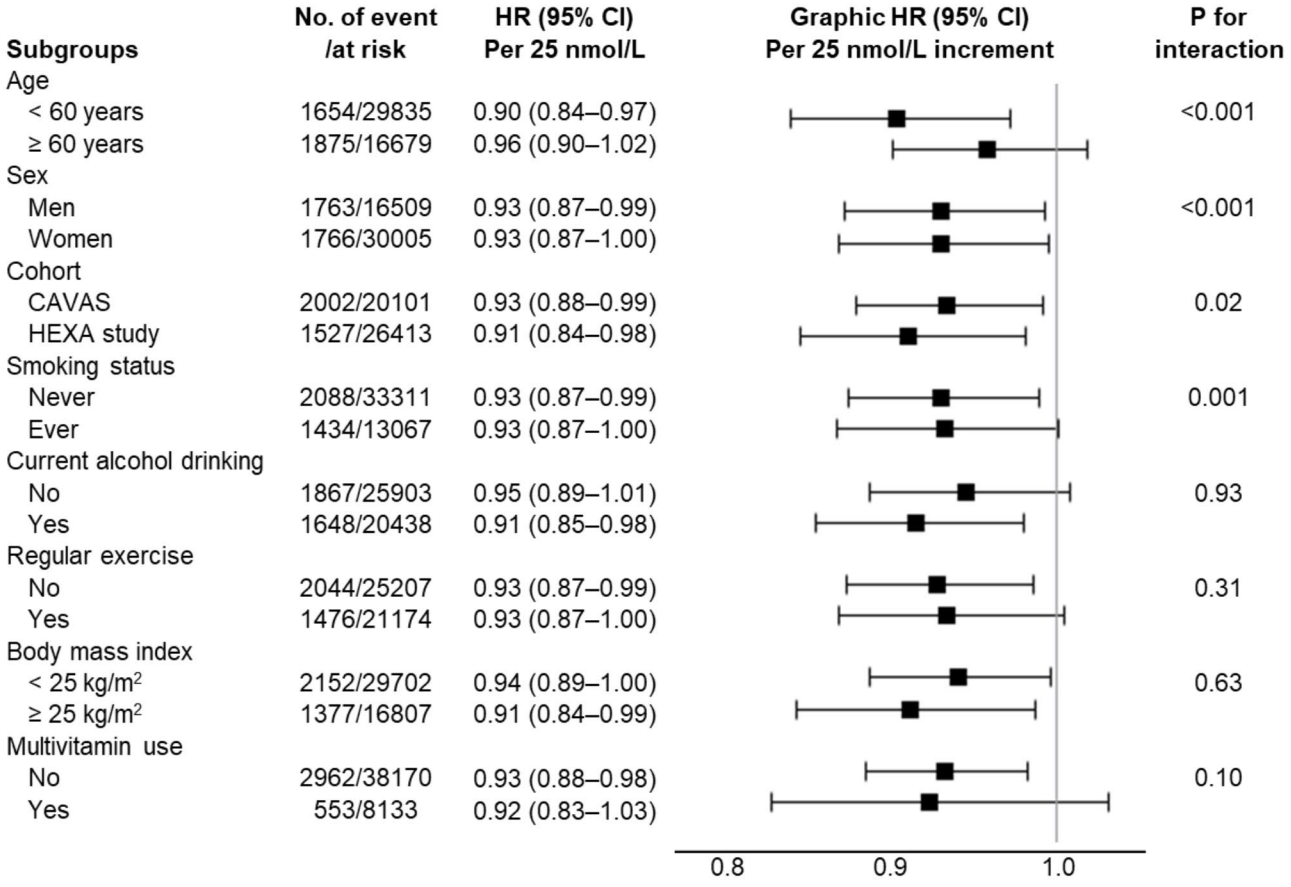

Fig. 1 Hazard ratios and 95% confidence intervals for overall cancer risk per 25 nmol/L increment in serum 25(OH)D by other factors. The model was adjusted for age in years, sex, cohort, educational level, cigarette smoking, alcohol drinking, regular exercise, body mass index, diabetes, and family history of cancer (as applicable). Abbreviations: 25(OH)D, 25-hydroxyvitamin D; HR, hazard ratio; CI, confidence interval; CAVAS, Cardiovascular Disease Association Study; HEXA, Health Examinees

conducted using sex- or cohort-specific quartiles. In sex-specific analyses, a significant inverse association was observed for liver cancer in both sexes and for lung cancer in men, while a non-significant inverse association was observed for colorectal cancer in women (Supplementary Table 3). In cohort-specific analyses, the inverse association between serum 25(OH)D levels and liver cancer was stronger in the HEXA study than in the CAVAS (Supplementary Table 4). In the HEXA study, the third quartile of serum 25(OH)D levels was associated with a higher risk of thyroid cancer compared with the first quartile. Additional subgroup analyses for selected site-specific cancers are presented in Supplementary Table 5. The association with liver cancer remained significant even after excluding participants with a history of liver disease. For lung cancer, a significant inverse association was limited to ever smokers. For prostate cancer, a non-significant positive association was observed among men aged ≥ 60 years. No significant association with breast cancer was observed when stratified by menopausal status.

Discussion

We examined the associations between 25(OH)D levels and the incidence of overall and major types of cancer in two population-based cohorts in Korea. Our findings indicate that higher serum 25(OH)D levels were associated with a lower risk of overall, colorectal, liver, and lung cancers.

A few Asian studies have examined the association between 25(OH)D levels and overall cancer risk. A large case–cohort study within the Japan Public Health Center-based Prospective (JPHC) Study, which included 3,301 incident cancer cases and 4,044 randomly selected subcohort participants, found that higher 25(OH)D levels were associated with a lower risk of overall cancer [21]. In that study, the fourth quartile of plasma 25(OH)D levels was associated with a lower risk of overall cancer compared with the first quartile (HR = 0.78; 95% CI = 0.67–0.91) [21], consistent with our results. Similarly, a small nested case–control study of Chinese adults with hypertension found that the combined second to fourth quartiles of serum 25(OH)D levels were associated

with a lower risk of overall cancer compared with the first quartile (odds ratio = 0.48; 95% CI = 0.28–0.83) [22]. Studies conducted in non-Asian populations have yielded inconsistent results. Prospective studies in American and Danish adults reported either an inverse [30, 31] or no association [32, 33] between 25(OH)D levels and overall cancer risk. Studies from Germany [34, 35], Norway [34], and Australia [36] did not support the hypothesis that higher 25(OH)D levels are associated with a lower risk of overall cancer incidence. A Swedish cohort study of older men found a U-shaped association between plasma 25(OH)D levels and overall cancer risk [37]. The inconsistency in these findings may be attributed to the heterogeneity of cancer types, differences in the race and age of study populations, and variations in follow-up duration, warranting additional investigation.

Evidence from in vitro and in vivo studies is suggestive of the antitumor activity of vitamin D against colorectal cancer, including its role in inhibiting cell proliferation and promoting epithelial differentiation through gene regulation and modulation of signaling pathways such as the Wnt/β-catenin pathway [38]. Observational studies generally support the protective role of vitamin D against colorectal cancer, particularly in women [13, 14]. In the International Pooling Project of 17 Cohorts from the United States ($n = 11$), Europe ($n = 5$), and Asia ($n = 1$; Japan), higher 25(OH)D levels were associated with a significantly lower risk of colorectal cancer in women (RR = 0.81; 95% CI = 0.75–0.87 per 25 nmol/L increment) and a non-significantly lower risk in men (RR = 0.93; 95% CI = 0.86–1.00) [14]. The reasons for these sex-based differences in the association between 25(OH)D and colorectal cancer remain unclear, and further research is needed. In this study, higher serum 25(OH)D levels were associated with a reduced risk of colorectal cancer in both men and women, with a non-significant inverse trend observed in women when analyzed separately. A recent study in Korean adults found a significant inverse association between serum 25(OH)D levels and colorectal cancer risk in both men and women: the HR (95% CI) comparing vitamin D levels ≥50 vs. <25 nmol/L was 0.43 (0.25–0.74) for women and 0.52 (0.32–0.84) for men [25]. However, in the JPHC case–cohort study, no significant association was found between plasma 25(OH)D levels and colorectal cancer risk in either sex [21].

Consistent with our study, a strong inverse association between 25(OH)D levels and liver cancer risk has been reported in nested case–control studies, including those from the European Prospective Investigation into Cancer and Nutrition cohort [39], the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [40], and the JPHC case-cohort study [21]. These studies, which included 138 to 202 liver cancer cases, found that the highest vitamin D category was associated with an approximately 49–55% lower risk of liver cancer compared to the lowest category. Similarly, a nested case–control study within the Linxian Nutrition Intervention Trial cohorts in China reported that participants in the highest quartile of serum 25(OH)D levels were associated with a lower risk of liver cancer compared to those in the second to third quartiles [41]. In addition to its role in regulating autophagy, inducing differentiation, and inhibiting proliferation, vitamin D is thought to exert anticancer effects by modulating cancer-associated fibroblasts [7]. In vitro and in vivo models have shown that VDR agonists exhibit antiproliferative and antifibrotic effects on liver fibrosis by antagonizing transforming growth factor β signaling [42, 43]. However, reverse causation is possible, as vitamin D is converted to 25(OH)D in the liver [3], and low vitamin D levels are common among patients with chronic liver disease [44]. A recent UK Biobank study found that serum 25(OH)D levels were inversely associated with the risk of severe liver disease, including hepatocellular carcinoma (HCC), a major type of liver cancer; however, no association was observed when HCC was analyzed separately [45]. In our study, the results remained robust when restricted to participants without a history of liver disease. However, further confirmation is warranted due to the limited number of cases and the potential effects of undiagnosed liver diseases.

A pooled analysis of 5,313 case–control pairs from 20 cohorts found no apparent association between 25(OH)D levels and lung cancer [46]. This study included participants from cohorts in the United States ($n = 11$), Europe ($n = 4$; Sweden, Finland, and Norway), Asia ($n = 4$; China), and Australia ($n = 1$) and adjusted for circulating cotinine levels. Subgroup analyses revealed no differences in associations by sex, smoking status, or histological subtype; however, an inverse association was observed in European cohorts [46]. Similarly, two large Danish cohort studies reported a significant inverse association between serum 25(OH)D levels and lung cancer risk [31, 47]. Although the interaction was not statistically significant, Afzal et al. observed an inverse association between plasma 25(OH)D levels and tobacco-related cancers among ever-smokers, but not among never-smokers [31], consistent with our findings. Residual confounding by smoking is unlikely to explain our findings, as serum 25(OH)D levels did not vary by smoking status or pack-years of smoking. In the JPHC study, which included proportions of women and never-smokers similar to our study, men in the upper quartiles and women in the second quartile of plasma 25(OH)D levels were associated with a lower risk of lung cancer compared with those in the first quartile [21]. These findings suggest a potential protective role of vitamin D in lung cancer, warranting further research, particularly focusing on the role of smoking.

Epidemiological evidence on the role of vitamin D in prostate and breast cancer remains inconclusive. In our study, a non-significant positive association was observed between serum 25(OH)D levels and prostate cancer risk among older men. This aligns with previous epidemiological studies reporting null or positive associations between 25(OH)D levels and prostate cancer risk [18, 19, 36, 47]. A study in the Nordic countries found that both low and high serum 25(OH)D concentrations were associated with increased prostate cancer risk, suggesting a U-shaped relationship [48]. Furthermore, a nested case–control study from the Prostate Cancer Prevention Trial suggested that vitamin D may have differential effects depending on the aggressiveness of prostate cancer; however, the biological mechanisms remain unclear [49]. In addition, since higher circulating 25(OH)D levels have been associated with improved survival in patients with prostate cancer [50], further research is warranted to clarify the potential role of vitamin D in prostate cancer prevention and treatment. A recent International Pooling Project of 17 cohorts from the United States and Europe found no significant association between 25(OH)D levels and breast cancer risk overall or in subgroups stratified by age at diagnosis, tumor characteristics, and lifestyle factors [51]. However, in the JPHC case-cohort study, premenopausal women in the third quartile of plasma 25(OH)D levels exhibited a lower risk of breast cancer compared with those in the first quartile, while no association was observed among postmenopausal women [21]. Furthermore, a pooled analysis of two RCTs and a prospective cohort of women (with a baseline median 25(OH)D level of 85 nmol/L) found a significant reduction in breast cancer risk for women with 25(OH)D levels > 150 nmol/L compared with those with < 50 nmol/L [52]. In our study, we observed no significant association between vitamin D levels and breast cancer risk, either overall or in subgroup analyses by menopausal status; however, this lack of significance may be due to limited statistical power, particularly for women with 25(OH)D levels above 100 nmol/L, highlighting the need for further investigation.

Current evidence from epidemiological studies does not support a beneficial role of vitamin D in gastric cancer. Consistent with our findings, two nested case–cohort studies from China [23] and Japan [21] found no significant association between 25(OH)D levels and gastric cancer risk. Similarly, the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers found no evidence linking 25(OH)D levels to esophageal and gastric cancer [53]. Preclinical data suggest possible benefits of vitamin D in thyroid cancer; however, human studies remain limited [54]. A recent meta-analysis reported that lower 25(OH)D levels were associated with a higher risk of thyroid cancer, although most included studies incorporated a case–control design [55]. The JPHC case–cohort study, which included a small number of thyroid cancer cases, found no significant association between plasma 25(OH)D levels and the risk of thyroid cancer [21]. In our study, higher 25(OH)D levels appeared to be associated with a higher risk of thyroid cancer, particularly among participants enrolled from health examination centers. These results should be interpreted with caution, as the follow-up period coincided with a sharp increase in thyroid cancer incidence, primarily due to overdiagnosis [56]. Future studies using repeated measurements of vitamin D and long-term follow-up in the Korean population are needed to confirm these findings.

The strengths of this study include its large sample size and registry-based follow-up over a substantial period. However, some limitations must be acknowledged. First, due to the observational design, the possibility of reverse causation and residual confounding cannot be ruled out. To mitigate reverse causation, we excluded participants diagnosed with cancer during the early follow-up period. Second, as with most prospective studies, 25(OH)D levels were measured at a single time point. However, long-term follow-up studies with repeated 25(OH)D measurements have demonstrated moderate reliability. For example, in the Northern Sweden Mammary Screening Cohort, the intraclass correlation coefficient for 25(OH)D levels measured 8 to 11.7 years apart was 0.63 [57]. Similarly, in the Tromsø Study, the correlation coefficient for serum 25(OH)D levels measured 14 years apart was 0.52 among participants whose samples were collected during the same season [58]. In that study, most individuals with low serum 25(OH)D levels were unlikely to experience substantial improvements in their vitamin D levels over time. Furthermore, although there is potential for underestimation of risk associations due to regression dilution in long-term follow-up [59], our study still observed significant associations between 25(OH)D levels and the risk of overall and site-specific cancers. Third, while serum 25(OH)D levels in both cohorts were measured using the gold standard method, differences in measurement tools could introduce variability. To address this, we estimated cohort-specific season-standardized 25(OH)D levels and adjusted for cohort in our analyses. Furthermore, stratified analyses by cohort were conducted to further assess the robustness of our findings. Fourth, the relatively small number of cases for some site-specific cancers may have limited the statistical power of our study. Finally, although participants were recruited from both rural and metropolitan areas, the generalizability of our findings may be slightly limited.

Conclusions

In conclusion, higher 25(OH)D levels were associated with a lower risk of overall and site-specific cancers, including colorectal, liver, and lung cancers, in Korean adults from two large cohort studies. Suggestive positive associations between 25(OH)D levels and the risk of prostate and thyroid cancer warrant further investigation. Our findings underscore the need for RCTs to establish a causal relationship between vitamin D and the risk of overall and site-specific cancers.

Abbreviations

25(OH)D	25-hydroxyvitamin D
HR	Hazard ratio
CI	Confidence interval
UVB	Ultraviolet B
VDR	Vitamin D receptor
RCT	Randomized controlled trial
KoGES	Korean Genome and Epidemiology Study
KDCA	Korea Disease Control and Prevention Agency
CAVAS	Cardiovascular Disease Association Study
HEXA	Health Examinees
IRB	Institutional review board
BMI	Body mass index
JPHC study	Japan Public Health Center-based Prospective study
RR	Relative risk
HCC	Hepatocellular carcinoma

Supplementary Information

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Supplementary Material 1

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Author contributions

SS and H-YP contributed to the study conception and design. SS performed statistical analyses and drafted the manuscript. HDW, JL, BMS, J-YL commented on previous versions of the manuscript. H-YP supervised the manuscript preparation. All authors read and approved the final manuscript.

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Data availability

The KoGES data are available from the Clinical & Omics Data Archive (CODA) [https://coda.nih.go.kr/frt/index.do], with the permission of the National Institute of Health in Korea. The cancer registry data linked to the KoGES data are not publicly available due to privacy and ethical restrictions.

Declarations

Ethics approval and consent to participate

The Korean Genome and Epidemiology Study (KoGES) was approved by the Institutional Review Boards (IRBs) of the KoGES group collaborators and the Korea Disease Control and Prevention Agency (KDCA). All participants provided written informed consent. This study was approved by the IRB of the KDCA (IRB No. 2022-07-07-C-A).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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