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Context: Circulating levels of 25-hydroxyvitamin D [25(OH)D] may affect the prognosis of cancer patients; however, the epidemiological results are not consistent.

Objective: To perform a meta-analysis of all published studies to assess the associations of circulating 25(OH)D levels measured at or near the time of diagnosis and outcomes for cancer patients.

Data Sources: Searches of the PubMed and MEDLINE databases were performed and updated to December 2013.

Study Selection: Studies reporting an association between circulating 25(OH)D levels at or near the time of diagnosis and outcomes for the patients were included.

Data Extraction: Data extraction was performed independently by two authors, and conflicts were resolved by a third investigator.

Data Synthesis: Included in the meta-analysis were 25 studies with 17,332 cases. Significant associations between circulating 25(OH)D levels at or near the time of diagnosis and the outcomes for cancer patients were found. The pooled hazard ratio for the highest vs the lowest quartile of circulating 25(OH)D levels was 0.55 (95% confidence interval [CI] = 0.33–0.91) for overall survival of colorectal cancer patients, 0.63 (95% CI = 0.51–0.77) for breast cancer patients, and 0.48 (95% CI = 0.36–0.64) for lymphoma patients. Higher 25(OH)D levels were significantly associated with reduced cancer-specific mortality for patients with colorectal cancer (P = .005) and lymphoma (P < .001) and improved disease-free survival for patients with breast cancer (P < .001) or lymphoma (P < .05). A 10-nmol/L increment in circulating 25(OH)D levels conferred a hazard ratio of 0.96 (95% CI = 0.95–0.97) for overall survival of the cancer patients.

Conclusions: The results indicate that cancer patients with higher circulating 25(OH)D levels at or near the time of diagnosis have better outcomes. (J Clin Endocrinol Metab 99: 2327–2336, 2014)

Vitamin D status is the result of cutaneous synthesis of vitamin D under UV irradiation and ingestion of food or vitamin D supplements. 25-Hydroxyvitamin D [25(OH)D], the major circulating metabolite of vitamin D, is derived from vitamin D via 25-hydroxylation in the liver. CYP27B1 (1α-hydroxylase), a mitochondrial enzyme present in renal proximal tubules (1), converts 25(OH)D into 1α,25-dihydroxyvitamin D [1α,25(OH)2D], the active hormonal form of vitamin D. Extrarenal expression of CYP27B1 is found in skin, colon, prostate, and breast

* M.L. and P.C. contributed equally to the study.

Abbreviations: CI, confidence interval; FL, follicular lymphoma; HR, hazard ratio; NSCLC, non-small cell lung carcinoma; 25(OH)D, 25-hydroxyvitamin D; 1α,25(OH)2D, 1α,25-dihydroxyvitamin D; RCT, randomized controlled trial; TCL, T-cell lymphoma.
Vitamin D and Cancer Prognosis

Selection strategy

Standardized inclusion criteria were applied to the retrieved studies. First, the included study should evaluate the outcomes for cancer patients, including the overall survival, cancer-specific mortality, or the disease-free survival, and patients who had their circulating 25(OH)D levels measured at or around the time of diagnosis, before any treatment. Second, each study should report the circulating 25(OH)D levels in categories for the studied population and the correlating estimated hazard ratio (HR) and its 95% confidence intervals (CIs) for the outcomes under the Cox proportional hazard model. If not, the included study should provide the HR and its 95% CI for the highest in contrast with the lowest quartile of circulating 25(OH)D level or provide sufficient data that could be used to calculate the HR and its 95% CI for the highest in contrast to the lowest quartile of circulating 25(OH)D level. Studies that reported the predicted, not determined, 25(OH)D levels were excluded. Third, eligible studies must be original reports; reviews, commentaries, case reports, and meta-analyses were excluded.

Data extraction

The following data were independently extracted from each study by two of the authors, and conflicts were resolved by a third investigator: last name of the first author, year of publication, study country, cancer type, disease stage, sample size, time of follow-up, time of blood collection, categorized circulating 25(OH)D levels, and the estimated HRs and corresponding 95% CIs for the overall survival, cancer-specific mortality, and disease-free survival that reflected the greatest degree of control for potential confounders for categories and the adjusted covariates in the statistical analysis.

Statistical analyses

The estimated HRs with their corresponding 95% CIs for the highest vs the lowest quartile of circulating 25(OH)D level were used to calculate the pooled estimates for the outcomes. To establish the appropriate weighting for each study, the SE for each logarithm HR (logHR) was calculated and was recognized as the estimated variance of the logHR. The generic inverse variance approach was applied for weighting. The DerSimonian and Laird random-effects model, which considers the variability within and between studies, was applied to calculate the pooled estimate and its 95% CI (39). Statistical heterogeneity between the studies was quantified with the Cochrane Q test, together with I² values (significance set at I² > 25%). Publication bias was represented as funnel plots and further assessed by the Egger’s linear test (40). Sensitivity studies were performed by excluding individual studies to identify any study that significantly affected the overall estimates. For those reports with subgroup study populations, the subgroup studies were recognized as individual studies.

To examine the dose effect of circulating 25(OH)D at diagnosis and the prognosis for cancer patients, we hypothesized a nonlinear dose-response relationship (41) between circulating 25(OH)D levels and overall survival of cancer patients by modeling 25(OH)D levels using the restricted cubic splines with four knots at fixed percentiles (5, 35, 65, and 95%) of the circulating 25(OH)D distribution. Those studies reported the circulating 25(OH)D levels at diagnosis in quartiles, in contrast to the lowest quartile, and providing the corresponding HR and its 95% CI for
the overall survival of cancer patients were included in the dose-response evaluation.

For each study, the median or mean level of circulating 25(OH)D for each category was assigned to its corresponding HR estimate. If the median or mean level for the category was not provided, the midpoint of the upper and lower boundaries in each category was assigned as the mean circulating level. If the lower boundary of the lowest category or the upper boundary of the highest category was not provided, it was assumed that both boundaries had the same amplitude as their closest category. Variance-weighted least-squares regressions were used to calculate the dose-response relationship for the circulating 25(OH)D levels and estimates for overall survival of the cancer patients. A \( P \) value for nonlinearity was calculated by testing the null hypothesis that the coefficients of the second and third spline transformations were equal to zero. \( P < .05 \) was considered as statistically significant. All statistical analyses were performed with Review Manager software (version 5.1) and STATA software (version 10.0; Stata Corporation).

Results

Study selection

A total of 2529 reports were identified through a systematic search of the PubMed and MEDLINE databases (Figure 1): 677 duplicates were excluded, resulting in 1852 unique reports; 1544 reports were excluded because the title and abstract failed to satisfy the inclusion criteria; and 308 potentially relevant studies were considered for evaluation. Of these, 75 nonpopulation studies, 62 nonoriginal articles, and 71 studies reporting no relevant survival outcomes were excluded. Twenty-four studies were excluded because no blood 25(OH)D levels were provided. Other studies examining diseases other than cancer, not performed with the Cox proportional hazard model, focused only on vitamin D receptor polymorphisms, or analyzing cancer mortality in the general population rather than cancer patients were also excluded (\( n = 51 \)). Thus, fully meeting the inclusion criteria were 25 studies, with a total of 17,332 cancer patients (21, 42–65) (Figure 1). Details of the characteristics of the studies are provided in Table 1. For the selected studies, five were related to colorectal cancer (21, 42–45), seven to breast cancer (45–51), three to prostate cancer (52–54), four to lung cancer (45, 55–57), two to head and neck cancer (58, 59), two to lymphoma (45, 60), two to leukemia (61, 62), one to melanoma (63), one to gastric cancer (64), and one to Merkel cell carcinoma (65). Ten studies were performed in the United States (42, 43, 50, 53–56, 60–62). Nine were conducted in European countries, including one in western Europe (44), two in Norway (45, 52), two in Germany (48, 51), one in Belgium (49), one in the United Kingdom (63), one in Austria (59), and one in France (65). Four were conducted in Asia, including one in Japan (21), one in Korea (47), and two in China (57, 64). Two studies were conducted in Canada (46, 58).

Circulating 25(OH)D levels and outcomes for colorectal cancer patients

Five studies (21, 42–45) evaluated the relationship between circulating 25(OH)D levels and the outcomes for colorectal cancer patients (Table 1). The pooled HR of the five studies (21, 42–45) under the random-effects model suggested a better overall survival for colorectal cancer patients with the highest quartile compared to those with the lowest quartile of circulating 25(OH)D levels (pooled HR = 0.55, 95% CI = 0.33–0.91, \( P = .02 \); Figure 2). Significant heterogeneity between the studies was found (\( Q = 35.87, df = 4, P < .001; I^2 = 89\% \)), but sensitivity studies suggested that no individual study significantly affected the overall estimate of the meta-analysis. As suggested by the Egger’s test, no significant publication bias was found for the included studies (\( P = .98 \). The risk for cancer-specific mortality was also found to be reduced by 35% for colorectal cancer patients with the highest quartile of circulating 25(OH)D level compared to those with the lowest quartile (pooled HR = 0.65, 95% CI = 0.47–
### Table 1. Characteristics of the 25 Included Case-Cohort Studies

<table>
<thead>
<tr>
<th>First Author, Year (Ref.)</th>
<th>Cancer Type</th>
<th>Tumor Stage, n</th>
<th>Follow-Up</th>
<th>Measure of Exposure</th>
<th>Time of Blood Collection</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ng, 2008 (42)</td>
<td>Colorectal cancer</td>
<td>HV, 304</td>
<td>Median, 78 mo</td>
<td>Mean plasma 100 ± 2 vs 41.25 ± 1 nmol/L</td>
<td>Pre-diagnosis</td>
<td>0.52 (0.29–0.94)</td>
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<tr>
<td></td>
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<td></td>
<td>Serum 40–90 vs 7.5–17.5 nmol/L</td>
<td>Perioperative period</td>
<td>0.84 (0.43–1.67)</td>
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<tr>
<td></td>
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<td></td>
<td>Plasma 68–188.5 vs 37.5–32.75 nmol/L</td>
<td>Post-diagnosis</td>
<td>0.80 (0.48–1.36)</td>
</tr>
<tr>
<td>Fedirko, 2012 (44)</td>
<td>Colorectal cancer</td>
<td>HV, 1202</td>
<td>Mean, 73 mo</td>
<td>Serum 60.6–76.8 vs &lt;36.3 nmol/L</td>
<td>Median of 46 mo before diagnosis</td>
<td>0.40 (0.1–1.6)</td>
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<tr>
<td></td>
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<td></td>
<td>Serum &gt;81 vs &lt;46 nmol/L</td>
<td>Median of 30.5 d after diagnosis</td>
<td>0.20 (0.04–1.1)</td>
</tr>
<tr>
<td>Treti, 2012 (45)</td>
<td>Colorectal cancer</td>
<td>Local, regional, distant, 52</td>
<td>From 1973–2007 to Dec 31, 2008</td>
<td>Serum &gt;81 vs &lt;46 nmol/L</td>
<td>Median of 33 d after diagnosis</td>
<td>0.37 (0.21–0.67)</td>
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<tr>
<td></td>
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<td></td>
<td>Mean of 36 d after diagnosis</td>
<td>Median of 45 d after diagnosis</td>
<td>0.18 (0.11–0.29)</td>
</tr>
<tr>
<td>Goodwin, 2009 (46)</td>
<td>Breast cancer</td>
<td>T1–3, N0–1, M0, 512</td>
<td>Mean, 11.6 y</td>
<td>Plasma &gt;72 vs &lt;50 nmol/L</td>
<td>Median of 41 d after diagnosis</td>
<td>0.33 (0.16–0.69)</td>
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<tr>
<td></td>
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<td></td>
<td>Mean of 36.4 d after diagnosis</td>
<td>Median of 116 d post-diagnosis</td>
<td>0.72 (0.53–1.16)</td>
</tr>
<tr>
<td>Kim, 2011 (47)</td>
<td>Breast cancer</td>
<td>T0-T3, 310, NR, 1295</td>
<td>Mean, 23 mo</td>
<td>Serum 75–375 vs &lt;50 nmol/L</td>
<td>Median of 30 d after diagnosis</td>
<td>0.64 (0.42–1.00)</td>
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<tr>
<td></td>
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<td></td>
<td>Serum 55 vs &lt;35 nmol/L</td>
<td>Median of 62.5 nmol/L within 120 d of diagnosis</td>
<td>0.24 (0.11–0.53)</td>
</tr>
<tr>
<td>Hame, 2012 (49)</td>
<td>Breast cancer</td>
<td>HI, 1800</td>
<td>Mean, 4.7 y</td>
<td>Serum 75 &gt; vs &lt;75 nmol/L</td>
<td>Mean of 116 d post-diagnosis</td>
<td>0.53 (0.33–0.86)</td>
</tr>
<tr>
<td>Villaseor, 2013 (50)</td>
<td>Breast cancer</td>
<td>Localized, regional, 565</td>
<td>Mean, 9.2 y</td>
<td>Serum &gt;75 vs &lt;50 nmol/L</td>
<td>Mean of 36 mo post-diagnosis</td>
<td>0.9 (0.5–1.61)</td>
</tr>
<tr>
<td>Vnelting, 2013 (51)</td>
<td>Breast cancer</td>
<td>HV, 2177</td>
<td>Mean, 5.3 y</td>
<td>Circulating 55 &gt; vs &lt;35 nmol/L</td>
<td>Median of 116 d post-diagnosis</td>
<td>0.72 (0.53–1.16)</td>
</tr>
<tr>
<td>Treti, 2009 (52)</td>
<td>Prostate cancer</td>
<td>NR, 160</td>
<td>Median, 44.0 mo</td>
<td>Serum &gt;80 vs &lt;50 nmol/L</td>
<td>Median of 116 d post-diagnosis</td>
<td>0.72 (0.53–1.16)</td>
</tr>
<tr>
<td>Fang, 2011 (53)</td>
<td>Prostate cancer</td>
<td>T1/T2,T3,T4/ N1/M1, 1822</td>
<td>Mean, 10 y</td>
<td>Mean plasma 95.875 ± 17.95 vs 40.475 ± 11.15 nmol/L</td>
<td>Median of 30.5 d after diagnosis</td>
<td>0.91 (0.72–1.15)</td>
</tr>
<tr>
<td>Holt, 2013 (54)</td>
<td>Prostate cancer</td>
<td>Localized, regional, 1476</td>
<td>Mean, 10.8 y</td>
<td>Serum &gt;127.5 vs &lt;30 nmol/L</td>
<td>Median of 116 d post-diagnosis</td>
<td>0.91 (0.72–1.15)</td>
</tr>
<tr>
<td>Zhou, 2007 (55)</td>
<td>NSCLC</td>
<td>IA, IB, 8A, 447</td>
<td>Mean, 72 mo</td>
<td>Serum (plasma) &gt;54 vs &lt;25.5 nmol/L</td>
<td>Median of 30 d after diagnosis</td>
<td>0.74 (0.5–1.1)</td>
</tr>
<tr>
<td>Heist, 2008 (56)</td>
<td>NSCLC</td>
<td>IIa, IIb, IV, 294</td>
<td>Mean, 42 mo</td>
<td>Serum (plasma) &gt;69.25 vs &lt;31.5 nmol/L</td>
<td>Median of 30 d after diagnosis</td>
<td>1.08 (0.75–1.57)</td>
</tr>
<tr>
<td>Liu, 2011 (57)</td>
<td>NSCLC</td>
<td>NR, 87</td>
<td>Mean, 72 mo</td>
<td>Serum (plasma) &gt;69.25 vs &lt;31.5 nmol/L</td>
<td>Median of 30 d after diagnosis</td>
<td>2.54 (1.01–6.41)</td>
</tr>
<tr>
<td>Meyer, 2011 (58)</td>
<td>Head and neck cancer</td>
<td>I, II, 522</td>
<td>Mean, 8.0 y</td>
<td>Serum &gt;78 vs &lt;48 nmol/L</td>
<td>Median of 30 d after diagnosis</td>
<td>0.85 (0.57–1.28)</td>
</tr>
<tr>
<td>Gugatschka, 2011 (59)</td>
<td>HNSCC</td>
<td>T1-T4, N0, M0, B8, NR, 370</td>
<td>Mean, 428 d</td>
<td>Serum &gt;62.5 vs &lt;62.5 nmol/L</td>
<td>Median of 30 d after diagnosis</td>
<td>0.89 (0.83–0.97)</td>
</tr>
<tr>
<td>Drake, 2010 (60)</td>
<td>DLBCL</td>
<td>NR, 70</td>
<td>Median, 34.8 mo</td>
<td>Serum &gt;62.5 vs &lt;62.5 nmol/L</td>
<td>Within 120 d of diagnosis</td>
<td>0.50 (0.32–0.79)</td>
</tr>
<tr>
<td></td>
<td>TCL</td>
<td>NR, 71</td>
<td>Median, 34.8 mo</td>
<td>Serum &gt;62.5 vs &lt;62.5 nmol/L</td>
<td>Within 120 d of diagnosis</td>
<td>0.42 (0.18–0.96)</td>
</tr>
<tr>
<td></td>
<td>MCL</td>
<td>NR, 285</td>
<td>Median, 34.8 mo</td>
<td>Serum &gt;62.5 vs &lt;62.5 nmol/L</td>
<td>Within 120 d of diagnosis</td>
<td>0.74 (0.29–1.89)</td>
</tr>
<tr>
<td></td>
<td>FL</td>
<td>NR, 109</td>
<td>Median, 34.8 mo</td>
<td>Serum &gt;62.5 vs &lt;62.5 nmol/L</td>
<td>Within 120 d of diagnosis</td>
<td>0.66 (0.26–1.67)</td>
</tr>
<tr>
<td></td>
<td>Post-FL</td>
<td>NR, 78</td>
<td>Median, 34.8 mo</td>
<td>Serum &gt;62.5 vs &lt;62.5 nmol/L</td>
<td>Within 120 d of diagnosis</td>
<td>0.36 (0.08–1.72)</td>
</tr>
<tr>
<td></td>
<td>ORHL</td>
<td>NR, 78</td>
<td>Median, 34.8 mo</td>
<td>Serum &gt;62.5 vs &lt;62.5 nmol/L</td>
<td>Within 120 d of diagnosis</td>
<td>0.48 (0.18–1.27)</td>
</tr>
<tr>
<td>Shanafelt, 2011 (61)</td>
<td>Chronic lymphocytic leukemia</td>
<td>0-Iv, 543</td>
<td>Mean, 36 or 118 mo</td>
<td>Serum &gt;62.5 vs &lt;62.5 nmol/L</td>
<td>Median of 2.5 or 3.2 mo post-diagnosis</td>
<td>0.68 (0.45–1.03)</td>
</tr>
</tbody>
</table>

(Continued)
No significant heterogeneity between the studies was identified ($P = .35$), and no significant publication bias was evident.

**Circulating 25(OH)D level and the outcomes for breast cancer patients**

Seven studies (45–51) evaluated the associations between circulating 25(OH)D levels at diagnosis and the outcomes for breast cancer patients. The pooled HR under the random-effects model suggested that women with the highest quartile of circulating 25(OH)D level at diagnosis showed a 37% reduced risk for all causes of death compared to those with the lowest quartile. The results were consistent between studies ($P = .32$). The estimate from four pooled studies (45, 49–51) indicated that breast cancer patients with the highest quartile of circulating 25(OH)D level had a 35% reduced risk for cancer-specific mortality relative to those with the lowest quartile of 25(OH)D level (pooled HR = 0.65, 95% CI = 0.44–0.98, $P = .04$; Figure 2). An analysis of the four pooled studies (46–49) showed a better disease-free survival for breast cancer patients with the highest quartile of circulating 25(OH)D level in contrast to those with the lowest quartile (pooled HR = 0.42, 95% CI = 0.29–0.62, $P < .001$; Figure 2). No heterogeneity between studies was identified, and no significant publication bias was found for the studies regarding the associations between the circulating 25(OH)D levels and the outcomes of breast cancer patients.

**Abbreviations:** OS, overall survival; CSM, cancer-specific mortality; DFS, disease-free survival; HNSCC, head and neck squamous cell carcinoma; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; ONHL, other non-Hodgkin’s lymphoma; NR, not reported; Ref, reference; NSCLC, non-small cell lung carcinoma.

**Table 1. Continued**

<table>
<thead>
<tr>
<th>First Author, Year (Ref.)</th>
<th>Cancer Type</th>
<th>Tumor Stage, n</th>
<th>Follow-Up</th>
<th>Measure of Exposure</th>
<th>Time of Blood Collection</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee, 2014 (62)</td>
<td>Acute myeloid leukemia</td>
<td>NR, 97</td>
<td>Median, 15.6 mo</td>
<td>Serum 80–250 vs &lt;50 nmol/L</td>
<td>Pretreatment</td>
<td>0.65 (0.25–1.67) NR 0.64 (0.26–1.56)</td>
</tr>
<tr>
<td>Newton-Bishop, 2009 (63)</td>
<td>Melanoma</td>
<td>N/A, 87</td>
<td>Medium, 4.7 y</td>
<td>Serum per 20 nmol/L increase</td>
<td>3 to 6 mo post-diagnosis</td>
<td>Post-diagnosis</td>
</tr>
<tr>
<td>Ren, 2012 (64)</td>
<td>Gastric cancer</td>
<td>N/A, 197</td>
<td>Mean, 5 y</td>
<td>Serum ≥ 50 vs &lt;50 nmol/L</td>
<td>Within 3 y after diagnosis</td>
<td>0.59 (0.37–0.91) NR NR</td>
</tr>
<tr>
<td>Samimi, 2014 (65)</td>
<td>Merkel cell carcinoma</td>
<td>NR, 89</td>
<td>Median, 10 mo</td>
<td>Serum ≥ 50 vs &lt;50 nmol/L</td>
<td>0.19 (0.03–1.33) NR NR</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Ln Hazard Ratio</th>
<th>NR, Random, 95% CI</th>
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<tbody>
<tr>
<td>Study or Subgroup</td>
<td>Weight</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>0.65 (0.25–1.67)</td>
</tr>
<tr>
<td>Newton-Bishop, 2009 (63)</td>
<td>0.83 (0.68–1.02)</td>
</tr>
<tr>
<td>Ren, 2012 (64)</td>
<td>0.59 (0.37–0.91)</td>
</tr>
<tr>
<td>Samimi, 2014 (65)</td>
<td>0.19 (0.03–1.33)</td>
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<th>Ln Hazard Ratio</th>
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<tr>
<td>Study or Subgroup</td>
<td>Weight</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>0.64 (0.26–1.56)</td>
</tr>
</tbody>
</table>

**Figure 2.** Forest plot for the highest quartile vs the lowest quartile of circulating 25(OH)D levels and outcomes for cancer patients.
Circulating 25(OH)D level and the outcomes for lung cancer patients

Patients with higher circulating 25(OH)D levels showed a better, but not statistically significant, overall survival (pooled HR = 0.75, 95% CI = 0.30–1.86, P = .54; Figure 2), as determined by pooling four studies (45, 55–57). Significant heterogeneity was evident (Q = 43.70, df = 3, P < .001; I² = 93%). Of the identified studies, Tretti et al (45) suggested that patients with higher circulating 25(OH)D levels showed a reduced risk for cancer-specific mortality (HR = 0.18, 95% CI = 0.11–0.29); however, another study, performed by Zhou et al (55), reported no significant association for circulating 25(OH)D levels at diagnosis and disease-free survival. Both studies were performed with a relatively small sample of patients. The association of circulating 25(OH)D levels with the outcomes for lung cancer patients needs further investigation.

Circulating 25(OH)D level and outcomes for lymphoma patients

Two studies (45, 60) evaluated the association between circulating 25(OH)D levels at diagnosis and the outcomes of lymphoma patients. Drake et al (60) stratified lymphoma patients into groups of diffuse large B cell lymphoma, mantle cell lymphoma, follicular lymphoma (FL), post-FL (including marginal zone and lymphoplasmacytic lymphoma), and T-cell lymphoma (TCL; including peripheral TCL, anaplastic large cell lymphoma, cutaneous TCL, and TCL not otherwise specified), as well as all other non-Hodgkin lymphomas. In the current analysis, each subgroup study was recognized as an individual study and was pooled to calculate the overall estimate. Lymphoma patients with high 25(OH)D levels were associated with better overall survival (pooled HR = 0.48, 95% CI = 0.36–0.64, P < .001; Figure 2) compared to those with the lowest quartile of 25(OH)D level, with no heterogeneity. Patients with the highest quartile of circulating 25(OH)D levels also showed a reduced risk of cancer-specific mortality (pooled HR = 0.50, 95% CI = 0.36–0.68, P < .001; Figure 2) and better disease-free survival (pooled HR = 0.80, 95% CI = 0.65–0.98, P = .04; Figure 2). No significant heterogeneity between studies was found for either study, and no significant publication bias was noticed.

Circulating 25(OH)D level and the outcomes for other cancer patients

A limited number of studies reported associations between circulating 25(OH)D levels (before or after diagnosis) and the outcomes for patients with prostate cancer (52–54), head and neck cancer (58, 59), leukemia (61, 62), melanoma (63), gastric cancer (64), or Merkel cell carcinoma (65). Tretti et al (52) found that prostate cancer patients with higher circulating 25(OH)D levels before any treatment showed a better overall survival and reduced risk for cancer-specific mortality. Fang et al (53) found that prostate cancer patients with a lower concentration of prediagnostic plasma 25(OH)D had a higher risk of developing fatal prostate cancer. Holt et al (54) reported that serum 25(OH)D levels, measured after diagnosis, were not associated with prostate cancer prognosis, but lower levels were associated with an increased risk of non-prostate cancer mortality. Gugatschka et al (59) reported that higher circulating 25(OH)D levels at diagnosis were positively associated with better disease-free survival and overall survival for patients with head and neck squamous cell carcinomas, while another study performed by Meyer et al (58) found no significant association between overall survival and the pretreatment levels of serum 25(OH)D. Two studies (61, 62) evaluated the association between survival of subtype leukemia patients and their circulating 25(OH)D levels at diagnosis. 25(OH)D insufficiency was associated with poor overall survival of patients with newly diagnosed chronic lymphocytic leukemia, although the P value was not statistically significant (P = .07) (61). For acute myeloid leukemia, patients with insufficient/deficient 25(OH)D levels had a worse relapse-free survival compared with those who had normal levels (62). Newton-Bishop et al (63) found that vitamin D reduced the risk of relapse from melanoma. For gastric cancer, Ren et al (64) reported that patients with high vitamin D levels (≥50 nmol/L) had a better overall survival compared with those with low levels (<50 nmol/L). Samimi et al (65) found that vitamin D deficiency was associated with greater tumor size at diagnosis and metastatic recurrence in patients with Merkel cell carcinoma, but not with death from this carcinoma. These studies suggested a protective effect for 25(OH)D in the outcomes for patients with various types of cancer; however, more epidemiological studies are warranted to validate the results.

Dose-response meta-analysis of circulating 25(OH)D levels and overall survival of cancer patients

Thirteen (21, 42–46, 48, 49, 53, 56–59) studies were included to assess the dose-response relationship between circulating 25(OH)D levels and overall survival of cancer patients. There was evidence of a statistically significant departure from linearity (P = .006) for the correlation between circulating 25(OH)D levels at diagnosis and overall survival. A 10-nmol/L increment in circulating 25(OH)D level at diagnosis was associated with a 4% reduction in deaths of all causes (pooled HR = 0.96, 95% CI = 0.95–0.97, P < .001; Figure 3) when 25(OH)D levels were in the range of 40–70 nmol/L compared to those with less than 19 nmol/L.
Discussion

Epidemiological studies have suggested that vitamin D decreases the risk of various types of cancer, although the results were not always consistent (66). Recently, the effects of vitamin D on the prognosis for cancer patients have been considered. In the current effort, 25 studies that evaluated associations between circulating 25(OH)D levels and the outcomes for cancer patients were systematically reviewed and assessed with meta-analysis methods. The results indicate that higher circulating 25(OH)D levels at diagnosis are significantly associated with better outcomes for patients with colorectal cancer, breast cancer, or lymphoma. Limited, but favorable, evidence was found for patients with lung cancer, gastric cancer, prostate cancer, leukemia, melanoma, or Merkel cell carcinoma. There was a nonlinear dose-effect relationship for blood 25(OH)D levels and the overall survival of cancer patients. These data indicate that circulating 25(OH)D levels could be an independent factor for prognosis of various types of cancers. However, the underlying mechanisms are unclear, and further investigations are warranted.

Ecological studies show that higher solar UVB exposure correlates with the mortality rate, rather than incidence, of cancers, indicating that dysfunctions of vitamin D may be involved in the progression of cancers (67, 68). There are several possible explanations for the associations between higher levels of circulating 25(OH)D and better outcomes for cancer patients. First, 1α,25(OH)2D and its analogs may reduce the progression of cancers by acting on tumor cells (69) and modulating the tumor microenvironment (70, 71). Moreover, considering the biological effects of vitamin D on bone health, patients with cancer types that are prone to bone metastases may benefit from the improvement of bone health by vitamin D. Second, vitamin D insufficiency is associated with many health conditions, including autoimmune diseases, diabetes, cardiovascular disease, infectious disease, and also with increased mortality (72, 73). Due to the limited data of randomized controlled trials (RCTs), it is unclear whether vitamin D status is causally related to diseases or if circulating 25(OH)D merely acts as a biomarker for health status of patients. Cancer patients with higher 25(OH)D levels had an improved overall survival, which was probably due to better health status. In addition, statistically significant associations between circulating 25(OH)D levels and cancer-specific mortality or disease-free survival were also found for patients with colorectal cancer, breast cancer, or lymphoma. However, the causal relationship for vitamin D and cancer prognosis needs to be established with RCTs. Third, cancer patients, especially those with advanced stages of disease, may have changed their lifestyle, including reduced physical activity and outdoor activities, which would decrease the body levels of vitamin D. However, this factor is not considered to be the major reason for the present findings because most patients recruited in the individual studies had their blood samples collected before or at the time of diagnosis and before any treatment. For those studies with blood samples collected after diagnosis, the samples were usually collected shortly after the diagnosis and before any treatment. Moreover, for most of the included studies, no significant difference in 25(OH)D levels was found for patients with early or later stages of the diseases, suggesting that the circulating 25(OH)D level at or around the time of diagnosis is an independent prognosis factor for cancer patients.

As determined by the meta-analysis, there was a consistent association between the circulating 25(OH)D levels and better overall survival for patients with breast cancer or lymphoma, as suggested by the Q-test and the I2 statistic. However, significant heterogeneity between the studies was found between the overall survival of colorectal cancer patients and circulating 25(OH)D levels. One study performed with metastatic colorectal cancer patients contributed most to the heterogeneity, suggesting a null association between circulating 25(OH)D levels and cancer outcomes (43). When this study was excluded, there was an improved overall survival for those colorectal patients with higher 25(OH)D levels (data not shown). Overall, these data suggest that vitamin D has a limited impact for patients with metastatic colorectal cancer. Loss of response of colon tumor cells to vitamin D may occur...
because vitamin D receptor expression is decreased in the late stages of the disease (74). Thus, the impact of vitamin D supplements would depend largely on the time when they are applied. In addition, considering that the follow-up time and the population size may influence the estimated HRs for vitamin D levels and the outcomes of cancer patients, meta-regression studies were applied as suggested by Harbord and Higgins (75) to determine whether the statistical heterogeneity between results was due in part to the follow-up time or the population size between the studies of colorectal cancer, breast cancer, and lung cancer patients. There was no significant correlation between the follow-up time or the population size and the logHRs for overall survival of the patients (highest vs lowest category), suggesting that follow-up time and the population size are not acting as codeterminant factors for the estimated HRs ($P > .05$; Supplemental Table 1). Similar results were found for the logHRs for disease-free survival and cancer-specific mortality (Supplemental Table 1).

Based on the rationale for vitamin D intervention in cancer prevention and treatment, intervention studies have been initiated. The recent Institute of Medicine report calls for 600 IU of vitamin D daily for people up to 70 years old and 800 IU thereafter, and the safe upper limit is raised to 4000 IU daily for adults (76). However, the recommended doses are largely dependent on bone health. The dose that could be effective for reducing cancer risk or preventing mortality is unknown. Intervention trials performed with cancer patients found a significant increase in 25(OH)D levels when they were provided with high dose vitamin D3 (eg, 10 000 IU daily; 50 000 IU weekly); there was no significant increase of 25(OH)D when 400 to 1000 IU vitamin D3 was provided (77–81). Thus, no significant physiological impact could be found when a low dose of vitamin D was given to the cancer patients. In addition to the effective dose, other issues such as intervention time, the intervention methods, and potential side effects need to be considered in clinical trials. Well-designed, randomized clinical trials are warranted to answer these questions.

Limitations of the current meta-analysis should be acknowledged. First, most of the studies evaluated only one measurement of circulating 25(OH)D levels, and the time for the blood sample collection was not always consistent. Because measurements of 25(OH)D levels were conducted by RIA or liquid chromatography-tandem mass spectrometry, systematic bias may exist between the measurement methods. Second, the quartiles of circulating 25(OH)D levels were different between studies. Through standardizing the circulating 25(OH)D levels and calculating the overall survival of cancer patients with dose-response methods, we found that a 10-nmol/L increment in blood 25(OH)D level conferred a 4% reduction of overall mortality of cancer patients, although there was considerable deviation from linearity for the dose-response. Third, the benefits of vitamin D on the prognosis of cancer patients were based on observational studies; randomized, placebo-controlled trials could elucidate the potential benefits of vitamin D on outcomes for cancer patients.

In conclusion, the present data suggest that cancer patients with higher circulating 25(OH)D levels, determined at or near the time of diagnosis and before any treatment, are associated with improved overall survival, reduced cancer-specific mortality, and better disease-free survival for various cancer types. However, more intervention studies are required to elucidate the clinical benefits of vitamin D supplements for cancer patients.

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**References**

5. Hsu JY, Feldman D, McNeal JE, Pechl DM. Reduced 1α-hydroxylase activity in human prostate cancer cells correlates with decreased


