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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Serum Levels of 25-Hydroxyvitamin D at Diagnosis Are Not Associated with Overall Survival in Esophageal Adenocarcinoma

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Abstract

Background: Higher levels of circulating 25-hydroxyvitamin D [25(OH)D] are associated with longer survival in several cancers, but the results have differed across cancer sites. The association between serum 25(OH)D levels and overall survival (OS) time in esophageal adenocarcinoma remains unclear.

Methods: We utilized serum samples from 476 patients with primary esophageal adenocarcinoma, recruited from Massachusetts General Hospital (Boston, MA) between 1999 and 2015. We used log-rank tests to test the difference in survival curves across quartiles of 25(OH)D levels and extended Cox modeling to estimate adjusted HRs. We tested for interactions between clinical stage or BMI on the association between 25(OH)D and OS. We additionally performed sensitivity analyses to determine whether race or timing of blood draw (relative to treatment) affected these results.

Results: We found no evidence that survival differed across quartiles of 25(OH)D (log rank $P = 0.48$). Adjusting for confounders, we found no evidence that the hazard of death among the highest quartile of 25(OH)D (quartile 1) differed from any other quartile [quartile 2 HR = 0.90, 95% confidence interval (CI), 0.67–1.23; quartile 3 HR = 1.03, 95% CI, 0.76–1.38; quartile 4 (lowest) HR = 0.98, 95% CI, 0.72–1.33]. Sensitivity analyses yielded consistent results when accounting for race or time between diagnosis and blood draw. Moreover, we did not find evidence of interaction between 25(OH)D and clinical stage or BMI on OS.

Conclusions: Serum level of 25(OH)D near time of diagnosis was not associated with OS in patients with esophageal adenocarcinoma.

Impact: Screening 25(OH)D levels among patients with esophageal adenocarcinoma at diagnosis is not clinically relevant to their cancer prognosis based on present evidence.

Introduction

Esophageal adenocarcinoma is the predominant subtype of esophageal cancer in western countries, with increasing incidence over the last five decades, particularly in White men (1–6). Esophageal adenocarcinoma remains a deadly disease with an average 5-year survival of less than 20% (2). The current best predictor of esophageal adenocarcinoma survival time is clinical stage at diagnosis (1, 2). Yet, even half of patients with stage I disease at diagnosis do not survive past five years (2). Few, if any, modifiable factors are known to improve prognosis after diagnosis. Thus, markers of prognosis, especially modifiable factors, are in high demand to identify both patients at risk of poor clinical outcomes and interventions that can improve patient outcomes.

Recently, *in vitro* and *in vivo* studies of the vitamin D pathway have demonstrated its oncosuppressive effects, including regulating pathways that inhibit proliferation, angiogenesis, and inflammation as well as pathways that promote cell adhesion and induce apoptosis (7–11). Hypothetically, if the downstream metabolite of vitamin D, [1,25(OH) $_2$D], directly regulates oncosuppressive cell signaling, then more intake of vitamin D should generate more downstream regulation and have a protective effect on the development and progression of cancer. With supplements that are cheap and readily available, vitamin D makes a particularly attractive potential intervention. This, coupled with the biologically plausible mechanism, has generated widespread interest in the role of the vitamin D pathway in cancer initiation and progression.

Clinically and in epidemiologic studies, 25-hydroxyvitamin D [25(OH)D], an upstream serum-circulating metabolite, reflective of both sun exposure and dietary intake (8, 12), is used as a marker of bioavailable vitamin D because it is more stable and consistently measured over time compared with 1,25(OH)$_2$D. Meta-analyses suggest that higher circulating 25(OH)D at diagnosis and vitamin D supplementation both protect against total cancer-specific mortality (13–15). A large Mendelian randomization study of genetic variants in two genes (*CYP2R1* and *DHCR7*) affecting plasma 25(OH)D levels also showed that genetically low

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25(OH)D was associated with increased risk of total cancer mortality (16). However, the results linking circulating 25(OH)D to cancer survival in specific cancer sites and across sites have been inconsistent (17).

Higher serum 25(OH)D levels at diagnosis have been associated with longer overall survival (OS) in colorectal cancer, lung, pancreatic, breast, melanoma, and prostate cancer, among others (17–27), but null findings have also been reported in studies of these same cancer sites (28–35). One recent study looked at the effect of 25(OH)D levels in patients with esophageal cancer, half of whom had adenocarcinoma, and found no association with OS, but the blood was drawn on average 6 years before cancer diagnosis (36). The role of circulating 25(OH)D at time of diagnosis on survival in esophageal adenocarcinoma is not established. There may be true variability in the effect of vitamin D on prognosis across cancer sites due to unique tumor biology at different cancer sites, or the effect of vitamin D on survival may be modified by cancer stage (18, 37–39), subtype (40), or by other metabolic factors in patients, such as obesity. These potential effect modifiers may be contributing to the modest reproducibility of results of the same cancer site across studies.

In this study, we tested whether higher levels of circulating 25(OH)D are associated with better OS among patients with esophageal adenocarcinoma. We additionally examined possible effect modification by clinical stage at diagnosis and BMI at diagnosis. Finally, we included several sensitivity analyses to assess whether timing of blood draw or race impacted our findings.

Methods

Study population

The ongoing Molecular Epidemiology of Esophageal Cancers study consists of patients with esophageal cancer recruited from Massachusetts General Hospital (MGH, Boston, MA) since January 1999 (41, 42). Patients were >18 years of age with histologically confirmed diagnosis. All patients provided written informed consent prior to study participation. At the time of enrollment, a trained interviewer obtained patients' demographic and lifestyle information via baseline questionnaire. The study was conducted in accordance with recognized ethical guidelines and was approved by the institutional review board at MGH and Harvard T.H. Chan School of Public Health (Boston, MA). We used electronic medical records to determine patients' clinical variables, including histology, treatment regimen, cancer stage, and relevant dates. The study population for this analysis was restricted to participants with histologically confirmed esophageal adenocarcinoma who were recruited at the time of their primary diagnosis between 1999 and September 2015 ($n = 587$), which was when serum samples were sent for analysis. For this analysis, we excluded patients who were recruited at the time of cancer recurrence or cancer remission, who had a concurrent cancer, who only presented to MGH for a second opinion, or who were diagnosed with stage 0 disease. Of the eligible patient participants, 495 patients had serum samples available for analysis, and 476 patients with complete information on all confounders who were included in the analyses (Fig. 1).

Vitamin D collection and measurement

When patients provided serum samples, the samples were stored at 4°C until processing and were processed within 24 hours of blood draw. Serum was isolated by centrifugation at 2,000 r.p.m. for 10 minutes at 4°C. Serum samples were then aliquoted and stored in −80°C freezers. In the fall of 2015, serum levels of 25(OH)D were sent in two batches, seven weeks apart, to be measured in the laboratory of Dr. Bruce Hollis (Medical University of South Carolina, Charleston, SC) by radioimmunoassay method (12, 43). We randomly selected and included blinded within-batch duplicates (4% of samples) and between-batch duplicates (5% samples) to be measured. Batch 1 had an intra-assay CV 9.3%, batch 2 had an intra-assay CV of 19.1%, and the between-batch replicates had an inter-assay CV of 29.4%. Of the samples included in this analysis, 90% serum vitamin D levels were measured in batch 1. Because serum levels of 25(OH)D fluctuate due to seasonal variability in sun exposure, we generated quartiles of 25(OH)D per month of blood draw. Simulations have shown that this adjustment reduces bias toward the null due to measurement misclassification without inducing bias away from the null, which can happen when adjusting for month of blood draw as a covariate in multivariable regression model (44). We additionally modeled 25(OH)D by clinical cut-off points (<10 ng/mL, 10–20 ng/mL, 20–30 ng/mL, 30–40 ng/mL, and ≥40 ng/mL) and continuously (ng/mL).

Outcome: OS

The outcome of interest in this study was OS, defined as the time from the date of blood draw until date of death or censored at date last known to be alive. We adjusted for the time between date of diagnosis and the date of blood draw. Data on outcome measures were collected from clinical records and hospital cancer registries.

Covariate collection and measurement

Cancer stage at diagnosis was defined by TNM staging system, where T refers to tumor size, N refers to lymph node status, and M refers to metastasis, for grouping esophageal adenocarcinoma into clinical stage I–IV and further categorized lymph node negative, lymph node positive, and metastatic. Date of diagnosis was considered date of pathology-confirmed cancer. In this study, treatment regimen was modeled as a series of binary variables: chemotherapy (yes/no), radiation (yes/no), and surgery (i.e., esophagectomy; yes/no), with surgery modeled as a time-dependent covariate. We chose to model surgery as time-dependent for several reasons. First, the timing of the operation is related to cancer prognosis up to the point of surgery. Patients with early-stage tumors receive esophagectomies as their first treatment, whereas locally advanced patients will receive esophagectomies pending their response to chemotherapy and/or radiation treatment. Second, the successful completion of the procedure is the most beneficial form of treatment for patients with esophageal adenocarcinoma and one of the best clinical indicators of prognosis. Third, the esophagectomy procedure has a huge impact on patients' diets and weight, and thus likely also affects their vitamin D levels. We did not have the date of chemotherapy or radiation initiation; therefore, we did not model chemotherapy or radiation as time-dependent covariates. We adjusted for year of diagnosis as a continuous variable, to account for slight modifications to treatment protocols throughout the study period. We also adjusted for crude cigarette smoking history as an ordinal variable (never, former, current), age as a continuous variable, and sex as a dichotomous variable. BMI at diagnosis was calculated as weight at diagnosis (kg) divided by height squared (meters^2).

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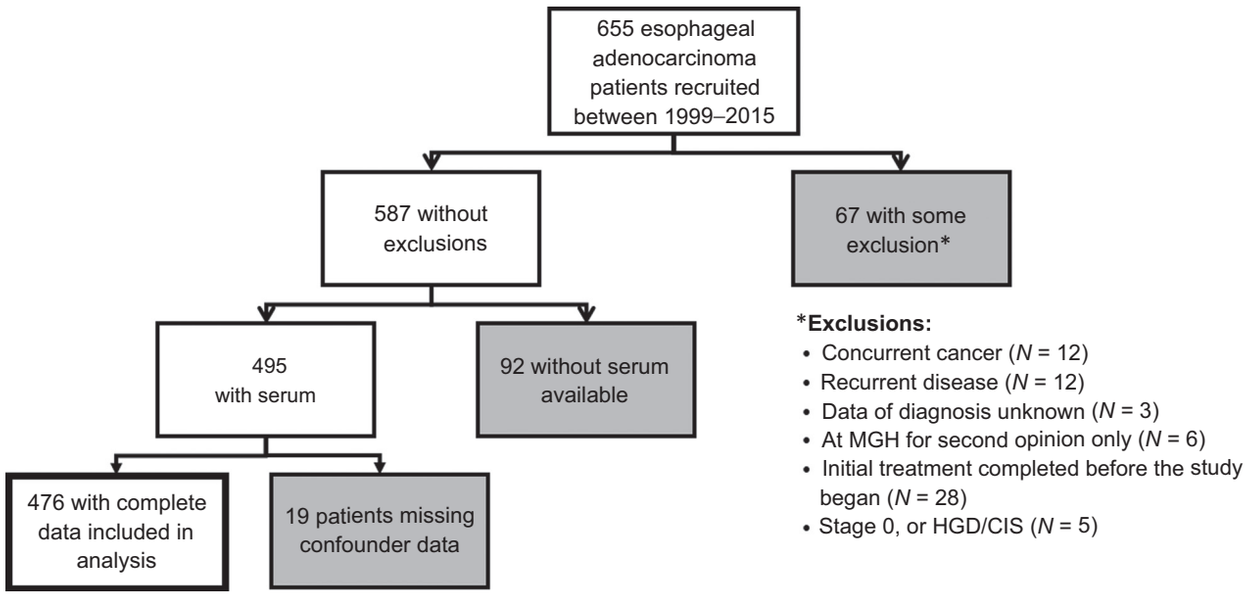

Figure 1.
Flowchart of patients included in the study and patients who were excluded from analysis.

Once calculated, BMI was categorized into four groups: BMI < 18.5, 18.5 $\leq$ BMI < 25, 25 $\leq$ BMI < 30, and BMI $\geq$ 30 kg/m^2.

Statistical analyses

Main analyses. We visualized survival time curves between quartiles of serum 25(OH)D and clinical stage using Kaplan–Meier plots. Univariate differences in survival curves were tested using log-rank tests. We used multivariable extended Cox regression models to estimate HRs of death by quartiles of 25(OH)D, adjusting for sex, age at diagnosis, BMI, smoking history, year of diagnosis, treatment modality (chemotherapy, radiation, and/or surgery) with surgery modeled as a time-dependent covariate, and stratifying baseline hazard by stage at diagnosis. When estimating the continuous association of 25(OH)D, we included season of blood draw in the model. Interactions between serum levels of 25(OH)D quartiles and BMI categories (excluding underweight patients) and clinical stage at diagnosis were tested independently by adding interaction terms to the model, with significance tested by the joint Wald Test [BMI categories and 25(OH)D quartiles with 6DF, and clinical stage with 25(OH)D quartiles with 6DF].

Sensitivity analyses. Most participants' blood samples were drawn close to the time of diagnosis, but many subjects had already initiated treatment at the time of serum draw. We suspected that chemotherapy, radiation, and especially surgical esophagectomy prior to blood draw could affect 25(OH)D levels at the time blood is drawn. Because we did not have the dates of first chemotherapy or radiation treatment, we could not account perfectly for the initiation of neoadjuvant or definitive chemotherapy and radiation treatment. However, we could determine how many weeks after diagnosis a patient's blood was drawn, and when blood was drawn in relation to surgery (for those patients who had surgery). We then assumed among patients who received chemotherapy and radiation, those whose blood was drawn $\geq$4 weeks after diagnosis likely had received some treatment, and patients whose blood was drawn <4 weeks after diagnosis had not initiated treatment yet. We then classified patients as having no treatment at the time of serum draw, having some chemotherapy and radiation treatment but no surgery at the time of serum draw, having had surgery within 12 weeks of the serum draw, and having serum drawn $\geq$ 12 weeks after surgery (Supplementary Table S1). We tested mean differences in 25(OH)D levels between these groups using ANOVA, and we repeated our main analysis restricting to patients who had not received treatment at the time their serum was drawn.

As an additional sensitivity analysis, we crudely imputed 25(OH)D levels at the time of diagnosis. For this imputed analysis, we restricted our study population to subjects with 25(OH)D levels with 3 standard deviations (SD) of the mean, and who had their blood drawn sometime within the week of their diagnosis up to one year past the date of diagnosis because the linear regression coefficient estimates might be unduly influenced by outliers. We additionally excluded those who were missing information about race, given the potential effect of skin pigmentation on vitamin D formation and circulating levels. Using this subpopulation, we generated a predictive linear regression model of serum 25(OH)D level as a function of time that included time between diagnosis and blood draw and adjusted for age at blood draw, sex, race, smoking status, month of blood draw, year of diagnosis, BMI, chemotherapy treatment, radiation treatment, and surgery (if surgery had occurred before blood draw). We then modeled the HR of the estimated diagnosis 25(OH)D level on OS.

Although race, as a proxy for skin pigmentation, is expected to be associated with uptake of vitamin D through sun exposure (45), >90% of our study population identified as White, and the remaining participants identified as a variety of races and ethnicities, with each group too small for meaningful statistical comparison. As a separate sensitivity analysis, we restricted our study population to patients who identified as non-Hispanic

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White to determine the potential effect of race on the effect of 25(OH)D and OS. All analyses were performed in SAS 9.4 (SAS Institute Inc.). *P* values were considered significant at an alpha level of 0.05.

Results

Study population demographics

A total of 495 patients had a serum samples available for 25(OH)D level measurement. Median time to serum draw was 7.6 weeks after diagnosis (interquartile range: 2.3–15.7 weeks). Patients who did not have serum available were more likely to be female and were less likely to have metastatic disease at diagnosis than the group with serum available (Table 1). Of the 495 patients with serum samples available, 476 patients had complete information for relevant covariates and were included in the analyses (Fig. 1). The overall mean 25(OH)D level was 20.6 ng/mL. The mean 25(OH)D level from highest (Q1) to lowest (Q4) quartile accounting for month of blood draw were 32.4 ng/mL (SD 11.0), 22.3 ng/mL (SD 2.5), 17.3 ng/mL (SD 2.8), and 10.8 ng/mL (SD 3.8). Median survival time (Kaplan–Meier) was 26.0 months [95% confidence interval (CI) 22.6–29.2].

Serum 25(OH)D levels and OS

We found no difference in unadjusted OS time across quartiles of 25(OH)D levels [Fig. 2; log rank $P = 0.48$; Q1 (REF); Q2 HR = 0.84, 95% CI, 0.62–1.13; Q3 HR = 0.89, 95% CI, 0.67–1.19; Q4 HR = 1.03, 95% CI, 0.77–1.38]. After adjusting for potential cofounders, we found no association between the highest quartile of 25(OH)D compared with the other quartiles of 25(OH)D and OS (Table 2; global $P = 0.86$), nor did we find an association between clinical cut-off points of 25(OH)D levels with OS (global $P = 0.32$) or continuous 25(OH)D levels with OS (Table 2; HR = 1.00; 95% CI, 0.99–1.01; $P = 0.47$).

Table 1. Study population characteristics

	Serum available (*N* = 495)	Serum not available (*N* = 92)
Men	440 (88.9%)	73 (79.4%)
Age	63.2 ± 11.0	64.8 ± 10.9
Race		
White	461 (93.1%)	85 (92.4%)
Black	2 (0.4%)	
Hispanic	6 (1.2%)	2 (2.2%)
Asian	4 (0.8%)	
Native American	5 (1.0%)	1 (1.1%)
Former smoker	313 (63.2%)	62 (67.4%)
Current smoker	73 (14.8%)	13 (14.2%)
BMI (kg/m^2)	27.4 ± 5.0	27.9 ± 5.9
Stage		
Lymph node negative (I–IIA)	157 (31.7%)	30 (32.6%)
Lymph node positive (IIA–IVA)	240 (48.5%)	48 (52.2%)
Metastatic (IVB)	98 (19.8%)	14 (15.2%)
Treatment[a]		
Surgery	358 (72.3%)	66 (71.7%)
Chemotherapy	392 (79.2%)	66 (71.7%)
Radiation	351 (70.9%)	60 (65.2%)
25(OH)D (ng/mL)	20.7 ± 10.2	
Death	377 (76.2%)	62 (67.4%)

NOTE: Values represent number (%) or mean ± SD.

[a]Treatment values are not mutually exclusive. One patient with vitamin D available was missing information on treatment. Among participants with serum available, information was missing about race ($n = 16$), smoking status ($n = 3$), BMI ($n = 18$), and treatment modality ($n = 1$). Among participants with serum not available, information was missing about race ($n = 4$) and BMI ($n = 2$).

Serum 25(OH)D level and clinical stage interaction with OS

Mean 25(OH)D levels for lymph node negative (19.4 ng/mL ± 8.1), lymph node positive (20.7 ng/mL ± 9.4), and metastatic disease (22.4 ng/mL ± 12.4) at time of diagnosis did not differ significantly (ANOVA, $P = 0.10$). In the multivariable extended Cox model, no significant interaction was found between lymph node status at diagnosis and 25(OH)D levels on the association with OS [Table 3; Wald (DF = 6), joint test of interaction term, $P = 0.87$].

Serum 25(OH)D level and BMI interaction with OS

Mean 25(OH)D levels for patients with BMI at time of diagnosis <18.5 kg/m^2 (15.8 ng/mL ± 5.9), 18.5 ≤ BMI < 25 kg/m^2 (20.8 ng/mL ± 10.1), 25 ≤ BMI < 30 kg/m^2 (21.6 ng/mL ± 10.5), and BMI ≥ 30 kg/m^2 (19.3 ng/mL ± 8.5) did not differ significantly (ANOVA $P = 0.10$). We additionally ran a multivariable survival model that included the interaction terms for BMI categories, excluding underweight patients due to small numbers, and quartiles of vitamin D adjusted for month of blood draw and found no evidence to support BMI as a modifier of the effect of vitamin D quartile on OS [Table 4; Wald joint test of interaction term (DF = 6), $P = 0.36$].

Sensitivity analysis accounting for time of blood draw

Mean 25(OH)D levels differed among patients with no treatment at the time of serum draw (22.6 ng/mL ± 10.5), patients who some chemotherapy and radiation treatment but no surgery (20.7 ng/mL ± 9.8), patients whose serum was drawn <12 weeks after surgery (18.7 ng/mL ± 9.1), and patients whose serum was drawn ≥ 12 weeks after surgery (20.3 ng/mL ± 8.4; ANOVA $P = 0.026$).

Among the 108 patients without treatment at the time of serum draw, we found no association between OS and 25(OH)D modeled as quartiles or continuous (Supplementary Table S2). When considered by clinical cut-off points, serum levels <40 ng/mL of vitamin D were significantly associated with higher hazard of all-cause death, but there was not an obvious pattern of association across cut-off points, and the sample sizes for these categories were very small, so these results should be considered cautiously.

When we further crudely imputed patients' 25(OH)D level at the time of diagnosis. We again did not see a significant association of the imputed diagnostic 25(OH)D levels on OS (Supplementary Table S3; $P = 0.30$).

Sensitivity analysis restricting to white patients

We additionally repeated all analyses, restricting the population to patients who identified as non-Hispanic White. The results for all analyses did not differ from the models where we used all subjects (Supplementary Table S4).

Discussion

We did not find evidence that levels of serum 25(OH)D around diagnosis are associated with OS in patients with esophageal adenocarcinoma. Nor did we find evidence that the association of 25(OH)D on OS in patients with esophageal adenocarcinoma differs by stage at diagnosis or BMI at diagnosis. Although serum levels of 25(OH)D did appear to differ according to treatment

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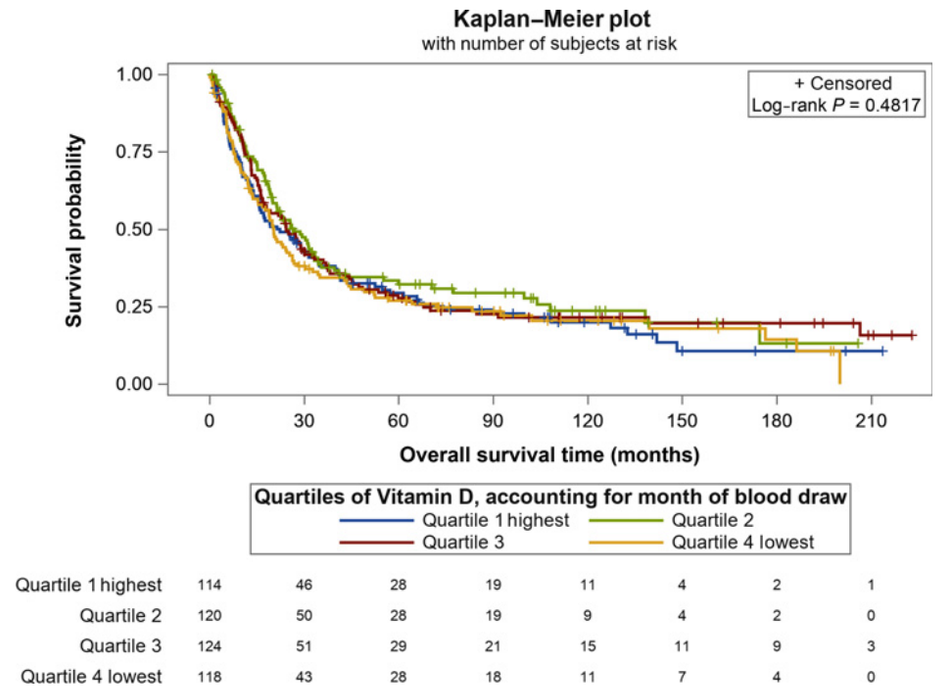

Figure 2.
Kaplan–Meier survival curve by quartiles of 25(OH)D accounting for month of blood draw. The Kaplan–Meier survival curve, and corresponding log-rank test, of OS among patients with esophageal adenocarcinoma stratified by quartiles of serum 25(OH)D levels, categorized accounting for month of blood draw. Q1 represents the highest 25(OH)D levels, and Q4 includes the lowest 25(OH)D levels.

status at the time of blood draw, treatment did not appear to alter the association between 25(OH)D levels and OS among patients with esophageal adenocarcinoma.

To our knowledge, this is the first study that has assessed the association between diagnostic 25(OH)D levels and OS exclusively among patients with esophageal adenocarcinoma. A pathologic study noted that high expression of vitamin D receptor (VDR) is common in esophageal adenocarcinoma tissues as well as the precancerous Barrett's esophagus tissues, but expression was rare in squamous cell carcinoma tissues, lending evidence that the pathway may be more relevant to the tumor biology in adenocarcinoma (46). Another recent study reported that tumor VDR expression was associated with longer OS among patients with esophageal adenocarcinoma (47). At least one study in esophageal squamous cell carcinoma reported patients with >10 ng/mL 25(OH)D at time of diagnosis had longer OS than those with <10 ng/mL, but they did not clearly report if or how they adjusted for the effects of seasonal variability of blood draw (48). More recently, a study from the European Prospective Investigation in Cancer and Nutrition prospective cohort examined circulating $25(OH)D_3$ levels from blood drawn many years before diagnosis of cancer on mortality among patients with head and neck and esophageal cancer (36). In the 147 patients with esophageal cancer included in the analysis (approximately 50% esophageal adenocarcinoma), they found no association between circulating $25(OH)D_3$ levels and OS or cancer-specific survival (36), consistent with our findings.

Table 2. Serum levels of 25(OH)D and OS[a] among patients with esophageal adenocarcinoma ($n = 476$)

25(OH)D Quartiles[b]	*N* deaths/patients	HR	95% CI	*P*
1 (highest)	90/114	REF		
2	82/120	0.90	(0.67–1.23)	0.51
3	95/124	1.03	(0.76–1.38)	0.87
4 (lowest)	93/118	0.98	(0.72–1.33)	0.90
				Global $P = 0.86$
25(OH)D Clinical cut-off points[c]				
≥40 ng/mL (≥100 nmol/L)	14/16	REF		
30–40 ng/mL (75–100 nmol/L)	31/39	1.29	(0.68–2.47)	0.44
20–30 ng/mL (50–75 nmol/L)	124/177	0.98	(0.55–1.73)	0.93
10–20 ng/mL (25–50 nmol/L)	159/201	1.22	(0.69–2.16)	0.49
<10 ng/mL (<25 nmol/L)	32/43	0.98	(0.50–1.92)	0.96
				Global $P = 0.32$
25(OH)D Continuous (ng/mL)[c]		1.00	(0.99–1.01)	0.54

[a]OS was calculated as time between date of blood draw and date of death or date last known to be alive.
[b]Estimates come from model that additionally adjusted for age, sex, smoking status, BMI categories, year of diagnosis, time between diagnosis and blood draw, chemotherapy, radiation, time-dependent surgery, and baseline treatment was stratified by tumor stage by lymph node status. Quartiles of vitamin D were determined accounting for month of blood draw.
[c]Estimates come from model that additionally adjusted for age, sex, smoking status, BMI categories, season of blood draw, year of diagnosis, time between diagnosis and blood draw, chemotherapy, radiation, time-dependent surgery, and baseline treatment was stratified by tumor stage by lymph node status.

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Table 3. Serum levels of 25(OH)D and OS[a] among patients with esophageal adenocarcinoma, stratified by clinical stage ($n = 476$)

	25(OH)D Quartiles[b]	*N* deaths/ patients	HR[c]	95% Confidence limits
Lymph node negative at diagnosis	Q1 (highest)	19/28	REF	
	Q2	21/41	0.93	0.49–1.76
	Q3	25/41	0.95	0.51–1.74
	Q4 (lowest)	27/41	1.00	0.55–1.82
Lymph node positive at diagnosis	Q1 (highest)	44/59	REF	
	Q2	39/57	0.95	0.61–1.47
	Q3	48/60	1.12	0.74–1.70
	Q4 (lowest)	42/53	1.19	0.77–1.83
Metastatic at diagnosis	Q1 (highest)	27/27	REF	
	Q2	22/22	0.80	0.45–1.42
	Q3	22/23	0.95	0.52–1.73
	Q4 (lowest)	24/24	0.69	0.39–1.24

[a]OS was calculated as time between date of blood draw and date of death or date last known to be alive.
[b]Quartiles of vitamin D were determined accounting for month of blood draw.
[c]Model adjusted for the main effect of vitamin D, age, sex, smoking status, the main effect of BMI categories, year of diagnosis, chemotherapy, radiation, time-dependent surgery, and baseline treatment, and baseline hazard was stratified by tumor stage by lymph node status.

Human observational studies, Mendelian randomization studies, and randomized controlled trials have reported that low levels of vitamin D are associated with increased risk of total cancer mortality (13, 14, 16, 49). Yet due to the unique biology of different cancers, we do not know whether the vitamin D pathway has the same prognostic impact in all cancer sites. There may also be a threshold effect of vitamin D. Several studies of various cancer sites have reported significantly shorter survival time among patients with very low levels of 25(OH)D (<12 ng/mL) compared with patients with even moderate levels (≥12–20 ng/mL; refs. 50–52). In our study, we found no evidence of association between OS and 25(OH)D, even at levels <10 ng/mL, in the whole population. When looking only among patients who had not initiated treatment at the time of serum draw, we did see that levels <40 ng/mL were associated with increased hazard of death. However, given the small sample sizes in these categories and extreme uncertainty of these estimates, coupled with the consistently null findings in other models, we cannot rule out that those associations are spurious.

Table 4. Serum levels of 25(OH)D and OS[a] among patients with esophageal adenocarcinoma, stratified by BMI ($n = 469$)

	25(OH)D Quartiles[b]	*N* deaths/ patients	HR[c]	95% Confidence limits
BMI (≥18.5 and <25)	Q1 (highest)	30/37	REF	
	Q2	26/38	0.68	0.40–1.17
	Q3	34/38	1.08	0.65–1.79
	Q4 (lowest)	33/36	0.74	0.44–1.25
BMI (≥25 and <30)	Q1 (highest)	45/56	REF	
	Q2	37/51	0.98	0.62–1.54
	Q3	37/50	0.83	0.53–1.29
	Q4 (lowest)	32/45	1.14	0.71–1.82
BMI (≥30)	Q1 (highest)	15/21	REF	
	Q2	18/29	1.32	0.65–2.67
	Q3	23/34	1.51	0.77–2.96
	Q4 (lowest)	25/34	1.22	0.63–2.36

[a]OS was calculated as time between date of blood draw and date of death or date last known to be alive.
[b]Quartiles of vitamin D were determined accounting for month of blood draw.
[c]Model estimates adjusted for the main effect of vitamin D, age, sex, smoking status, the main effect of BMI categories, year of diagnosis, chemotherapy, radiation, time-dependent surgery, and baseline hazard was stratified by tumor stage by lymph node status.

Epidemiologic studies in lung and pancreatic cancers have reported differences by stage in the association of 25(OH)D level on OS (18, 37, 38). Biologically, vitamin D is thought to slow tumor growth and inhibit metastases, among other things, so we hypothesized that the association with 25(OH)D would be weaker among patients with metastatic disease. However, we found no evidence of interaction between 25(OH)D and clinical stage on OS in this population.

High BMI (>30 kg/m^2) is a known risk factor developing esophageal adenocarcinoma but associated with better prognosis after diagnosis (53–56). BMI is also related to vitamin D, as vitamin D through sun exposure and diet can be stored in the fat cells of a person rather than being converted into circulating 25(OH)D. Thus people with more adiposity tend to have lower serum circulating 25(OH)D than someone with less body fat but the same intake of vitamin D (57). We did not find evidence of BMI as an effect modifier in this study. In healthy individuals, BMI is an adequate measure of adiposity, but sick cancer patients potentially have underlying sarcopenia or cachexia, so low BMI may indicate low lean mass and not necessarily low adiposity. Thus, the relationship between BMI and vitamin D in esophageal adenocarcinoma survival may be more complex than we were able to capture here.

We acknowledge limitations to our study. First, we did not have information on esophageal adenocarcinoma–specific mortality, but due to the aggressive pattern of esophageal adenocarcinoma, we infer that the vast majority of patients in our study died from their cancer and not with it. Second, like many studies, we only have one measure of 25(OH)D from close to the time of diagnosis. Although we accounted for seasonal variability at the time of blood draw, we cannot account for intraindividual changes to 25(OH)D levels over follow-up time, including seasonally, during treatment, or after treatment is completed. In the absence of taking vitamin D supplementation, healthy adults' 25(OH)D levels do not vary dramatically over a few years but tend to decrease notably across a decade (58–60). However, this decrease in 25(OH)D levels tracks with age and does not modify the association with all-cause mortality (61). Few studies have examined the impact of cancer treatment on 25(OH)D levels. Patients with breast cancer have shown significantly decreased 25(OH)D levels after neoadjuvant chemotherapy, but even accounting for that change, neither baseline nor posttreatment 25(OH)D levels have been associated with pathologic response to treatment (62, 63). In contrast, another recent longitudinal study of patients with melanoma found that baseline levels of 25(OH)D were not associated with risk of relapse but change in 25(OH)D during follow-up (both increased and decreased) was associated with worse prognosis, although they did not report change in vitamin D status per specific treatment modality (64). Our findings cannot rule out that trajectories of 25(OH)D levels throughout treatment may be associated with esophageal adenocarcinoma survival. Longitudinal studies tracking 25(OH)D levels throughout the course of treatment would further inform recommendations for patients.

A third, related, limitation of our study is that the timing of the blood draw in relation to cancer diagnosis differed across patients,

which means although blood draw occurred close to the time of diagnosis, patients were at varying points of their treatment regimen at the time of blood draw. This is a common problem in the study of prognostic biomarkers. We attempted to address this by considering numerous ways in which the timing of the blood draw might have affected measured levels of 25(OH)D. While mean 25(OH)D levels were statistically significantly different depending on the treatment patients had received at the time of blood draw, the levels across different groups actually did not deviate much from the overall population mean, and the timing of blood draw in relation to treatment does not appear to have impacted the main results. Moreover, the consistently null findings in almost all analysis and the *P* values consistently close to 1 support the null hypothesis, and mean that potential residual confounding from the above mentioned factors is unlikely to change the results of our analyses.

There are several strengths to our study. To our knowledge, this is the largest study to examine the effect of 25(OH)D levels as a prognostic factor in esophageal adenocarcinoma, and the first to look exclusively at esophageal adenocarcinoma. We were able to consider possible effect modifiers and many relevant confounders in addition to the main effect. In addition, our study population demographics are similar to the demographics of patients with esophageal adenocarcinoma across the United States, supporting generalizability of our findings.

Despite the biologic evidence that the vitamin D pathway suppresses tumor progression via a number of mechanism and the epidemiologic evidence that higher levels of vitamin D are protective against total cancer mortality, the evidence for 25(OH)D serum levels as a marker of prognosis of specific cancer sites in humans has been equivocal. We found no evidence that circulating 25(OH)D levels are associated with OS among patients with esophageal adenocarcinoma, accounting for a number of potential confounders and effect modifiers. A recent trial of vitamin D supplementation found those taking supplementation had reduced risk of cancer mortality, and the association was strongest after excluding the first 2 years of follow-up after cancer diagnosis (49). Our consistently null associations between serum 25(OH)D levels and OS among patients with esophageal adenocarcinoma may indicate that the aggressive nature of this cancer precludes any potential protective benefits of vitamin D.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: E. Loehrer, B.W. Hollis, D.C. Christiani
Development of methodology: B.W. Hollis, D.C. Christiani
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L. Su, A. Shafer, B.W. Hollis, D.C. Christiani
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): E. Loehrer, R.A. Betensky, B.W. Hollis, D.C. Christiani
Writing, review, and/or revision of the manuscript: E. Loehrer, R.A. Betensky, E.L. Giovannucci, B.W. Hollis, D.C. Christiani
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): E. Loehrer, A. Shafer, D.C. Christiani
Study supervision: D.C. Christiani

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