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Vitamin D and the Epidemiology of Upper Gastrointestinal Cancers: A Critical Analysis of the Current Evidence

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Abstract

Prospective analyses have yet to uncover a consistent relationship between vitamin D status and incidence and mortality of rarer cancers including esophageal and upper gastrointestinal cancers. We searched PubMed for literature regarding the epidemiology of upper gastrointestinal cancers and vitamin D published over the last decade and then summarized and critiqued the results of these studies in this review. The search yielded nine relevant studies. Overall, no consistent relationship was reported between serum vitamin D levels or a surrogate and upper gastrointestinal cancers. Four studies reported negative correlations between vitamin D status and upper gastrointestinal cancer, three reported positive correlations, one reported no correlation, and one reported both positive and negative correlations. No relationship has been established based on epidemiological data, but studies examining sun exposure consistently report an inverse association with esophageal cancer. The current literature is limited by the methods used to assess vitamin D status, lack of specific data for the types of upper gastrointestinal cancer, and failure to establish a temporal relationship between vitamin D status assessment and presentation of upper gastrointestinal cancer. It is possible that the lack of a consistent relationship is a consequence of inaccurate and imprecise assessment of vitamin D status.

Keywords

Cancer; Epidemiology; Esophagus; Gastrointestinal; Vitamin D

Introduction

The association between vitamin D status and cancer epidemiology is currently a heavily researched topic, and equally as heavily debated. Low serum 25-hydroxyvitamin D levels have been associated with increased risk of breast (1, 2) colon (2, 3) and bladder cancer (4) among others. The association of vitamin D status with cancer of the prostate (2) and skin (5) is less clear. Increasing 25-hydroxyvitamin D levels may be associated with an increased risk of prostate cancer (6, 7) and are associated with increased risk of melanoma and non-melanoma skin cancer (5, 8, 9). However, with respect to melanoma this may be confounded by the carcinogenic affects of ultraviolet radiation on the skin. In fact, in those with a diagnosis of malignant melanoma higher 25-hydroxyvitamin D levels have been associated

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Conflicts of Interest
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with less advanced tumor stage and decreased tumor depth (10). Additionally, some have suggested that there may be a role for vitamin D in controlling the progression of cutaneous malignancies (11), thus, highlighting the equipoise that exists regarding cancer and vitamin D.

A suggested link between ultraviolet-B radiation exposure and reduced risk of cancer has been proposed based on ecological evidence (12) but prospective analyses have yet to uncover a consistent relationship between vitamin D status and cancer mortality in general (13). This is especially true for rarer cancers including esophageal and upper gastrointestinal cancers for which an association has not been established (14), although no adequate summary of the epidemiological evidence exists. We have a particular interest in vitamin D and its importance in the esophagus and the development and treatment of esophageal adenocarcinoma (15, 16), and set out to summarize the current literature regarding the epidemiology of upper gastrointestinal cancers and vitamin D status in this review.

Methods

We searched PubMed for publications listed under the MeSH terms “Vitamin D” and “Esophagus” and “Adenocarcinoma” which yielded no results. We then expanded our search to include literature addressing vitamin D and sun exposure and any esophageal malignancies or gastric carcinomas published in the past decade. Abstracts of search results were surveyed for studies that examined the epidemiology of serum 25-hydroxyvitamin D levels or surrogates thereof and any of the above-mentioned cancers. These publications were then examined in more detail for their methods, results, and conclusions, which we report in this review. This is neither a meta-analysis nor a systematic review.

Results

Overall, nine observational studies examining the relationship between 25-hydroxyvitamin D levels (or a surrogate for 25-hydroxyvitamin D levels) and upper gastrointestinal cancer were reviewed (17–27). The results are summarized in Tables 1 and 2. One of these studies examined esophageal squamous cell dysplasia and was included because of the disease’s relationship to esophageal cancer. No consistent relationship was reported between serum 25-hydroxyvitamin D levels or a surrogate and upper gastrointestinal cancers; four studies reported negative correlations between vitamin D status and upper gastrointestinal cancer, three reported positive correlations, one reported no correlation, and one reported both positive and negative correlations. The results did not appear to trend systematically with the year of publication. All three studies examining esophageal cancer and ultraviolet radiation exposure reported negative correlations.

The four studies that reported lower incidence of upper gastrointestinal cancer with higher levels of 25-hydroxyvitamin D or surrogates thereof were Tran et al. (18), Lipworth et al. (25), Giovannucci et al. (23), and Boscoe and Schymura (17). Tran et al. (18) assessed cumulative ambient ultraviolet-B radiation exposure and its relationship to esophageal cancer. Investigators reported an 18% decrease in risk for esophageal adenocarcinoma, a 17% decrease for esophago-gastric junction adenocarcinoma, and a non-statistically significant decrease in esophageal squamous cell carcinoma for each standard deviation increase in ultraviolet-B irradiance, which was 10^7 J/m^2. Lipworth et al. (25), in a case-control study in Italy, reported a 16% decrease in esophageal squamous cell carcinoma for each 1.14 μg/day increase in dietary vitamin D intake prior to diagnosis, the standard deviation amongst controls. This study did not examine adenocarcinoma of the esophagus. In both studies by Tran et al. (18) and Lipworth et al. (25), relationships were stronger when assessment of vitamin D status, by ultraviolet-B irradiance or dietary vitamin D intake, was

reported as a categorical variable by tertile (Table 1). Giovannucci and colleagues (23) discovered a statistically significant inverse correlation between predicted serum 25-hydroxyvitamin D and incidence of esophageal cancer in the Health Professionals Follow-up Cohort. The cohort is composed of 51,529 males and has been followed since 1986 with information updates every 2–4 years. Investigators used data from this population to construct a model to predict 25-hydroxyvitamin D serum concentrations. Each 25 nmol/L increase in predicted 25-hydroxyvitamin D corresponded to a 63% decrease in esophageal cancer incidence. Finally, Boscoe and Schymura (17) reported a 27% increase in incidence and 36% increase in mortality of esophageal cancer in populations receiving an annual average of 650 kJ/m^2-year UV exposure versus 1540 kJ/m^2-year, albeit in non-Hispanic white males only. A weaker relationship was reported in non-Hispanic white females. The authors report that this relationship is proportional so that populations receiving 1100 kJ/m^2-year could be expected to have half the increased risk displayed by those receiving 650 kJ/m^2-year. The authors analyzed a black cohort separately and reported limited data because of the inconsistency of the results, but did note that the esophagus was the only cancer site that displayed a higher relative risk of cancer in the north versus south United States, in males and females, for both incidence and mortality. In this study, relative risks ranged from 1.3–1.5 (17).

The three studies that reported higher incidence of upper gastrointestinal cancer with higher vitamin D status were Mulholland et al. (26), Chen et al. (22), and Abnet et al. (19). Most recently, Mulholland and colleagues (26) evaluated the relationship between vitamin D intake and incidence of esophageal adenocarcinoma in a case-control study using an Ireland-based population cohort, called “Factors Influencing the Barrett’s Adenocarcinoma Relationship (FINBAR)”. A positive association was reported between the highest and lowest tertile of vitamin D intake and esophageal adenocarcinoma with OR 1.99 CI 1.03–3.86. This association did not persist for normal weight individuals, individuals negative for *H. pylori*, or those who never smoked, but the authors reported no interaction between these variables and vitamin D intake (26). Pre-trial 25-hydroxyvitamin D levels were correlated to subsequent development of ESCC in men in a 2007 case-control study by Chen et al. (22). There was no significant correlation between pre-trial serum 25-hydroxyvitamin D and development of gastric carcinoma, but in men pre-trial 25-hydroxyvitamin D level was positively correlated with esophageal squamous cell carcinoma development. Abnet and colleagues (19) examined the association between serum 25(OH)D and esophageal squamous cell dysplasia in the same population used by Chen et al. (22). They found a positive correlation between the two variables in both men and women with RR 1.86, CI 1.35–2.62. The relative risk was greater for women than in men, in contrast to the statistic reported by Chen and colleagues (22), which found a positive correlation between vitamin D and esophageal squamous cell cancer only in men.

Abnet and co-investigators (20) reported no correlation between serum 25-hydroxyvitamin D levels and upper gastrointestinal cancer, although analysis did yield some statistically significant trends in certain subgroups.(20) This nested case-control design utilized the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers and examined the relationship between upper gastrointestinal cancer and circulating serum 25-hydroxyvitamin D in 1,065 cases. In a subgroup analysis of 256 cases of esophageal cancer, no statistically significant trend was found over six levels of serum 25-hydroxyvitamin D status. The same was true when the 142 cases of squamous cell carcinoma and 104 cases of adenocarcinoma were looked at separately. Likewise, there was no statistically significant trend for any type of gastric cancer, although statistically significant odds ratios were calculated for certain comparisons between categories of serum 25-hydroxyvitamin D levels (20).

Chen and colleagues (21) reported both positive and negative correlations in a study taking place in China that looked for an ecological relationship between the geographic distribution of ambient ultraviolet-B (UVB) irradiance, measured in milliwatts per meter squared (mW/m^2), and incidence and mortality of esophageal and gastric cancer. Esophageal cancer mortality decreased by 8% and incidence by 27% for each 10 mW/m^2 increase in UVB irradiance. However, the inverse relationship between UVB irradiance and esophageal cancer mortality and incidence was restricted to rural counties. In these counties, each 10 mW/m^2 increase in UVB irradiance predicted an 11% and a 58% decrease in esophageal cancer mortality and incidence, respectively (21). In contrast, in urban counties each 10 mW/m^2 increase in UVB irradiance predicted no change in mortality and a 12% increase in esophageal cancer incidence. In comparison, gastric cancer mortality decreased by 3% and incidence by 13% for each 10 mW/m^2 increase in UVB irradiance. When stratified by county (urban or rural) UVB irradiance was inversely correlated with gastric cancer mortality only in urban counties, and with gastric cancer incidence only in rural counties; it was positively correlated with gastric cancer incidence in urban counties (21).

Discussion

The most apparent limitation to the existing literature is the methods used to estimate vitamin D status. Only three of the nine publications utilized serum 25-hydroxyvitamin D as a measure, the most accurate way to estimate vitamin D status (28). A single blood sample obtained in the spring or fall offers a reasonable estimate of the average serum 25-hydroxyvitamin D over a one year period (29). However, using a single serum sample still has its limitations, possibly underestimating statistical relationships (29). As Giovannucci and co-investigators (23) pointed out, one time serum 25-hydroxyvitamin D measurements can be transiently high or low. Tran and colleagues (18) contest that they may not account for the impact of vitamin D on esophageal carcinogenesis which may take place over a lifetime and exhibit a latency period with respect to this impact.

Furthermore, these studies pose the issue of temporality. The methods used in the published data did not allow for a calculation of the amount of time elapsed between evaluation of serum 25-hydroxyvitamin D and diagnosis of upper gastrointestinal cancer. This was exemplified in the study of Chen and colleagues (22). After obtaining pre-trial serum 25-hydroxyvitamin D levels, subjects were followed over a five-year period, establishing a prospective timeline between the serum 25-hydroxyvitamin D measurement and development of upper gastrointestinal cancer. This is a strength of the study; however, neither follow-up serum samples nor samples at the time of cancer mortality or incidence were assayed. Only the initial serum 25-hydroyvitamin D level was used as a predictor with possibly considerable variability in the time between this measurement and the identification of disease among subjects. Giovannucci and colleagues (23) made attempts to address this by tracking surrogate measurements of serum 25-hydroxyvitamin D and analyzing for correlations over time.

One point worthy of mention in the study of Abnet and co-investigators (19) is the method used to identify squamous cell dysplasia. Investigators used a staining test that had a range of specificity of 40% to 95% for the detection of higher-grade dysplasia or early neoplasia, and an even lower specificity for dysplasia of lower grades. This wide range of specificity along with the fact that subjects with any grade of dysplasia were included allows for the potential of false positive results. This could exaggerate the relative risk or lead to a falsely increased relative risk if a sufficient number of subjects with 25-hydroxyvitamin D levels in the upper quartiles had misclassified esophageal disease.

Two studies utilized food frequency questionnaires (FFQs) to estimate a subject's vitamin D status, a method purported by one group of authors to have high reproducibility and validity (25). Evidence suggests that surrogates such as dietary intake and vitamin supplementation are poor predictors of vitamin D status. A model utilizing physical inactivity, skin pigmentation, dietary intake, BMI, and region could account for only 28% of the variability in serum 25-hydroxyvitamin D levels (23). In this model, physical inactivity and skin pigmentation were the best predictors. This is logical when one considers that approximately 80–90% of vitamin D may be obtained from synthesis in the skin (30). In a study of a Sydney, Australia population, variables typically considered as surrogates of sun exposure, physical activity and smoking, were documented as significant predictors of serum 25-hydroxyvitamin D levels (31). Interestingly, the same study did not yield sun exposure itself as a significant predictive factor of vitamin D status.

It is likely that factors predicting vitamin D status differ according to race. In a Chicago, Illinois study, predictors of vitamin D status were different for men of European versus African descent. In European American men the strongest predictors were season and lifetime sun exposure followed by income and BMI. In African American men, dietary and supplemental vitamin D intake were major predictors (32). A global report on hypovitaminosis D concluded that not only skin pigmentation but also cultural differences like certain clothing practices significantly influence vitamin D status (33). The impact of skin color on the studies presented in this review is likely limited, however, considering most of the cohorts examined were largely non-black. Studies that did not report on race were conducted in Irish, Italian, and Chinese populations and presumably consisted of a negligible percentage of black subjects considering the demographics of these countries (19, 21, 22, 25, 26). Furthermore, two of the studies not reporting on race utilized 25-hydroxyvitamin D levels obviating the need to use skin color as predictor of vitamin D status. Boscoe and Schymura (17) analyzed non-Hispanic white and black cohorts separately to control for the impact of skin color on vitamin D status.

Predictors of vitamin D status and vitamin D status itself may also differ by gender; indeed two studies reviewed here reported correlations that differed between men and women (17, 22). In a Netherlands study, gender and season were the major predictors of vitamin D status. Men tended to have higher serum 25-hydroxyvitamin D levels than women. When parsed by gender, physical activity and season remained as correlates in men whereas physical activity and estradiol levels were the main determinants in women (34).

Additional evidence supports winter season, low vitamin D dietary and supplement intake, high BMI, physical inactivity, and low milk and calcium intake as major determinants of low vitamin D status (35), highlighting the myriad of opinions regarding predictors of vitamin D and the complexity of using surrogate markers to predict vitamin D status. Additionally, FFQs allow for the potential of recall bias. This is exemplified in the report by Mulholland and colleagues (26) in which study participants were asked to report dietary habits and BMI for a 12 month period beginning 5 years prior to the administration of the FFQ. This should be considered when interpreting these results.

Three studies examined the correlation of UV exposure to incidence and mortality of esophageal cancer. Interestingly, all three studies reported inverse correlation between UV exposure, a proposed surrogate for vitamin D status, and esophageal cancer. However, this method imposes some limitations. Measurements of ambient UVB irradiance may not reliably approximate serum 25-hydroxyvitamin D levels or even UVB exposure. Additionally, Chen and colleagues (21) did little to control for significant confounding variables, including smoking, alcohol intake, and BMI. But, these investigators reported both positive and negative correlations between UVB exposure and upper gastrointestinal

cancer. Esophageal cancer mortality and incidence was inversely correlated to UVB irradiance only in rural counties, a restriction that could reflect the increased amount of UVB exposure that the agrarian worker presumably gets. This would strengthen the inference that higher vitamin D status may help limit esophageal cancer mortality and incidence, as the authors point out. However, it could also reflect other lifestyle factors associated with the agrarian lifestyle that could protect against esophageal cancer mortality and incidence, confounding its relationship to UVB exposure.

The inconsistency of the relationship should be reiterated: UVB irradiance was inversely correlated with esophageal and gastric cancer incidence in rural counties, but positively correlated in urban counties, and an inverse correlation to gastric cancer mortality was only present in urban counties. These differences could be a consequence of different neoplastic process between esophageal and gastric cancer; or, statistically significant relationships could have been found serendipitously because of the increased probability of making a type 1 error when conducting numerous tests for significance. Nevertheless, there may be merit to using UVB irradiance as a surrogate for vitamin D status. Even at high latitudes season influenced vitamin D more than diet, ethnicity, and vitamin intake suggesting that sun exposure is the major determinant of vitamin D status (36).

The study by Tran and colleagues (18) was also limited by the possibility that UVB irradiance does not accurately predict vitamin D status. However, investigators were able to more accurately estimate UVB exposure by approximating individual lifetime exposure to UVB and collecting data on many confounding variables. Additionally, they examined UVB exposure at different age periods for each subject in an attempt to evaluate the contribution of estimated vitamin D status to the prevention of esophageal cancer over one's lifetime. This is a strength afforded by this study design and a limitation of study designs that assess serum 25-hydroxyvitamin D status at one particular instance, thus failing to account for the possibility of a latent period for esophageal carcinogenesis.

Two studies published in the last decade, a meta-analysis and a systematic review, examined the risk of subsequent cancer after diagnosis of skin cancer, essentially using prior skin cancer as a surrogate for ultraviolet irradiance. After previous diagnosis of squamous cell carcinoma, basal cell carcinoma, or non-melanoma skin cancer, Grant (24) reported relative risks for developing gastric cancer and esophageal cancer of 0.67 and 0.60, respectively. Wheless and colleagues (27) reported no association between previous diagnosis of skin cancer and subsequent esophageal cancer. This review included the data published in the study by Grant (24).

The discrepancy in the results of the investigators may be explained by the suggestion that the absence of a skin cancer diagnosis does not preclude adequate exposure to UVB light. If this is the case – that subjects with adequate UVB exposure are significantly represented in the group without a skin cancer diagnosis – then the inverse correlation reported by Grant (24) would attenuate. Nevertheless, if in fact sun exposure is linked to high vitamin D status, the findings by Grant (24) support the hypothesis that vitamin D plays a role in the prevention of cancer. In addition, Grant (24) astutely excluded melanocytic skin cancers, which are associated with intermittent and blistering sun exposure at an early age (37) and the presence of melanocytic nevi (38), the factors that may correlate less closely with overall sun exposure.

Despite a particular interest in adenocarcinoma of the esophagus, we decided to include all upper gastrointestinal cancers in this review because of the limited information on the topic. However, it has been suggested that adenocarcinoma of the esophagus and gastric cardia share many similar risk factors that they may be considered together, and may even be of the

same etiology (39). Other sources suggest otherwise (40), and this could be one of the limitations of this review.

The mechanism by which vitamin D may impact carcinogenesis in the upper gastrointestinal tract, in particular adenocarcinoma of the esophagus, is uncertain, but may involve the immunomodulatory role of vitamin D in the regulation of immune cells involved in reflux-related esophageal disease including CD4+ T cells (41–46), macrophages (43, 47, 48), and dendritic cells (49–52), and key signaling pathways including Wnt (53, 54), Hedgehog (55–57), NFκ-B (58), and IL-6-JAK-STAT (59, 60). The discrepancy between the role of vitamin D in cancers of lower gastrointestinal tract, including colorectal cancer where there is strong evidence of a protective effect (61, 62), and upper gastrointestinal cancers, including esophageal adenocarcinoma where the relationship is still unclear, may be explained by different pathogeneses of these two diseases. Esophageal adenocarcinoma is thought to arise from a metaplasia-neoplasia sequence as a consequence of chronic inflammation induced by bile and acid reflux (63), whereas it is generally accepted that colorectal cancer progresses through an adenoma-carcinoma sequence (64). The role of inflammation in these two disease states is also likely different and could impact the response to vitamin D status.

In summary, the current literature is limited in many cases by the method used to assess vitamin D status, lack of specific data for the types of upper gastrointestinal cancer including subtypes of esophageal cancer, and failure to establish a temporal relationship between vitamin D status assessment and presentation of upper gastrointestinal cancer. The most weight should be placed on the three studies utilizing serum 25-hydroxyvitamin D to assess vitamin D status as this limits confounding and misclassification. However, still there was no consensus relationship among these three data sets. Furthermore, there is merit to ecological studies and studies examining UV exposure that attempt to estimate an individual's vitamin D status over a lifetime. This may better predict the impact of vitamin D status on esophageal cancer if longterm vitamin D status is more relevant to carcinogenesis than current or recent vitamin D status. Future studies should aim to combine individual data regarding lifetime sun exposure, surrogate markers for vitamin D status, and serum 25-hydroxyvitamin D levels, ideally at multiple intervals throughout the study period.

It is possible that the lack of a consistent relationship reported across the nine studies reviewed is a consequence of study design. Inaccurate and imprecise assessment of vitamin D status could certainly attenuate, exaggerate, or obscure relationships, but this would require methods that systematically under assessed or over assessed vitamin D status. It is likely that studies using measurements other than serum 25-hydroxyvitamin D to assess vitamin D status are both inaccurate and imprecise. Additionally, each different subtype of upper gastrointestinal cancer – including esophageal adenocarcinoma and squamous cell carcinoma, which have distinctly different pathologies – may exhibit a different relationship with vitamin D levels and should be assessed separately. In conclusion, no consistent relationship between vitamin D status and upper gastrointestinal cancers is currently evident, but studies utilizing sun exposure as a main measurement consistently report lower rates of esophageal cancer with higher levels of ultraviolet irradiance.

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Table 1

Characteristics and outcomes of the nine studies surveyed.

Author	Study Design; # Cancer Cases; Skin Type	Study Location; Study Period	Vitamin D Status Assessment	Confounding Variables Included in Analysis	Correlation Reported, HR/OR/RR (95% CI)
Tran et al 2012	Case-control; 995; 95% + white	Australia; 2002–2005	UVB irradiance (J/m^2)	age, sex, BMI, state of residence at recruitment, heartburn, reflux symptoms, education, smoking, alcohol, h. pylori serostatus	**EAC: OR 0.82[a] (0.72–0.93); OR 0.59[b] (0.35–0.99)** **EGJAC: OR 0.83[a] (0.73–0.94); OR 0.55[b] (0.34–0.90)** ESCC: OR 0.94[a] (0.82–1.09); OR 0.91[b] (0.51–1.64)
Mulholland 2011	Case-control; 218; not reported	Ireland; 2002–2005	FFQ	age, sex energy intake, smoking, education, BMI, occupation, alcohol, NSAID use, h. pylori serostatus, glycemic index intake, saturated fat intake, location	**EAC: OR 1.99 (1.03–3.86)**
Abnet et al 2010	Case-control; 1065; 61% white, 33% asian, 3% black	China, Finland, U.S. including Hawaii; 1974–2006	25OHD	smoking, alcohol, education, BMI, history of gastric surgery	EAC: P for trend 0.70 ESCC: P for trend 0.77 GCA: P for trend 0.88 GNCA: P for trend 0.083
Chen et al 2010[c]	Ecological; --; not reported	China; 1988–1992	UVB irradiance (mW/m^2)	only sex, rural v urban county, ultraviolet irradiance, and cancer incidence/mortality were examined	**EC incidence ratio: 0.73 (0.68–0.78)** **EC mortality ratio: 0.92 (0.90–0.94)** **GC incidence ratio: 0.87 (0.83–0.91)** **GC mortality ratio: 0.97 (0.95–0.99)[d]**
Lipworth et al 2009	Case-control; 304; not reported	Italy; 1992–1997	FFQ	age, sex, study center, education, smoking, alcohol, energy intake	**ESCC: OR 0.84[e] (0.71–0.99)** **OR 0.58[f] (0.40–0.85)**
Chen et al 2007	Case-control with prospective component; 979; not reported	China: 1986–1991	25OHD	age, sex, BMI, smoking, alcohol, serum selenium, cholesterol and retinol, cholesterol and α-tocopherol	**ESCC: HR 1.06 (1.01–1.13)** GCA: 1.03 (0.96–1.10) GNCA: 0.98 (0.86–1.12)
Abnet et al 2007	Case-control with prospective component; 230; not reported	China: 1986–1991	25OHD	age, sex, height, weight, tooth loss	**ESCD: RR 1.86[g] (1.35–2.62)**
Giovannucci et al 2006	Prospective cohort; 93; mainly white cohort	U.S.; 1986–2000	Model predicting 25OHD; model included skin color	age, height, smoking, calorie intake, alcohol, red meat, calcium, retinol, total fruits and vegetables	**EC: RR 0.37 (0.17–0.80)** GC: RR 0.58 (0.26–1.33)
Boscoe and Schymura 2006[h]	Ecological; --; blacks and whites were analyzed separately	North America; 1993–2002	UVB irradiance (kJ/m^2-year)	age, poverty, income, smoking, exercise, alcohol, outdoor occupation, urban/rural, air quality	**EC: Incidence ratio 1.27[i] (1.21–1.34)** **Mortality ratio 1.36[i] (1.31–1.41)** **EC (blacks): RR 1.3–1.5[i]**

25OHD = 25-Hydroxyvitamin D; EAC = Esophageal Adenocarcinoma; EC = Esophageal Cancer; EGJAC = Esophagogastric Junction Adenocarcinoma ESCC = Esophageal Squamous Cell Carcinoma; ESCD = Esophageal Squamous Cell Dysplasia; FFQ = Food Frequency Questionnaire; GC = Gastric Cancer; GCA = Gastric Cardia Adenocarcinoma; GNCA = Gastric Non-cardia Adenocarcinoma UVB = Ultraviolet B

Statistically significant values are bolded.

[a] This OR is for each increase in 10^7 J/m^2 of cumulative ambient UVB exposure. See text for further explanation.

[b] This OR is for highest v. lowest tertile. See text for further explanation.

[c] A total of 424,088 cancer cases were used including nasopharynx, esophagus, stomach, colon, rectal, liver, lung, breast, cervix, bladder, leukemia. Exact figures for esophagus and gastric cancers were not published.

[d] These are statistics reported for overall incidence and mortality ratios, but these ratios varied depending on urban or rural counties. See text and table 2 for further detail.

[e] This OR is for vitamin D status reported as a continuous variable.

[f] This OR is with respect to the lowest tertile of vitamin D status.

[g] Highest quartile vs. lowest quartile.

[h] This study examined over 3 million cancer cases of all types but did not specify numbers of individual types of cancer.

[i] Ratio was reported for receiving annual average 650 kJ/m^2 versus 1540 kJ/m^2. See text for further explanation.

[j] Authors did not report specifics on this risk ratio. See text for details.

Table 2

Negative and Positive Correlations between vitamin D and upper gastrointestinal cancer reported in nine studies.

	Negative						Positive					
	EC	**EAC**	**EGJAC**	**ESCC**	**GC**	**GNCA**	**EC**	**EAC**	**ESCC**	**ESCD**	**GC**	**GCA**
Tran et al 2012		**0.82**[a], **0.59**[b]	**0.83**[a], **0.55**[b]	0.94[a], 0.91[b]								
Mulholland 2011								**1.99**				
Abnet et al 2010			No correlation						No correlation			
Chen et al 2010	**0.42**[c], **0.89**[d]				**0.62**[c], 0.99[d]		**1.12**[e], 1.00[f]				**1.08**[e], **0.92**[f]	
Lipworth et al 2009				**0.84**[g], **0.58**[h]								
Chen et al 2007						0.98			**1.07**			1.03
Abnet et al 2007[a]										**1.86**		
Giovannucci et al 2006	**0.37**				0.58							
Boscoe and Schymura 2006	**1.27**[i], **1.36**[j]											

EAC = Esophageal Adenocarcinoma; EC = Esophageal Cancer; EGJAC = Esophagogastric Junction Adenocarcinoma; ESCC = Esophageal Squamous Cell Carcinoma; GC = Gastric Cancer

Statistically significant values are bolded. The absence of a value in a field indicates this statistic was not evaluated by the study.

[a] This OR is for each increase in 10^7 J/m^2 of cumulative ambient UVB exposure. See text for further explanation.

[b] This OR is for highest v. lowest tertile. See text for further explanation.

[c] Rural incidence ratio

[d] Rural mortality ratio

[e] Urban incidence ratio

[f] Urban mortality ratio

[g] This OR is for vitamin D status reported as a continuous variable.

[h] This OR is with respect to the lowest tertile of vitamin D status.

[i] Incidence ratio

[j] Mortality ratio