Markers of Vitamin D Exposure and Esophageal Cancer Risk: A Systematic Review and Meta-analysis

Lina Zgaga¹, Fiona O’Sullivan¹, Marie M. Cantwell², Liam J. Murray², Prashanthi N. Thota³, and Helen G. Coleman²

Abstract

Vitamin D has been associated with reduced risk of many cancers, but evidence for esophageal cancer is mixed. To clarify the role of vitamin D, we performed a systematic review and meta-analysis to evaluate the association of vitamin D exposures and esophageal neoplasia, including adenocarcinoma, squamous cell carcinoma (SCC), Barrett’s esophagus, and squamous dysplasia. Ovid MEDLINE, EMBASE, and Web of Science were searched from inception to September 2015. Fifteen publications in relation to circulating 25-hydroxyvitamin D [25(OH)D; n = 4], UVB exposure (n = 1), and genetic factors (n = 7) were retrieved. Higher [25(OH)D] was associated with increased risk of cancer [adenocarcinoma or SCC, OR = 1.39; 95% confidence interval (CI), 1.04–1.74], with the majority of participants coming from China. No association was observed between vitamin D intake and risk of cancer overall (OR, 1.03; 0.65–1.42); however, a nonsignificantly increased risk for adenocarcinoma (OR, 1.45; 0.65–2.24) and nonsignificantly decreased risk for SCC (OR, 0.80; 0.48–1.12) were observed. One study reported a decreased risk of adenocarcinoma with higher UVB exposure. A decreased risk was found for VDR haplotype rs2238135(G)/rs198990(T) carriers (OR, 0.45; 0.00–0.91), and a suggestive association was observed for rs2107301. In conclusion, no consistent associations were observed between vitamin D exposures and occurrence of esophageal lesions. Further adequately powered, well-designed studies are needed before conclusions can be made.

Introduction

It is estimated that 456,000 new esophageal cancer cases and 400,000 deaths occur annually in the world (1). Esophageal cancer is the sixth most common cause of cancer-related death worldwide, largely due to a particularly poor prognosis: 5-year survival rates are barely 10% in Europe (2, 3). Esophageal cancer has a distinctive epidemiologic pattern according to its most common histologic subtypes: adenocarcinoma and squamous cell carcinoma (SCC). Differing patterns of incidence suggest differential risk factors that may influence these cancer subtypes. Adenocarcinoma affects the lower third of the esophagus and is thought to arise due to repetitive gastro-esophageal reflux causing alterations to the native squamous epithelium that can lead to Barrett’s esophagus and cancer. Western regions have witnessed a rapid increase in esophageal adenocarcinoma incidence (4): a threefold increase has been observed since the 1970s (5). This increase has been associated with lifestyle factors, including obesity and tobacco smoking (6–8).

In contrast, incidence rates of SCC, which typically affects the upper esophagus, appear to be declining in some Western countries (9, 10). However, SCC remains the predominant esophageal cancer type in developing countries and is endemic in parts of Asia or the "esophageal cancer belt" stretching from Northern Iran to North central China (11). SCC can be largely attributed to consumption of alcohol, hot mate, pickled vegetables, opium, tobacco smoking, or chewing of nass (12–14).

Adequate vitamin D status has been linked with reduced risks of colorectal, breast, and other cancers (15–21). The tentatively causal relationship is supported by an abundance of in vitro evidence that has demonstrated several effects of vitamin D on the "hallmarks" of cancer, including regulation of apoptosis, promotion of cell differentiation, and suppression of cell proliferation (19, 22). Synthesis in the skin following exposure to sunshine and dietary intake are the main sources of vitamin D. Very few foods naturally contain vitamin D, so supplements constitute the most important dietary source (23). Once vitamin D is synthesized or ingested, it is hydroxylated in the liver to form 25-hydroxyvitamin D [25(OH)D], the main circulating form of vitamin D and best predictor of vitamin D status (24). After a second hydroxylation reaction, the active form 1,25-dihydroxyvitamin D [1,25(OH)₂D] is created. 1,25(OH)₂D can bind to the vitamin D receptor (VDR) and this complex has the ability to exert downstream biologic effects. Therefore, it is hypothesized that it is not only the availability of vitamin D but also the availability and structure of VDR that determine molecular actions.
The role of vitamin D in occurrence of rarer cancers is less clear; in particular, conflicting findings have been reported for the risk of esophageal cancer (25). Because vitamin D status is easily modifiable, understanding the role of vitamin D for cancer occurrence is highly relevant for making informed decisions about primary prevention. The aim of this systematic review and meta-analyses is to provide a comprehensive summary of the published literature on the risk of esophageal cancer and precursor lesions in relation to vitamin D exposures: 25(OH)D, vitamin D intake, UIVB radiation, vitamin D–related genetic variation, and VDR expression. To our knowledge, this is the first systematic review on this topic.

Materials and Methods

Search strategy

The bibliographic databases Ovid MEDLINE (US National Library of Medicine, Bethesda, Maryland), EMBASE (Reed Elsevier PLC, Amsterdam, Netherlands), and Web of Science (Thomson Reuters, Times Square, New York) were searched from inception to September 8, 2015, for literature related to vitamin D or related exposures and esophageal neoplasia risk.

The search strategy identified studies that contained at least one keyword or Medical Subject Heading (MeSH) term from each of the following exposures: (i) vitamin D, cholecalciferol, ergocalciferol, 25(OH)D, vitamin D receptor(s), or calcitriol receptor(s), or any of these terms combined with SNP(s) or genetic polymorphism(s), or sun exposure, ultraviolet, UIVB, solar radiation, sunlight, latitude or geographic variation, combined with terms for the outcomes: (ii) Barrett’s esophagus, esophageal cancer, adenocarcinoma, SCC, tumor(s), or neoplasm(s). The search strategy also incorporated limits to studies conducted on humans; however, no language restrictions were specified. Review articles were excluded but checked for references. The systematic review protocol is registered on PROSPERO database 2014:CRD42014007630 (26) and in compliance with MOOSE guidelines (27).

Data extraction

Titles and abstracts were independently examined by two of three reviewers (L. Zgaga, F. O’Sullivan, and H.G. Coleman) to assess eligibility for the review using “PICO” criteria:

(i) Participants: Individuals of any age who have received a diagnosis of cancer or premalignant conditions of the esophagus (and corresponding control populations) were included in the review.

(ii) Intervention: Assessment of vitamin D status, UIVB exposure, vitamin D intake (from foods and/or supplements), VDR expression, and vitamin D–related genetic polymorphisms of the study participants.

(iii) Comparators: Comparisons will be made between vitamin D status and vitamin D–related exposures outlined above with individuals who have not received a diagnosis of cancer or premalignant conditions of the esophagus.

(iv) Outcome: Risk of esophageal cancer, including the histologic subtypes adenocarcinoma and/or SCC, and/or premalignant lesions of the esophagus, Barrett’s esophagus, and squamous dysplasia.

With regard to study design, observational (case–control, retrospective and prospective cohorts, cross-sectional) and interventional studies were included in the review; ecologic studies and case reports were not eligible for inclusion.

The reviewers initially screened titles and abstracts to remove obviously irrelevant articles and screened full text articles independently to identify studies for inclusion in the systematic review. Discrepancies were resolved by discussion with a fourth reviewer (M.M. Cantwell). Reference lists of included articles were also searched for other relevant studies. Methodologic quality for case–control and cohort studies was evaluated using the Newcastle–Ottawa Scale (28). For the cross-sectional study, we used an adapted version of the Newcastle–Ottawa Scale (29).

A standardized data collection protocol was used for gathering data: apart from results, study authors, publication year, residence of participants, proportion of Caucasians, age and gender distribution, study design, number of cases and controls, measurement method or definition of vitamin D exposure and outcome examined, details of the adjustment for confounders, and other variables were recorded. Corresponding authors were contacted for extra study details to enable evaluation and/or analysis if these were not reported in the articles, such as OR values for each of the SNPs investigated (typically only significant associations were reported), or covariates used in the analysis.

Statistical analysis

The associations between esophageal lesion risk and vitamin D exposures were summarized in meta-analyses by comparing risk in the highest to the lowest reported category of exposure (the lowest exposure level was the reference). If the original article used the highest category as the reference, the ORs were inverted or recalculated.

ORs and their corresponding 95% confidence intervals (CI) adjusted for the maximum number of confounding variables were extracted from published reports. In some studies, relative risk (RR) estimates were used, whereas adjusted HRs were extracted from cohort studies. These measures were used in the meta-analysis as given, because the HR, OR, and RR are approximate to one another when event rates are small, as is the case with esophageal cancer (30). Random-effects models were used to calculate pooled OR estimates. We used forest plots to show study-specific risk estimates and to present summary ORs where a minimum of two studies were published for: (i) per esophageal lesion subtype (adenocarcinoma, SCC, squamous dysplasia, and Barrett’s esophagus) and (ii) for esophageal cancer overall (adenocarcinoma and SCC). Although stratified analysis by gender, ethnicity, and geographic location was planned, lack of studies precluded this.

The I² statistic was calculated to quantify the degree of heterogeneity between studies: larger I² values indicate greater heterogeneity (31). Risk of publication and selection bias was evaluated by checking for asymmetry in the funnel plots of the study OR against the standard error of the logarithm of the OR (32). Analysis was conducted using R software and the ‘metaphor’ package (33).

Results

Flowchart for study selection is shown in Fig. 1. Following initial screening of 690 titles and abstracts (n = 475 after removing duplicates), and then 45 full text articles, we identified 15 articles (34–48) that examined relationship between vitamin D
exposures and esophageal neoplasms. These publications related to risk of esophageal cancer or precursor lesions, and: [25(OH)D] concentration (n = 3), vitamin D intake (n = 4), UVB radiation (n = 1), and/or vitamin D–related genetic variants or molecular expression (n = 7), as outlined in Table 1. Further specific limitations of the original study designs are outlined in Supplementary Table S1.

Vitamin D status

Only two studies investigated the role of [25(OH)D] in SCC occurrence (39, 40). In the meta-analysis, we found a nonsignificantly increased SCC risk when comparing the high versus low levels of circulating [25(OH)D]; OR, 1.20 (95% CI, 0.77–1.63). Esophageal adenocarcinoma risk was investigated in a single nested case–control study (39), and squamous dysplasia risk in a single cross-sectional study (38). We found an increased risk of esophageal cancer overall (adenocarcinoma and SCC) when comparing high versus low levels of [25(OH)D] level in the meta-analysis (OR, 1.39; 95% CI, 1.03–1.74; Fig. 2).

Vitamin D intake

Four studies have reported on the association between vitamin D intake from food (supplement use not considered) and esophageal neoplastic lesion risk: two studies examined risk of adenocarcinoma (35, 37), three examined risk of SCC (34–36), and a single study examined risk of Barrett’s esophagus (37). A nonsignificantly increased risk was found in the meta-analysis for adenocarcinoma (OR, 1.45; 95% CI, 0.65–2.24) and nonsignificantly decreased risk for SCC (OR, 0.80; 95% CI, 0.48–1.12; Fig. 3) with higher vitamin D intakes. No association was observed overall between vitamin D intake and risk of cancer (OR, 1.03, 95% CI, 0.65–1.42). No associa-

Copyright © 2016 American Association for Cancer Research. Published OnlineFirst March 30, 2016. DOI: 10.1158/1055-9965.EPI-15-1162
Table 1. Characteristics of studies of vitamin D-related exposures and the risk of esophageal cancer and premalignant conditions

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design</th>
<th>Study location</th>
<th>NO score</th>
<th>Vitamin D exposure</th>
<th>Outcomes</th>
<th>Cases</th>
<th>Control/cohorts</th>
<th>Adjuled confounders</th>
<th>Age</th>
<th>Sex</th>
<th>Energy</th>
<th>BMI</th>
<th>Smoking</th>
<th>Alcohol</th>
<th>NSAIDs</th>
<th>Reflux</th>
<th>Education</th>
<th>SE status</th>
<th>PA</th>
<th>H. pylori</th>
<th>Race</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qian et al. (2007)</td>
<td>Case-cohort</td>
<td>China</td>
<td>8</td>
<td>Serum 25(OH)D SCC</td>
<td>SCC</td>
<td>545</td>
<td>1,105</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnet et al. (2010)</td>
<td>Nested</td>
<td>China, Finland, USA</td>
<td>8 Serum/plasma SCC</td>
<td>SCC</td>
<td>545</td>
<td>1,105</td>
<td>√</td>
<td></td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Launoy et al. (1998)</td>
<td>Hospital-based case-control</td>
<td>France</td>
<td>5</td>
<td>Interv. diet history SCC</td>
<td>208</td>
<td>399</td>
<td>M</td>
<td></td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meyn et al. (2011)</td>
<td>Population-based case-control</td>
<td>Italy</td>
<td>6</td>
<td>Dietary intake SCC</td>
<td>206</td>
<td>399</td>
<td>M</td>
<td></td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upchurch et al. (2009)</td>
<td>Population-based case-control</td>
<td>Ireland</td>
<td>7</td>
<td>Dietary intake SCC</td>
<td>206</td>
<td>399</td>
<td>M</td>
<td></td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muldoon et al. (2017)</td>
<td>Population-based case-control</td>
<td>Australia</td>
<td>8</td>
<td>Lifetime daily SCC</td>
<td>206</td>
<td>399</td>
<td>M</td>
<td></td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D-related genetic variants/ molecular expression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Gattardi et al. (2006)</td>
<td>Cross-sectional</td>
<td>Switzerland</td>
<td>4</td>
<td>VDR expression (mRNA) SCC</td>
<td>206</td>
<td>399</td>
<td>M</td>
<td></td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li et al. (2008)</td>
<td>Case-control</td>
<td>China</td>
<td>6</td>
<td>VDR F37 polymorphism SCC</td>
<td>206</td>
<td>399</td>
<td>M</td>
<td></td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van der Wilt et al. (2009)</td>
<td>Case-control</td>
<td>Netherlands</td>
<td>N/A</td>
<td>VDR polymorphisms SCC</td>
<td>206</td>
<td>399</td>
<td>M</td>
<td></td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al. (2011)</td>
<td>Population-based case-control</td>
<td>Ireland</td>
<td>8</td>
<td>VDR polymorphisms SCC</td>
<td>206</td>
<td>399</td>
<td>M</td>
<td></td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guo et al. (2014)</td>
<td>Hospital-based case-control</td>
<td>China</td>
<td>7</td>
<td>VDR polymorphisms SCC</td>
<td>206</td>
<td>399</td>
<td>M</td>
<td></td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jemmal et al. (2015)</td>
<td>Case-control</td>
<td>Netherlands</td>
<td>6</td>
<td>VDR polymorphisms SCC</td>
<td>206</td>
<td>399</td>
<td>M</td>
<td></td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang et al. (2015)</td>
<td>Case-control</td>
<td>China</td>
<td>7</td>
<td>Vitamin D level SCC</td>
<td>206</td>
<td>399</td>
<td>M</td>
<td></td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Adjusted confounders: Energy, energy intake; reflux, gastro-esophageal reflux symptoms; SE status, socioeconomic status; PA, physical activity; H. pylori, Helicobacter pylori infection; FFQ, food frequency questionnaire; NO score, Newcastle-Ottawa quality scale score (maximum score: 9).

*All male cohort.

# Covariate considered but removed from the final model.

# New Zealand-Ottawa quality score could not be derived because of insufficient detail (only abstract available).

# An adapted version of the Newcastle-Ottawa quality scale was used for this study as it was cross-sectional.

# Same cohort (shared controls).
Vitamin D and Esophageal Cancer Risk: A Review

One Chinese case–control study, assessed 12 SNPs that were shown to modify vitamin D status in relation to risk of SCC. In this relatively large study comprising about 4,000 participants (1,942 cases), no significant associations were found between any of these SNPs individually or their genetic score and the risk of SCC (48).

Discussion

In this systematic review, we attempt to summarize all available evidence to give the most comprehensive overview of the associations between vitamin D exposures and esophageal neoplastic lesions to date. Our effort has been limited by the scarcity and quality of published studies, and the use of different vitamin D exposures and outcomes, which makes interpretation and comparisons difficult.

Vitamin D status

Although we observed increased esophageal lesion risk associated with higher [25(OH)D] concentration in the meta-analysis, at this time, we are reluctant to suggest that higher [25(OH)D] increases the risk of esophageal cancer. The small number of published studies, the limitations of their designs (Supplementary Table S1), and possibility of population-specific effects raise concerns. Nonetheless, current evidence exposes a possibility that population subgroups may exist where risk of esophageal cancer is increased with higher [25(OH)D] concentration.

Figure 2.

Meta-analysis of studies looking at serum [25(OH)D] and esophageal neoplasia using adjusted OR estimates. SCC: \( \hat{I}^2 = 21.93\%, \hat{Q} = 128, P = 0.25 \). Overall cancer: \( \hat{I}^2 = 60.54\%, \hat{Q}(df=2) = 5.0679, P = 0.079 \). Weights are shown for overall cancer. *, this study was a cross-sectional study, whereas the others were case–control; †, total number of upper gastrointestinal cancer cases from each study given for the Cohort Consortium: Finland: 416, China: 313, USA: 296. Number of geometric means of vitamin D levels per quantiles: Chen and colleagues (2007): 25th, 19.9 nmol/L; 75th, 57.2 nmol/L and Abnet and colleagues (2007): 25th, 24.1 nmol/L; 75th, 48.2 nmol/L. #, Q1 versus Q4, quartile 1 versus quartile 4.

We found a nonsignificantly increased risk of adenocarcinoma and nonsignificantly decreased risk of SCC for higher dietary vitamin D intakes—this is contradictory to nonsignificantly
increased risk of SCC found for higher [25(OH)D] levels. As subtypes of esophageal cancer seem to have different etiology, it is plausible to hypothesize that vitamin D could have a beneficial effect on one while having no effect or a detrimental effect on another subtype. Overall, only four studies investigated the relationship between vitamin D intake and neoplastic lesions of the esophagus. Notably, none of these studies collected information on vitamin D supplementations, which make a major contribution to vitamin D status for individuals choosing to take these (23). Widespread vitamin D supplementation is not currently advocated; however, with increasing prevalence of use, it is plausible to hypothesize that vitamin D could have a beneficial effect. VDR and other vitamin D–related genetic factors

The advantage of studying genetic polymorphisms is that the exposure is constant and present throughout life. However, genetic effects are typically small and very large cohorts are needed to achieve sufficient power for effect detection. The majority of studies included in this review had small sample sizes (median number of cases was 141). There has been some evidence to suggest different polymorphisms in the VDR gene (and consequential variations in the VDR protein) can modify activity of vitamin D due to its location in the VDR gene (and consequential variations in the VDR protein) can modify activity of vitamin D (55). For example, rs11568820 was found to directly influence transcriptional activity due to its location in the VDR promoter region (56), and rs10735810 has been shown to affect the translational start site of 1,25-dihydroxycholecalciferol (57). Therefore, VDR polymorphisms or altered expression can potentially lead to the modification of cancer risk and survival (58–60). To date, polymorphisms in VDR gene have

UVB radiation

A single article reported on measures of lifetime UV radiation exposure and esophageal cancer risk in an Australian population–based case–control study (47). Individuals with the highest tertile of mean lifetime daily UV radiation exposure had a reduced risk of esophageal adenocarcinoma and esophago-gastric junctional tumors. In addition, an inverse association was also found between the number of nevi (another marker of sun exposure) and adenocarcinoma in the same study. This is in contrast to no association observed in a single [25(OH)D] study and contradictory to the increased adenocarcinoma risk found for higher dietary vitamin D intake. Similarly, no association was found between SCC and UVB, but a suggestive positive association was observed in [25(OH)D] studies. The inconsistency between these results may be due to the underlying population differences which we are not able to address at this time due to the lack of published studies.

It is worth mentioning that multiple ecological studies examined UVB radiation exposure and esophageal cancer risk (these were ineligible for inclusion in our review due to study design). However, they found a significantly lower esophageal cancer risk and mortality in regions with higher UVB irradiance (47, 51, 52). Boscoe and colleagues used satellite-measured solar UVB levels and found a reduced esophageal cancer risk (RR, 0.79; 95% CI, 0.75–0.83) and lower mortality rates (RR, 0.74, 95% CI, 0.71–0.76) when looking at solar UVB exposure in Southern versus Northern United States. Similar correlations with incidence and mortality were observed with latitude, with an index of UVB intensity in France (53) and with mortality in China (54).

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Cases</th>
<th>Controls</th>
<th>Population</th>
<th>Diet</th>
<th>Suppl</th>
<th>Exposure (µg/d)</th>
<th>Weight</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayne, 2001</td>
<td>282</td>
<td>687</td>
<td>USA</td>
<td>✓</td>
<td>X</td>
<td>75th vs. 25th %</td>
<td>22%</td>
<td>1.10 (0.86–1.40)</td>
</tr>
<tr>
<td>Mulholland, 2011</td>
<td>218</td>
<td>252</td>
<td>Ireland</td>
<td>✓</td>
<td>X</td>
<td>&gt;3 vs. &lt;2.05</td>
<td>73%</td>
<td>1.92 (0.98–3.76)</td>
</tr>
<tr>
<td>Overall AC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.45 (0.65–2.24)</td>
</tr>
<tr>
<td>Mayne, 2001</td>
<td>206</td>
<td>687</td>
<td>USA</td>
<td>✓</td>
<td>X</td>
<td>75th vs. 25th %</td>
<td>24.1%</td>
<td>1.00 (0.74–1.36)</td>
</tr>
<tr>
<td>Launoy, 2009</td>
<td>208</td>
<td>399</td>
<td>France</td>
<td>✓</td>
<td>X</td>
<td>&gt;7 vs. &lt;3</td>
<td>75.3%</td>
<td>0.70 (0.32–1.54)</td>
</tr>
<tr>
<td>Lipworth, 2009</td>
<td>304</td>
<td>743</td>
<td>Italy</td>
<td>✓</td>
<td>X</td>
<td>T3 vs. T1 †</td>
<td>25.6%</td>
<td>0.58 (0.39–0.86)</td>
</tr>
<tr>
<td>Overall SCC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.80 (0.48–1.12)</td>
</tr>
<tr>
<td>Mulholland, 2011</td>
<td>212</td>
<td>252</td>
<td>Ireland</td>
<td>✓</td>
<td>X</td>
<td>&gt;3 vs. &lt;2.05</td>
<td>1.18</td>
<td>0.61–2.29</td>
</tr>
</tbody>
</table>

Figure 3. Meta-analysis of studies looking at dietary vitamin D intake and esophageal neoplasia using adjusted OR estimates. Adenocarcinoma: I² = 80%, Q = 5.07, P = 0.024, SCC: I² = 38%, Q = 2.8, P = 0.24. Overall cancer: I² = 77%, Q(df = 5) = 12.75, P = 0.012. †, 75th versus 25th percentiles: mean vitamin D intake for each quartile not specified in article; †, T1 versus T3: the 33rd and 67th percentiles of vitamin D reported in this article were 2.51 and 3.51 µg/d, respectively.
been linked to risk of cancers, including prostate (61), breast (62), skin and colorectal (63, 64), and high VDR expression has been linked to increased survival in prostate and breast cancers (65–67).

VDR polymorphisms. In the meta-analysis, an association was found for VDR haplotype rs2238135/rs1989969 G/T and esophageal neoplasia risk; while there was suggestive association for variant rs2107301. In accordance with this, previous studies have also reported a reduced risk in prostate cancer for individuals who have the more common G allele, when compared with those with the rarer C allele for variant rs2238135 (OR, 0.51; 95% CI, 0.29–0.85; ref. 68). Contrastingly however, this article also found an increased risk of prostate cancer with variant rs2107301 T versus C (OR, 2.47; 95% CI, 1.52–4.0; ref. 68), whereas Anic and colleagues found no association between rs2107301 and risk of glioma (69).

VDR expression. It had previously been suggested that apoptosis mechanisms were important for the transformation of Barrett’s esophagus into adenocarcinoma and that expression of VDR in the esophagus was important in regulating apoptosis (70). It has further been shown that high expression of VDR can impact disease progression and overall survival of prostate, colon, and breast cancers (65, 67, 71). In a very small study by De Gottardi and colleagues, no difference in VDR expression was observed in esophageal biopsies from patients with normal mucosa, Barrett’s esophagus, or adenocarcinoma (42).

It has previously been suggested that apoptosis mechanisms were important for the transformation of Barrett’s esophagus into adenocarcinoma and that expression of VDR in the esophagus was important in regulating apoptosis (70). It has further been shown that high expression of VDR can impact disease progression and overall survival of prostate, colon, and breast cancers (65, 67, 71). In a very small study by De Gottardi and colleagues, no difference in VDR expression was observed in esophageal biopsies from patients with normal mucosa, Barrett’s esophagus, or adenocarcinoma (42). Towbridge and colleagues have also published a series of articles on VDR expression in esophageal tissue, but these were not eligible for inclusion in our review due to the lack of risk estimates presented, or inability to calculate these. In their studies, a change in VDR expression has been noted in columnar metaplasia but not in native squamous epithelium of the esophagus (72, 73). This suggests that vitamin D does not have an opportunity to bind locally in the esophagus and therefore exert any biologic effects, unless the cell lining has undergone the metaplastic transition and may explain discrepancies in results by histologic subtype.

Vitamin D level–related genetic variation. Finally, Wang and colleagues (2015) found no associations between 12 genetic variants associated with vitamin D status and risk of SSC in their Chinese case–control study. However, it may be inappropriate to assess these SNPs that were shown to modify vitamin D status in GWAS in individuals of European ancestry (74) in the Chinese population (48).

In summary, because of the small sample size of most studies and an overall scarcity of published articles, evidence available at this time is deficient and meaningful conclusions cannot be made.
However, results presented here do suggest vitamin D–related genetic variation is worthy of further examination, in larger, adequately powered studies.

**Strengths, limitations, and recommendations for future research**

This is the first systematic review that has examined the relationship between vitamin D and related exposures and esophageal neoplasia risk. A strong point of this review is that all major environmental and genetic vitamin D–related exposures have been considered. Dietary vitamin D intake is known to correlate only weakly with [25(OH)D], the best biomarker for exposure to vitamin D. This is probably due to the fact that dietary sources of vitamin D are scarce, and accurate assessment of vitamin D intake over time is difficult. Therefore, the associations observed may in fact reflect the effect of additional exposures other than vitamin D.

The major limitation relates to the published information; namely, only a small number of studies that suffer from various methodologic limitations and typically include small sample sizes were available. It cannot be excluded that reported findings arose due to unmeasured or residual confounding, as the level of adjustment varied across retrieved studies. Moreover, we noted relatively large heterogeneity in meta-analyses and our capacity to detect publication bias is limited (Supplementary Figs. S2–S5) because meta-analyses were based on a small number of studies (75).

Future studies should be sufficiently powered and aim to measure 25(OH)D (ideally at multiple time points), collect accurate data on vitamin D intake (in particular, information on vitamin D supplementation), attempt to approximate individual UVB exposure, and assess genetic factors relevant for vitamin D metabolism, to provide comprehensive evidence. Information on important confounders should be collected and included. Associations should ideally be examined in a cohort (particularly for vitamin D intake and UVB) or case–control (genetic factors) studies and designed carefully to minimize the possibility of confounding and reverse causation. Different esophageal neoplastic lesions should be examined separately due to the known differences in their etiology.

**Conclusion**

This is the first systematic review which has examined the relationship between esophageal neoplasia risk and vitamin D exposures; we present the most comprehensive overview of available evidence to date by including all major personal, environmental, and genetic factors related to vitamin D. While vitamin D has generally been shown to be protective for most other cancers, we found that higher [25(OH)D] concentration was associated with an increased risk of esophageal cancer, in predominantly Chinese populations. Interestingly, albeit non-significantly, dietary vitamin D intake was associated with a decreased risk of SCC, but an increased risk of adenocarcinoma. One study reported higher lifetime UVB exposure was associated with a decreased risk of adenocarcinoma. There is some evidence to suggest VDR polymorphisms modify the risk;
however, no consistent associations were detected. Hence, results are strikingly inconsistent and we are unable to make any firm conclusions with respect to the role of vitamin D in esophageal neoplasia at this time.

Because vitamin D deficiency is common, pressure exists to promote vitamin D supplementation. Our findings have implications for the guidelines on supplementation and population-wide interventions that are currently being revisited and debated in many countries, because results suggest that population subgroups may exist where attempts to increase [25(OH)D] concentration could be harmful. Issues like this need to be considered and harmful effect clarified before interventions are put in place.

Therefore, it is critical to examine the suggested detrimental effects of vitamin D on health in well-designed adequately powered studies, before public health measures aimed at increasing [25(OH)D] are introduced.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Grant Support
F O'Sullivan is funded via FP7-PEOPLE-2013-CIG-SOGVID, project number 631041. H.G. Coleman is supported by a Cancer Research UK Population Research Postdoctoral Fellowship (A15333).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received November 10, 2015; revised February 11, 2016; accepted March 20, 2016, published OnlineFirst March 30, 2016.

References

12. Islami F, Ren JS, Taylor PR, Kamangar F. Pickled vegetables and the risk of esophageal neoplasia at this time.


Markers of Vitamin D Exposure and Esophageal Cancer Risk: A Systematic Review and Meta-analysis

Lina Zgaga, Fiona O'Sullivan, Marie M. Cantwell, et al.


Updated version
Access the most recent version of this article at:
doi:10.1158/1055-9965.EPI-15-1162

Supplementary Material
Access the most recent supplemental material at:
http://cebp.aacrjournals.org/content/suppl/2016/03/30/1055-9965.EPI-15-1162.DC1

Cited articles
This article cites 72 articles, 17 of which you can access for free at:
http://cebp.aacrjournals.org/content/25/6/877.full#ref-list-1

Citing articles
This article has been cited by 1 HighWire-hosted articles. Access the articles at:
http://cebp.aacrjournals.org/content/25/6/877.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.