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Markers of vitamin D exposure and oesophageal cancer risk: a systematic review and meta-analysis.

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Abstract

Vitamin D has been associated with reduced risk of many cancers, but evidence for oesophageal 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 oesophageal neoplasia, including adenocarcinoma, squamous cell carcinoma (SCC), Barrett's oesophagus 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 (n=3), Vitamin D intake (n=4), UVB exposure (n=1), and genetic factors (n=7) were retrieved. Higher 25-OHD was associated with increased risk of cancer (adenocarcinoma or SCC, OR=1.39;95%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 non-significantly increased risk for adenocarcinoma (OR=1.45;0.65-2.24) and non-significantly 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)/rs1989969(T) carriers, OR=0.45;0.00-0.91, and a suggestive association was observed for rs2107301. No consistent associations were observed between Vitamin D exposures and occurrence of oesophageal lesions. Further adequately powered, well-designed studies are needed before conclusions can be made.

Introduction

It is estimated that 456,000 new oesophageal cancer cases and 400,000 deaths occur annually in the world (1). Oesophageal cancer is the 6th most common cause of cancer death worldwide, largely due to a particularly poor prognosis: 5-year survival rates are barely 10% in Europe (2, 3). Oesophageal cancer has a distinctive epidemiological pattern according to its most common histological subtypes: adenocarcinoma (AC) and squamous cell carcinoma (SCC). Differing patterns of incidence suggest differential risk factors that may influence these cancer subtypes.

AC affects the lower third of the oesophagus and is thought to arise due to repetitive gastro-oesophageal reflux causing alterations to the native squamous epithelium that can lead to Barrett's oesophagus (BO) and cancer. Western regions have witnessed a rapid increase in oesophageal AC 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 oesophagus, appear to be declining in some western countries (9, 10). However, SCC remains the predominant oesophageal cancer type in developing countries, and is endemic in parts of Asia or the "oesophageal 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 synthetized 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 biological effects. Therefore, it is hypothesised that it is not only the availability of vitamin D but also 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 oesophageal 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 oesophageal cancer and pre-cursor lesions in relation to vitamin D exposures: 25(OH)D, vitamin D intake, UVB 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 (Thompson Reuters, Times Square, New York, USA) were searched from inception to 8th September 2015 for literature related to vitamin D or related exposures and oesophageal 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 single nucleotide polymorphism(s) or genetic polymorphism(s), or sun exposure, ultraviolet, UVB, solar radiation, sunlight, latitude or geographic variation, combined with terms for the outcomes: (ii) Barrett's (o)esophagus, (o)esophageal cancer, AC, SCC, tumour(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 (LZ, FOS and HC) to assess eligibility for the review using 'PICO' criteria:

(i) **P**articipants: Individuals of any age who have received a diagnosis of cancer or pre-malignant conditions of the oesophagus (and corresponding control populations) were included in the review.

(ii) **I**ntervention: Assessment of vitamin D status, UVB exposure, vitamin D intake (from foods and/or supplements), VDR expression, and vitamin D-related genetic polymorphisms of the study participants.

(iii) **C**omparators: 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 pre-malignant conditions of the oesophagus.

(iv) **O**utcome: Risk of oesophageal cancer, including the histological subtypes AC and/or SCC, and/or pre-malignant lesions of the oesophagus, BO and squamous dysplasia (SD).

With regard to study design, observational (case-control, retrospective and prospective cohort, cross-sectional) and interventional studies were included in the review; ecological 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 (MC). Reference lists of included articles were also searched for other relevant studies. Methodological 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 standardised 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 paper, such as OR values for each of the SNPs investigated (typically only significant associations were reported), or co-variates used in the analysis.

Statistical analysis

The associations between oesophageal lesion risk and vitamin D exposures were summarised 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 paper used the highest category as the reference, the odds ratios were inverted or recalculated.

Odds ratios (OR) 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 estimates (RR) were used, whereas adjusted hazard rate ratios (HR) 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 oesophageal 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 odds ratios where a minimum of two studies were published for: (i) per oesophageal lesion subtype (AC, SCC, SD and BO), and (ii) for oesophageal cancer overall (AC and SCC). Although stratified analysis by gender, ethnicity and geographic location was planned, lack of studies precluded this.

The I^2 statistic was calculated to quantify the degree of heterogeneity between studies: larger I^2 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 **Figure 1**. Following initial screening of 690 titles and abstracts (n=475 after removing duplicates), and then 45 full text articles, we identified fifteen articles (34-48) that examined relationship between vitamin D exposures and oesophageal neoplasms. These publications related to risk of oesophageal cancer or pre-cursor 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 non-significantly increased SCC risk when comparing the high vs. low levels of circulating 25(OH)D, OR=1.20 (95%CI: 0.77-1.63). Oesophageal AC risk was investigated in a single nested case-control study (39), and SD risk in a single cross-sectional study (38). We found a an increased risk of oesophageal cancer overall (AC and SCC) when comparing high vs. low levels of 25(OH)D level in the meta-analysis, OR=1.39 (95%CI: 1.03-1.74, **Figure 2**).

Vitamin D intake

Four studies have reported on the association between vitamin D intake from food (supplement use not considered) and oesophageal neoplastic lesion risk: two studies examined risk of AC (35, 37), three examined risk of SCC (34-36) and a single study examined risk of BO (37). A non-significantly *increased* risk was found in the meta-analysis for AC (OR=1.45; 95%CI: 0.65-2.24) and non-significantly *decreased* risk for SCC (OR=0.80; 95%CI: 0.48-1.12, **Figure 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 associations with vitamin D and BO were found in an Ireland based study (37).

UVB

Only a single study examined the relationship between oesophageal cancer and UVB (47). This study found decreased risk of oesophageal AC (OR=0.49; 95%CI: 0.31-0.79) and oesophago-gastric junction AC (OR=0.52; 95%CI: 0.33-0.81) in individuals with higher lifetime mean daily UV radiation exposure, but not with SCC (OR=0.95; 95%CI: 0.57-1.59). For meta-analysis across cancer types from this study see **Supplementary Figure S1**.

VDR and other vitamin D related genetic factors

Risk of oesophageal neoplasia was investigated in relation to VDR polymorphisms (5 studies), VDR expression (single study) and vitamin D level-related genetic variation (single study).

Haplotype rs2238135/rs1989969 was examined using the same cohort in relation to SCC and also BO and AC. We found a decreased cancer risk in G/T haplotype carriers in meta-analysis of unadjusted findings, OR=0.45 (95%CI: 0.00-0.91) (**Figure 4**).

A suggestive association was also found between oesophageal cancer risk and variant rs2107301 T vs. G in a meta-analysis of two studies adjusted OR estimates, OR=0.66 (95%CI: 0.28-1.05) (**Figure 4 and Figure 5**). No association was found between TaqI or FokI and oesophageal neoplasia, OR=1.31 (95%CI: 0.41-2.20) and OR=1.03 (95%CI: 0.72-1.33), respectively.

A single study did not find any differences in VDR expression between BO, AC or normal mucosa samples analysed, although this investigation was restricted to only six biopsies samples per disease state (42).

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 ~4000 participants (1942 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 summarise all available evidence to give the most comprehensive overview of the associations between vitamin D exposures and oesophageal 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 oesophageal 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 oesophageal 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 oesophageal cancer is increased with higher 25(OH)D concentration. All three studies contained a large proportion of the Han Chinese population, of which two were in Linxian China. The Linxian region in China has among the highest rates of oesophageal SCC in the world (38-40). It is not clear whether any region-specific environmental or genetic exposures (or their interactions) drive these high rates. Some authors suggest that vitamin D may be increasing cancer risk in this population by affecting the metabolism of polycyclic aromatic hydrocarbons (high use of coal in the region leads to high exposure to these toxins) (38). Hence, the majority of evidence to date comes from studies conducted in China, where distribution of 25(OH)D and aetiology of oesophageal lesions are likely to be different to that of the Western populations (49). The notion that the effect of vitamin D on oesophageal cancer may vary by ethnicity has implications for vitamin D supplementation recommendations aimed at increasing 25(OH)D level. In conclusion, further studies in different populations are needed and population-specific effects of 25(OH)D cannot be excluded at this time.

Vitamin D Intake

We found a non-significantly *increased* risk of AC, and non-significantly *decreased* risk of SCC for higher dietary vitamin D intakes – this is contradictory to non-significantly *increased* risk of SCC found

for higher 25(OH)D levels. As subtypes of oesophageal cancer seem to have different aetiology, it is plausible to hypothesize that vitamin D could have a beneficial effect on one, while having no or a detrimental effect on another subtype. Overall, only four studies investigated the relationship between vitamin D intake and neoplastic lesions of the oesophagus. Notably, none of these studies collected information on vitamin D supplementation, which make a major contribution to status for individuals choosing to take these (23). Widespread vitamin D supplementation is not currently advocated; however, with increasing prevalence of use it is important for contemporary studies to assess this as part of vitamin D intake data.

It is worth mentioning the study of Giovannucci et al. that measured *predicted* 25(OH)D concentration in a large cohort (N=47,800), by modelling multiple factors that influence vitamin D status, such as UVB, diet, supplements, skin pigmentation and body mass index (BMI). A prediction equation was then developed and it was found that higher levels of predicted 25(OH)D were associated with a *decreased* risk of oesophageal cancer (RR=0.37, 95%CI: 0.17-0.80) (50); however, factors used to predict 25(OH)D could affect cancer risk independent from their association to vitamin D status, for example BMI.

UVB radiation

A single paper reported on measures of lifetime UV radiation exposure and oesophageal 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 oesophageal AC and oesophago-gastric junctional tumours. In addition, an inverse association was also found between the number of nevi (another marker of sun exposure) and AC in the same study. This is in contrast to no association observed in a single 25(OH)D study and contradictory to the increased AC 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 oesophageal cancer risk (these were ineligible for inclusion in our review due to study design). However, they found a significantly lower oesophageal cancer risk and mortality in regions with higher UVB irradiance (47, 51, 52). Boscoe et al. used satellite-measured solar UVB levels and found a reduced oesophageal 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).

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-VDR complex (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 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 oesophageal 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 to those with the rarer C allele for variant rs2238135 (OR=0.51, 95%CI: 0.29-0.85) (68). Contrastingly however, this paper also

found an increased risk of prostate cancer with variant rs2107301 TvsC (OR=2.47, 95%CI: 1.52-4.0) (68), while Anic et al 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 BO into AC and that expression of VDR in the oesophagus 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 et al., no difference in VDR expression was observed in oesophageal biopsies from patients with normal mucosa, BO or AC (42). Trowbridge et al, have also published a series of papers on VDR expression in oesophageal 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 oesophagus (72, 73). This suggests that vitamin D does not have an opportunity to bind locally in the oesophagus, and therefore exert any biological effects, unless the cell lining has undergone the metaplastic transition and may explain discrepancies in results by histological subtype.

Vitamin D level-related genetic variation. Finally, Wang et al. (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, due to the small sample size of most studies and an overall scarcity of published papers, 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 oesophageal 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 methodological 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 Figures 2-5**) 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, designed carefully to minimise the possibility of confounding and reverse causation. Different oesophageal neoplastic lesions should be examined separately due to the known differences in their aetiology.

Conclusion

This is the first systematic review which has examined the relationship between oesophageal 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 oesophageal 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 AC. One study reported higher lifetime UVB exposure was associated with a *decreased* risk of AC. 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 oesophageal 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 suggests that population subgroups may exist where attempts to increase 25-OHD 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.

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Table 1. Characteristics of studies of vitamin D related exposures and the risk of oesophageal cancer and pre-malignant conditions. Adjusted confounders: *Energy*: Energy intake; *BMI*: Body mass index; *Reflux*: Gastro-oesophageal 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).
m: all male cohort; ˣ covariate considered but removed from the final model; †: Newcastle-Ottawa quality score could not be derived due to 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).

Study and location	Study design	Study location	NO score	Vitamin D exposure	Outcomes	Cases	Controls/ Cohort	Adjusted confounders												
								Age	Sex	Energy	BMI	Smoking	Alcohol	NSAIDs	Reflux	Education	SE Status	PA	H. pylori	Race
VITAMIN D STATUS																				
Chen et al. (2007),	Case-cohort	China	8	Serum 25(OH)D	Squamous cell carcinoma	545	1,105	✓	✓		ˣ✓	✓	✓							
Abnet et al. (2007),	Cross-sectional	China	8≠	Serum 25(OH)D	Squamous dysplasia	230	490	✓	✓		✓									
Abnet et al. (2010),	Nested case-control	China, Finland, USA	8	Serum/ plasma 25(OH)D	All oesophageal cancer	265	264	✓	✓		ˣ✓	✓	✓			✓				✓
					Adenocarcinoma	104	103	✓	✓		ˣ✓	✓	✓			✓				✓
					Squamous cell carcinoma	142	142	✓	✓		ˣ✓	✓	✓			✓				✓
VITAMIN D INTAKE																				
Launoy et al. (1998),	Hospital-based case-control	France	5	Interview diet history	Squamous cell carcinoma	208	399	✓	*m*	✓		✓	✓							
Mayne et al. (2001),	Population-based case-control	USA	6	Dietary intake (104-item FFQ)	Adenocarcinoma	282	687	✓	✓	✓	✓	✓	✓			✓				✓
					Squamous cell carcinoma	206	687	✓	✓	✓	✓	✓	✓			✓				✓
Lipworth et al. (2009),	Hospital-based case-control	Italy	6	Dietary intake (78-item FFQ)	Squamous cell carcinoma	304	743	✓	✓		✓	✓	✓			✓				
Mulholland et al. (2011),	Population-based case-control	Ireland	7	Dietary intake (101-item FFQ)	Adenocarcinoma	218	252	✓	✓	✓	✓	✓	✓	✓	ˣ✓	✓			✓	
					Barrett's oesophagus	212	252	✓	✓	✓	✓	✓	✓	✓	ˣ✓	✓			✓	

Study and location	Study design	Study location	NO score	Vitamin D exposure	Outcomes	Cases	Controls/ Cohort size	Adjusted confounders: Age	Sex	Energy	BMI	Smoking	Alcohol	NSAIDs	Reflux	Educatio	SE Status	PA	H. pylori	Race
UVB RADIATION																				
Tran et al. (2012),	Population-based case-control	Australia	8	Lifetime daily mean ambient UV radiation	Adenocarcinoma	330	1,417	✓	✓		✓	✓	✓		✓	✓		*✓	✓	
					Squamous cell carcinoma	279	1,417	✓	✓		✓	✓	✓		✓	✓		*✓	✓	
					Junctional tumours	386	1,417	✓	✓		✓	✓	✓		✓	✓		*✓	✓	
VITAMIN D RELATED GENETIC VARIANTS/MOLECULAR EXPRESSION																				
De Gottardi et al. (2006),	Cross-sectional	Switzerland	4	VDR expression (tissue)	Barrett's oesophagus	6	6	none												
					Adenocarcinoma	6	6	none												
Li et al. (2008),	Case-control	China	6	VDR *TaqI* polymorphism	Squamous cell carcinoma	126	169	✓	✓							✓				
					Squamous dysplasia	127	169	✓	✓							✓				
Van den Winkel et al. (2009),	Case-control	Netherlands[$]	N/A[†]	VDR polymorphisms	Squamous cell carcinoma	64	202	none												
Chang et al. (2012),	Population-based case-control	Ireland	8	VDR polymorphisms	Adenocarcinoma	224	256	✓	✓	✓	✓	✓	✓		✓	✓	✓			
Gu et al. (2014),	Hospital-based case-control	China	7	VDR polymorphisms	Squamous cell carcinoma	629	686	✓	✓			✓	✓							
Janmaat et al. (2015),	Case-control	Netherlands[$]	6	VDR polymorphisms	Barrett's oesophagus	260+150	202	none												
					Adenocarcinoma	141	202	none												
Wang et al (2015),	Case-control	China	7	Vitamin D level-related polymorphisms	Squamous cell carcinoma	1942	2111	✓	✓											

Figure Legends:

Figure 1. Flow diagram of search strategy.

Figure 2. Meta-analysis of studies looking at serum 25(OH)D and oesophageal neoplasia using adjusted OR estimates. Squamous cell carcinoma (SCC) I^2 = 21.93%, Q-value=1.28, p-value= 0.25. Overall Cancer I^2: 60.54% Q(df = 2) = 5.0679, p-value = 0.079. Weights are shown for overall cancer. * This study was a cross-sectional study, while 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. # Geometric means of vitamin D levels per quantiles: Chen et al (2007): 25th: 19.9 nmol/l, 75^{th}: 57.2nmol/l. and Abnet et al (2007) 25^{th}: 24.1 nmol/l 75^{th}: 48.2 nmol/l. Q1 vs Q4: quartile 1 vs quartile 4

Figure 3. Meta-analysis of studies looking at dietary vitamin D intake and oesophageal neoplasia using adjusted OR estimates. Adenocarcinoma (AC): I^2 = 80%, Q-value=5.07, p-value= 0.024. Squamous cell carcinoma (SCC) I^2 = 38%, Q-value=2.8, p-value= 0.24. Overall Cancer I^2: 77%, Q (df = 5) = 12.75, p-value = 0.012.
* 75^{th} vs 25^{th} percentiles: Mean vitamin D intake for each quartile not specified in paper, † T1 vs T3: the 33^{rd} and 67^{th} percentiles of vitamin D reported in this paper were 2.51 and 3.51µg/d respectively.

Figure 4. Meta-analysis of studies looking at selected VDR polymorphisms and oesophageal neoplasia using crude OR estimates. BO: Barrett's oesophagus, AC: adenocarcinoma, SCC: squamous cell carcinoma.† OR values calculated from Allele frequencies given in paper, # Replication Barrett's oesophagus cohort used in paper, * same control cohort used in these studies. Weights are shown for overall cancer.

Figure 5. Meta-analyses of studies looking at selected VDR polymorphisms and oesophageal neoplasia using adjusted OR estimates. SD: Squamous dysplasia, AC: adenocarcinoma, SCC: squamous cell carcinoma. Weights are shown for overall cancer.