original article

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Dietary vitamin D and cancers of the oral cavity and esophagus

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Background: Data on the association between vitamin D and upper digestive tract neoplasms are limited.
Methods: In two case–control studies in Italy, we examined the relation between dietary vitamin D intake and squamous cell carcinoma of the esophagus (SCCE; 304 cases) and oral/pharyngeal cancer (804 cases). Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by multiple logistic regression.
Results: Adjusted ORs for SCCE and oral/pharyngeal cancer were 0.58 (95% CI 0.39–0.86) and 0.76 (95% CI 0.60–0.94), respectively, for the highest tertile of vitamin D intake. Using a reference group of those in the highest tertile of vitamin D who were never/former smokers, ORs were 8.7 (95% CI 4.1–18.7) for SCCE and 10.4 (95% CI 6.9–15.5) for oral/pharyngeal cancer among heavy smokers in the lowest vitamin D tertile; similarly, compared with those in the highest tertile of vitamin D who drank <3 alcoholic drinks/day, corresponding ORs were 41.9 (95% CI 13.7–128.6) for SCCE and 8.5 (95% CI 5.7–12.5) for oral/pharyngeal cancer, among heavy alcohol drinkers in the lowest vitamin D tertile.
Conclusion: We observed inverse associations between dietary vitamin D intake and risk of SCCE and, perhaps, oral/pharyngeal cancer, which were most pronounced among heavy current smokers and heavy consumers of alcohol.
Key words: cancer, epidemiology, esophageal, oral, pharyngeal, vitamin D

original article

introduction

Since Garland and Garland [1] first suggested that vitamin D status may explain inverse ecologic associations between colon cancer mortality and solar UVB radiation exposure, similar associations have been hypothesized for breast, ovarian, and prostate cancers. Inverse ecologic correlations have been reported between regional solar UVB radiation, latitude, and other indicators of UV radiation in the United States, Europe, and Asia and mortality rates for numerous types of cancer, including colon, rectum, breast, ovary, prostate, stomach, esophagus, pancreas, and non-Hodgkin's lymphoma [2–5]. In one calculation, >23 000 premature cancer deaths in the United States were estimated to occur annually due to low solar UVB radiation, the majority of which are cancers of digestive system organs [2]. In a similar ecologic study in Japan, Mizoue [6] demonstrated an inverse correlation between average annual solar radiation levels and mortality from digestive system cancers but not other types of cancer. Despite these ecologic findings, there has been very little epidemiologic research on the association between vitamin D and upper digestive tract neoplasms (oral, pharyngeal, and esophageal cancer).

We previously examined the influence of dietary intake of numerous micronutrients on the risk of developing squamous cell carcinoma of the esophagus (SCCE) [7] and oral and pharyngeal cancers [8], and we reported modest protective effects of vitamin D intake. In the present analysis, we have examined the association between vitamin D and esophageal and oral and pharyngeal cancers according to categories of cigarette smoking and alcohol consumption, both strong risk factors for these cancers, to determine whether there may be stronger evidence of a protective effect.

methods

Detailed descriptions of the methods of the case–control studies have been previously published [7, 9]. The study of SCCE was conducted from 1992 to

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1997 in the provinces of Pordenone and Padua in northeast Italy and the greater Milan area in north Italy and includes 304 cases (275 men and 29 women) with a median age of 60 years (range 39–77 years). The study of oral and pharyngeal cancers was conducted from 1992 to 2005 in the provinces of Pordenone in northeast Italy, Rome and Latina in central Italy, and the greater Milan area in north Italy and includes 804 patients (658 men and 146 women) with a median age of 58 years (range 22–78 years); of these, 405 had cancer of the oral cavity and 399 had cancer of the pharynx. In both studies, cases were patients with incident, histologically confirmed cancer and with no prior history of cancer. Controls were admitted for a variety of acute illnesses to major teaching and general hospitals drawing from the same study base as the cases. Diseases related to tobacco smoking (e.g. chronic obstructive bronchitis and cardiovascular disease) or alcohol abuse (e.g. cirrhosis and pancreatitis) were excluded as causes of hospital admission, but not as comorbidities, in order to avoid overrepresentation of smokers and heavy drinkers compared with the source population. For esophageal cancer, a control-to-case ratio of 5 was chosen for women and 2 for men to compensate for the rarity of SCCE among women; controls were 743 patients (593 men and 150 women), frequency matched to esophageal cancer cases by gender, age quinquennia, and area of residence, with a median age of 60 years (range 36–77 years) and with no history of cancer. Twenty-nine percent of controls were admitted for trauma, mostly sprains and fractures, 36% for other orthopedic disorders, 12% for acute surgical conditions, 13% for eye diseases, and 9% for other acute conditions. For oral and pharyngeal cancers, controls were 2080 patients (1302 men and 778 women) with a median age of 58 years (range 19–79 years), admitted for traumas (25%), other orthopedic disorders (30%), acute surgical conditions (19%), eye diseases (9%), and other acute conditions (17%). Overall, <5% of cases and controls contacted refused to participate.

Cases and controls were interviewed in the hospital by trained personnel using the same standard structured questionnaire designed to collect information on sociodemographic characteristics, lifetime smoking and alcohol drinking habits, physical activity, anthropometric measures, personal medical history, and family history of cancer. Usual diet during the 2 years before diagnosis, or hospital admission for controls, was assessed using an interviewer-administered food frequency questionnaire (FFQ) with high reproducibility and validity [10, 11]. The FFQ included 78 foods, groups of food, or recipes. The FFQ was divided into seven sections: (i) bread, cereals, and first courses; (ii) second courses (e.g. meat and other main dishes); (iii) side dishes (i.e. vegetables); (iv) fruits; (v) sweets, desserts, and soft drinks; (vi) milk, hot beverages, and sweeteners; and (vii) alcoholic beverages. To compute energy and nutrient intakes, including vitamin D intake, an Italian food composition database as well as information from additional sources were used [8, 12, 13]. Use of vitamin supplements was uncommon in this population during the study period [14].

The data were modeled using unconditional multiple logistic regression to compute odds ratios (ORs) and corresponding 95% confidence intervals (CIs) [15]. Adjusted models included terms for quinquennia of age, sex, study center, education, cigarette smoking, alcohol consumption, and nonalcohol energy intake. Adjustment for energy was carried out using the residuals model [16]. We also fitted models across strata of age (< or ≥60 years), sex, and calcium intake (< or ≥median value among controls), as well as cigarette smoking and alcohol consumption. Vitamin D was entered into the models as tertiles of intake (based on the distribution among controls) or as a continuous variable (with the increment of intake set as the standard deviation among controls = 1.14 μg/day for SCCE and 1.21 μg/day for oral and pharyngeal cancers). Trend tests for risk of cancer according to tertiles of vitamin D intake were based on a likelihood ratio test between models with and without a linear term for the vitamin D tertiles.

results

Cases of SCCE and oral and pharyngeal cancers smoked cigarettes and drank alcohol substantially more heavily than their corresponding controls. Level of education was lower among esophageal cancer cases than controls, but was similar among oral and pharyngeal cancer cases and controls. Nonalcohol energy intake was lower among male esophageal cancer cases and among oral and pharyngeal cancer cases compared with controls, but was higher among female esophageal cancer cases than their corresponding controls.

Table 1 shows the distribution of esophageal and oral and pharyngeal cancer cases and controls, as well as multiple logistic regression-derived ORs and corresponding 95% CIs, according to tertiles of vitamin D intake and continuous increments of intake. For both SCCE and oral and pharyngeal cancers, we observed a significant trend of decreasing ORs with increasing

Table 1. Multiple logistic regression-derived ORs[a] and corresponding 95% CIs for esophageal and oral and pharyngeal cancers, according to tertiles of intake of vitamin D (Italy, 1992–1997)

	Tertiles of vitamin D intake[b]			*P* value (trend)	Continuous OR[c]
	1 (low)[d]	2	3 (high)		
Esophageal cancer					
Cases : controls	133 : 247	101 : 247	70 : 249		
OR (95% CI)	1.0	0.58 (0.40–0.85)	0.58 (0.39–0.86)	0.003	0.84 (0.71–0.99)
Oral and pharyngeal cancers					
Cases : controls	344 : 692	245 : 694	215 : 694		
OR (95% CI)	1.0	0.82 (0.66–1.02)	0.76 (0.60–0.94)	0.012	0.91 (0.83–1.00)

[a]Adjusted for age, sex, study center, education, cigarette smoking, alcohol consumption, and total energy intake.
[b]Tertiles based on distribution among controls; the 33rd and 67th percentiles of estimated vitamin D intake were 2.51 and 3.51 μg/day, respectively, for esophageal cancer and 2.44 and 3.42 μg/day, respectively, for oral and pharyngeal cancers.
[c]Estimated for an increment of intake equal to one standard deviation among controls (=1.14 μg/day for esophageal cancer and 1.21 μg/day for oral and pharyngeal cancers).
[d]Reference category.
OR, odds ratio; CI, confidence interval.

intake of vitamin D (P trend = 0.003 and 0.012, respectively). Adjusted ORs for esophageal cancer were 0.58 (95% CI 0.40–0.85) for the second tertile and 0.58 (95% CI 0.39–0.86) for the highest tertile of vitamin D intake compared with the lowest; the continuous OR per 1.14 μg increase in vitamin D intake was 0.84 (95% CI 0.71–0.99). For oral and pharyngeal cancers, corresponding adjusted ORs for the second and third tertile of vitamin D intake were 0.82 (95% CI 0.66–1.02) and 0.76 (95% CI 0.60–0.94), respectively, and the OR per 1.21 μg increase in vitamin D intake was 0.91 (95% CI 0.83–1.00).

The relation with vitamin D was examined separately by strata of age, calcium intake, and sex (the latter for oral and pharyngeal cancers only since there were too few female cases of esophageal cancer for meaningful evaluation) (Table 2). For esophageal cancer, the inverse association with vitamin D was stronger and statistically significant among those aged >60 years, while the opposite appeared true for oral and pharyngeal cancers. There was little evidence of effect modification by calcium intake for either cancer type, and none of the tests for heterogeneity of the ORs was statistically significant.

We evaluated the interaction between vitamin D intake and both cigarette smoking and alcohol consumption (Table 3). For esophageal cancer, an inverse association with vitamin D was apparent among all groups except those who drank <3 drinks/day, while for oral and pharyngeal cancers, the protective effect of vitamin D was to a large extent confined to heaviest smokers and drinkers. Using a common reference group of those in the highest tertile of vitamin D intake who were never smokers or former smokers who quit >10 years ago, there was an almost nine-fold increase in esophageal cancer risk among heavy smokers of ≥20 cigarettes/day who were in the lowest tertile of vitamin D intake (OR = 8.7; 95% CI 4.1–18.7). Similarly, using a common reference group of those in the highest tertile of vitamin D intake who drank <3 alcoholic drinks/day, an OR of 41.9 (95% CI 13.7–128.6) for esophageal cancer was observed among heavy drinkers of ≥7 drinks/day who were in the lowest tertile of vitamin D intake. For oral and pharyngeal cancers, using the same common reference groups, the corresponding ORs were 10.4 (95% CI 6.9–15.5) for heavy smokers in the lowest tertile of vitamin D and 8.5 (95% CI 5.7–12.5) for heavy alcohol drinkers in the lowest tertile of vitamin D intake.

discussion

Our results suggest that dietary vitamin D intake is associated with a decreased risk of SCCE and, somewhat less clearly, with a decreased risk of oral and pharyngeal cancers. In this study population, those in the highest tertile of vitamin D intake, corresponding to intake >3.5 μg/day, had risk reductions of ∼40% for esophageal cancer and 25% for oral and pharyngeal cancers. The inverse association of both cancers with vitamin D intake was most pronounced among, or confined to, those who were heavy current smokers (≥20 cigarettes/day) and heavy consumers of alcohol (≥7 drinks/day).

A large number of epidemiologic studies have fairly consistently demonstrated an inverse association between dietary or supplementary vitamin D intake, as well as serum 25(OH)D levels, and colorectal cancer [17–19]. In those studies, risk reductions for the highest categories of intake (generally corresponding to a mean of 17.5–20 μg/day) versus the lowest ones have ranged between 30% and 50% [17, 18]. As

Table 2. Multiple logistic regression-derived ORs[a] and corresponding 95% CIs for esophageal and oral and pharyngeal cancers, according to tertiles of intake of vitamin D across strata of age, calcium intake, and sex (Italy, 1992–1997)

	Cases : controls	Tertiles of vitamin D intake[b]		
		1[c]	2	3
Esophageal cancer				
Age (years)				
<60	141 : 344	1	0.68 (0.39–1.19)	0.69 (0.38–1.26)
≥60	163 : 399	1	0.55 (0.32–0.93)	0.52 (0.29–0.91)
Calcium (mg/day)				
<1036.9	178 : 372	1	0.51 (0.31–0.86)	0.72 (0.41–1.27)
≥1036.9	126 : 371	1	0.67 (0.38–1.19)	0.47 (0.25–0.86)
Oral and pharyngeal cancers				
Age (years)				
<60	433 : 1132	1	0.91 (0.67–1.22)	0.66 (0.48–0.91)
≥60	371 : 948	1	0.73 (0.53–1.01)	0.90 (0.65–1.25)
Calcium (mg/day)				
<884.0	464 : 1040	1	0.84 (0.63–1.11)	0.74 (0.54–1.01)
≥884.0	340 : 1040	1	0.82 (0.59–1.14)	0.76 (0.54–1.07)
Sex				
Male	658 : 1301	1	0.68 (0.53–0.88)	0.77 (0.59–1.00)
Female	146 : 779	1	1.55 (0.99–2.43)	0.83 (0.51–1.34)

[a]Adjusted for age, sex, study center, education, cigarette smoking, alcohol consumption, and total energy intake.
[b]Tertiles based on distribution among controls.
[c]Reference category.
OR, odds ratio; CI, confidence interval.

Table 3. Multiple logistic regression-derived ORs[a] and corresponding 95% CIs for esophageal and oral and pharyngeal cancers, according to intake of vitamin D across strata of cigarette smoking and alcohol consumption (Italy, 1992–1997)

	Cases : controls	Tertiles of vitamin D intake[b]		
		3 (high)	2	1 (low)
Esophageal cancer				
Cigarette smoking				
Never smokers + former smokers ≥10 years	80 : 434	1.0 (ref)	1.1 (0.5–2.4)	2.5 (1.2–4.9)
Former smokers <10 years + current smokers <20 cigarettes/day	121 : 216	4.3 (2.1–9.1)	3.2 (1.5–6.8)	5.1 (2.5–10.3)
Current smokers ≥20 cigarettes/day	103 : 93	3.9 (1.6–9.6)	7.5 (3.3–17.2)	8.7 (4.1–18.7)
Alcohol consumption				
≤2 drinks/day	28 : 298	1.0 (ref)	1.1 (0.4–3.0)	1.6 (0.6–4.3)
3–6 drinks/day	102 : 295	8.3 (2.6–26.7)	11.2 (3.6–34.9)	16.1 (5.2–50.2)
≥7 drinks/day	174 : 150	28.1 (8.5–92.4)	19.3 (6.0–62.0)	41.9 (13.7–128.6)
Oral and pharyngeal cancers				
Cigarette smoking				
Never smokers + former smokers ≥10 years	188 : 1261	1.0 (ref)	0.9 (0.6–1.3)	0.9 (0.6–1.4)
Former smokers <10 years + current smokers <20 cigarettes/day	353 : 601	2.7 (1.9–4.0)	3.4 (2.4–4.8)	4.5 (3.1–6.3)
Current smokers ≥20 cigarettes/day	263 : 218	6.7 (4.3–10.4)	6.8 (4.4–10.6)	10.4 (6.9–15.5)
Alcohol consumption				
≤2 drinks/day	224 : 1331	1.0 (ref)	1.0 (0.7–1.3)	0.9 (0.6–1.3)
3–6 drinks/day	183 : 546	1.6 (1.0–2.4)	1.6 (1.0–2.4)	1.8 (1.2–2.7)
≥7 drinks/day	397 : 221	5.8 (3.6–9.3)	6.9 (4.5–10.7)	8.5 (5.7–12.5)

[a]Adjusted for age, sex, study center, education, total energy intake, alcohol consumption (in models stratified by cigarette smoking), and cigarette smoking (in models stratified by alcohol consumption).
[b]Tertiles based on distribution among controls.
OR, odds ratio; CI, confidence interval.

expected, the levels of dietary vitamin D intake were substantially lower in our Italian population; the main dietary sources of vitamin D in this population were fish (49.4%), meat (25.8%), eggs (7.2%), and cheese (4.9%), with little food fortification or use of supplements. It is therefore surprising that the magnitudes of the risk reductions we observed for esophageal and oral and pharyngeal cancers were similar to those observed for colorectal cancer in other populations with much higher levels of intake. We did not have measurements of circulating levels of 25(OH)D, which is a biomarker for vitamin D status [20]. It has been demonstrated that dietary (and supplemental) vitamin D intake predicts only a relatively small proportion of the variation in 25(OH)D levels, while skin pigmentation, outdoor sunlight exposure, geographic region of residence, season, body mass index, and genetic differences in vitamin D receptor expression are strong predictors of 25(OH)D levels [21, 22].

Evidence for a protective effect of vitamin D on cancer other than colorectal cancer, in particular SCCE or oral and pharyngeal cancers, is substantially more limited. Most dietary studies of oral and pharyngeal cancers have focused on nutrients correlated with diets rich in fruits and vegetables, which have been shown to be inversely associated with these types of cancer. In a recent meta-analysis of ecologic studies, reduced risk of esophageal cancer was reported following a diagnosis of nonmelanoma skin cancer, used as a surrogate for high cumulative UVB irradiance [23]. A few observational studies have generally presented relevant results for cancers of the digestive system combined, due to small numbers of esophageal cancer cases. Freedman et al. [24] recently conducted a prospective study of serum 25(OH)D levels and cancer mortality among 16 818 participants in the Third National Health and Nutrition Examination Survey (NHANES III). Those with serum 25(OH)D levels >50 nmol/l had a significantly lower risk of colorectal cancer mortality compared with lower levels, but there was no relation between 25(OH)D level and total cancer mortality or cancer at digestive sites other than the colon.

In the Health Professionals Follow-up Study [25], black men had substantially higher risk of digestive system (oral cavity, esophagus, stomach, pancreas, colon, and rectum combined) cancer incidence and mortality compared with whites. Blacks in the United States have been shown to have lower levels of vitamin D compared with whites [24, 26, 27], and this vitamin D insufficiency has been hypothesized as a possible explanation for excess cancer incidence and mortality among blacks [28]. Giovannucci et al. [21] also computed a predicted level of 25(OH)D for men in the Health Professionals Follow-up Study, based on the combined influence of various major determinants of 25(OH)D, including race, dietary and supplementary vitamin D, body mass index, and geographic region of residence. An increment of 25 nmol/l in the predicted 25(OH)D level (which approximates the difference between the highest and lowest decile in that population) was inversely associated with total cancer incidence and mortality as well as risk for the major digestive organ cancers, including esophageal cancer (relative risk (RR) = 0.37; 95% CI 0.17–0.80) and oral and pharyngeal cancers (RR = 0.30; 95% CI 0.11–0.81).

In a prospective study in Linxian, China, in a population with very high rates of SCCE and low dietary intake of vitamin

D, increasing serum 25(OH)D concentrations were unexpectedly associated with increased risk of SCCE among men, but not among women [29]. Further, increased serum 25(OH)D levels were also associated with significantly increased risk among both men and women for esophageal squamous dysplasia, the precursor lesion for SCCE, in a cross-sectional analysis [30]. In that population, mean serum 25(OH)D levels were 33.3 nmol/l among men and 40.1 nmol/l among men who developed SCCE [29], substantially lower than the mean serum concentration of 83 nmol/l among USA white males in the NHANES III study [31] and most likely lower than that of our Italian population. There is no immediate explanation for the apparent discrepancy between the results of the Chinese study, the first to examine an association between vitamin D and esophageal cancer using serum 25(OH)D, and those of other studies, including the present one, but further research is needed before speculating on the possibility of a U-shaped association.

Alcohol consumption and tobacco smoking represent the predominant risk factors for both SCCE and oral and pharyngeal cancers in our study population. Compared with never/former smokers with the highest vitamin D intake (those presumably at lowest baseline risk for SCCE and oral and pharyngeal cancers), we observed a 9- to 10-fold increased risk for esophageal and oral and pharyngeal cancers among heavy smokers with low vitamin D intake. Similarly, compared with never or light drinkers with high vitamin D intake, heavy drinkers with low vitamin D intake had an OR of 41.9 for esophageal cancer and 8.5 for oral and pharyngeal cancers. To our knowledge, only one other study, a case–control study of SCCE in France, has evaluated the interaction between alcohol consumption and vitamin D intake [32], and they reported a significant protective effect of dietary vitamin D among heavy drinkers but not among moderate drinkers. In our study, the favorable effect was observed across strata of tobacco and alcohol intakes.

Our study was sufficiently large to obtain reasonably precise risk estimates for vitamin D intake. Cases and controls came from comparable catchment areas, participation was virtually complete, and both cases and controls were interviewed in the hospital setting, thereby reducing potential selection and recall bias [33]. However, it is well established that vitamin D is essential to bone health, and low vitamin D levels are associated with osteoporosis and osteomalacia, as well as muscle strength and falls [34–36]. Since >50% of controls in our studies were admitted to hospital for traumas or other orthopedic disorders, we cannot rule out the possibility that low vitamin D intake among those controls may have biased our esophageal or oral and pharyngeal cancer ORs away from the null. However, the inverse association was not materially different when comparison was made separately using different categories of hospital controls.

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references

1. Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? Int J Epidemiol 1980; 9: 227–231.
2. Grant WB. An estimate of premature cancer mortality in the US due to inadequate doses of solar ultraviolet-B radiation. Cancer 2002; 94: 1867–1875.
3. Grant WB. Ecologic studies of solar UV-B radiation and cancer mortality rates. Recent Results Cancer Res 2003; 164: 371–377.
4. Grant WB. Does solar ultraviolet irradiation affect cancer mortality rates in China. Asian Pac J Cancer Prev 2007; 8: 236–242.
5. Freedman D, Dosemeci M, McGlynn K. Sunlight and mortality from breast, ovarian, colon, prostate and non-melanoma skin cancer: a composite death certificate based case-control study. Occup Environ Med 2002; 59: 257–262.
6. Mizoue T. Ecological study of solar radiation and cancer mortality in Japan. Health Phys 2004; 87: 532–538.
7. Franceschi S, Bidoli E, Negri E et al. Role of macronutrients, vitamins and minerals in the aetiology of squamous-cell carcinoma of the oesophagus. Int J Cancer 2000; 86: 626–631.
8. Negri E, Franceschi S, Bosetti C et al. Selected micronutrients and oral and pharyngeal cancer. Int J Cancer 2000; 86: 122–127.
9. Rossi M, Garavello W, Talamini R et al. Flavonoids and the risk of oral and pharyngeal cancer: a case-control study from Italy. Cancer Epidemiol Biomarkers Prev 2007; 16: 1621–1625.
10. Decarli A, Franceschi S, Ferraroni M et al. Validation of a food-frequency questionnaire to assess dietary intakes in cancer studies in Italy. Results for specific nutrients. Ann Epidemiol 1996; 6: 110–118.
11. Franceschi S, Negri E, Salvini S et al. Reproducibility of an Italian food frequency questionnaire for cancer studies: results for specific food items. Eur J Cancer 1993; 29A: 2298–2305.
12. Gnagnarella P, Parpinel M, Salvini S et al. The update of the Italian food composition database. J Food Compost Anal 2004; 17: 509–522.
13. Salvini S, Parpinel M, Gnagnarella P et al. Banca di composizione degli alimenti per studi epidemiologici in Italia. Milano, Italia: Istituto Europeo di Oncologia 1998.
14. Istituto Nazionale di Statistica. Indagine Multiscopo sulle famiglie: stili di vita e condizioni di salute. ISTAT, editor [5]. Rome, Italy: ISTAT 2005.
15. Breslow NE, Day NE. Statistical Methods in Cancer Research. Volume I—The Analysis of Case-Control Studies. IARC Sci Publ 32. Lyon, France: International Agency for Research on Cancer 1980.
16. Willett WC, Stampfer MJ. Total energy intake: implications for epidemiologic analysis. Am J Epidemiol 1986; 124: 17–27.
17. Giovannucci E. The epidemiology of vitamin D and cancer incidence and mortality: a review (United States). Cancer Causes Control 2005; 16: 83–95.
18. Grant WB, Garland CF. A critical review of studies on vitamin D in relation to colorectal cancer. Nutr Cancer 2004; 48: 115–123.
19. Lipworth L, Bender T, Rossi M et al. Dietary vitamin D intake and cancers of the colon and rectum: a case-control study in Italy. Nutr Cancer 2009; 61: 70–75.
20. Holick MF. Vitamin D status: measurement, interpretation, and clinical application. Ann Epidemiol 2009; 19: 73–78.
21. Giovannucci E, Liu Y, Rimm EB et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. J Natl Cancer Inst 2006; 98: 451–459.
22. Heaney RP, Davies KM, Chen TC et al. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr 2003; 77: 204–210.
23. Grant WB. A meta-analysis of second cancers after a diagnosis of nonmelanoma skin cancer: additional evidence that solar ultraviolet-B irradiance reduces the risk of internal cancers. J Steroid Biochem Mol Biol 2007; 103: 668–674.

24. Freedman DM, Looker AC, Chang SC, Braubard BI. Prospective study of serum vitamin D and cancer mortality in the United States. J Natl Cancer Inst 2007; 99: 1594–1602.
25. Giovannucci E, Liu Y, Willett WC. Cancer incidence and mortality and vitamin D in black and white male health professionals. Cancer Epidemiol Biomarkers Prev 2006; 15: 2467–2472.
26. Looker AC, Dawson-Hughes B, Calvo MS et al. Serum 25-hydroxyvitamin D status of adolescents and adults in two seasonal subpopulations from NHANES III. Bone 2002; 30: 771–777.
27. Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. Arch Intern Med 2008; 168: 1629–1637.
28. Egan KM, Signorello LB, Munro HM et al. Vitamin D insufficiency among African-Americans in the southeastern United States: implications for cancer disparities. Cancer Causes Control 2008; 19: 527–535.
29. Chen W, Dawsey SM, Qiao YL et al. Prospective study of serum 25(OH)-vitamin D concentration and risk of oesophageal and gastric cancers. Br J Cancer 2007; 97: 123–128.
30. Abnet CC, Chen W, Dawsey SM et al. Serum 25(OH)-vitamin D concentration and risk of esophageal squamous dysplasia. Cancer Epidemiol Biomarkers Prev 2007; 16: 1889–1893.
31. Zadshir A, Tareen N, Pan D et al. The prevalence of hypovitaminosis D among US adults: data from the NHANES III. Ethn Dis 2005; 15: S5–S101.
32. Launoy G, Milan C, Day NE et al. Diet and squamous cell cancer of the oesophagus: a French multicentre case-control study. Int J Cancer 1998; 76: 7–12.
33. D'Avanzo B, La Vecchia C, Katsouyanni K et al. An assessment, and reproducibility of food frequency data provided by hospital controls. Eur J Cancer Prev 1997; 6: 288–293.
34. Holick MF. Vitamin D: its role in cancer prevention and treatment. Prog Biophys Mol Biol 2006; 92: 49–59.
35. Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc 2006; 81: 353–373.
36. Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357: 266–281.