



Dietary vitamin D intake and risk of non-small cell lung cancer: a matched case-control study

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Background: Several studies indicated that serum vitamin D (Vit D) level was associated with lung cancer development and prognosis. To investigate the association between dietary Vit D and the risk of non-small cell lung cancer (NSCLC), a case-control study was conducted.

Methods: Dietary Vit D intake was ascertained in 200 NSCLC cases and 200 controls in the 1:1 matched case-control study. Face-to-face interviews were conducted to collect dietary information using a food frequency questionnaire (FFQ). Logistic regression was used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI) between dietary Vit D intake and the risk of NSCLC.

Results: Dietary Vit D intake was associated with a risk reduction relative to NSCLC. The adjusted OR for NSCLC of the second to fourth quartile levels of Vit D were 0.63 (range, 0.41–0.89), 0.48 (range, 0.25–0.67), and 0.37 (range, 0.14–0.53) according to the first quartile levels respectively.

Conclusions: This study indicated that dietary Vit D intake insufficiency might be a risk factor for NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); food frequency questionnaire (FFQ); Vitamin D (Vit D); case-control study

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Introduction

Lung cancer is the leading cause of malignant tumor-related deaths, and non-small cell lung cancer (NSCLC) reportedly comprises approximately 85% of all lung cancer cases (1). Lung cancer is believed to be caused by the interaction of both environment and hereditary factors. Environmental interventions targeting dietary and lifestyle may be the major means for preventing lung cancer. Vitamin D (Vit D) is a steroid-derived vitamin and its metabolites in cancer have become highly regarded recently (2-7). Vit D exerted important functions in tumor development by regulating

cell proliferation, facilitating apoptosis, promoting cell differentiation, and inhibiting angiogenesis (8,9), as well as the optimal 25(OH)D concentration for preventing and surviving cancer appears to be above 75–100 nmol/L (10). Epidemiological studies indicated that serum Vit D level was inversely associated with lung cancer development and prognosis (11-13). However, reports are lacking on the association between dietary intake of Vit D and the risk of lung cancer in Chinese populations. Here we performed a 1:1 matched case control study to investigate the association between dietary Vit D and the risk of NSCLC in the Qingdao area.

Methods

A total of 200 NSCLC patients (153 men, 47 women) who were admitted to the Affiliated Hospital of Qingdao University, Qingdao Hiser hospital, and Pingdu City Hospital of Traditional Chinese Medicine were recruited between December 2014 and March 2015 according to the diagnostic criteria of the “Standard for Diagnosis and Treatment of Primary Lung Cancer by the Ministry of Health” issued in 2011. All of the patients were diagnosed with primary lung cancer by pathologic examination, and the diagnoses included squamous cell carcinoma in 102 patients (51%), adenocarcinoma in 93 (46.5%), adenosquamous carcinoma in 4 (2%), and carcinoid in 1 (1%). Tumor stages were classified according to the International Association for the Study of Lung Cancer (IASLC 2009), 7th edition and included: stage I in 39 patients (19.5%), stage II in 57 (28.5%), stage III in 93 (46.5%), and stage IV in 11 (5.5%). All of the patients were diagnosed within 1 month prior to completing the interview and questionnaire. The exclusion criteria included: (I) insufficient liver and kidney functions, diabetes, thyroid dysfunction, and other nutrient metabolism disorders; (II) taking Vit D supplements; and (III) receiving glucocorticoid treatment. A total of 200 age (± 3 years) and sex-matched controls from three hospitals were also included. All participants provided written informed consent. The study was approved by the Institutional Ethics Committee of Medical College of Qingdao University.

Face-to-face interviews were conducted to collect general and dietary information. The food intake information during the past 1 year was collected using a food frequency questionnaire (FFQ) designed for residents in north China which has been proven reliability and validity (14). The FFQ includes 81 total items in seven frequency categories as follows: (I) almost never eat or drink; (II) less than once per week; (III) once a week; (IV) 2–3 times per week; (V) 4–6 times per week; (VI) once a day; (VII) twice or more per day. The amount of food was estimated using a collection of illustrative pictures of food or dishware to which the participants referred for guidance.

Statistical analysis

The questionnaire was uploaded and checked by two persons in EpiData 3.1, and analyses by SPSS version 17.0 software (SPSS Inc, Chicago, IL, USA). The *t* test or χ^2 test was utilized to compare data of the patients and healthy controls. The case control set was divided into quartiles by Vit D daily

intake. The association between Vit D intake (Q1–Q4) and NSCLC risk was analyzed by logistic regression. The value of Q1 was set as a reference, the odds ratios (OR), adjusted OR and 95% confidence intervals (CI) of the other groups were calculated. Multivariate conditional logistic regression analysis was used to adjust for age, gender, body mass index, education level, profession, family income, smoking, secondary smoking, drinking, outdoor activities, family tumor history.

Results

General information

The average ages of the patients and healthy controls were 58.23 ± 11.30 and 56.72 ± 10.15 years, respectively; there were no significant differences in age, sex, or profession between the two groups (*Table 1*). Compared with the healthy controls, the patients had relatively lower body mass index ($P=0.048$), higher education level ($P<0.001$), less family income ($P<0.001$), spent less time engaging in outdoor activities ($P=0.021$), and were less likely to receive dietary guidance ($P<0.001$). Meanwhile, a family tumor history ($P=0.003$), smoking ($P<0.001$), and secondary smoking ($P<0.05$) were more commonly found in patients than in controls.

Inverse association between daily dietary Vit D and NSCLC

The daily intakes of Vit D were 5.4 ± 1.2 and 7.5 ± 1.6 μg for patients and healthy controls, respectively, and the daily mean intake of Vit D from dietary sources was lower in patients than in healthy controls ($P<0.001$). The incidence OR of NSCLC was gradually decreased along with the increase of daily dietary Vit D intake, indicating that dietary Vit D was a protective factor for NSCLC. The association between Vit D intake and NSCLC remained unchanged after the adjustment for confounding factors including age, gender, body mass index, education level, profession, family income, smoking, secondary smoking, drinking, outdoor activities, family tumor history, and received dietary health guidance (*Table 2*).

Stratification analysis

The stratification analysis indicated that Vit D intake was inverse associated with NSCLC in the ≤ 60 years old group, while no association in the >60 years old group.

Table 1 General characteristics of the patients and healthy controls

Variants	Patients (n=200)	Healthy controls (n=200)	P
Age (year)	58.23±11.30	56.72±10.15	0.820
BMI (kg/m ²)	20.27±3.05	22.46±3.63	0.048
Education level, n (%)			<0.001
Junior high school and below	83 (41.5)	126 (63.0)	
High school or technical secondary school	38 (19.0)	24 (12.0)	
College degree or above	79 (39.5)	50 (25.0)	
Family income (RMB/people/month), n (%)			<0.001
≤500	25 (12.3)	5 (2.5)	
501–2,000	79 (39.6)	54 (27.0)	
2,000–3,000	66 (33.2)	93 (46.5)	
>3,000	30 (15.0)	48 (24.0)	
Profession, n (%)			0.764
Pure mental work	45 (22.5)	54 (27.0)	
Mental work	53 (26.5)	47 (23.5)	
Pure manual labor	27 (13.5)	26 (13.0)	
Manual labor	60 (30.0)	62 (31.0)	
Other	15 (7.5)	11 (5.5)	
Tumor family history, n (%)	24 (12.0)	8 (4.0)	0.003
Smoking, n (%)	118 (59.0)	61 (30.5)	<0.001
Passive smoking, n (%)	94 (47.0)	42 (21.0)	<0.050
Drinking, n (%)	54 (27.0)	47 (23.5)	0.420
Outdoor activities (hours/week)	4.6±4.1	5.0±3.5	0.021
Received dietary health guidance, n (%)	24 (12.0)	87 (43.5)	<0.001

Table 2 Odds ratios (OR) (95% CI) of non-small cell lung cancer (NSCLC) according to dietary Vit D intake quartile

Quartile	Vit D intake (μg/d)	N _{patient} /N _{healthy controls}	OR (95% CI) [#]	Adjusted OR (95% CI) [*]
Q1	<4	60/39	1	1
Q2	4–7	49/47	0.67 (0.37–1.18)	0.68 (0.41–0.89)
Q3	7–10	50/58	0.56 (0.32–0.97)	0.43 (0.25–0.67)
Q4	>10	41/56	0.48 (0.27–0.85)	0.37 (0.14–0.53)

[#], univariate logistic regression; ^{*}, multiple factor logistic regression. Adjusted factors including age, gender, body mass index, education level, profession, family income, smoking, secondary smoking, drinking, outdoor activities, family tumor history, and received dietary health guidance.

Table 3 Odds ratios (OR) (95% CI) of non-small cell lung cancer (NSCLC) according to dietary Vit D intake quartile

Stratified variables	Quartiles of dietary Vit D intake			
	Q1	Q2	Q3	Q4
Gender				
Male	1.00	0.76 (0.44–0.94)	0.69 (0.31–0.89)	0.25 (0.10–0.61)
Female	1.00	0.43 (0.29–0.63)	0.39 (0.26–0.59)	0.32 (0.21–0.49)
Age				
>60	1.00	1.01 (0.38–2.72)	0.98 (0.29–2.69)	0.64 (0.21–1.92)
≤60	1.00	0.52 (0.37–0.72)	0.52 (0.37–0.74)	0.38 (0.26–0.54)
Smoking status				
Smoker	1.00	0.62 (0.44–0.87)	0.66 (0.47–0.94)	0.43 (0.30–0.62)
No smoker	1.00	0.27 (0.09–0.77)	0.18 (0.06–0.60)	0.26 (0.08–0.88)
Drinking status				
Drinking	1.00	0.49 (0.30–0.79)	0.44 (0.27–0.71)	0.32 (0.20–0.51)
No drinking	1.00	0.55 (0.35–0.86)	0.55 (0.34–0.88)	0.36 (0.20–0.63)
Dietary guidance				
No	1.00	0.62 (0.42–0.91)	0.63 (0.42–0.94)	0.51 (0.33–0.79)
Yes	1.00	0.47 (0.26–0.83)	0.46 (0.25–0.86)	0.22 (0.12–0.42)

There was an consistently inverse association between dietary Vit D intake and NSCLC when stratified by other factors including smoking, drinking, and dietary guidance received (*Table 3*).

Discussion

Our findings indicated that the OR of NSCLC was decreased along with the increase in dietary Vit D intake, implying that Vit D deficiency might be a risk factor for NSCLC. The inverse association between Vit D and NSCLC remained unchanged when the confounding factors were adjusted, including age, gender, body mass index, education level, profession, family income, smoking, secondary smoking, drinking, outdoor activities, family tumor history, and received dietary health guidance. This finding was consistent with other studies. Cheng *et al.* found that serum Vit D level was negatively correlated with death rate in non-smoking lung cancer patients (15). Zhou reported that serum 25(OH)D level and Vit D intake were positively associated with total survival period of patients with early-stage NSCLC (16). A meta-analysis of prospective studies conducted by Chen suggested that

25(OH)D may be associated with reduced risk of lung cancer (12). It was also reported that Vit D acquired by solar ultraviolet-B (UVB) exposure could decrease one's risk of lung cancer; for instance, Chen found that mortality rates for lung cancer were inversely correlated with ambient UVB (17); Grant reported that the UVB index, which formed by lip cancer less lung cancer standardized incidence radios, was significantly inversely correlated with lung cancer (18). Above studies presented indirect evidence that dietary Vit D could decrease the risk of lung cancer.

Major studies reported that Vit D exerted its anti-cancer effects by targeting cancer or normal cells with the potential to transform into cancer cells. The anti-tumor mechanism of Vit D might be associated with its abilities to suppress cellular proliferation, promote cellular apoptosis, and inhibit angiogenesis (8,19). Vit D also regulates immune function, inhibits the production of prostaglandin, protease, and pro-inflammatory cytokines, all of which are mediators that can promote tumor development and progression (19,20). Shin *et al.* recently showed that Vit D deficiency was closely associated with epidermal growth factor receptor (EGFR) mutation in patients with adenocarcinoma (21). All these findings indicate a novel direction for Vit D anti-cancer

mechanism research.

UVB exposure is normally the major source of Vit D for humans; however, Vit D deficiency is reportedly as low as 40% in residents of Northeast China (22). Therefore, dietary Vit D is the major source for people living at high latitudes or during winter or spring. Qingdao and Dalian are located north of 36 and 39 degrees latitude, respectively, and the Vit D deficiency rates for people from the Dalian area were reportedly 40% (22). The consumption of sea fish as food more than four times a week by Japanese women was reported to effectively prevent Vit D deficiency (23). Therefore, from the perspective of cancer prevention, the increased ingestion of dietary Vit D-rich food such as fish, animal liver, dairy products, and mushrooms was recommended in addition to increased daylight exposure.

Conclusions

This study indicated that dietary Vit D intake insufficiency might be a risk factor for NSCLC. But, this study's retrospective nature may not completely exclude the bias introduced by participant recall, and serum Vit D levels were not determined. Therefore, further cohort studies are needed to investigate whether insufficient dietary Vit D intake increases one's risk of lung cancer.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2016.07.19>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee of Medical College of Qingdao University of No. 20140421 and written informed consent was obtained from all patients.

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