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Vitamin D Deficiency as a Risk Factor in Non-Squamous Lung Cancer Subgroups - A Preliminary Study

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Abstract

Background: It has been known that smoking is the primary causative factor of lung cancer, but other factors also play roles. Epidemiological studies demonstrate an increase of cancer in people lower exposure to sunlight and which has an impact in the synthesis of active 25(OH)D. The aim of study was to determinate the potential role of 25(OH)D etiologic factor in subtypes of lung cancer.

Methods: There were 140 participants of which 100 were men (71.4%) and 40 (28.6%) were women. The study group was 60 lung cancer before any treatment participants (48 male, 12 female) and control group was 80 (52 male, 28 female). The study group was divided into three histologic subtypes; small cell lung cancer (SCLC) (13 pts, 21.7%), squamous cell lung cancer (SqCC) (18 pts, 30%) and non-squamous (23 adenocarcinoma, 6 others; total 29 pts, 48.3%).

Results: There was significant difference between smoking and histologic subgroups ($p<0.001$). While the SCLC ($p=0.002$) and the SqCC ($p<0.001$) group had a significantly more pack/year smoking; no difference in non-squamous subgroup ($p=0.114$). 25(OH)D levels was significantly less in non-squamous cell subgroups ($p<0.001$). Smoking group has less 25(OH)D levels than non-smoker group significantly ($p=0.006$).

Conclusion: Meanwhile smoking is a risk factor for SCLC and SqCC; in non-squamous subtype 25(OH)D deficiency could be a causative factor. Our findings may be supported with further studies including larger patient populations.

Keywords: Vitamin D deficiency; 25 (OH)D; Cancer; Smoking; Non-squamous cell carcinoma; Lung cancer

Introduction

Lung cancer is the leading cause of cancer mortality in both men and women, and it has been known for decades that smoking is the primary causative factor [1]. However, lung cancer does not develop in all smokers and can occur in non-smokers as well, suggesting that other factors can play a role in the development of lung cancer [2]. Large-scale epidemiological studies have demonstrated an increase in some types of cancer in individuals who live in high-altitude countries and have lower exposure to sunlight [3,4]. Because the ultraviolet B beams in natural sunlight play a role in the synthesis of active vitamin D, researchers have focused on the role of 25-hydroxyvitamin D3 (25(OH) D) in cancer development [5]. In the last decade, the relationship between 25(OH)D and many different types of cancers, including breast, pancreas, colon and prostate, has been shown [4,6]. The aim of this preliminary study was to determinate the role of 25(OH)D as an etiologic factor in subgroups of lung cancer.

Methods

From January 2008 to December 2014, 140 participants, of whom 100 were men (71.4%) and 40 (28.6%) were women, were entered into the study. The study group, which comprised participants who had been diagnosed with lung cancer, contained 60 individuals (48 males and 12 females), and the control group contained 80 individuals (52 males and 28 females). Blood samples were collected from newly diagnosed lung cancer patients prior to any treatment. The control group consisted of well-matched individuals whose 25(OH)D levels were measured for other reasons. Participants who had been diagnosed with any other type of cancer, chronic kidney disease, stem cell transplant recipients and, who had been given 25(OH)D treatment or whose specimens had hemolysis prior to analysis were excluded from the control group.

Age, sex, smoking status, serum 25(OH)D levels and cancer type were also recorded for the study group. For participants who were smokers, the pack-years of cigarette smoking were recorded as the year. The study group was divided into three histologic subgroups: small cell lung cancer (SCLC) (13 patients, 21.7%), squamous cell lung cancer (SqCC) (18 patients, 30%) and non-squamous non-small cell lung carcinoma (23 adenocarcinoma, 4 large cell, 1 sarcomatoid and 1 neuroendocrine; a total of 29 patients; 48.3%).

Venous blood samples were obtained after an overnight fast, and samples underwent centrifugation at 1,500 rpm for 5 minutes and were stored at -70°C until the date of analysis. 25(OH)D was measured using an Architect i2000 automated chemiluminescent immunoassay analyzer (Abbott Laboratories, Abbott Park, IL, USA). 25(OH)D deficiency was defined as a level < 20 ng/ml. The study was approved by the local ethics committee.

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Statistical analysis

Statistical analysis was conducted using SPSS for Windows software (ver. 20.0; SPSS Inc., Chicago, IL, USA). All statistical tests were performed at the two-sided 0.05 level. A p value less than 0.05 was considered to indicate a statistically significant difference. Demographic and clinical variables were compared using Pearson's chi-square tests for categorical variables, Pearson correlation coefficients to analyze the relation between the dependent variables and Mann-Whitney U tests for continuous variables, where appropriate.

Results

The study group contained 48 (80%) men and 12 women (20%), while the control group contained 52 men (65%) and 28 women (35%). The mean age of the study group was 60.03 ± 9.62 years (range: 38–80 years) while that of the control group was 59.18 ± 11.44 years (range: 32–81 years). There was no statistically significant difference in age (p=0.644) or sex (p=0.052) between the two groups. The percentage of smokers was 78.3% and 36.3% in the study and the control group, respectively. However, there was no significant difference in the percentage of smokers between two groups (p>0.05, Table 1).

Among the pathologic subgroups, SCLC and SqCC have significantly higher amounts of smoking pack per year than control group (p= 0.002, p<0.001, respectively). However, there was no significant difference in the amounts of smoking pack per year between non-squamous subgroup and control group (p>0.05, Table 2).

The average level of 25(OH) D was 15.78 ± 6.58 ng/dL and 25.29 ± 12 ng/dL, in the study and control group respectively, with a significant difference between two groups (p<0.001) (Table 3).

There was a significant difference serum 25(OH)D levels in histopathologic subgroups (p<0.001). In the post-hoc tests, the difference was found between the control and non-squamous group (Table 4). 25(OH)D levels were decreased in non-squamous group than control group significantly (p<0.001).

The smoking group showed significantly lower vitamin 25(OH) D levels than the non-smoker group (p=0.005). There was a negative correlation between cigarette smoking and serum 25(OH)D level (p<0.001) (r = -0.305) (Figure 1).

	Non-smoker (%)	Smoker (%)	Total (%)	*p*
Study group	13 (21.7)	47 (78.3)	60 (100)	>0.05
Control group	51 (63.7)	29 (36.3)	80 (100)	
Total	64 (45.7)	76 (54.3)	140 (100)	

Table 1: Cancer and smoking status.

	Mean	Std. Deviation	*p*
SCLC	31,62	16,17	**0.002**
SqCC	35,67	12,38	**<0.001**
NON-SQU	21,38	18,70	0.112
Control	11,31	16,87	
SCLC: Small Cell Lung Cancer; SqCC: Squamous Cell Lung Cancer; NON-SQU: Non- Squamous Cell Lung Cancer.			

Table 2: Lung cancer subgroups and smoking pack/year.

	n	Vitamin D ng/mL	Std. Deviation	Range	*p*
Study	60	15.78	6.58	4.9 – 42.7	**<0.001**
Control	80	25.29	12.00	8.2 – 65.92	

Table 3: Serum 25(OH)D levels and lung cancer.

	n	25(OH)D	Std. Deviation	Range	*p*
SCLC	13	17.54	7.22	10 - 34.3	0.058
SqCC	18	17.16	5.75	5.1 – 29.9	0.66
NON-SQU	29	14.12	6.57	4.9 – 32.7	**<0.001**
Control	80	25.29	12.00	8.2 – 65.92	
SCLC: Small Cell Lung Cancer; SqCC: Squamous Cell Lung Cancer; NON-SQU: Non- Squamous Cell Lung Cancer.					

Table 4: Serum 25(OH)D levels (ng/dL) and lung cancer subgroups.

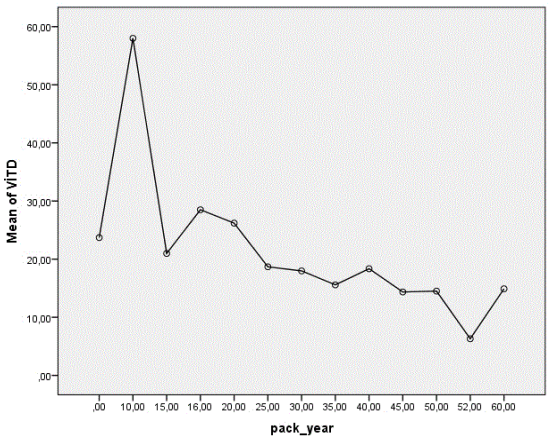

Figure 1: Cigarette smoking amount and serum 25(OH)D levels.

Discussion

Lung cancer is the leading cause of cancer-related deaths in western countries [1]. In Turkey, lung cancer is the second most common type of cancer in men after prostate cancer. It is the second most common type of cancer in women in the US, and the sixth most common cancer in women in Turkey [1,7]. Smoking alone is responsible for 75% to 85% of all lung cancer cases [2]. However, as lung cancer does not develop in all smokers, and lung cancer can occur in non-smokers, there must be other factors playing a role in cancer development. Among non-smokers with lung cancer, 15–25% shows many etiologic factors, some gene mutations (EGFR, ALK genes), or certain environmental factors, such as radon and asbestos exposure [8].

Since the 1940s, it was observed that individuals living at higher latitudes, who have lower exposure to sunlight, were at a higher risk of cancer [9]. In 1980, Garland and Garland first proved the association between latitude and colon cancer from 25(OH)D deficiency as a result of reduced sun exposure [4]. Based on those findings, large epidemiological studies have confirmed the importance of 25(OH)D to cancer risk (3,6,10). In addition to dietary intake, another important determinant of 25(OH)D levels is exposure to sunlight, which plays an important role in 25(OH)D synthesis [10].

25(OH)D is a steroid hormone that is synthesized in the skin from 7-dehydrocholesterol through solar UV-B exposure, or obtained through dietary sources and supplements. It is metabolized in the liver to make 25(OH)D, and in the kidney to make its active form, 1,25-dihydroxyvitamin D3 (1,25(OH)$_2$D) [10,11].

The hormonal activity of 25(OH)D is mediated by vitamin D receptors (VDR) within the nuclei of cells. The active form of 1,25(OH)$_2$D binds to VDRs and, upon ligand binding, dimerizes with the retinoic acid X receptor [11]. This complex binds to vitamin D-responsive elements

(VDRE) within the promoter regions of vitamin D-responsive genes causes subsequent changes in the activity of genes involved in cell division, cell adhesion, and other functions [12,13]. Brain, prostate, breast, and colon tissues, as well as immune cells, have vitamin D receptors and respond to the active form of 1,25(OH)D.

Apart from its primary role in maintaining the homeostasis of calcium and phosphorus, 25(OH)D has many non-skeletal actions in the whole body. Furthermore, autoimmune diseases, cardiovascular diseases, diabetes, schizophrenia, depression, osteoarthritis, and asthma, as well as some types of cancer, are associated with 25(OH) D status [14]. 25(OH)D is thought to protect against carcinogenesis by promoting cell differentiation and apoptosis, inhibiting cell proliferation, and modulating inflammation and immunity [15].

The recommended cutoff for 25(OH)D deficiency is 20 ng/dL (equivalent to 50 nmol/L) in a broad range of epidemiological studies [16]. In our study, we also accepted 20 nmol/L as the cutoff for 25(OH) D deficiency. While the city in which the study was carried out was on the Mediterranean coast of Turkey, which is sunny for nearly 10 months each year, the participants' average 25(OH)D level was 21.25 ng/dL, and only 43.6% of participants had levels higher than 20 ng/L.

Pazdiora et al. investigated the 25(OH)D serum levels of 170 patients with different types of cancer (28 prostate, 43 breast, 49 colorectal, and 50 lung cancer patients) and 214 healthy individuals used as controls. They found that serum 25(OH)D levels were significantly lower in the study group than the control group [17]. In our study, the 25(OH)D levels of the participants with lung cancer were significantly lower than those of the control group ($p<0.001$).

A meta-analysis concerning 25(OH)D and breast cancer prevention demonstrated a 45% decrease in breast cancer risk for those in the highest quartile of 25(OH)D compared with those in the lowest quartile [18].

Despite of these protective effects of vitamin D, International Agency for Research on Cancer (IARC) report on prostate cancer, no protective effect could be determined. Furthermore, polymorphisms of the VDR gene may modify the biological activity of vitamin D, resulting in varying susceptibility to prostate cancer, as well as local metabolism of hormonal 25(OH)D, which seems to play an important role in the development and progression of prostate cancer [19].

Kassi et al. demonstrated a high prevalence of 25(OH)D deficiency in a young and middle-aged male population. Smoking is a significant determinant of serum 25(OH)D; as smoking increases, 25(OH)D deficiency occurs more frequently [20]. We also found a negative correlation between cigarette smoking and 25(OH)D level ($p<0.001$) ($r = -0.317$) (Figure 2). The decrease in 25(OH)D levels in smokers can be explained by two hypotheses: the first one posits that cigarette smoking reduces 25(OH)D, and the second posits that smokers do not pay attention to their eating habits.

In another study, the serum level of 25(OH)D were compared among the groups of non-smokers and smokers with lung cancer and control group; significant differences were found in 25(OH)D level among the groups. Interestingly, it was observed that a high intake of vitamin D was associated with a lower risk for non-small cell lung cancer in former smokers [21]. In our study, the level of 25(OH)D in the non-smoker group was significantly higher than that in the smoker group ($p=0.006$).

Some previous investigations and meta-analysis suggest an inverse association between serum 25(OH)D and lung cancer risk [21,22],

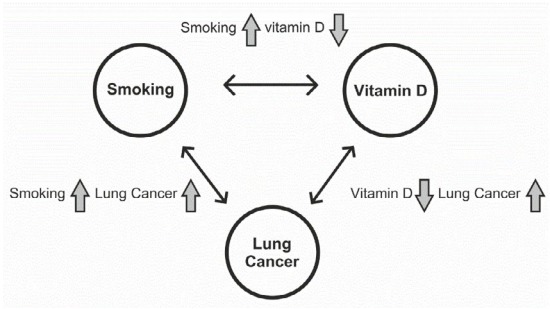

Figure 2: Relationships among smoking, 25(OH)D level and lung cancer.

however in our study we emphasize on the subtypes of lung cancer. We found a relationship between histopathologic subgroup and 25(OH) D levels in our study ($p<0.001$). In the post-hoc tests, a significant difference in the serum levels of 25(OH)D was found between the control group and the non-squamous group ($p<0.001$). It seems that low level of 25(OH)D is more of a risk factor instead of smoking in the non-squamous group.

Several limitations in this study must be addressed. First, the study used a single-center cohort design conducted on a relatively small scale; thus, replication studies with large, independent cohorts are warranted. Second, we did not detect VDR expression in either serum or cancer tissue. This association should be evaluated in other prospective studies. Furthermore, the potential differences in 25(OH)D levels between histopathologic subtypes suggested by our study should be examined further.

Conclusion

Although smoking is an important risk factor for SCLC and SqCC, 25(OH)D deficiency could be a causative factor for non-squamous subtype of lung cancer. This preliminary study was only a small-scale investigation of the relationship between 25(OH)D and subtypes of lung cancer however, our findings may be supported with further studies including larger patient populations hence, may provide a guidance for epidemiologic studies.

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