RESEARCH ARTICLE

Does Sunlight Exposure Improve Survival in Patients with Non-small Cell Lung Cancer?

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Abstract

<u>Background:</u> Some epidemiological studies reported that sunlight exposure and highvitamin D levels may decrease the morbidity and mortality related to cancer. We aimed to evaluate whether sunlight exposure has an impact on survival in patients with non small cell lung cancer. <u>Materials and Methods:</u> A total of 546 patients with NSCLC from two different regions (Kayseri and Adana) differing according to sunlight exposure were analysed retrospectively. <u>Results:</u> The median overall survival (OS) rates were 11. 6 (CI: 9.50-13.6) and 15.6 months (CI: 12.4-18.8) for Kayseri and Adana, respectively, in all patients (p=0.880). <u>Conclusions:</u> There were no differences between groups in terms of OS. While there is strong evidence regarding inverse relationship between cancer incidence and sunlight exposure, it is still controversial whether sunlight exposure is a good prognostic factor for survival in patients with lung cancer.

Keywords: Lung cancer - sunlight - survival - season

Introduction

Lung cancer is the leading cause of cancer related deaths in both men and women (Jemal et al., 2011; Demirci et al., 2013). Of lung cancers, 85% are non small cell lung cancer (NSCLC) and the 5-year-survival rate is approximately 75% in TNM stage I and it is only 13% in stage IV (Goldstraw et al., 2007; Oguz et al., 2013). Unfortunately, of all patients with NSCLC 15% survive five years. Age, sex, histological type, stage, performance status, some genetic mutations and smoking are known as common prognostic factors (Hoang et al., 2005; Riquet et al., 2007; Albain et al., 2009; Caglar et al., 2009; Alimujiang et al., 2013; Kamsa-Ard et al., 2013; Pan et al., 2013). Some epidemiological studies evaluated whether epidemiologic properties had an effect on mortality or morbidity of cancer (Mutlu et al., 2011; 2013; Fuhrman et al., 2013; Holick et al., 2013). Generally, it was speculated that sufficient solar light exposure and vitamin D level may decrease the morbidity and mortality related to cancer. When it was evaluated some studies about the relationship between geographical or seasonal differences and lung cancer, in a study, it was reported that the lower levels of ultraviolet B irradiance were independently associated with higher incidence rates of lung cancer in

111 countries (Mohr et al., 2008). The other study said that the sun induced vitamin D status at time of lung cancer diagnosis may have a prognostic value (Norton et al., 2012). Turkey include a lot of region those have different climate. Adana city is in the Mediterranean region having a warmer climate, whereas Kayseri is in inner Anatolia having a colder climate. The ratio of sunny days and annual sunlight exposure are much more in Adana than Kayseri city.

In our study, we aimed to evaluated whether there was a difference regarding the overall survival in patients with NSCLC living Kayseri and Adana cities those have different sunlight exposure.

Materials and Methods

Totally of 546 patients with NSCLC from Acıbadem Kayseri Hospital and Kayseri Research and Training Hospital in Kayseri and Acıbadem Adana Hospital in Adana were analysed retrospectively, using hospital records between 2009-2012. The patients were divided into two groups; Kayseri city having a colder climate (n: 426) and Adana with a warmer climate and more sunlight exposure (n: 120). Staging was made according to the 7th version of TNM lung cancer staging system. Age,

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sex, histological subtypes, stage, comorbidity, smoking status were recorded to Statistical Package for the Social Sciences 16.0 (SPSS Inc., Chicago, IL, USA) (SPSS16.0) statistical software for analysis. Also the date of diagnosis and date of death were recorded in SPSS 16.0.

To determine the characteristics of patients, descriptive statistics (frequency analysis and crosstabs) and independent samples t test were performed. To evaluate the prognostic factors between these groups, a chi-square test was performed. To evaluate overall survival, Kaplan-Meier statistical methods using log rank test were used. The p<0.05 was considered to be statistically significant.

Results

Annual solar light exposure was more intensive in the Mediterranean region than the internal region and the hours of sunshine per day for Kayseri and Adana region were given in Table 1 and shown in Figure 1. The characteristics of patients were given in Table 2. Mean age of patients were 62.5±10.0 and 61.8±10.0 years. for Kayseri and Adana. respectively (p=0.461). The male and female ratio were similar (p=0.934). There was

no significant difference regarding histology of cancer (p=0.131). comorbidity (p=0.577). smoking status (p=0.116). There was a significant difference for stage between the groups (p=0.006). The ratio of patients with stage 4 was more in Kayseri (43% vs 34%). the ratio of patients with stage 2 were more in Adana (17% vs 9%). The median OS were 11.56 (CI: 9.50-13.62) and 15.60 months (CI: 12.41-18.78) for Kayseri and Adana. respectively. in all patients (p=0.880). In patients with stage 1, 2, 3, the median OS were 19.38 (CI: 15.92-22.84) and 19.41 months (CI: 14.73-27.09) for Kayseri and Adana. respectively (p=0.962). In patients with stage 4. the median OS were 8.11 (CI: 6.32-9.90) and 10.77 months (CI: 5.60-15.94) for Kayseri and Adana. respectively,

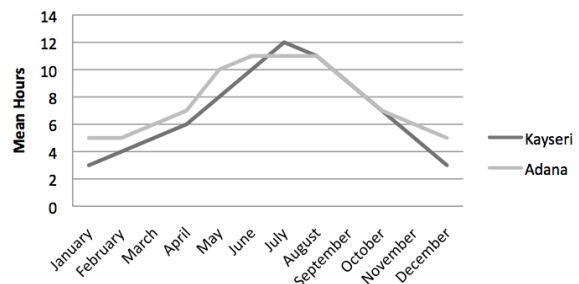### Table 1. Hours of Sunshine Per Day for Kayseri and Adana (p=0.475)

Months	Kayseri	Adana
	Hours of sunshine per day	Hours of sunshine per day
January	3	5
February	4	5
March	5	6
April	6	7
May	8	10
June	10	11
July	12	11
August	11	11
September	9	9
October	7	7
November	5	6
December	3	5
Mean hours (month)/Total hours (year)		
	210.9/2531	237.9/2855

Table 2. Demographic Properties

Parameters		Kayseri (n:426)	Adana (n:120)	p value
Age (mean)		62.5±10.0	61.8±10.0	0.461
Sex	Male	395	111	0.934
	Female	31	9	
Histology	Adenocancer	111	39	0.131
	Squamous Cell	186	39	
	Other	12	6	
	Nonspecified	117	36	
Stage	1	5 (1%)	5 (4%)	0.006
	2	36 (9%)	20 (17%)	
	3	189 (44%)	51 (43%)	
	4	183 (43%)	41 (34%)	
	Unknown	13 (3%)	3 (2%)	
Comorbidity	Diabetes	24	6	0.577
	ASHD	28	8	
	Hypertension	26	6	
	Others	26	3	
	No	322	97	
Smoking	Yes	344	89	0.116
	No	82	31	

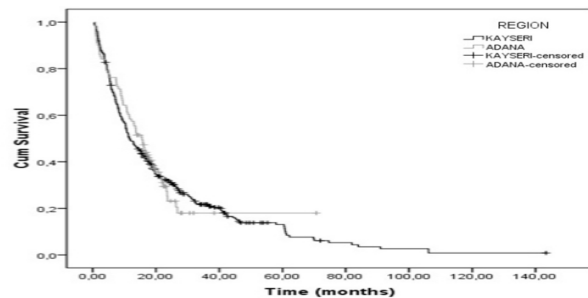**Figure 1. Sunlight Exposure for Kayseri and Adana Regions**

Figure 2. The Overall Survival Curves According to all Patients

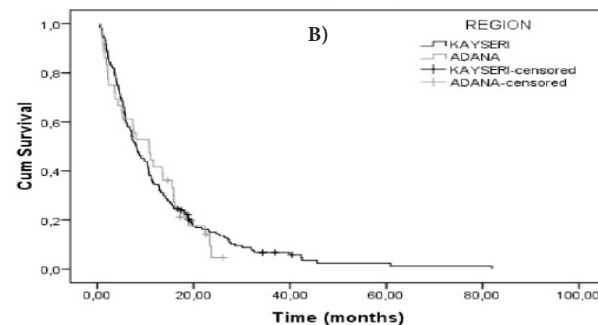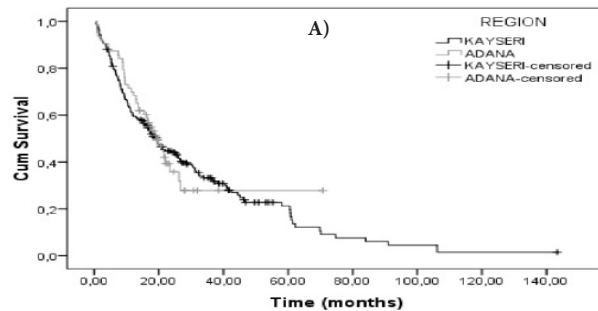**Figure 3. The Overall Survival Curves According to the Patients with A) Local or Locally Advanced Disease; and B) Metastatic Disease**

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(p=0.849). The OS curves were shown is in Figure 2, Figure 3 and Figure 4 according to all patients, patients with local or locally advanced disease and patients with metastatic disease, respectively.

Discussion

In study presented, we evaluated whether sunlight exposure had an impact on prognosis in patients with NSCLC. According our results, there was no differences between groups in terms of overall survival.

Some *in vitro* studies showed vitamin D3 (1.25-dihydroxyvitamin D3(1.25(OH)2D3)) inhibits lung cancer growth (Nakagawa et al., 2004; Norton et al., 2012). In other in vitro studies, it was shown 1α, 25-dihydroxyvitamin D3 24-hydroxylase (CYP24) considering a candidate oncogene was frequently over-expressed and vitamin D receptor (VDR) was modestly down-regulated in lung tumors (Albertson et al., 2000; Anderson et al., 2006). In addition vitamin D3/erlotinib combination resulted in significantly greater growth inhibition than either single agent in both the erlotinib-sensitive HCC827 cell line and the erlotinib-resistant H1975 cell line (Zhang et al., 2012). In order to product vitamin D3 in the body, sunlight exposure is essential. Some studies have evaluated the relationship between sunlight and cancer prognosis. One of them have reported that the patients with NSCLC diagnosed in summer and autumn associated with improved survival compared with that in winter (Lim et al., 2006). In others, it was reported that ultraviolet exposure was related to reduce overall cancer risk (Chen et al., 2010; Yang et al., 2011; Grant, 2013).

Kayseri and Adana cities are similar regarding socioeconomic and dietary habits. Thus in patients with NSCLC living in Kayseri and Adana, the most important environmental factor may be sunlight exposure, especially for production of vitamin D3 considering having an impact on prognosis in patients with cancer. Perhaps we may expect that the patients with NSCLC have higher survival rates in Adana region than Kayseri region because the sunlight exposure is more in Adana region than Kayseri region. Despite of the difference regarding patients with stage IV NSCLC between region (43% vs 34% for Kayseri and Adana region, respectively), we did not find the significant difference between region.

There is strongly evidence regarding inverse relationship between cancer incidence and sunlight exposure through vitamin D3 except for skin cancer. But it is still controversial whether sunlight exposure is a good prognostic factor for overall survival in patients with cancer. In our study we found that there was no difference between patients with NSCLC with differ sunlight exposure. The further studies are warranted to evaluate the relationship between sunlight exposure and mortality of lung cancer.

References

Albain KS, Swann RS, Rusch VW, et al (2009). Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet*, **374**, 379-86.

Albertson DG, Yistra B, Segraves R, et al (2000). Quantitative mapping of amplicon structure by array CGH identifies CYP24 as a candidate oncogene. *Nature Genetics*, **25**, 144-6.

Alimujiang S, Zhang T, Han ZG, et al (2013). Epidermal growth factor receptor tyrosine kinase inhibitor versus placebo as maintenance therapy for advanced non- small-cell lung cancer: a meta-analysis of randomized controlled trials. *Asian Pac J Cancer Prev*, **14**, 2413-9.

Anderson MG, Nakane M, Ruan X, Kroeger PE, Wu-Wong JR (2006). Expression of VDR and CYP24A1 mRNA in human tumors. *Cancer Chemother Pharmacol*, **57**, 234-40.

Caglar HB, Baldini EH, Othus M, et al (2009). Outcomes of patients with stage III nonsmall cell lung cancer treated with chemotherapy and radiation with and without surgery. *Cancer*, **115**, 4156-66.

Chen W, Clements M, Rahman B, et al (2010) Relationship between cancer mortality/incidence and ambient ultraviolet B irradiance in China. *Cancer Causes Control*, **21**, 1701-9.

Demirci E, Daloglu F, Gundogdu C, et al (2013). Incidence and clinicopathologic features of primary lung cancer: a north-eastern anatolia region study in Turkey (2006-2012). *Asian Pac J Cancer Prev*, **14**, 1989-93.

Fuhrman BJ, Freedman DM, Bhatti P, et al (2013). Sunlight, polymorphisms of vitamin D-related genes and risk of breast cancer. *Anticancer Res*, **33**, 543-51.

Grant WB (2013). Update on evidence that support a role of solar ultraviolet-B irradiance in reducing cancer risk. *Anticancer Agents Med Chem*, **13**, 140-6.

Goldstraw P, Crowley J, Chansky K, et al (2007). The IASLC lung cancer staging project: proposals for the revision of the TNM stage groupings in the forthcoming (7th) edition of the TNM classification of malignant tumours. *J Thorac Oncol*, **2**, 706-14.

Hoang T, Xu R, Schiller JH, Bonomi P, Johnson DH (2005). Clinical model to predict survival in chemonaive patients with advanced non-small-cell lung cancer treated with third-generation chemotherapy regimens based on eastern cooperative oncology group data. *J Clin Oncol*, **23**, 175-83.

Holick MF (2013). Vitamin D, sunlight and cancer connection. *Anticancer Agents Med Chem*, **13**, 70-82.

Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. *CA Cancer J Clin*, **61**, 69-90.

Kamsa-Ard S, Promthet S, Lewington S, et al (2013). Association between smoking and mortality: Khon Kaen cohort study, Thailand. *Asian Pac J Cancer Prev*, **14**, 2643-47.

Lim HS, Roychoudhuri R, Peto J, et al (2006). Cancer survival is dependent on season of diagnosis and sunlight exposure. *Int J Cancer*, **119**, 1530-36.

Mohr SB, Garland CF, Gorham ED, Grant WB, Garland FC (2008). Could ultraviolet B irradiance and vitamin D be associated with lower incidence rates of lung cancer? *J Epidemiol Community Health*, **62**, 69-74.

Mutlu H, Akca Z, Cihan YB, et al (2013). Is season a prognostic factor in breast cancer? *Asian Pac J Cancer Prev*, **14**, 743-6.

Mutlu H, Colak T, Ozdoğan M, Altuner Torun Y, Akça Z (2011). The effect of seasonal differences on prognostic factors in Turkish patients with breast cancer. *Eur J Cancer Prev*, **20**, 475-7.

Nakagawa K, Kawaura A, Kato S, Takeda E, Okano T (2004). Metastatic growth of lung cancer cells is extremely reduced in vitamin D receptor knockout mice. *J Steroid Biochem Mol Biol*, **89-90**, 545-7.

Norton R, O'Connell M (2012). Vitamin D potential in the prevention and treatment of lung cancer. *Anticancer Res*, **32**, 211-22.

Oguz A, Unal D, Tasdemir A, et al (2013). Lack of any association between blood groups and lung cancer, independent of histology. *Asian Pac J Cancer Prev*, **14**, 453-6.

Pan JB, Hou YH, Zhang GJ (2013). Correlation between EGFR mutations and serum tumor markers in lung adenocarcinoma patients. *Asian Pac J Cancer Prev*, **14**, 695-700.

Riquet M, Bagan P, Le Pimpec Barthes F, et al (2007). Completely resected non-small cell lung cancer: reconsidering prognostic value and significance of N2 metastases. *Ann Thorac Surgery*, **84**, 1818-24.

Yang L, Veierod MB, Lof M, et al (2011). Prospective study of UV exposure and cancer incidence among Swedish women. *Cancer Epidemiol Biomarkers Prev*, **20**, 1358-67

Zhang Q, Kanterewicz B, Shoemaker S, et al (2012). Differential response to 1α,25-dihydroxyvitamin D(3) (1α,25(OH)(2)D(3)) in non-small cell lung cancer cells with distinct oncogene mutations. *J Steroid Biochem Mol Biol*. [Epub ahead of print].