AKCİĞER KANSERİNDE AİLE ÖYKÜSÜ ÖNEMLİ MİDİR? TÜRKİYE'DEN RETROSPEKTİF KOHORT ÇALIŞMA

IS FAMILY HISTORY IN LUNG CANCER PATIENTS IMPORTANT? RETROSPECTIVE COHORT STUDY FROM TURKEY

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Anahtar sözcükler: Akciğer kanseri, aile öyküsü, risk faktörleri, ailesel yatkınlık

Keywords: Lung cancer, family history, risk factors, familial predisposition

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ÖZ

Amaç: *Akciğer kanseri, her yıl kanserden kaynaklanan ölümlerin yarısından fazlasının nedenidir. Ailesel risk, akciğer kanserinde hastalığın genetik temeli hala net olmasa da önemlidir. Çalışmanın amacı, göğüs hastalıkları kliniğinde eski ve yeni tanı konmuş akciğer kanseri olgularında akciğer ve akciğer dışı kanser türleri açısından ailesel bir yatkınlık olup olmadığı, bu yatkınlığın histopatolojik tip, hastalığın evresi, cinsiyet gibi demografik faktörlerle ilişkisini araştırmaktır.*

Yöntem ve Gereç: *Çalışma Nisan 2013 – Aralık 2014 tarihleri arasında Göğüs Hastalıkları Kliniğine başvuran yeni ve eski tanı almış 350 akciğer kanserli hasta ve 350 akciğer kanseri ve/veya herhangi bir kanseri olmayan hastalardan oluşan kontrol grubu dahil edilmiştir. Hastaların cinsiyeti, yaşı, sigara içme durumları, sigara paket yılı, akciğer kanseri ve akciğer dışı kanser türleri açısından ailesel yatkınlıkları kaydedilerek her iki grup özellikleri karşılaştırıldı.*

Bulgular: *Akciğer kanserli birinci derece ve ikinci derece akrabalarda aile öyküsü olmayanlara göre akciğer kanseri riskinin sırasıyla 2.18 ve 3.14 kat artış gösterdiğini tespit ettik.*

ABSTRACT

Aim: *Lung cancer is the cause of more than the half of deaths caused by cancer, each year. Familial risk is significantly present although the genetic basis of the disease is still unclear in lung cancer. The aim of study was to investigate presence and degree of familial predisposition for lung or extra-pulmonary cancers in cases with previously or newly diagnosed lung cancer, and the presence of a relationship of this predisposition with the histopathological type, the stage of the disease, and demographic factors such as gender, in the pulmonary diseases clinic.*

Material and Methods: *The study was performed between April 2013 - December 2014 at a pulmonary diseases clinic which included 350 patients with previously and newly diagnosed lung cancer and 350 patients as the control group with no lung cancer and/or any cancer presenting to the pulmonary diseases clinic. The gender, age, smoking status, pack-years of smoking, familial predisposition for lung cancer or non-lung cancers of the patients were recorded and both groups were compared.*

Results: *Determining that first-degree and second-degree relatives with lung cancer had a*

Sonuç: *Bu çalışma akciğer kanseri ve herhangi bir kanser aile öyküsü ile akciğer kanseri riski arasında pozitif ilişki olduğunu göstermektedir.*

2.18-fold and a 3.14 fold increase in the risk of lung cancer, respectively, compared to individuals without a family history.

Conclusion: *This study show that a positive association between the risk of lung cancer and a family history of lung cancer and any cancer in relatives.*

INTRODUCTION

Cancer is the most important cause of deaths worldwide, constituting the cause of death of 8.2 million people and 14.1 million new cancer cases were detected in 2012. Lung cancer is the cause of more than the half of deaths caused by cancer, each year (1). Smoking is defined as a major etiologic risk factor for lung cancer, and there is a 10-fold increased risk in long-term smokers compared to non-smokers (2). Familial risk is significantly present although the genetic basis of the disease is still unclear in lung cancer (3,4). There are many studies on the increased frequency of lung cancer in patients whose first-degree relatives have been diagnosed with lung cancer compared to the patients with no family history (5-8). Furthermore, in many studies, the first-degree relatives of patients diagnosed with lung cancer were shown to have an increased risk of non-lung cancer compared to the control group (5,6,9).

The aim in this study was to investigate presence and degree of familial predisposition for lung or extra-pulmonary cancers in cases with previously or newly diagnosed lung cancer, and the presence of a relationship of this predisposition with the histopathological type, the stage of the disease, and demographic factors such as gender, in the pulmonary diseases clinic.

METHODS

This retrospective cohort study was performed between April 2013 – December 2014 at a pulmonary diseases clinic. Presenting to pulmonary disease clinic during th study period; 350 patients with all previously diagnosed and newly diagnosed lung cancer and 350 patients as the control group with no lung cancer and/or any cancer selected by complete randomization method to prevent bias and provide appropriate sample size, were included into our study (Figure 1).

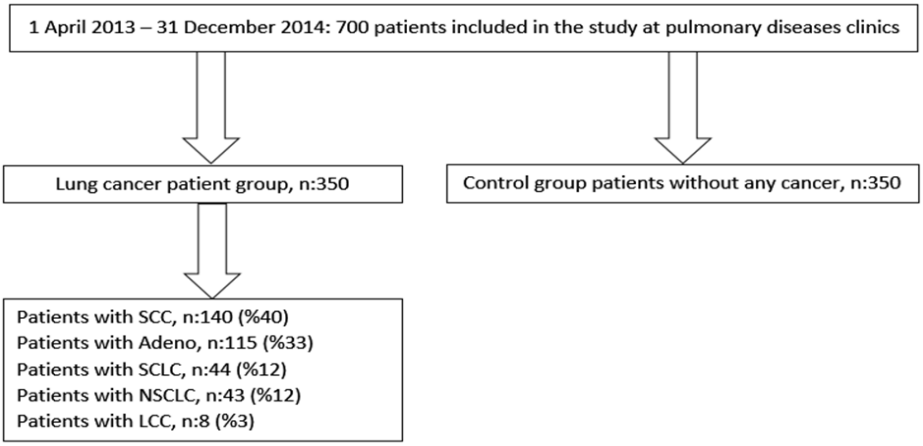

Figure 1. Flow chart of the study.
Abbreviations: SCC, squamous cell carcinoma; Adeno, adenocarcinoma; SCLC, small cell carcinoma; NSCLC, non small cell carcinoma; LCC, large cell carcinoma

Figure 1.

The gender, age, smoking status, pack-years of smoking, familial predisposition for lung cancer or non-lung cancers of the patients were recorded in the patient group and in the control group, while in the patient group with lung cancer, the tumor histopathology and the stage of the disease of the cases were recorded.

A first-degree relative is defined as a close blood relative, which includes the individual's parents, full siblings, or children. A second-degree relative is defined as a blood relative, which includes the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces or half-siblings. A third-degree relative is defined as a blood relative, which includes the individual's first-cousins, great-grandparents or great grandchildren.

This study was approved by the local ethics committee of the state training and research hospital (Istanbul – Turkey-10.02.2015. No:89513307/1009/405).

The data were collected from the files of the patients and the operating systems of the hospital. The data received from the hospital database were organized and converted to Microsoft Excel tables. The data that showed normal and homogeneous distribution in the study were given as the average value ± standard deviation, and the data that did not show normal and homogeneous distribution were given as median (min-max) values, and also with numbers and percentage values. The distribution of the variables was checked with the Shapiro-Wilk test, and their homogeneity was checked using the One-way Anova. The analyses on the non-parametric data were performed with the Mann-Whitney U test, and the Chi-square test was used for the categorical data analysis. The odds ratio and the confidence intervals were calculated in the patient group and in the control group. The results were assessed in the 95% confidence interval, and the significance level was set at a p value of <0.05. The SPSS (Statistical Package for Social Sciences) for Windows 21.0 program was used for the statistical analysis in the evaluation of the results obtained in the study.

RESULTS

In the patient group, 140 (40%) cases who had been diagnosed with squamous cell lung cancer, 115 (32.9%) cases with adenocarcinoma, 44 (12.6%) cases with small cell lung cancer, 41 (12.2%) with non-small cell lung cancer, 8 (2.3%) with large cell lung cancer, and in the control group, 350 cases who had not been diagnosed with any cancer, were evaluated in the study.

Of the 350 lung cancer cases, 89.1% were men and among the 350 hospital controls, 80% were men. The median age of the patients in the study group was 61.0 (40-86) years, while in the control group, the median age was determined as 62.0 (30-87) years.

Squamous cell carcinoma and adenocarcinoma were the most frequent types of lung cancer among the male patients and the female patients in the study group, respectively. 71.8% of the lung cancer cases constituted advanced stages (Stage 3-4), and 28.2% constituted early stages (Stage 1-2) of the disease.

There was a highly significant difference in terms of the smoking status between the patients and the control groups (P<0.001). The median packet-year value of the cases in the patient group was 45 (3-180), and in the control group it was 25 (1-130); this difference between the groups was found to be highly statistically significant (P<0.001). The demographic characteristics of the cases in both groups in our study have been summarized in Table 1.

No relationship was determined between the histological type and the family history of lung or non-lung cancer in cases with lung cancer in our study (P=0.614, P=0.495) (Table 2).

In 141 (40.2%) cases with lung cancer, there was family history positivity in terms of any cancer, while in the control group, 94 (26.8%) cases had a family history in terms of cancer, and this difference was highly statistically significant (P<0.001).

While there was family history positivity in terms of lung cancer in 94 (26.8%) cases, in the control group, 41 (14%) cases had a positive family history in terms of lung cancer, and this difference was highly statistically significant (P<0.001) (Table 3).

Table 1. The demographic characteristics of the cases

	Patient group n:350	**Control group n:350**	**P value**
Gender			
Male, n(%)	312 (89)	280 (80)	0,25#
Female, n(%)	48 (11)	70 (20)	
Median age	61.0 (40-86)	62.0 (30-87)	0,53*
Smoking status			
Never smoked, n(%)	19 (5.4)	155 (44.3)	<0.001#
Ex smoker, n(%)	242 (69.1)	137 (39.2)	<0.001#
Current smoker, n(%)	89 (25.5)	58 (16.5)	<0.001#
Cigarettes packet-year, median (min-max)	45 (3-180)	25 (1-130)	<0.001*
* Mann Whitney U test, # Chi-Square test			

Table 2. The relationship between the type of the lung cancer and the familial cancer history in cases in the patient group

		Lung Cancer Subtype					*P* value
		Adeno	SCC	SCLC	Large cell	NSCLC	
Family history of extra-pulmonary cancer?	Yes	28	43	11	4	12	0.495
	No	87	97	33	4	31	
Family history of lung cancer?	Yes	30	38	10	1	15	0.614
	No	85	102	34	7	28	
Adeno: Adenocarcinoma of lung, SCC: Squamous cell lung carcinoma, SCLC: small cell lung carcinoma, Large cell: Large cell lung carcinoma, NSCLC: Non small cell lung carcinoma							

Table 3. Lung cancer risk associated with family history of cancer

Family history		**Lung Cancer Patients Group, n:350**	**Control Patients Group, n:350**	**OR**	**95% CI**
Any cancer	Present, n (%)	141 (40.2)	96 (27.4)	1.78	1.29-2.45
	Absent, n (%)	209 (59.8)	254 (72.6)		
Lung cancer	Present, n (%)	94 (26.8)	49 (14)	2.25	1.53-3.31
	Absent, n (%)	256 (73.2)	301 (86)		
Extra-pulmonary cancer	Present, n (%)	98 (28)	63 (18)	1.77	1.23-2.53
	Absent, n (%)	252 (72)	287 (82)		
Lung cancerin the first-degree relative	Present, n (%)	39 (11)	19 (5.4)	2.18	1.23-3.86
	Absent, n (%)	311 (89)	331 (94.6)		
Lung cancer int the second-degree relative	Present, n (%)	51 (14.5)	18 (5.1)	3.14	1.79-5.50
	Absent, n (%)	299 (85.5)	332 (94.9)		
Lung cancer in the third-degree relative	Present, n (%)	20 (5.7)	19 (5.4)	1.05	0.55-2.01
	Absent, n (%)	330 (94.3)	331 (94.6)		
OR= odds ratio; CI= confidence interval					

The most frequently determined extra-pulmonary cancer types in the patient group were gastrointestinal system (GIS) cancers, breast cancer and genitourinary system (GUS) cancers; in the control group, the most frequently determined extra-pulmonary cancer types were GIS cancers and leukemia. Extra-pulmonary cancer history positivity was more frequent in the patient group compared to the control group, and this rate was statistically significant (P=0.0210) (Table 4).

Comparison of the lung cancer history in the relatives of cases with lung cancer and the cases in the control group has been summarized in Table 4.

Individuals with first-degree and second-degree relatives with lung cancer had a 2.18-fold and a 3.14 fold increase in the risk of lung cancer, respectively, compared to individuals without a family history (95% CI=1.23-3.86, 95% CI=1.79-5.50). The risk of lung cancer associated with having a family history of lung cancer and any cancer in relatives has been presented in Table 4.

DISCUSSION

The results of this study show a positive association between the risk of lung cancer and a family history of lung cancer and any cancer in relatives. The study revealed a 2.25-fold higher risk of lung cancer among individuals whose relative was affected by lung cancer. Furthermore, our results show a positive association between the risk of lung cancer and a history of reported lung cancer in first-degree relatives (OR=2.18, 95% CI=1.23-3.86).

Environmental and genetic factors are concurrently involved in the etiology of lung cancer. The most important etiological agent in lung cancer is smoking. Besides smoking, environmental and occupational factors such as ionizing radiation, asbestos, radon, and silica, and previous lung diseases play roles in the development of lung cancer (4,10-14).

Smoking has been held responsible for 90% of cases developing lung cancer (3). The risk for development of lung cancer in an individual, who has smoked one pack a day for 40 years, has been determined to be 20 times higher compared to an individual who has never smoked (15). In our study, a history of smoking was present in 94.5% of patients with lung cancer; in addition, the rate of smoking and the median pack-year value of patients with lung cancer were determined to be significantly higher, compared to the control group (P<0.001).

Table 4. Extra-pulmonary cancer types in cases in the patient and control group

		The patient group		Total n:700	*P* value#
		Lung cancer group n: 350	Control group n:350		
Site of the extra pulmonary cancer	**Breast, n(%)**	20 (5.7)	4 (1.1)	24 (3.4)	**0.0008**
	Larynx, n(%)	11 (3.1)	4 (1.1)	15 (2.1)	0.06
	Brain, n(%)	5 (1.4)	6 (1.7)	11 (1.5)	0.76
	GIS, n(%)	32 (9.1)	34 (9.7)	66 (9.4)	0.79
	Leukemia, n(%)	10 (2.8)	11 (3.1)	21 (3)	0.82
	Lymphoma, n(%)	3 (0.8)	3 (0.8)	6 (0.8)	1
	GUS, n(%)	20 (5.7)	8 (2.2)	28 (4)	**0.02**
	Gynecological, n(%)	2 (0.5)	4 (1.1)	6 (0.8)	0.41
	Other, n(%)	4 (1.1)	6 (1.7)	10 (1.4)	0.52
Total, n(%)		107 (30.5)	80 (22.8)	187 (26)	**0.0210**

GIS: gastrointestinal system, GUS: genitourinary system, # Chi-square

In studies evaluating the histological type of the lung cancer and the familial cancer risk, an increased familial cancer risk was determined in squamous cell lung cancer and adenocarcinoma cases, compared to the other histological types (5,8,16,17). However, in our study, no correlation was found between the histological type and the family history of lung cancer, and family history of extra-pulmonary cancer (p =0.614, p=0.495). This may be explained by the fact that in developing countries like ours, squamous cell carcinoma, which is strongly related to smoking, is more common than compare to adenocarcinoma which is associated with family history (18,19).

In spite of the fact that no molecular predisposition causing an increase in familial cancer risk has been demonstrated yet, thanks to the advances in molecular epidemiology, some

individuals are suggested to be more prone to environmental carcinogens, both genetically and due to acquired reasons as well (20). In many studies investigating the genetic factors that play another important role in the development of lung cancer, the first-degree relatives of patients with lung cancer were shown to have an increased risk of lung cancer and extra-pulmonary cancers (21-23). In two other studies from our country, a positive family history had been determined in 38-40% of cases with lung cancer (5,9). In our study, in 40.2% of cases with lung cancer, a positive family history was determined in terms of any cancer, and this rate was significantly higher than the control group. In addition, in the first-degree relatives of cases with lung cancer, a positive lung cancer history was determined at a higher rate than the control group (P<0.001).

In studies evaluating the association of lung cancer with other cancers, clustering has been determined between the lung cancer and GIS cancers (5,9,24). In terms of familial clustering of lung cancer, several studies have demonstrated an increase in the risk for relatives of lung cancer patients (23,25-28). In our study, in the relatives of cases with lung cancer, the risk of lung cancer was found to be increased by 2.25 (95% CI: 1.53-3.31)-fold, compared to the patients without a family history (Table 4). Consistent with the literature, in our study, familial clustering was determined in lung and breast cancers (P<0.005, P=0.0008).

In the study of Coté et al. in 2012, on first-degree relatives of cases with lung cancer, they stated that they had determined the lung cancer risk to be increased by 1.51 (95% CI: 1.39-1.63)-fold, compared to cases without a family history (25). In our study, however, in the first-degree relative of cases with lung cancer, the risk of lung cancer was determined to be increased by 2.18 (95% CI: 1.23-3.86) fold, compared to cases without a family history. Etiological heterogeneity, number of our cases, dietary habits, ethnic and genetic differences may be the main reasons of this difference.

Retrospective nature of this study is one of the limitations. The limitations of our study; this is also gathering family history from patients own declaration may affect accuracy. Besides, socioeconomic living conditions, mutation analysis, infection and ethnic characteristics have not been identified. Our main strength; concerning the lack of adequate data in our country regarding the family story in lung cancer, results we obtained are important sources for our country. The results we have obtained are a source for our country.

CONCLUSION

In lung cancer, the etiology of which environmental and genetic factors play a role, the risk of lung cancer incidence increases in the case of a positive family history of lung cancer. Therefore, the relatives of cases with lung cancer should be monitored carefully for possible malignancies.

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