

# The changing epidemiological trends for carcinoma of the lung in Turkey

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## ABSTRACT

**الأهداف:** مقارنة القياسات الوبائية لسرطان الرئة في العقدين الماضيين (1986م - 1995م مقابل 1996م - 2005م).

**الطريقة:** تم الحصول على بيانات الصفات السكانية والأنواع الفرعية النسيجية للمرضى المصابين بسرطان الرئة بشكل استعادي بواسطة مراجعة لوحة البيانات بمستشفى جامعة كومهوربيت - تركيا للفترة من 1993م إلى 2005م. تم البحث عن جميع الأوراق التي تحتوي على نص كامل يذكر بيانات وبائية لسرطان الرئة بتركيا للتحليل بطريقة ميتا.

**النتائج:** تم تحليل إجمالي عدد 25.604 مريضاً خلال العقدين الماضيين. بلغ متوسط العمر عند التشخيص في ذلك الوقت 59.4 عاماً و92.5% من المرضى كانوا من الذكور. في العقد الماضي، انخفض معدل السرطان الغدي ذو الخلايا الحشرية من 61% إلى 50% ولكن معدل السرطان الغدي ذو الخلايا الصغيرة قد ازداد من 19% إلى 24%، ومعدل الورم الغدي السرطاني من 20% إلى 26%.

**خاتمة:** كان هنالك تغير في نسبة الذكور / الإناث في تركيا. انخفض معدل الورم السرطاني الغدي الحشري ولكن ازداد الورم السرطاني الغدي ذو الخلايا الصغيرة والورم الغدي السرطاني.

**Objective:** To compare epidemiological parameters for lung cancer in the last 2 decades (1986-1995 versus 1996-2005).

**Methods:** Data on demographic characteristics, and histological subtype of lung cancer patients were retrospectively collected by a chart review in Cumhuriyet University Hospital, Sivas, Turkey for the period of 1993-2005. All other full-text papers that report epidemiological data for lung cancer in Turkey were also searched for meta-analysis.

**Results:** A total of 25,604 patients were analyzed in the last 2 decades. The mean age at the time of diagnosis was 59.4 years, and 92.5% of the patients were males. In the last decade, the rate of squamous

cell carcinoma decreased from 61-50%, however, the rate of small cell carcinoma increased from 19-24%, and the rate of adenocarcinoma from 20-26%.

**Conclusion:** There was a shift in the male/female ratio in Turkey. The rate of squamous cell carcinoma decreased, however, small cell carcinoma and adenocarcinoma increased progressively.

*Saudi Med J 2008; Vol. 29 (5): 749-753*

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*Received 16th November 2007. Accepted 18th March 2008.*

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Although environmental exposure to asbestos is a known factor for lung cancer in Turkey, smoking is the most important factor for the development of the disease.<sup>1</sup> Both population-based<sup>2</sup> and hospital-based studies<sup>3</sup> suggest a real and international change in the histopathology of lung cancer. Squamous cell carcinoma, which was formerly the most common type in men, is now getting rarer, and adenocarcinomas are becoming relatively more common, especially among men. Most of the temporal and geographical variations in lung cancer rates are generally related to different patterns of past smoking behavior and cigarette design. The understanding of the relationship between histological

**Disclosure:** The authors of this article declare that this undertaking was not supported by any foundation.

trend and epidemiological parameters can help in the pathogenesis of lung cancer. Such studies can reveal the active components responsible for the pathogenesis, and help to identify potential therapeutic targets. There are no data on the trend in histopathology of lung cancer in Turkey. The aim of this study was to evaluate epidemiological parameters and histopathologic changes for lung cancer over the last 2 decades.

**Methods.** We conducted a retrospective study to determine the pattern of lung cancer in our region (Sivas) and in Turkey. Data on demographic characteristics and histological type were retrospectively obtained by screening of the chart records of patients with lung cancer in the Department of Chest Diseases, and the archives of the hospital. We included only pathologically proven primary lung cancers between January 1993 and January 2005. Metastatic lung neoplasms, carcinoids and pleural malignancies were excluded from the study. Histological classification was carried out according to the World Health Organization.<sup>4</sup> We calculated only 3 major histologic subtypes such as squamous cell carcinoma, small cell carcinoma, and adenocarcinoma. The local ethics committee approved the study (2005-5/1). In addition, we searched the related papers on the demographic characteristics of lung cancer in Turkey. We investigated full-text articles, however, not on meeting abstracts, in the periodical journals covered by the Turkish Medical Index and Index Medicus. We inspected all the articles that have key words such as lung cancer, or lung tumors, or lung carcinoma, or bronchial carcinoma. The studies consisting of more than 100 patients in each were included in the meta-analysis. All patients included in the meta-analysis had pathologically proven lung cancer. For better understanding of changing trends in epidemiological parameters in our country, we compared both decades (1986-1995 versus 1996-2005).

Chi-square test was used for the comparison of the decades. A *p*-value less than 0.05 was considered significant. Statistical Package for Social Sciences (SPSS) version 10.0 was employed for data analysis.

**Results.** The mean age of 407 patients was 59.9, and 90.6% were males. There were 96 patients with small cell carcinoma (81 males), 209 patients with squamous cell carcinoma (200 males), 44 adenocarcinoma (34 males), 53 undefined non-small cell carcinoma (49 males), and 5 large cell carcinoma (all males) between 1993 and 2005 in Cumhuriyet University Hospital, Sivas, Turkey. For the meta-analysis, there were 31 eligible studies,<sup>5-35</sup> and a total of 25,604 patients were reviewed in the last 2 decades. There were 9 studies for the period of 1986-

1995, and 11 studies for the period of 1995-2004. One trial spans over the 2 time periods,<sup>16</sup> however, all the selected trials do not contain overlapping population. The mean age at the time of diagnosis was 59.4 years, and 92.5% of the patients were males (Table 1). Table 1 showed that the most common major types were squamous cell, small cell, and adenocarcinoma. When compared to the period 1986-1995, the ratio of males decreased from 93.3-91.8% ( $\chi^2$ : 24.6,  $p < 0.01$ ), however, the mean age increased from 58.5-59.8 years in the period 1996-2005. In last decade, the rate of squamous cell carcinoma decreased from 63-50%, however, the rate of small cell carcinoma increased from 16-24%, and the rate of adenocarcinoma from 21-26% ( $\chi^2$ : 173.52,  $p < 0.01$ ). In males, the rates of squamous cell carcinoma were 55.5%, small cell carcinoma was 24.9%, and adenocarcinoma was 19.6%. In females, these rates were 25.7% for squamous cell carcinoma, 25% for small cell carcinoma, and 49.3% for adenocarcinoma. The number of patients according to gender in each decade is shown in Table 2.

**Discussion.** The epidemiology of lung cancer is changing in many parts of the world. In the industrialized countries, the incidence of the disease increases in women, while it decreases in men.<sup>3</sup> Our meta-analysis showed that the rate of females increased significantly in the last decade. This finding may be due to increasing prevalence of smoking in women.<sup>13,27</sup> The prevalence of smoking in Turkey has increased during the past 3 decades. Cigarette consumption increased by 10% from 1970 to 1985, however, this consumption went up to 44% in 1988 with a smoking prevalence of 63% for males and 24% for females.<sup>1,13</sup> Additionally, it has been suggested that female smokers are more susceptible to lung cancer than male smokers.<sup>36</sup>

In the present study, squamous cell carcinoma remains the most common type in males. However, Table 2 demonstrated that there was a decreasing incidence trend for squamous cell carcinomas, significant among males. In women, adenocarcinomas have always been the most common type, and remains so. Endocrine factors can contribute to the predominance of adenocarcinoma in women.<sup>37</sup> Although the increased incidence of adenocarcinoma might be explained by advances in diagnostic technology such as increased ability to perform biopsies on tumors in smaller, more distal airways, and immunohistochemical stains,<sup>36</sup> it has been reported that the increase in this cancer is associated with changes in smoking behavior and cigarette design.<sup>38</sup> Smokers of low-yield filter-tipped cigarettes have to take more frequent and larger puffs to fulfill their needs of nicotine. This allows the cigarette smoke to reach the distant branches of bronchiolar tree

**Table 1** - The information of gender, age, and number of patients according to the major histological subtypes in the studies originating from Turkey.

Study period	City	Number of patients	Males	Females	Mean age	Squamous cell carcinoma	Small cell carcinoma	Adenocarcinoma
1985-1991 <sup>5</sup>	Istanbul	1000	975	25	-	538	336	176
1986-1991 <sup>6</sup>	Istanbul	165	153	12	59.9	101	28	36
1987-1994 <sup>7</sup>	Ankara	627	587	40	56.2	431	84	72
1988-1991 <sup>8</sup>	Izmir	350	333	17	-	225	80	37
1989-2003 <sup>9</sup>	Eskisehir	1068	980	88	60.5	461	286	194
1990-1992 <sup>10</sup>	Erzurum	116	90	26	59.5	56	23	19
1990-1993 <sup>11</sup>	Istanbul	391	364	27	-	243	61	68
1990-1994 <sup>12</sup>	Istanbul	216	201	15	56.9	119	52	45
1990-1996 <sup>13</sup>	Ankara	1046	966	80	56.7	441	269	166
1990-1999 <sup>14</sup>	Diyarbakir	181	168	13	56.7	122	28	21
1991-2002 <sup>15</sup>	Ankara	343	309	34	59.7	158	77	26
1992 <sup>16</sup>	Istanbul	960	895	65	56.4	582	175	130
1992-1993 <sup>17</sup>	Izmir	1962	1868	94	60.1	-	-	-
1992-1995 <sup>18</sup>	Bursa	108	101	7	61.0	-	-	-
1992-1999 <sup>19</sup>	Trabzon	226	217	9	61.3	151	34	23
1992-2001 <sup>20</sup>	Edirne	521	497	24	60.8	258	155	64
1993-1997 <sup>21</sup>	Istanbul	393	349	44	-	-	-	-
1993-2005 (this study)	Sivas	407	369 (90.6%)	38	59.9	209 (60%)	96 (28%)	44 (12%)
1994-1995 <sup>22</sup>	Istanbul	250	231	17	55.8	172	22	19
1994-1999 <sup>23</sup>	Ankara	571	536	35	-	236	150	103
1994-2004 <sup>24</sup>	Elazig	323	279	44	63.2	116	55	42
1995 <sup>16</sup>	Istanbul	1184	1089	95	-	595	162	352
1995-2000 <sup>25</sup>	Ankara	1500	1379	121	59.9	769	358	309
1996-1997 <sup>26</sup>	Ankara	1291	1195	96	62.3	553	242	224
1997-2000 <sup>27</sup>	Ankara	2216	1992	224	57.3	898	344	566
1997-2003 <sup>28</sup>	Izmir	1297	1159	138	62.0	351	252	93
1998 <sup>16</sup>	Istanbul	1287	1178	109	57.9	640	158	398
1998-2000 <sup>29</sup>	Antalya	225	204	21	59.7	86	57	42
1999-2003 <sup>30</sup>	Istanbul	971	897	74	57.7	348	283	185
1999-2005 <sup>31</sup>	Izmir	2144	2088	56	62.2	421	364	224
2001-2002 <sup>32</sup>	Samsun	227	213	14	60.6	-	-	-
2001-2003 <sup>33</sup>	Istanbul	144	144	-	60.0	64	31	39
2002 <sup>34</sup>	Ankara	493	441	52	58.7	173	91	122
2004 <sup>35</sup>	Istanbul	1403	1238	165	59.1	577	184	359
<b>Total</b>		<b>25604</b>	<b>23685 (92.5%)</b>	<b>1919</b>	<b>59.4</b>	<b>10094 (54%)</b>	<b>4537 (24%)</b>	<b>4198 (22%)</b>

**Table 2** - Number of patients according to gender in each decade.

Study period	Gender	Squamous cell carcinoma	Small cell carcinoma n (%)	Adenocarcinoma	References
1986-1995	Males	617 (66)	188 (20)	129 (14)	6,8,10,11
	Females	28 (36)	16 (21)	33 (43)	
1996-2005	Males	2071 (51)	1040 (26)	943 (23)	26,27,30,34
	Females	90 (24)	86 (23)	196 (53)	

Females  $\chi^2 = 4.94$ ,  $p > 0.05$ , Males  $\chi^2 = 72.47$ ,  $p < 0.01$

where adenocarcinoma usually occurs.<sup>1,27,38</sup> Blended reconstituted tobacco releases higher concentrations of nitrosamines from tobacco stems than did products made predominantly from tobacco leaves.<sup>39</sup> The observation of similar trends in esophageal cancers supported this hypothesis. Smoking is also a risk factor for esophageal cancers. For esophageal cancer, the rate of squamous cell carcinoma declined, however, the incidence of adenocarcinoma increased.<sup>39</sup> The nitrosamine 4-(methyl nitrosamine)-1-(3-pyridyl)-1-butanone, is known to stimulate adenocarcinoma in animal models, and its quantity in cigarettes has increased over time, almost doubling between 1980 and 1996. Simultaneously, concentrations of polycyclic aromatic hydrocarbons, implicated primarily for squamous cell carcinoma, has declined over time (having been reduced nearly 50% between 1960 and 1996), which may explain in part the decreasing incidence of squamous cell lung cancers while adenocarcinomas of the lung continue to increase.<sup>39</sup> According to the Institute of Statistics of Turkey, there was a striking tendency to use filtered cigarettes in Turkey. The shift between squamous cell carcinoma and adenocarcinoma may be explained partly by the socioeconomic factors. Lower income and education levels have been associated with a higher rate of exposure to environmental pollutants, higher smoking prevalence, and nicotine dependence rates, and greater usage of non filter, high-tar cigarettes.<sup>2,40</sup> In our region, the relative incidence of adenocarcinoma was 12%, while this rate was 22% in Turkey. This finding was probably due to low socioeconomic conditions of our province.

The results of the largest data review in Turkey show that there was a striking decrease in the rate of squamous cell carcinoma, however, a rapid increase in the rate of adenocarcinoma, especially in men. This trend is the same as in Europe, Japan, and the United States. In contrast, while the proportion of patients with small cell carcinoma has decreased from 17.4% in 1986 to 13.8% in 1998,<sup>41</sup> it is increasing in Turkey, especially in the last decade. However, while smoking incidence is low or lowering in the above-mentioned countries, this rate continues to increase due to negative promotions of foreign tobacco companies.

The exact cause of the increase of the proportion of small cell carcinoma is unclear. The studies included for meta-analysis do not surely represent the entire country. This finding may be due to patient selection as we used clinical trial data. In addition, we included only the studies consisting of more than 100 patients in the meta-analysis. Consequently, this is a biased population. Note that 20 of the 31 studies included came from 2 cities (Istanbul and Ankara) although these are the biggest cities in Turkey. On the other hand,

there is no population based cancer registry (similar to surveillance epidemiology and end results) available for more accurate analysis of trends over time with regard to lung cancer in Turkey. Occupational risks for small cell cancer include exposure to vinyl chloride, nickel, asbestos, and cadmium.<sup>42</sup> Environmental exposure to asbestos or erionite (a volcanic carcinogenic mineral) in Turkey may be responsible for the increase of the rate of small cell cancer. The increase in air pollution in Turkey may be another cause of this trend as industrial nations in general have an increased incidence of small cell cancer, possible from higher levels of air pollutants.<sup>42</sup>

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