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Smoking and lung cancer

Tevfik ÖZLÜ, Yılmaz BÜLBÜL

Karadeniz Teknik Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Trabzon.

ÖZET

Sigara ve akciğer kanseri

Günümüzde erişkinlerin yaklaşık üçte birinin sigara içtiği ve kadın nüfusunda sigara içme oranının arttığı bilinmektedir. Tütün kullanımıyla ilişkilendirilebilir ölümlerin 2025 yılında 10 milyona çıkacağı tahmin edilmektedir ve tüm erişkin ölümlerinin üçte birinin sigara içmekten kaynaklanacağı öngörülmektir. Sigara ve akciğer kanseri arasındaki ilişki geniş kapsamlı çalışmalarla ispatlanmıştır. Tütün kullanımı erkeklerin %90'ında, kadınların ise %79'unda akciğer kanserinin ana nedeni olarak bildirilmiştir. Akciğer kanserinden ölümlerin %90'ının sigara içmeyle ilişkisi olduğu tahmin edilmektedir. Sigara içenlerde akciğer kanseri gelişme riski sigara içmeyenlerle karşılaştırıldığında 20-40 kat daha yüksektir. Çevresel sigara içilmesine maruz kalma ve sigara içişinin farklı tipleri, akciğer kanserine sebep olarak gösterilmiştir. Son dekadlarda, kadın popülasyonu arasında sigara içme oranlarının artması ve "light" sigara kullanımının artmasından dolayı skuamöz ve küçük hücreli akciğer kanseri tipinden adenokarsinomaya bir değişme vardır. Sigarayı bıraktıktan sonra, akciğer kanserinden kümülatif ölüm riski azalmaktadır. Sigara içmeye devam eden hastanın kanser tedavisinde daha büyük zorluklar olmaktadır. Sigarayı bırakmak, kanserli hastalarda hayatta kalma süresini uzatabilir ve akciğer kanseri nüks riskini azaltabilir. Hekimler, güvenli yaşamak ve sigarayla ilişkili tehlikelerden korunmak için kanserli ve sağlıklı bireylerin hepsine sigarayı bırakmayı tavsiye etmelidir.

Anahtar Kelimeler: *Kanser, akciğer kanseri, sigara bırakma, sigara.*

SUMMARY

Smoking and lung cancer

Ozlu T, Bulbul Y

Department of Chest Diseases, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey.

Nowadays, around one-third of adults are known to be smokers, and smoking rates are increasing among the female population. It is estimated that deaths attributable to tobacco use will rise to 10 million by 2025, and one-third of all adult deaths are expected to be related to cigarette smoking. The association between cigarettes and lung cancer has been proven by large cohort studies. Tobacco use has been reported to be the main cause of 90% of male and 79% of female lung cancers. 90% of deaths from lung cancer are estimated to be due to smoking. The risk of lung cancer development is 20-40 times higher in lifelong smokers compared to non-smokers. Environmental cigarette smoke exposure and different types of smoking have been shown to cause pulmonary carcinoma. DNA adducts, the metabolites of smoke carcinogens bound co-

Yazışma Adresi (Address for Correspondence):

Dr. Tevfik ÖZLÜ, Karadeniz Teknik Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, TRABZON - TURKEY

e-mail: tozlu@meds.ktu.edu.tr

valently with DNA, are regarded as an indicator of cancer risk in smokers. In recent decades, there has been a shift from squamous and small cell lung cancer types to adenocarcinoma, due to increasing rates of smoking among female population and rising light cigarette usage. After smoking cessation, the cumulative death risk from lung cancer decreases. Patients who continue smoking experience greater difficulties during cancer treatment. Stopping smoking may prolong survival in cancer patients, and also decreases the risk of recurrent pulmonary carcinoma. In order to save lives and prevent smoking related hazards, physicians should advise both healthy individuals and those with cancer of the benefits of stopping smoking.

Key Words: *Cancer, lung cancer, smoking, smoking cessation, tobacco.*

SMOKING: A HISTORICAL PERSPECTIVE

The history of tobacco goes back more than 4000 years. It was used as a narcotic substance by Native Americans. In 1493, it was brought back to Europe by Christopher Columbus. Tobacco growing soon started in Spain, and the use of tobacco spread rapidly in Europe during the 16^{th} and 17^{th} centuries. Annual consumption of tobacco in United States rose from 5 billion in 1905 to 17 and 90 billion in 1915 and 1925, respectively.

As its harmful effects became understood, campaigns against tobacco started during the 1950s. At the same time, cigarette companies began to produce filter cigarettes in order to neutralize the negative effects of those campaigns. Light cigarettes containing low tar and nicotine were put on the market during the 1970s, following filter cigarettes.

SMOKING EPIDEMIOLOGY

Nowadays, one-third of adults (1.3 billion people) are known to be smokers. While 25% of females smoke, the level rises up to 50% among males (1). Approximately 6 trillion cigarettes per year are smoked worldwide, and the age at which people take up smoking is decreasing all over the world (1,2). Interestingly, 75% of smokers live in poor countries. However, smokers enjoy low socio-economic conditions whether they live in rich or poor countries (3). While the number of cigarettes consumed has declined in the United States and in some European countries, such as England and Finland, over the last 30 years, the trend in China and in other Asian countries is rising. Currently, half of the world's cigarette production is consumed in Asia. China is the largest consumer of tobacco related products, and smoking related deaths are consequently most common there. The number of smokers in China is about 320 million, and there was a 7.2% increase in tobacco consumption from 1980 to 1990 (4). One interesting statistic from China is that while two-thirds of males smoke, smoking levels among females are less than 5% (4).

SMOKING and HEALTH

Approximately 5 million people die from smoking related disorders each year, and one-tenth of all adult deaths are related to tobacco use. It is estimated that deaths attributable to tobacco use will rise to 10 million by 2025, and one-third of all adult deaths are expected to be related to cigarette smoking (5). 50% of smokers die from smoking related disorders (6). Smoking is known to be the cause of some 30 diseases, mainly cardio-vascular and cerebro-vascular disorders, chronic obstructive pulmonary diseases (COPD) and cancers. 30% of all cancer deaths, 75% of all COPD deaths and 25% of all atherosclerotic hearth diseases are attributed to smoking (7). Life expectancies of people who smoke at least 20 cigarettes per day for 25 years are estimated to be 25% shorter than those of non-smokers (6).

SMOKING and CANCER

Rottman first claimed that lung cancer might stem from tobacco use in 1898 (8). Decades later this hypothesis was proved by Roffo, who produced skin cancer in mice, using cigarette tar, in 1931 (8). The epidemiological relation between cigarette smoke and lung cancer was first reported by Muller in 1939 (8). In the wake of Muller's report, large case control studies

from the United States and Great Britain also proved the scientific basis for an association between cigarette smoking and lung cancer in the 1950s (9,10). Consequently, the main cause of lung cancer in males was reported to be cigarette smoking in the Surgeon General's Report in 1964 (11). Interestingly, a similar relation concerning females was only proved in 1980.

Over 4000 bioactive chemical compounds have been isolated from cigarette smoke, of which more than 60 are carcinogens (12). Topical, intrathracheal or subcutaneous administration of polyaromatic hydrocarbons, found in cigarette smoke, may produce cancer in animals. Tobacco chewing and snuff taking have also been reported to cause oral, esophageal, laryngeal and pharyngeal cancers (13).

Lung, larynx, pharynx, esophagus, oral cavity, pancreas, urinary bladder and renal pelvic cancers are strongly related to tobacco use. Tobacco is known to be the causative factor in the development of colorectal, sinonazal, adrenal, gastric, uterine, cervical and liver cancers, as well as of myeloid leukemia. However, it is not known whether there is a causative association between tobacco use and such carcinomas as prostate, brain, skin and breast carcinomas, testicular and endometrial cancers, soft tissue sarcomas, lymphomas and melanomas (14).

In developed countries, one-third of all cancer deaths (47% of male and 14% of female cancer deaths) are associated with cigarette smoking (1,15). Deaths from cancer are twice as high in smokers compared to non-smokers. Moreover, if the number of cigarettes smoked per day exceeds 20, death rates are four times higher compared to non-smokers (16).

SMOKING and LUNG CANCER

Lung cancer accounts for 12.8% of all cancers worldwide and it is highly lethal among both males and females. More than 90% of patients with lung cancer die. Of cancer deaths, 17.8% are attributed to pulmonary carcinoma and 5-year survival rates are less than 10%. The number of lung cancer related deaths was reported to be 1 million in 1990 (17,18). In contrast to most cancers, the incidence and mortality of lung cancer are gradually increasing. Death rates for pulmonary carcinoma have been reported to have risen by 400% between 1950 and 1990 (19).

Tobacco use has been reported to be the main cause of 90% of male and 79% of female lung cancers (20). 90% of lung cancer deaths are estimated to be due to smoking (21,22). Compared to non-smokers, the risk of the development of lung cancer in lifelong smokers is 20-40 times higher (23,24). The synergy between cigarette smoking and exposure to asbestos, arsenic and radon has been shown to increase the risk of pulmonary carcinoma (25-28).

The association between cigarette smoking and lung cancer has been proven by large cohort studies (29,30). 20% of smokers develop pulmonary carcinoma and approximately 90% of patients with lung cancer are smoker (31,32). Capewell et al. showed that only 2% of patients with lung cancer were non-smokers (33). The association between cigarette and lung cancer is stronger for squamous cell and small cell types other than adenocarcinoma and large cell carcinoma (24). The association between lung cancer and smoking is also more dominant in the male population compared to females (Table 1).

The risk of pulmonary carcinoma in smokers increases with commencing smoking at an early age, the number of cigarettes consumed per day and the depth of cigarette smoke inhalation (31,33,34). Geographical variations and gender differences in the incidence of lung cancer are also related to frequency of tobacco use (24,28,35-39).

Types of Cigarette Smoked

The risk of cancer development may vary according to the type of cigarette smoked. The risk decreases with the use of filter cigarettes (40). Engeland et al reported a higher risk with hand-rolled cigarettes compared to factory made cigarettes (34). At the same time, Chinese cigarette brands were found to be less mutagenic than Western brands (41).

Table 1. Relative risk of lung cancer in Europe according to smoking status and the sex (adapted from Simonato L, et al. Int J Cancer 2001).

	Male		Female	
Smoking status	**Squamous cell**	**Adenocarcinoma**	**Squamous/small cell Ca.**	**Adenocarcinoma**
Non-smoker	1.0	1.0	1.0	1.0
Stopped	16.2*	3.5*	3.8*	1.1
Smoker	57.9*	8.0*	18.2*	4.1*

* p< 0.05.

Cigar and pipe smoking increase the risk of lung cancer seven times (42). The carcinogens found in cigars and pipes are reported to be the same as those in cigarettes (43). However, those studies that have reported a reduced risk with cigars and pipes may be related to limited use and shallow inhalation (42). In fact, the risk of lung cancer in cigar and pipe smokers in Denmark and Holland, where cigar and pipe smoking involves deeper inhalation, was found to be the same as that among cigarette smokers (16).

Because of their higher tar content and carcinogen levels, mentholated cigarettes may increase the risk of lung cancer. Moreover, menthol facilitates carbon monoxide absorption and causes retention of cigarette smoke in the lung by restricting ventilation (44-50).

Light cigarettes, which were produced to enhance safety, do not lower the risk of cancer. During the last 30 years, the increasing trend of consuming cigarettes containing low tar and nicotine levels has caused a predomination of peripherally located adenocarcinomas, in contrast to centrally located squamous cell cancers (21,51,52). Because real cigarette smoking may differ from smoking simulated by machine, light cigarette users smoke a greater number of cigarettes per day and make deep inhalations to restore their previous nicotine levels. Consequently, the smoke and carcinogens reach more distal areas and cause peripheral lung cancers (21,52,53).

Environmental Smoke Exposure and Lung Cancer

Environmental cigarette smoke exposure has been shown to cause pulmonary carcinoma in several studies (54-58). Exposure to smoke alters the risk of lung cancer by 15-25% (56,57,59). Indeed, it has been shown that non-smokers exposed to cigarette smoke have some metabolites of tobacco carcinogens (60-63). Squamous cell lung cancer is the most common histological type among non-smokers exposed to environmental smoke (58). In addition, deaths due to lung cancer in non-smoking women whose husbands smoke are 20% higher than in women whose husbands are non-smokers (54). Cardenas et al. reported a higher risk in women whose husbands smoke more than two packets a day (64). It was also reported that the risk of lung cancer rises by 30% in non-smokers living with smokers (19). The risk of lung cancer is twice as high in individuals exposed to indoor cigarette smoke during childhood and adolescence (19).

Smoking Related Carcinogenesis

The balance between the metabolic activation and detoxification of the carcinogens in smoke determines the risk of individual cancer development. Metabolites occurring during the activation of carcinogens bind covalently with DNA, and this produces DNA adducts. DNA adducts are regarded as an indicator of cancer risk in smokers. The level of DNA adducts is directly related to the intensity of cigarettes smoked (65,66). However, DNA adduct levels gradually decrease after stopping smoking, and previously produced DNA adducts return to a normal DNA structure, by means of DNA repair mechanisms (67). However, some DNA adducts escaping the repair mechanisms may cause miscoding. If miscoded cells are not killed by apoptotic mechanisms, mutations are inevitable. On the other hand, free radicals in cigarette smoke cause oxi-

dative damage to and mutations in DNA. Some mutations activate oncogenes and inhibit tumor suppressor genes.

The most important event in the pathogenesis of lung cancer is mutation in the TP53 gene. TP53 protein is involved in several processes including cell cycle control, DNA synthesis/repair, cell differentiation, gene transcription and programmed cell death. TP53 gene mutations are detected in 50% of NSCLC and 70% of SCLC patients (68-71). The characteristics of cigarette smoke related lung cancer are G:C and T:A transversions (72-74). These mutations are more frequent in females who smoke (68). Vahakangas et al. determined those mutations in both current and past smokers (74). Mutant TP53 and K-RAS genes may be detected in sputum several months before the diagnosis of lung cancer of smokers (75). Ahrendt et al. also reported that TP 53 gene mutations are facilitated by the joint use of tobacco and alcohol (76). These data suggest that alcohol may increase the mutagenicity of cigarettes.

Smoking Related Lung Cancers in Women

Currently, the incidence of lung cancer in females is not as high as that in males, mostly due to the lower smoking rates among females. However, while lung cancer deaths have been declining in the USA and Europe, they have been rising among females for the last 20 years (20,77). The rate of deaths due to pulmonary carcinoma increased by 600% in the USA female population from 1930 to 1997 (78). Irrespective of levels of exposure to cigarette smoke, the TP 53 gene, G:C and T:A mutations and DNA adduct levels in females were reported to be higher than in males (68,79-81). Mollerup et al. also showed altered CYP1A1 gene expression in females compared to males (81). Activation of polycyclic aromatic hydrocarbons by means of the CYP1A1 gene causes the formation of increased DNA adducts (82). Polymorphism in the glutathione S-transferase M1 (GSTM1) gene, involving the metabolism of carcinogens activated by the CYP1A1 gene and also blocking free radical formation, is encountered more frequently in female smokers than in males (83,84). DNA repair capacity is lower and K-ras mutations in NSCLC are also higher in females (85,86).

G:C and T:A transversions, which are more common in lung cancer due to cigarette smoking, are more frequent in female smokers compared to non-smoking females. However, G:C and T:A transversion frequencies are not significantly different between male smokers and non-smokers (68).

Some studies suggest that the risk of lung cancer development in females who smoke the same number of cigarettes as males is higher than that in males (87-89). The risk of small cell lung cancer development is reported to be higher in females who smoke the same amount as males, while the risk of squamous cell lung cancer is reported to be the same in both the male and female populations (90,91). However, reports presenting contrary findings also exist (77,92). The inconsistencies between studies may originate from differences in the smoking behavior of females compared to that of males. Indeed, the higher frequency of adenocarcinoma in females was found to be related to female smoking patterns (21,93,94). Women smoke due to negative feelings, in contrast to males, in whom addiction is predominant (95). Depression among female smokers is more common than in males (95). This different motivation and behavior may be related to females taking more puffs and inhaling more deeply, which subsequently causes carcinogens to reach the lung periphery. Again, starting smoking at later ages and the use of filter cigarettes among females may be responsible for the higher incidence of adenocarcinoma in women.

Without respect to the total number of cigarettes smoked, the risk of lung cancer increases if the age at which smoking begins is lower than 20 for males and 25 for females (96). Estrogen replacement at more advanced ages also increases the risk of lung cancer, especially adenocarcinoma in women (88,97,98). These data predict the role of hormonal factors in the development of cancer due to tobacco use. Taioli reported a relationship between increased risk of adenocarcinomas and estrogens, endogenous or exogeno-

us (99). Although the clinical significance is unknown, some authors have reported increased alpha type estrogen receptors in human lung cancer (100-102).

In a study analyzing indoor cigarette smoke exposure between husbands and wives, lung cancer mortality in non-smoking wives exposed to their husbands' cigarette smoke were interestingly found to be three times higher than that in non-smoking husbands exposed to their wives' cigarette smoke (103). This may be related to the duration of indoor exposure experienced by females since they spend longer at home, and may also be related to intense exposure to other indoor pollutants from cooking, heating etc.

Quit Smoking and Lung Cancer

After smoking cessation, the cumulative death risk from lung cancer decreases. Peto et al. showed that the earlier cigarette smoking stops the greater the decline in lung cancer mortality (23). For instance, while the cumulative lung cancer mortality risk is 9.9% in subjects who stop smoking at the age of 60, the risk is only 3% in those who stop smoking at 40 (23). A study by Simonato et al. carried out in six European countries shown that the risk of lung cancer development decreases gradually in the years following stopping smoking (Table 2) (24). The data presented here were also supported by large, prospective studies performed on British male doctors and US veterans (29,30).

Table 2. Relationship between stop smoking and lung cancer (adapted from Simonato L, et al. Int J Cancer 2001).

	Relative risk	
Time after cessation	**Male**	**Female**
2-9 years	0.66*	0.41*
10-19 years	0.27*	0.19*
20-29 years	0.170	0.08*
> 30 years	0.08*	0.13*
Never smoked	0.04*	0.11*
Current smoker	1.00	1.00

* p< 0.05.

Quit Smoking and Lung Cancer Treatment

Of all cancer patients, 46-75% have been reported to be smokers at the time of diagnosis. Of these patients, 14-58% continue smoking (104). It has been reported that physicians who smoke do not sufficiently encourage their patients to stop smoking (104). Davitson et al. reported that some physicians think that patients receiving cancer treatment cannot tolerate stopping smoking (105). Despite the evidence regarding the negative and harmful effects of cigarette smoking during cancer treatment, some physicians claim that "It is too late", "It is too difficult" to "stop on their own" and that "stopping rates under therapy are low" (104).

Patients who continue smoking experience greater difficulties during cancer treatment (106,107). Tumor response to chemotherapy decreases and the risk of radiotherapy related pulmonary fibrosis increases by 20% in patients who continue smoking (108,109). An enhanced risk of recurrent pulmonary carcinoma in these patients was reported in several studies (110-113). Survival time is also shorter compared to that of ex-smokers (113-117). Postoperative complications and lung function loss after pulmonary resection are also higher in cancer patients who continuing smoking (104).

However, postoperative complications in patients who stop smoking decline (118). Blood pressure, heart rate and carbon monoxide levels are known to return to normal levels in a matter of hours after giving up smoking. Sense of taste, circulation and respiratory system recovery takes days, while metabolic functions and the immune system require months (119). Quality of life, general health conditions, cognitive functions, anxiety and physiologic functions improve and cancer treatment becomes more effective in ex-smokers (119,120). Improvements in respiratory distress, weakness, daily activities, appetite, sleep and pulmonary functions have also been reported (119). Toxicity due to cancer treatment has also been reported to decline in former smokers (121). Johnston-Early et al. showed prolonged survival in SCLC patients after stop smoking, and another study reported hig-

her chemo-resistance rates in NSCLC (especially squamous cell) patients who continued smoking (116,121). Cigarette smoking lowers therapeutic drug levels by changing hepatic metabolism, which may have a negative impact on chemotherapeutic drugs.

Approximately one-third of patients start smoking cigarettes again after cancer diagnosis (122). Interestingly, 13% of patients go back to smoking after thoracotomy (123). These data suggest that physicians should ask cancer patients about smoking, and should encourage them to quit and provide technical support. Professional approaches supported by physicians are known to be more effective and to enjoy higher success rates (124).

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