Cigarette Smoking and the Risk of Pulmonary Metastasis from Breast Cancer: A Case-Control Study

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Abstract

Aiming to evaluate the association between cigarette smoking and risk of pulmonary metastasis from breast cancer, 98 female patients with unilateral breast cancer which had metastasized to the lung (study group) and 199 female patients who had primary breast cancer without pulmonary metastasis (control group) were investigated. The two groups were compared for cigarette smoking history, age at diagnosis, menopausal status, family history, other organ metastasis. Chi-square and Fisher's exact tests were used in the analyses. There were no statistical differences between the study and control groups in age at diagnosis, menopausal status, family history and other organ metastasis. When the two groups were compared for smoking behavior; the number of eversmoker patients in the control group was found to be greater than that in the study group, but the difference was not of statistical significance.

In conclusion, a statistical difference was not found between cigarette smoking and the development of pulmonary metastatic disease in breast cancer.

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Introduction

Primary breast cancer is the most common cancer among women in Europe and the United States (1). This is also true for Turkey, where the incidence is reported as 24.4/100. 000 (2).

Until 1985, primary breast cancer was also the number one cause of cancer deaths in women, but at present it is in second rank, being outnumber by lung cancer, which currently is at the top of the list (3).

Relapses and metastases to other organ are frequent in primary breast cancer despite treatment. Lung, bone, liver and brain are the most commonly involved organs (4,5).

Lung is a common site of metastasis from breast cancer and any other primary tumors. It is not clear why metastases to the lung are so common. Smokers have been reported to have an increased rate of death from breast cancer in several epidemiological studies. It can be speculated that, smoking, through its pulmonary or systemic effects, adversely affects the natural history of breast cancer (6,7). In some studies it was also reported that, smoking increases the risk of pulmonary metastases from breast cancer (8,9,10).

The aim of this study was to examine the relationship between cigarette smoking and pulmonary metastases in unilateral, invasive breast cancer patients.

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Table 1. Features of the study and control groups			
	Case patients (n : 98)	Control patients (n: 199)	p
Age at diagnosis, yr	46 + 12	48 + 11.5	*
Postmenopausal %	66.2	63.8	*
Family history breast cancer %	6.1	10.1	*
CT[1] + RT[1] +Surgery,%	45	50.3	*
CT + RT + Hormone, %	-	1.0	*
CT + Surgery + Hormone,%	-	1.5	*
CT+RT+Surgery+Hormone,%	8.2	14.6	*
Other organ involvement,%	33	67	**
Smoking,%	11.2	20.1	*
[1]CT: Chemotherapy, [1]RT: Radiotherapy *p>0.05 , **p<0.05			

Materials and Methods

The study group consisted of 98 female patients admitted to our hospital from 1994 to 2001 and who were diagnosed as primary unilateral breast cancer with pulmonary metastases. The control group was defined as women with unilateral, invasive breast cancer who did not have pulmonary metastases and consisted of 199 female patients.

The patients were accepted to have pulmonary metastases if they fulfilled one of the following criteria:

1) Presence of unilateral malignant pleural effusion on the same side as the primary tumor or contralaterally
2) Bilateral malignant pleural effusion
3) Metastatic pulmonary nodule with pathological evidence
4) Multiple pulmonary nodules on the chest radiograph or CT scan, interpreted by clinician and radiologist to be metastatic in etiology, regardless of availability of biopsy findings
5) Lymphangitic carcinomatosis on the chest radiograph or CT scan (as interpreted by the radiologist)

The medical records of the study group and of control patients were reviewed retrospectively and, when possible, the patients were also interviewed directly. Information on age at diagnosis, menopausal status, family history of breast cancer, breast cancer treatment (chemotherapy, radiation therapy, surgery, hormone therapy), type of the pulmonary metastasis, existence of other organ involvement, smoking habits, was recorded on a structured data sheet.

All patients were classified as ever smokers (consisting of current smokers and ex-smokers) and nonsmokers.

Current smokers were those individuals who had smoked at least one cigarette daily or an equivalent amount of tobacco until the time of diagnosis.

Ex-smokers were those who had stopped smoking for at least one year prior to diagnosis.

Nonsmokers were individuals who smoked less than 100 cigarettes in their lifetime.

χ^2 and Fisher's Exact tests were used for the comparison of the study and control groups. Age at diagnosis, menopausal status, family history of breast cancer, type of pulmonary metastasis, other organ involvement and, smoking habita were compared in the two groups. A p value of <0.05 was considered significant. The analyses were done using a SPSS 10.0 Windows software.

Results

The study group consisted of 98 female patients who had primary unilateral breast cancer and had pulmonary metastases. The mean age of the group was 50±12 years and mean age at the time of diagnosis was 46±12 years. The control group consisted of 199 women. The mean age of the control group was 51±11 years and mean age at the time of diagnosis was 48±11.5 years (Table 1).

In the study group, 66.2% of the women were postmenopausal. This ratio was 63.8% in the control group. A family history of breast cancer was found in 6.1% of the study group and in 10.1% of the control group. Forty five percent of the patients in the study group and 50.3% of those in the control group underwent chemotherapy(CT)+ Radiation therapy (RT)+ surgery. In the study group, 8.2% of the patients also received hormone therapy. This ratio was 14.6% in patients in the control group. Other organ involvement was high in control group (p<0.05) (Table 1).

Thirty three percent of patients in the study group and 67% of those in the control group had metastatic involvement of other organs.

There were no significant differences between the study and control groups ion age at time of diagnosis, menopausal sta-

Table 2. Types and frequency of pulmonary metastatic involvement		
	No:	(%)*
Parenchymal nodules	48	41.4
Pleural effusion on the same side	31	30.6
Bilateral pleural effusion	22	22.4
Pleural effusion on the contalateral side	15	15.2
Solitary nodule	5	5.1
Lymphangitic carcinomatosis	2	2.0
*Percentages total>100% as categories not mutually exclusive		

Table 3. Smoking status of the study and control groups			
	Case patients	Control patients	P
Smoking Status	n:98	n:199	*
Nonsmoker, %	88.8	79.9	*
Current smoker, %	–	7.5	*
Ex-smoker, %	11.2	12.6	
Ever-smoker, %	11.2	20.1	
*p<0.05			

tus, family history of breast cancer, or treatment modalities (p>0.05).

When the study group was evaluated as to type and frequency of pulmonary metastases; it was found that there was more than one pulmonary nodule in 48 (41.4%) patients, pleural effusion on the same side in 31(30.6%) patients, bilateral pleural effusion in 22 (22.4 %) patients, pleural effusion on the contralateral side in 15 (15.2%) patients, a solitary nodule in 5 (5.1%) patients and lymphangitic carcinomatosis in 2 (2.0%) patients (Table 2). The categories were not mutually exclusive.

In the study group, 11.2% of the patients were ever-smokers. This ratio was 20.1% in the control patients. The ratio of nonsmokers was 88.8% in the study group versus 79.9% in the control patients, while the ratio of ex-smokers in the study group was, 11.2% versus 12.6% in the controls (Table 3). In the study group, mean pack-years was 12±8 years and, this ratio was 15±10 years in the control patients.

When the study and control groups were compared for ever smoking status, the number of smoker patients was higher in the control group, but this difference was not statistically significant (p>0.05). Regarding current smoking status, no patient in the study group was currently smoking, while 7.5% of the control patients were current smokers (p<0.05) (Table 3).

Discussion

In this study, we could not find a relationship of statistical significance between cigarette smoking and the development of pulmonary metastatic disease among women with breast cancer. The number of smoker patients was higher in the control group who had primary breast cancer without pulmonary metastasis than in the study group. On the other hand, other organ involvement was significantly higher in the control group as compared to the patients in the study group.

Smoking leads to important changes in the lung, including increased permeability and altered local immune function and is associated with changes in the incidence and natural history of a broad variety of lung diseases (11,12). Smoking causes mild lung injury and, in animal models of cancer, it has been shown that lung injury from a variety of causes, such as hyperoxia, radiation and bleomycine exposure, increases the likelihood of pulmonary metastatic disease (10).

Scanlon suggested that all tumor types expand in the same way. The cells from a primary tumor follow the less resistant way along the basal membrane of the interstitial compartment and enter the systemic circulation via the interstitial tissue. While most of the tumor cells die in this travel, a small group survives. It is possible that the effect of smoking on metastasis is not limited to the lung. Smoking has systemic effects that could affect tumor defense mechanisms external to the lung. For example, the number of circulating natural killer cells is reversibly decreased in active smokers. Smoking also affects platelet function and coagulability, factors that are believed to play a role in the body's defense against tumor cells lodged within capillary beds (13).

Most of the primary cancers and especially breast cancer in women, for reasons which are not clear, metastasize to the lung.

The studies performed among women with breast cancer suggested that cigarette smoking is a risk factor for the development of metastatic pulmonary disease (8,9).

In contrast to our study, Murin et al. found that 24.1% of their patients with pulmonary metastases and 15.3% of their control patients were ever-smokers. Based on these results, these authors suggested that smoking increased the development of pulmonary metastases in breast cancer patients (8).

Scanlon et al also, based on their series of 835 women diagnosed as primary malignant unilateral breast cancer, stated that, smoking was a risk factor for the development of pulmonary metastases in female patients with primary breast cancer (9).

In contrast to these two reports, we were not able to establish a statistical difference between cigarette smoking and the development of pulmonary metastatic disease in breast cancer in our study. In fact, smoking prevalence was higher in the control group than in the study group. The reason for why smoking prevalence was high in the control group may

be explained by the higher number of current smokers.
In our study, we were also unable to establish any relationships between development of pulmonary metastasis and different treatment modalities in relation to smoking.
Other lifestyle factors such as diet and physical activity may confound the relationship between smoking and metastatic disease (14). We were not able to investigate the effect of these factors in this study.
The phenomenon of an adverse impact of cigarette smoking on the course and outcome of cancer may not be limited to breast cancer, in that smoking has been suggested as a predictor of a more lethal course for other cancers as well (15). The relationship between smoking and cancer outcome deserves further studies.
Primary tumor factor (T factor) and nodal metastasis factor (N factor) are the most important factors for determination of risk of metastasis and of prognosis in breast cancer (16). These factors could not be taken into account in our study because of the defects in the patients' follow-up files. This was one of the weak points of this study. Due to this lack of follow-up information, a multivariate analysis could not be performed and also it has not been possible to evaluate other organ metastasis in follow-ups.
In conclusion, no statistical difference was found between cigarette smoking and the development of pulmonary metastatic disease among women with breast cancer in this study study. An inverse relationship was found between pulmonary metastasis and other organ involvement. There were more nonsmoker patients in the study group as compared to the control patients, so we were not able to state that smoking is a risk factor for pulmonary metastatic disease. Systemic effects of smoking, rather than localized pulmonary effects may play a role in influencing the course of breast and other cancers and confounding by unrecognized smoking-associated factors cannot be excluded. The effect of smoking on the natural history of breast cancer and other nonpulmonary malignancies warrants further investigations.

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