Cigarette Smoking and Malignant Melanoma

Prognostic Implications

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In a prospective study of 178 patients with malignant melanoma, a subset of 33 patients (18.5%) was identified to be at significantly higher risk for developing metastatic disease based on history of cigarette smoking. Patients in this high-risk group (current smokers with a >15 pack-years of smoking history) had two-year disease-free survival rates of 74.2%, versus 92.3% for the remaining patients (p = 0.008). A possible explanation of this phenomenon is that chronic smoking diminishes host defense mechanisms and results in an adverse effect on the biologic behavior of established malignant melanomas.

INTRODUCTION

Cigarette smokers have been shown to be more likely to develop certain malignancies and to have poorer prognoses compared to non-smokers.[1] Such smoking has also been shown to result in significant alterations in immunologic function,[2-4] which may play a role in aggressiveness of malignant neoplasms. This study was designed to determine whether cigarette smoking influences the potential of malignant melanomas to metastasize.

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MATERIALS

During the years 1972 through 1980, histories of cigarette smoking from 178 patients with primary cutaneous malignant melanomas were prospectively gathered by the Melanoma Cooperative Group of the New York University Medical Center. All of these patients were examined for metastases at regular intervals after surgical ablation of their primary lesions. Evidence for distant spread of the malignancies (nodal or visceral) was based on clinical examination and laboratory study. Since almost 80% of the recurrences in our study appeared in the first 24 months following locally definitive surgery, a two-year metastasis-free rate was used in the calculations described below.

t-Test comparisons and chi-square analyses were used to evaluate differences between observed and expected values.[5] Life-table analysis by the method of Kaplan and Meier[6] was used for deriving metastatic (nodal or visceral) disease-free rates. Comparisons of life-table disease-free curves were made by the Mantel test.[7]

RESULTS

Of the 178 patients in this study, 48 (27%) were currently cigarette smokers, 68 (38.2%) were former smokers, but not smokers currently, and 62 (34.8%)

Table 1
Attributes and Prognoses of Patients with Malignant Melanomas Related to Histories of Smoking

	High Risk*	Low Risk**	*p* Value of Difference
Number of patients	33 (18.5%)	145 (81.5%)	—
Number of metastases	8 (24%)	11 (8%)	0.014
Two-year disease-free survival after surgical ablation of primary lesions	74.2%	92.3%	0.008
Thickness of lesion	2.04 ± 1.87 mm	1.60 ± 1.40 mm	0.28
Age	50.1 ± 12.6 years	49.9 ± 16.1 years	0.9
Sex			
Male	19 (55.9%)	80 (55.2%)	0.6
Female	14 (44.1%)	65 (44.8%)	

* Current smokers with histories of more than 15 pack-years.

** Non-smokers, former smokers, and current smokers with histories of less than 15 pack-years.

had never smoked. Nineteen (10.7%) of the 178 patients developed metastases within the period of this study.

The patients were divided into a high-risk group (those who were currently smokers and had histories of more than 15 pack-years* of smoking) and a low-risk group (non-smokers, former smokers, and current smokers with histories of less than or equal to 15 pack-years of smoking). The high-risk group consisted of 33 (18.5%) of the 178 patients; the low-risk group, of 145 (81.5%). There were 19 instances of metastases in all. However, while only 18% of the patients fell into the high-risk group, 8 (42%) of the recurrences occurred in this subset. In contrast, the low-risk group, comprising 81% of the patients, had only 11 (58%) of the metastases. This difference in "expected versus observed metastases" in the two groups was statistically significant ($p = 0.014$). Life-table analysis showed a two-year metastatic-disease-free rate of 74.2% for patients in the high-risk group, compared to 92.3% for low-risk patients ($p = 0.008$). The mean thickness of lesions for high-risk and low-risk patients was 2.04 ± 1.87 mm and 1.60 ± 1.40 mm, respectively. Although the high-risk patients had thicker lesions than those in the low-risk group, this difference was not statistically significant ($p = 0.28$) and could not explain the difference in prognosis found in the two groups (Table 1). No significant differences were found between the high-risk and low-risk groups with respect to age (50.1 vs. 49.6 years) or sex (55.9% females vs. 55.2% males). No statistically significant difference in prognosis was found between absolute non-smokers and former smokers.

* A pack-year is defined as smoking one pack of cigarettes per day for one year.

DISCUSSION

It is known that cigarette smokers are more likely to develop malignant neoplasms than are non-smokers. They are at greater risk for development of carcinomas of the lungs, oropharynx, esophagus, and bladder.[1] Shaw et al.[8] have shown that malignant melanomas metastasize with greater frequency in men who smoke than in men who do not smoke. Holt et al.[2] have presented evidence suggesting that the increased incidence of infection in smokers may be related to impaired immunologic mechanisms. The propensity for more rapid growth of malignant neoplasms in smokers may also be related to alterations in the immune system. Chretien[3] has shown that in both experimental animals and man chronic inhalation of tobacco smoke leads to significant changes in cellular and humoral immunity. Mice exposed daily to tobacco smoke develop an initial increase in reactivity of lymphocytes to phytohemagglutinin in vitro and increased lymphocyte cytotoxicity specific to malignancies. These changes

are seen only during the first 4 to 10 weeks of exposure to cigarette smoke. In mice continuously exposed to cigarette smoke for longer than 10 weeks, lymphocyte reactivity to phytohemagglutinin in vitro declines, lymphocyte cytotoxicity diminishes, and the number of innocula of malignant cells that survive and grow is greater compared to control groups. In humans, studies of the effect of chronic inhalation of cigarette smoke on cellular immunity have been limited to measurement of the effects of reactivity of lymphocytes to phytohemagglutinin and peripheral T-cell levels.[3] It has been found that in adults with less than a 20 pack-year history of smoking, reactivity of lymphocytes to phytohemagglutinin and peripheral blood T-cell levels are higher than in age-matched controls.[3] In those with a greater than 20 pack-year history, reactivity of lymphocytes to phytohemagglutinin declines, although peripheral blood T-cell levels remain elevated.[3] In animals and humans with shorter times of exposure to cigarette smoke (i.e., less than a 20 pack-year history), the changes in reactivity of lymphocytes to phytohemagglutinin were found to be reversible. In animals and humans with prolonged exposure to cigarette smoke in which decreased reactivity of lymphocytes to phytohemagglutinin had occurred, cessation of smoking did not lead to reversal of the immune deficiency. The mechanisms involved in the initial increase in cellular immunity associated with inhalation of tobacco smoke are not known. Chretien[3] postulates that the subsequent decline in immunity upon prolonged exposure to cigarette smoke may be due to exhaustion of the immune system. He also suggests that metastatic spread of disease may be enhanced in this manner.

Ferson et al.[4] have shown that, in age- and sex-matched smokers and non-smokers who have malignant melanomas, the natural killing activity of blood leukocytes in both normal subjects and patients with malignant melanomas who smoke is significantly lower against cells from malignant melanomas in culture than is activity of leukocytes obtained from non-smokers. Smokers were also shown to have lower levels of IgG and IgA in their sera compared to levels in non-smokers. These results also suggest a possible role of smoking in decreasing immune surveillance.

In summary, our findings indicate an increased risk of metastases in patients with malignant melanomas who currently are smokers with greater than 15 pack-year histories compared to those with less than or equal to 15 pack-year histories, former smokers, and non-smokers. These findings also relate to immunologic theories of protective surveillance. They indicate that alterations in the immune system may play a significant role in the potential for metastases in patients with malignant melanomas who have been and continue to be heavy smokers of cigarettes.

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