

## INFLUENCE OF CIGARETTE SMOKING ON THE EFFICACY OF RADIATION THERAPY IN HEAD AND NECK CANCER

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**Abstract Background.** Smoking is a risk factor for several cancers and may also limit the efficacy of treatment. In this study, we evaluated the influence of cigarette smoking during radiation therapy on the efficacy of treatment in patients with head and neck cancer.

**Methods.** Using a questionnaire, we obtained information on smoking behavior at base line and weekly during therapy in 115 patients with head and neck cancer who were treated with radiation therapy with or without fluorouracil. The side effects of therapy were evaluated weekly, and response was assessed 13 weeks after treatment was completed. The main outcomes measured were treatment response and survival.

**Results.** The prognostic variables were similar among the patients who smoked and those who did not smoke during treatment. The 53 patients who continued to smoke during radiation therapy had a lower rate of complete response (45 percent vs. 74 percent,  $P = 0.008$ ) and poorer two-year survival (39 percent vs. 66 percent,  $P = 0.005$ ) than the 62 patients who did not smoke or who had quit be-

fore treatment. Among the nonsmoking patients, mortality was influenced by the length of time between quitting and treatment, with a risk reduction (relative to that for patients who continued to smoke) of 40 percent for patients who had quit less than 12 weeks before diagnosis and of 70 percent for patients who had quit more than 1 year before diagnosis. After adjustment for other variables with proportional-hazards regression analysis, smoking remained an independent prognostic factor ( $P = 0.002$ ), with a relative risk of 2.5 (95 percent confidence interval, 1.4 to 4.4) favoring the patients who abstained from smoking. The results could not be explained by the type of chemotherapy received, the presence of coexisting morbid conditions, differences in the side effects of radiation, or the number of interruptions of treatment.

**Conclusions.** Patients with head and neck cancer who continue to smoke during radiation therapy have lower rates of response and survival than patients who do not smoke during radiation therapy. (N Engl J Med 1993; 328:159-63.)

CIGARETTE smoking is an important risk factor for the development of squamous-cell cancers of the head and neck.<sup>1,2</sup> There is also evidence that patients with other forms of cancer who have a history of smoking have more advanced disease at the time of diagnosis than nonsmokers,<sup>3,4</sup> and that smokers with cancer have a worse prognosis than nonsmokers.<sup>4-8</sup> In one study, patients with small-cell lung cancer who continued to smoke during combination therapy had a poorer prognosis than those who did not smoke during therapy, regardless of their previous smoking habits.<sup>9</sup> These results, however, were not confirmed in a subsequent study.<sup>10</sup> Stevens et al. reported that the survival of patients with head and neck cancer who continued to smoke after diagnosis was poorer than that of patients who quit smoking at the time of diagnosis.<sup>11</sup>

We hypothesized that smoking during radiation therapy might influence the response to treatment in patients with squamous-cell cancer of the head and neck. We were also interested in learning whether smoking during radiation therapy would influence the short-term side effects of therapy, as has radiation therapy given according to an accelerated fractionation schedule.<sup>12</sup> To address these questions, we studied the smoking habits of patients while they received

radiation therapy for locally advanced cancer of the oral cavity, oropharynx, hypopharynx, and larynx. These patients were enrolled in a randomized trial in which fluorouracil or placebo was administered for 72 hours during the first and third weeks of radiation therapy. Several indexes of side effects were measured, and information on smoking was obtained weekly during therapy by an interviewer-administered questionnaire. The results suggest that patients with head and neck cancer who continue to smoke during radiation therapy are less likely to respond to therapy and have a lower rate of survival than patients who do not smoke during treatment.

### METHODS

#### Study Patients and Treatment

The study subjects were 115 consecutive patients of a total of 175 with histologically confirmed localized stage III or IV (according to the American Joint Committee on Staging classification) squamous-cell carcinoma of the head and neck (oral cavity, oropharynx, hypopharynx, and larynx) who had entered a randomized trial of treatment with radiation and fluorouracil or placebo. These 115 patients were seen at one of the two institutions at which the treatment study was conducted. To be eligible for the study, the patients had to have normal renal and hepatic function, normal blood counts, an Eastern Cooperative Oncology Group performance status of  $\leq 2$ , a serum albumin concentration of  $\geq 35$  g per liter, and no other active cancer. All patients were treated with external-beam radiation with single daily fractions of 200 rad (equivalent to 200 cGy) to large fields five days per week for five weeks (total, 5000 rad) followed by a boost of 1600 rad over a period of eight days. The treatment thus delivered a total dose of 6600 rad in 33 fractions over a period of 6½ weeks. During the first and third weeks of treatment, the patients assigned to receive fluorouracil were given 1.2 g per square meter of body-surface area per day for 72 hours as a continuous infusion, starting 6 hours after the first dose of radiation; the other patients received a saline infusion.

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The study was approved by the local institutional review board, and all patients gave written informed consent.

### Assessment of Smoking Behavior, Side Effects, and Response

All patients who participated in this study were seen by the same interviewer and completed a smoking questionnaire at base line about smoking status, smoking history, and history of alcohol intake. They also completed a separate questionnaire each week during therapy, which ascertained the average number of cigarettes smoked each day during the preceding week. All patients were also seen weekly by the radiation oncologist for a general evaluation and by the trial nurse coordinator to evaluate side effects during treatment and for four weeks after treatment. Patients who admitted smoking at least one cigarette during the 6½ weeks of radiation therapy were classified as smokers, and those who denied smoking during treatment were classified as abstainers. Side effects were assessed weekly with several scales, including the World Health Organization (WHO) stomatitis and skin-toxicity indexes (five-point scales in which side effects are classified as ranging from absent to severe),<sup>13</sup> and by monitoring body weight, serum albumin levels, and the Eastern Cooperative Oncology Group performance status (a five-point scale in which the patient's ability is classified as ranging from normal to severely impaired).<sup>14</sup>

The response of the tumor was determined 13 weeks after the completion of radiation therapy, with histologic confirmation of residual disease that was identified clinically. Patients were classified as having a complete response (no clinical evidence of disease) or no response (less than a complete response). The patients were then followed at regular intervals according to a prescribed schedule.

### Statistical Analysis

The chi-square test was used to compare proportions. Means were compared with Student's *t*-test. The weekly side-effects scores were compared with repeated-measures analysis of variance. Survival curves were calculated according to the life-table method and were compared with use of the log-rank test.<sup>15</sup> Proportional-hazards regression analysis was used to adjust the observed smoking effect for other important potential prognostic factors and to determine the independent influence of these other variables on the prognosis, expressed as the relative risk at 18 months.<sup>16</sup> This relative risk was computed from the exponential of the  $\beta$  coefficient in the regression model.

## RESULTS

Among the 115 patients, 62 reported that they did not smoke during radiation therapy and were classified as abstainers. Of these 62 abstainers, 4 (6 percent) had never smoked, 26 (42 percent) had quit more than 1 year before the diagnosis, and 32 (52 percent) had quit less than 12 weeks before the diagnosis. None of the patients had quit between 12 weeks and 1 year before the diagnosis. Fifty-three patients smoked at least one cigarette during radiation therapy and were classified as smokers. Tumor response, side effects, and survival could be evaluated in all patients.

Tables 1 and 2 show the characteristics of the two groups at base line. The groups were well balanced with respect to sex, age, body weight, performance status, serum albumin and hemoglobin concentrations, tumor stage, node stage, disease stage, and primary site. The groups were also well balanced according to the treatment they received (fluorouracil or placebo). The mean ( $\pm$ SD) number of pack-years smoked was  $55 \pm 28$  in the group that abstained from

**Table 1. Base-Line Characteristics of the Patients with Head and Neck Cancer Treated with Radiation and Fluorouracil or Placebo, According to Smoking Status.\***

CHARACTERISTIC	SMOKED (N = 53)	DID NOT SMOKE (N = 62)
Treatment group (no.)		
Fluorouracil	26 (49)	31 (50)
Placebo	27 (51)	31 (50)
Sex (no.)		
Male	44 (83)	49 (79)
Female	9 (17)	13 (21)
Age (yr)	61 $\pm$ 9	62 $\pm$ 11
Weight (kg)	69 $\pm$ 14	72 $\pm$ 14
Serum albumin (g/liter)	41 $\pm$ 5	42 $\pm$ 3
Hemoglobin (g/liter)	144 $\pm$ 15	142 $\pm$ 15
ECOG performance status†	0.8 $\pm$ 0.1	0.8 $\pm$ 0.1

\*Plus-minus values are means  $\pm$ SD. Percentages are given in parentheses.

†ECOG denotes Eastern Cooperative Oncology Group. On this scale a score of 0 indicates that the patient is fully active without symptoms; a score of 1, the patient is restricted from strenuous activity; a score of 2, the patient is ambulatory more than 50 percent of waking hours but unable to carry out any work; a score of 3, the patient is confined to bed or a chair more than 50 percent of waking hours and has a limited ability to take care of himself or herself; and a score of 4, the patient is completely disabled and confined to bed or a chair.

smoking during treatment and  $66 \pm 30$  in the group that continued to smoke ( $P = 0.46$ ).

Among the 53 patients who continued to smoke during radiation therapy, only 24 (45 percent) had a complete response, as compared with 46 of the 62 patients (74 percent) who abstained from smoking ( $P = 0.008$ ). The two-year survival rate was 66 percent in the group that did not smoke, as compared with 39 percent in the group that smoked ( $P = 0.005$ ) (Fig. 1). The median survival was 30 months in the group that did not smoke and 16 months in the group that smoked.

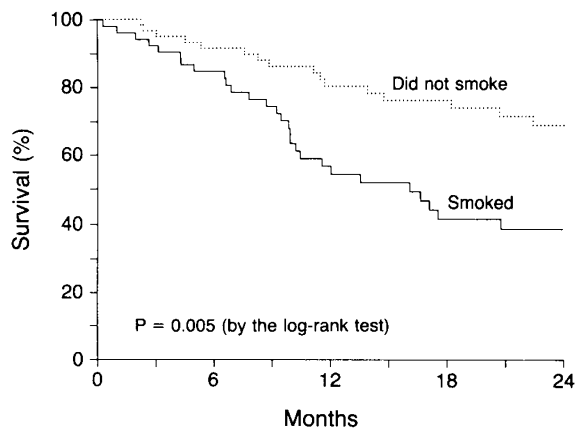
To determine whether the superior results among

**Table 2. Base-Line Characteristics of the Head and Neck Cancers in the Study Patients, According to Smoking Status.\***

CHARACTERISTIC	SMOKED (N = 53)	DID NOT SMOKE (N = 62)
	<i>number (percent)</i>	
Site		
Oral cavity	7 (13)	8 (13)
Oropharynx	23 (43)	31 (50)
Hypopharynx	5 (9)	9 (15)
Larynx	18 (34)	14 (23)
Tumor stage		
T1	4 (8)	7 (11)
T2	12 (23)	15 (24)
T3	29 (55)	38 (61)
T4	8 (15)	2 (3)
Node stage		
N0	12 (23)	20 (32)
N1	16 (30)	13 (21)
N2	14 (26)	20 (32)
N3	11 (21)	9 (15)
Disease stage†		
III	23 (43)	33 (53)
IV	30 (57)	29 (47)

\*Because of rounding, not all categories total 100 percent.

†Stage III cancer is T3, N0 or T1-3, N1; and stage IV (localized) is T4, N0 or T any stage, N2-3.



GROUP	0	6	12	18	24
Smoked	53	49	43	36	24
Did not smoke	62	58	51	44	40

Figure 1. Survival among Patients with Head and Neck Cancer, According to Whether They Continued to Smoke or Abstained from Smoking during Radiation Therapy.

The numbers beneath the graph are the numbers of patients in each group who were at risk at each time point.

the patients who did not smoke applied both to those who had quit smoking less than 12 weeks before the diagnosis and to those who had quit more than 1 year before the diagnosis, we calculated the survival of these two groups and their mortality relative to that of the smokers. The difference in survival (Fig. 2) was statistically significant ( $P = 0.005$ ) and was related to the length of time between quitting and treatment. As compared with the smokers, the risk of mortality 18 months after treatment was 0.4 (95 percent confidence interval, 0.2 to 0.7) for the entire group of abstainers, 0.3 (95 percent confidence interval, 0.1 to 0.7) for patients who had not smoked for more than a year before the diagnosis, and 0.6 (95 percent confidence interval, 0.3 to 1.0) for patients who had quit smoking less than 12 weeks before the diagnosis. The risk of mortality was not significantly different in the two subgroups of nonsmokers ( $P = 0.31$ ).

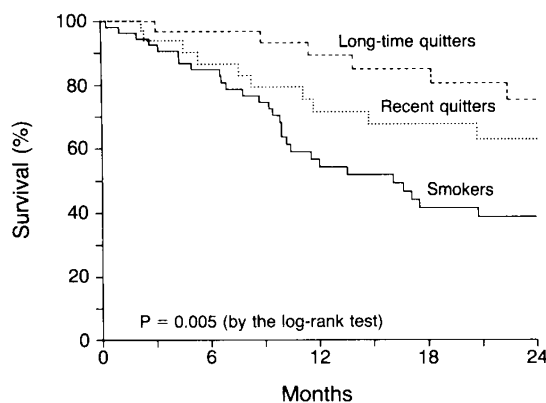
Since the groups being compared were not allocated according to their randomization assignment, we were concerned that the observed results might be related to other factors. The main factors of concern were the side effects (smokers could have had more severe side effects, leading to more frequent interruptions of either radiation therapy or chemotherapy and thus compromising the effectiveness of treatment), coexisting conditions (smokers might have had other morbid conditions that contributed to their poorer prognosis), and the possibility that the distribution of other prognostic variables was skewed, favoring the group of patients that did not smoke during treatment.

The mean ( $\pm$ SD) number of days required for the completion of radiation therapy was almost identical in the two groups:  $45 \pm 5$  for the smokers and  $46 \pm 5$  for those who did not smoke. There were six interruptions of radiation therapy among patients who smoked and

three among patients who abstained, and four interruptions of chemotherapy among the smokers as compared with two among those who abstained. Although these differences in the frequency of interruptions of treatment could be important if the trend continued in a larger study group, it is unlikely that the number of these events accounts for the magnitude of the differences in therapeutic outcomes. Figure 3 shows the weekly scores of the WHO stomatitis and skin-toxicity indexes for the two groups; the differences in the scores were not significant.

Of the 31 deaths among the smokers, 29 were related to cancer, as compared with 21 of the 25 deaths among the patients who abstained from smoking during treatment; thus, the poorer survival among the smokers is not explained by an excess number of deaths from coexisting morbid conditions. The six deaths that were not related to cancer were attributed to second cancers (two patients), myocardial infarction (three patients), and pneumonia (one patient).

Included in the regression model for survival were age, tumor stage, tumor site, treatment group (fluorouracil or placebo), and smoking status during treatment. On the basis of proportional-hazards regression analysis, smoking during radiation therapy emerged as the only significant variable independently associated with survival ( $P = 0.002$ ), with a relative risk of 2.5 (95 percent confidence interval, 1.4 to 4.4) in favor of those who did not smoke during treatment. We also examined all potential interactions of the variables contained in the model. No interaction terms were significant, and with the introduction of the interaction terms, smoking remained an independent predictor of survival, with a relative risk of 2.3 (95 percent confidence interval, 1.2 to 4.2;  $P = 0.008$ ) in favor of those who did not smoke during radiation therapy.



GROUP	0	6	12	18	24
Smokers	53	49	43	36	24
Recent quitters	32	28	24	20	18
Long-time quitters	30	30	27	24	22

Figure 2. Survival among Patients with Head and Neck Cancer, According to Whether They Continued to Smoke during Radiation Therapy, Had Quit Smoking Less Than 12 Weeks before Diagnosis, or Had Not Smoked for at Least 1 Year before Diagnosis.

The numbers beneath the graph are the numbers of patients in each group who were at risk at each time point.

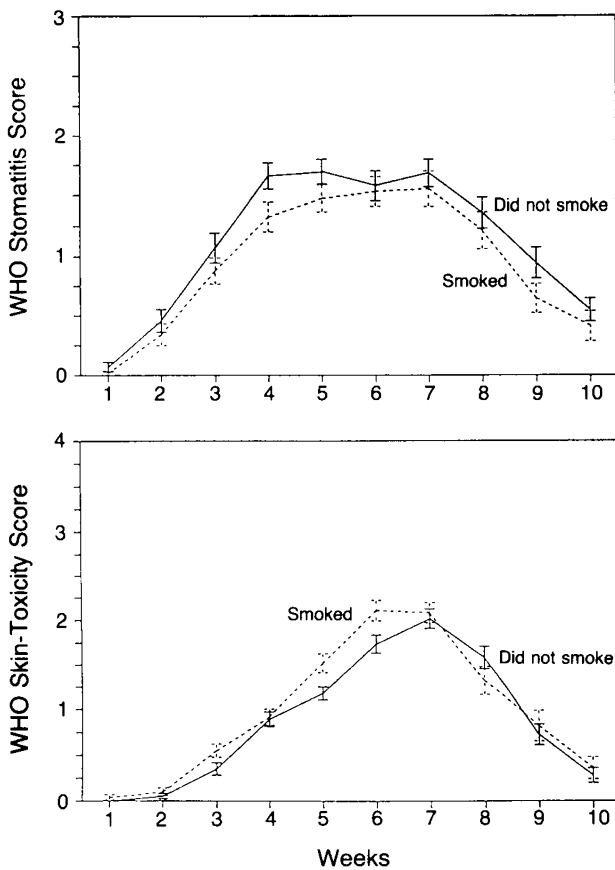


Figure 3. The Mean ( $\pm$ SD) Weekly WHO Stomatitis and Skin-Toxicity Scores among the Patients Who Continued to Smoke during Radiation Therapy and Those Who Did Not Smoke during Treatment.

According to the WHO stomatitis index, a grade of 0 indicates no stomatitis; a grade of 1, soreness and erythema; a grade of 2, erythema, ulcers, and an ability to eat solids; a grade of 3, ulcers and an ability to eat only a liquid diet; and a grade of 4, a total inability to eat. According to the WHO skin-toxicity index, a grade of 0 indicates no side effects; a grade of 1, erythema; a grade of 2, dry desquamation, vesiculation, and pruritus; a grade of 3, moist desquamation and ulceration; and a grade of 4, exfoliative dermatitis and necrosis requiring surgical intervention.

When the variables related to alcohol intake during treatment and smoking history (based on the number of packs smoked per day and the number of years of smoking) were entered into the model, the number of years of smoking was identified as an additional factor associated with survival (relative risk, 1.0 per year of smoking;  $P = 0.033$ ).

### DISCUSSION

Among the patients with locally advanced stage III or IV squamous-cell cancer of the head and neck who were treated with radiation therapy (with or without fluorouracil), those who admitted continuing to smoke during therapy had a lower rate of response and survival than those who claimed to have abstained from smoking during treatment. The number of years spent smoking was also a significant prognostic variable.

The effect of smoking could not be explained by an imbalance of patient-related and tumor-related characteristics at base line and, in a regression model, was found to be independent of other known prognostic variables and of chemotherapy. It is possible that the difference in survival between the smokers and those who abstained from smoking during treatment was related to other unknown variables. For example, the intake and serum concentrations of nutrients such as beta carotene and vitamin A, which may protect against the development of epithelial cancers, are reduced among smokers,<sup>17-19</sup> and the treatment of head and neck cancer with analogues of vitamin A reduces the incidence of second cancers.<sup>20</sup> However, all but two of the deaths from cancer were related to the primary tumor, rendering this explanation of the difference in survival between the two groups unlikely. Since the smoking data were obtained prospectively, before we had any knowledge of the patients' response, we can exclude bias based on knowledge of outcomes as a factor in the ascertainment of smoking behavior during therapy. Conversely, those assessing tumor response were unaware of the results of the smoking questionnaires.

Although several studies have examined the association between tumor prognosis and smoking history, smoking behavior during cancer treatment has been studied only twice. Among patients with small-cell lung cancer who were treated with combined therapy in one study, those who did not smoke during therapy survived longer on average than those who continued to smoke.<sup>9</sup> The results were similar among the subgroups that received chemotherapy only. In the other study, no difference in survival attributable to smoking behavior was found in patients with small-cell lung cancer who were treated with combination chemotherapy.<sup>10</sup>

Several biologic mechanisms could theoretically contribute to the results of our study. Smokers have lower levels of natural-killer-cell activity in peripheral blood than nonsmokers,<sup>21,22</sup> and in mice exposure to cigarette smoke reduces cell-mediated immunity and is associated with accelerated tumor progression.<sup>23</sup> Cigarette smoking is associated with increased blood carboxyhemoglobin concentrations, which cause a leftward shift of the hemoglobin-oxygen dissociation curve. This could produce relative tissue hypoxia, which interferes with the oxygen-dependent effects of radiation.<sup>24</sup>

The smoking behavior reported by the patients we studied was not validated biochemically. However, we do not believe that the veracity of the smoking responses elicited by the questionnaire is crucial for the interpretation of this study, since it is unlikely that prognosis would be related to statements about smoking behavior independently of the behavior itself. This factor would be of greater concern if no relation between smoking status and outcome had been found. If the patients misled investigators about their smoking habits, it is likely that the direction of this effect would

be to include smokers in the group that abstained from smoking, since it is less likely that those who did not smoke during treatment would claim to have smoked. This potential bias in the reporting of smoking behavior suggests that our estimates of the effect of smoking on tumor response and survival are likely to be conservative. Nevertheless, it would be desirable to obtain confirmation of smoking behavior in future studies.

We conclude that patients with head and neck cancer who continue to smoke cigarettes during therapy have a reduced response to radiation therapy. These results should encourage therapists to advise patients to stop smoking, and investigators should be aware that smoking behavior may be an important confounding variable in clinical trials of radiation therapy in patients with head and neck cancer.

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