The Impact of Smoking Status, Disease Stage, and Index Tumor Site on Second Primary Tumor Incidence and Tumor Recurrence in the Head and Neck Retinoid Chemoprevention Trial

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The Impact of Smoking Status, Disease Stage, and Index Tumor Site on Second Primary Tumor Incidence and Tumor Recurrence in the Head and Neck Retinoid Chemoprevention Trial[1]

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Abstract

Second primary tumors (SPTs) develop at an annual rate of 3–7% in patients with head and neck squamous cell cancer (HNSCC). In a previous Phase III study, we observed that high doses of 13-*cis*-retinoic acid reduced the SPT rate in this disease. In 1991, we launched an intergroup, placebo-controlled, double-blind study to evaluate the efficacy of low-dose 13-*cis*-retinoic acid in the prevention of SPTs in patients with stage I or II squamous cell carcinoma of the larynx, oral cavity, or pharynx who had been previously successfully treated with surgery, radiotherapy, or both, and whose diagnoses had been established within 36 months of study entry. As of September 16, 1999, the Retinoid Head and Neck Second Primary (HNSP) Trial had completed accrual with 1384 registered patients and 1191 patients randomized and eligible. All of the patients were followed for survival, SPT development, and index cancer recurrence. Smoking status was assessed at study entry and during study. Smoking cessation was confirmed biochemically by measurement of serum cotinine levels. The annual rate of SPT development was analyzed in terms of smoking status and tumor stage. As of May 1, 2000, SPTs have developed in 172 patients. Of these, 121 (70.3%) were tobacco-related SPTs, including 113 in the aerodigestive tract (57 lung SPTs, 50 HNSCC SPTs, and 6 esophageal SPTs) and 8 bladder SPTs. The remaining 51 cases included 23 prostate adenocarcinomas, 8 gastrointestinal malignancies, 6 breast cancers, 3 melanomas, and 11 other cancers. The annual rate of SPT development observed in our study has been 5.1%. SPT development related to smoking status was marginally significant (active *versus* never, 5.7% *versus* 3.5%; $P = 0.053$). Significantly different smoking-related SPT development rates were observed in current, former, and never smokers (annual rate = 4.2%, 3.2%, and 1.9%, respectively, overall $P = 0.034$; current *versus* never smokers, $P = 0.018$). Stage II HNSCC had a higher overall annual rate of SPT development (6.4%) than did stage I disease (4.3%; $P = 0.004$). When evaluating the development of smoking-related SPTs, stage was also highly significant (4.8% for stage II *versus* 2.7% for stage I; $P = 0.001$). Smoking-related SPT incidence was significant for site as well (larynx *versus* oral cavity, $P = 0.015$; larynx *versus* pharynx, $P = 0.011$). Primary tumors recurred at an annual rate of 2.8% in a total of 97 patients. The rate of recurrence was higher in patients with stage II disease (4.1% *versus* 2.2%, $P = 0.004$) as well as oral cavity site when compared with larynx ($P = 0.002$). This is the first large-scale prospective chemoprevention study evaluating smoking status and its impact on SPT development and recurrence rate in HNSCC. The results indicate significantly higher SPT rates in active smokers *versus* never smokers and significantly higher smoking-related SPT rates in active smokers *versus* never smokers, with intermediate rates for former smokers.

Introduction

HNSCC[3] is a major cause of worldwide cancer death, with more than 500,000 cases of head and neck cancer estimated in 2000. In the United States alone, 40,000 new cases are anticipated in the calendar year 2000 with ~12,500 deaths (1). Although surgery and radiotherapy are highly effective treatments for early-stage disease with cure rates ranging from 70 to 85% for stages I and II HNSCC, advanced disease (stage III, IV) remains difficult to control, with estimated 5-year survival rates of 30–40% (2, 3).

Head and neck cancer patients are at a significantly elevated risk for developing SPTs, regardless of initial treatment. SPTs have the greatest impact in patients treated for early-stage disease (stage I or II). Because surgery and radiation therapy are usually effective therapies in early-stage disease, a major cause

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[3] The abbreviations used are: HNSCC, head and neck squamous cell cancer; SPT, second primary tumor; 13cRA, 13-*cis* retinoic acid; CCOP, Clinical Community Oncology Program.

Table 1 Patient characteristics for randomized, eligible patients and those with available follow-up data

Total	1191	1127
Gender		
Male	942 (79.1%)	893 (79.2%)
Female	249 (20.9%)	234 (20.8%)
Race		
White	1085 (91.1%)	1024 (90.9%)
Black	49 (4.1%)	47 (4.2%)
Hispanic	41 (3.4%)	40 (3.5%)
Asian	7 (0.6%)	7 (0.6%)
Other	9 (0.8%)	9 (0.8%)
Age (yr)		
Median	62	62
<30	8 (0.7%)	8 (0.7%)
31–40	51 (4.3%)	51 (4.5%)
41–50	170 (14.3%)	159 (14.1%)
51–60	305 (25.6%)	290 (25.7%)
61–70	438 (36.8%)	414 (36.7%)
>71	219 (18.4%)	205 (18.3%)
Smoking status		
Never	160 (13.4%)	154 (13.7%)
Former, quit >1 yr	576 (48.4%)	540 (47.9%)
Current		
Quit <1 yr	214 (18.0%)	206 (18.3%)
Active	241 (20.2%)	227 (20.1%)
Prior treatment		
Surgery only	289 (24.3%)	273 (24.2%)
Radiation only	733 (61.5%)	701 (62.2%)
Both	163 (13.7%)	147 (13.0%)
Neither	6 (0.5%)	6 (0.6%)
Time to registration after diagnosis		
<1 yr	691 (58.0%)	646 (57.3%)
1–2 yr	317 (26.6%)	304 (27.0%)
2–3 yr	183 (15.4%)	177 (15.7%)

Table 2 Baseline cotinine levels by smoking status for randomized, eligible patients with follow-up data

	Active smoker	Quit ≤1 yr	Quit >1 yr	Nonsmoker
Analyzed	191 (84.1%)	174 (84.5%)	462 (85.6%)	124 (80.5%)
0–15 (ng/ml)	7 (3.2%)	106 (60.9%)	426 (92.1%)	119 (96.0%)
>15 (ng/ml)	184 (96.8%)	68 (39.1%)	36 (7.9%)	5 (4.0%)
Not analyzed	36 (15.9%)	32 (15.5%)	78 (14.4%)	30 (19.5%)
Total	227	206	540	154

of morbidity and mortality is the development of SPTs (4). Vikram (4) demonstrated in a careful retrospective analysis in 1983 that, after 3 years, the leading cause for cancer-related mortality in head and neck cancers is actually the development of SPTs.

Chemoprevention was defined by Sporn *et al.* (5) as an attempt to reverse, suppress, or delay carcinogenic disease progression to invasive cancer. This was based on extensive prior data from Wolbach and Howe linking Vitamin A deficiency with carcinogenesis in animals (6). In 1990, Hong *et al.* demonstrated that high-dose 13cRA (50–100 mg/m^2) was capable of preventing the development of SPTs in patients treated for squamous cell carcinoma of the head and neck (7). On additional follow-up, patients who received 1 year of high-dose 13cRA did not develop smoking-related malignancies *versus* those taking placebo. The effect of the retinoid lasted for ~2 years after completion of 13cRA, after which SPT rates were identical in both the 13cRA and placebo arms (8). However, patients treated with high-dose 13cRA endured substantial toxic effects, with the vast majority of patients requiring a dose reduction because of grade II or III cheilitis, conjunctivitis, or skin toxicities.

In 1991, we launched a randomized, placebo-controlled trial of daily low-dose (30 mg/day) 13cRA (isotretinoin) *versus* placebo in patients definitively treated with surgery or radiation therapy or both. In this study, patients with stage I and II head and neck cancer of the larynx, oral cavity, or pharynx were randomized to receive either low-dose 13cRA at 30 mg/day or placebo for 3 years followed by 4 years of observation. The primary end point of this study was to evaluate whether a daily low dose of 13cRA for 3 years prevents SPTs. The secondary end point was to qualitatively and quantitatively evaluate the toxicity of low-dose 13cRA given over the prolonged period of time of 3 years. This is an interim analysis of the study evaluating the impact of smoking status, stage, and site on SPTs.

Patients and Methods

This study was launched in November of 1991 and closed to new patient registration on June 30, 1999. Patients were registered on this trial through the Radiation Therapy Oncology Group, the University of Texas M. D. Anderson Cancer Center, the CCOP, the Southwest Oncology Group, and the Cancer and Leukemia Group B as well as the Texas Community Oncology Network, which later became part of the CCOP. Patients placed on this protocol were given a thorough head and neck examination prior to registration and randomization. Only those who were free of disease were eligible to be randomized. All of the patients were required to sign an informed consent form that was approved by both the institution's cooperative group and its institutional review board. Patients who were registered onto the study were blinded to a run-in period of 8 weeks, during which they all received placebos. The assumption is that most of the participants who manifest signs of poor compliance will do so early in the study (9–11). Depending on compliance measured at the end of the run-in period, the patients were either dropped from the study or randomized. The run-in compliance requirements included keeping clinic appointments, taking 75% of the study medication, and remaining disease-free. The length of the run-in was selected to give patients ample time to become accustomed to taking the study drug and making notations on their study calendars, but was not so long that the run-in lengthened the study excessively. Placebos were used to measure possible iatrogenic side effects, suggested by the consent form, which would disqualify the patient from study participation. Participation in this trial required patients to take either the study drug 13cRA or placebo for a total of 3 years followed by 4 years of follow-up. Patients were seen for evaluation at 3, 6, 9, 12, 16, 20, 24, 28, 32, and 36 months after randomization during the study. Neither the patient nor the physician/investigator was aware of which study agent was being taken. After completing treatment, patients were assigned to follow-up care at 6-month intervals for an additional 4 years.

Any patient noted to have an event, defined as either a possible tumor recurrence or SPT, was required to have tissue samples of both the primary tumor and either the recurrent tumor or the SPT, including all pertinent radiographic examinations forwarded to an End Point Review Committee at M. D. Anderson Cancer Center. The End Point Review Committee was chaired by a head and neck surgeon (H. G.). The criteria for classifying SPTs follow the Warren and Gates criteria (12). A new cancer of different histological type, one of identical his-

Table 3 SPT by site in randomized, eligible patients with available follow-up data ($n = 172$)

Site	*n* (%)
Lung	57 (33.1)
Oral cavity	26 (15.1)
Larynx	15 (8.7)
Pharynx	9 (5.2)
Esophagus	6 (3.5)
Bladder	8 (4.7)
Prostate	23 (13.4)
Colorectal	6 (3.5)
Breast	6 (3.5)
Kidney	2 (1.2)
Other	14 (8.1)

Table 4 Overall annual SPT rate in person-years including 95% confidence interval (CI) estimates by smoking status

	Overall (95% CI)	Smoking-related (95% CI)
Smoking status		
Current smokers	5.7% (4.6–7.2%) $^{74}/_{433}$[a]	4.2% (3.3–5.5%) $^{56}/_{433}$
Former smokers	4.9% (3.9–6.0%) $^{82}/_{540}$	3.2% (2.5–4.2%) $^{56}/_{540}$
Nonsmokers	3.5% (2.1–5.6%) $^{16}/_{154}$	1.9% (1.0–3.6%) $^{9}/_{154}$
Overall annual SPT rate	5.1% (4.3–5.8%) $^{172}/_{1127}$	3.5% (2.9–4.1%) $^{121}/_{1127}$
*P*s for comparing the SPT development by smoking groups		
Overall comparison	0.112	0.034
Pair-wise comparison		
Current *vs.* former smokers	0.233	0.121
Current *vs.* nonsmokers	0.053	0.018
Former *vs.* nonsmokers	0.181	0.110

[a] Number of events/patients.

tological type occurring more than 3 years after therapy of the primary tumor, or one separated from the initial primary tumor by more than 2 cm of clinically normal epithelium are all considered SPTs (12). A local recurrence was defined as any tumor of similar histology appearing within 2 cm or 3 years of the primary tumor. Cervical lymph nodes were classified similarly as either distant or regional recurrence. These guidelines as well as the clinical characteristics of the patient were used by the End point Committee to assign tumors as recurrence or SPT. Once determination of the event was made, the results of the committee decision were faxed to the central office of the respective cooperative group, which immediately informed the individual institution of the decision. Patients who had disease recurrence while on study were required to remain on the drug unless they were treated with systemic chemotherapy or clinically deteriorated to the point at which they were unable to continue on study. However, patients who developed SPTs had mandatory discontinuation of their investigational drug and were taken off study. Patients with grade II, III, or IV toxic effects had the drug held until such effects were lessened to grade 0 or 1. The drug dose was then reduced by 10 mg from the previous level and restarted.

The stratification criteria for randomization included the primary site of the tumor (index primary tumors of the larynx, oral cavity, and pharynx), tumor stage (stage I or II), and smoking status (current, former, or never smoker). Former smokers were defined as individuals who had successfully ceased smoking for at least 1 year at the time of study registration. Never smokers were defined as individuals who had <20 total cigarettes during their lifetime.

Smoking status was assessed by questionnaire and serum cotinine levels. The study was initially designed to test whether 13cRA could decrease by 50% the incidence rate of second primary cancers with 80% power. A planned interim analysis of this data were completed in November 1999. This did not meet the planned early-stopping criteria ($P = 0.001$). The overall objective of the head and neck SPT trial was to establish whether low-dose 13cRA given as long-term treatment was a useful chemopreventive agent for head and neck cancer, thereby defining a new standard of care for this patient population.

Statistical Considerations. Descriptive statistics were applied to summarize the distribution of variables. The SPT and recurrence rates were computed by person-years. Nonparametric averaging with a window of ± 1.5 years was used to compute the rate at a specific time. The log-rank test was used to compare the development of SPT or recurrence among various groups. All of the *P*s reported were based on two-sided tests.

Results

As of September 16, 1999, a total of 1384 patients were registered and 1191 patients randomized. A description of the randomized and eligible patients is listed in Table 1. For the 1191 patients randomized and eligible, a median follow-up of 36 months was available at the time of this analysis on May 2, 2000. Patients were registered through the Radiation Therapy Oncology Group [$n = 958$ (69.2%)], the University of Texas M. D. Anderson Cancer Center [$n = 176$ (12.7%)], the CCOP [$n = 135$ (9.8%)], the Southwest Oncology Group [$n = 69$ (5.0%)], the Cancer and Leukemia Group B [$n = 35$ (2.5%)], and the Texas Community Oncology Network [$n = 11$ (0.8%)]. Follow-up was available and current on the first 1127 of the 1191 randomized and eligible patients. Sixty-four cases were too early in their therapy or had insufficient data at the time of this analysis. The median and the upper quartiles of the follow-up time were 36 and 56 months, respectively. Table 2 shows baseline cotinine levels by smoking status for our patients. Generally, there was good agreement between cotinine levels and self-reporting in our study population. To validate the self-reporting smoking status, baseline serum cotinine level in 951 patients (84.4%) was analyzed and reported in Table 2. The cotinine level in 176 patients (15.6%) was not available mainly because of pending blood specimen or samples yet to be received and analyzed in batch samples. Among patients with available cotinine levels, 96.8% of the active smokers and only 4.0% of the nonsmokers had a cotinine level of greater than 15 ng/ml. For patients who quit smoking, 39.1% of patients who quit within 1 year and 7.9% of those who quit for >1 year had >15 ng/ml cotinine. Taking self-reporting smoking status as the gold standard and using 15 ng/ml as a cutoff point, we had a 96.8% sensitivity in active smokers and a 96.0% specificity in nonsmokers. The result was comparable with what was reported in the literature (13, 14). From these 1127 patients, a total of 276 end point determinations were identified for analysis. These included 172 SPTs and 97 cases of recurrent disease. The 172 second-primary cases included 14 cases that also had relapsed primary tumors. The sites of the SPTs are shown in Table 3. One hundred twenty-one (70.3%) of the SPTs were smoking-related (head and neck, lung, esophageal, and bladder cancers), whereas the remaining 51 (29.7%) were not. In this study thus far, 132 patients have been lost to follow-up and 24 patients have refused further treatment.

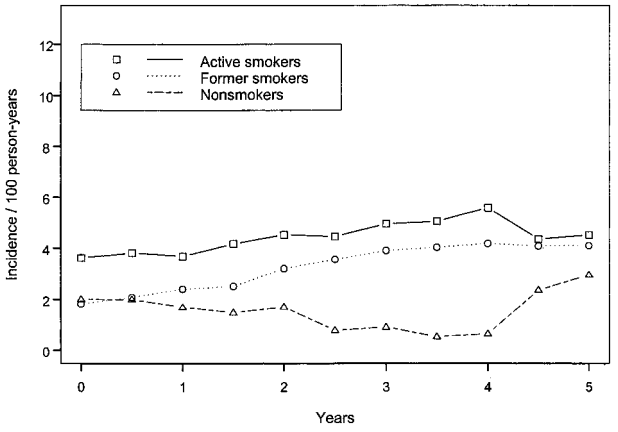

Fig. 1. Annual smoking-related SPT rate by smoking status.

Annual SPT Rate by Smoking Status. Table 4 lists the annual SPT rate by smoking status. In the study population, the overall annual SPT rate was 5.1%, with 172 cases of 1127 evaluable cases with adequate length of follow-up. The annual rate of smoking-related SPTs was 3.5% (121/1127). Although the overall comparison of the SPT development among the three smoking groups was not statistically significant (P = 0.112), the rates of developing smoking-related SPTs were significant by smoking status (P = 0.034). The highest individual rate of SPT development was seen in 5.7% (74/433) of current smokers *versus* the lowest rate of 3.5% (16/154) in nonsmokers. The difference was marginally significant (P = 0.053). Former smokers, on the other hand had an intermediate rate of 4.9% (82/540; Table 4). However, when one analyzes only the incidence of smoking-related SPTs, the difference was more striking. Statistically significant differences were observed among current, former, and never smokers (P = 0.034). The annual incidence of smoking-related SPTs among current smokers was 4.2% (56/433) *versus* a rate of only 1.9% in nonsmokers (9/154), and this was also statistically significant (P = 0.018; Table 4; Fig. 1). The incidence of smoking-related SPTs among former smokers was 3.2% and, when compared with current smokers, was not statistically significant (P = 0.121).

Annual SPT Rate by Site. When assessing individual disease sites and their annual SPT rates (Table 5), the SPT development was marginally significant (P = 0.060) among the three index primary tumor sites. The highest annual incidence of SPTs, 7.4% (28/124), was in those individuals who had an index primary pharyngeal cancer. However, this annual rate of smoking-related SPTs was only 5.1% (20/124). The site of lowest annual incidence of smoking-related SPTs was the larynx; the rate was 2.7% (57/665) with an overall annual SPT rate in larynx cancers of 4.5% (92/665). The oral cavity had intermediate rates of overall annual SPT (5.1%; 52/338) as well as smoking-related SPT (4.3%; 44/338). The overall comparison of the annual smoking-related SPT rate among the primary tumor sites was statistically significant (P = 0.012). The pairwise comparison was statistically significant when smoking-related SPT incidence in the larynx and the oral cavity were compared (P = 0.015) and when the larynx and pharynx smoking-related SPT rates were compared (P = 0.011). Fig. 2 compares the annual smoking-related SPT rates by site.

Annual SPT Rate by Disease Stage. Annual SPT rate by stage (Table 6) was strikingly higher in patients with stage II disease than it was in patients with stage I disease. This was more notable when one looks only at smoking-related SPT rates, in which an annual incidence of 4.8% was seen in patients with stage II disease (58/403) compared with only 2.7% annually in patients with stage I disease (63/724); this was highly statistically significant (P = 0.001; Fig. 3). The overall annual SPT rate by stage was also significantly higher in the stage II than in the stage I tumors at 6.4% (75/403) compared with 4.3% (97/724; P = 0.004; Fig. 4).

Table 5 Overall annual SPT rate in person-years by tumor site

	Overall (95% CI[a])	Smoking-related (95% CI)
Site		
Larynx	4.5% (3.7–5.5%) 92/665[b]	2.7% (2.1–3.5%) 57/665
Oral cavity	5.1% (3.9–6.7%) 52/338	4.3% (3.2–5.7%) 44/338
Pharynx	7.4% (5.1–10.8%) 28/124	5.1% (3.3–7.9%) 20/124
*P*s for comparing the SPT development by site		
Overall comparison	0.060	0.012
Pair-wise comparison		
Larynx *vs.* oral cavity	0.372	0.015
Larynx *vs.* pharynx	0.016	0.011
Oral cavity *vs.* pharynx	0.148	0.649

[a] CI, confidence interval.
[b] Number of events/patients.

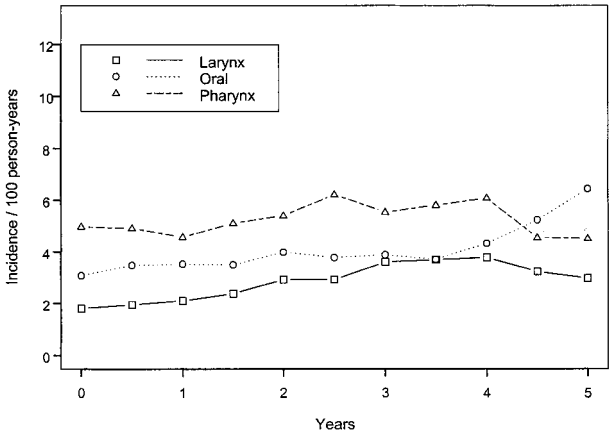

Fig. 2. Annual smoking-related SPT rate by site.

Table 6 Overall annual SPT rate in person-years by disease stage

	Overall (95% CI[a])	Smoking-related (95% CI)
Stage I	4.3% (3.5–5.2%) 97/724[b]	2.7% (2.1–3.5%) 63/724
Stage II	6.4% (5.1–8.1%) 75/403	4.8% (3.7–6.2%) 58/403
*P*s for comparing the SPT development by stage		
Stage I *vs.* stage II	0.004	0.001

[a] CI, confidence interval.
[b] Number of events/patients.

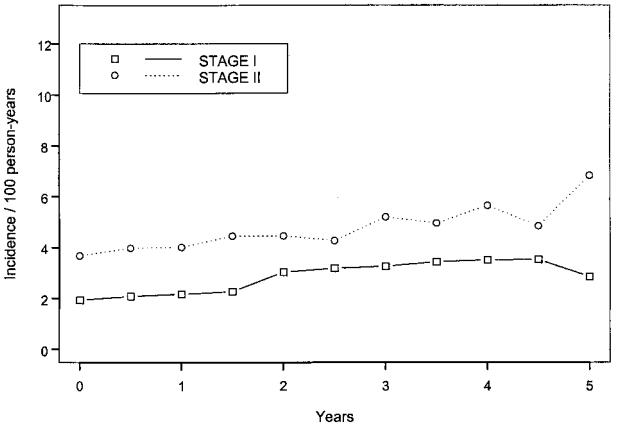

Fig. 3. Annual smoking-related SPT rate by stage.

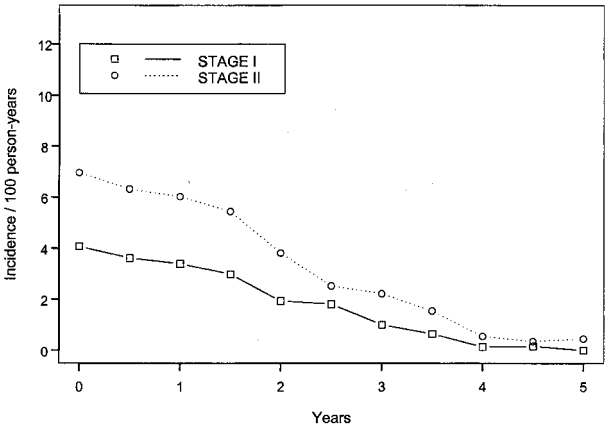

Fig. 5. Annual recurrence rate by stage.

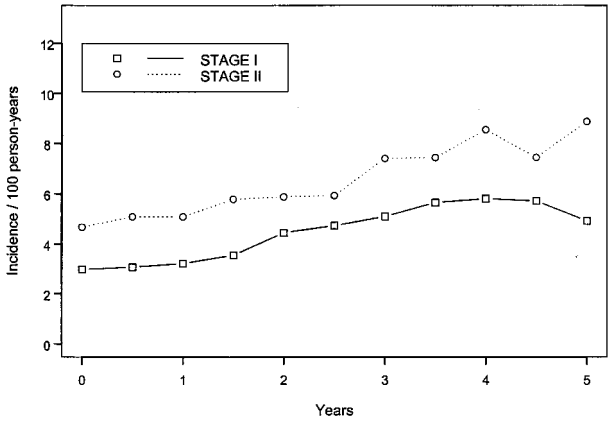

Fig. 4. Annual SPT rate by stage.

Overall Annual Recurrence Rate by Smoking Status, Site, and Disease Stage. The overall annual rate of primary tumor recurrence on this study was low at 2.8% (97/1127). Differences were seen in recurrence rates according to stratification criteria. Not surprisingly, the recurrence rate was significantly higher in patients with stage II disease (4.1% annually or 47/403 patients) than those with stage I disease (2.2% or 50/724; $P = 0.004$; Fig. 5). Recurrence rates were not significantly different in terms of smoking status; it was highest (3.4%) in current smokers, followed by, interestingly, nonsmokers (3.3%), and finally former smokers (2.3%). However, when recurrence rates were assessed by site, the highest incidence of recurrence (4.3%) was in oral cavity cancers (42/338), which was significantly higher than the recurrence rate for laryngeal cancers [annual rate, 2.1% (43/665); $P = 0.002$]. Patients with pharyngeal cancers had an intermediate annual rate of 3.2% (12/124).

Discussion

Analysis of these preliminary results from our trial demonstrates that smoking plays an important role in SPT incidence. The goal of the study, unlike the antecedent trial by Hong *et al.* (7) was to decrease SPT incidence in a population of patients treated with curative intent for early stage-disease. A concern of the previous Hong trial was that, despite a pronounced difference in SPT rates, given the fact that most patients died from primary tumor recurrence or metastasis, no impact was seen on survival. Here, we deliberately assayed a patient population with earlier-stage disease, for which SPT events are far more likely to be the ultimate determinants of survival. Although we recognize that results in early-stage head and neck cancer in terms of SPT incidence and smoking status are essentially reflections of early-stage disease, we believe that the SPT rates that we have reported in this article are in keeping with the rates reported in the literature for more advanced disease. Analysis of the data to date suggests that, in those individuals who develop smoking-related SPTs, continued smoking appears to portend a higher likelihood of tumorigenesis in the aerodigestive tract or in the bladder. This is not particularly surprising, because the etiology of the primary-index cancers in the 154 never smokers on this trial is unclear, and they represent a subpopulation of patients with head and neck cancer in which tobacco apparently plays little etiopathogenetic role. Recent data indicate that these cancers in nonsmokers may be caused by viruses such as human papillomavirus 16 and 18 (15, 16). Those data have essentially focused on the etiology of tonsillar and laryngeal cancers. The 154 never smokers in this study included individuals who had 51 laryngeal cancers, 89 oral cavity cancers, and 14 pharyngeal tumors. The low SPT rates among these never smokers is at least somewhat reassuring, lending further credence to the hypothesis that carcinogenesis of the head and neck in these nonsmokers proceeds via alternative pathways.

At this point in the study, with the investigators and patients still blinded, we cannot assess whether the retinoid has had any significant impact on the prevention of SPTs. However, stage, site, and smoking status are stratification factors in randomization, and the treatment assignments will be balanced within each stratum. Therefore, we are able to estimate the effect of stratification factors on the end points without knowing the treatment effect and assuming no interaction between the treatment and stratification factors. An interim analysis was performed on completion of accrual, and as early-stopping rules were not met, the trial continues pending the final analysis in September 2002, when the last randomized patient will have completed 3 years of drug. Large randomized clinical trials, however, remain the only definitive way to assess the efficacy of chemopreventive agents while addressing appropriate clinical issues.

SPTs, by definition, are currently assigned according to the Warren and Gates criteria, which was published in the 1930s (12). Research today focuses on delineating the origin of these tumors of the head and neck. Development of multiple tumors is alternatively hypothesized to be attributable to independently occurring genetic events or from the transformation of a single cell that gives rise to genetically related tumors from mucosal spread. Molecular testing attempts to identify characteristics of the primary tumor and compares them with subsequent tumors, recurrence, and/or SPTs. Microsatellite analysis has been used to analyze tissue specimens, but further work is needed to determine whether these tumors are metachronous or of clonal origin (17–21).

Whereas our study represents the largest randomized trial conducted in head and neck cancer alone, recently published data from the EUROSCAN study encompassed 2,592 patients. This study demonstrated no benefit of chemopreventive agents in patients with head and neck or lung cancer in terms of survival, event-free survival, or SPT (22). In the EUROSCAN study, patients were randomized to receive supplementation with retinyl palmitate, *N*-acetylcysteine, both drugs in combination, or placebo for 2 years. Sixty % of patients had a history of head and neck cancer, and 40% had a history of lung cancer. Patients were grouped as current/former (93.5%) smokers and never (6.5%) smokers. However, data regarding smoking status, verification thereof (cotinine levels), and its impact relative to SPTs and recurrence were not presented.

Much of the prior work assessing annual SPT rates was based on archival data and is, thus, retrospective in nature. Our study emerges as a large prospective study evaluating SPT incidence and recurrence rates in a randomized interventional setting. The data, although not unblinded by intervention, are nevertheless highly useful in defining annual rates of SPT incidence as well as recurrence rates in populations with early-stage head and neck disease. What we have learned is especially useful in prospectively evaluating the impact of stage, primary site, and, particularly, smoking status on SPT development.

Controversy persists about the role of continued smoking in the development of SPTs. Whereas most studies do suggest that smoking cessation leads to a reduction in the risk of SPTs (23–28), difficulties in collecting accurate data on factors relating to smoking and a lack of biochemical confirmation (*e.g.*, measurement of serum cotinine levels) have impeded conclusive determination. Some investigators continue to question the association between smoking and the risk of SPTs (29). Most current data used screening of ongoing smoking habits and tended to indicate that continued smoking appears to increase the likelihood of SPT development (21–26). Recent SEER data that reviews long-term SPT incidence in patients with prior laryngeal cancers may be helpful in this regard (30).

Since the Surgeon General's report in 1964, >40,000,000 Americans have quit smoking. However, 50,000,000 individuals continue to smoke in the year 2000. Recent studies have shown that several new agents and techniques are effective in helping people quit smoking (31). The introduction of the transdermal nicotine patch and particularly the drug bupropion has helped smoking cessation (32). This was later verified by studies that found that the combination of nicotine patch and bupropion was superior to either alone. Additional studies are needed to assess the long-term efficacy of these interventions (33). These techniques and medications need to be encouraged in patients with head and neck cancer who can be potentially cured of primary disease and yet face a lifelong risk of SPT development.

13cRA remains a promising agent in the prevention of SPTs, although the optimal dose is not yet known. Adjuvant therapy in advanced head and neck cancer has also been recently reported in a Phase II study (34). Combination 13cRA (50 mg/m^2/day), IFN-α (3 MU/m^2/three times a week), and α-tocopherol (1200 IU/day) was given for 12 months. Of 45 evaluable patients with definitively treated stage III/IV head and neck cancer, 39 have no evidence of disease and only 6 had recurrences at 21 months median follow-up. The 2-year disease-free survival of the study is 84%. This suggests that perhaps in those patients with higher risk of developing recurrence or SPTs, more aggressive therapies for prevention are warranted.

The final results of this trial will help tremendously in establishing the optimal, posttherapeutic intervention in this patient population. Should the results be positive and the incidence of SPTs be decreased in those individuals who receive 13cRA instead of the placebo, a new, unequivocal standard of care will be set: low-dose 13cRA for patients treated definitively for their primary head and neck cancer. Should the results reveal no difference between the two arms, then there will be no compelling proof that low-dose 13cRA impacts on SPT incidence, and its use cannot be encouraged in patients rendered free of disease because of the moderate side effects.[4] However, the public health implications of the data reported herein are significant. For people who can be treated definitively for a primary early-stage (I or II) HNSCC, smoking cessation may have an impact on reducing the SPT incidence.

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