Relation Between Smoking and Skin Cancer

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Purpose: **Tobacco smoking is a risk factor for several cancers. The risk of cutaneous malignancies related to smoking, however, is relatively unknown. We investigated the possible association between smoking and skin cancer.**

Patients and Methods: **A hospital-based case-control study was performed that included 161 patients with squamous cell carcinoma, 301 with nodular basal cell carcinoma, 153 with superficial multifocal basal cell carcinoma, 125 with malignant melanoma, and 386 controls. Information on smoking history was collected in personal interviews. Relative risks were estimated using exposure odds ratios from cross-tabulation and logistic regression.**

Results: **An association between smoking and squamous cell carcinoma of the skin was found (relative risk, 2.3; 95% confidence interval, 1.5 to 3.6; *P* = .0001), with a higher risk for current smokers (relative risk, 3.3; 95% confidence interval, 1.9 to 5.5) than for former smokers (relative risk, 1.9; 95% confidence interval, 1.2 to 3.0). After adjustment for age, sex, and sun exposure, the relative risk of squamous cell carcinoma was 2.0 (95% confidence interval, 1.2 to 3.2; *P* = .008). There was a dose-response relationship with number of cigarettes and pipes smoked. No significant association was found between smoking and nodular basal cell carcinoma, superficial multifocal basal cell carcinoma, or malignant melanoma.**

Conclusion: **Tobacco smoking is an independent risk factor for cutaneous squamous cell carcinoma.**

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THE EFFECTS OF SMOKING on internal organs have been studied extensively, and the association between smoking and cancers of the lung, bladder, and cervix is well established.[1] Smoking is also a potentially important risk factor for the development of cutaneous squamous cell carcinoma.[2-4] Surprisingly, this has not generated a lot of attention, although this association has been reported repeatedly and may have a high impact on skin cancer morbidity.

Since 1985, several studies have reported significantly higher risks of developing cutaneous squamous cell carcinoma among smokers[2,3] and elevated risks for a subsequent squamous cell carcinoma in persons who had ever smoked.[4] An association between smoking and cutaneous squamous cell carcinoma, however, could not always be established.[5] Studies were published showing that smoking does not increase the risk of malignant melanoma, but smokers were reported to have a poorer prognosis after they were diagnosed with malignant melanoma, because they have an increased risk of metastases.[6,7] Finally, no clear relationship between smoking and basal cell carcinoma was found.[2-4]

Skin cancers are the most common malignant tumors among the white population. Cutaneous squamous cell carcinoma and basal cell carcinoma, together commonly called nonmelanoma skin cancers, on the one hand, and malignant melanoma, on the other hand, account for over 90% of cutaneous malignancies.[8-11] During the past decennia, a marked increase in incidence of these three cancers has been noted.[12,13] Malignant melanoma is associated with significant mortality. Although the annual mortality rate from nonmelanoma skin cancers is relatively low, due to the high prevalence and substantial degree of morbidity, these tumors present a significant and costly health problem.[14]

Exposure to sunlight is generally considered to be the most important risk factor for cutaneous squamous cell carcinoma.[8,10,15] The effects of smoking on the development of this type of skin cancer, however, are still less well known.

The purpose of this study was to address the association between smoking and the different types of skin cancer in a well-defined group of patients and controls. There is increasing evidence that nodular basal cell carcinomas and superficial multifocal basal cell carcinomas are different types of tumors[16]; therefore, data on these tumors were collected and analyzed separately.

PATIENTS AND METHODS

Study Population

The Leiden Skin Cancer Study was initiated in 1997 as a case-control study of the causes of skin cancer in the Dutch population. The medical ethics committee approved the protocol and all participants gave informed consent.

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The Leiden University Medical Center (LUMC) has a yearly number of first outpatient visits of 71,000, of which 70% are of regional origin (within 50 km of Leiden) and 30% of supraregional origin (rest of the Netherlands; the total population of the Netherlands is 16 million). All newly diagnosed cases with squamous cell carcinoma and basal cell carcinoma of the skin from January 1, 1985, through December 31, 1997, were obtained from the registration system of LUMC. All skin cancers were histologically confirmed. This resulted in potentially 560 patients with squamous cell carcinoma and 1,765 with basal cell carcinoma. To reduce recall bias, we decided to exclude persons who were older than 80 years of age. This limitation affected our recruitment of cases with squamous cell carcinoma, since these individuals seemed to be older than 80 years quite frequently. To enlarge our population of cases with squamous cell carcinoma, we therefore decided to also recruit patients with squamous cell carcinoma in hospitals within 50 km of Leiden that were within the referral area of LUMC (34 patients in the St Franciscus Hospital in Rotterdam, 24 in the Rijnland Hospital in Leiderdorp, and eight in the Westeinde Hospital in The Hague). These patients did not differ regarding their baseline characteristics from the patients with squamous cell carcinoma who were selected in LUMC (data not shown). All patients with squamous cell carcinoma who were younger than 80 years of age were invited to participate. Patients with basal cell carcinoma in the same age category were invited starting with those with the most recently occurring skin cancer. Of the 601 patients with nonmelanoma skin cancer who were invited to participate in the study, 491 (81.7%) agreed to visit our clinic.

From January 1991 onward, all cases of nonfamilial cutaneous malignant melanoma at LUMC have been identified. All malignant melanomas were histologically confirmed. There were 155 patients with malignant melanoma who were eligible for the study. A total of 130 (83.9%) participated in the study.

Controls, aged 28 through 80, were recruited at the ophthalmology outpatient clinic at LUMC. This group was chosen because it consists of patients of the same University Hospital, living in the same region. Furthermore, eye conditions are usually not related to smoking and are not associated with skin cancer. Controls were excluded when they had either an intraocular melanoma or any skin cancer in their history. Both cases and controls were excluded when they were transplant recipients or suffered from rare hereditary skin disorders, such as xeroderma pigmentosum or basal cell nevus syndrome, since these persons are at a highly increased risk of developing skin cancer. Dark-skinned persons (skin type $\geq$ V, according to the Fitzpatrick classification),[17] both case subjects and controls, were also excluded, since persons with these skin types rarely develop skin cancers.

All participants who were eligible for the study were sent a letter with an invitation to make an appointment at the dermatology outpatient clinic. Along with the letter a so-called residence work calendar was sent. In this form, every change in residence or working habit during the participant's lifetime had to be marked. All participants were asked to complete the residence work calendar at home and bring it to their outpatient visit to facilitate the assessment of pattern of sun exposure during the interview. Participants were asked not to reveal during their interview and skin examination whether or not they had previously been treated for skin cancer. During the interview, relevant events in the medical history were assessed, excluding treatments of skin cancer.

Collection of Data on Risk Factors for Cutaneous Malignancies

The visit to the dermatology outpatient clinic was identical for all case subjects and controls, lasted about 90 minutes, and consisted of a standardized interview and a physical examination.

A trained interviewer collected data on smoking history and many other potential risk factors of skin cancer. Smokers were asked which type of tobacco they used (cigarettes, cigars, pipe, or a combination of these products), at what age they started smoking, and if applicable, at what age they had quit. The numbers of cigarettes, pipes, and cigars per day per age period were noted. The total amount of tobacco products smoked was calculated by multiplying the daily tobacco consumption by the time period when the participants smoked. We did not inform the participants about the research question of the possible association between smoking and skin cancer.

The interviewer collected information on ethnic background, medical history, exposure to carcinogens (arsenic, asbestos, pesticides, and polycyclic aromatic hydrocarbons), propensity to burn rather than tan (skin type), freckling in childhood, natural hair color at the age of 20, painful sunburns and blistering, as well as sun exposure, using a standardized questionnaire (obtainable from J.N.B.B.). Hours spent outdoors were recorded for working and nonworking days between 9 AM and 5 PM in the months May through September. The whole year was taken into account when people had lived near the equator. Sun exposure during winter holidays to sunny regions or ski resorts was also recorded. The residence work calendar was used for to help participants better remember past sun exposure.

During the physical examination, a dermatologist recorded eye and hair color, amount of ephelides and lentigines, number of normal and clinically atypical nevi, number and localization of actinic keratoses and seborrheic warts, amount of elastosis and telangiectasia (using a four-point scale ranging from none to severe), and the presence of skin cancer.

Occasionally (seven times), controls seemed to have a skin cancer at physical examination that was subsequently confirmed by histologic examination. These persons were then considered as case subjects.

Statistical Analysis

All calculations were performed with JMP version 2 statistical software (SAS Institute, Inc, Cary, NC). The data were analyzed using Student's t test and the χ^2 test. Relative risks were estimated using exposure odds ratios from cross-tabulation and logistic regression analyses. Multivariate logistic regression analysis was used to adjust for confounding variables.

Because only 18 of 646 persons were exposed to tobacco products other than cigarettes, we did not give different weights to the use of the different forms of tobacco, and all current and former smokers were pooled regardless of the tobacco products they used. Excluding these 18 persons from the analyses did not change the results. In analyses of the number of cigarettes smoked per day, however, these 18 persons were excluded and the numbers of cigars and or pipes smoked by the different individuals were not included.

A confounding variable had to be a risk factor for the disease and had to be associated with the exposure but could not be an intermediate step in the causal path between the exposure and the disease. For the association between smoking and skin cancer, we adjusted for age, sex, and total amount of sun exposure. No adjustments were made for actinic keratoses, seborrheic warts, elastosis, and telangiectasia, because these factors are potentially within the causal pathway or are indicators of the final outcome. Adjustments for skin type, eye color, and hair color were not made, because these factors are generally not associated with smoking and these factors were also not significantly associated with smoking in this set of data.

Table 1. Basic Characteristics of the Study Population

Category	Controls		Squamous Cell Carcinoma		Nodular Basal Cell Carcinoma		Superficial Multifocal Basal Cell Carcinoma		Malignant Melanoma		P, Compared With Controls
	No.*	%	No.	%	No.	%	No.	%	No.	%	
Total no.	386		161		301		153		125		
Age											SCC: < .00001
Mean ± SD	58.6 ± 11.2		65.9 ± 8.4		63.1 ± 9.2		60.2 ± 10.6		49.7 ± 12.1		NBCC: < .00001
Range	28.6-79.9		36.9-78.2		31.7-78.2		31.7-78.2		24.1-77.5		SMBCC: .11
											MM: < .00001
Sex											SCC: < .00001
Male	164	42.5	103	64.0	170	56.5	79	51.6	47	37.6	NBCC: .0003
Female	222	57.5	58	36.0	131	43.5	74	48.4	78	62.4	SMBCC: .055
											MM: .33
Skin type											
IV	24	6.2	7	4.3	15	5.0	10	6.5	3	2.4	SCC: < .00001
III	181	46.9	47	29.2	110	36.5	52	34.0	34	27.2	NBCC: .0007
II	156	40.4	80	49.7	131	43.5	66	43.1	76	60.8	SMBCC: .0018
I	25	6.5	27	16.8	45	15.0	25	16.4	12	9.6	MM: .0001
Sun exposure, hours per year											SCC: .0001
Mean ± SD	538 ± 161		603 ± 208		579 ± 177		583 ± 201		498 ± 151		NBCC: .0017
Range	200-1,569		198-1,764		198-1,331		198-1,764		194-1,023		SMBCC: .0072
											MM: .015
Smoking status											
Nonsmoker	136	35.2	31	19.2	87	28.9	62	40.5	51	40.8	SCC: < .00001
Ex-smoker	180	46.7	78	48.5	151	50.2	65	42.5	47	37.6	NBCC: .20
Current smoker	70	18.1	52	32.3	63	20.9	26	17.0	27	21.6	SMBCC: .51
											MM: .21

Abbreviations: SCC, squamous cell carcinoma; NBCC, nodular basal cell carcinoma; SMBCC, superficial multifocal basal cell carcinoma; MM, malignant melanoma.

*No. = number of patients.

RESULTS

Altogether, 1,019 patients were interviewed and examined. For the current analysis, we excluded 53 patients (41 case subjects and 12 controls). Some of them met one of the exclusion criteria (11 subjects with intraocular melanoma, five with familial malignant melanoma, two renal transplant recipients, two subjects with basal cell nevus syndrome, and two subjects with skin type V). Others (31 subjects) were excluded because they had a histologic subtype of basal cell carcinoma different from a nodular or a superficial multifocal basal cell carcinoma; we were interested in possible differences between these two subtypes of basal cell carcinoma only.

The group of 966 subjects who were eligible for the study was composed of 580 patients with skin cancer (161 patients with squamous cell carcinoma, 301 with nodular basal cell carcinoma, 153 with superficial multifocal basal cell carcinoma, and 125 with malignant melanoma) and 386 controls. A total of 135 patients had two or more different types of skin cancer. Therefore, the data were analyzed twice. First, all patients with a certain type of skin cancer were analyzed, regardless of the presence of other types of skin cancer; second, only patients with just one type of skin cancer were analyzed.

In this group of 966 individuals, 320 had never smoked cigarettes, cigars, or pipes; 561 had smoked only cigarettes; 10 had smoked only cigars; six had smoked only pipes; 43 had smoked both cigarettes and cigars; 12 had smoked both cigarettes and pipes; two had smoked both cigars and pipes; and 12 had smoked all three types of tobacco products.

The basic characteristics of the study cohort, which are relevant for this study, are listed in Table 1. Case subjects with squamous cell carcinoma and nodular basal cell carcinoma were significantly older at physical examination than controls, whereas case subjects with malignant melanoma were significantly younger. Males were overrepresented among case subjects with squamous cell carcinoma and the two types of basal cell carcinoma compared with controls. As expected, fair skin type was associated with an increased risk of skin cancer (Table 1). Blue or light-colored eyes and red or blond hair were associated with squamous cell carcinoma and malignant melanoma and to a lesser extent with basal cell carcinoma (data not shown). Furthermore, hours of sun exposure per year were associated with

Table 2. Estimated Relative Risks of Skin Cancer According to Smoking in All Patients With the Specific Type of Skin Cancer, Regardless of Other Skin Cancers

	Nonsmokers		Smokers		Crude Odds Ratio	95% CI	Adjusted Odds Ratio*	95% CI
	No.	%	No.	%				
Controls	136	35.2	250	64.8				
Squamous cell carcinoma	31	19.3	130	80.7	2.3	1.5-3.6	2.0	1.2-3.2
Nodular basal cell carcinoma	87	28.9	214	71.1	1.3	0.97-1.9	1.1	0.79-1.6
Superficial multifocal basal cell carcinoma	62	40.5	91	49.5	0.80	0.54-1.2	0.66	0.44-1.0
Malignant melanoma	51	40.8	74	59.2	0.79	0.52-1.2	0.78	0.50-1.2

*The odds ratios are adjusted for age, sex, and total cumulative amount of sun exposure.

squamous cell carcinoma, nodular basal cell carcinoma, and superficial multifocal basal cell carcinoma but inversely with malignant melanoma (Table 1). By contrast, painful sunburns before the age of 20 were significantly associated with malignant melanoma (data not shown). The inverse relation between chronic sun exposure and malignant melanoma and the positive association with painful sunburns are in agreement with the literature.[18] Squamous cell carcinoma and both types of basal cell carcinoma were also associated with degree of elastosis and telangiectasia and number of actinic keratoses, whereas malignant melanoma was associated with number of nevi (data not shown).

A strong association between smoking and squamous cell carcinoma (regardless of other skin cancers) was observed (Tables 1, 2, and 3), with an estimated relative risk of 2.3 (95% confidence interval, 1.5 to 3.6) of developing squamous cell carcinoma among smokers (Table 2). Analyzing patients with only squamous cell carcinoma did not change this relative risk substantially (Table 3). Therefore, all additional analyses were performed with squamous cell carcinoma, regardless of other skin cancers.

Smoking was highly associated with sex. Twenty-three percent of the men were current smokers and 58% were ex-smokers. Among the women, these figures were 17% and 36%, respectively. There was also a significant difference in hours of yearly sun exposure between smokers and nonsmokers. Current smokers spent 574 ± 198 (mean ± SD) hours per year in the sun, ex-smokers, 562 ± 169 hours, and nonsmokers, 531 ± 162 hours ($P = .01$). After adjustment for age, sex, and sun exposure, the relative risk of squamous cell carcinoma in smokers was 2.0 (95% confidence interval, 1.2 to 3.2) (Table 2). Smoking was also associated with degree of elastosis and number of actinic keratoses (data not shown).

With respect to both types of basal cell carcinoma and malignant melanoma, our initial analyses did not suggest a significant relationship with smoking (Tables 1 and 2). In a subgroup analysis of 57 case subjects who had only superficial multifocal basal cell carcinoma, however, we found a statistically significant negative association between smoking and the development of this tumor (Table 3). This subgroup consisted more often of young women (57.9%) with less sun exposure. Analyses were conducted of the whole group of 153 case subjects with superficial multifocal basal cell carcinoma (Table 2) and of the subgroup of 96 (153 minus 57) case subjects with superficial multifocal basal cell carcinoma who had a history of squamous cell carcinoma, nodular basal cell carcinoma, and/or malignant basal cell carcinoma, excluding those subjects without additional skin cancers. These analyses found no association between smoking and superficial multifocal basal cell carcinoma (odds ratio, 1.1; 95% confidence interval, 0.69 to 1.9).

The risk of squamous cell carcinoma was higher among current smokers (relative risk, 3.3; 95% confidence interval, 1.9 to 5.5) than among former smokers (relative risk, 1.9; 95% confidence interval 1.2 to 3.0) compared with nonsmokers, which was also apparent after adjustment for age,

Table 3. Estimated Relative Risks of Skin Cancer According to Smoking in Patients With One Type of Skin Cancer

	Nonsmokers		Smokers		Crude Odds Ratio	95% CI	Adjusted Odds Ratio*	95% CI
	No.	%	No.	%				
Controls	136	35.2	250	64.8				
Squamous cell carcinoma	19	18.3	85	81.7	2.4	1.4-4.2	2.3	1.2-4.1
Nodular basal cell carcinoma	53	29.1	129	70.9	1.3	0.90-1.9	1.2	0.77-1.7
Superficial multifocal basal cell carcinoma	31	54.4	26	45.6	0.46	0.26-0.80	0.42	0.23-0.75
Malignant melanoma	41	40.2	61	59.8	0.81	0.52-1.3	0.81	0.50-1.3

*The odds ratios are adjusted for age, sex, and total cumulative amount of sun exposure.

Table 4. Estimated Relative Risks of Squamous Cell Carcinoma in Relation to Smoking Characteristics

	Controls		Squamous Cell Carcinoma		Crude Odds Ratio	95% CI	Adjusted Odds Ratio*	95% CI
	No.	%	No.	%				
Smoking status								
Never smoked	136	35.2	31	19.3				
Former smoker	180	46.7	78	48.4	1.9	1.2-3.0	1.8	1.0-3.0
Current smoker	70	18.1	52	32.3	3.3	1.9-5.5	2.9	1.5-5.6
Duration of smoking among former and current smokers, compared with those who never smoked								
0 years	136	35.2	31	19.3				
1-19 years	74	19.2	21	13.0	1.2	0.67-2.3	1.8	0.90-3.7
20-39 years	116	30.1	52	32.3	2.0	1.2-3.3	2.0	1.1-3.6
40 and more	60	15.5	57	35.4	4.2	2.4-7.1	1.7	0.87-3.3
		Test for trend†			$P < .00001$		$P = .08$	
No. of cigarettes smoked per day among current smokers, compared with those who never smoked								
0	136	66.1	31	38.3				
1-10	22	10.7	15	18.5	3.0	1.4-6.4	2.4	0.99-6.0
11-20	31	15.0	18	22.2	2.5	1.3-5.1	3.0	1.3-7.1
21 and more	17	8.2	17	21.0	4.4	2.0-9.5	4.1	1.5-11.5
		Test for trend†			$P = .0002$		$P = .0044$	
Type of smoking‡								
No smoking	136		31					
Smoking cigarette	249		124		2.2	1.4-3.4	2.0	1.2-3.3
Smoking pipe	7		16		10.0	3.8-26.5	6.7	1.9-23.8
Smoking cigar	26		14		2.4	1.1-5.0	1.6	0.62-4.2

*The odds ratios are adjusted for age, sex, and total cumulative amount of sun exposure.

†We tested for trends by entering duration of smoking or the number of cigarettes as a continuous variable in the logistic model.

‡Some cases and controls smoked different sorts of tobacco products; this fact is reflected here by overlapping of the numbers of cases and controls in these categories.

sex, and sun exposure (Table 4). The relative risk of squamous cell carcinoma among current smokers compared with former smokers was 1.7 (95% confidence interval, 1.1 to 2.8). A dose-response relationship was observed between risk of squamous cell carcinoma and number of cigarettes currently smoked (Table 4). A dose-response relationship was also observed between risk of squamous cell carcinoma and duration of smoking, but this effect almost completely disappeared after adjustment for age, sex, and cumulative amount of sun exposure (Table 4). Considering the type of smoking, there was a striking presence of pipe smokers among squamous cell carcinoma patients compared with controls. The relative risk of developing a squamous cell carcinoma in pipe smokers was 10.0 (95% confidence interval, 3.8 to 26.5). After adjustment for age, sex, and sun exposure, the relative risk was still 6.7 (95% confidence interval, 1.9 to 23.8). After adjustment for age, sex, and sun exposure, the relative risk of squamous cell carcinoma among persons who had ever smoked cigarettes was 2.0 (95% confidence interval, 1.2 to 2.8), whereas cigar smoking was not significantly associated with squamous cell carcinoma (Table 4). Squamous cell carcinomas among pipe smokers were localized in the head and neck region in nine (56%) of 16 patients, which was not substantially different from the location of the squamous cell carcinomas among the other patients (104 of 145 case subjects, or 72%). Only two of the squamous cell carcinomas among pipe smokers were located on the lip.

DISCUSSION

In this case-control study of a variety of skin cancers, a significant association was found between tobacco smoking and cutaneous squamous cell carcinoma, with a higher risk for current smokers than for former smokers. A clear relationship with the number of cigarettes currently smoked was observed. In particular, cigarette and pipe smokers seemed to have a high risk of developing squamous cell carcinoma, whereas cigar smokers were not at a significantly increased risk.

In general, no significant association was observed between tobacco smoking and nodular basal cell carcinoma, superficial multifocal basal cell carcinoma, or malignant melanoma. However, in a small subgroup of case subjects, ie, those who did not develop other types of skin cancer in addition to the superficial multifocal basal cell carcinoma, a negative association between smoking and this type of skin cancer was found. If true, the apparent protective effect of smoking on superficial multifocal basal cell carcinoma should be confirmed in an independent study. An alternative and more likely explanation for the negative association between smoking and superficial multifocal basal cell carcinoma may be that this is due to chance, caused by the multiple testing of several subgroups. The fact that no such negative association was found in the case subjects with superficial multifocal basal cell carcinoma who had additional types of skin cancer is an important argument in favor of the latter explanation.

The association between smoking and cutaneous squamous cell carcinoma is in agreement with earlier studies. A smaller-sized case-control study in the Montreal, Canada, region also showed a statistically significant association (relative risk, 2.3; 95% confidence interval, 1.3 to 4.2).[2] In a prospective study of new primary squamous cell carcinoma in a cohort with at least one prior squamous cell carcinoma, an elevated risk of a subsequent squamous cell carcinoma was observed for current smokers (relative risk, 2.0; 95% confidence interval, 1.2 to 3.3) and former smokers (relative risk, 1.6; 95% confidence interval, 1.1 to 2.5). The risks increased with duration (years) of smoking and number of cigarettes smoked.[4] Finally, a follow-up study showed current cigarette smokers to have a 50% increase in the risk of squamous cell carcinoma compared with persons who had never smoked (relative risk, 1.5; 95% confidence interval, 1.1 to 2.1).[3]

Individuals with a disease tend to think about the causes of their disease or to have heard about the possible causes of their disease and are thus more likely to remember their exposure histories differently compared with controls. To reduce bias, the procedure used to obtain information was similar among patients and controls, and the patients were requested not to inform the interviewers and dermatologist as to whether they were a patient or a control. The public's awareness of the association between smoking and skin cancer is low.[19] Moreover, if recall bias had played a role, then patients with basal cell carcinoma and malignant melanoma would have experienced a degree of recall bias similar to that among the squamous cell carcinoma patients. Exposure to smoking, however, was much higher among squamous cell carcinoma patients compared with basal cell carcinoma and malignant melanoma patients.

Smokers had significantly more hours of yearly sun exposure than nonsmokers did. A possible explanation could be that the proportion of smokers is greater among outdoor workers, or that people who smoke tend to be less concerned about their health and thus neglect the dangers of sun exposure. The higher exposure to sunlight among smokers, however, did not materially influence the association between smoking and skin cancer.

The current study is hospital-based. For that reason, it cannot be automatically extrapolated to the population at large. There are, however, no adequate arguments to assume that the relationship between smoking and skin cancer is intrinsically different in hospital patients than in patients who reside in the population.

The effects of smoking on the development of skin cancer can potentially be explained in a number of different ways. First, tobacco smoke may act as a skin carcinogen, either directly on the skin or through a systemic carcinogenic effect. In experiments with mice and rabbits, applying smoke to the skin induced squamous cell carcinoma.[20] The association between several malignancies at sites remote from direct smoke contact, such as the bladder,[21] pancreas,[22] and cervix,[23] may suggest systemic carcinogenic effects of tobacco smoke. Tobacco smoke contains several classes of compounds with demonstrated carcinogenic or cocarcinogenic activity, including nitrosamines, polycyclic aromatic hydrocarbons, aromatic amines, unsaturated aldehydes, and phenolic compounds.[24] Among these, benzo[a]pyrene, the prototype compound of polycyclic aromatic hydrocarbons, is metabolically activated to the ultimate carcinogen benzo[a]pyrene diolepoxide, which may form DNA adducts; this is generally thought to be the basis of the carcinogenic effect.[25,26] Several mouse studies have shown the binding of benzo[a]pyrene diolepoxide to DNA to correlate with the initiation of skin carcinogenesis.[27] Numerous reports have pointed out the importance of the *p53* tumor suppressor gene in the process of carcinogenesis.[28-30] Mutations of the *p53* gene have been linked to tobacco smoking in squamous cell carcinoma of the head and neck, as well as on esophageal, lung, and bladder cancer.[29,31] Indeed, certain carcinogens seem to induce particular *p53* mutations, thus leaving a "fingerprint"-like pattern, both in terms of mutation type and codon specificity.[32] Benzo[a]pyrene has been shown to produce preferentially G→T transversions.[33] The involvement of ultraviolet (UV) light in inducing *p53* mutations in skin carcinomas at sun-exposed sites is indicated by the presence of CC→TT double-base changes and C→T transitions at dipyrimidine sites.[15] Recently, multiple and distinct p53 mutations were detected in tumor and adjacent nonmalignant skin samples from patients with nonmelanoma skin cancer of the head

and neck.[30] The mutations consisted of C→T transitions at dipyrimidine sequences, T→C transitions, and G→T transversions, suggesting that other carcinogens may act along with UV radiation in the development of NMSC. In addition to substantial exposure to UV radiation, most patients had a history of smoking.[30] Thus, the induction of specific mutations in the *p53* gene could be a way by which tobacco smoke exerts its carcinogen effect on human skin.

A second possible effect of smoking in the development of cutaneous squamous cell carcinoma could be loss of immune surveillance, since tobacco smoke has been shown to suppress immunologic functions,[34-38] and immunosuppressed patients (eg, renal transplant patients) are known to have an increased risk of squamous cell carcinoma.[39,40] The high prevalence of human papillomavirus (HPV) DNA detected in squamous cell carcinomas of immunosuppressed patients suggests a potential role for HPV infection in the etiology of these lesions.[41] Remarkably, cervical cancer is also associated with tobacco smoking, and HPV infection is a well-established risk factor for this malignancy.[42] A hypothetical explanation could be that tobacco smoking, through its effect on the immune system, enhances HPV infection.

In conclusion, this study identified tobacco smoking, especially cigarette and pipe smoking, as a risk factor for cutaneous squamous cell carcinoma. The strength of the association, the dose dependency, the experimental evidence, the biologic plausibility, and the analogy with squamous cell carcinoma of the lung, larynx, bladder, and cervix suggests causality and supports the growing evidence of smoking as a risk factor for squamous cell carcinoma in general. In order to reduce the risk of cutaneous squamous cell carcinoma, not only should sun exposure be reduced but smoking should be discouraged as well.

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APPENDIX
Members of the Leiden Skin Cancer Study Group

Members of the Leiden Skin Cancer Study Group are, in alphabetical order, Nathalie van Amsterdam, Maarten T. Bastiaens, Wilma Bergman, Marjo J.P. Berkhout, Jan N. Bouwes Bavinck, Ingeborg L.A. Boxman, René Broer, Jan A. Bruijn, Marianne Crijns, Mariet Feltkamp, Nelleke A. Gruis, Sofie A.E. De Hertog, Juliette J. Hoefnagel, Jeanet A.C. ter Huurne, Kees Kennedy, Christine J. Kielich, Iris Kuijken, Sjan P.M. Lavrijsen, Linda H.C. Mulder, Marloes Polderman, Marinus C.G. van Praag, Jan ter Schegget, Caesar Sterk, Linda Struijk, Jan P. Vandenbroucke, Bert J. Vermeer, Christianne A.H. Wensveen, and Rudi G.J. Westendorp.

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