

INCIDENCE OF ORAL CARCINOMA IN PATIENTS WITH LEUKOPLAKIA OF THE ORAL MUCOSA

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A series of 782 patients with a clinical diagnosis of oral or lip leukoplakia was followed with regular checks for 1 to 44 years (mean 12 years). Oral carcinoma developed in 2.4% of the patients in 10 years and in 4% in 20 years. The prevalence in the various age groups was about 50 to 100 times greater than for the Swedish population according to the 1959 Cancer Registry. It was primarily the small group of cases of leukoplakia in persons not using tobacco that were responsible for the excess morbidity from oral carcinoma; among tobacco users with leukoplakia the figure was considerably lower. There is no evidence that the incidence of oral carcinoma can be diminished by surgical removal of the leukoplakia but this does not mean that the operation should be abandoned, mainly for histologic diagnosis. The prevalence of other malignant tumors than oral and lip carcinoma in cases of oral leukoplakia did not differ from that of malignant tumors in the Swedish population as a whole.

THAT MALIGNANT TRANSFORMATION OCCURS in some cases of oral leukoplakia is generally agreed but estimates of the proportion so affected vary widely.^{5, 6, 8, 17, 18, 20} The purpose of the present study is to determine the incidence of carcinoma among cases of leukoplakia of the oral mucosa and to ascertain whether there is a specially high morbidity in any particular group of these patients.

MATERIAL AND METHODS

Between 1920 and 1960, 832 patients were seen at Radiumhemmet for alterations in the mucosa of the oral cavity or the lip, diagnosed clinically by the examining physician as leukoplakia. In 256 cases the diagnosis was supplemented by histologic examination. The patients were followed up by annual examinations at Radiumhemmet or the Depart-

ment of Otorhinolaryngology or by regular correspondence, either direct or through a physician who annually examined the patient. This follow-up was supplemented in 1965 by two questionnaires, by evaluation of autopsy reports or record sheets from other hospitals where the patients had been treated during the follow-up period and in 117 cases by a new examination of the patient, supplemented where it was deemed necessary by a new biopsy examination of the oral leukoplakia.

Fifty of the patients were followed up for less than one year and were not available for examination when the case series was compiled; none of them is known to have developed oral carcinoma. The remaining 782 patients—comprising 94% of the series—were followed up from 1 to 44 years; the mean follow-up time was 11.7 years. Of these 782 patients 522 were men and 260 were women.

An oral tumor was defined as a discrete clinically or histologically malignant neoplasm situated on the tongue, buccal mucosa, palate, floor or elsewhere in the mouth and discovered during life. Tumors of the lip, pharynx, tonsils, parotid and submandibular glands were not included among the oral tumors.

A tobacco user was defined as any person who regularly chewed tobacco or smoked a pipe or who regularly smoked at least five

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cigarettes a day. The vast majority of the tobacco users were cigarette smokers consuming more than ten cigarettes a day. Eighty-three per cent of the patients used tobacco and 17% did not. The mean age of the tobacco users was 51 years and of nonusers was 54 years.

A patient recorded as operated on was one in whom an attempt had been made to remove the leukoplakia by wide excision or electrocoagulation within 3 months after the first examination but not when only a biopsy specimen was taken. Surgical removal of the leukoplakia was performed in 313 cases; the mean age of these patients was 54 years and of the others was 52 years.

In 728 cases the dental status was assessed at the first examination. In 252 of them the leukoplakia was ascribed to chafing by a tooth; this usually was corrected by a dentist.

Fifty-five patients received radiotherapy for the leukoplakia. Two of them developed oral carcinoma. After a long observation (15 to 20 years) there was no difference between the irradiated patients and the others in this respect but the former group is too small to permit of comparison.

In the calculation of the prevalence of malignancy, account was taken of the follow-up period for each patient. The probability of developing carcinoma within m years after diagnosis of leukoplakia (r_m) was calculated from the expression:

$$r_m = 1 - q_1 q_2 q_3 \cdots q_m$$

in which

$$q_i = \frac{n_i - a_i - \frac{d_i}{2}}{n_i - \frac{d_i}{2}}$$

where

n_i denotes the number of patients at the beginning of year i ,

a_i the number of new cases of carcinoma in year i and

d_i the number of patients withdrawn from follow-up during year i .

The statistical methods used have been dealt with elsewhere.³

RESULTS

During the first three years 1.3% of the patients developed oral carcinoma (about

0.4% per annum) and thereafter a mean of 0.1% every year. After 10 years 2.4% of the patients had oral carcinoma and after 20 years 4% (Table 1). The incidence of lip carcinoma in this series is given in a preliminary report.⁴

The prevalence of oral carcinoma in the various age groups is given in Tables 2 and 3. Oral and lip carcinoma constituted 28% of all malignant tumors observed in cases of leukoplakia of the oral cavity (Table 4). The incidence of other types of malignant tumors is given in Table 5.

The prevalence of oral carcinoma among the cases of leukoplakia was considerably lower among tobacco-users than others (Table 6).

There was no difference in the prevalence of malignant tumors of the oral cavity in patients in whom the leukoplakia was ascribed to chafing by one tooth than in other patients; after 5 years the frequencies of oral tumors in these two groups were 1.7 and 1.3%.

The prevalence of oral carcinoma in patients in whom an attempt was made to remove the leukoplakia by wide excision or electrocoagulation was not lower than in those not operated on (Table 7).

There was no appreciable difference in the prevalence of oral carcinoma between men and women with leukoplakia of the oral mucosa.

DISCUSSION

There is a great deal of confusion regarding the microscopic vs. the clinical use of the word "leukoplakia." It is considered by some to cover any white patch on the mucosa that cannot be rubbed off and that cannot be ascribed to any other disease (e.g. lichen planus and stomatitis) while others base the diagnosis on histologic criteria; however, these differ widely from one author to another. If, for instance, the presence of dyskeratosis is required,^{1, 5, 6, 19} a higher prevalence of carcinoma will be recorded. Owing to misunderstandings arising from varying use of the word

TABLE 1. Cumulative Frequency of Oral Carcinoma in Cases of Oral Leukoplakia

	Observation period, years				
	1	3	5	10	20
No. of cases of leukoplakia	782	736	691	447	126
% with oral carcinoma	0.5	1.3	1.6	2.4	4.0

TABLE 2. Annual Incidence of Oral Carcinoma for the First Five Years after Diagnosis of Oral Leukoplakia

Age	No. of patients	Observation—years	Cases of carcinoma	Annual incidence (%)	
				Present series	Swedish population*
20-49	274	1301	2	0.2	0.001
50-69	399	1890	3	0.2	0.004
70-89	109	489	7	1.5	0.016
TOTAL	782	3680	12	0.3	0.003

* According to the 1959 Swedish Cancer Registry.

"leukoplakia" in microscopic diagnosis, it has been suggested that the term should be avoided as a histologic entity.^{7,16} Even in a series where the term has only a clinical implication, the criteria for the diagnosis are subjective; however, the results will depend above all on the origin of the patients—for instance mass health examinations, dental reception centers or patients referred to a cancer hospital for further examination; in the last case the material will be a selected one.

In the present study "leukoplakia" is used in the clinically descriptive sense; all patients had a white patch on the mucous membrane of the lip or oral cavity that was judged on a clinical basis to be leukoplakia and that could not be attributed to any other disease either at initial examination or during the follow-up period. In only one third of the cases was it confirmed microscopically at the initial examination that the change was not attributable to any other defined disease such as lichen planus, stomatitis or carcinoma.

The prevalence of oral carcinoma among the cases of leukoplakia of the oral cavity is lower than has usually been reported.^{9,13,20} This in spite of the long observation period, the high proportion of cases followed up and the probable presence of a selective factor, the series consisting of patients referred to a cancer hospital for examination.^{2,6,10,11,13-15}

Just as for the population as a whole, the risk of developing carcinoma is greater for older persons with leukoplakia. Of the patients aged 70 to 89 years 7.5% developed oral carcinoma during the first 5 years; for the patients younger than 50 years the corresponding figure is 1% and in the subsequent 5-year period about 0.5% (Tables 2 and 3). This frequency is by no means negligible but in our series of young cases of leukoplakia (< 50 years) only one case of oral carcinoma was found among 130 patients followed up for 5 years.

To be able to judge whether the prevalence of oral carcinoma in cases of oral leukoplakia is greater than can be ascribed to chance, it is necessary to have access to a comparable control series of the same age and preferably from the same period. No such series was available to us nor to any other author engaged with these problems, however, a comparison in this study was made with the prevalence of oral carcinoma for the same age group according to the 1959 Cancer Registry. The cases of leukoplakia were observed from 1920 to 1965; they are compared here with a large control series, which, however, was followed up only for a small part of this period. As the age-specific carcinoma incidence in Sweden changes with time, only large differences between the groups can be ascribed any significance.

A comparison of the leukoplakia series with the age-specific incidence of malignant tumors according to 1959 Swedish Cancer Registry¹² shows that the prevalence of oral carcinoma in the various age groups of cases of leukoplakia is 50 to 100 times greater than among the whole population of Sweden (Table 2). As biopsy specimens were taken only in one third of the series, it might be difficult to know what proportion of the cases had carcinoma at the outset;¹⁵ however, even if the first 5 years after the diagnosis of leukopla-

TABLE 3. Annual Incidence of Oral Carcinoma more than Five Years after Diagnosis of Oral Leukoplakia

Age	Observation—years	Cases of carcinoma	Annual incidence (%)	
			Present series	Swedish population*
20-49	995	1	0.1	0.001
50-69	2997	3	0.1	0.004
70-89	1472	6	0.4	0.016
TOTAL	5464	10	0.2	0.003

* According to the 1959 Swedish Cancer Registry.

TABLE 4. Percentage Distribution of Primary Malignant Tumors According to Site

Site	Present series		Whole population*	
	No. of cases	%	No. of cases	%
All sites exc. skin	98	100	19,495	100
Mouth	22	22	162	0.8
Lip	6	6	178	0.9

* According to the 1959 Swedish Cancer Registry.

kia are disregarded, the prevalence of oral carcinoma in the various age groups is 30 to 100 times greater among cases of leukoplakia than for the whole population of Sweden (Table 3). The incidence of oral carcinoma is many times greater for the cases of oral leukoplakia, even a long time after the diagnosis of this condition (Table 3) but the prevalence of all other forms of tumor when oral and lip carcinoma are excluded is almost identical in the present series and the Swedish population (Table 5).

Oral leukoplakia is much more common among tobacco users than nonusers; only 17% of the patients of the present series did not use tobacco but the frequency of malignant tumors in patients contracting oral leukoplakia even though they did not use tobacco was eight times greater than for tobacco users with leukoplakia; the former group, in spite of its small size, was responsible for the greater part of the excess morbidity in oral carcinoma for

TABLE 5. Annual Incidence of Malignant Tumors in Cases of Oral Leukoplakia, Oral and Lip Carcinoma Excluded

Age	Observation—years	Cases of carcinoma	Annual incidence (%)	
			Present series	Swedish population*
20-49	2296	3	0.1	0.1
50-69	4887	26	0.5	0.5
70-89	1948	41	2.1	1.3
TOTAL	9131	70		

* According to the 1959 Swedish Cancer Registry.

TABLE 6. Cumulative Incidence of Oral Carcinoma in Tobacco Users and Nonusers with Oral Leukoplakia

Observation period	Tobacco	
	Users	Nonusers
2 yr.	0.2	1.1
5 yr.	0.4	3.1

the whole series. The leukoplakia in tobacco users seems not to be of great precancerous significance; in only one of 250 cases did oral carcinoma develop in the first 5 years (Table 6). It must be seriously considered whether this prevalence justifies the suffering often inflicted on inveterate smokers through the discovery of leukoplakia. It is also questionable to what extent this prevalence might be reduced by prohibition of smoking.

In 40% of the series an attempt was made to remove the leukoplakia by excision or electrocoagulation. A study was made to find whether this operation reduces the risk of oral carcinoma. No reduction in the prevalence of oral carcinoma could be shown in the surgically treated patients; on the contrary, the incidence of oral carcinoma was greater for those undergoing operation (Table 7). This is probably because these patients were selected. Even if the operation could not be shown to reduce the risk of subsequent development of oral carcinoma, the surgical removal of leukoplakia is often indicated as a means of obtaining histologic confirmation that there is no carcinoma.

TABLE 7. Cumulative Probability of a Malignant Tumor of the Mouth Occurring Among Cases of Oral Leukoplakia

Follow-up period (yr.)	Leukoplakia removed surgically (%)	
	No operation (%)	
2	1.6	0.4
5	2.3	1.1
15	4.6	2.5

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Professional Program

Ellis Fischel State Cancer Hospital and Cancer Research Center

The semiannual professional program of the Ellis Fischel State Cancer Hospital and Cancer Research Center will be presented on December 16, 1967. To convene at the Ellis Fischel State Cancer Hospital, the fall program will explore two areas of interest:

1. Management of nonsurgical malignancies;
2. Current concepts of the prevention and management of cancer of the skin.

Visiting guest speakers include Matthew H. Block, MD, Denver, Colo.; W. Mage Honeycutt, MD, Little Rock, Ark.; Carl V. Moore, MD, St. Louis, Mo.; Robert Olson, MD, Oklahoma City, Okla.; Jesse Steinfeld, MD, Los Angeles, Calif.; E. S. Schewe, MD, Columbia, Mo.; and Howard B. Latourette, MD, Iowa City, Iowa.

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