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Multiple Primary Cancers in Patients with Squamous Cell Carcinoma of the Oral Cavity

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During the 27 years between 1962 and 1988, 984 patients visited the National Cancer Center Hospital for previously untreated squamous cell carcinoma of the oral cavity and lip. The records of all these 984 patients were reviewed to determine the incidence of additional primary carcinoma. 1) One hundred and thirty-five additional carcinomas developed in 111 patients (11.2%) during 5,689.2 person-years of observation. The incidence of additional primary carcinoma was 23.7 per 1,000 person-years. 2) The cumulative rate of additional primary carcinoma during the first five years of observation showed a tendency to increase in the most recently treated patients (from 1980 to 1988). 3) The observed-to-expected ratio (O/E ratio) for all sites was 2.77 and this is significantly high ($P<0.01$). The calculation of the O/E ratio for each site revealed significantly high risks in the oral cavity and pharynx, esophagus and skin. The O/E ratio for the oral cavity and pharynx was extremely high (79.45). 4) The O/E ratio for all sites in each year of follow-up was the highest in the first year, stayed nearly constant from the second to 14th years, and decreased gradually afterwards. Significantly high risk was observed until the 13th year of follow-up. Patients with oral squamous cell carcinoma must be under frequent and regular examination for almost 15 years.

Key words: Multiple primary cancer — Squamous cell carcinoma of the oral cavity — Observed-to-expected ratio

It is now well documented that patients with squamous cell carcinoma of the oral cavity develop additional malignancies very frequently.[1-8] The reported incidence of additional carcinoma seems to be increasing, being as high as 10 to 20% in recent studies[3,5-7] and even up to 27% in one series.[4]

We ourselves had the impression that recently multiple cancer cases were increasing in number. To see if this is indeed the case, we selected 984 cases of previously untreated oral squamous cell carcinoma and reviewed the records of all these cases to determine the incidence of additional primary carcinoma. We also estimated the risk of additional carcinoma for each site and in each year of follow-up.

PATIENTS AND METHODS

During the 27 years ranging from 1962 to 1988, 1,305 patients received radical treatment for squamous cell carcinoma of the oral cavity and lip in the National Cancer Center Hospital. Nine hundred and eighty-four had previously untreated disease. The records of these 984 patients were reviewed to determine the incidence of additional primary carcinoma. Table I shows the sex and age distribution of the patients and site and stage of the original oral, or index, cancers. Oral squamous cell carcinoma was most frequent in the sixth and seventh decades, with the average age of 57.5 years; 72.8% of patients were 50 years old or above.

As the criteria of additional primary carcinoma, we used those originally proposed by Warren and Gates[10]: 1) each of the tumors must present a definite picture of malignancy, 2) each must be distinct, and 3) the probability that one was a metastatic lesion from the other must be excluded. These criteria were sometimes difficult to meet, especially when another squamous cell carcinoma arose in the oral cavity. In this case we included the second lesion as additional carcinoma only when the site of the new lesion was distinct from that of the index cancer and no continuity was observed clinically or histopathologically. A lesion of squamous cell carcinoma found at the same site as the index cancer was regarded as a recurrence and was not included in this series, even if there was a more than five-year interval between these two lesions. We excluded carcinomas found unexpectedly at autopsy. Carcinoma found in another hospital was included as an additional carcinoma when we could obtain detailed information on the lesion through the hospital, the patient, or his/her family, or when there was no doubt that the lesion met in full the criteria of Warren and Gates.

Additional carcinomas were considered to be synchronous when found at the same time as or within a six-month period after diagnosis of the primary cancer. Carcinomas found after six months were referred to as metachronous carcinomas.

Observation was begun on the day a patient first visited our hospital for the index cancer and was continued until

Table I. 984 Patients with Previously Untreated Squamous Cell Carcinoma of the Oral Cavity and Lip

Sex		Age		Site		Stage[c]	
Male	700	0–9	0	Tongue	642	I	236
Female	284	10–19	1	Oral floor	108	II	315
(male to female		20–29	19	Lower gingiva	87	III	193
ratio 2.46:1)		30–39	83	Buccal mucosa[a]	55	IV	222
		40–49	165	Upper gingiva	30	Unknown	18
		50–59	247	Lip	22		
		60–69	293	Hard palate	20		
		70–79	137	Retromolar area	17		
		80–89	39	Oral cavity, NOS[b]	3		
		90–	0				

a) Not including the retromolar area.
b) Not otherwise specified.
c) The stage of each tumor was determined by the TNM system of the International Union Against Cancer (4th edition, 1987).[9]

the earliest of the next three times: April 1, 1989, the patient's death, or his/her loss to observation. The follow-up period of each patient ranged from 18 days to 9,633 days. The average was 2,110.3 days, or five years nine months and 15.3 days. The total of the follow-up period of all patients was 2,076,556 person-days, or 5,689.2 person-years. Six hundred and twenty-eight cases (63.8%) were completely followed up.

To study the recent change in the incidence of additional primary carcinoma, we divided the patients into three groups according to the year of their first visit to our hospital: from 1962 to 1970, from 1971 to 1979, and from 1980 to 1988. The 1962–1970 group included 248 patients. The 1971–1979 group and the 1980–1988 group included 328 and 408 cases, respectively. We not only calculated the incidence of additional carcinoma in each group, but also computed cumulative rates of additional primary carcinoma by yearly interval for each group. To calculate the cumulative rate of additional primary carcinoma in each year of follow-up, we first computed an additional primary carcinoma-free rate in each year by the life table method and subtracted that value from one.

To obtain the expected number of additional primary carcinomas by site, we calculated person-years in each patient by means of the method proposed by Schoenberg and Myers,[11] applied the person-years to the age-, sex-, site-, and year-specific cancer incidence tables in Japan and totaled the resulting numbers for all the patients. Observation between 1962 and 1979 was considered applicable to the cancer incidence table in Japan in 1975[12] and that between 1980 and 1989 to the cancer incidence table in Japan in 1985.[13] Then, observed-to-expected ratios (O/E ratios) were calculated and their statistical significance was tested on the assumption of a Poisson distribution with the significance factor table produced by Bailar and Ederer.[14] The expected number of additional carcinomas and the O/E ratio in each year of follow-up were calculated by using the same method as stated above, based on person-years in each patient in each year of follow-up.

RESULTS

After the index cancers, 135 new malignancies developed in 111 patients (11.2%) during 5,689.2 person-years of observation; that is, the incidence of additional primary carcinoma was 23.7 per 1,000 person-years.

Table II shows the site distribution of additional primary carcinomas observed after the index cancers. Of 58 additional carcinomas in the oral cavity and pharynx, 48 carcinomas developed in the oral cavity and lip (15 in the tongue, 12 in the gingiva, 7 in the buccal mucosa, 5 in the oral floor, 5 in the hard palate, 3 in the lip, and 1 in the retromolar area) and 10 in the pharynx (8 in the mesopharynx and 2 in the hypopharynx). The "Others" category includes two cases of renal cancer and one case each of carcinoma of the gallbladder, rectum, breast, uterus, ureter, thyroid and submandibular gland, melanoma of the nasal cavity and osteosarcoma.

The most frequent site of additional primary carcinoma was the oral cavity and lip (48 cases, 35.6%). This was followed by the stomach (18 cases), esophagus (13 cases), and pharynx (10 cases) in this order. Twenty-one cancers (15.6%) were synchronous and 114 were metachronous. Four carcinomas were found incidentally in resection specimens, and their sites were the submandibular gland, kidney, prostate and colon.

Forty-five carcinomas had been observed before the index cancers. Their site distribution is shown in Table

Table II. Additional Primary Carcinomas Observed after the Index Cancers

	Observed number (O)	Expected number (E)	O/E ratio
All sites	135	48.73	2.77 ($P<0.01$)
Oral cavity & pharynx	58	0.73	79.45 ($P<0.01$)
Stomach	18	16.39	1.10
Esophagus	13	1.66	7.83 ($P<0.01$)
Liver	7	3.92	1.79
Lung	6	6.61	0.91
Colon	6	3.07	1.95
Skin	4	0.57	7.02 ($P<0.01$)
Larynx	2	0.58	3.45
Pancreas	2	1.75	1.14
Bladder	2	1.43	1.40
Prostate	2	1.36	1.47
Leukemia	2	0.67	2.99
Malignant lymphoma	2	1.18	1.69
Others	11		

Table III. Additional Primary Carcinomas Observed before the Index Cancers

Total	45	
Stomach	8	
Esophagus	8	
Pharynx	6	
Mesopharynx		5
Hypopharynx		1
Larynx	6	
Oral cavity & lip	5	
Tongue		1
Buccal mucosa[a)]		1
Retromolar area		1
Hard palate		1
Lip		1
Uterus	3	
Lung	2	
Breast	2	
Others	5	

a) Not including the retromolar area.

III. The "Others" category includes one case each of carcinoma of the maxillary sinus, skin, prostate and ovary, and malignant fibrous histiocytoma.

In total, 180 additional carcinomas developed in 145 patients. Of these 145 patients there were 16 cases with two addi-tional carcinomas, five cases with three additional carcinomas, and three cases with four additional carcinomas.

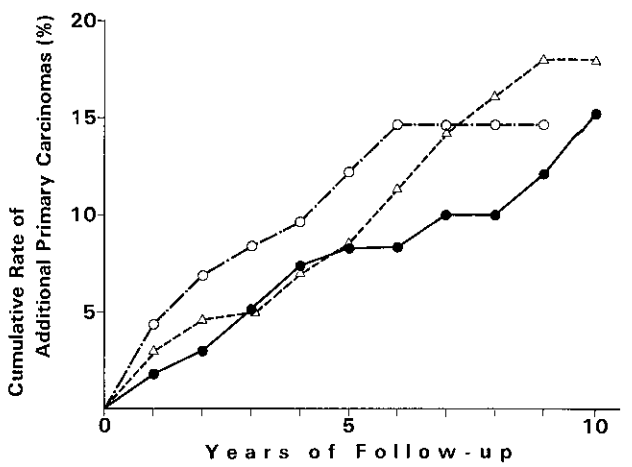

Fig. 1. Cumulative rates of additional primary carcinoma by yearly interval for three groups: patients first seen from 1962 to 1970 (●), from 1971 to 1979 (△), and from 1980 to 1988 (○).

In the 1962–1970 group, the incidence of additional primary carcinoma was 19.4 per 1,000 person-years. It was 22.2 per 1,000 person-years in the 1971–1979 group, and 33.1 per 1,000 person-years in the 1980–1988 group. The incidence of additional carcinomas thus became higher in the more recently treated patients.

The cumulative rates of additional primary carcinoma by yearly interval are illustrated in Fig. 1. Here we can see that the cumulative rate curve of the 1980–1988 group showed a plateau after the sixth year because of the shortness of the observation period, which indicates that comparison of the three cumulative rate curves should be carried out only for the first five years. During this period the 1980–1988 group showed much higher cumulative rates of additional primary carcinoma than the other two groups. Although the difference in the cumulative rates between the 1980–1988 group and the 1962–1970 group, or that between the 1980–1988 group and the 1971–1979 group, was not statistically significant by any of the Mantel-Haenszel test, logrank test, generalized Wilcoxon test, and Cox-Mantel test, we can at least state that the cumulative rate of additional primary carcinoma during the first five years of observation showed a tendency to increase in the most recently treated (1980–1988) group.

For each site, the observed (O) and expected (E) numbers of carcinoma and their ratio (observed-to-expected ratio, O/E ratio) were calculated (Table II). Because the cancer incidence tables we used[12, 13] classified all carcinomas of the oral cavity and pharynx into one category, we could not estimate the expected cancer

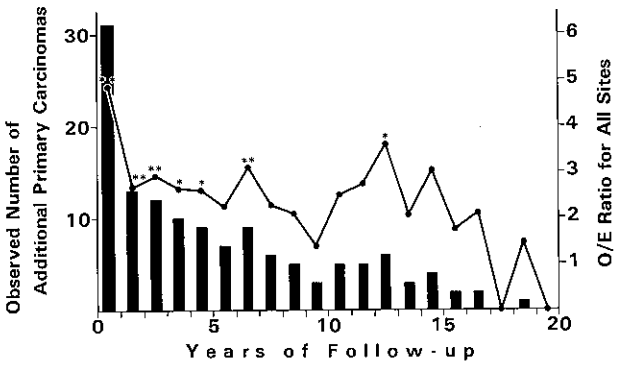

Fig. 2. The annual change of the observed number of additional primary carcinomas (■) and the O/E ratio for all sites (●). ** $P<0.01$, * $P<0.05$.

occurrence or O/E ratio of each subsite in the oral cavity and pharynx.

The O/E ratio for all sites was 2.77 and this is statistically significant ($P<0.01$). The O/E ratio for the oral cavity and pharynx was extremely high (79.45), and statistically significant ($P<0.01$). Significantly high O/E ratios were also observed for the esophagus and skin. The occurrence of stomach cancer, lung cancer, or laryngeal cancer was not significantly high.

Figure 2 shows the observed number of additional primary carcinomas and the O/E ratio for all sites in each year of follow-up. Usually the observed number of additional primary carcinomas is the highest at the beginning of observation and decreases with the lapse of time, which exactly corresponded to our result.

Regarding the annual change of additional carcinoma risk, the O/E ratio gives the most accurate information. As can be seen in Fig. 2, the O/E ratio was the highest (4.83) in the first year of follow-up, stayed nearly constant (between 2 and 3) from the second to 14th years and decreased gradually afterwards. The last part of the curve was rather unstable because of the small number of patients observed: 115, 89, 72, 60 and 48 patients were followed up in the 16th, 17th, 18th, 19th and 20th years, respectively. Statistical significance was found in the first five years, and the seventh and 13th years. The most important result is that significantly high risk for additional primary carcinoma was recognized as late as in the 13th year of follow-up ($P<0.05$).

The five-year cumulative survival rate of the 984 index cancers was 61.8% with the standard error of 1.6%. The five-year cumulative survival of 145 patients with additional primary carcinoma was 61.1%, and that of 839 patients without additional carcinoma was 62.2%. There was no significance in the difference between these two survival curves by any of the Mantel-Haenszel test, logrank test, generalized Wilcoxon test, and Cox-Mantel test.

DISCUSSION

In 1932, Warren and Gates[10] reported that they had encountered 3.7% of multiple cancer cases in their 1,078 malignant disease autopsies. As information on multiple primary cancer has accumulated, the reported incidence has increased. Vrabec (1979)[2] found that 11.5% of 1,518 head and neck cancer patients had multiple cancers. For the incidence of multiple primary carcinoma in oral cancer patients, even higher figures have been presented in recent reports, such as 17.7% by Gluckman *et al.* (1980),[3] 18.5% by Gluckman and Crissman (1983),[5] 18.0% by Kinzie *et al.* (1984),[6] and 17.6% by De Vries *et al.* (1986).[7] Tepperman and Fitzpatrick (1981)[4] reported that out of 377 patients with squamous cell carcinoma of the floor of the mouth, 27% developed second cancers. In Japan, Shibuya *et al.* (1987)[8] found that the incidence of additional carcinoma in oral cancer patients was 8.2%.

In all these reports, the incidence of additional primary carcinoma was expressed as the percentage of patients who developed additional carcinoma. The incidence in our series expressed in this way is 11.2%. This figure is lower than those reported in the United States or Europe, but higher than that reported by Shibuya *et al.*[8]

The incidence of additional primary carcinoma in our series can be expressed in another way: 23.7 per 1,000 person-years; that is, we could observe 23.7 additional primary carcinomas in the follow-up of 1,000 patients for one year. In other words, about one case of additional carcinoma developed every year when 40 oral cancer patients were followed up. We think that the incidence expressed as occurrences per 1,000 person-years gives more precise information than the percentage because the former is not influenced by the difference in the observation period.

As we had suspected, the occurrence of additional carcinoma showed a tendency to increase in the most recently treated patients. This trend can be explained by several factors: a greater awareness of the multiple cancer phenomenon which has stimulated a more extensive search,[5] more complete pathologic study of the operative and autopsy specimens,[2] better treatment methods which have resulted in an increased number of successfully treated patients with longer follow-up periods,[2] and a possibly true increase in the occurrence of additional carcinoma. Because our strategies for examination and treatment of oral carcinoma have not changed substantially during the past 27 years, a true increase in the occurrence of additional carcinoma from an unknown cause is strongly suspected.

The fact that additional carcinomas in oral cancer patients most frequently developed in the same area as the index cancer is consistent with several reports.[2, 4, 7, 8] However, we must be careful in the evaluation of this result because, although we excluded all lesions found at the same site as the index cancer and all doubtful lesions, there still remains a possibility that some recurrent lesions were erroneously included as additional malignancies. Another difficult problem with this result is the effect of radiotherapy. Because many patients received radiotherapy for the initial oral squamous cell carcinoma, radiation-induced cancer could develop in the radiation field, which would account for the high frequency of additional malignancies in the oral cavity and pharynx. This hypothesis cannot either be accepted or rejected because presently we do not have any established method to demonstrate that a cancer lesion is truly radiation-induced. Individual studies are necessary to establish the true effect of radiotherapy on the development of additional carcinoma.

With calculation of the expected number of additional primary carcinomas by the person-year method and comparison of this expected number with the observed number of additional malignancies according to the Poisson distribution, we could establish that the high frequency of additional primary carcinoma in oral cancer patients is statistically significant. Although there have been many reports on this subject, only two reports[4, 8] approached the problem with the same statistical analyses.

It is noteworthy that these two reports define the statistically high risk area in somewhat different ways from ours. Tepperman and Fitzpatrick[4] showed that significantly high O/E ratios were observed for the oral cavity, upper respiratory area (including the nasal cavity, sinuses, nasopharynx, mesopharynx, hypopharynx, and larynx), lung and esophagus. Shibuya *et al.*[8] indicated that the statistically high risk area included the oral cavity and pharynx, esophagus, lung, larynx and skin. In our series, significant risk was observed for the oral cavity and pharynx, esophagus and skin. The occurrence of lung cancer or laryngeal cancer was not statistically significant in our study. Significantly high risk for the oral cavity, mesopharynx, hypopharynx and esophagus was common in all these reports.

Although the reason for the high frequency of additional malignancies in oral cancer patients is yet to be identified, the most convincing hypothesis is the "field cancerization" theory originally proposed by Slaughter *et al.*[1]; several carcinogens act on areas of squamous mucosa, producing an irreversible change toward cancer extensively, but not uniformly. Cancer develops first where the carcinogenic stimuli have been maximal and more cancers develop later in areas subjected to lesser carcinogenic stimuli. This theory corresponds very well to clinical situations where multiple primary cancers are observed. According to the reports of Tepperman and Fitzpatrick[4] and Shibuya *et al.*,[8] carcinogens acting on the oral cavity also affect the entire respiratory and upper digestive tracts. Our result, however, confines the effect of the carcinogens to the oral cavity, mesopharynx, hypopharynx, and esophagus.

The high risk of additional carcinoma in the skin in our series could result from an irrelevantly low morbidity listed in the cancer incidence tables, as stated by Shibuya *et al.*[8]

The O/E ratio for all sites in each year of follow-up remained between 2 and 3 until the 14th year. After the 15th year the reliability of the calculated O/E ratio must be very low, because the number of observed patients was rather small. We cannot, therefore, decide whether the overall gradual decrease in the O/E ratio after the 15th year is reflecting a natural course in the occurrence of additional primary carcinoma, or is just a result of insufficient data. The most important result is that second carcinoma risk was significantly high as late as in the 13th year of follow-up. We can conclude that patients with oral squamous cell carcinoma have higher risk of developing additional primary carcinoma for more than ten years and must be under frequent and regular examination, especially of the high risk area, for almost 15 years.

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