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# The Prognostic Effect of Tobacco and Alcohol Consumption in Intra-oral Squamous Cell Carcinoma

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**The aim of this study was to assess the potential prognostic value of tobacco and alcohol consumption in 161 consecutive patients with intra-oral squamous cell carcinoma. The patients were included in a prospective clinico-experimental and epidemiological study to secure valid data on tobacco and alcohol consumption. Univariate analysis showed that patients with an alcohol consumption above the median had a significantly ($P=0.03$) poorer prognosis than other patients, with 5-year cause-specific survivals of $54 \pm 6$ and $33 \pm 6\%$, respectively. Similarly, patients with a tobacco consumption above the median had a worse prognosis than other patients, with 5-year cause-specific survivals of $55 \pm 6$ and $39 \pm 6\%$, respectively. This difference was on the borderline of significance, $P=0.056$. Tobacco and alcohol consumption were correlated and each of them correlated with sex, males having a higher consumption than females. T-stage, N-stage, clinical stage, tumour size and sex all had a significant prognostic impact. To elucidate whether tobacco and alcohol consumption had an independent prognostic value, a multivariate analysis by means of the Cox proportional hazards regression analysis was performed. This analysis showed that clinical stage ($P=2 \times 10^{-5}$), tumour size ($P=0.007$) and tobacco consumption ($P=0.046$), but not alcohol consumption, had significant influences on prognosis. Thus, smoking cessation programmes seem warranted both from a prophylactic and a therapeutic point of view.**

**Keywords: oral carcinoma, prognosis, tobacco consumption, alcohol consumption**

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## INTRODUCTION

INTRA-ORAL CANCER accounts for a little less than 1% of all reported cancers in Denmark and the histology is planocellular (including verrucous) carcinoma in some 90% [1]. The incidence has been rising steadily in both sexes since the beginning of the 1960s [2]. Although this period has seen therapeutic and diagnostic advances in oncology in general, the prognosis remains poor in intra-oral squamous cell carcinoma [3]. The rise in its incidence has thus been matched by a parallel increase in its mortality in Denmark [1].

Tobacco and alcohol consumption have been established as independent risk factors for the development of intra-oral squamous cell carcinoma [4, 5], and a Danish study has demonstrated that the rise in incidence has coincided with a significant increase in alcohol consumption since the 1960s [2].

The prognostic evaluation of intra-oral squamous cell carcinoma and, by implication, its management is mainly based on the TNM system. However, in recent years a number of non-therapeutic factors have been added to the list of prognostically relevant parameters. They include age, sex, tumour histology and cellular and molecular parameters; factors that may reflect a specific tumour's biology and, therefore, may be a valuable supplement to the TNM system [6, 7].

The connection between tobacco and alcohol consumption and intra-oral squamous cell carcinoma has been well known for years. Still then, only a few studies [8–10] have studied how such consumption affects the prognosis and none have applied a multiple factor analysis.

Browman *et al.* [11] have shown that patients with head-and-neck cancer who continue smoking during radiotherapy have a significantly lower response rate and poorer survival than other patients. Silverman *et al.* [12], following 160 patients with head-and-neck cancer, observed a reduced risk for second primary oral/oropharyngeal cancer among patients who either reduced their smoking or quitted altogether. In a recent study by Pradier *et al.* [13], alcohol consumption was found to give significant, independent prognostic information about survival in patients with laryngeal carcinoma.

Studies of cancers outside the head and neck have established a relationship between tobacco consumption and

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prognosis [14–17], and other studies have shown that smokers tend to present with more advanced disease [18, 19].

The purpose of the present study is to test if tobacco and alcohol consumption affects the prognosis of intra-oral squamous cell carcinoma in a well-defined consecutive group of patients on whom reliable information about tobacco and alcohol consumption was available. If this is so, whether this could be explained by a tendency for these patients to present with more advanced disease.

## PATIENTS AND METHODS

In the period 1 January 1986 to 1 November 1990 a total of 162 patients, 98 males and 64 females, were treated at the Aarhus University Hospital for primary intra-oral squamous cell carcinoma. The hospital's catchment area counts some 1.4 million inhabitants and the study period saw a total number of 167 newly diagnosed cases. 5 patients received primary therapy at another hospital and 1 patient (male) was excluded from the present study because of uncertainty about the reported history. All 161 patients were included in a prospectively-designed combined clinico-experimental and epidemiological study. The clinical examination involved a meticulous observation of the oral cavity including TNM classification and measurement of the tumour's maximum diameter (T size). Additional parameters included sex and age.

The status of all patients was evaluated in May 1993, resulting in a follow-up period ranging between 2.5 and 7.4 years in patients who were still alive at the time. Outcome was assessed by corrected (cause-specific) survival. The endpoint was defined as death with disease, whether or not this was the primary cause of death.

*Assessment of tobacco and alcohol consumption*

The patients were asked to fill in a questionnaire on admission in order to establish their exposure to tobacco and alcohol. To facilitate calculation of the life-time consumption, patients were asked for major changes in their consumption and the number of years with a specific level of consumption. Patients were asked for their daily consumption of cigarettes, cheroots, cigars and pipe tobacco. Tobacco exposure was expressed as grams of tobacco per day (cigarette equivalents): 1 cigarette was set to the equivalent of 1 g of tobacco, 1 cheroot 1.2 g, 1 cigar 8.0 g and 1 pack of pipe tobacco 50 g. Similarly, patients were asked for their daily consumption of beer, wine and strong alcohol. Alcohol exposure was assessed as the number of drinks per day: 1 beer was set to the equivalent of one drink, 2 cl of strong alcohol one drink, and 1 bottle of wine six drinks. In the present paper, the patients' current alcohol and tobacco habits were analysed. The motivation for doing this was that this parameter is readily available from the patient. Patients who ceased smoking or drinking less than 2 years before the diagnosis were assigned a current consumption equal to what they had immediately before quitting. In

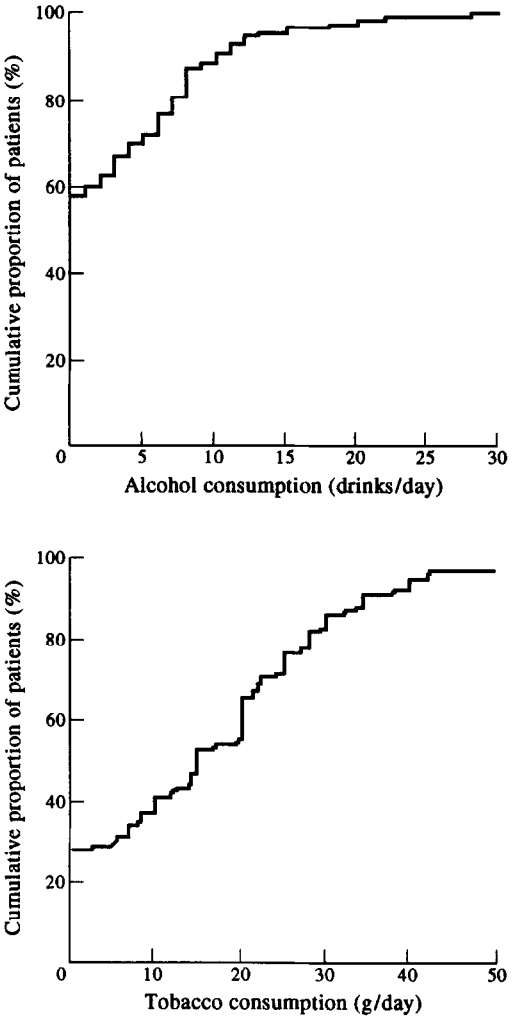


**Fig. 1. Cumulative distribution of patients according to alcohol consumption ($n=157$) and tobacco consumption ($n=153$).**

*Table 1. Single-factor analysis of prognostic clinical parameters, tobacco and alcohol consumption in 161 patients with intra-oral squamous cell carcinoma*

| Prognostic parameter | Groups/cut-off points | No. of cases in each group | 5-year corrected survival (%) | *P*-value |
|---|---|---|---|---|
| T-stage | 1vs. 2 vs. 3 vs. 4 | 62/59/23/17 | 66/38/25/24 | $5\times10^{-8}$ |
| N-stage | $N_0$ vs. $N_+$ | 125/36 | 53/21 | $5\times10^{-7}$ |
| Tumour size (mm) | ≤25 vs. >25 | 82/79 | 66/24 | $<10^{-8}$ |
| Stage | I vs. II vs. III vs. IV | 55/48/27/31 | 69/44/41/12 | $<10^{-8}$ |
| Sex | Female vs. male | 64/97 | 63/33 | 0.005 |
| Age (years) | ≤66 vs. >66 | 82/79 | 42/49 | 0.7 |
| Alcohol consumption (drinks/day) | 0 vs. >0 | 91/66 | 54/33 | 0.030 |
| Tobacco consumption (g/day) | ≤15 vs. >15 | 81/72 | 55/39 | 0.056 |

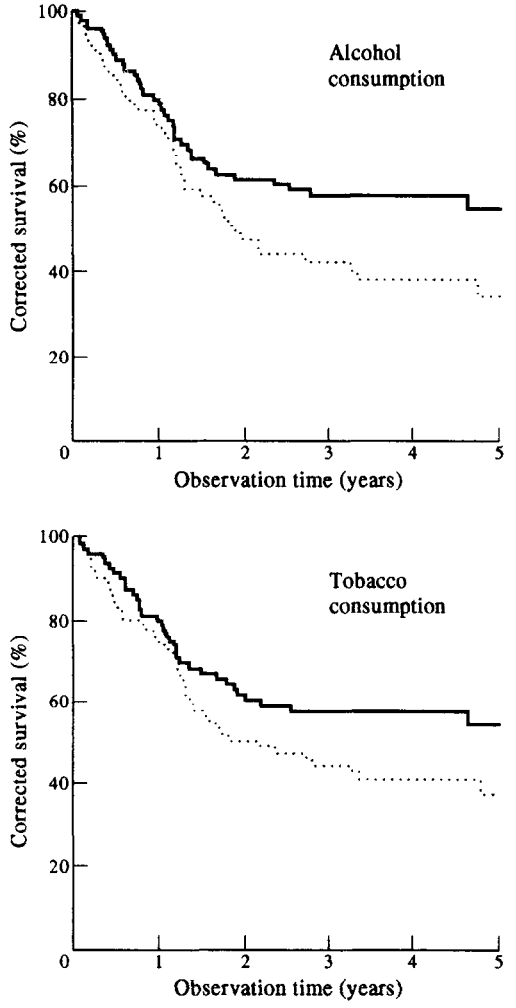


**Fig. 2. Corrected survival according to alcohol (top) and tobacco (bottom) consumption. Cut-off points represent overall median of alcohol and tobacco consumption, respectively. Solid lines indicate a consumption below or at the median and the dotted lines indicate a consumption above the median.**

9 patients the information about current consumption of either tobacco or alcohol was not available. This left 152 patients to be included in the analysis.

*Statistics*

The non-parametric Spearman's rank correlation was used to test the association between alcohol and tobacco consumption on one hand and clinical characteristics on the other. Cause-specific survival was estimated by the Kaplan–Meier method [20]. Univariate tests for the prognostic importance of life-style and patients' characteristics were performed by means of the Mantel–Cox log rank test [21], or, in case of ordered multiple categories, the associated test-for-trend [22]. For univariate testing of the continuous variables, tobacco and alcohol consumptions and tumour size, the patient population was grouped according to the median value of the relevant variable.

The Cox proportional hazards model [23] was employed for multivariate analysis of prognostic factors [24]. The proportional hazards assumption was tested graphically according to the method of Bentzen *et al.* [25]. The log-linear dependence between relative risk and the value of continuous variables was tested by including the square of the variable among the possible prognostic characteristics. As an alternative, a dummy variable indicating values below and above the median was tested for each of the continuous variables. The final model was established by stepwise regression using forward selection of the prognostic factors.

In any case, statistical significance was tested at the 5% level.

## RESULTS

Figure 1 shows the cumulative distribution of the current alcohol and tobacco consumption among the patients. The zero level represents the patients who had not smoked within the past 2 years. For alcohol consumption, the zero level represents the patients who had not enjoyed alcohol on a daily basis within the past 2 years. A total of 24 patients had never smoked and 84 patients had never consumed alcohol on a daily basis. The study included 23 non-users, i.e. patients who had never smoked or consumed alcohol on a daily basis.

Table 1 shows the distribution of the clinical variables and the results of the univariate analysis. T-stage, N-stage, clinical stage, tumour size, sex and alcohol consumption were all statistically significant predictors of survival ($P<0.05$), and tobacco consumption was borderline significant ($P=0.056$).

Figure 2 depicts the corrected survival according to current tobacco consumption and current alcohol consumption.

Tobacco and alcohol consumption and the parameters having a prognostic impact in the single-factor analysis were evaluated by means of a multivariate Cox analysis. Patients on whom data were missing for any of the variables ($n=9$) were excluded from this analysis.

The multivariate analysis (Table 2) showed that only clinical stage, tumour size and current tobacco consumption carried significant independent prognostic information. The

*Table 2. Multivariate analysis of prognostic clinical parameters, tobacco and alcohol consumption in 152 patients with intra-oral squamous cell carcinoma*

| Characteristic | Score | β | Relative risk | *P*-value |
|---|---|---|---|---|
| Clinical stage | 1/2/3/4 | 0.55 | 1.7* | $2\times10^{-5}$ |
| Size below/above median | 0/1 | 0.72 | 2.1 | 0.007 |
| Tobacco consumption | 0.01 × square of consumption (g/day) | 0.026 | 1.26† | 0.046 |
| Alcohol consumption | 0.01 × square of consumption (drinks/day) | n.e. | n.e. | 0.29 |

n.e., not estimated. * Relative risk for a specific stage relative to the preceeding stage (e.g. III vs. II). † Relative risk from smoking 30 cigarettes per day vs. no smoking.

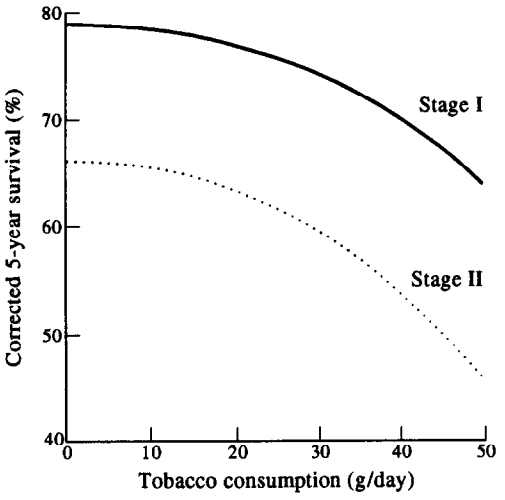


**Fig. 3. Survival according to tobacco consumption. Model-predicted survival curves for patients with stage I and II intraoral squamous cell carcinoma and with tumour diameter lower than or equal to the median.**

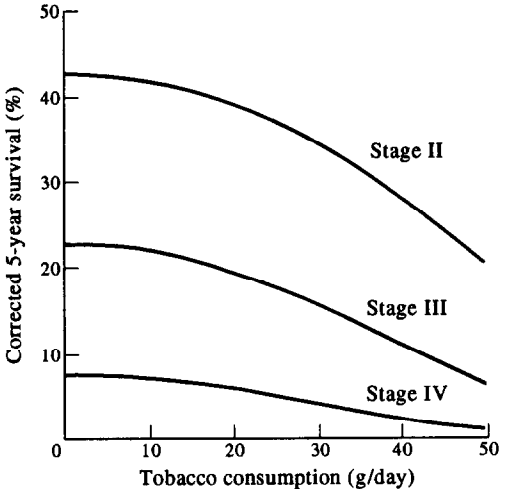


**Fig. 4. Survival according to tobacco consumption. Model predicted survival curves for patients with stage II, III and IV intraoral squamous cell carcinoma and with tumour diameter greater than the median.**

optimal method of representation of these characteristics was to dichotomise tumour size (below/above the median), and to use the square of the tobacco consumption. The correlation between T-stage and tumour diameter eliminated the possibility that the former would be an independent significant prognostic parameter and the correlation between clinical stage and N stage also eliminated the N-stage as a significant independent prognostic marker.

Figures 3 and 4 depict the relationship between corrected survival and tobacco consumption. Figure 3 shows the survival course in patients with stage I and II tumours with a tumour size that is smaller than the overall median. Figure 4 shows the survival among patients with stages II, III and IV tumours and tumour size that is larger than the overall median.

Testing the relationship between the parameters examined revealed a significant correlation between sex and tobacco ($P = 5 \times 10^{-5}$) and between sex and alcohol ($P = 2 \times 10^{-6}$). Likewise, there was a highly significant correlation ($P < 10^{-8}$) between tobacco and alcohol consumption (Table 3). A high intake of alcohol was almost invariably accompanied by a high tobacco consumption, whereas the reverse was not necessarily true (Figure 5).

## DISCUSSION

The study demonstrates that consumption of alcohol and tobacco is closely associated not only with the development of oral cancer, but also with the course of the disease. The univariate analysis established that both alcohol consumption and tobacco consumption were associated with a poor prognosis. So were the conventional clinical parameters: T-stage, N-stage, clinical stage, tumour diameter and sex. This confirms the utility of the TNM system as a predictor of survival in intra-oral cancer.

The multivariate analysis eliminated alcohol consumption and sex as independent prognostic markers. As is apparent from Table 3, the association between alcohol consumption and T-stage, N-stage and disease stage was non-significant. Inversely, the association between alcohol and tobacco was highly significant. The significant prognostic impact of alcohol on survival, as demonstrated in the single factor analysis, may possibly be ascribed to the strong correlation between alcohol and tobacco consumption, that is the effect of alcohol is confounded by tobacco consumption.

The analysis demonstrates that tobacco consumption has a significant prognostic impact in itself. Thus, as shown in Figure 3, tobacco consumption considerably affects the prog-

*Table 3. Correlation between tobacco/alcohol consumption and clinical parameters in 152 patients with intra-oral squamous cell carcinoma*

| | Tobacco consumption | | Alcohol consumption | |
|---|---|---|---|---|
| | Spearman's rank correlation coefficient | *P*-value | Spearman's rank correlation coefficient | *P*-value |
| T-stage | 0.11 | 0.17 | 0.11 | 0.18 |
| N-stage | 0.05 | 0.5 | 0.06 | 0.43 |
| Stage | 0.13 | 0.11 | 0.12 | 0.13 |
| Sex* | 0.32 | $5 \times 10^{-5}$ | 0.37 | $2 \times 10^{-6}$ |
| Alcohol consumption | 0.46 | $< 10^{-8}$ | — | — |

*Males had a greater consumption than females.

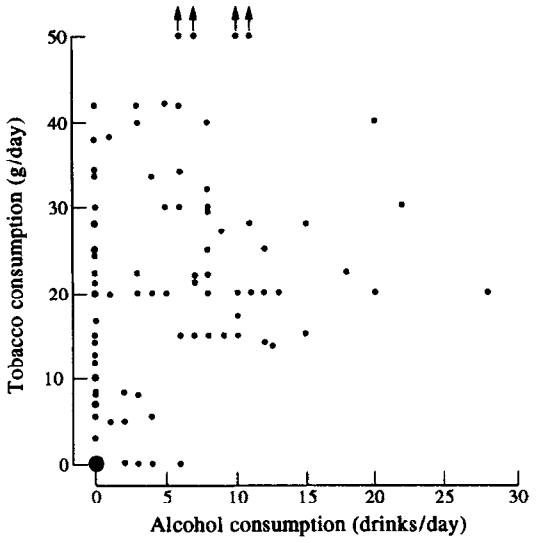


**Fig. 5. Scatterplot of the tobacco consumption vs. the alcohol consumption in patients with intra-oral squamous cell carcinoma ($P < 10^{-8}$). The area of each circle is proportional to the number of patients represented by the point.**

nosis, namely a patient in stage I with a tobacco consumption of about 45 g/day has the same prognosis as a non-smoker in stage II. This also applies when the disease has progressed to later stages (Fig. 4).

The multivariate analysis has so far only found little use [26, 27] in studies of the prognosis in oral cancer, and none of the available studies have included tobacco and alcohol consumption among their parameters. In a retrospective study of 176 patients with oral carcinoma, Tytor *et al.* [26] were not able to assess the impact of alcohol because their data were insufficient, nor were they able to significantly relate tobacco exposure to survival when stratifying their population into smokers and non-smokers.

Epidemiological studies have clarified the most important aetiological risk factors involved in the development of intra-oral squamous cell carcinoma [4, 5, 28]. A direct dose-related carcinogenic effect, as well as a synergic effect of tobacco and alcohol has been shown. The number of tobacco-associated cancers that occurs throughout the world is related to the long-term dose of carcinogens in tobacco, and tobacco is associated to many neoplastic and non-neoplastic diseases. An association between the prognosis of cancer of the tongue and tobacco and/or alcohol use has been reported by Johnston *et al.* [9]. Thus, users had a higher mortality from intercurrent diseases than non-users, they had a higher frequency of second primary tumours, and a higher mortality from primary tumours and/or second primary tumours. However, in our study corrected survival was used.

The individual prognostic impact of tobacco consumption suggests that apart from being an aetiological determinant, tobacco might also affect the tumour–host relationship in patients with intra-oral carcinoma. It is well known that smoking alters a person's immunological profile [29, 30] and exposure to smoke from cigarettes has been shown to accelerate tumour progression in animal studies [31]. Smoking increases the carboxyhaemoglobin content of the blood and the left-shift of the haemoglobin–oxygen dissociation curve may cause a relative tissue hypoxia which may reduce the effect of radiotherapy [11]. In this study, the patients tobacco habits after the diagnosis was not investigated. Yet, the current tobacco consumption at the time of diagnosis had an independent prognostic impact on all patients irrespective of the chosen treatment modality.

All data on tobacco and alcohol consumption were gathered at the time of diagnosis, i.e. without any knowledge of the course of the disease. Any such bias may, therefore, be exluded. It is possible, though, that the differences in survival associated with tobacco consumption are related to other unknown factors. Still, the endpoint used was death with oral cancer (corrected survival).

Prognostic variables that can be used in conjunction with the TNM system are valuable to the planning of treatment for oral cancer. Histological grading, DNA content and various cellular characteristics have previously been shown to hold independent prognostic information. In this paper, tobacco consumption has been shown to be yet another prognostic predictor which is even easy to establish when taking the patient's history. Previous studies have established that alterations of the oral mucosa after radiotherapy correlate with smoking during and/or after therapy [32] just as cigarette smoking has been shown to have a negative effect on the result of radiotherapy [11]. The present study shows that a stable tobacco consumption up until the time of diagnosis, in itself has an effect on the prognosis in intraoral carcinoma. A focusing on tobacco consumption would thus seem warranted both from a prophylactic and a therapeutic point of view because it influences the therapeutic strategy to be adopted (a massive exposure to tobacco corresponds, prognostically speaking, to a more advanced disease stage) and because of its relevance to the design and analysis of head-and-neck cancer protocols.


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