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# Case-control study of squamous cell cancer of the oral cavity in Denmark

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**A population-based case-control study was designed to examine if the risk of developing intra-oral squamous-cell carcinoma in Denmark was associated with occupation, marital status, residence, dental status, and exposure to coffee, tea, tobacco, and alcohol. Cases consisted of 161 consecutively-admitted incident patients with histologically verified, primary, intra-oral squamous-cell carcinoma treated at the Aarhus University Hospital from January 1986 to November 1990. For each case, three controls of the same gender and age were selected randomly from among nonhospitalized residents in the hospital's catchment area (some 1.4 m inhabitants). Four hundred of the selected 483 controls participated in the study. Risk was associated significantly with marital status, residence, dental status, alcohol consumption, and exposure to tobacco. When correcting for tobacco and alcohol consumption, only marital status and dental status remained significant. The association between risk and marital status was particularly prominent among divorced compared with married persons (odds ratio [OR] = 2.3, 95 percent confidence interval [CI] = 1.1-4.6). Persons with less than five teeth had an OR of 2.4 (CI 1.3-4.1) compared with persons with 15 or more teeth. Tobacco and alcohol exposure were the strongest individual risk-indicators in both lifetime and current consumption estimates, and their composite effect was particularly strong. Compared with nonusers, OR for tobacco (> 20 g/d) adjusted for alcohol = 5.8 (CI = 3.1-10.9); OR for alcohol (> 5 drinks/d) adjusted for tobacco = 8.4 (CI = 4.0-17.6). The OR for heavy users of tobacco and alcohol (> 20 g tobacco/d and > 5 drinks/d) was 80.7 (CI = 21.8-298.8). These results confirm that tobacco and alcohol contribute significantly to the risk of developing oral cancer. There were no significant differences between the risk estimates for the two genders or young and old persons. Two simulation studies indicate that the observed risk associated with tobacco and alcohol consumption cannot be explained reasonably by a high consumption among the 83 nonrespondents.** *Cancer Causes and Control* 1995, 6, 57–67

*Key words:* Alcohol, Denmark, dental status, intra-oral cancer, population-based study, tobacco.

## Introduction

In Denmark, intra-oral cancer currently accounts for 0.9 percent of all reported cancers among men and 0.6 percent among women.[1] The past decades have seen a steep rise in its incidence.[1] The failure to raise the relative survival from this disease has caused a parallel increase in the mortality, both in Denmark and other west European countries.[2]

In 1989, Møller[3] reported a more than threefold

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**Table 1.** Oral squamous-cell cancer in Denmark: tumor location among 161 consecutive cases

| Site | No. |
|---|---|
| Retromolar area | 9 |
| Buccal mucosa[a] | 21 |
| Floor of mouth | 41 |
| Hard palate | 6 |
| Upper alveolus | 8 |
| Lower alveolus | 27 |
| Tongue | 49 |
| Total | 161 |

[a] Including mucosal surfaces of upper and lower lips.

increase in the cumulative incidence of intra-oral cancer from 1958-62 to 1983-85 in both genders, aged 75 years and under. The incidence of tongue cancers doubled among women and rose by a factor of 2.5 among men.

Intra-oral cancer, in Denmark, is treated either by surgery or radiotherapy, alone or in combination. Such treatment may give rise to serious functional discomfort.[4] Available therapeutic techniques unfortunately remain somewhat unsatisfactory although many attempts have been made recently to evaluate prognostic parameters that will predict more safely the likelihood of survival. The present case-control study includes all patients with intra-oral cancer drawn from a catchment area of 1.4 m inhabitants over a five-year period and a randomly drawn, gender and age-matched control group of nonhospitalized volunteers. The purpose of the study is to evaluate how risk estimates correlate with occupation, dental status, consumption of coffee and tea, marital status, residence (urban/rural), and tobacco and alcohol consumption.

## Materials and methods

From 1 January 1986 to 1 November 1990, 162 patients with newly diagnosed, primary, intra-oral squamous-cell cancer (buccal mucosa, upper alveolus and gingiva, lower alveolus and gingiva, hard palate, tongue, retromolar area and floor of mouth) were treated at the Aarhus University Hospital. (The hospital's catchment area counts some 1.4 m inhabitants.) Five more patients during that period received primary therapy at another hospital and therefore were excluded from the study. One patient at Aarhus Hospital was excluded because of uncertainty about the reported history. Thus, a total of 161 of the 167 incident cases drawn from the hospital's catchment area were enrolled in the study, which includes only histologically verified,

**Table 2.** Age and gender distribution in cases and controls, Denmark

| Age (yrs) | Males | | Females | | Total |
|---|---|---|---|---|---|
| | Cases | Controls | Cases | Controls | |
| ≤ 45 | 8 | 20 | 1 | 3 | 32 |
| 46-55 | 24 | 64 | 9 | 22 | 119 |
| 56-65 | 23 | 60 | 9 | 25 | 117 |
| 66-75 | 27 | 74 | 29 | 62 | 192 |
| > 75 | 15 | 32 | 16 | 38 | 101 |
| Total | 97 | 250 | 64 | 150 | 561 |

primary, squamous cell carcinomas and verrucous carcinomas. The distribution of tumors according to site is given in Table 1. All patients completed a lifestyle questionnaire on admission.

For each case, three gender- and age-matched controls from the same geographic area were drawn randomly from the Danish Central Population Register. A questionnaire was distributed to the nonhospitalized controls identical to that filled out by the cases, with the same wording and same order of questions. The reference period was the same for both groups. Four hundred (83 percent) of the 483 selected controls responded, some 50 percent when first invited to do so, and the rest after having been prompted either in writing or by phone. Table 2 shows the distribution of cases and controls.

Cases and controls were asked a number of questions whose rationale has been explained in previous papers.[5-12] The questions concerned:

- Occupation: beverage industry, tobacco industry, textile industry, clothing industry, graphics industry, paper industry, tanning and leather industry, chemical industry, tailor's workshop, typographer, and waiter;
- Occupational exposure: wood dust, welding fumes, welding fumes from stainless steel welding, organic solvents, textile fibers, and asbestos fibers. Both the time and duration (in years) of the exposure was recorded;
- Tobacco consumption: Registration included consumption of cigarettes, cheroots, cigars, and pipe tobacco. We recorded the quantity of daily consumption, years of such consumption, or number of years since stopping. The analysis uses both life consumption (kg tobacco) and current tobacco consumption (daily consumption, grams of tobacco/day). Tobacco exposure was expressed as 'gram tobacco per day' (cigarette equivalents: one cigarette is equivalent to 1 g of tobacco). One cigarette was set

to the equivalent of 1 g of tobacco, 1 cheroot to 2.8 g, 1 cigar to 8.0 g, and 1 (50 g) pack of pipe tobacco to 50 g. With respect to cigars and cheroots, we have estimated the tobacco content on the basis of information about the most used sorts of cheroots and cigars in Denmark. Participants who quit smoking within the past two years before diagnosis, were set to a daily consumption corresponding to their actual consumption at the time they stopped;

- Chewing tobacco and snuff: Registration included weekly consumption, years at this consumption level, or number of years since quitting;
- Alcohol consumption: Alcohol exposure was assessed as the number of drinks per day and the number of years of exposure. We recorded the use of beer, wine, and spirits. Alcohol exposure was assessed as the number of drinks: one beer was set to the equivalent of one drink; 2 cl (0.7 fluid ozs) of alcohol equals one drink, and one bottle of wine equals six drinks. We recorded the patient's daily alcohol intake (number of drinks/day) and estimated lifetime consumption (total number of drinks). Participants who quit drinking within the past two years before diagnosis were set to a daily consumption corresponding to their actual consumption at the time they stopped;
- Coffee and tea: Registration included daily consumption, years at this consumption level, or, if relevant, the number of years since quitting;
- Dental status: Dental status of upper and lower jaws was described as: own teeth and no dentures; dentures; no teeth and no dentures; partial plastics denture; and partial plastics denture with metal frame. We also recorded the number of own teeth in both upper and lower jaw and the number of years the participants had been using a possible denture;
- Dental check-ups: 'Regular dental check-ups' was defined as visits to the dentist at least once a year. The number of months between check-ups was recorded for participants who visited their dentist regularly.

*Statistics*

The data according to the way controls were selected, were stratified into 10 strata consisting of five age groups for each gender. All statistical analyses used this stratification, *i.e.*, all associations are corrected for gender and age. Initially, the risk associated with each of the factors was estimated by univariate conditional logistic regression. Second, the risk associated with each factor was estimated by trivariate conditional logistic regression adjusting for lifetime consumption of tobacco and alcohol. A multivariate conditional logistic regression model was fitted on the basis of these results and knowledge of the subject matter. The question of a possible synergistic effect of tobacco and alcohol was tested by introduction of a interaction between these factors. The prognostic value of the different ways to report the tobacco and alcohol consumption was evaluated by comparing the fit of multiplicative models.

In general, the results reported here assume that the risk associated with each factor is independent of gender and age. The appropriateness of the assumption was checked by fitting both the univariate and the multivariate models with interaction between gender and each factor, and age and each factor. These analyses showed no substantial interaction between any factor and gender or age ($\leq$ 65 yrs *cf* $>$ 65 yrs).

Bias may have resulted from the fact that not all the eligible controls participated in the study; however, these were analyzed by means of simulation. Pseudo-controls for the 83 nonrespondents were generated in two different ways: (i) a pseudo-control was taken as a random case from the appropriate age and gender strata and assigned the characteristics of this case (for each set of 83 pseudo-controls, a multiplicative model containing life consumption of tobacco and alcohol and dental status was fitted); and (ii) a pseudo-control was taken as a random control from the correct strata and assigned the same number of teeth of this control, while the tobacco and alcohol consumptions were doubled. This was repeated 1,000 times for each of the two ways of generating pseudo-controls and the results were compared with the one obtained on the original dataset.

Risk factors with more than two levels were tested by likelihood ratio tests. The level of statistical significance is set to five percent. The main part of the statistical analysis was performed using the EPICURE program package.[13]

## Results

Table 3 shows the main results of the univariate analyses.

*Marital status*

The study population was divided into four categories: married, unmarried, divorced, widow/widower. The univariate analysis showed that the risk of intra-oral cancer was associated significantly with marital status ($P < 0.001$), particularly for divorced (odds ratio [OR] = 4.0, 95 percent confidence interval [CI] = 2.2-7.3) compared with married persons. Adjusting for tobacco and alcohol exposure did reduce this association, but the association was still significant.

**Table 3.** Odds ratio (OR) for intra-oral cancer, Denmark

| Factor | Group | Cases/controls | Crude | | Corrected[a] | |
|---|---|---|---|---|---|---|
| | | | OR | (CI)[b] | OR | (CI)[b] |
| Marital status | Married | 90/258 | 1 | — | 1 | — |
| | Unmarried | 11/32 | 1.0 | (0.5-2.0) | 1.2 | (0.5-2.7) |
| | Divorced | 30/24 | 4.0 | (2.2-7.3) | 2.3 | (1.1-4.6) |
| | Widow/widower | 30/84 | 0.9 | (0.5-1.5) | 0.6 | (0.3-1.1) |
| | | | | $P < 0.001$ | | $P = 0.02$ |
| Residence | Rural area | 13/55 | 1 | — | 1 | — |
| | City <1000 inhab. | 21/65 | 1.3 | (0.6-2.9) | 1.1 | (0.5-2.7) |
| | 1,000-<10,000 inhab. | 29/101 | 1.2 | (0.6-2.5) | 1.7 | (0.7-3.9) |
| | 10,000-<100,000 inhab. | 72/121 | 2.5 | (1.3-4.8) | 1.1 | (0.5-2.4) |
| | 100,000+ inhab. | 26/58 | 1.9 | (0.9-4.0) | 1.2 | (0.4-2.9) |
| | | | | $P = 0.008$ | | $P = 0.5$ |
| Textile worker | No | 148/381 | 1 | — | 1 | — |
| | Yes | 13/19 | 1.7 | (0.8-3.6) | 1.4 | (0.6-3.1) |
| Waiter | No | 154/397 | 1 | $P = 0.2$ | 1 | $P = 0.4$ |
| | Yes | 7/3 | 5.8 | (1.5-23.0) | 2.9 | (0.6-13.5) |
| | | | | $P = 0.007$ | | $P = 0.2$ |
| Coffee | Nondrinker | 5/17 | 1 | — | 1 | — |
| | Drinker | 155/378 | 1.4 | (0.5-3.8) | 1.4 | (0.4-4.5) |
| | | | | $P = 0.5$ | | $P = 0.6$ |
| Tea | Nondrinker | 109/239 | 1 | — | 1 | — |
| | Drinker | 51/151 | 0.7 | (0.5-1.1) | 0.9 | (0.6-1.4) |
| | | | | $P = 0.1$ | | $P = 0.6$ |
| Number of teeth | 15+ | 42/165 | 1 | — | 1 | — |
| | 5-14 | 31/66 | 2.0 | (1.2-3.6) | 1.9 | (1.1-3.4) |
| | 0-4 | 88/167 | 2.4 | (1.5-4.0) | 2.4 | (1.3-4.1) |
| | | | | $P = 0.001$ | | $P = 0.008$ |
| Dental check-up | Regularly | 56/203 | 1 | — | 1 | — |
| | Not regularly | 105/196 | 2.1 | (1.4-3.2) | 2.1 | (1.3-3.3) |
| | | | | $P < 0.001$ | | $P = 0.002$ |
| Tobacco[c] | 0 | 25/136 | 1 | — | 1 | — |
| (Lifetime consumption) | 1-135 kg | 30/116 | 1.8 | (1.0-3.3) | 1.7 | (0.9-3.2) |
| | 136-235 kg | 32/76 | 3.3 | (1.7-6.3) | 2.5 | (1.3-5.0) |
| | 236+ kg | 73/68 | 11.3 | (5.9-21.8) | 6.3 | (3.1-12.9) |
| | | | | $P < 0.001$ | | $P < 0.001$ |
| Tobacco[c] | 0 | 43/228 | 1 | — | 1 | — |
| (Current consumption) | 1-20g/day | 58/128 | 2.7 | (1.7-4.3) | 2.1 | (1.3-3.5) |
| | 21+ g/day | 52/41 | 9.1 | (5.1-16.1) | 5.8 | (3.1-10.9) |
| | | | | $P < 0.001$ | | $P < 0.001$ |
| Alcohol | 0 | 84/310 | 1 | — | 1 | — |
| (Lifetime consumption) | 1-<40,000 drinks | 24/70 | 1.5 | (0.9-2.6) | 1.1 | (0.6-2.0) |
| | 40,000+ drinks | 53/19 | 14.3 | (7.6-26.7) | 7.5 | (3.9-14.7) |
| | | | | $P < 0.001$ | | $P < 0.001$ |
| Alcohol | 0 | 91/318 | 1 | — | 1 | — |
| (Current consumption) | 1-5 drinks/day | 22/67 | 1.3 | (0.7-2.3) | 0.9 | (0.5-1.7) |
| | 6+ drinks/day | 44/13 | 15.6 | (7.8-31.4) | 8.4 | (4.0-17.6) |
| | | | | $P < 0.001$ | | $P < 0.001$ |

[a]Corrected for lifetime consumption of tobacco and alcohol.
[b]CI = 95% confidence interval.
[c]1 g tobacco equals one cigarette.

*Residence*

Cases and controls were stratified into five groups according to the following criteria: residing in a rural area or village (< 1,000 inhabitants), small town (1,000-< 10,000 inhabitants), town (10,000-< 100,000 inhabitants), or city (100,000 + inhabitants). The univariate analysis showed a significant association between place of habitation and risk ($P = 0.008$). However, this

significance disappeared when adjusting for alcohol and tobacco exposure.

*Occupation*

Only participants employed in textiles or as waiters seemed to have an elevated risk, but as the study contained only a moderate number of such persons, the results are uncertain. Univariate analysis showed no significant increase in the risk for textile employees, but occupation as a waiter implied a significantly increased risk ($P = 0.007$). However, this significance disappeared when adjusting for alcohol and tobacco exposure.

*Coffee and tea*

Neither coffee nor tea exposure could be linked to the development of intra-oral cancer.

*Chewing tobacco and snuff*

Very few participants from either study group reported a current or previous consumption of chewing tobacco and snuff. Eight patients and 14 controls were using or had used chewing tobacco. No one in either group was using snuff and very few individuals had a previous history of snuff exposure. A single patient had a carcinoma at precisely the site in the oral cavity where he had habitually put his chewing tobacco for the past 20 years.

*Dental status*

Controls had more teeth in both upper and lower jaws than cases. Inversely, the proportion of individuals wearing a denture was higher among cases than among controls. This trend applied for all age groups.

We observed a significant association between the risk of intra-oral cancer and the number of own teeth ($P < 0.001$). The OR was 2.4 (CI = 1.5-4.0) when comparing persons with less than five teeth with persons with 15 or more teeth. This association remained significant when corrected for alcohol and tobacco consumption.

Thirty-five percent of the cases had regular dental check-ups compared with 51 percent of controls. A univariate analysis corrected for alcohol and tobacco exposure established a corresponding risk association of OR = 2.1 (CI = 1.3-3.3).

*Tobacco*

Single-factor analysis on cases and controls grouped as smokers and nonsmokers, established the significant association between risk and smoking in general, and cigarette and cheroot smoking in particular. Among cases, 98 smoked cigarettes, 55 smoked cheroots, and 39 and seven smoked pipes and cigars, respectively. The OR for lifetime consumption of cigarettes greater than 235 kg was 5.5 (CI = 2.9-10.5). The OR for life consumption of cheroots greater than 135 kg was 3.1 (CI = 1.8-5.4). There was a significant correlation between life consumption of tobacco and daily consumption at the time of the interview. The risk was associated positively with consumption, as shown in Table 3.

*Alcohol*

Alcohol exposure showed the strongest association with intra-oral cancer, whether analyzed by single-factor analysis or multivariate analysis. The risk was increased significantly among daily users compared with non-daily users of alcohol. Risk was associated positively with consumption, as shown in Table 3.

A significant risk was associated with daily consumption of beer (yes/no) (OR = 4.0, CI = 2.6-6.2) and spirits (yes/no) (OR = 2.6, CI = 1.5-4.5), but not wine (12 cases and 24 controls consumed wine on a daily basis). Beer was, by far, the most important source of alcohol (66 cases and 70 controls were drinking beer daily), and the OR for a lifetime consumption of 40,000 or more drinks of beer was 16.0 (CI = 7.6-32.2) compared with nondrinkers.

Patients with advanced-stage onset of intra-oral carcinoma (Stage IV) were not exposed significantly more to tobacco and alcohol than patients whose onset was diagnosed at earlier stages (daily tobacco consumption $P = 0.2$, daily alcohol consumption $P = 0.7$).

*Multivariate analysis*

The results of a multivariate analysis including the main risk factors is shown in Table 4. These results indicate that the important risk factors for intra-oral cancer are tobacco and alcohol consumption and dental status. As there is a very close association between the number of own teeth and regular dental check-ups (Table 5) only one of these factors (number of teeth) was used in a multivariate analysis. The results, when including regular dental check-ups, is analogous.

Table 6 shows the risk estimates for combinations of tobacco and alcohol consumption. It appears from the table that there is a close relationship between tobacco and alcohol exposure, as virtually all who drink alcohol also smoke. The data showed no indication of deviation from a multiplicative effect tobacco and alcohol consumption.

We have used three different measures of exposure to alcohol and tobacco: users/nonusers, current daily consumption, and lifetime consumption. Table 7 contains a comparison of these three measures as risk indicators, adjusted for the other significant risk factors listed in Table 4. It is seen that current consumption and lifetime consumption yield similar fit, while the more

**Table 4.** Odds ratio (OR) for intra-oral cancer, results of multiple analysis including the listed factors, Denmark

| Factor | Group | OR | CI[a] |
|---|---|---|---|
| Marital status | Married | 1 | — |
| | Unmarried | 1.1 | (0.5-2.7) |
| | Divorced | 2.0 | (1.0-4.2) |
| | Widow/widower | 0.6 | (0.3-1.0) |
| | | | $P = 0.03$ |
| Residence | Rural area | 1 | — |
| | City < 1000 inhab. | 1.1 | (0.5-2.7) |
| | 1,000-< 10,000 inhab. | 1.2 | (0.5-2.8) |
| | 10,000-< 100,000 inhab. | 1.7 | (0.8-3.7) |
| | 100,000 + inhab. | 1.2 | (0.5-3.0) |
| | | | $P = 0.6$ |
| Number of teeth | 15 | 1 | — |
| | 5-14 | 2.1 | (1.1-4.0) |
| | 0.4 | 2.4 | (1.4-4.3) |
| | | | $P = 0.007$ |
| Tobacco[b] | 0 kg | 1 | — |
| (Lifetime consumption) | 1-135 kg | 1.7 | (0.9-3.4) |
| | 136-235 kg | 2.2 | (1.1-4.5) |
| | 236+ kg | 6.1 | (2.8-13.0) |
| | | | $P < 0.001$ |
| Alcohol | 0 | 1 | — |
| (Lifetime consumption) | 1-<40,000 drinks | 1.2 | (0.7-2.2) |
| | 40,000+ drinks | 6.7 | (3.3-13.4) |
| | | | $P < 0.001$ |

[a]CI = 95% confidence interval.
[b]1 g tobacco equals one cigarette.

crude division into users and nonusers does not give quite as good a fit.

*Possible selection bias*

The number of participants in the study was reduced by 83 of the 483 control persons drawn for the study. One could expect the alcohol and tobacco consumption among these nonrespondents to be higher than among the responders. This would result in an overestimation of the risk associated with tobacco and alcohol consumption. The potential bias that nonresponders may have introduced into the control material was assessed by two simulation studies, as described earlier.

**Table 5.** Association between the number of teeth and regular dental check-ups, Denmark

| Regular dental check-ups | Number of teeth | | | |
|---|---|---|---|---|
| | 0-4 | 5-14 | 15-32 | Total |
| Yes | 20 | 52 | 186 | 258 |
| No | 234 | 45 | 21 | 300 |
| Total | 254 | 97 | 207 | 558 |

The results pooled in Table 8 show that tobacco, alcohol, and dental status kept their status as significant risk indicators even when nonresponders were set to a high level of tobacco and alcohol consumption.

## Discussion

This Danish population-based case-control study of risk factors of intra-oral squamous-cell carcinoma has confirmed the general picture of a greatly exacerbated risk by alcohol and tobacco consumption and has furnished contributory evidence to the role of dental status and the importance of regular dental check-ups reported by other studies.[12,14,15] Correcting for these factors, we also report a significant association with marital status, which would seem to indicate that intra-oral cancer is to a large extent a 'lifestyle malady.'[16] Both dental and marital status, however, may be related to factors we have not analyzed, such as nutritional status, vitamin supplementation, etc. Other studies have established a link between these factors and intra-oral cancer.[17,18] The present study has not been able to pinpoint specific occupational risk-factors. Still, having corrected for alcohol and tobacco consumption, we

**Table 6a** Odds ratio (OR) for intra-oral cancer dependent on life consumption of tobacco and alcohol, Denmark

| Life consumption of tobacco[a] | Alcohol | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0 drinks | | | <40 000 drinks | | | 40 000 + drinks | | |
| | Ca/co[b] | OR[c] | (CI)[d] | Ca/co[b] | OR[c] | (CI)[d] | Ca/co[b] | OR[c] | (CI)[d] |
| 0 kg | 24/128 | 1 | — | 1/8 | 1.1 | (0.1-10.0) | 0/0 | — | — |
| 1-135 kg | 21/91 | 1.6 | (0.8-3.2) | 7/22 | 2.6 | (1.0-7.2) | 2/3 | 6.7 | (1.0-45.6) |
| 136-235 kg | 18/52 | 2.8 | (1.3-5.9) | 4/18 | 1.9 | (0.6-6.4) | 10/6 | 18.7 | (5.7-61.0) |
| 236+ kg | 20/36 | 6.0 | (2.7-13.4) | 12/21 | 6.8 | (2.7-17.4) | 41/10 | 52.3 | (20.7-131.9) |

[a]1 g tobacco equals one cigarette.
[b]Ca/co = cases/controls.
[c]Reference: 0 g/day and 0 drinks/day.
[d]CI = 95% confidence interval.

**Table 6b.** Odds ratio (OR) for intra-oral cancer dependent on current consumption of tobacco and alcohol, Denmark

| Current consumption of tobacco[a] | Alcohol | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0 drinks/day | | | 1–5 drinks/day | | | > 5 drinks/day | | |
| | Ca/co[b] | OR[c] | (CI)[d] | Ca/co[b] | OR[c] | (CI)[d] | Ca/co[b] | OR[c] | (CI)[d] |
| 0 g/day | 37/199 | 1 | — | 5/25 | 1.4 | (0.5-4.1) | 1/4 | 2.6 | (0.3-24.3) |
| 1-20 g/day | 32/93 | 2.2 | (1.2-3.8) | 10/29 | 2.2 | (1.0-5.1) | 15/6 | 22.5 | (7.8-64.7) |
| 21+ g/day | 21/24 | 6.8 | (3.2-14.2) | 7/12 | 5.7 | (2.0-16.5) | 24/3 | 80.7 | (21.8-298.8) |

[a]1 g tobacco equals one cigarette.
[b]Ca/co = cases/controls.
[c]Reference: 0 g/day and 0 drinks/day.
[d]CI = 95% confidence interval.

**Table 6c.** Odds ratio (OR) for intra-oral cancer dependent on use of tobacco and alcohol, Denmark

| Ever-user of tobacco | Alcohol | | | | | |
|---|---|---|---|---|---|---|
| | No | | | Yes | | |
| | Ca/co[a] | OR[b] | (CI)[c] | Ca/co[a] | OR[b] | (CI)[c] |
| No | 23/128 | 1 | — | 1/8 | 1.0 | (0.1-8.5) |
| Yes | 61/182 | 2.5 | (1.4-4.4) | 76/82 | 8.1 | (4.3-15.2) |

[a]Ca/co = cases/controls.
[b]Reference: never users.
[c]CI = 95% confidence interval.

observed a trend between the service trade and cancer of the oral cavity (OR = 2.9, CI = 0.6-13.5). Although other studies have made a similar observation, interpretation of this finding remains difficult.[19] The passive smoking suffered by employees of this trade may carry some explanatory weight.[7] Still, the size of the present study population would not seem to allow an in-depth analysis of the relative risk associated with the trades in question, and we have focused only on specific occupations. Several of the previous studies reporting an increased mortality from intra-oral cancer in specific trades, have failed to correct for tobacco and smoking exposure.[9,10]

We confirm the reported lack of any association between intra-oral cancer and coffee and tea consumption.[11]

**Table 7.** Comparison of three ways of modeling the association between intra-oral cancer and tobacco and alcohol consumption, [a]Denmark

| | $\chi^2$ | df[b] |
|---|---|---|
| Ever-user (yes/no) | 35.1 | 2 |
| Current consumption (0, 1-20, 21+ g tobacco/day and 0, 1–5, 6+ drinks/day) | 80.7 | 4 |
| Life consumption (0-135, 136-235, 236+ tobacco kg and 0,-40,000, >40,000 drinks) | 81.2 | 5 |

[a]Models, including the factors listed in Table 4 and with no interaction between tobacco and alcohol were fitted to 541 persons with full information on the factors.
[b]Degrees of freedom.

In Denmark, consumption of chewing tobacco and snuff has undergone a drastic decline since the 1920s and is now at a very low level.[20] Very few patients in our study were exposed to chewing tobacco or snuff. Twenty-two persons had a history of using chewing tobacco. Twelve of these had a daily consumption of tobacco and 11 had a daily consumption of alcohol.

We may infer from the figures that chewing tobacco and snuff hardly can have played any quantitatively significant role in the development of intra-oral carcinoma in Denmark. (A single patient developed a carcinoma at precisely the site in the oral cavity where he had habitually put his chewing tobacco for the past 20 years.) However, the public should be advised against lowering the use of smoke tobacco by shifting to chewing tobacco.[21]

Thirty-two cases neither drank alcohol on a daily basis nor smoked (nonusers). This group has been described in another paper.[22] A total of 128 controls were nonusers. We did not observe any gender-related difference in risk (estimated as OR) between users and nonusers, although nonusers, as expected, were far more numerous among females than among males.

Our study shows a significant relationship between the number of teeth and the development of oral cancer ($P = 0.001$). Graham *et al*[12] have described an association between dental status (decayed, missing, or repaired teeth) and the development of intra-oral cancer. A recent work[14] has demonstrated a significantly enhanced risk where teeth are lost but not replaced by dentures, even after statistical allowance for tobacco and alcohol consumption. We confirm this, reporting a significant association between enhanced risk and lost teeth after correction for tobacco and alcohol exposure. Still, many factors presumably related to dental status remain unanalyzed, in particular, nutritional status and the composition of diets.

In line with previous reports, we find that dental status is a less significant risk-factor than tobacco and alcohol.[14] Regular dental check-ups also were associated significantly with the risk of squamous cell carcinoma of the oral cavity (increasing risk with fewer check-ups). Still, by virtue of the close relationship between the number of own teeth and the regularity of dental check-ups (Table 5), either factor is a confounder for the other and the multivariate analysis only allows one of the two to be a significant risk indicator. We have chosen here 'number of own teeth' which is a reliable, objective

**Table 8.** Results of two simulation studies evaluating the effect of nonrespondents

| | | Actual estimates OR[c] | Simulation (i)[a] 1,000 simulations geometric average OR[c] | Simulation (ii)[b] 1,000 simulations geometric average OR[c] |
|---|---|---|---|---|
| Current alcohol | 1-5 drinks/day | 1.1 | 1.2 | 0.9 |
| | 6+ drinks/day | 9.7[d] | 4.5[d] | 7.2[d] |
| Current tobacco | 1-20 g/day | 2.0[d] | 1.8[d] | 1.2 |
| | 21+ g/day | 6.3[d] | 3.7[d] | 4.4[d] |
| Number of teeth | 5-14 | 1.5 | 1.4 | 1.3 |
| | 0-4 | 2.1[d] | 1.9[d] | 1.6[d] |

[a]Pseudo-controls taken as random cases.
[b]Pseudo-controls taken as random control, but with double the tobacco and alcohol consumption.
[c]OR = odds ratio (reference: 0 drinks/day, 0 g tobacco/day, 15-32 teeth).
[d]$P < 0.05$.

parameter. The dental status of patients and controls has been described more thoroughly in another study.[23]

We evaluated patients' lifetime consumption of tobacco and alcohol and their daily consumption at the time of examination. Valid data on both exposure variables were available for 545 participants (152 cases, 393 controls). In 541 participants (152 cases and 389 controls), valid data on all the listed parameters in Table 4 were available. Chi-square values (log OR) are shown in Table 7. Daily consumption and lifetime consumption data were equally valid ($\chi^2 = 80.7$ *cf* 81.2). Risk estimation on the basis of daily consumption therefore appears to be a rational approach not only because a history is obtained more easily and grouping more expedient, but also because the data obtained in this way largely match those that reflect lifetime consumption.

It was possible to estimate lifetime consumption of alcohol in all 161 cases and in 399 controls. For tobacco, the corresponding figures were 160 and 396, respectively. In the evaluation of daily consumption of the patients, we had to exclude eight users of tobacco and four users of alcohol because they could not tell precisely when they became nonusers. The corresponding figures for the controls were three (tobacco) and one (alcohol). In order to minimize the number of excluded cases, we based the multivariate analysis (Table 4) on lifetime-consumption data on tobacco and alcohol, but there was no apparent difference in risk estimates based on lifetime consumption and daily consumption.

The beginning of this century saw the first reports of a heavy use of alcohol and tobacco among patients with intra-oral cancer.[24] Later cohort studies have established an increased mortality from oropharyngeal cancer among smokers compared with nonsmokers.[25] Case-control studies have reported an association between a somewhat increased risk of oral cancer and tobacco and alcohol.[26-28]

The present study documents the presence of a very strong correlation between oral cancer and tobacco and alcohol exposure. These risk factors are connected closely because almost all who drink on a daily basis also are exposed to tobacco. Consequently, the sparsity of participants who drink but are not exposed to tobacco weakens our data for this combination.

In Denmark, tobacco and alcohol consumption have been rising steadily since the 1960s.[3] This trend has been parallelled by a similar rise in the national incidence of intra-oral cancer.[1,3] Our results therefore support the claim that tobacco and alcohol exposure are the strongest risk indicators for intra-oral cancer in Denmark. In a recent collaborative study among the five Nordic cancer registries,[29] it was estimated that the incidence of cancer of the oral cavity and pharynx would account for the largest relative increase in cancers among men in Denmark.[29] The estimated annual rise would be in the magnitude of 100 percent among men and 45 percent among women. This increase is due, in part, to changes in the age composition of the population, but mainly to an altered risk-profile. The increased risk of oral cancer is related to large-scale consumption of alcohol (hard liquor, beer, and wine), which may indicate that ethanol exercises an active role in carcinogenesis. However, experimental studies have failed to demonstrate a carcinogenic effect of ethanol, but it can be hypothesized that it does act as a promoter via other mechanisms: nutritional deficit associated with large alcohol intake, induction of microsomal enzymes, and a direct topic action with a toxic effect on epithelial respiratory enzymes. It is also possible that other components in alcoholic beverages (*e.g.*, nitrosamines in beer and whisky) are involved in the carcinogenic process.

We found a significant association between cancer of the oral cavity and daily consumption of beer and spirits, but not wine. This observation confirms previous reports of lower risk estimates for wine than for other alcoholic beverages.[27,30] It should be stressed that other (*e.g.*, social) factors also may play a role, as the number of wine drinkers in the study was very small. The results of previous studies are not consistent regarding type of alcoholic beverages. Many studies from European countries suggest a stronger effect from wine, indicating that wine *per se* can cause cancer of the oral cavity, and it appears that the most frequently used alcoholic-beverage in each area tends to be the most important determinant.[31,32] This is consistent with our findings, and suggests that all the different types of alcoholic drinks are carcinogenic, and differences in risk estimates are due partly to different levels of drinking patterns in various populations. The relative risk for heavy drinkers seems high in our study, but changing the cut-off points in the analysis does not change appreciably this observation.

Cigarette and cheroot smoking were significant individual parameters and there was a significant link between lifetime consumption and development of oral cancer for each parameter. As for alcohol consumption by smokers, it seems that the most frequently used sort of tobacco tends to be the strongest risk factor.

The strongest risk estimates are found for the aggregate exposure to both tobacco and alcohol, both measured as life consumption and daily consumption. We can confirm previous reports of a higher OR at increasing consumption and a multiplicative enhancement of risk for the combination of tobacco and alcohol exposure, a combination which is a persistent finding among individuals who are heavy users of alcohol.

In another study based on the same material,[33] we have shown that tobacco and alcohol also affect the prognosis in oral cancer, and that tobacco can be an independent prognostic parameter.

The strength of the present study lies mainly in the high participation rate of the cases (161 of 167 consecutive incident cases from a population of 1.4 m inhabitants). None of the cases were real nonresponders, but some were excluded because they failed to meet the inclusion criteria. Further, the controls were non-hospitalized individuals randomly drawn from the central state index of names. Cases and controls filled in identical questionnaires. A participation ratio in the order of 83 percent is certainly acceptable. Still, there is a considerable potential for bias insofar as those who declined the invitation to participate may have a high alcohol exposure (and thereby a high exposure to tobacco). Nonresponders who were contacted by telephone gave widely different reasons for their nonparticipation. We can see from Table 2 that many nonresponders were located in the higher age strata, which, presumably, are not exposed excessively to alcohol. Apart from gender and age, we had no information on nonresponders. The effect of a nonresponder bias on the overall risk estimates for tobacco, alcohol, and dental status, was assessed via simulation studies as shown in Table 8. It appears from the table that the risk remained significant, even if nonresponder consumption levels were set relatively high.

We have established that the majority of the intra-oral cancers diagnosed were associated with tobacco and alcohol exposure. However, other factors do play a contributory role. Thus, in this study, 23 patients had intra-oral cancer without having been exposed to tobacco and alcohol. Recent years have seen a growing focus on the role of the human papilloma virus (HPV) in carcinogenesis, including intra-oral squamous cell carcinoma.[34] A sample of nonusers, users, and patients with multiple cancers will be drawn from the present material for further analysis of the potential presence of human papilloma virus (HPV)-DNA in the intra-oral cancer. Still, the significance of these contributory factors is negligent compared with that of tobacco and alcohol consumption.

Most European countries have witnessed a rising incidence of cancer of the oral cavity and pharynx. The incidence is fairly stable in Scandinavia—except in Denmark where both incidence and mortality from this malady have been rising since Pindborg in 1963[35]— showed that the oral cancer morbidity rate in Denmark was unchanged over a 14-year period, in contrast to the decreasing mortality rates in other western countries. Age-specific incidence scores demonstrate a noticeable increase in the incidence in younger age groups in most European countries, Denmark included. Tobacco and alcohol long have been suspected of being the most important risk factors in cancer of the oral cavity and pharynx in Europe. Therefore, it is regrettable that a disease whose epidemiology has been recognized for years is taking a continuously rising toll, particularly among the younger age strata. The failure of current treatment techniques in combatting this disease is reflected in the survival rates which have remained poor for decades. Prophylactic efforts to make people stop smoking and the dissemination of information about the adverse effects of excessive alcohol consumption currently would seem to be the best strategy for a long-term reduction of morbidity and mortality from this disease.

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