Clin Investig (1992) 70:320–327

Original Article

The Clinical Investigator

Tobacco and alcohol and the risk of head and neck cancer

H. Maier[1], A. Dietz[1], U. Gewelke[1], W.-D. Heller[2], and H. Weidauer[1]

[1] Hals-Nasen-Ohren-Klinik der Universität Heidelberg

[2] Institut für Statistik und mathematische Wirtschaftstheorie der Universität Karlsruhe

Summary. We carried out two case-control studies on the relative risk of head and neck cancer in association with tobacco and alcohol consumption. The first study carried out at the ENT Department of the University hospitals of Heidelberg and Giessen (FRG) comprised 200 male patients with squamous cell cancer of the head and neck and 800 control subjects matched for sex, age, and residential area (1:4 matching design). Of the tumour patients, 4.5% had never smoked, in contrast to 29.5% of the control group. The average tobacco and alcohol consumption of the patients was approximately twice as high as in the control subjects. The highest alcohol and tobacco consumption was observed in patients suffering from oropharyngeal cancer. Tobacco and alcohol increased the risk of head and neck cancer in a dose-dependent fashion and acted as independent risk factors. In heavy smokers (>60 pack-years) a relative risk of 23.4 (alcohol adjusted) was calculated. Combined alcohol and tobacco consumption showed a synergistic effect. The risk ratio increased more in a multiplicative than in an additive manner. Oral and laryngeal cancer were associated with the highest tobacco-associated risk values. The highest ethanol-associated risk values were associated with oropharyngeal and laryngeal cancer. The second study was carried out at the ENT Department of the University of Heidelberg on 164 males with squamous cell carcinoma of the larynx and 656 control subjects matched for sex, age and residential area (1:4 matching design). Of the cases, 4.2% had never smoked, compared with 28.5% of the control subjects. The risk of laryngeal cancer by tobacco consumption was dose dependent, reaching a maximum value of 9.1 (adjusted for alcohol) for a consumption of more than 50 tobacco-years (TY). The relative risk of laryngeal cancer associated with alcohol intake was also dose dependent, reaching a value of 9.0 (adjusted for tobacco) for a mean daily consumption of more than 75 g alcohol. An analysis of subsite specific risks showed that heavy smokers (>50 TY) carried a nearly ten times higher risk of supraglottic cancer than of glottic cancer. The risk of supraglottic cancer from alcohol consumption was also higher than that of glottic cancer.

Key words: Tobacco – Alcohol – Head and neck cancer – Risk factors

The pathogenesis of approximatelly 90% of squamous cell carcinomas of the head and neck is firmly linked to environmental risk factors. A considerable amount of epidemiological evidence has been built up over decades to implicate occupation, social status, diet, smoking and chronic consumption of alcohol in the aetiology of head and neck cancer.

Tobacco smoking and alcohol consumption have been identified as the strongest determinants in a great number of epidemiological studies conducted in many countries all over the world. It is surprising that in Germany until recently no studies investigating the tobacco- and/or alcohol-associated risk for this type of cancer had been performed.

We report on the first case-control studies on the role of smoking and drinking in the aetiology of squamous cell carcinoma of the head and neck conducted in a German population.

Methods and materials

The first case-control study was performed at two centres, the departments of ENT of the Universities of Heidelberg and Giessen. The number of

cases in each centre was limited to 100 subjects with histologically confirmed squamous cell carcinoma of the oral cavity, the oropharynx, the hypopharynx or the larynx, resulting in a total number of cases of 200. Females cases were few in number and therefore excluded. We attempted to recruit all patients who attended the centres for treatment or follow-up examination between 1 September 1987 and 31 December 1987 (Giessen) and 1 February 1988 and 30 May 1988 (Heidelberg). In order to reduce the possibility of selection and/or bias only patients in whom the interval between diagnosis of the tumour and interview was not longer than 3 years were eligible.

A total of 800 male subjects without known cancer served as controls. The control subjects were selected within the same time periods from the outpatient clinics of the department of ENT ($n=200$) and internal medicine (200) of each study centre. Cases and controls were matched for age and residential area using a 1:4 matching design.

All interviews were conducted in the abovementioned hospitals by the same interviewer (A.D.), using a structured questionnaire. The interview took approximately 30–60 minutes and covered, besides smoking and drinking habits, occupational history, dietary habits, social status, prior medical conditions, use of certain drugs and family history of certain diseases. In the present paper we want to focus exclusively on tobacco and alcohol consumption. Tobacco consumption was described by the term 'tobacco year' (TY) which was defined as a daily consumption of 20 cigarettes, four cigars or five pipes for 1 year. Alcohol consumption was described as total intake of ethanol (g/day). The calculation of this value was based on an average ethanol content of 4 vol% in beer, 10 vol% in wine and 40 vol% in spirits.

The second case-control study was conducted in 164 male subjects with histologically proven squamous cell carcinoma of the larynx who attended the ENT-clinic of the University of Heidelberg for treatment or follow-up examination between 1 February 1988 and 30 May 1988 and between 1 November 1988 and 1 May 1989. In order to reduce the possibility of selection and/or bias, again only patients in whom the interval between diagnosis of the tumour and interview was not longer than 3 years were eligible. A total of 656 control subjects were selected within the same time periods from the out-patient clinics of the department of ENT ($n=328$) and internal medicine (328) of the University of Heidelberg using identical selection criteria as in the first study. In view of our experience in the first study, the occupational part of the questionnaire was redesigned, but the alcohol and tobacco part remained unchanged.

The analysis of the questionnaire data was performed by means of the statistical package SAS using the procedures LOGIST and MCSTRAT [33, 39]. Risk estimates and corresponding confidence intervals were calculated by means of logistic models of regression.

Results

Case-control study on squamous cell carcinoma of the head and neck

The mean age of the cases was 57.5 years (range 33–89 years). The most frequent cancer site was the larynx (44.5%), followed by the oropharynx (24.5%), the oral cavity (23%), and the hypopharynx (8%). Only 4.5% of the cases had never smoked in contrast to 29.5% of the controls. Previous smokers were 48.5% of the cases and 44.5% of the controls, and active smokers were 47% of the cases and 27% of the controls. The mean tobacco consumption calculated for the cases amounted to 43.2 ± 27.9 TY compared with 20.1 ± 26.7 TY in the controls ($P<0.0001$). In Table 1 the mean tobacco consumption for patients with various tumour sites is listed. The highest consumption was found in patients with oropharyngeal cancer (51.2 ± 28.8 TY). The risk ratios associated with tobacco consumption are shown in Table 2. Since only nine cases had never smoked, the referent category included smokers with less

Table 1. Consumption of tobacco (in tobacco-years) in patients with tumours at various sites

Oral cavity ($n=47$)	Oropharynx ($n=46$)	Hypopharynx ($n=12$)	Larynx ($n=95$)
Patients			
40.0 ± 19.3	51.2 ± 28.8	36.3 ± 24.7	41.9 ± 30.9
Controls			
18.7 ± 36.6	21.3 ± 24.8	17.1 ± 16.9	20.6 ± 22.6

Table 2. Tobacco-associated risk of head and neck cancer (adjusted for alcohol) ($n=200$)

Tobacco-years	RR	*P* value	95% C.I.
< 5	1.0		
5–20	1.9	<0.12	(0.8; 4.3)
20–40	10.6	<0.0001	(5.5; 20.4)
40–60	13.0	<0.0001	(6.4; 26.4)
>60	23.4	<0.0001	(11.0; 49.9)

Table 3. Tobacco-associated risk of cancer (expressed as risk ratios) for different sites of the head and neck (adjusted for alcohol)

Tobacco years	Oral cavity ($n=47$)	Oropharynx ($n=46$)	Hypopharynx ($n=12$)	Larynx ($n=95$)
<5	1.0	1.0	1.0	1.0
5–50	17.1 (3.4–85.3)	–	–	5.4 (2.2–13.0)
>50	77.5 (11.0–545.6)	–	–	11.9 (4.3–32.8)

Values in parentheses are 95% confidence intervals, – Number of cases too small for calculation of risk

Table 4. Consumption of alcohol (g/day) in patients with tumours at various sites

Oral cavity ($n=47$)	Oropharynx ($n=46$)	Hypopharynx ($n=12$)	Larynx ($n=95$)
Patients			
66.1±60.5	80.5±79.2	69.9±35.9	65.1±46.1
Controls			
28.9±29.3	31.2±30.1	30.8±27.9	29.4±25.2

Table 5. Alcohol-associated risk of head and neck cancer (tobacco adjusted) ($n=200$)

Alcohol (g/day)	Risk ratio	P value	95% C.I.
<25	1.0		
25–50	1.7	<0.04	(1.0; 2.7)
50–75	6.7	<0.0001	(3.9; 11.3)
75–100	16.2	<0.0001	(7.1; 36.8)
>100	21.4	<0.0001	(11.2; 40.6)

Table 6. Alcohol-associated risk of cancer (expressed as risk ratios) for different sites of the head and neck (adjusted for tobacco)

Alcohol consumption (g/day)	Oral cavity ($n=47$)	Oropharynx ($n=46$)	Hypopharynx ($n=12$)	Larynx ($n=95$)
<25	1.0	1.0	1.0	1.0
25–75	2.8 (1.1–7.0)	0.9 (0.3–2.3)	2.9 (0.4–22.9)	3.5 (1.9–6.4)
>75	14.9 (4.2–53.7)	12.5 (3.2–49.3)	–	15.7 (6.6–37.3)

Values in parentheses are 95% confidence intervals, – Number of cases too small for calculation of risk

than 5 TY. There was a clear dose response relationship displaying a 23-fold increase in risk (adjusted for alcohol consumption) for heavy smokers (>60 TY). Because of small sample sizes in this study the tobacco associated risk could be calculated only for two different tumour sites (oral cavity and larynx) (Table 3). The risk of oral cancer increased 77-fold ($P<0.0001$) and of laryngeal cancer 12-fold ($P<0.0001$) in heavy smokers (>50 TY).

Regular, consumption of alcohol was admitted by 89% of the cases and by 88% of the controls. The total daily intake of ethanol differed significantly between groups. The cases averaged 69.2± 58.1 g/day in contrast to 29.8±27.5 g/day ($P<$ 0.001). Table 4 displays the mean alcohol consumption for patients with various tumour sites. The highest consumption was found in patients with oropharyngeal cancer (80.5±79.2 g). The risk ratios associated with alcohol consumption are shown in Table 5. Since only 12 patients did not report a regular alcohol consumption, the referent category included subjects with a daily consumption of less than 25 g/day. There was a clear dose-response relationship displaying a 21-fold increase in risk (adjusted for tobacco consumption) for heavy drinkers (>100 g/day).

The alcohol-associated risk for different tumour sites is shown in Table 6. After adjustment for tobacco consumption the risk of oral cancer increased 15-fold ($P<0.0001$), of oropharyngeal cancer 12-fold and of laryngeal cancer 16-fold ($P<$ 0.0001) in heavy drinkers (>75 g/day).

Combined consumption of alcohol and tobacco increased the risk more in a multiplicative than in an additive manner (Table 7). The relative risk of head and neck cancer associated with a daily ethanol consumption of 75 g or more and a tobacco consumption of more than 50 TY was 146 times greater than the referent group.

Case-control study on squamous cell carcinoma of the larynx

The mean age of the cases was 58.15 years (range 39.9–85.8 years). Of the cases, 4.2% and of the

Table 7. Interaction of alcohol and tobacco on the risk of head and neck cancer expressed as risk ratios (95% C.I.). Patient/control numbers in each category are shown beneath the risk ratios values

Tobacco years	Alcohol consumption (g/day)		
	<25	25–75	>75
<5	1.0 (5/178)	2.3 (0.6; 8.8) (5/97)	10.3 (1.9; 55.8) (3/10)
5–50	5.7 (1.9; 17.3) (27/246)	14.6 (4.8; 43.9) (50/180)	153.2 (44.1; 532) (44/19)
>50	23.3 (6.6; 82.5) (14/33)	52.8 (15.8; 176.6) (27/28)	146.2 (37.7; 566) (25/9)

Table 8. Consumption of tobacco (expressed as tobacco years) by patients with laryngeal cancer and control subjects

	Laryngeal cancer ($n=164$)	Controls ($n=656$)
Min	0	0
Max	173.3	141.3
Mean	44.2	22.2
25% quantile	26.2	0
50% quantile	38.9	14.0
75% quantile	64.3	35.2

control subjects 28.5%, had never smoked. Previous smokers and active smokers were 95.8% of the cases and 71.5% of the control subjects. Cigarette smokers were 96.5% of the cases and 91.5% of the controls. Of the cigarette smokers in the tumour group 70%, and in the control group 87.8%, preferred filter-tipped cigarettes.

The tobacco consumption of the cases and the control subjects is listed in Table 8. The mean tobacco consumption calculated for the cases amounted to 44.2 TY compared with 22.2 TY for the controls ($P<0.0001$). The risk of laryngeal cancer associated with tobacco consumption is shown in Table 9. The referent category included smokers with less than 5 TY. There was a clear dose-response relationship displaying a nine-fold increase in risk (adjusted for alcohol consumption) for heavy smokers (>50 TY). The tobacco-associated risk was different for supraglottic and glottic cancer (Table 10) and increased fourfold ($P<0.005$) for glottic cancer and for supraglottic cancer 33-fold ($P<0.0001$) in heavy smokers (>50 TY).

The alcohol consumption of the cases and the control subjects is listed in Table 11. The mean alcohol consumption calculated for the cases amounted to 64.1 g/day compared with 29.2 g/day in the control group ($P<0.0001$). The risk of laryngeal cancer associated with alcohol consumption is shown in Table 9. The referent category included

Table 9. Alcohol- and tobacco-associated risk of laryngeal cancer (adjusted for tobacco and alcohol) ($n=164$)

Alcohol 25–75 g/day	RR *P* C.I.	2.6 0.0001 1.63–3.99
Alcohol >75 g/day	RR *P* C.I.	9.0 0.0001 5.21–15.53
Tobacco years 5–50	RR *P* C.I.	5.6 0.0001 2.87–10.93
Tobacco years >50	RR *P* C.I.	9.1 0.001 4.46–18.71

RR, risk ratio

Table 10. Alcohol- and tobacco-associated risk of supraglottic and glottic cancer (adjusted for tobacco and alcohol)

		Glottic cancer ($n=72$)	Supraglottic cancer ($n=73$)
Alcohol 25–75 g/day	RR *P* C.I.	3.6 0.0002 1.83–7.05	1.6 0.16 0.83–3.13
Alcohol >75 g/day	RR *P* C.I.	7.92 0.0001 3.53–17.77	11.76 0.0001 4.48–29.58
Tobacco years 5–50	RR *P* C.I.	2.3 0.04 1.83–7.05	20.2 0.0001 4.48–91.49
Tobacco years >50	RR *P* C.I.	3.7 0.005 1.49–9.0	32.7 0.0001 6.88–155.56

RR, risk ratio

alcohol consumers of less than 25 g/day. There was a clear dose-response relationship displaying a ninefold increase in risk (adjusted for tobacco consumption) for heavy drinkers (>75 g/day). The alcohol-associated risk was slightly different for su-

Table 11. Consumption of alcohol (expressed as g/day) by patients with laryngeal cancer and control subjects

	Laryngeal cancer ($n=164$)	Controls ($n=656$)
Min	0	0
Max	261.4	188.5
Mean	64.1	29.2
25% quantile	24.3	4.3
50% quantile	52.1	20.4
75% quantile	93.9	41.0

praglottic and glottic cancer (Table 10) and increased eightfold ($P<0.0001$) for glottic cancer and, for supraglottic cancer, 12-fold ($P<0.0001$) in heavy drinkers (>75 g/day).

Discussion

Clinically a link between chronic consumption of tobacco and/or alcohol and head and neck cancer has been observed for many years. This observation has been supported by numerous epidemiological studies indicating that heavy smoking or drinking, and especially the combination of the two, increases the risk of squamous cell carcinoma of the oral cavity, the pharynx and the larynx [2, 5, 6, 8, 10, 28, 29, 31, 32, 37, 40, 45, 46, 47]. The tobacco-associated cancer risk has been explained by the fact that tobacco smoke contains more than 30 different carcinogenic compounds, for example polycyclic aromatic hydrocarbons, and tobacco-specific nitrosamines some being capable of local carcinogenic action [12]. While there has been general agreement that tobacco is the major risk factor for this type of cancer, the role of chronic alcohol consumption has been underestimated for a long time. Alcohol per se is not a carcinogen, but acts as a co-carcinogen [14, 36]. It is capable of affecting carcinogenesis at different stages during initiation and promotion [36]. More than 90% of environmental carcinogens occur in their procarcinogenic form and require further activation by microsomal cytochrome P-450-dependent enzymes [43]. Chronic ethanol consumption increases procarcinogen-activating enzyme activities [9, 11]. In animal experiments it has been shown that alcohol may affect carcinogenesis via an inhibition of DNA repair [26]. The upper digestive tract is exposed to ethanol concentrations several times higher than other tissues, thus leading to direct cell alterations there. Such cellular injury is usually answered by cellular hyper-regenerativity, a state in which tissues exhibit an increased sensitivity toward chemical carcinogens [44]. Further, alcohol acts as a solvent for certain carcinogens, thus increasing their cellular uptake [36]. Acute and chronic ethanol administration decreases the production and secretion of saliva [15, 18, 19]. This may result in higher local concentrations of procarcinogens or carcinogens and a reduced clearance of the mucosal surface. Besides alcohol beverages may contain a variety of procarcinogens [16, 23, 38]. Finally alcoholism is often associated with malnutrition and deficiencies in vitamins (A, B_1, B_2, B_6, E, folic acid) and trace elements (Mg, Zn, Fe) [16, 22, 24, 34, 35, 36].

In the present investigation, for the first time in a German population the relative risk for head and neck cancer associated with tobacco and alcohol consumption has been evaluated. Since tobacco and alcohol consumption are positively correlated, it was necessary to examine the effects of smoking unconfounded by alcohol and vice versa.

Most, but not all, of the cancer patients enrolled into the studies were active or previous smokers (95.5% in the first, and 95.8% in the second, study). Among the control subjects, the percentage of active or previous smokers was also rather high (70.5% in the first, and 71.5% in the second, study). It is remarkable that a regular consumption of alcohol was admitted by 89% of the cases and also by 88% of the controls. However, the tobacco as well as the alcohol consumption of the cancer patients in both studies was twice that of the control subjects. This in itself indicated a possible dose-response relationship between tobacco consumption, as well as alcohol consumption, and cancer risk. The calculation of relative risks for head and neck cancer in general, associated with tobacco consumption, confirmed this first impression: compared with the referent category (<5 TY) there was a significant dose-response relationship displaying a 23-fold increase in the risk for heavy smokers (>60 TY; adjusted for alcohol). A similar situation was observed for the alcohol-associated risk: compared with the referent category (<25 g/day) there was a significant dose-response relationship displaying a 21-fold increase in the risk for heavy drinkers (>100 g/day; adjusted for tobacco).

There is general agreement that tobacco consumption acts as an independent risk factor for head and neck cancer [2, 5, 6, 28, 29, 40]. This was confirmed in the present study. Concerning alcohol, there is some disagreement. In most previous studies alcohol has been described as a risk enhancer in smokers, but not as an independent risk factor [45, 46]. On the contrary, most recent

investigations [2, 6, 13, 40], and also both of our case-control studies, provide strong evidence that alcohol acts as an independent risk factor of head and neck cancer.

Since most of the patients suffering from head and neck cancer smoke and drink heavily it is important to investigate the joint effect of tobacco and alcohol on the cancer risk. Attempts have been made to describe the interaction of both in terms of an additive or multiplicative model. In one of the first studies analysing this question, Wynder et al. [47] found an additive effect. However, several other more recent studies have described a greater than additive effect [2, 5, 6, 10, 28, 29, 32, 40]. The present study also provides evidence that alcohol and tobacco act in a synergistic manner: the relative risk associated with combined heavy alcohol and tobacco consumption was 146 times higher compared with the referent group. However, this risk value has been established on data from only 200 cases, and thus should be interpreted cautiously. For a detailed description of the interaction of alcohol and tobacco on the risk for head and neck cancer a greater number of cases than 200 is recommended [3, 4].

Several case-control studies have provided evidence that tobacco- as well as alcohol-associated cancer risk varies for different anatomical sites in the head and neck region [2, 5, 6, 40]. Similar observations were made in our studies: the risk (adjusted for alcohol) of oral cancer increased 77-fold ($P<0.0001$), and of laryngeal cancer 12-fold ($P<0.0001$), in heavy smokers (>50 TY). While the relative risk value calculated for laryngeal cancer is in agreement with the risk values reported by other authors, the value for oral cancer was surprisingly high. The site-dependent risks from alcohol of head and neck cancer were only slightly different. After adjustment for tobacco consumption, the relative risk of oral cancer increased 15-fold ($P<0.0001$), of oropharyngeal cancer 12-fold and of laryngeal cancer 16-fold ($P<0.0001$), in heavy drinkers (>75 g/day). However, it should be mentioned that the latter values were derived from a small number of cases and need to be confirmed, as we have done in our second study, concerning laryngeal cancer.

Again there was a clear dose-dependent increase in risk, reaching a value of 9.1 for heavy smokers (>50 TY) and for heavy drinkers (>75 g/day). One has to recognise that laryngeal cancer includes cancers arising from different parts of the larynx. The most common types of laryngeal cancer are glottic cancer, which arises from the vocal fold, and supraglottic cancer, which arises above the vocal fold. In our study the tobacco-associated risk of glottic cancer showed a moderate dose-dependent increase reaching a value of 3.7 for heavy smokers (adjusted for alcohol). The risk ratio calculated for supraglottic cancer, however, was nearly ten times higher, reaching a value of 32.7 for heavy smokers (>50 TY; adjusted for alcohol). The subsite-specific risks from alcohol consumption were only slightly different. The alcohol-associated risk of glottic cancer reached a value of 7.9 and of supraglottic cancer, 11.8 for heavy drinkers (adjusted for tobacco). Similar subsite-specific relative risks from tobacco as well as from alcohol consumption have been reported by other authors [2, 6, 8, 40]. The high subsite-specific risk from tobacco consumption for supraglottic cancer is surprising since the exposure to tobacco smoke is similar for both the supraglottic and glottic region. It therefore appears likely that the mucosa of the supraglottic structures, like the epiglottis or the aryepiglottic folds, are rendered more susceptible to the carcinogenic effect of certain tobacco smoke compounds by other noxae, for example alcohol. While glottic mucosal structures are normally exposed only to alcohol via the blood stream or expired air – i.e. to low concentrations – the supraglottic structures mentioned may be in direct contact with alcoholic beverages while these are ingested.

In confirmation of previous epidemiological investigations, the two case-control studies presented in this paper provide strong evidence for a major role of tobacco and alcohol consumption as risk factors of head and neck cancer in general, and of laryngeal cancer in particular. However, one should keep in mind that the aetiology of head and neck cancer is multifactorial. It is noteworthy that comparatively few smokers and drinkers develop this disease, although tobacco and alcohol consumption are rather common habits among the adult German population. There are additional aspects to the causation of head and neck cancer that science is just beginning to unravel, for example poor diet [1, 17, 25, 27, 30], occupational exposure to carcinogens [20, 21], social status [7, 8], viral infections [41] and genetic predisposition [42]. Further investigations of these risk factors in the field of epidemiology, toxicology, and especially molecular biology, are necessary for a better understanding of the pathogenesis of head and neck cancer.

References

1. Barch DH, Iannaccone PM (1986) Role of zinc deficiency in carcinogenesis. In: Newberne PM, Poirier LA, Pariza

MW (eds) Essential nutrients in carcinogenesis. Plenum Press, New York, pp 517–527
2. Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, Bernstein L, Schoenberg JB, Stemhagen A, Fraumeni JF jr (1988) Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res 48:1282–1287
3. Breslow N (1986) Use of the power transform to discriminate between additive and multiplicative models in epidemiologic research. In: Moolgavkar SH, Prentice RL (eds) Modern statistical methods in chronic disease epidemiology. Wiley, New York, pp 181–196
4. Breslow NE, Storer BE (1985) General risk functions for case-control studies. Am J Epidemiol 122:149–162
5. Brownson RC, Chang JC (1987) Exposure to alcohol and tobacco and risk of laryngeal cancer. Arch Environ Health 42:192–196
6. Brugere J, Guenel P, Leclerc A, Rodriguez J (1986) Differential effects of tobacco and alcohol in cancer of the larynx, pharynx and mouth. Cancer 57:391–395
7. Dietz A, Heller WD, Maier H (1991) Plattenepithelkarzinome des oberen Aerodigestivtraktes – eine Erkrankung der unteren sozialen Schichten? In: Maier H, Weidauer H (eds) Krebsrisiken im Kopf-/Halsbereich. Springer, Berlin Heidelberg New York
8. Ellwood JM, Pearson JCG, Skippen DH, Jackson SM (1984) Alcohol, smoking, social and occupational factors in the etiology of cancer of the oral cavity, pharynx and larynx. Int J Cancer 34:603–612
9. Farinati F, Zhou Z, Bellah J, Lieber CS, Garro AJ (1985) Effect of chronic ethanol consumption on activation of nitrosopyrrolidine to a mutagen by rat upper alimentary tract, lung and hepatic tissue. Drug Metab Dispos 13:210–214
10. Flanders WD, Rothman KJ (1982) Interaction of alcohol and tobacco in laryngeal cancer. Am J Epidemiol 115:371–379
11. Garro AJ, Seitz HK, Lieber CS (1981) Enhancement of dimethylnitrosamine metabolism and activation to a mutagen following chronic ethanol consumption. Cancer Res 41:120–124
12. Hoffmann D, Melkian A, Adams JD, Brunnemann ND, Haley ND (1985) New aspects of tobacco carcinogenesis. Carcinogenesis 8:239–256
13. International Agency for Research on Cancer (1988) Alcohol drinking (IARC Mononographs on the evaluation of carcinogenic risks to humans, 44) International Agency for Research on Cancer, Lyons
14. Ketcham AS, Wexler H, Mantel N (1963) Effects of alcohol on mouse neoplasia. Cancer Res 23:1015–1023
15. Kissin B, Kaley MM (1974) Alcohol and cancer. In: Kissin B, Begleiter H (eds) The biology of alcoholism, vol 3. Plenum Press, New York, pp 481–511
16. Lieber CS, Garro AJ, Leo MA, Mak KM, Worner TM (1986) Alcohol and cancer. Hepatology 6:1005–1019
17. Mackerras D, Buffler PA, Randall DE, Nichaman MZ, Pickle LW, Mason TJ (1988) Carotene intake and risk of laryngeal cancer in coastal Texas. Am J Epidemiol 128:980–988
18. Maier H, Born IA, Veith S, Adler D, Seitz HK (1986) The effect of chronic ethanol consumption on salivary gland morphology and function in the rat. Alcoholism Clin Exp Res 10:425–427
19. Maier H, Born IA, Mall G (1988) Effect of chronic ethanol and nicotine consumption on the function and morphology of the salivary glands. Klin Wochenschr [Suppl XI] 66:140–150
20. Maier H, deVries N, Weidauer H (1990) Beruf und Krebs im Bereich von Mundhöhle, Pharynx und Larynx. HNO 38:271–278
21. Maier H, Dietz A, Gewelke U, Heller WD (1991) Berufliche Exposition gegenüber Schadstoffen und Krebsrisiko im Bereich von Mundhöhle, Oropharynx, Hypopharynx und Larynx – eine Fall-Kontrollstudie. Laryngol Rhinol Otol 70:93–98
22. Mak KM, Leo MA, Lieber CS (1987) Effect of ethanol and vitamine A deficiency on epithelial cell proliferation and structure in the rat esophagus. Gastroenterology 93:362–370
23. Marshall E (1979) Carcinogens in Scotch. Science 205:768–769
24. McClain CS, Su LC (1983) Zinc deficiency in the alcoholic: a review. Alcoholism Clin Exp Res 7:5–10
25. McLaughlin JK, Gridley G, Block G, Winn DM, Preston-Martin S, Schoenberg JB, Greenberg RS, Stemhagen A, Austin DF, Ershow AG, Blot WJ, Fraumeni JF jr (1988) Dietary factors in oral and pharyngeal cancer. J Natl Cancer Inst 80:1237–1243
26. Mufti SJ, Lieber CS, Garro AJ (1981) Effect of chronic ethanol consumption on the extent and persistence of DMN-induced DNA-alkylation (abstract). Cancer Res 21:58
27. Notani PN, Jayant K (1987) Role of diet in upper aerodigestive tract cancers. Nutr Cancer 10:103–113
28. Olsen J, Sabroe S, Fasting U (1985) Interaction of alcohol and tobacco as risk factors in cancer of the laryngeal region. J Epidemiol Community Health 39:165–168
29. Olsen J, Sabroe S, Ipsen J (1985) Effect of combined alcohol and tobacco exposure on risk of cancer of the hypopharynx. J Epidemiol Community Health 39:304–307
30. Peto R, Doll R, Buckley JD, Sporn MB (1981) Can dietary beta-carotene materially reduce human cancer rates? Nature 290:201–208
31. Phillips RL (1975) Role of life-style and dietary habits in risk of cancer among Seventh Day Adventists. Cancer Res 35:3513–3523
32. Rothman K, Keller A (1972) The effect of joint exposure to alcohol and tobacco on risk of cancer of the mouth and pharynx. J Chron Dis 25:711–716
33. SAS Users' Guide: Statistics. SAS Institute Inc, 1985
34. Seitz HK, Kommerell B (1990) Alkoholismus als häufigste Ursache für Mangelernährung. Dtsch Ärzteblatt 87:497–500
35. Seitz HK, Simanowski UA (1987) Metabolic and nutritional effects of ethanol. In: Hathcock JN (ed) Nutritional Toxicology, vol II. Academic Press, Orlando, pp 63–104
36. Seitz HK, Simanowski UA (1988) Alcohol and carcinogenesis. Annu Rev Nutr 8:99–119
37. Smith EM (1979) Epidemiology of oral and pharyngeal cancers in the United States. Review of recent literature. J Natl Cancer Inst 63:1189–1195
38. Spiegelhalder B, Eisenbrand G, Preussmann R (1979) Contamination of beer with trace quantities of N-nitroso-dimethylamine. Food Cosmet Toxicol 17:29–31
39. SUGI, Supplemental Library Users' Guide, 5th edn. SAS Institute Inc 1985, Cary, North Carolina, USA
40. Tuyns AJ, Esteve J, Raymond R, Berrino F, Benhamou E, Blanchet F, Boffetta P, Crosignani P, Del Moral A, Lehmann W, Merletti F, Pequignot G, Riboli E, Sancho-Garnier H, Terracini B, Zubiri A, Zubiri L (1988) Cancer of the larynx/hypopharynx, tobacco, and alcohol: IARC international case-control study in Turin and Varese (Italy), Zaragossa and Navarra (Spain), Geneva (Switzerland) and Calvados (France). Int J Cancer 41:483–491
41. de Villiers EM, Weidauer H, Le YJ, Neumann C, zur Hau-

sen H (1986) Papillomviren in benignen und malignen Tumoren des Mundes und des oberen Respirationstraktes. Laryngol Rhinol Otol 65:177–179
42. de Vries N (1990) The magnitude of the problem. In: de Vries N, Gluckman JL (eds) Multiple primary tumors in the head and neck. Thieme, Stuttgart New York, pp 1–29
43. Weisburger JH (1975) Chemical carcinogens. In: Casarett LJ, Duoll J (eds) Toxicology, the basic science of poisons. Macmillan, New York, pp 333–378
44. Wright NA (1983) The histogenesis of gastrointestinal cancer. In: Hodgson HJF, Blum SR (eds) Gastrointestinal and hepatobiliary cancer. Chapman and Hall, London, pp 79–118
45. Wynder ED, Mabuchi K (1972) Etiological and preventive aspects of human cancer. Prev Med 1:300–334
46. Wynder EL, Bross IDJ, Day E (1956) A study of environmental factors in cancer of the larynx. Cancer 9:86–110
47. Wynder ED, Bross IJ, Feldmann R (1957) A study of etiological factors in cancer of the mouth. Cancer 10:1300–1323

Received: July 15, 1991
Accepted: September 3, 1991

Priv.-Doz. Dr. H. Maier
Universitäts-HNO-Klinik
Im Neuenheimer Feld 400
W-6900 Heidelberg, FRG