European Journal of Clinical Nutrition (1998) 52, 271–278

Malignant epithelial tumours in the upper digestive tract: a dietary and socio-medical case-control and survival study

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Objective: The aim of the present study was to elucidate the influence of social, dietary and environmental factors on the incidence of malignant epithelial tumours in the upper digestive tract and on the prognosis of patients with these cancers.
Design: A population-based case-control study was carried out, and the patients in the study were included in a survival analysis.
Setting: The study was carried out at the Department of Otorhinolaryngology at Ullevål University Hospital, Oslo, Norway.
Subjects: In the case-control study, 84 patients and 89 controls were included. Only the patients were included in the survival analysis.
Results: Smoking showed the highest odds ratio (OR) for morbidity (OR = 29). The patients had in general a lower social status, and a higher alcohol intake (OR = 6.6). For both β-carotene and vitamin C, the ORs decreased with increasing intake (OR = 0.2 and 0.3, respectively). Increased ORs were associated with low values for haemoglobin, iron, TIBC, folic acid, magnesium and especially for albumin (OR = 14), and with high values for ferritin, vitamin B12 and thiocyanate (a marker for smoking). Stage of the disease was an important prognostic factor. The relative risk (RR) of dying for disseminated *vs* localised tumours being 3.2. A poorer prognosis was linked to higher age, to smoking *vs* no smoking (RR = 2.3), and to lower levels of haemoglobin, albumin, magnesium and thiocyanate.
Conclusions: Strong beer, liquor, consumption of milk and table fat, low social status and smoking seemed to have a negative impact on both disease and survival. Fruit and vegetables might, however, reduce the risk. Whereas low serum albumin, iron and magnesium indicated a high OR for cancer, vitamin C and β-carotene had the opposite implication. No significant implications on survival could be detected in blood chemistry beyond the stage of disease.
Consent procedures: The study was approved by the Norwegian Data Inspectorate. No remarks were given from the Hospitals ethical committee.
Sponsorship: The study was supported by the Norwegian Cancer Society.
Descriptors: Upper digestive tract cancer; diet; social class; morbidity; mortality

Introduction

In Norway, the incidence of cancer of the upper digestive tract constitutes 2.7% of the total cancer incidence among men and 1.3% among women (Cancer Registry of Norway, 1995). Squamous cell carcinomas accounted for about 85%, adenocarcinomas for 10% and others for 5%. The incidence rate in Oslo, the capital city, is about 1.6 times the average national incidence rate.

It is well known that tobacco and alcohol are heavily implicated in the aetiology of upper digestive tract cancers (Tomatis *et al*, 1990; International Agency for Research on Cancer, 1986). Nutritional studies have suggested that poor diet may also influence the risk (Marshall & Boyle, 1996; Cheng & Day, 1996), and so may even socio-medical and environmental factors (Bundgaard *et al*, 1995). Patients with cancer of the upper digestive tract have a poor prognosis. In Norway, the five-year relative survival rate for this group of cancers was less than 40% in 1988 through 1992 (Cancer Registry of Norway, 1995).

Especially in Oslo, an increasing rate, has been observed for cancers of the upper digestive tract. The aim of the present study was therefore to elucidate the possible influence of social, dietary and environmental factors on this incidence. All patients investigated were hospitalised at the Department of Otorhinolaryngology (ORL) at the Ullevål University Hospital, during the five-year period December 1987 to December 1992. This department is the sole institution treating head and neck cancers for the city of Oslo. The study was designed as a population-based case-control study, but also the survival of the patients was evaluated with respect to the variables included. The basis for this issue was to evaluate if diet and socio-medical factors might influence survival beyond the stage of disease. Types of diet and consumption might be reflected in blood biochemistry. A relatively broad screening, i.e. laboratory analyses, were therefore conducted in order to

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Received 3 July 1997; revised 23 October 1997; accepted 22 November 1997

detect eventual predictors and prognostics for malignant disease.

Subjects and methods

Subjects

From December 1987 to December 1992, 84 patients, native Norwegians (65 men and 19 women), all Caucasians, with newly diagnosed malignant epithelial tumours, mainly squamous cell carcinomas (89%), of the upper digestive tract, were hospitalised and treated at the Department of ORL at Ullevål University Hospital. The patients were 27–73 y old with a median age of 61 y. The age and sex distributions of the cases are shown in Table 1, and the distribution according to WHOs International Classification of Diseases, ninth revision (ICD-9) in Table 2 (World Health Organization, 1977). All the cases except one were histologically verified, namely only by fine needle aspiration (FNA).

For each case, sex- and age-matched controls for the same area of Oslo were obtained from the Norwegian Central Population Registry. The city of Oslo is divided in 27 regions ranging from 949–27 939 inhabitants, percentage distribution about equal for men and women and ages (1992). Stratification in urban areas was done assuming that location and type of habitat could possibly influence daily life, social standard and daily consumption. Anticipating that social status could also influence daily consumption, we graded social status in three classes, namely low, medium and high. This was based on a simplified issue from Standard classification of socio-economic status made by Statistics Norway (Statistics Norway, 1984). The study was originally designed as a 1:2 matching. However, quite a high number of the stratified selected controls appeared to be ethnically incompatible or did not meet for examination and interview. Altogether 89 controls were included. Due to the low number of controls, the cases and controls were grouped to form sets with both cases and controls included. The groupings were performed by adding cases with no controls to sets with the same sex and birth year within the two years before or after the birth year of the index case. One of the cases, a women in the age group 30–39 y, did not fit into any of these groups, and was therefore excluded from the case-control analysis.

Methods

Both cases and controls were examined clinically by an ORL-specialist, and were asked about smoking habits, education, occupation, social status and their height and weight 10 y prior to the examination. Present height and weight were measured. In addition, a blood sample was taken. A clinical dietician interviewed all the patients and controls about their dietary habits. Eight of the patients were not interviewed due to practical problems. The patients were interviewed about their premorbid diet in order to exclude eventual influence from the disease itself, namely their regular adult diet. Each interview lasted about one hour, and was performed by using a food frequency questionnaire designed for the study. Due to previous review studies, most attention was paid to the consumption of vegetables, fruits and alcoholic beverages (Block *et al*, 1992).

Table 1 Age distribution of the cases

Age	*Males*	*Females*	*Total*
27–29	1	0	1
30–39	2	1	3
40–49	6	2	8
50–59	12	9	21
60–69	39	7	46
70–73	5	0	5
Total	65	19	84

Table 2 Distribution of the cases according to WHOs International Classification of Diseases, ninth revision (ICD-9) (WHO) World Health Organization, 1977

ICD-9	*Site*	*Males*	*Females*	*Total*
141	Tongue	12	11	23
144	Floor of mouth	3	0	3
145	Other parts of mouth	11	2	13
146	Mesopharynx	15	4	19
148	Hypopharynx	15	2	17
149	Pharynx, unspecified	1	0	1
150	Oesophagus, upper part	8	0	8
Total		65	19	84

Whole blood and serum samples were taken in the fasting state on the first morning after the patient's admission to the hospital; before exposure to the hospital diet and prior to treatment. Samples were taken from the controls in the fasting state as early as possible on the day of investigation. Their interviews also took place at the hospital.

The people were categorised by daily smoking habits during the last five years into four categories. Those who had not smoked during the last five years were termed 'non-smokers'. Those who were current smokers or had stopped smoking less than five years ago were categorised by average tobacco consumption into three groups; 1–9 g/d, 10–19 g/d and more than 19 g/d. The weight of one cigarette was set to 1 g, one cigar to 3 g and one package of pipe tobacco to 50 g.

Information on diet was obtained by interview/questionnaire on one months average consumption. Scores for intake of vitamin C and β-carotene were estimated from the different sources containing these two nutrients. For vitamin C the following items were included: broccoli, brussel sprouts, cabbage, cauliflower, grapefruit, mandarin, orange, paprika, potatoes, swede, turnip and tomato, and for β-carotene: banana, broccoli, brussel sprouts, carrot, curly kale, frozen mixed vegetables, paprika, tomato and tomato ketchup.

The scores were estimated by calculating the reported number of portions per day for each food item and the nutrient content per portion. The weights for the portion sizes were mainly base on Norwegian standard amounts for foods (Blaker & Aarsland, 1989). The content of nutrients in foods was taken from the official Norwegian food table (National Nutrition Council, 1995).

The intake of alcohol per day was calculated from the given frequency of daily consumption and the amount of beer, wine and spirits consumed each time.

In the survival analysis, the patients were followed from the date of diagnosis to the date of death or to the end of June 1995, except for one patient who was censored at the date of his emigration. The cancer cases were grouped according to stage of the disease into localised and non-localised tumours. Thirty-eight (45%) of the cancers were localised tumours.

Laboratory analyses

In order to get biochemical knowledge, and thereby perhaps also be able to confirm the data obtained by the dietary

questionnaire, a number of laboratory analyses were conducted.

Haemoglobin concentration was measured in an Ortho Elt 800® analyser. Serum albumin was measured in a Hitachi 737® analyser. Iron/total iron binding capacity (TIBC) and thiocyanate were determined by colorimetry in a Cobas Bio®, ferritin by immunometry in an Abbott IMX®. Magnesium was measured by atomic absorption spectrometry. Vitamin B_{12} and folic acid were determined by radioimmune assay (RIA). Total retinol (retinol + retinyl esters) was determined by HPLC after hydrolysis with potassium hydroxide (10%) in ethanol and extraction into hexane (Blomhoff *et al*, 1985). Retinol binding protein (RBP) was assayed by immunodiffusion (Behring Institute, Marburg, Germany). For the detection of mononucleosis antibodies the Monospot® screening test was used; if positive, it was followed by the Paul & Bunnell test, both being performed at the Department of Microbiology, Ullevål University Hospital. Locally established reference values were used for the evaluation of the laboratory test results.

Statistical methods

In the case-control analysis, odds ratios (ORs) and their 95% confidence intervals (95% CIs) were derived from multivariate conditional logistic regression models. In the survival analysis, hazard ratios, here termed relative risks (RRs), and their 95% confidence intervals were derived from Cox proportional hazards survival analysis. The crude survival probability was estimated by the product-limit method (Kaplan & Meier, 1958). The analysis was performed using the program package EGRET (Statistics and Epidemiology Research Corporation, 1988).

Throughout the analysis, a significance level of 5% was used. People with missing information on one or more variables were excluded from the analyses when these variables were included, resulting in varying numbers of patients and controls in the tables presented.

Results

Case-control study

The relationship between tobacco consumption and cancer of the upper digestive tract is shown in Table 3. More than half of the patients were heavy smokers, with a consumption of more than 19 g/d. The OR for the heavy smokers compared to the non-smokers was 29 (95% CI = 9.3–87).

Patients and controls were matched on age, sex and sector of the city. However, anticipating that social status could differ inside a particular section, this parameter was also considered. Table 3 also shows a clear difference in the distribution of social status in patients and controls. Most of the patients were manual labourers, whereas about one third of the controls belonged to the group of employees of higher social levels (data not shown). In the lower social status all but one were patients, whereas few patients belonged to the higher social status. Only minor changes were seen in the ORs when adjusting for smoking.

The distribution of body mass index 10 y before the present examination (BMI_{10}) was almost the same in both groups except for a few more heavy weight persons among the patients (Table 3). BMI for the patients at the time of hospitalisation showed highest risk in persons with low BMI. This might, however, only reflect the disease itself (data not shown).

Table 4 shows the intake of alcohol, β-carotene and vitamin C. The alcohol consumption was higher in patients than among controls. The crude OR was 6.6 (95% CI = 2.3–19) when drinking 30 g or more alcohol per day as compared to intake less than 10 g. When smoking was taken into account, an increasing risk by alcohol consumption was still seen, although the ORs were not significant. Different types and amount of alcohol consumed were relatively distinct between the two populations. Light beer, lager and table wine were more often used by the controls (data not shown). One type of beverage, however, differed markedly from the other. About 20% of the patients consumed export beer, namely strong beer, with an average consumption of 6.6 l/week, while none of the controls reported any use of this alcoholic beverage. For all the alcoholic beverages reported, the average consumption in the users was higher in the patients than in the controls.

For β-carotene as well as for vitamin C, the OR decreased with increasing intake to 0.2 and 0.3, respectively. However, when adjusting for smoking the possible influence of these nutrients was no longer significant.

More patients than controls (50% *vs* 22%) reported use of whole milk as drinking milk. The ORs without and with adjustment for smoking were 4.1 (95% CI = 1.9–8.9) and 2.8 (95% CI = 1.1–7.3), respectively. Patients also more often used butter on their bread than did the controls. The total amount of table fat on bread (all kinds) was on

Table 3 Number of patients (Np) and controls (Nc) and odds ratios (OR) with 95% confidence intervals (95% CI) by smoking habits, social status and body-mass index

	Not adjusted for smoking				*Adjusted for smoking*			
Variable	*Np*	*Nc*	*OR*	*95% CI*	*Np*	*Nc*	*OR*	*95% CI*
Smoking								
non-smoker	8	59	1.0	Referent				
1–9 g/d	9	8	8.5	(2.2–32)				
10–19 g/d	23	15	8.8	(3.1–24)				
> 19 g/d	41	7	29	(9.3–87)				
Social status								
below average	23	1	47	(5.7–390)	23	1	35	(3.5–360)
average	53	71	1.0	Referent	53	71	1.0	Referent
above average	5	17	0.3	(0.1–1.1)	5	17	0.5	(0.1–2.0)
Body-mass index (10 y before examination)								
< 20	10	6	1.3	(0.4, 3.9)	10	6	0.7	(0.2, 3.3)
20–24.9	57	59	1.0	Referent	56	59	1.0	Referent
25–29.9	12	22	0.5	(0.2–1.2)	11	22	0.7	(0.2–2.1)
≥30	4	1	4.7	(0.5–46)	4	1	17	(1.1–270)

Table 4 Number of patients (Np) and controls (Nc) and odds ratios (OR) with 95% confidence intervals (95% CI) by categories of consumption of alcohol, β-carotene and vitamin C

	Not adjusted for smoking				*Adjusted for smoking*			
Variable	*Np*	*Nc*	*OR*	*95% CI*	*Np*	*Nc*	*OR*	*95% CI*
Alcohol								
<10 g/d	32	65	1.0	Referent	31	65	1.0	Referent
10–29 g/d	22	18	2.2	(1.0–4.8)	21	18	1.4	(0.5–4.0)
≥ 30 g/d	19	6	6.6	(2.3–19)	19	6	2.3	(0.6–8.8)
β-carotene								
<2568 µg/d	29	21	1.0	Referent	28	21	1.0	Referent
2568–4631 µg/d	36	45	0.4	(0.2–0.9)	36	45	0.8	(0.3–2.1)
≥ 4632 µg/d	10	22	0.2	(0.1–0.7)	9	22	0.5	(0.1–1.7)
Vitamin C								
<76 mg/d	42	22	1.0	Referent	41	22	1.0	Referent
76–115 mg/d	23	45	0.3	(0.1–0.6)	22	45	0.3	(0.1–0.8)
≥ 116 mg/d	10	22	0.3	(0.1–0.9)	10	22	0.4	(0.1–1.1)

average somewhat (6 g) higher in the patient group. Butter used as gravy on main meal dishes was more common among the patients than the controls.

In Table 5, results are given for the relevant haematological and clinical chemical measurements in the patients and controls. The following altered haematological parameters dominate among the patients: elevated ferritin and vitamin B_{12}, lowered haemoglobin, serum iron, TIBC and folic acid. Altered clinical chemical parameters dominating among the patients were: elevated thiocyanate and lowered magnesium and albumin.

There was no difference between patients and controls with respect to total retinol. However, three patients had values of total retinol which were pathological. Retinol

Table 5 Number of patients (Np) and controls (Nc), means, standard deviations (Sd) and odds ratios (OR) with 95% confidence intervals (95% CI) by different levels of blood parameters

	Patients			*Controls*				
Variable	*Np*	*Mean*	*Sd*	*Nc*	*Mean*	*Sd*	*OR*	*95% CI*
Haemoglobin (HG) (g/100 ml)								
M: <12.5, F: <11.5	15	11	1.4	0	—	—	—	
M: 12.5–16.5, F: 11.5–15.5	65	14	1.0	82	15	0.9	1.0	Referent
M: >16.5, F: >15.5	2	17	0.21	6	17	0.46	0.5	(0.1–2.5)
Iron (µmol/l)								
M: <15, F: <10	40	9.3	3.4	25	12	2.0	2.6	(1.3–5.0)
M: 15–30, F: 10–25	37	20	4.9	59	21	4.5	1.0	Referent
M: >30, F: >25	6	30	2.4	5	34	3.6	1.6	(0.4–6.8)
Iron binding capacity (µmol/l)								
<55	43	46	6.8	27	49	4.4	2.4	(1.2–4.7)
55–90	39	63	6.9	61	64	7.0	1.0	Referent
>90	0	—	—	1	120	—	—	
Ferritin (µg/l)								
M: <25, F: <10	3	16	6.7	4	18	4.8	1.4	(0.3–7.1)
M: 25–200, F: 10–110	44	110	48	69	97	47	1.0	Referent
M: >200, F: >110	32	280	140	16	290	110	3.1	(1.5–6.7)
Vitamin B_{12} (pmol/l)								
<140	2	120	14	2	80	71	1.5	(0.2–12)
140–600	73	320	110	84	290	100	1.0	Referent
>600	7	1200	840	2	1100	600	3.4	(0.7–18)
Folic acid (nmol/l)								
<6	8	4.7	1.1	2	5	1.0	4.2	(0.9–21)
6–24	60	14	5.1	77	14	4.4	1.0	Referent
>24	15	30	8.0	10	30	5.9	1.7	(0.7–4.1)
Magnesium (mmol/l)								
<0.70	34	0.62	0.06	11	0.68	0.02	5.5	(2.4–13)
0.70–0.95	46	0.78	0.05	76	0.78	0.05	1.0	Referent
>0.95	2	1.1	0.01	2	0.97	0.01	2.2	(0.3–20)
Thiocyanate (µmol/l)								
0–70	42	25	20	69	30	16	1.0	Referent
>70	34	120	42	18	130	43	2.7	(1.2–5.8)
Albumin (g/l)								
Less than 50 y: <40, Above 50 y: <37	34	34	2.6	6	36	1.5	14	(4.5–46)
Less than 50 y: 40–51, Above 50 y: 37–58	45	41	2.8	82	42	2.5	1.0	Referent
Total retinol (µmol/l)								
<0.7	3	0.6	0.01	0	—	—	—	
0.7–2.2	36	1.5	0.37	32	1.7	0.33	1.0	Referent
>2.2	41	3.0	0.62	42	3.2	0.79	0.7	(0.4–1.5)
Retinol binding protein (mg/l)								
4.7–47	53	31	12	34	37	7.0	1.0	Referent
>47	27	69	43	40	60	13	0.5	(0.2–1.0)

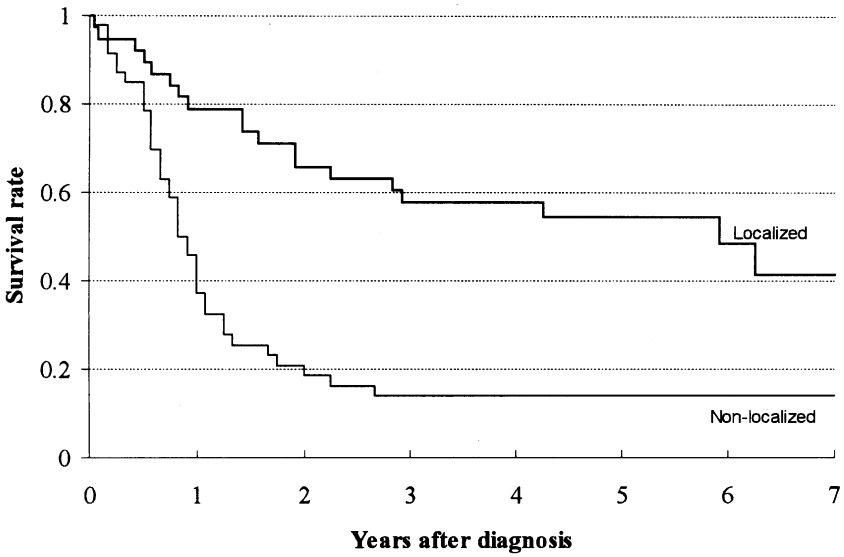

Figure 1 Survival rates by time since diagnosis for patients with localised and non-localised tumours.

binding protein was slightly higher in the control group than in the patients (borderline significance). Two patients and one control showed a positive test for mononucleosis antibodies.

Survival analysis

All 84 cancer patients were included in the survival analysis. The end of follow-up was 2.5 y after the last case was diagnosed. Fifty-eight of the patients died during the follow-up period. The overall median survival time was 16 months.

Stage of the disease appeared as an important prognostic factor (Figure 1). Those with a non-localised tumour had a relative risk (RR) of 3.2 (95% CI = 1.8–5.6) compared to those with a localised tumour. Unless otherwise stated, the RRs in the following are adjusted for stage.

Difference in survival was observed between males and females. The median survival time after diagnosis in the male patients was one year, while the median time in female patients was five years and 11 months. The RR in females compared to males was 0.6 (95% CI = 0.3–1.3) (Table 6). Due to the small number of cases, it was not possible to adjust for the different cancer sites (Table 2).

All but two patients received radiation. Fifty of the patients had surgery (35 males and 15 females), and showed a higher survival rate than the others, although the difference was not significant (Table 6).

The patients aged 65 y or more tended to have a poorer prognosis than patients younger than 50 y (Table 6). No significant differences were observed for social status or BMI. A poorer prognosis was indicated for smokers compared to non-smokers (RR = 2.3, 95% CI = 0.7–7.4) but no trend was observed in the survival by tobacco consumption (Table 7). No difference in the survival was observed in patients as to consumption of alcohol, β-carotene or vitamin C.

In Table 8, RRs in patients at different levels of various blood parameters are listed. Poor prognosis was related to low levels of haemoglobin, thiocyanate, albumin and magnesium. High level of thiocyanate is a marker for smoking. Since it seemed contradictory that smokers had poorer prognosis than non-smokers while high level of thiocyanate was connected to good prognosis for the patients, a more detailed analysis was needed. None of the non-smokers had a high level of thiocyanate, while among smokers there were persons with both high and low levels. Restricting the analysis to smokers only, the RR for patients with a high level of thiocyanate compared to patients with a low level of thiocyanate was 0.4 (95% CI = 0.2–0.8). Total retinol and RBP did not influence survival.

Discussion

The number of controls was not as high as preferred. Due to relative poor response from drawn controls, we ended up with an approximate 1:1 matching. This must be considered but need not substantially inflict on the results. The call for controls were made from the Central Population Registry, stratified in respect to urban regions, sex and age. Two controls were called for each patients but with no reminder when no answer. Ethnic incompatible controls had to be rejected in order to avoid both impact of genetics and special tastes of food, namely 17 subjects. On the other hand, some bias has to be taken into account for the otherwise relatively poor response. Some unexpected selection might be intimated by the responders social status and concern for the investigation.

A social status below the average seem to indicate a high risk for cancer in the upper digestive tract even if adjusted for smoking (OR = 35, 95% CI = 3.5–360). Alcohol and smoking make the larger impact in the statistics. Smoking by itself has an OR of 29 (95% CI = 9.3–87) when consuming > 19 g of tobacco per day. However, even 1–9 cigarettes daily augments the risk considerably (Table 3). This is in accordance with other studies (International Agency for Research on Cancer, 1986; International Agency for Research on Cancer, 1988; MacFarlane *et al*, 1995).

The alcohol intake was higher among patients than in controls. The crude OR was 6.6 (95% CI = 2.3–19) at an intake of 30 g or more alcohol per day when compared to an intake of less than 10 g/d. The ratio became, however, considerably reduced when adjusting for smoking (OR = 2.3, 95% CI = 0.6–8.8). The consumption of strong beer among the patients seems conspicuous. It is possible that alcohol *per se* does not have a direct carcinogenic effect but rather that additional components in the beverage are involved, namely nitrosamins and mycotoxins. This

Table 6 Number of patients (*n*) and relative risk of dying (*RR*) with 95% confidence intervals (95% CI) by age, gender, surgery, education, occupation, social status and body mass index

Variable	*n*	*Deaths*	*RR*[a]	*95% CI*
Gender				
Males	65	48	1.0	Referent
Females	19	10	0.6	(0.3–1.3)
Age				
< 50	12	6	1.0	Referent
50–64	42	28	1.2	(0.5–2.9)
> 65	30	24	2.0	(0.8–4.9)
Surgery				
No	34	30	1.0	Referent
Yes	50	28	0.6	(0.4–1.1)
Social status				
Below average	23	17	1.1	(0.6–2.0)
Average	54	37	1.0	Referent
Above average	5	3	0.8	(0.2–2.5)
Body-mass index (at diagnosis)				
< 20	24	20	1.5	(0.9–2.6)
20–24.9	47	32	1.0	Referent
25–29.9	11	5	0.7	(0.3–1.8)
≥ 30	2	1	1.0	(0.1–7.9)

[a]Adjusted for stage of cancer at the time of diagnosis.

Table 7 Number of patients (*n*) and relative risk of dying (*RR*) with 95% confidence intervals (95% CI) by categories of consumption of smoking, alcohol, *β*-carotene and vitamin C

Variable	*n*	*Deaths*	*RR*[a]	*95% CI*
Smoking				
Non-smoker	9	3	1.0	Referent
1–9 g/d	9	6	1.9	(0.5–7.9)
10–19 g/d	23	17	2.5	(0.7–8.6)
> 19 g/d	41	31	2.2	(0.7–7.4)
Alcohol				
< 10 g/d	33	23	1.0	Referent
10–29 g/d	22	14	0.9	(0.4–1.7)
≥30 g/d	19	13	1.2	(0.6–2.4)
β-carotene				
< 2568 μg/d	29	19	1.0	Referent
2568–4631 μg/d	36	25	1.2	(0.6–2.1)
≥4632 μg/d	11	8	0.8	(0.3–1.8)
Vitamin C				
< 76 mg/d	42	28	1.0	Referent
76–115 mg/d	24	17	1.0	(0.5–1.8)
≥116 mg/d	10	7	0.8	(0.3–1.9)

[a]Adjusted for stage of cancer at the time of diagnosis.

finding is consistent with the remarks of Bundgaard *et al*, 1995. On the other hand, an unbalanced diet due to a high intake of alcohol must also be considered. It has been found in animal studies, that acute alcohol intoxication promotes tumour metastasis (Ben-Eliyahu *et al*, 1996). It has to be noticed that table wine was more often used by the controls though with a smaller average intake. It is an open question if this is beneficial or not. In studies of the relation between alcohol intake and cancers of the upper digestive tract, an increasing risk has been found by increasing consumption of alcohol (Winn, 1995). The results in the present study also indicate an increasing risk by alcohol consumption.

Great methodological problems are associated with obtaining valid data from diet 20–30 y ago (McKeown-Eyssen *et al*, 1986). However, the current dietary habits are found to provide as good information about the past diet as evaluating the habits by retrospective methods (Jensen *et al*, 1984). On this basis, we decided to get information about the diet from the time before the disease was manifest. The interviews were concentrated about the time before the disease was known for the patients. Nevertheless, it may well be that the patients' answers were influenced by their current dietary habits, since some of them were in poor health and had chewing problems.

The calculated indexes for the intake of *β*-carotene and vitamin C reflected intake of different fruits and vegetables. Both *β*-carotene and vitamin C indicated a negative association with the disease, though not significant when adjusting for smoking. In most of the published studies a reduced risk has been found by increasing intake of these nutrients (Winn, 1995; Block *et al*, 1992). It seemed that the effect of vitamin C levelled out in the highest category of intake (Table 4). Among smokers the requirement has been estimated to be as much as twice that of non-smokers. At least 100 mg of vitamin C a day are recommended for regular smokers (National Research Council, 1989).

Our results may indicate that the people developing a cancer of the upper digestive tract had different food preferences than the controls, since we found more frequent use of whole milk and butter among the patients. Drinking milk and table fat have for years been the main sources for total fat as well as for saturated fat in the Norwegian diet (Lund-Larsen, 1994). In a case-control study conducted in Western New York, it was found that intake of fat was more likely to be related to risk than protein and carbohydrates (Marshall *et al*, 1992).

Some years ago it was reported that supplementation with *β*-carotene and vitamin A reduced the proportion of micronucleated (micronucleus formation is a marker for chromosome breakage) buccal mucosal cells in betel nut and tobacco chewers, suggesting that the supplementation reduced oral cancer risk (Stich *et al*, 1984). Furthermore, observational epidemiological studies suggest that people who consume much fruits and vegetables containing *β*-carotene have lower risk of certain types of cancer (Peto *et al*, 1981; Block *et al*, 1992). *β*-carotene could influence the cancer risk both as an antioxidant and as precursor for retinol (Burton & Ingold, 1984). On this background several prospective studies have been initiated. Till now, results of three studies have been published, and none of them could demonstrate a beneficial effect of *β*-carotene (Omenn *et al*, 1996; Hennekens *et al*, 1996; The Alpha-Tocopherol, 1994). The content of *β*-carotene and vitamin C in the diet may therefore only reflect the intake of fruits and vegetables. Which compounds in the fruits and vegetables are the real protective agents is not known.

β-carotene is a precursor of both retinol and retinoic acid. The latter compound in high doses, has been shown to be effective in the treatment of oral leukoplakia (Hong *et al*, 1986), and also inhibits new primaries in patients with this disease (Hong *et al*, 1990).

Although abnormalities in laboratory test results were dominating among the patients, some pathological laboratory findings were obtained also among the control persons for the various analyses. This may in part reflect the way of establishing reference limits; which usually represent 95% of the total reference population. However, most of the pathology in laboratory results among the controls may present minor disease also in this group.

Of all laboratory parameters investigated in the present case-control study, low serum albumin levels caused the highest OR (14) for cancer. A low serum albumin concentration has been earlier found in patients with oesophageal cancer (Prasad *et al*, 1992).

Fifteen of the cases, and none of the controls, had anaemia, as judged from the haemoglobin determination.

Table 8 Number of patients (*n*) and relative risk of dying (*RR*) with 95% confidence intervals (95% CI) by different levels of blood parameters

Variable	*Mean*	*n*	*Deaths*	*RR*[a]	*95% CI*
Haemoglobin (g/100 ml)					
M: < 12.5, F: < 11.5	11	15	14	3.4	(1.8–6.4)
M: 12.5–16.5, F: 11.5–15.5	14	66	42	1.0	Referent
M: > 16.5, F: > 15.5	17	2	1	1.3	(0.2–10)
Iron (μmol/l)					
M: < 15, F: < 10	9.3	40	31	1.5	(1.8–2.5)
M: 15–30, F: 10–25	19	38	25	1.0	Referent
M: > 30, F: > 25	30	6	2	0.6	(0.1–2.7)
Iron binding capacity (μmol/l)					
< 55	46	43	31	1.0	(0.6–1.7)
55–90	63	40	26	1.0	Referent
Ferritin (μg/l)					
M: < 25, F: < 10	16	3	3	3.1	(0.9–11)
M: 25–200, F: 10–110	110	44	31	1.0	Referent
M: > 200, F: > 110	280	33	20	0.9	(0.5–1.5)
Vitamin B_{12} (pmol/l)					
< 140	120	2	1	1.2	(0.2–9.2)
140–600	320	73	50	1.0	Referent
> 600	1100	8	6	1.0	(0.4–2.3)
Folic acid (nmol/l)					
< 6	4.7	8	7	2.4	(1.0–5.4)
6–24	14	60	40	1.0	Referent
> 24	30	16	11	1.5	(0.8–3.0)
Magnesium (mmol/l)					
< 0.70	0.62	34	28	1.9	(1.1–3.3)
0.70–0.95	0.78	47	27	1.0	Referent
> 0.95	1.1	2	2	8.0	(1.8–36)
Thiocyanate (μmol/l)					
0–70	24	43	32	1.0	Referent
> 70	120	34	21	0.6	(0.3–1.0)
Albumin (g/l)					
Less than 50 y: < 40, Above 50 y: < 37	34	35	30	2.2	(1.3–3.8)
Less than 50 y: 40–51, Above 50 y: 37–58	41	45	24	1.0	Referent
Total retinol (μmol/l)					
< 0.7	0.56	3	3	1.9	(0.6–6.4)
0.7–2.2	1.5	36	26	1.0	Referent
> 2.2	3.0	41	26	0.8	(0.4–1.3)
Retinol binding protein (mg/l)					
4.7–47	30	53	35	1.0	Referent
> 47	69	27	20	1.2	(0.7–2.0)

[a] Adjusted for stage of cancer at the time of diagnosis.

By case history and serum ferritin measurements bleeding as a cause of the anaemia were ruled out in most of these patients. Ferritin, however, often being elevated in stress situations, may have been 'falsely' high in some of the cases. Probably in most anaemic cases some alimentary deficiencies lay behind. Half of the cases had low serum iron and magnesium contents, eight had low folic acid levels. Half of the cases reported a high alcohol intake (Table 4), which may displace the intake of foods containing important or essential nutrients and trace elements.

The frequently elevated serum ferritin concentrations observed among the patients could theoretically be caused by a toxic liver cell ferritin 'leakage'. However, any significant correlation between alcohol intake and ferritin could not be demonstrated.

Serum thiocyanate, being a marker for smoking, was elevated in less than half of the cases and one quarter of the controls. None of the non-smokers had a high level of thiocyanate, while among smokers there were persons at both levels of thiocyanate.

In two of the cases and one control person the mononucleosis antibody test was positive. By experience this test is positive in a limited period of time after virus exposure. Our findings confirm that mononucleosis antibody testing does not contribute to knowledge about the role of Epstein–Barr virus as a pathogenic factor in cancer of the upper digestive tract.

The survival analysis was carried out looking for possible prognostic indication of any of the measured variables in the case-control part of the study. Since the disease process itself may influence the variables directly all the analyses include stage of the disease at the time of diagnosis. This means that the prognostic indications presented may be thought of as an additional effect when stage is taken into account.

The tendency to a worse prognosis for those who were smoking at the time of diagnosis is in accordance with previous studies (Mak Kregar *et al*, 1992; Browman *et al*, 1993). In contrast we do not know whether our patients smoked during treatment. There was no clear dose-response between number of cigarettes smoked and survival and it was confusing that thiocyanate was inversely related to survival. However, an explanation may be that the smokers in the most serious condition of the disease stopped smoking and hence lowered their thiocyanate level.

Of the other variables only pretherapy haemoglobin and albumin showed a significant prognostic effect when stage of the disease was taken into account. Hannisdal has looked at the prognostic effect of haemoglobin for several types of cancer and found in univariate analyses a positive relation, but this effect usually disappeared in multivariate analyses when other prognostic factors were included (Hannisdal,

1994). Low values of albumin are shown to be related to a worse prognosis (Mick *et al*, 1991). Although we have adjusted for stage of the disease it may be a too rough adjustment. Theoretically, a low serum albumin concentration could express undernourishment and be in accordance with the tendency of worse prognosis for those with lowest BMI at the time of diagnosis. However, any significant correlation between albumin concentration and the BMI could not be shown in the present material.

Conclusions

In the present study, a variety of blood chemistry variables, dietary habits, smoking, alcohol consumption and socio-economic status were investigated in order to evaluate possible influences on oro-pharyngeal cancer and survival. Some prognostics were revealed broadly harmonising with other studies. Smoking, strong beer and liquor, low social status and consumption of butter and milk had a negative influence on the disease. Fruit and vegetables, particularly focused on, appeared to have a beneficial effect. Low serum albumin, iron and magnesium indicated a high OR for cancer, whereas vitamin C and β-carotene had the opposite implication. No significant implications on survival could be detected in blood chemistry beyond the stage of disease.

Acknowledgements—The assistance of K. Noreik in the formation of socio-economical questionnaires is gratefully acknowledged

We also appreciate, in particular, the initiative of Prof. Emeritus G. Djupesland who conceived the idea for this study.

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