Occupational exposures and squamous cell carcinoma of the oral cavity, pharynx, larynx, and oesophagus: a case-control study in Sweden

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Abstract

***Objectives*—This community based case-referent study was initiated to investigate aetiological factors for squamous cell carcinoma of the upper gastrointestinal tract.**

***Methods*—The study was based on all Swedish men aged 40–79 living in two regions of Sweden during 1988–90. Within that base, efforts were made to identify all incident cases of squamous cell carcinoma of the oral cavity, oropharynx and hypopharynx, larynx, and oesophagus. Referents were selected as a stratified (age, region) random sample of the base. The response was 90% among cases and 85% among referents. There were 545 cases and 641 referents in the final study group. The study subjects were interviewed about several lifestyle factors and a life history of occupations and work tasks. The exposure to 17 specific agents were coded by an occupational hygienist. The relative risk (RR) of cancer was calculated by logistic regression, standardising for age, geographical region, and alcohol and tobacco consumption.**

***Results*—Exposure to asbestos was associated with an increased risk of laryngeal cancer, and a dose-response relation was present. The RR was 1.8 (95% confidence interval (95% CI) 1.1 to 3.0) in the highest exposure group. More than eight years of exposure to welding fumes was associated with an increased risk of pharyngeal cancer (RR 2.3 (1.1 to 4.7)), and laryngeal cancer (RR 2.0 (1.0 to 3.7)). There were indications of a dose-response for duration of exposure. Associations were also found for high exposure to polycyclic aromatic hydrocarbons (PAHs) and oesophageal cancer, RR 1.9 (1.1 to 3.2). Exposure to wood dust was associated with a decreased risk of cancer at the studied sites.**

***Conclusions*—Some of the present findings confirm known or suspected associations—such as asbestos and laryngeal cancer. The study indicates that welding may cause an increased risk of pharyngeal as well as laryngeal cancer. The findings corroborate an association between exposure to PAHs and oesophageal cancer.**

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There are large variations in the incidence of cancer of the head and neck over the world. In western countries, these tumours to a large extent depend on tobacco smoking and alcohol habits,[1–4] and recent studies indicate that a high intake of fruit and vegetables may have a protective effect.[5]

In Sweden, where the incidence of these tumours is comparatively low, there are around 1000 new cases of cancer of the oral cavity, oropharynx and hypopharynx, oesophagus, and larynx each year, 700 among men and 350 among women. The age standardised incidences are 16.0 and 6.0 $\times 10^{-5}$ a year, for men and women respectively, and are higher in urban than in rural areas. Over the past 20 years, there has been an increase in cancer of the oral cavity, pharynx, and oesophagus among men, whereas the laryngeal cancer rate has decreased slowly.[6]

Occupational risk factors for cancer at these sites are less well established. Nickel, chromium, and mustard gas have been reported as risk factors, and increased risks have also been reported among workers in the leather industry, in isopropyl alcohol manufacturing, and after exposure to acid mist.[4] There are some studies indicating that asbestos exposure may cause laryngeal cancer, but several reviews consider the association as uncertain.[7–10] Oesophageal cancer has been noted to be in excess among workers exposed to combustion products,[11] and in the rubber industry,[12] although the possibility of confounding effects from alcohol and tobacco was not ruled out. For cancer of the oral cavity, oropharynx, and hypopharynx, there are sporadic reports of occupational associations, but no firm evidence exists.

This study was initiated to investigate aetiological factors for cancer of the upper aerodigestive tract, including lifestyle factors—such as alcohol, tobacco, diet, snuff, oral hygiene, and occupational exposures. The study was restricted to squamous cell carcinomas as this is the most common histological subtype. The study was restricted to men as use of oral snuff in Sweden is mostly restricted to men, and occupational exposures are also much more common among men. Also, the incidence among women is much lower, which would give the study a low power to detect differences in risk due to sex. The study was performed in two densely populated areas of Sweden, comprising around 37% of the Swedish population.

Table 1 Number of cases and referents by geographical region

Region	Referents	Cases				
		All sites	*Oral cancer*	*Pharyngeal cancer*	*Oesophageal cancer*	*Laryngeal cancer*
Stockholm	352	299	76	87	70	66
Southern region	289	246	52	51	52	91
Total	641	545	128	138	122	157

In the design of the study, attention was paid to early identification of the cases to obtain exposure information from the subjects themselves. Referents were selected from the population. Personal face to face interviews were performed to obtain a detailed assessment of the exposure to known risk factors—such as alcohol and tobacco smoking, as well as an assessment of dietary habits, and a lifetime history of occupations and work tasks.

This report deals with occupational exposures. The intensity of the exposure to 17 specific occupational exposure factors was assessed by an occupational hygienist. Occupational titles were also recorded, but this article focuses on the risk associated with exposure factors rather than occupations.

The study aimed at an evaluation of the role of several known or suspected occupational carcinogens in the aetiology of squamous cell carcinoma of the oral cavity, oropharynx and hypopharynx, oesophagus, and larynx.

Material and methods

STUDY BASE

The study was based on all men aged 40–79, born in Sweden and living in (and included in the population registers of) the county of Stockholm or in the southern healthcare region, comprising the counties of Malmöhus, Kristianstad, Blekinge, Kronoberg, and parts of Halland. This population, comprising around 750 000 men, was followed from 1 January 1988 to 31 January 1991.

CASES AND REFERENTS

Efforts were made to identify all incident cases of squamous cell carcinoma of the head and neck that occurred in the study base. Cases of cancer at the following sites were included: oral cavity, oropharynx and hypopharynx, oesophagus, and larynx, which corresponded to code numbers 141, 143, 144, 145, 146, 148, 150, and 161, of the ninth revision of the international classifications of diseases (ICD-9). Cases were identified by weekly reports from departments of otorhinolaryngology, oncology, and surgery. Cases not identified by this procedure were obtained from the regional cancer registries in Stockholm and in the southern healthcare region. Cancers identified incidentally at necropsy were not included.

Referents were selected by stratified random sampling from computerised population registers in each of the two regions. Sampling was performed every six months. The referent series was frequency matched to the cases for region (Stockholm and the southern healthcare region) and age group (40–54, 55–64, and 65–79 years).

In all, 605 cases and 756 referents were identified. Exposure histories were obtained from 90% of the cases and 85% of the referents. There were 545 cases and 641 referents in the final study group. Table 1 shows the numbers of cases by cancer site and referents in each region.

EXPOSURE INFORMATION

Cases and referents were asked to participate in an interview on lifestyle and environmental factors. All interviews were conducted by two nurses, one in each region. The interview followed a structured questionnaire on smoking history, use of oral snuff, alcohol habits, and occupational history, as well as other lifestyle and environmental factors. Most cases were interviewed at the wards and the referents were usually interviewed in their homes. The nurses were specially trained for interviews on lifestyle factors and occupational histories. The nurses could not be blinded to the case-referent status of the subjects, but were trained to aim at the same level of detail in the exposure histories for both cases and referents.

The smoking history recorded the use of cigarettes, cigarillos, cigars, and pipe tobacco over the lifetime. The average intake of beer, wine, and liquor during the past five years was converted to g alcohol/week. Several indicators of oral hygiene were used—such as frequency of visits to a dentist, and how often the subject changed tooth brush.

OCCUPATIONAL EXPOSURES

The occupational history included all jobs held for more than one year over the lifetime, recording the times of starting and stopping, job title, job tasks, and company for each job. The nurses were trained to specify work tasks, materials used, etc for jobs of special relevance for the exposures under study. The work histories were reviewed by an occupational hygienist (RJ), who coded the occupations according to the Swedish standard classification of occupations, NYK 1983, and the intensity and probability of the exposure to 17 specific occupational exposure factors, for each job held. The hygienist was blinded to the case-referent status of the men.

The following occupational exposures were assessed (the percentage of referents ever exposed are given in parentheses): polycyclic aromatic hydrocarbons (PAHs, with benzo(a)pyrene (BaP) as an indicator for the assessment, 44.3%), asbestos (27.6%), general dust (based on levels of total suspended particles, 24.0%), wood dust (18.2%), quartz (16.4%), metal dust (16.1%), oil mist (15.0%), welding fumes (12.9%), formaldehyde (9.4%), man made mineral fibres (MMMF, 6.7%), paper dust (5.3%), textile dust (3.9%), chromium (hexavalent Cr, 3.7%), phenoxy acids (3.4%), nickel (elemental or in compounds, 3.3%), acid mist (2.0%), and leather dust (1.7%).

The exposure assessments were based on a literature survey of exposure data for different occupations. The assessments aimed to estimate the exposure intensity on a relative scale,

Table 2 Relative risk of cancer among those ever exposed v never exposed to each exposure factor, calculated by unconditional logistic regression accounting for region, age, alcohol consumption (four classes) and smoking habits (never/ex/current smoker) (low and high exposure refers to a cut off at the median of the cumulative dose among the exposed referents)

	All sites			*Oral cavity*			*Pharynx*			*Oesophagus*			*Larynx*		
	Cases (n)	*RR*	*95% CI*	*Cases (n)*	*RR*	*95% CI*	*Cases (n)*	*RR*	*95% CI*	*Cases (n)*	*RR*	*95% CI*	*Cases (n)*	*RR*	*95% CI*
PAHs (low)	109	1.08	(0.78 to 1.51)	25	0.99	(0.57 to 1.73)	28	1.06	(0.61 to 1.82)	32	2.01	(1.16 to 3.48)	26	0.77	(0.46 to 1.28)
PAHs (high)	175	1.48	(1.09 to 2.01)	41	1.39	(0.86 to 2.25)	44	1.52	(0.94 to 2.45)	37	1.87	(1.11 to 3.16)	53	1.47	(0.96 to 2.24)
Asbestos (low)	89	1.08	(0.75 to 1.55)	17	0.64	(0.35 to 1.20)	24	1.01	(0.57 to 1.80)	22	1.21	(0.67 to 2.17)	28	1.21	(0.73 to 2.02)
Asbestos (high)	95	1.15	(0.80 to 1.65)	16	0.67	(0.36 to 1.25)	22	1.08	(0.62 to 1.91)	21	1.00	(0.54 to 1.82)	34	1.69	(1.05 to 2.74)
Dust (low)	75	1.40	(0.95 to 2.05)	21	1.76	(0.98 to 3.16)	15	1.06	(0.55 to 2.05)	16	1.48	(0.77 to 2.85)	23	1.24	(0.73 to 2.12)
Dust (high)	76	1.33	(0.90 to 1.97)	16	1.35	(0.70 to 2.60)	17	1.42	(0.74 to 2.72)	20	2.16	(1.15 to 4.05)	23	1.27	(0.74 to 2.20)
Wood dust	69	0.62	(0.43 to 0.90)	16	0.70	(0.38 to 1.29)	14	0.52	(0.27 to 0.99)	19	0.88	(0.49 to 1.59)	20	0.54	(0.32 to 0.93)
Quartz	94	0.95	(0.68 to 1.34)	20	0.85	(0.48 to 1.50)	27	1.29	(0.77 to 2.18)	23	1.16	(0.66 to 2.03)	24	0.78	(0.47 to 1.29)
Metal dust	114	1.33	(0.95 to 1.85)	19	0.76	(0.43 to 1.36)	31	1.40	(0.84 to 2.33)	23	1.26	(0.72 to 2.20)	41	1.66	(1.07 to 2.57)
Oil mist	75	0.79	(0.55 to 1.13)	15	0.69	(0.37 to 1.29)	19	0.78	(0.43 to 1.41)	13	0.66	(0.34 to 1.29)	28	1.10	(0.68 to 1.80)
Welding fumes	97	1.37	(0.95 to 1.95)	18	0.88	(0.48 to 1.60)	28	1.57	(0.91 to 2.71)	19	1.15	(0.62 to 2.12)	32	1.56	(0.97 to 2.53)
Formaldehyde	69	1.42	(0.94 to 2.15)	14	1.28	(0.64 to 2.54)	13	1.01	(0.49 to 2.07)	19	1.90	(0.99 to 3.63)	23	1.45	(0.83 to 2.51)
MMMF	28	0.53	(0.31 to 0.93)	6	0.51	(0.20 to 1.32)	7	0.56	(0.23 to 1.38)	5	0.46	(0.17 to 1.29)	10	0.71	(0.34 to 1.50)
Paper dust	28	0.82	(0.46 to 1.45)	6	0.63	(0.24 to 1.64)	7	0.68	(0.27 to 1.69)	8	1.15	(0.47 to 2.80)	7	0.69	(0.29 to 1.62)
Textile dust	18	0.76	(0.39 to 1.49)	4	0.80	(0.26 to 2.48)	3	0.53	(0.14 to 1.93)	3	0.54	(0.14 to 2.01)	8	1.06	(0.45 to 2.53)
Chromium	20	1.04	(0.54 to 2.02)	7	1.60	(0.63 to 4.06)	3	0.66	(0.18 to 2.41)	5	1.40	(0.48 to 4.05)	5	0.78	(0.29 to 2.13)
Phenoxy acids	11	0.45	(0.20 to 1.02)	7	1.61	(0.61 to 4.24)	0	—	—	1	0.22	(0.03 to 1.75)	3	0.36	(0.10 to 1.26)
Nickel	16	0.94	(0.46 to 1.95)	6	1.53	(0.57 to 4.16)	2	0.45	(0.10 to 2.11)	4	1.15	(0.36 to 3.70)	4	0.68	(0.22 to 2.06)
Acid mist	12	1.23	(0.52 to 2.93)	3	1.39	(0.34 to 5.58)	4	1.21	(0.35 to 4.23)	1	0.42	(0.05 to 3.63)	4	1.31	(0.41 to 4.22)
Leather dust	16	2.06	(0.87 to 4.89)	3	2.15	(0.54 to 8.67)	5	2.83	(0.79 to 10.20)	3	2.61	(0.64 to 10.65)	5	2.08	(0.65 to 6.62)

reflecting time specific annual average exposure levels. The exposure intensities were assessed on a four level ratio scale (exposure class 0,1,2,3). Exposure class 0 was used for unexposed work periods.

Exposure class 3 represented exposures higher than one third of the Swedish threshold limit value (TLV) in 1992 for all exposures but PAHs, formaldehyde, welding, and phenoxy acids. For exposure to PAHs, BaP was used as an indicator and class 3 represented exposures higher than one fifth of the TLV for BaP. Formaldehyde class 3 represented exposures higher than three times the TLV, and for welding and phenoxy acids arbitrary exposure units were used, based on work tasks.

The ratio between classes 1, 2, and 3 were 1:3:5 for all exposures but PAHs (1:10:100), welding (1:5:10), and phenoxy acids (1:4:15). Examples of the classification of PAHs and asbestos in some typical occupations are given in the discussion section. The methods developed for the exposure classification will be presented in detail elsewhere.

The probability of exposure for each person and work period was assessed as >70%, 33%–70%, or <33%, with 0.85, 0.50, and 0.20 as point estimates. In some situations, a person could have both a low but certain exposure to a substance, and a low probability of a higher exposure to the same substance. In this case, priority was given to a high probability in the estimation. Of all exposure assessments in exposure class 3, 95% of the assessments were assigned the highest probability, the corresponding proportion in class 2 was 93%, and in exposure class 1 48% of the assessments had a high probability.

The cumulative exposure to each of the 17 substances was calculated as the product of the exposure intensity, the probability of exposure, and the duration of the exposure, and by adding the contributions over the entire work history.

The obtained index of cumulative exposure was classified, based on the distribution among exposed referents, with medians, tertiles, etc as cut off points. The number of classes were reduced to obtain reasonably large groups; subgroups comprising <5% of exposed referents were avoided.

DATA ANALYSIS

The relative risk of developing cancer (the incidence rate ratio, RR) was calculated by unconditional logistic regression.[13] Indicator variables for geographical region (Stockholm or the southern healthcare region) and age class (40–54, 55–64, 65–79 years) were included in all regression models, to account for variables included in the study design. Alcohol and tobacco smoking were accounted for in all analyses. Based on exploratory analyses, alcohol was expressed by indicator variables representing the average level of alcohol intake during the past five years (0–10 g, 11–20 g, 21–50 g, and >50 g of ethanol a week). The influence from tobacco smoking could largely be accounted for by subdivision into current smokers, ex-smokers, and never smokers. Use of oral snuff did not influence the cancer risk and was not included in the standard model for control of confounding.

As a check of residual confounding, certain analyses were also adjusted for age in five-year categories, duration of smoking (never smoked, 1–20, 21–40, and >40 years of smoking), eight categories of lifetime tobacco consumption (never smoked and seven equally large classes of increasing lifetime tobacco consumption), eight categories of alcohol intake (by splitting each of the existing four classes into two), oral hygiene (dichotomous), intake of vitamin C (four classes), and intake of carotene (four classes).

The SPSS computer program[14] was used for data processing.

ANALYTICAL APPROACHES

The regression models were kept as unrestricted as possible, with indicator variables rather than continuous variables. In the basic analyses, the cancer risk among people ever

Table 3 Asbestos exposure and laryngeal cancer, analysis of dose-response

Model (n)		*Unexposed to asbestos*	*Asbestos exposure, cumulative*			
			Quartile I	*Quartile II*	*Quartile III*	*Quartile IV*
	Cases (n)	95	13	15	16	18
	Referents (n)	464	43	45	44	45
I	Crude RR, adjusted for age and region	(1.0)	1.44	1.65	1.78	1.98
	95% CI		(0.74 to 2.80)	(0.87 to 3.10)	(0.96 to 3.30)	(1.09 to 3.61)
II	RR adjusted for age, region, alcohol, and tobacco. Asbestos exposure was represented by four indicator variables	(1.0)	0.99	1.57	1.53	1.77
	95% CI		(0.49 to 1.98)	(0.80 to 3.08)	(0.79 to 2.93)	(0.94 to 3.31)
III	RR adjusted for age, region, alcohol, and tobacco. One variable was used to represent the asbestos exposure class.* Fitted values of RR and 95% CI are shown	(1.0)	1.16	1.35	1.56	1.82
	95% CI		(1.02 to 1.32)	(1.04 to 1.74)	(1.06 to 2.30)	(1.08 to 3.04)

The cumulative dose of asbestos was categorised on a scale with five levels; unexposed and four levels of increasing cumulative doses, based on the quartiles of the distribution of cumulative dose among the exposed referents. Unconditional logistic regression accounted for age, region, alcohol consumption (four classes) and tobacco smoking (never/ex/current smokers).
*Model III gave a p for trend = 0.02.

exposed to one of the occupational factors was compared with that among those never exposed to the factor. For evaluation of dose-response, the indicator of cumulative exposure was categorised, based on the distribution among the exposed referents, as already described. For a test of significance of trend, the classes of increasing exposure were assigned the numbers 0, 1, 2, 3, and 4, representing the exposure in one variable. For some analyses, the cumulative exposure index as such was included as a continuous variable.

The use of cumulative dose in the calculation of dose-response was based on the assumption that cancer risk is proportional to cumulative dose, which may be a reasonable assumption but may not always be true. A short but high exposure may have a stronger effect than a prolonged low exposure, although both may sum up to the same cumulative dose. In the absence of initial knowledge on the best way to combine intensity and time, we used a simple linear combination. Other models would probably result in several additional dose-response associations, but interpretation is hampered if models are selected for special purposes. For some exposures, dose response was also tested with duration of exposure.

Results

Table 2 shows the relative risk of cancer by site, associated with each of the 17 occupational exposures. The risk of cancer at all sites combined (head and neck cancer) was increased after high exposure to PAHs, and to some extent also to general dust, welding fumes, and formaldehyde. Exposure to wood dust was associated with a reduced risk of head and neck cancer.

High exposure to PAHs was associated with an increased risk of oesophageal cancer, although the point estimates for low and high exposure did not indicate an exposure-response trend. High exposure to asbestos was associated with an increased risk of laryngeal cancer. There were no indications of increased risk for any of the other sites after exposure to asbestos. High exposure to general (total) dust was associated with an increased risk of oesophageal cancer.

Exposure to metal dust as well as welding fumes was associated with an increased risk of laryngeal cancer. However, these two exposures were closely correlated, and it was not possible to separate exposure to metal dust from welding fumes. There was also some association between exposure to formaldehyde and oesophageal cancer.

Many exploratory analyses were performed to investigate the main findings of table 2 further. The material allows many models and hypotheses to be tested. In this paper we have focused on dose as a linear combination of time and intensity. Duration of exposure was analysed for welding and formaldehyde, but not for the other exposure factors.

LARYNGEAL CANCER AND EXPOSURE TO ASBESTOS, DOSE-RESPONSE, AND INTERACTION

Table 3 shows the relative risk of laryngeal cancer subdivided by cumulative exposure to asbestos. Three models for investigation of dose-response relations are presented. Model I is the crude RR, adjusted only for age and region, to account for the study design for sampling of referents. Model II presents the RR adjusted for age, region, alcohol and tobacco, incorporating the cumulative dose of asbestos as four indicator variables, with unexposed men as reference. Model II gave indications of a dose-response relation. In model III, the asbestos dose class number (0,1,2,3, or 4) was introduced in the regression as one variable. The increase in RR for each successive increase in dose (the $\exp(\beta)$) was 1.16, and the p value for trend was 0.02. Inclusion of cumulative dose of asbestos as a continuous variable (not shown in table) also confirmed a dose-response relation ($p = 0.008$).

Inclusion of indicator variables for oral hygiene, intake of vitamin C, carotene, and eight classes to represent smoking habits did not change the risk estimates materially (the RRs for quartiles 1–4 of increasing asbestos exposure were 1.07, 1.36, 1.67, 1.69).

Table 4 shows an analysis of the interaction between tobacco smoking and asbestos in the causation of laryngeal cancer. Ex-smokers and never-smokers were combined in one group and contrasted with current smokers to obtain larger groups. Men exposed to asbestos were

Table 4 RRs from regression model for test of deviation from multiplicative interaction between asbestos and tobacco smoking for risk of laryngeal cancer (the model also included age, region, and alcohol)

	Asbestos exposure	
Smoking status	*No*	*Yes*
Current smoking:		
No	(1)*	1.81
Yes	3.87	4.78

*The number of cases or referents in each cell were: asbestos only 21/97, current smoking only 57/134, both exposures 41/80, neither exposure 38/330.
Expected RR among current smokers exposed to asbestos according to: multiplicative model 1.81×3.87=7.00; additive model 3.87+(1.81−1)=4.68.

contrasted with those unexposed. The interaction term for the combined effect of asbestos and smoking was non-significant with a point estimate of 0.68 (0.32 to 1.47), indicating that the combined effect of smoking and asbestos was smaller than that predicted by a multiplicative model. The RRs predicted by a purely multiplicative as well as additive interaction model are also shown.[15] The observed RR among current smokers exposed to asbestos was close to that predicted by an additive model.

WELDING FUMES

Exposure to welding fumes seemed to increase the RRs for both pharyngeal and laryngeal cancer (table 2). The risk correlated with number of years exposed for both pharyngeal and laryngeal cancer (table 5), but there was no obvious dose-response pattern with cumulative dose. The risk of cancer at both sites was significantly increased after more than eight years of exposure to welding fumes (the median exposure time among exposed referents). Adjustment for concurrent exposure to asbestos changed the risk estimates only marginally.

EXPOSURE TO PAHS

Exposure to PAHs was associated with an increased risk of oesophageal cancer, and there were also indications of increased risk for the other sites among the highly exposed men (table 2). Subdivision of the exposed group into four classes of increasing cumulative exposure gave no indications of a dose-response trend for oesophageal cancer, but for all sites combined, the RR increased with increasing cumulative exposure to PAHs. These RRs were 1.15 (0.75 to 1.78), 1.02 (0.66 to 1.57), 1.40 (0.94 to 2.09), 1.56 (1.06 to 2.29), for successively increasing levels of cumulative exposure to PAHs, standardising for age, region, alcohol, and tobacco.

Table 5 Duration of exposure to welding fumes and RR of cancer of the pharynx and larynx

		Duration of welding		
	Unexposed	*1–8 y*	*>8 y*	*Trend test*
Pharyngeal cancer, (RR)	(1.0)	1.12	2.26	p=0.04*
95% CI		0.53–2.35	1.09–4.68	
Laryngeal cancer, (RR)	(1.0)	1.25	1.95	p=0.04†
95% CI		0.65–2.42	1.03–3.69	

Unconditional logistic regression accounting for age, region, alcohol consumption (four classes) and tobacco smoking (never/ex/current smokers).
*The class number (0, 1, or 2), representing unexposed, >0–8 y and >8 y of exposure was included as one variable in the regression model. The exp(β) was 1.43 (1.02–2.01).
†The class number (0, 1, or 2), representing unexposed, >0–8 y and >8 y of exposure was included as one variable in the regression model. The exp(β) was 1.37 (1.02–1.85).

FORMALDEHYDE

Table 2 indicated some association between oesophageal cancer and formaldehyde. There was no dose-response trend based on cumulative dose or on number of years exposed (data not shown).

WOOD DUST

Exposure to wood dust was associated with a decreased risk of cancer, for all studied sites (table 2). The risk of head and neck cancer was decreased among men exposed to wood dust both in Stockholm, RR 0.78 (0.43 to 1.40) and in the southern region, RR 0.56 (0.35 to 0.89). A striking interaction with smoking was present, as exposure to wood dust was associated with a lowered risk of head and neck cancer among current smokers (RR 0.59 (0.36 to 0.97)), and ex-smokers (RR 0.39 (0.20 to 0.78)), whereas exposure to wood dust was associated with an increased cancer risk when the regression was restricted to people who had never smoked, RR 2.27 (0.96 to 5.38).

GENERAL DUST

Exposure to general dust was associated with an increased risk of oesophageal cancer and possibly also of oral cancer (table 2). However, there were no indications of dose-response, and the RR decreased considerably when other occupational exposure factors as well as an indicator of oral hygiene were included in the model. This indicates that the risk excess was not caused by exposure to dust in itself.

Discussion

This study involved four cancer sites and 17 occupational exposure factors, giving many combinations of exposures and outcomes. We shall discuss possible systematical errors in the risk assessments, generalisability, and statistical power. The most important associations are discussed in detail, but it is not possible to make a detailed analysis and discussion of all 68 combinations. Future work will focus on concepts of dose other than the cumulative dose used here, and also include analyses based on occupational titles.

SYSTEMATIC ERRORS

The quality and the completeness of the tumour diagnoses in the Swedish cancer registry is high. Notification of new cases of cancer is compulsory for both clinical physicians and pathologists in Sweden, and the notification rate for cancer at these sites is high, 99%.[6 16] All cases were histologically verified as squamous cell carcinomas by the pathologists at the hospitals. Thus, the potential problem of misclassification of the outcome was small in this study. Referents were selected from continuously updated registers of the base population, thus obtaining a representative sample of the person-time that generated the cases. The response rate was high, both among cases and referents.

The classification of occupational exposures was based on occupational histories, and could not account for variation in the exposure that was not reflected in the job titles or description of work tasks in the interviews. It is probable that there is imprecision in the classification of the intensity of occupational exposures, even if the histories were obtained directly from the men rather than from surrogates. However, the hygienist performing the classifications was blinded to the case-referent status of the men, and any exposure misclassification is likely to be non-differential for outcome and give an attenuation of the RRs towards unity.

Both tobacco smoking and alcohol consumption are important risk factors for cancer at the studied sites, and efforts were made to obtain high quality in the exposure information on these factors. There was a tendency to positive confounding from both alcohol and tobacco for many of the associations, implying that the exposed people had smoked more and drunk more alcohol than the referents. The confounding from both tobacco and alcohol was controlled by a relatively simple model, based on smoking classified as never-smokers, ex-smokers, and current smokers only. Additional models were tested, including the duration and intensity of smoking and a finer stratification of g alcohol/week. This did not affect the RRs materially, indicating that there is no important residual confounding due to smoking or alcohol.

STATISTICAL POWER AND GENERALISABILITY, GENERAL REMARKS

Six of the 17 exposures were comparatively rare. These were textile dust, chromium, phenoxy acids, nickel, acid mist, and leather dust. Our study would be able to detect only large risks for these exposures, so moderate excesses in risk cannot be excluded.

The study was community based—that is, cases and referents were selected from a geographically defined area. The average exposure levels for most factors would tend to be low, and the fraction of men with very high exposures would also be low.

ASBESTOS

Exposure to asbestos was associated with an increased risk of laryngeal cancer, and a dose-response relation was present, when cumulative dose was used as a measure of dose. The same type of dose-response relation has been shown in the causation of lung cancer by asbestos.[17]

It is not feasible to calculate dose-response in terms of fibre concentrations or fibre-years from the data in its present form. Dose estimations were based on quantitative assessments of the intensity of the exposure (annual average fibre concentration) as well as the probability of exposure. It is not immediately justified to calculate backwards what absolute asbestos concentrations that were associated with an increased risk without disentangling the contributions from intensity, probability of exposure, and time.

To be included in the highest cumulative exposure group an insulator (with the highest intensity and probability of asbestos exposure) would have to have worked for at least four years. The mean exposure among the exposed referents in the highest cumulative class corresponded to 10 years of work as an insulator. A car mechanic or bricklayer (typically in the lowest asbestos intensity class) would have to work for at least 20 years to be included in the highest cumulative exposure group, and on average would have worked 50 years, provided that the exposure was assigned a high probability.

Among the referents, 27.6% were ever exposed to asbestos. The two higher quartiles of cumulative exposure to asbestos showed indications of an increased risk of laryngeal cancer (table 3). These quartiles comprise 12.1%, 12.5%, and 14.7% of the age groups 40–54, 55–64, 65–79, respectively, among the referents. Thus, the findings indicate that about 13% of the male population aged 40–79 in the studied areas have had an occupational exposure to asbestos high enough to increase the risk of laryngeal cancer by 60%. Laryngeal cancer should not be overlooked when the public health impact from exposure to asbestos is assessed.

Reviews of the role of asbestos in the aetiology of laryngeal cancer have arrived at markedly different conclusions; in their extensive review of health effects from asbestos, Doll and Peto[17] considered the evidence for a causal relation to be strong, which was also the conclusion of Smith *et al*.[18] Several other reviewers have considered the evidence as weak or non-existent.[7–10]

The present data give strong support for asbestos as a risk factor for cancer of the larynx. The relation was robust for different models with standardisation for alcohol, tobacco, and oral hygiene, as well as other occupational exposures.

WELDING FUMES

There were increased risks of cancer of the larynx and pharynx after more than eight years of exposure to welding fumes. Welding involves exposure to many chemicals, including metal dust, irritant gases, and PAHs. Welding in stainless steel is associated with an increased risk of lung cancer, due to exposure to hexavalent chromium.[19] Welding in other materials has not been consistently shown to be associated with an increased risk of lung cancer. The present data indicate that other components of welding fumes may be carcinogenic as well, as regression models of risk of laryngeal cancer, incorporating welding, asbestos, and chromium showed independent effects of both asbestos and welding. Eleven per cent of the welders among the referents were ever exposed to chromium, which corresponds with other investigations, showing that on the average 7% of Swedish welders are exposed to chromium (N Plato, personal communication). This indicates that exposure to chromium among the welders in this study has not been missed, and the excess of laryngeal and pharyngeal cancer

cannot be attributed solely to exposure to chromium during stainless steel welding.

There are some earlier observations of increased risk of laryngeal cancer among welders,[20 21] although it is possible that exposure to asbestos may have contributed to the excess, as stated by Tola *et al*.[21]

PAHS

There was an increased risk of head and neck cancer after exposure to PAHs, and the risk increased with increasing cumulative dose. To obtain a cumulative dose of PAHs in the highest class a person would have to work for at least four months as a coke or gas worker (exposure intensity class 3) or at least three years as a steel or foundry worker (typically in class 2). The mean exposure among exposed referents in the highest exposure class corresponded to one year as a gas or coke worker, or 10 years as a steel or foundry worker. Men with a lower intensity exposure to PAHs—such as car repairers, garage workers, or iron miners (all in exposure intensity class 1)—would never accumulate a high enough exposure to PAHs to be included in the group with the highest cumulative dose.

The PAHs are a mixture of compounds of which some are carcinogenic to humans.[22] An increased risk of lung and bladder cancer after exposure to PAHs has been found in several investigations, and there are also sporadic reports of increased risk of cancer of the buccal cavity, pharynx, larynx,[23] and oesophagus.[11] The present data add to the evidence that PAHs are carcinogens and can produce cancer of the head and neck.

FORMALDEHYDE

Formaldehyde was classified as probably carcinogenic by the International Agency for Research on Cancer (IARC),[24] partly based on observations of increased risk of nasopharyngeal cancer among exposed humans. The present findings of an increased risk of oesophageal cancer after exposure to formaldehyde give no strong evidence in the absence of a dose-response. It may be a chance finding, or another concept of dose than cumulative dose or duration of exposure should be tested.

WOOD DUST

Exposure to wood dust was associated with a decreased risk of cancer for all the studied sites. Tobacco smoking is often not allowed in the wood industry due to the fire hazard, and it could be speculated that the lowered risk was due to residual confounding from low smoking habits among those exposed to wood dust. To investigate this, additional regressions were performed, subdividing smoking habits into eight classes of successively increasing cumulative dose of tobacco. However, the low RRs associated with exposure to wood dust persisted.

An interaction with tobacco smoking was found, in that a decreased risk of head and neck cancer was present among current smokers and ex-smokers only, but there was an increased risk after exposure to wood dust among those who had never smoked. There is a strongly increased risk of sinonasal cancer among workers exposed to wood dust.[24] However, epidemiological data on laryngeal cancer are contradictory: an excess of head and neck cancer was found among workers exposed to wood dust in Spain,[25] whereas a recent review concluded that there is no definite evidence for such an association.[26] The IARC concluded that occupational exposure to wood dust does not seem to have a causal role in cancers of the oropharynx or hypopharynx as opposed to nasal and nasopharyngeal cancer.[24] The interaction with smoking that was found in this study has not been reported previously and further investigations are needed to explore the nature and causes of this interaction.

AETIOLOGICAL FRACTION FOR CANCER OF THE PHARYNX AND LARYNX DUE TO WELDING

The RR of pharyngeal as well as laryngeal cancer was increased to about 2.0 after more than eight years of welding. The proportion of men having welded for more than eight years among the referents was 6.5% (6.1%, 6.3%, and 6.9% in age-groups 40–54, 55–64, and 65–79, respectively). There are around 280 cases of cancer of the larynx and pharynx among men in Sweden annually. Assuming that the observed association is causal, around $280\times(2-1)/(2+1/0.065-1) = 17$ cases of laryngeal and pharyngeal cancer could be prevented every year in Sweden if the exposure was removed.[15]

This is an occupational hazard not previously fully recognised. If the association is causal, which must be confirmed by other studies, it is necessary to reduce air pollution levels during welding. A recent investigation of exposure to welding fumes in Stockholm showed that exposure levels were still as high as in the 1970s for certain workplaces.[27]

OTHER EXPOSURES

Exposure to quartz, oil mist, MMMF, or paper dust did not seem to increase the risk of cancer of the head and neck. However, risk excesses in highly exposed subgroups cannot be ruled out.

Conclusions

Exposure to asbestos was associated with an increased risk of laryngeal cancer. There were indications of a dose-response trend for cumulative dose of asbestos. Tobacco smoking, alcohol consumption, oral hygiene, or exposure to welding fumes did not explain the findings.

Exposure to welding fumes was associated with increased risk of pharyngeal as well as laryngeal cancer. There were indications of a dose-response trend for number of years of exposure. Tobacco smoking, alcohol consumption, oral hygiene, or exposure to asbestos did not explain the findings.

The findings corroborate an association between exposure to PAHs and oesophageal cancer, as well as head and neck cancer in general. The relation between oesophageal cancer and exposure to formaldehyde needs further evaluation.

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