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Nasal and sinonasal cancer

Connection with occupational exposures in Denmark, Finland and Sweden

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HERNBERG S, WESTERHOLM P, SCHULTZ-LARSEN K, DEGERTH R, KUOSMA E, ENGLUND A, ENGZELL U, SAND HANSEN H, MUTANEN P. Nasal and sinonasal cancer: Connection with occupational exposures in Denmark, Finland and Sweden. *Scand j work environ health* 9 (1983) 315–326. A joint Danish-Finnish-Swedish case-referent investigation was initiated in 1977 in order to study the connection between nasal and sinonasal cancer and various occupational exposures. All new cases of nasal and sinonasal cancer were collected from the national cancer registers (Finland and Sweden) or from the hospitals (Denmark). Those still alive who agreed to an interview (N = 167) were individually matched for age and sex with patients with colonic or rectal cancer. A detailed telephone interview was made according to standardized forms. Both cases and referents thought that their condition was the one under study. The exposures were coded blindly by an industrial hygienist. The results showed associations between nasal and sinonasal cancer and exposure to (i) hardwood or mixed wood dust (discordant pairs 14: 2), (ii) softwood dust alone (13: 4), (iii) chromium (16: 6), (iv) nickel (12: 5, not significant), (v) welding, flame-cutting and soldering (17: 6), and (vi) lacquers and paints (14: 0). The last finding was probably due to confounding from wood dust exposure. Hardwood dust exposure was associated with adenocarcinoma. Softwood dust exposure alone was associated with epidermoid and anaplastic carcinomas. No associations were found for a number of exposures, including agricultural chemicals, textile dust, asbestos, quartz dust, organic solvents and leather work. Possible exposure to formaldehyde was evenly distributed between the cases and referents.

Key terms: chromium, epidemiology, furniture industry, nickel, sawmill industry, welding, wood dust.

Nasal and sinonasal cancers have been associated with several occupational exposures, among them dust from hardwood (1, 2, 3, 4, 5, 10, 11, 12, 15, 19, 22, 25), nickel production (3, 9, 13, 14, 24, 28, 29), cutting

oils (26), phenoxyacids and chlorophenols (18), and unspecified exposures in the boot and shoe industry (1, 4). Quite recently, experimental data have indicated that exposure to formaldehyde causes nasal cancer in rats (30).

Especially nasal adenocarcinoma, a rare tumor with an incidence of about 1 case per 1,000,000 person-years, has shown a very strong connection with occupational exposure to hardwood dust in the furniture industry (1, 2, 3, 4, 5, 6, 10, 11, 19, 22, 25). In addition some other types of nasal cancer may occur in excess among furniture workers, but the association is not yet quite clear (4, 22). It is also unclear whether exposure to softwood dust, eg, pine and spruce dust, can cause nasal cancer (19). In order to elucidate these

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Table 1. Distribution of identified cases by country.

	Denmark	Finland	Sweden	Total
Died	12	14	19	45
Could not be located or refused to cooperate	33	26	10	69
Number of interviewed cases without referent	2	3	1	6
Number of cases included in the analysis	69	24	74	167
Total number of identified cases	116	67	104	287

Table 2. Histopathological type of tumors.

Type	N
Epidermoid carcinoma	95
Adenocarcinoma	18
Anaplastic carcinoma	17
Malignant tumor of the salivary gland	9
Malignant melanoma	11
Lymphoma	8
Malignant mesenchymal tumor	3
Other malignant tumor	6
Total	167

problems further, a joint Nordic study was initiated in 1977. Because of its case-referent design, several factors other than exposure to wood dust could also be studied simultaneously.

Subjects

The Nordic countries all have national cancer registers with nearly 100 % coverage. Because the comparatively small size of the population in any single Nordic country limits the study of etiological factors for a rare tumor like nasal cancer, a joint study covering all the Nordic countries was planned initially. However, the population of Iceland was considered too small to make the extra costs of translation, attending meetings, etc, worthwhile. Unfortunately, it turned out later that Norway could not join the study, either, because the Norwegian cancer register considered it unethical to place data on referents at our disposal. For these reasons the study had to be undertaken with the participation of Denmark, Finland, and Sweden only.

All new patients with primary malignant tumors of the nasal cavity and paranasal sinuses [International Classification of Diseases (ICD) 160.00–160.99] diagnosed

in Denmark, Finland, and Sweden between 1 July 1977 and 31 December 1980 and reported to the national cancer registers were primarily selected as cases. However, because of a rather long reporting delay to the Danish register, it proved to be more practical to locate the cases from those four of the five existing oncological centers in Denmark which were prepared to collaborate.

After the cases (and the referents, see the last paragraph of this section) had been identified, a consent to contact the patients was obtained from the chief medical officer of the hospital or department where the patient had been treated. Table 1 shows the loss of material due to death, nonresponse, etc. In order to ensure that the quality of the information was good, we included only those patients who were still alive at the time of identification from the registers. Altogether 167 cases (Denmark 69, Finland 24, Sweden 74) remained when deceased patients and nonrespondents had been omitted (see the last paragraph of this section). The most common reasons for nonresponse were poor health and lack of telephone. Copies of the hospital records of the cases were borrowed from the hospitals and reviewed by the investigators for exact information of the primary site and the extent of the tumor. The original histopathological slides of all the cases were collected and evaluated by an experienced pathologist from each country and reexamined at joint meetings in which a consensus on the histopathological diagnoses was reached in all cases. The histopathological diagnoses were then classified into eight categories (table 2).

The mean age of the interviewed cases was 64.1 (SD 11.7, range 36–88) years for the 110 male patients and 62.5 (SD 14.0, range 29–88) years for the 57 female patients. The mean age of those cases not interviewed did not differ significantly

Table 3. Mean age and sex distribution of identified cases by country.

Sex of patient	Mean age (years)					
	Denmark		Finland		Sweden	
	Interviewed	Not interviewed	Interviewed	Not interviewed	Interviewed	Not interviewed
Male	64.8	65.1	58.3	59.7	65.2	65.8
Female	58.5	59.0	57.9	64.0	66.8	69.6
Total	63.1	62.6	57.9	61.7	65.8	66.9

from the ages of the interviewed ones (table 3). The mean age of the interviewed cases was the lowest in Finland (58 years). The Danish cases had the highest male:female ratio, or 2.6. Table 4 shows how those interviewed and those not interviewed were distributed according to primary site. Patients with cancer of the maxillary sinus contributed the highest proportion of dropouts. Table 5 shows the same distribution according to histological classification. No remarkable pattern emerged.

Each case was matched for country, sex, and age at diagnosis (within ± 3 years) with alive patients having malignant tumors of the colon and rectum (ICD 211.3 & 211.4). These patient-referents were all extracted from the national cancer registers, and they represented the same period as the cases. The first patient found who complied with the matching criteria was always selected as the referent. However, at the same time, another referent was also selected according to the same criteria to be used should the first referent be dead or otherwise unavailable. In spite of this procedure six cases for which referents were not available had to be left out of the material (table 1).

Methods

Interview

After the consent to contact the patient had been obtained from the hospital, a short standardized note describing the study and explaining that a telephone interview was to follow was sent to all the cases and referents. About one week later the patients were contacted by telephone and interviewed according to a standardized form. The patients were all told that

Table 4. Identified cases according to the primary site of tumor.

Site	Inter-viewed	Not interviewed
Vestibulum or cavum nasi or ethmoidal sinus	97	49
Maxillar sinus	28	46
Others	42	25
Total	167	120

Table 5. Identified cases according to the histopathological type of cancer.

Type of cancer	Inter-viewed	Not interviewed
Epidermoid carcinoma	95	59
Adenocarcinoma	18	13
Anaplastic carcinoma	17	9
Others	37	27
Missing information	—	12
Total	167	120

the aim of the study was to explore connections between occupational factors and various diseases in general (cancer was not mentioned at all), and hence they had no knowledge of whether they were cases or referents. The standardized interview forms had been worked out in Swedish at joint meetings and were then translated into Finnish and Danish. Although the occupational history was the primary objective, the patients were also asked questions about personal habits such as smoking, snuff consumption, and hobbies. Table 6 shows the smoking habits of the cases and referents 10 years before diagnosis. There were slightly more non-smokers among the referents. Snuff consumption occurred rather rarely; besides, in the Nordic countries, snuff is usually not inhaled through the nose, but taken

Table 6. Cigarette smoking status 10 years before the diagnosis.

Status	Case	Referent
Nonsmoker	76	91
Smoker		
1-9 cigarettes/d	32	26
10-19 cigarettes/d	38	29
≥20 cigarettes/d	21	21

Table 7. The interviewers' assessment of the quality of the interview.

Country	Good	Intermediate	Poor	Total
Denmark				
Case	43	22	4	69
Referent	54	14	1	69
Finland				
Case	18	5	1	24
Referent	18	5	1	24
Sweden				
Case	55	13	6	74
Referent	55	14	5	74
Total				
Case	116	40	11	167
Referent	127	33	7	167

under the lip or tongue.

A detailed occupational history was taken for each separate occupation of more than one year's duration. However, the last 10 years were not accounted for in order to allow for a latency period. The respondent was asked to indicate the calendar time of employment, the name of the company, the products produced by the company, his or her main occupational task, and if he or she was usually exposed to fumes, dust, smoke, or chemicals. Depending on the answers, one or more of six standardized special forms were then used for each period of employment in the following occupations: wood work, farming and forestry, textile work, metal work, construction work, and "other" work with exposure to chemicals.

For the same patient one or more special forms were filled out, sometimes the same form several times, depending on the number of employments, whereas the general form was, of course, filled out only once. All the accumulated data were considered when the exposure histories were coded. Each special form contained 6 to 10 specific questions regarding both the patient's own tasks and those of other workers in his/her vicinity. Both work processes (eg,

welding, soldering, electroplating) and specific agents (eg, cadmium, chromium, nickel) were explored with detailed questions. Such a procedure meant that those who had not worked in any of the specific environments of interest answered the general form only, while those who had worked in such exposures had a longer interview. It appeared that the preliminary letter contact greatly helped the patients to remember, and the interviewers did not get the impression that the patients became exhausted. The interviewers' assessment of the quality of the interview is shown in table 7. No major differences occurred between the cases and referents.

Classification of exposure

The interviewers met personally several times during the study and discussed the uniformity and symmetry of their techniques. The Swedish interviewer was a medical secretary with training in medical interviews, the Finnish interviewer was a nurse with long experience in research work, while the Danish interviewer was a physician (KS-L). In order to obtain a good appraisal of the data collected, and to allow for an assessment of historical data, an industrial hygienist (RD) evaluated the quality of exposure and did the final coding for the data analyses in collaboration with the interviewers. She did the coding blindly to secure symmetry for the cases and referents. Exposure was classified according to intensity, duration, and calendar time. The same person could have had several exposure periods of different intensity. The intensity of exposure was classified into no exposure, moderate exposure (assessed to be approximately below the American Conference of Governmental Industrial Hygienist's threshold limit values), and heavy exposure (levels above these standards). Because the exposures had taken place from more than 60 to 10 years ago, the conditions must have changed much over time. Hence visits to workplaces or measurements of air impurities as of today were judged meaningless, and the classification was based on estimates.

Exposures to wood dust in the furniture industry were classified as heavy when the work included grinding, drilling, and planing. The exposures to softwood dust for

sawmill workers and carpenters at construction sites were classified as moderate. Birch and aspen were included in the group of softwoods together with spruce and pine, to separate typically Nordic kinds of wood. All other kinds of wood, eg, oak, beech, mahogany, teak, palisander, walnut, etc, were classified as hardwood. All farmer exposures (fertilizers, animal dust, grain or hay dust, pesticides) for which no hygienic standards exist were classified as moderate. Examples of occupations which were classified as being nonexposed include teacher, salesman, clerk, housewife (knitting and lacemaking were not coded as "exposed"), fisherman, and lumberjack. In this presentation "exposed" is made up of "moderate" and "heavy" exposure combined.

Statistical methods

The comparisons were then made with regard to different exposure variables constructed from data on 26 specific agents or exposures. When the exposure variable was nominal with two categories, a matched pair analysis was performed using the McNemar test. The effect of exposure was estimated as the odds ratio. For dichotomous variables the odds ratio was estimated as the rate of discordant pairs, and its confidence limits were calculated as outlined by Miettinen (23). When subjects were stratified according to other variables (eg, smoking habits), the matching was ignored, and the Mantel-Haenszel procedure for significance testing and for calculation of the summary strength of association was used.

Results

Among both the cases and the referents the selection of occupational titles was great, comprising altogether about 100 different categories. The largest group with an almost equal case : referent ratio was farmers (48 : 41), followed by sales personnel, housewives, taxi drivers and chauffeurs, and office staff. Cabinetmakers (9 : 1) and mechanical engineering shop workers (17 : 8) were those who showed the most remarkable differences. However, since the study was designed to highlight detailed data on occupational expo-

sure, not merely occupations, only specific exposure data have been analyzed in the present communication.

Table 8 shows how the discordant pairs were distributed with regard to exposure to various kinds of wood dust. Exposure to hardwood dust was usually accompanied by exposure to softwood dust also, because exposure had occurred in the furniture industry. On the other hand, those who had been exposed to softwood dust alone had usually worked as sawmill workers and carpenters at construction sites, and their exposure did not include any hardwood dust (table 9). Two cases, but no referents, had probably also been exposed to wood preservatives consisting of chlorinated phenols and arsenicals in sawmills. Table 9 shows a list of the types of exposures that had occurred.

Exposure to paints and lacquers also showed a strong association with nasal and sinonasal cancer (distribution of discordant pairs 12 : 10), but this exposure often occurred together with exposure to hardwood or mixed wood dust. As can be seen from table 10, there were seven cases and three referents exposed to hardwood or mixed wood dust only, while two cases and no referents had been exposed to lacquers and paints but not to wood dust. Of them, one had also been exposed to chromium and nickel and one to chemicals in the leather industry. Two additional cases (both painters) had been exposed both to softwood (but not hardwood) dust and to paints. Eight cases and no referents had been exposed both to hardwood or mixed wood dust and to paints and lacquers. The association between nasal and sinonasal cancer and exposure to hardwood, softwood, or mixed wood dusts was the same also when only exposures occurring more than 20 or 30 years before the time of diagnosis were considered. The

Table 8. Distribution of discordant pairs for exposure to wood dusts.

Type of exposure	Discordant pairs	Odds ratio	95 % confidence limits
Hardwood dust only	2 : 1	2.0	0.2-21.0
Softwood dust only	13 : 4	3.3	1.1- 9.4
Hardwood + softwood dusts	12 : 1	12.0	2.4-59.2

Table 9. Exposure histories for those cases and referents classified as having been exposed to hardwood, mixed wood, or softwood dust.

Subject	Type of cancer ^a	Type of exposure	Period	Number of years
Hardwood				
Case 1	Ad	Sawing and sorting of oak parquet	1935–1943	8
Case 2	Ad	Cabinetmaking	1933–1975	42
Referent 1		Production of wagons	1922–1933	11
Mixed wood				
Case 1	Ad	Cabinetmaking	1934–1965	31
Case 2	E	Cabinetmaking	1931–1937	6
Case 3	E	Cabinetmaking	1940–1978	38
Case 4	Ad	Cabinetmaking	1942–1970	28
Case 5	Ad	Cabinetmaking	1926–1959	33
Case 6	E	Carpentry as a hobby, 4–6 h/week	1940–1980	40
Case 7	E	Cabinetmaking	1915–1927	12
Case 8	E	Construction carpentry	1927–1931	4
		Unskilled worker in furniture plant	1952–1955	3
Case 9	Ad	Cabinetmaking	1932–1967	35
Case 10	Ad	Cabinetmaking	1921–1945	24
Case 11	Ad	Pattern making (boats)	1930–1976	46
Case 12	Ad	Sanding of parquet floors	1954–1959	5
Case 13	Ad	Cabinetmaking	1925–1975	50
Referent 1		Sawing	1939–1950	11
Referent 2		Cabinetmaking	1929–1963	34
Softwood				
Case 1	E	Sawmill worker	1943–1944	1
Case 2	O	Construction carpenter	1920–1960	40
Case 3	E	Packing of glass in wood-wool	1963–1978	15
Case 4	An	Insulation work	1950–1952	12
Case 5	O	Construction work	1968–1978	
		Construction carpenter	1965–1967	2
Case 6	E	Sawmill worker	1945–1953	8
Case 7	E	Construction carpenter	1958–1969	11
		Construction work	1930–1943	13
Case 8	E	Sawmill worker	1946–1951	5
Case 9	E	Construction carpenter	1951–1979	28
		Construction carpenter	1943–1958	15
Case 10	E	Sawmill worker	1954–1973	19
Case 11	Mel	Sawmill worker	1926–1933	7
		Packing of glass in wood-wool	1950–1967	17
Case 12	An	Cabinetmaking (own firm, no hardwood)	1920–1970	50
Case 13	E	Matchmaking	1945–1964	19
Referent 1		Sawmill worker	1939–1968	29
Referent 2		Sawmill worker (carrying timber, transport of sawdust)	1929–1949	20
Referent 3		Construction carpenter	1933–1968	35
Referent 4		Construction carpenter	1925–1958	33

^a Ad = adenocarcinoma, An = anaplastic carcinoma, E = epidermoid carcinoma, Mel = malignant melanoma, O = other malignant tumor.

Table 10. Combined exposure to hardwood or mixed wood dusts and lacquers and paints.

Type of exposure	Number of cases	Number of referents
Wood dust	15	3
Only wood dusts	7	3
Lacquers and paints	12	–
Only lacquers and paints	2	–

stability within the occupations explains most of this consistency. Accounting for the total duration of exposure did not change these results, either. Smokers had higher odds ratios than nonsmokers (table 11), an occurrence which may suggest a synergistic effect, although the numbers are too small for any definite conclusion. This analysis was performed with the

Table 11. Connection between nasal and sinonasal cancers and exposure to wood dusts by smoking status 10 years before the diagnosis (unmatched data).

Type of exposure	Nonsmokers		Smokers		Total	
	Odds ratio	95 % confidence limits	Odds ratio	95 % confidence limits	Odds ratio	95 % confidence limits
Hardwood dust only	2.0	0.3–15.7	0.8	0.02–42.6	1.7	0.3–9.9
Softwood dust only	1.2	0.2–6.1	9.3	1.2–74.1	3.4	1.1–10.3
Hardwood + softwood dust	5.0	0.5–45.7	8.2	1.0–66.5	6.7	1.8–25.5

matching broken, which explains why the odds ratios for the whole material shown in table 11 differ from those in table 8.

The total series of cases also included some types of cancer with a less likely connection to dust exposures. In order to sharpen the analysis, the 18 cases of adenocarcinoma on one hand, and the 112 cases of epidermoid and anaplastic carcinoma on the other, were scrutinized separately. As can be seen from table 12, exposure to hardwood dust, either alone or in combination with softwood dust, was found to be associated with adenocarcinoma. However, the results also suggest an association between exposure to mixed wood dust and risk for epidermoid and anaplastic carcinoma.

Exposure to softwood dust only showed no association at all with adenocarcinoma. All 13 cases occurring in this exposure category were of other types, 10 of them being epidermoid or anaplastic carcinomas. Although this finding did not reach statistical significance, it suggests that softwood dust exposure may also have carcinogenic properties but that it causes other types of cancer than adenocarcinoma.

Table 13 shows the association between nasal carcinomas and exposure to some metals. The category "welding, flame-cutting and soldering," which represents mixed exposure, was significantly asso-

Table 12. Exposure to wood dusts according to histopathological type of cancer – Distribution of discordant pairs.

Type of exposure	Expidermoid and anaplastic carcinoma	Adenocarcinoma
Hardwood dust only	0:1	2:0
Softwood dust only	10:4	0:0
Softwood + hardwood dust	5:0	7:0*

* $p < 0.05$ (Mc Nemar).

ciated with nasal and sinonasal cancers. The same is true for exposure to chromium. Exposure to nickel also showed an excess nearly achieving statistical significance at the 5 % level. (Many of these cases fall into two or more categories.) Chromium and nickel exposure often consisted of the welding of stainless steel, which contains up to 30 % chromium and some nickel. These exposures mostly occurred together and can therefore not be separated statistically. Smokers and nonsmokers had roughly the same odds ratios. The most common types of cancer were epidermoid and anaplastic carcinoma. It is of interest to note that only one case had been engaged in the production of nickel. None had worked in the production of chromates. The results hence indicate that also other types of nickel and

Table 13. Exposure to some metals – Distribution of discordant pairs. The categories are not exclusive.

Type of exposure	Discordant pairs	Odds ratio	95 % confidence limits
Welding, flame-cutting and soldering	17:6	2.8	1.2–6.9
Same, but only those with exposure to chromium and/or nickel	13:4	3.3	1.1–9.4
Electroplating	9:6	1.5	0.5–4.2
Chromium	16:6	2.7	1.1–6.6
Nickel	12:5	2.4	0.9–6.6

chromium exposure may be carcinogenic. Table 14 shows the types of exposure in this category.

None of the other exposures investigated showed any significant associations with nasal or sinonasal cancer. For some exposures the study was uninformative because of the rareness of occurrence (eg, cadmium, arsenic, oil mist, bitumen, leather work), but in other instances more convincing negative results emerged. These include exposure to agricultural chemicals (including fertilizers and pesticides, distribution of discordant pairs 21:22), grain and hay dust (26:26), stone dust, mineral wool dust and cement dust combined (14:13), and organic solvent vapors (11:11). Asbestos exposure showed a discordant pair ratio of 9:5 (nonsignificant). However, in this respect the reference series was probably inadequate in view of the connection between asbestos exposure and colonic cancer found in some studies (20). With the present design, such a bias would tend to mask an increased risk for nasal or sinonasal cancer.

A scrutiny of occupations where expo-

sure to formaldehyde may have occurred gave no indication of any association. None of the cases or referents had worked in the particle board or plywood industry or in the production of formaldehyde or formaldehyde-based glues. The only possible exception was the category "painting, lacquering and glueing," for which 18 exposed cases and 6 exposed referents were found. Minimal exposure to formaldehyde could have arisen from formaldehyde-resin paints. However, 15 of the cases but no referents had also been exposed to wood dust. Because of this dual exposure and in view of the shaky data on formaldehyde exposure, no conclusions can be drawn as far as formaldehyde is concerned. Two cases and no referents had probably been exposed to wood preservatives (together with softwood dust) in the sawmill industry. Six cases and 11 referents had been exposed to pesticides. Two referents but no cases had sprayed herbicides.

Continuous use of pesticides occurs in greenhouses. Three cases and one referent had worked in greenhouses, the cases from

Table 14. Exposure histories for those cases and referents classified as having been exposed to welding, flame-cutting, soldering, chromium (Cr), and nickel (Ni).

Subject	Welding, flame-cutting & soldering	Cr ^a	Ni ^a
Case 1	Welder	+	+
Case 2	Metal grinder	+	+
Case 3	Blacksmith	-	-
Case 4	Car mechanic	-	-
Case 5	Machine mechanic	-	-
Case 6	Plumber (area heating)	+	+
Case 7	Welder, blacksmith	+	+
Case 8	Welder, turner	-	-
Case 9	Machine mechanic	+	+
Case 10	Steelworker	+	-
Case 11	Mechanic	+	+
Case 12	Repairman	+	+
Case 13	Repairman	+	+
Case 14	Attending ball-mill in nickel refinery	-	+
Case 15	Soft soldering (electronics)	-	-
Case 16	Repairman, mechanic	-	-
Case 17	Telephone mechanic	-	-
Case 18	Welding of agricultural machines, spray painting with chromates	+	-
Case 19	Welding	-	-
Case 20	Welding	+	+
Case 21	Mechanical engineering shop, grinding	+	+
Referent 1	Electrician	-	-
Referent 2	Teacher (metal works)	+	+
Referent 3	Goldsmith	-	-
Referent 4	Car mechanic	-	-
Referent 5	Trade school (mechanics)	-	-
Referent 6	Painting, farming (welding)	+	+
Referent 7	Car mechanic	+	+
Referent 8	Mechanical engineering (welding, soldering, grinding)	+	+
Referent 9	Service works in nickel mine	-	+

^a + = exposed, - = nonexposed.

12 to 53 years and the referent for six years.

Most of the exposed cases and referents were men. Because of the very low number of exposed (to any exposure) women, it was not possible to analyze their data separately.

Discussion

When the results of epidemiologic studies in general and case-referent studies in particular are being evaluated, the first question is: "Are these results unbiased?"

In case-referent studies all types of validity problems, ie, selection, information, and comparison validity, must be considered. Selection validity means that the likelihood of being selected into the study is similar for cases and referents. Our original plans involved including all cases of nasal and sinonasal cancer occurring during a certain time period and selecting referents for them from the cancer registers according to a few matching criteria, but with no knowledge of past exposures. Colonic and rectal cancer was selected as the reference category for reasons of information bias control (see the following paragraph). While this procedure could have introduced confounding, it could not conceivably introduce any selection bias since the source population of the referents was the same as the cases, ie, the entire populations of Denmark, Finland and Sweden. The fact that as many as 40 % of the cases could not be interviewed, by contrast, for various reasons (table 1) could in principle introduce selection bias, but only provided that the nonrespondents differed systematically from those interviewed with regard to exposure status. This occurrence could of course not be checked for the nonrespondents, but some indirect support in favor of symmetry was gained (table 3 & 5). It should be added that social status, which may be connected with occupation, does not influence the availability and quality of treatment in the Nordic countries. There is also no reason to assume that the exposure status would have influenced either the availability for interview (eg, access to telephone) or the course of the disease. Hence it is hard to see why there should be systematic differences between the respondents and nonrespondents.

Information bias is a well-known problem of case-referent studies. It can be subdivided into observer bias, ie, the interviewers collect an asymmetrical history, and recall bias, ie, cases and referents "remember" asymmetrically. To avoid observer bias, the interviewers were carefully instructed in interview techniques. Blinding them would have been desirable, but in view of the long interviews required this procedure was deemed unrealistic. Furthermore, the relevant exposures were of many years' duration (see table 9), and an observer bias influencing information on such substantial exposures does not seem likely. The same can be said of recall bias, and even the fact that a connection between nasal and sinonasal cancer and exposure to hardwood dust in the furniture industry was known in advance can hardly influence "remembering" exposures of several years', even decades', duration. Furthermore the very reason for selecting cancer patients as referents was to secure a symmetrical quality of information. Both the cases and referents thought they were the primary focus of interest. Objections may, of course, be raised against the use of cancer referents. However, in our view, recall bias giving rise to asymmetrical information is the most severe source of error in a study like the present one, and cancer referents are more likely than other referents to give a history of similar quality as the cases. The reason for excluding dead cases was also one of improving the quality of information. Because this study was concerned with detailed exposure histories, not only occupational titles, it was not considered likely that a next-of-kin would remember or even know about specific exposures 20-50 years in the past. However, this practice of course reduced the number of cases available for analysis, which no doubt was a drawback from the point of view of study efficiency.

Confounding becomes a problem if the referents' condition is one which is either caused or prevented by the exposure(s) in question, or by some factor(s) statistically associated with the exposure(s). In a semi-specific study like the present one, dealing with a great variety of exposures, it is hard to ensure complete unrelatedness of all exposures to the reference condition in question. However, we were

especially interested in exposure to wood dust and some metals, and colonic and rectal cancers were not known to be associated with any such exposure at the start of the study in 1977. As already mentioned before, asbestos exposure may not fulfill the criterion of unrelatedness to the referent condition and may have therefore caused negative confounding. On these grounds the suitability of our reference population for testing this particular hypothesis is not the best. Therefore we must refrain from drawing any conclusions as far as asbestos exposure is concerned.

The most important finding in this study was the association between wood dust and nasal and sinonasal cancer. As shown in table 8, combined exposure to dusts from hard- and softwoods had occurred significantly more often among the cases than among the referents. Softwood dust exposure alone also occurred in excess among the cases.

In view of what has already been demonstrated by other authors, the relation between nasal and sinonasal cancer and exposure to wood dust containing hardwood is not a surprising finding [for literature reviews, see Acheson (1) and the International Agency for Research on Cancer (IARC) (19)]. Sinonasal adenocarcinoma in furniture workers has been especially ascribed to exposure to hardwood dust in this particular industry. Acheson (1) has provided data suggesting that beech and oak are the primary causal factors; however, he does not rule out the possibility that other kinds of wood could carry the same type of risk, because these were the only two woods for which he had occupational histories of men exposed to one type of timber only. This aspect has also been emphasized by, eg, Leroux-Robert (21). As far as exposure to softwood dust is concerned, there are a few inconclusive studies suggesting that the risk for nasal and sinonasal cancer increases (8, 26). However, according to IARC (19), "the epidemiologic data are not sufficient to make a definite assessment of the carcinogenic risks of employment in the lumber and sawmill industries."

In our study exposure to hardwood dust usually occurred together with exposure to softwood dust. Most of these workers had been employed in the furniture industry, and their main type of tumor was

adenocarcinoma. Those with exposure to softwood only had a completely different occupational distribution (table 9). Most of them were construction or sawmill workers. Such categories do not usually handle hardwood in the Nordic countries. However, it should be noted that birch dust was classified as a soft type of wood. In the Nordic countries exposure to spruce and pine dust is almost always combined with exposure to birch dust. But pine and spruce are much more prevalent, and therefore dust from these woods constitutes the dominating component of this type of mixed exposure.

The data of the present study also suggest that the risk may not be restricted to one particular histopathological type of cancer, the adenocarcinoma. The risk may also concern other types of cancer, ie, the epidermoid and anaplastic cancer types. This possibility is suggested by the data presented in table 12. Exposure to softwood dust alone was especially associated with these cancer types, but also mixed wood dust exposure was overrepresented. The numbers are small, however, and the possibility of random events cannot be disregarded.

There was also a high prevalence of exposure to lacquers and paints among the cases of nasal and sinonasal cancers. The results serve as a reminder that also other air pollutants may occur in wood manufacturing industries. Wood dust may act as a carrier of other airborne pollutants with carcinogenic properties. In this study most of those exposed to lacquers and paints had had concomitant exposure to wood dusts, and those two who had not, had been exposed to other potentially carcinogenic substances. Therefore, these results cannot be taken to incriminate paints and lacquers as etiologic agents.

A noteworthy finding is the observed association between welding, flame-cutting or soldering and nasal and sinonasal cancer. Welding of stainless steel involves exposure to composite mixtures of air pollutants and particulate dusts, including chromium trioxide and chromates. An excess of nasal and sinonasal cancer among welders has not been reported to our knowledge, but there is strong evidence that exposure to many hexavalent chromium compounds leads to excess lung cancer (16, 28). The bulk of evidence comes

from studies of workers engaged in the production and/or use of chromates, but some recent studies have also suggested that chromeplating workers experience excess mortality from lung cancer (eg, 7, 17, 27, 31). As far as nickel is concerned, it is recognized that several inorganic nickel compounds are carcinogenic. In the nickel refining industry epidemiologic studies have demonstrated an excess of both nasal-sinonasal cancer and lung cancer (eg, 13, 14, 24, 28). However, it is not exactly clear which ones of the particular compounds or groups of compounds are responsible for the excess, and other types of nickel exposure have not been studied enough. When scrutinizing the lists of occupations among cases and referents, one will find that only one of the cases had been engaged in the production of nickel and none in chromate production, which does not occur in the Nordic countries. Hence our results suggest that exposure to a mixture of chromium and nickel compounds in welding fumes and flame-cutting operations and other exposed tasks also causes an increased risk of nasal and sinonasal cancer. Because of the mixed patterns, including exposure to nitrous oxides and ozone, our data do not allow a separation of chromium and nickel exposures, not to speak of the possibility of incriminating specific compounds.

Smoking must in principle be considered a potential confounder in studies of respiratory cancer. As can be seen from table 6, there were so small differences in smoking habits between the series that significant confounding can be ruled out. Possible synergism between smoking and other carcinogenic exposures is another matter to be looked at. The data shown in table 11 suggest that some synergism may occur, but the material is too small for any definite conclusions.

The first reports of a connection between nasal cancer in rats and exposure to formaldehyde were published when this study was well under way (30). By that time it was not possible to change the study protocol in order to explore past exposure to this agent in sufficient detail. However, during the analyses the occupations and work processes in which formaldehyde had most likely occurred were considered to be the particle board or plywood industry, the production of formal-

dehyde and formaldehyde-based glues, and possibly "painting, lacquering and glueing." These later-formed exposure categories must be considered far more uncertain than those accounted for at the planning stage. The fact that no differences were found between the series with regard to possible formaldehyde exposure can be cautiously interpreted as a negative finding, with reservations for the weaknesses of the aforementioned exposure classification. Neither were exposures to chlorinated phenols or phenoxyacids suspected in particular in 1977. Such exposures may occur in the sawmill industry and in forestry, respectively. In the evaluation of exposure in sawmills, an attempt was made to separate tasks occurring before and after impregnation, but this division could not be exact without specific data. The finding of a case-referent ratio of 2:0 says nothing in itself, but, taken together with the results of Hardell and his co-workers (18), they provide motivation for more specific studies on larger populations. Exposure to pesticides in agriculture could be better evaluated because one of the items in the "agricultural" form specifically concerned the handling of pesticides. However, because of the low number of exposed cases, the study must be considered too small to be informative in this respect.

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