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Nasal cancer and occupational exposures

Preliminary report of a joint Nordic case-referent study

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HERNBERG S, COLLAN Y, DEGERTH R, ENGLUND A, ENGZELL U, KUOSMA E, MUTANEN P, NORDLINDER H, SAND HANSEN H, SCHULTZ-LARSEN K, SØGAARD H, WESTERHOLM P. Nasal cancer and occupational exposures: Preliminary report of a joint Nordic case-referent study. *Scand j work environ health* 9 (1983) 208—213. Nasal and sinus paranasal cancers have been associated with several occupational exposures, for example, dust from hardwood, nickel and unspecific agents occurring in the boot and shoe industry. A joint Danish-Finnish-Swedish case-referent investigation was initiated in 1977 to study further the connection between nasal and sinus paranasal cancers and various occupational exposures. All new cases of these cancers were collected from the national cancer registers (Finland & Sweden) or from hospitals (Denmark). Those still alive who agreed to the interview (N = 167) were individually matched for age and sex with patients with colonic or rectal cancer. A detailed telephone interview was performed according to a standardized procedure. Both the cases and referents thought that their condition was the one under study. The exposures were coded blindly by an experienced industrial hygienist. The results showed associations between nasal or sinus paranasal cancer and exposure to hardwood or mixed wood dust (discordant pairs 14/2); softwood dust alone (13/4); chromium (16/6); nickel (12/5, not significant); welding, flamecutting and soldering (17/6); and lacquers and paints (12/0). Hardwood dust exposure showed a connection 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, nickel, solvents, welding, wood dust.

Nasal adenocarcinoma, a rare tumor with an incidence of about one case per million person-years, has shown a very strong connection with occupational exposure to hardwood dust in the furniture industry (1, 2, 3, 4, 5, 7, 8, 9, 10, 12, 14). Some other types of nasal cancer may also occur in excess among furniture workers, but no association has yet been clearly established (2, 12). Not only wood dust, but also several other occupational exposures, are associated with an increased risk of nasal cancer. These include, eg, the production of nickel (15) and exposure to

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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

unspecified factors in the boot and shoe industry (2). Also textile dust has been incriminated (6).

The Nordic countries all have national cancer registers with nearly 100 % coverage. However, the comparatively small size of the population in any single country limits the study of etiologic factors for a rare tumor like nasal cancer. Therefore it was considered practical to initiate a joint Nordic study in 1977 to explore further the connection between nasal cancer and occupational exposures. The population of Iceland was considered too small to make the extra costs of translation, the joining meeting, etc, worthwhile. For various reasons Norway could not take part in the study, and therefore the investigation had to be undertaken with the participation of Denmark, Finland, and Sweden only.

Materials and methods

All new patients with primary malignant tumors of the nasal cavity and paranasal sinuses (ICD 160.00—160.99) in Denmark, Finland, and Sweden in 1978, 1979, and 1980 and reported to the national cancer registries were primarily selected as cases. However, in Denmark, it proved to be more practical to locate the cases from four of the five existing oncologic centers. After the cases (and the referents) were 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 an attempt to ensure the quality of the information collected, only those patients were included who were still alive when identified from the registers. Altogether 167 cases (Denmark 69, Finland 24, Sweden 74) remained when deceased patients and nonrespondents had been omitted. Copies of the hospital records of the cases were ordered from the hospitals and reviewed by the investigators to get exact information on 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 (YC, HN & HS) 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).

Table 2. Histopathological type of tumors at the time of diagnosis.

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

The mean age of the 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. Each case was matched for country, sex, and age at diagnosis (within ± 3 years) with alive patients having malignant tumors of

the colon or rectum (ICD 211.3 & 211.4). The referents were also obtained from the national cancer registries. Cancer patients were selected as referents in order to secure a symmetrical quality of information, and colonic and rectal cancer were not known to be associated with any occupational exposure at the start of the study in 1977, perhaps with the exception of asbestos.

After the consent to contact the patient had been obtained from the hospital, a short standardized note describing the study and informing 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 did not know whether they were a case or a referent. They were all told that the objective of the study was to explore connections between occupational factors and various diseases in general. (Cancer was not mentioned at all.) 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 interest, the patients were also asked questions about personal habits such as smoking, snuff consumption, and hobbies. A detailed occupational history was obtained for each separate occupation of more than one year's duration up to 10 years before the diagnosis. In other words the 10 last years were not accounted for at all in order to allow for a latency period. The respondent was asked to indicate the time of employment, 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. Each form contained questions on specific exposures.

The interviewers were carefully instructed in interview techniques in order to obtain information free from interviewer bias. They met several times during the study and discussed the equality of the methods. 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).

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 as "no", "moderate" (assessed to be approximately below the American Conference of Governmental Industrial Hygienist's threshold limit values), and "heavy" (levels above these standards) exposure. However, the exposures had taken place more than 10 to 60 years ago. Thus exposure conditions must have changed much over time, and visits to workplaces or measurements of air impurities as of today were meaningless. Therefore the classification had to be based on estimates.

For example, exposure to wood dust in the furniture industry was classified as heavy when the work included grinding, drilling and planing. Exposure to softwood dust for sawmill workers and carpenters at construction sites was classified as moderate. Birch and aspen were included in the group of softwoods, together with spruce and pine, while all other kinds of wood 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 occupational titles classified as nonexposed include teacher, salesman, clerk, housewife, fisherman, and lumberjack. In this presentation "exposed" is made up of "moderate" and "heavy" exposure combined.

The comparisons were then made with regard to different exposure variables constructed from data on 26 specific agents or exposures. When the exposure

Table 3. 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 dust	12/1	12.0	2.4—59.2

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 (13). 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 and comments

Table 3 shows the discordant pairs of 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 only had worked as sawmill workers and carpenters at construction sites, and their exposure did not include any hardwood dust or solvents. Only two cases and no referent had probably also been exposed to wood preservatives (in sawmills). Exposure to paints and lacquers showed a strong association with nasal cancer (distribution of discordant pairs: 12/0) but also with exposure to hardwood or mixed wood dust (8/0). As can be seen from table 4, there were seven cases exposed to hardwood or mixed wood dust only, while two cases had been exposed to lacquers and paints but not to wood dust. Eight cases and no referents had been exposed to both wood dust and paints and lacquers and the results cannot be used to delineate between wood dust and paints and lacquers as the causative agents. The association between nasal cancer and exposure to hardwood, softwood or mixed wood dusts was the same also when only exposures occurring 20 or 30 years or earlier before the time of diagnosis were considered. The stability within the occupations explains most of this consistency. Smokers had higher odds ratios than nonsmokers. Table 5 shows the distribution of discordant pairs according to the most common histopathological types of cancer. Exposure to hardwood dust, either alone or in combination with softwood dust, was mainly associated with adenocarcinoma. However the results also suggest an association between exposure to mixed wood dust and risk of epidermoid and anaplastic carcinoma. Exposure to soft wood 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

Table 4. 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 dust		7		3
Lacquers and paints	12		—	
Only lacquers and paints		2		—

Table 5. Exposure to wood dusts according to histopathological type of cancer. Distribution of discordant pairs.

Type of exposure	Expidermoid and anaplastic cancer	Adeno-carcinoma
Hardwood dust only	0/1	2/0
Softwood dust only	10/4	0/0
Hardwood + softwood dust	5/0	7/0 *

* $p < 0.05$ (McNemar).

Table 6. Exposure to some metals. Distribution of discordant pairs. The categories are not exclusive.

Type of exposure	Discordant pairs	Odds ratio	95 % confidence limits
Welding, flamecutting and soldering	17/6	2.8	1.2—6.9
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

anaplastic carcinomas. Hence these results suggest that also softwood dust exposure may have carcinogenic properties but that it causes other types of cancer than adenocarcinoma.

Table 6 shows the association between nasal carcinomas and exposure to some metals. As can be seen, the category welding, flamecutting and soldering, which represents a mixed exposure, was significantly associated with nasal carcinomas. The same is true for exposure to chromium and nickel. (Many of these cases fall into two or more categories.) Chromium and nickel exposure consisted mainly of the welding of stainless steel, which contains up to 30 % chromium and some nickel. These exposures mostly occurred together and could not easily be separated statistically. The most common types of cancer were epidermoid and anaplastic carcinoma. It is of interest to note that only one of these cases had been engaged in the *production* of nickel and none in the production of chromates. The results hence suggest that also other types of nickel and chromium exposure may be carcinogenic.

None of the other exposures investigated showed any significant associations with nasal cancer. For some exposures the study was quite uninformative because of their rare 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 ensilage), grain and hay dust, stone dust, mineral wool dust, cement dust, organic solvent vapors, and "other" chemicals. Asbestos exposure showed a discordant pair ratio of 9/5 (nonsignificant). However, in this respect, the reference series could be considered inadequate in view of the connection between asbestos exposure and colonic cancer found in some studies (11). The first reports of a connection between nasal cancer in rats and exposure to formaldehyde were published when this study was well under way. By that time it was not possible to change the study protocol in order to explore past exposure to formaldehyde in sufficient detail. However, a scrutiny of occupations for which exposure to formaldehyde possibly may have occurred gave no indication of any association. None of the cases or referents had been working in the particle board or plywood industry or in the production of formaldehyde or formaldehyde-resin paints. The only possible exception was the category "painting, lacquering and glueing" which contained 18 exposed cases and 6 exposed referents. However 15 of the cases, but none of the referents, had also been exposed to hardwood dust. In the presence of such a strong carcinogen, no conclusions can be drawn as far as formaldehyde is concerned.

In conclusion this investigation supports earlier studies as far as the connection between adenocarcinoma and hardwood dust is concerned, and in addition it suggests softwood dust as an etiologic factor for other types of nasal and sinus paranasal cancer. It also may suggest that not only the production of nickel and chromates, but also exposure to these metals in other occupations, may cause nasal cancer.

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