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## Nasal cancer in leather workers: an occupational disease

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**Abstract** Nasal cancer has a number of causative agents; exposures to most of the established nasal carcinogens occur in the workplace. An increased risk of nasal cancer has been ascertained in shoe-making and shoe-repairing, but the results for leather goods manufacture and leather tanning don't provide adequate evidence of carcinogenicity. Findings from two epidemiological studies carried out in Italy (a case/control study and a case/series report) add further information on this issue. The case/control study was performed in the provinces of Siena (Tuscany), Verona and Vicenza (Venetia) including 96 cases and 378 controls. A significant increased risk (Odds Ratio: 6.8; 90% C.I. = 1.9–25) of sinonasal cancer was found for the employ in the whole leather industry; Odds Ratio of 8.3 (C.I. = 1.9–36) and 5.0 (C.I. = 0.92–28) were associated with shoe-making and leather tanning. The case/series report is based on 110 patients accepted in some Italian hospitals during last three years (1990–1993): 26 cases had worked in the leather industry; adenocarcinoma is the most frequent type observed. Chromium salts and natural tannins are indicated as possible aetiological agents.

**Key words** Nasal cancer · Occupation · Leather industry  
Case/control study · Case · Series report

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The Editors

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### Introduction

Malignant epithelial neoplasm of the nasal cavities and paranasal sinuses (simply referred to here as nasal cancer) is a relatively rare disease, the annual incidence in most European countries ranging between 0.5 per 100 000 and 1.5 per 100 000 in men and between 0.1 per 100 000 and 0.5 per 100 000 in women (Muir et al., 1987).

Nasal cancer is a usually fatal disease, 5-year survival being currently estimated around 30% (Bush and Bagshaw 1982; Isaacs et al. 1990), and the quality of life of survivors is severely affected. Nasal cancer has a number of ascertained causative agents, among them tobacco snuffing (Keen et al. 1955), radiation (Kligerman et al. 1960), and occupational exposure to chromium (Hueper 1966), nickel (Doll 1958), mustard gas (Wada et al. 1968), or wood dust (Macbeth 1965; Acheson et al. 1967; Nylander and Dement 1993).

Furthermore, an increased risk of nasal cancer has been reported in shoemakers (Acheson et al. 1970a, b), textile workers (IARC 1990a), metal workers (Olsen 1988; Comba et al. 1992a), construction workers (Roush et al. 1980), farmers (Olsen 1988) and in various occupations implying exposure to large amounts of organic and inorganic dust (Comba et al. 1992b).

The aetiological fraction of nasal cancer associated with occupation has been estimated to be as high as 60% (Comba et al. 1992b). Given the high fatality of this disease and the elevated aetiological fraction related to occupation, primary prevention appears to be of the utmost relevance.

As was previously mentioned, an area of industry characterized by an increased risk of nasal cancer and by the presence of various potential causal agents, is the leather industry; in this term we include tanning, leather goods manufacture and boot and shoe production and repair. The purpose of the present paper is to review the existing epidemiological evidence on this topic and to support the recognition of nasal cancer in leather workers as an occupational disease.

**Table 1** Number of case reports and epidemiological studies on nasal cancer in leather workers by year of publication. This table is based on the following references: Acheson et al. 1972, 1970a, b; 1981, 1982; Bimbi et al. 1988; Bross et al. 1978; Cecchi et al. 1980; Decoufflé and Walrath 1983; Engzell et al. 1978; Fukuda and Shibata 1988; Gardner

and Winter 1984; Hayes et al. 1986 a, b; Loi et al. 1989; Magnani et al. 1989; Malker et al. 1986; Merler et al. 1986; Olsen 1988; Pippard and Acheson 1985; Pippard et al. 1985; Rüttner and Makek 1985; Vetrugno and Comba 1987

Source and type of information	No. of reports						Total
	1961–1965	1966–1970	1971–1975	1976–1980	1981–1985	1986–1990	
Case Report				1	2	1	4
Incidence in areas of interest		1			2	3	6
Geographical correlation					1		1
Cohort					1		1
Case control			1	2		5	8
PMR*					1		1
Total		1	1	3	7	9	21

\* PMR, proportional mortality ratio

**Table 2** Number of case reports and epidemiological studies on nasal cancer in leather workers by country. This table is based on the following references: Acheson et al. 1972, 1970a, b, 1981, 1982; Bimbi et al. 1988; Bross et al. 1978; Cecchi et al. 1980; Decoufflé and Walrath 1983; Engzell et al. 1978; Fukuda and Shibata 1988; Gardner

and Winter 1984; Hayes et al. 1986 a, b; Loi et al. 1989; Magnani et al. 1989; Malker et al. 1986; Merler et al. 1986; Olsen 1988; Pippard and Acheson 1985; Pippard et al. 1985; Rüttner and Makek 1985; Vetrugno and Comba 1987.

Source and type of information	No. of reports								
	Denmark	Italy	Japan	Netherland	Sweden	Switzerland	United Kingdom	USA	Total
Case report		1			1	1	1		4
Incidence in areas of interest	1	1			1		3		6
Geographical correlation							1		1
Cohort							1		1
Case control		4	1	1			1	1	8
PMR*								1	1
Total	1	6	1	1	2	1	7	2	21

\* PMR, proportional mortality ratio

The initial observation of a cluster of cases in Northamptonshire prompted the implementation of an epidemiological study aimed at detecting possible causal factors (Acheson et al. 1970a, b). Almost 60% of male patients diagnosed from 1953 to 1967 appeared to have worked in the boot and shoe industry, compared to 17% of the adult male population; relative risks were 8 for all histological types and 35 for adenocarcinoma. Most of the cases had worked in the preparation or in the finishing departments, where particularly heavy exposure to dust had taken place. The risk of nasal cancer in the leather industry has been further confirmed in a survey on nasal cancer and occupation in England and Wales (Acheson et al. 1972), and in several other studies conducted in Great Britain and other countries (Tables 1, 2).

Latency periods seem to be very long. From the published data of 53 adenocarcinomas we found a mean latency of 47 years with a minimal period of 30 and maximal one of 74 years (Maier 1993). From the respective data of 16 squamous cell carcinomas a mean latency was calculated to be 43 years with a minimal period of 33 and a maximal one of 62 years (Maier 1993).

Studies in the United States (Brinton et al. 1984), Japan (Takasaka et al. 1987), the Netherlands (Hayes et al. 1986 b) and France (Luce et al. 1992) did not confirm the often reported excess of sinonasal cancer among workers exposed to leather dust. As emphasized by Leclerc and Luce (1993), this does not necessarily mean that there is no risk. Since leather-dust-related occupations are rare in some regions, the impact of some studies may be low because only a small number of cases were observed.

In Western Germany between 1979 and 1984 altogether 1975 cases of sinonasal adenocarcinomas were reported from more than 160 hospitals (Grimm et al. 1984; Wolf et al. 1986). The evaluation of potential occupational causes suggested a strong influence of wood dust exposure but in no case of adenocarcinoma could exposure to leather dust be found in the working histories. This lack of evidence may be due to a very low risk in Western Germany.

According to the International Agency for Research on Cancer (IARC 1987), evidence of carcinogenicity associated with employment in the leather industry can be evaluated as follows.

**Table 3** Number of cases of nasal cancer in leather workers observed in some Italian hospitals

Occupation	Florence 1976–1992	Siena 1982–1993	Pisa 1983–1990	Lucca 1982–1990	Varese 1980–1990	Total	% Observed cases (% of total)
Tanner	1	1				2	7.8
Repairing	6				1	7	26.9
Shoemaker	5		3	2	6	16	61.5
Vegetable-tanning extraction						1	3.8
Total	12	1	3	2	7	26	

**Table 4** Histological type and main occupational categories at risk in the complete series of cases observed in some Italian hospitals

Cancer	Wood-workers	Leather industry	Others
Adenocarcinoma	26	21	19
Spino-cellular	5	3	52
Others	4	2	39

Boot and shoe manufacture and repair: there is sufficient evidence of carcinogenicity associated with employment in the boot and shoe manufacturing and repairing industries, the risk of nasal cancer being higher for those exposed to high levels of leather dust. An increased risk can be detected especially for adenocarcinoma as well as for other histotypes.

Leather goods manufacture: there is inadequate evidence of carcinogenicity associated with the manufacture of leather goods other than boots and shoes, the number of reported cases of nasal cancer being insufficient for an evaluation.

Leather tanning and processing: there is inadequate evidence of carcinogenicity associated with leather tanning and processing, and no evidence of an increased risk of nasal cancer.

Some recent findings from Italy add further information on this issue.

## Patients and methods

A multicentre case/control study on nasal cancer and occupation was performed in the provinces of Siena, Tuscany, and Verona and Vicenza, Venetia (Comba et al. 1992b). The study population was defined as living in the catchment areas of the hospitals of Verona and Vicenza (Verona study) and Siena (Siena study). Cases of malignant epithelial neoplasms of the nose and paranasal sinuses diagnosed between 1982 and 1987 in these areas were enrolled in the study. The WHO classification of histotypes was adopted (Shanmugaratnam and Sobin 1978). Six potential controls were matched to each case taking into account sex, age ( $\pm 5$  years), residence and time of admission to hospital. All diagnoses were accepted except chronic rhinosinus disease and acute nasal bleeding, as possibly early symptoms of a malignancy. Four controls were finally enrolled in the study, while the two others were taken as substitutes in case of refusal to respond by any of the primarily chosen controls. Information on work history was collected by interviewers from subjects still in hospitals and from subjects living in Siena and in Verona. For the other subjects, questionnaires were sent by mail. The questionnaire included an open section on occupational history and specific questions concerning work in mining and quarrying, the chemical industry, metal industry, textile and garment industry, agriculture, wood and furniture

industry and leather industry. Information on smoking habits was collected. Altogether, 96 cases and 378 controls were enrolled in the study. In Siena 100% of the cases and 93.4% of the controls were interviewed; in Verona the corresponding figures were 76.6% and 60.6%. The overall response rate was thus 70%, mailed questionnaires included.

Data were analysed using the Biomedical Data Program statistical package (Dixon 1988). Stratified analysis was performed according to the procedure by Mantel and Haenszel (1959). Multiple logistic regression analysis was applied according to the BMDP program, and it was decided to use the 90% confidence interval of the odds ratio, in order to decrease the possibility of identifying falsely negative results (Ahlbom et al. 1990).

## Results

A significantly increased risk of nasal cancer was associated with employment in the whole leather industry (odds ratio: 6.8; 90% confidence interval: 1.9–25); an odds ratio of 8.3 (1.9–36) was associated with shoemaking, while leather tanners had an odds ratio of 5.0 (0.92–28) based on two exposed cases.

During the last 3 years (1990–1993) we have carried out a review of the cases of nasal cancer diagnosed by pathologists, at different times, in the hospitals of Siena, Pisa, Lucca, Firenze (Tuscany) and Varese (Lombardy). The size of the general population in these two areas is about 2 800 000 people. In Tuscany all craft activities are well represented, while the province of Varese is characterized by the presence of a relevant shoe industry.

By interviews with the patients (30%) and their relatives (70%) we collected information on 172 subjects. According to most reports, in our data-series, also woodworkers constitute the largest occupational group.

The 26 cases from the leather industry were 15.1% of the total recorded number (only 2 were women); Table 3 shows the distribution of cases by specific jobs in the leather industry; 32% were smokers, 32% ex-smokers and 36% non-smokers. The mean age at diagnosis was 64.9 years (SD = 9.2); the period of exposure could be estimated to be as long as 31.2 years (SD = 15.8) and the induction/latency time was 47.6 years (SD = 8.5). Adenocarcinoma and spino-cellular types were the most frequently observed cancers (table 4).

Shoe manufacture and repair were the occupations in the majority of cases, in accord with the distribution of the workforce in the leather industry, while tanners and other specific jobs are quite rare in the evaluation.

In Italy in the past, work in this industry has been described as very dusty, because of narrow workplaces and the nature of the preparing and finishing phases (leather and sole storage, cutting, blasting, smoothing etc.); exhaust systems were lacking nearly everywhere until the 1970s.

It is interesting to note one case detected by us: the patient was employed in tannin extraction from wood, an industrial process that involves exposure both to tannin vapours and to wood dust; very few workers are likely to be employed in these processes.

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## Discussion

Nasal cancer in leather workers seems to affect mainly those exposed to dust in the preparation and finishing of heels and soles, which in many countries are usually tanned with vegetable extracts including extracts of wood (Acheson et al. 1982).

It should be noted, though, that a small proportion of soles and heels could also be chromium tanned. Randell (1990) discussed the different occurrence of nasal cancer in US leather workers (low risk) and UK leather workers (high risk). In the US, finishing of vegetable-tanned leather soles is performed by applying animal oils, which can be abraded in subsequent phases of the manufacture; in the UK, instead, mineral oils are mainly used. The presence of mineral oils in leather dust in the UK, but not in the US, might account for the striking differences in risk between these countries.

Other hypotheses explaining the differences found in studies from two countries are discussed by Decouflé and Walrath (1987), mainly with reference to issues in study design, however. In our series we have a small number of cases from the leather industry, so the odds ratio associated with these jobs always proved not significant.

A pooled re-analysis of data collected in various European cohort and case control studies is being carried out at IARC (P. Boffetta, personal communication). A comparison of the findings and of the working conditions in countries with higher and lower risk should be helpful to clarify the causes of this kind of occupational cancer.

Even if the ultimate carcinogens have not yet been defined, prevention of nasal cancer in the leather industry could certainly be accomplished through improvements of the exhaust systems. No comprehensive survey on the dust levels in leather and shoemaking industries is available, because most of the activity of the Health Authorities in various countries has been mainly directed towards preventing solvent-induced neuropathy in shoemakers.

Compensation for nasal cancer is contemplated in the European list of occupational diseases (Commission des Communautés Européennes 1990) for woodworkers, and in several countries there is no particular problem for these categories, even though some uncertainties about the specific carcinogenic agent also still persist in the furniture industry (Nylander and Dement 1993).

In the leather industry, chromium or natural tannins are indicated as possible aetiological agents: chromium salts are classified in the first group of carcinogenic substances by IARC (1990b); tannins, especially those not hydrolysing, are proven to be experimentally carcinogenic (Badaway et al. 1969; Hausen 1981; Kirby 1960; Korpassy 1961; O'Gara 1968; O'Gara et al. 1971, 1974; Reddy et al. 1970; Hueper 1965, 1966).

Finally, it has to be considered that:

1. Nasal cancer is, in fact, rare even in the occupational groups at greatest risk; in the shoe industry the crude incidence rate has been estimated as  $7 \times 10^{-5}$  for workers in the press and finishing departments and as  $1 \times 10^{-5}$  for workers employed in other jobs within the same industry (Acheson et al. 1970).
2. The disease is very severe, high mortality and heavy impairment affecting the residual life of patients.
3. Adenocarcinoma is the most frequent type of cancer recorded in the occupational series; however, it has to be considered that a carcinogenic agent is usually defined as a substance that statically increases the spontaneous incidence of a malignant and/or benign neoplasm (Montesano 1981; Crump et al. 1976) so we were unable to restrict our discussion to a specific histological type. Furthermore, some difficulties may exist in pathology diagnoses (Brugère et al. 1981).

Consequently, although some uncertainties persist about the specific aetiological agent in the leather industry, it seems reasonable to consider eligible for compensation all the cases of malignant epithelial neoplasm of the nose and accessory sinuses that come out from the leather industry, without any distinction of histological type.

On the basis of the epidemiological evidence from shoe manufacture and repair, where the leather dusts and tannins are mostly suspected, analogous criteria could also be applied to the few cases expected from tanning and other jobs in or related to the leather industry.

In our opinion, it would nowadays be useful to standardize, at least in European countries, the insurance legislation, taking into account the IARC evaluations and the politics of social welfare.

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