Sinonasal Cancer

7

Kirsti Husgafvel-Pursiainen, Matthieu Carton, Danièle Luce, C. Henrik J. Wolff, Reetta Holmila, Vivi Schlünssen, Jette Bornholdt, and Johnni Hansen

Keywords
Sinonasal cancer • Epidemiology • Pathology • Occupational factors • Wood dust exposure • Genotoxicity • Molecular markers • Mechanisms of carcinogenesis

Introduction

Sinonasal cancer, the cancer of the nose and paranasal cavities (ICD 10 codes C30.0 and C31.0 to C31.9), is a rare form of cancer. Its incidence varies between men (0.5–1.5 new cases annually per 100,000) and women (0.1–0.6/100,000) and also from country to country. For example, age-standardized incidence rates among men during 1998–2002 in some European countries were 0.8–1.6 in France, 0.4–1.4 in Italy, 0.9 in Denmark, 0.8 in the Netherlands, 0.8 in Norway, 0.3–0.7 in the UK, 0.5–0.6 in Germany, 0.5 in Finland, and 0.4 in Sweden; in the USA the incidence rate was 0.7 (in Blacks) and 0.6 (in Whites). The corresponding rates in each country were lower for women [1]. There has also been some variation in the incidence rates over time [2–4]. It is currently seen that by far the most important factor explaining such variation in incidence is exposure, in particular occupational exposure, whereas individual factors, such as genetic susceptibility, play only a very minor role [2, 4].

Anatomically, the sinonasal region is located in the mid-portion of the face and is composed of the centrally located paired nasal cavities surrounded by paired paranasal sinuses (maxillary, frontal, ethmoidal, and sphenoidal) (Fig. 7.1) [5]. The airspace within the sinuses is connected to that of the nasal cavities via narrow passages.

In the most anterior part of the nasal cavity, the superior and lateral walls are composed of the soft tissues of the nasal wings; this area is called the nasal vestibule. The lining of the vestibule consists of an extension of the skin with keratinizing stratified epithelium and secondary appendages. This lining extends 1–2 cm from the external rim of the nose into the nostrils. The mucocutaneous junction is the location where the respiratory mucosa (referred to as the Schneiderian membrane) begins. The nasal cavity with the turbinates and the paranasal sinuses are lined with this epithelium. The superior, middle, and inferior turbinates (conchae) hang into the nasal lumen along the lateral wall of the nasal cavity. Posteriorly, the turbinates end approximately one cm anterior to the choanal orifice where the nasal cavity leads into the anterior opening of the nasopharynx.

K. Husgafvel-Pursiainen, PhD (✉)
Health and Work Ability, Systems Toxicology,
Finnish Institute of Occupational Health,
Topeliuksenkatu 41a A, FI-00250, Helsinki, Finland
e-mail: kirsti.husgafvel-pursiainen@ttl.fi

M. Carton, MD
UMS 011, Population-based Epidemiologic Cohorts Unit,
Inserm – Versailles St-Quentin University, Villejuif, France

D. Luce, PhD
Inserm UMR 1085 – Irset,
Inserm (French National Institute of Health and Medical Research),
Pointe-à-Pitre, Guadeloupe, French West Indies

C.H.J. Wolff, MD
Health and Work Ability, Systems Toxicology/Pathology,
Finnish Institute of Occupational Health,
Helsinki, Finland

R. Holmila, PhD
Section of Molecular Carcinogenesis, International Agency for Research on Cancer, Lyon, France

V. Schlünssen, MD, PhD
Department of Public Health, Section for Environmental and Occupational Medicine, Aarhus University, Aarhus, Denmark

J. Bornholdt, PhD
Department of Biology, The Bioinformatics Centre,
University of Copenhagen, Copenhagen, Denmark

J. Hansen, PhD
Research Center, Danish Cancer Society,
Copenhagen, Denmark

S. Anttila, P. Boffetta (eds.), *Occupational Cancers*,
DOI 10.1007/978-1-4471-2825-0_7, © Springer-Verlag London 2014

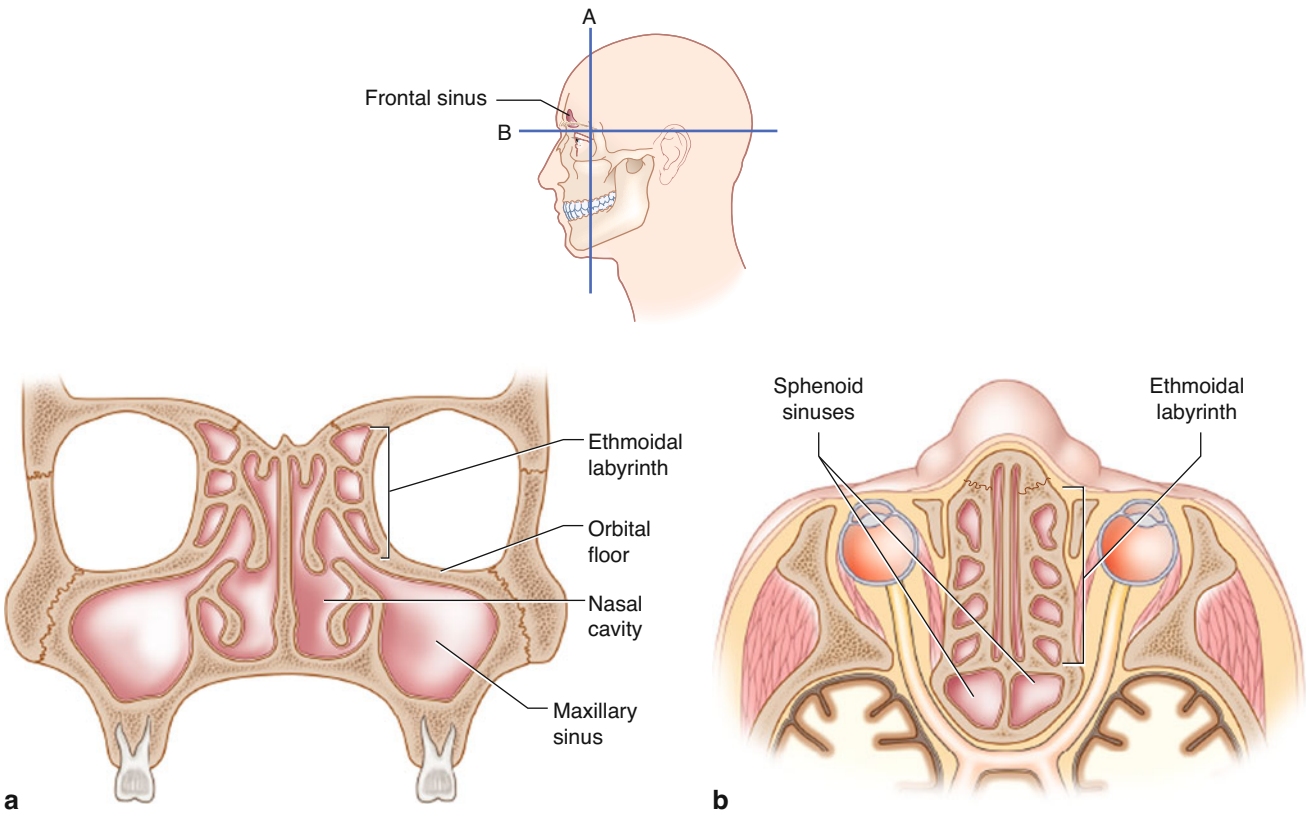


Fig. 7.1 Nasal cavities and paranasal sinuses shown in (**a**) coronal and (**b**) transverse sections. The orientation of the sections is illustrated in the middle where the frontal sinus is also shown. The ethmoidal labyrinth is a frequent target of sinonasal adenocarcinoma (Adapted from Gnepp [5])

The ethmoid labyrinth in the adult is a completely pneumonized complex of 3–18 cells per side. The roof of the labyrinth is adjacent to the anterior cranial fossa. The maxillary sinus is the largest of the sinuses, and it encompasses the majority of the body of the maxilla. The frontal and sphenoidal sinuses (Fig. 7.1) are of less importance for the topic of this chapter; these are described in more detail elsewhere [6].

This chapter will give an overview and discuss studies on sinonasal cancer dealing with epidemiological findings and various occupational risk factors, exposure levels and other exposure characteristics, tumor pathology, the molecular cancer mechanisms likely to be involved in the development of the disease, and, finally, molecular alterations observed in tumors and available as potential molecular markers. The main studies and their findings as well as the principal pathological features of sinonasal tumors are summarized in tables and exemplified in illustrations.

Epidemiology and Occupational Risk Factors

Sinonasal cancer is a rare type of cancer with 0.5–1.5 new cases per year per 100,000 in men and 0.1–0.6/100,000 in women. The incidence has been relatively stable in the last decades but varies markedly between the countries and even within the same country, from one region to another [7, 8] (see Introduction for some detail). Two main histological types of sinonasal cancer (squamous cell carcinomas and adenocarcinoma; see also Section on Pathology) exist with somewhat different etiologies and epidemiology. The 5-year relative survival of sinonasal cancer is about 50–60 % in Europe and the USA [8–12].

Occupational Risk Factors

Several occupational exposures are known to increase the risk of sinonasal cancer. According to the recent review of human carcinogens compiled by the International Agency for Research on Cancer [4, 13–15], wood dust, leather dust, nickel compounds, radium-226, and work in isopropanol production cause sinonasal cancer. Positive associations have also been observed between sinonasal cancer and exposure to chromium VI compounds, to formaldehyde, and work in the textile industry, although the evidence remains limited in humans [16]. The following Section on Exposure Characteristics characterizes the exposures involved, giving more detail in estimated numbers of those exposed at work,

exposure levels, exposure-response relationships, as well as industries and occupations relevant.

Since sinonasal cancer is a rare disease, cohort studies may often lack the statistical power to detect even moderate excess risks. In addition, as many occupational cohort studies are based on mortality data, no reliable information on histology is available. Therefore, most information on risk factors for sinonasal cancer has emerged from case-control studies. For such a rare disease, however, even case-control studies tend to involve a relatively small number of cases (generally less than 100), precluding detection of associations with specific jobs or exposure to specific substances.

This section will thus focus on the results of a pooled reanalysis of 12 case-control studies on sinonasal cancer conducted in seven countries [17–19]. These studies were selected on the basis of the availability of information on histological type, age, sex, smoking, and occupational histories. The pooled dataset consisted of 930 patients with sinonasal cancer (680 men and 250 women) and 3,136 controls (2,349 men and 787 women). The cases included 195 adenocarcinomas (169 men, 26 women) and 432 squamous cell carcinomas (330 men, 102 women). The proportion of adenocarcinomas was distinctly higher in the studies carried out in France (49 %), Italy (between 22 and 69 %), and the Netherlands (25 %) compared to those performed in the USA (between 3 and 14 %). The occupational histories were coded and exposures were assessed through a job-exposure matrix. The main advantage of the pooled analysis is that it provides sufficient statistical power to realistically examine the risks according to histological type, sex, work, exposure category, and exposure duration.

The analyses from the pooled dataset focused on the associations with wood dust [17], formaldehyde, silica, textile dust, coal dust, flour dust, asbestos, man-made vitreous fibers [19], and various occupations and industries [18]. An analysis was also conducted restricted to the 8 European studies included in the pooled dataset, dealing with exposure to wood dust, leather dust, and formaldehyde [20]. The main characteristics of the 12 studies are summarized in Table 7.1. Specific results from the original studies as well as results from case-control studies not included in the pooled dataset (Table 7.2) or from cohort studies will be also presented and discussed when they add relevant information.

Wood Dust

The causal role of exposure to wood dust in the genesis of sinonasal cancer has long been unambiguously established by numerous epidemiological studies, carried out in populations in different geographical origin, who were exposed for different periods and in several fields of activity [2, 4, 14].

Demers and coworkers [17] analyzed the pooled data from 12 case-control investigations presented above and summarized in Table 7.1. Seven categories of woodworkers were investigated. The levels of exposure to wood dust were classified into 4 categories (none, low, medium, and high), corresponding approximately to the following estimated concentrations: equal to zero, less than 1 mg/m^3, between 1 and 5 mg/m^3 and above 5 mg/m^3. The distribution of histological types varied markedly between studies.

Adenocarcinoma

The results from the pooled analysis [17] revealed that there was a sizeable risk of adenocarcinoma (Fig. 7.2). The study showed a high risk in men working with a wood-related job (OR 13.5; 95 % confidence interval [CI] 9.0–20.0). This risk was particularly high in the case of cabinetmakers and men employed in furniture factories (OR 41.1; 95 % CI 24.5–68.7). No increase in the risk of adenocarcinoma was shown for lumberjacks, foresters, or employees in paper pulp plants. The risk for saw mill employees was intermediate (OR 19.7; 95 % CI 11.1–35.1) and slightly lower after eliminating those who had worked in furniture factories (OR 14.9; 95 % CI 8.0–28.7).

For men, the risk of adenocarcinoma increased with the intensity of exposure (OR 0.6, 95 % CI 0.1–4.7 for low exposures; OR 3.1, 95 % CI 1.6–6.1 for moderate exposures; and OR 45.5, 95 % CI 28.3–72.9 for high exposures), and with exposure duration (OR 1.08, 95 % CI 1.07–1.09 per year; OR 5.3, 95 % CI 2.5–11.1 for duration shorter than 5 years; OR 10.7, 95 % CI 5.2–11.8 for duration of 10–19 years; and OR 36.7, 95 % CI 22.0–61.3 for duration of 30 years or more). The data provided evidence for a latency period, in the order of at least 20 years.

The results for women were less conclusive: the increase in the risk of adenocarcinoma for women with wood-related jobs (OR 2.78; 95 % CI 0.75–10.3) was smaller than that seen in men. As with men, the risk was greatest for women employed in furniture factories (OR 4.6; 95 % CI 1.16–18.3). No increase in risk was observed with an increase in the intensity of exposure in women, regardless of the histological type. However, the small number of cases precluded any detailed analysis.

Squamous Cell Carcinoma

The findings from the pooled analysis [17] were more ambiguous for squamous cell cancers than for adenocarcinomas (Fig. 7.2). The risk for women only was approximately doubled, particularly for women who had worked in moderately or highly exposed jobs; an exposure-effect relationship was evident with respect to the exposure duration. It has to be noted that the results for women were based on small numbers. For men, the risk of squamous cell carcinoma was not related to being exposed at the job nor to the intensity or the duration of exposure. Overall, the results showed the risk estimates for squamous cell carcinomas to be distinctly lower than those for adenocarcinomas.

Table 7.1 Main characteristics of the 12 case-control studies included in the pooled analyses by Demers et al. [17], Leclerc et al. [18], 't Mannetje et al. [20], and Luce et al. [19]

Country/reference	Source of information, exposure evaluation	Studied agents	Cases sex: *n* (%AC/%SCC)	Controls
China (Shanghai)/ Zheng et al. [21]	In-person interview	Asbestos, silica, metal, coal, wood, textile, petroleum products, benzene/paint, chromium, pesticide, formaldehyde, chromium	Population-based cancer registry of Shanghai diagnosed between 01/1988 and 02/1990	Randomly selected from the Shanghai Resident Registry
	Self-reported exposures	Job titles	Men: 39 (16/72)	Men: 269
	Job titles		Women: 21 (18/55)	Women: 145
France/Leclerc et al. [22], Luce et al. [23–25]	Interviewed by trained physicians	Job titles	Diagnosed between 01/1986 and 02/1988 in 27 participating hospitals in France	Selected from patients of the same hospital with cancer from another site and neighborhood of cases
	Detailed occupational history	Industry titles	Men: 167 (49/36)	Men: 320
	Job titles and industries coded ISCO and ISIC	WD, formaldehyde, leather dust, textile dust, flour dust, sugar dust, coal/coke dust, nickel, chromium, chromium VI, welding fumes, soldering fumes, cutting oils, paints, varnishes and lacquers, glues, adhesives	Women: 40(13/45)	Women: 89
	Specific questionnaire for substances, compounds, or procedures			
	Assessment by industrial hygienist			
Germany (Hessen)/ Bolm-Audorff et al. [26]	Occupational history collected through interview	Wood dust, leather dust, welding fumes, pesticides, other dusts (stone, building site, cereal)	Diagnosed between 01/1983 and 12/1985 in hospitals in Hessen	Selected from patient with nonoccupational bone fractures matched for each case on age, sex, and residence
			Men: 33 (9/39)	Men: 33
			Women: 21 (5/33)	Women: 21
Italy (Verona, Vicenza)/Comba et al. [27]	Interviewed or mailed questionnaire	Wood dust, leather dust, metal, textile, mining and construction, farming	Diagnosed between 1982 and 1987 in hospitals of Verona, Vicenza, and Siena provinces	Selected from patient admitted for diseases other than sinonasal diseases, matched for each case on age, sex, and residence
	General occupational history		Men: 55 (25/47)	Men: 184
	Detailed work description in 7 industries		Women: 23 (14/36)	Women: 70
Italy (Brescia)/ Comba et al. [28]	Detailed occupational history	Wood dust, leather dust, metal, textile, mining and construction, farming	Diagnosed between 1980 and 1989 in Brescia Hospital	Selected from patients treated in the same hospital for benign and malignant tumors of the head and neck (excluding cases localization) matched for each case on age, sex
	Specific items concerning work in metal, leather, and wood industries		Men: 23 (22/52)	Men: 70
			Women: 11 (10/50)	Women: 32
Italy (Biella)/ Magnani et al. [29]	Detailed occupational history	Wood dust, leather dust, metal, textile, mining and construction, farming	Diagnosed between 1976 and 1988 among residents of Biella and Cossato	Selected from patient with diagnoses other than respiratory cancer, matched for each case on age, sex
	Specific items concerning work in textile, garment, furniture, shoe, leather, metalworking, agriculture	Formaldehyde (job-exposure matrix and industrial hygienist)	Men: 22 (43/38)	Men: 92
			Women: 4 (33/67)	Women: 19

Table 7.1 (continued)

Country/reference	Source of information, exposure evaluation	Studied agents	Cases sex: *n* (%AC/%SCC)	Controls
Italy (Vigevano)/ Merler et al. [30]	Occupational history, interviews	Leather dust, solvents, rubber, wood dust, polycyclic aromatic hydrocarbons, nickel, benzene	Diagnosed between 1968 and 1982 and identified through cancer registry	Selected from electoral roll (living controls) and mortality records (dead controls) matched for age, sex, vital status, year of death if dead
	Blind evaluation by 2 occupational physicians on the basis of recorded interviews		Men: 16 Women: 5 Men+Women: 21 (69/6)	Men: 29 Women: 10
The Netherlands/ Hayes et al. [31, 32]	Job history	Wood dust	Diagnosed in men aged 35–79 years between 1978 and 1981 in 6 major hospitals which treat head and neck tumors	Random sample of living and dead males in the Netherlands in 1981 selected from municipal resident registries and records of the Central Bureau of Genealogy
	Interviews by trained interviewers Job titles and industries coded SICM of US Census and tasks with the US DOT Job history reviewed and classified according to level and probability of WD exposure and formaldehyde (blinded to case-control status)	Formaldehyde	Men: 91 (25/55) Women: –	Men: 195 Women: –
Sweden/Hardell et al. [33]	Mailed questionnaire completed by telephone interviews	Asbestos, chlorophenols, DDT, glass fibers, leather work, organic solvents, woodwork, particle board production	Diagnosed between 1970 and 1979 and reported to the Swedish Cancer Registry Men: 44 (7/70) Women: –	Referents of a previous study of soft tissue sarcoma and lymphoma Men: 541 Women: –
USA (Virginia, North Carolina)/ Brinton et al. [34, 35]	Telephone interviews	Wood dust, leather, nickel, chromium, asbestos, petroleum products, formaldehyde	Admitted to four hospitals in North Carolina and Virginia between 1970 and 1980	Selected from living hospital cases matched for year of admission, age, sex, race, and area of residence
	Occupational exposures, medical and family history		Men: 93 (15/61) Women: 67 (17/52)	Men: 181 Women: 106
USA (Los Angeles)/ Mack et Preston-Martin[a]	Telephone interviews		Diagnosed between 1979 and 1985 and reported to a tumor registry	Neighborhoods
	Occupational history, job titles		Men: 64 (3/63) Women: 38 (3/41)	Men: 108 Women: 70
USA (Seattle)/ Vaughan and Davis [36]	Telephone interviews	Wood dust, formaldehyde (study specific JEM)	Diagnosed between 1979 and 1983 and identified from a population-based tumor registry	Selected by random digit dialing and matched for sex and age
	Occupational history, job titles		Men: 33 (3/59) Women: 20 (5/35)	Men: 327 Women: 225

(continued)

Table 7.1 (continued)

Country/reference	Source of information, exposure evaluation	Studied agents	Cases sex: *n* (%AC/%SCC)	Controls
Pooled analysis of 12 international case-control studies IARC/Demers et al. [17], Luce et al. [19]	Occupational history, job titles, and industries coded by ISCO and ISIC	Wood dust, leather dust, formaldehyde, flour dust, coal dust, silica dust, textile dust, asbestos, mineral wools, ceramic fibers	Cases of the 12 above studies	Controls of the 12 above studies
	Job-exposure matrix		Men: 680 (25/48)	Men: 2,349
			Women: 250 (10/40)	Women: 787
Pooled analysis of eight European case-control studies/'t Mannetje et al. [20]	Occupational history, Job titles and industries coded by ISCO and ISIC	Wood dust, leather, formaldehyde	Cases of the 8 European studies above (France, Germany, Italy, the Netherlands, Sweden)	Controls of the 8 European studies above (France, Germany, Italy, the Netherlands, Sweden)
	Job-exposure matrix	Other high-risk occupations/ industries	Men: 451 (33/44)	Men: 1,464
			Women: 104 (11/39)	Women: 241

[a]Mack W, Preston-Martin S, Case-control study of cancers of the nasal sinuses and nasopharynx among non-Asians in Los Angeles county, 1995, unpublished work
AC adenocarcinomas, *SCC* squamous cell carcinomas

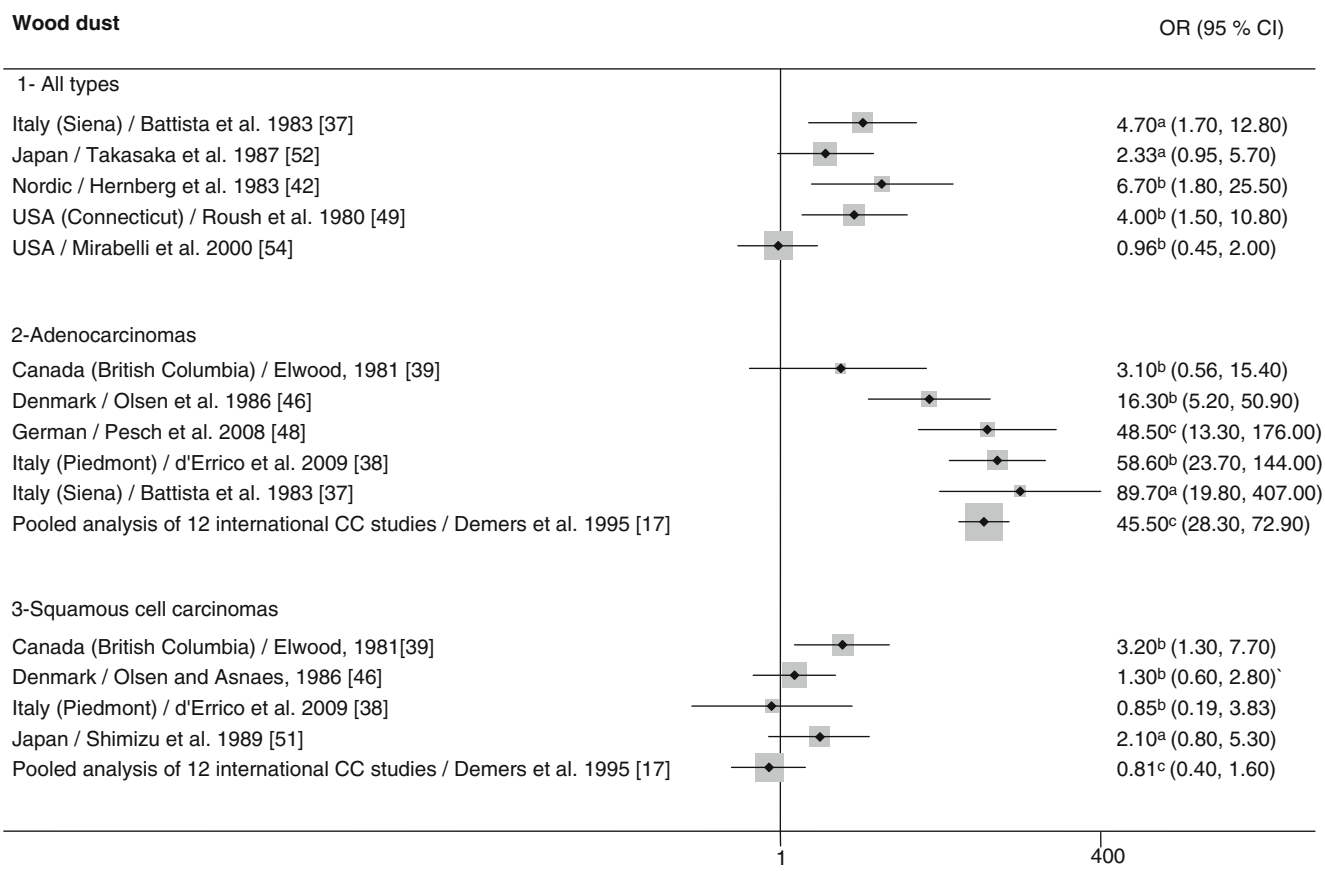
Table 7.2 Main characteristics of other case-control studies (not included in the pooled analyses)

Country/reference	Source of information, exposure evaluation	Studied agents	Cases sex: *n* (%AC/%SCC)	Controls
Italy (Siena)/ Battista et al. [37]	Occupational history and specific questions about having ever worked in wood industry, furniture industry, and leather industry	Wood dust, leather	Diagnosed between 1963 and 1981 in Siena hospital	Selected from men admitted for other diseases, matched for age
			Men: 36 (14/47)	Men: 164
			Women: –	Women: –
Italy (Piedmont)/ d'Errico et al. [38]	Occupational history, jobs, and tasks description	Wood dust, leather dust, arsenic, nickel, chromium, PAH, welding fumes, oil mists, formaldehyde, flour, cocoa powder, textile dusts, silica, coal dust, paint mists, strong-acid mists, and organic solvent vapors	Diagnosed or treated between 1996 and 2000 in all Piedmont hospitals	Selected from departments of ENT and orthopedics, frequency matched for age, sex and residence
	Job-exposure matrix		Men: 76 (59/16)	Men: 234
	Exposure evaluated by occupational physicians		Women: 37 (22/68)	Women: 102
Canada (British Columbia)/Elwood [39]	Occupational history	Wood dust	Diagnosed between 1939 and 1977 in the main cancer treatment center in British Columbia	Selected from patients with cancer considered unrelated to smoking or outdoor work, matched for age and year of diagnosis
			Men: 121 (9/50)	Men: 363
			Women: –	Women: –
Japan (Hokkaido)/ Fukuda and Shibata [40], Fukuda et al. [41]	Postal questionnaire	Woodworking (carpenters, joiners, furniture workers, and others woodworkers)	Diagnosed between 1982 and 1986 in all Hokkaido hospitals, aged 40 to 79,	Selected from telephone directory, matched for sex, age, and residence
	Occupational history, history of nasal disease		Men: 81 (?/91)	Men: 162
			Women: 25 (?/83)	Women: 50
Nordic/Hernberg et al. [42]	Telephone interviews	Woodwork, farming, forestry, textile work, metal work, construction work	Diagnosed between 07/1977 and 12/1980 and reported to national cancer registries of Denmark, Finland, and Sweden	Patients with tumors of colon and rectum, matched for country, sex, and age at diagnosis
	Occupational history, tasks, exposure to dust, smoke, fumes, or chemicals	Specific agents: cadmium, chromium, nickel	Men: 110	Men: 110
	Assessment of exposure by an industrial hygienist		Women: 57	Women: 57
			Men+Women: 167 (11/57)	

Table 7.2 (continued)

Country/reference	Source of information, exposure evaluation	Studied agents	Cases sex: *n* (%AC/%SCC)	Controls
Hong Kong/Ng [43]	Occupational history	Job titles	Diagnosed between 1974 and 1981 and reported to the Cancer Registry in Hong Kong	Two groups: nasopharyngeal carcinomas and other cancers selected in random order from the same registry and matched for treatment center, year of admission, age, sex, race, and resident status
		Industries titles	Men: 157	Men: 159 + 158
			Women: 68	Women: 65 + 68
			Men+Women: 225 (2/53)	
Denmark/Olsen et al. [44], Olsen and Jensen [45], Olsen and Asnaes [46], Olsen [47]	Occupational history	Formaldehyde, wood dust, leather dust, nickel-chromium, chlorophenols, textile dust, asbestos, metal work, man-made mineral fibers, paint, lacquer and glue manufacture, plastic manufacture, silage manufacture	Diagnosed between 1970 and 1982 and identified by the Danish Cancer Registry	Patients with cancers of colon, rectum, prostate/breast diagnosed during the same period
	Exposure assessed by industrial hygienists		Men: 345 (13/69)	Men: 1,631
			Women: 180 (8/66)	Women: 834
Germany/Pesch et al. [48]	Occupational history	Wood dust, varnishes, pigments stains, formaldehyde	Workers of woodworking industries with SNC recognized as occupational disease between 1994 and 2003	Workers of woodworking industries with recognized accidents and falls frequency matched for age
	JEM based on personal measurements in the German woodworking industries: mg/m^3 and mg/m^3.years		Men: 86 (100/0)	Men: 204
			Women: –	Women: –
USA (Connecticut)/ Roush et al. [49, 50]	Job title at 1, 10, 20, 25, 30, 40, 50 years prior to death or until the subject was less than 20 years of age	Nickel, cutting oils, wood dust	Identified through the Connecticut Tumor Registry, aged 35 years or older, and died between 1935 and 1975 in Connecticut	Randomly selected from population of males dying in Connecticut from 1935 to 1975 at age 35 or older
			Men: 198 (10/55)	Men: 605
			Women: –	Women: –
Japan/Shimizu et al. [51]	Occupational history	List of occupations in relation with wood	SCC of maxillary sinus diagnosed in six hospitals in north-eastern Japan between 10/1983 and 10/1985	Random sample of residents in the same area from telephone directories, matched for age and sex
			Men: 45 (0/100)	Men: 90
			Women: 21 (0/100)	Women: 42
Japan/Takasaka et al. [52]	Complete history of experience in woodworking and detailed tasks	List of occupations (forestry worker, coal miner, nickel worker, wood sawyer, chipperman, veneer maker, wood machinist, wood furniture maker and joiner, leather worker, carpenter)	Admitted to Tohoku University Hospital in Japan between 1971 and 1982	Admitted to the same hospital with other otorhinolaryngological diseases, matched for sex, age, and date of admission
			Men: 107 (6/80)	Men: 413
			Women: –	Women: –
USA/Caplan et al. [53], Mirabelli et al. [54], Zhu et al. [55]	Telephone interviews	Pesticides/herbicides, dry cleaning, wood preservatives, wood dust, asbestos, leather, chlorophenols, formaldehyde	Selected from the Selected Cancers Study (Vietnam veterans), born between 1929 and 1953 and reported to eight cancer registries in the USA between 12/1984 and 11/1988	Selected by random digit dialing
	Occupational history		Men: 70 (20/59)	Men: 1,910
	Estimation of exposures by industrial hygienist		Women: –	Women: –

AC adenocarcinomas, *SCC* squamous cell carcinomas



- For each study, when ORs were reported for specific histological types, the OR for the category "All types" is not presented.
- Results from individual studies included in the pooled analysis are not presented.
- Exposure categories:[a]Wood workers or cabinet makers,[b]Wood dust,[c]Wood dust ≥ 5 mg/m^3

Fig. 7.2 Exposure to wood dust. Estimated relative risks from case-control (*CC*) studies (Forest plot) for sinonasal cancer associated with occupational exposure, by main histological types. *Diamonds* represent the estimated ORs, *horizontal lines* represent the 95 % CIs, and the size of the *gray squares* indicates the relative size of the study population in each stratum. *OR*, odds ratio; *95 % CI*, 95 % confidence interval

Case-control studies not included in the pooled analysis confirmed the role of wood dust exposure in sinonasal cancer risk, the association with exposure to wood dust being much stronger for adenocarcinomas than for squamous cell carcinomas (Fig. 7.2).

Cohort Studies

An elevated risk of sinonasal cancer was also found in cohorts of woodworkers, but there was no information available on histological type. Demers and coworkers [56] performed also a pooled analysis of five cohorts of workers exposed to wood dust. A significant excess in the number of deaths from sinonasal cancer (11 cases; standard mortality ratio [SMR] 3.1; 95 % CI 1.6–5.6) was found, with a clear increase of the SMR with the exposure probability. The excess risk was limited to workers in the furniture industry and no sinonasal cancer deaths were observed in the plywood industry cohorts. The excess risk was limited to those workers who had begun their employment before 1940 and to those whose exposure had begun more than 20 years earlier. In this pooled analysis, the results were strongly influenced by the number of deaths from sinonasal cancer in the group of furniture industry workers from England (ten out of the 11 deaths from sinonasal cancer).

Summary of Studies on Wood Dust

There are epidemiological data indicating that exposure to wood dust is related to extremely high relative risks for sinonasal cancer. Adenocarcinoma represents a variable proportion of sinonasal cancers (between 10 and 50 %, depending on the country). The link between the onset of this histological form and exposure to wood dust is very clear and the association is stronger for adenocarcinomas than for squamous cell carcinomas. Thus, the excess risks reported for all the histological types together could be explained largely by the results relating to adenocarcinoma.

Even though the results for adenocarcinoma were on the whole consistent across the studies, the relative risk was much higher in Europe (especially France and Italy) than in

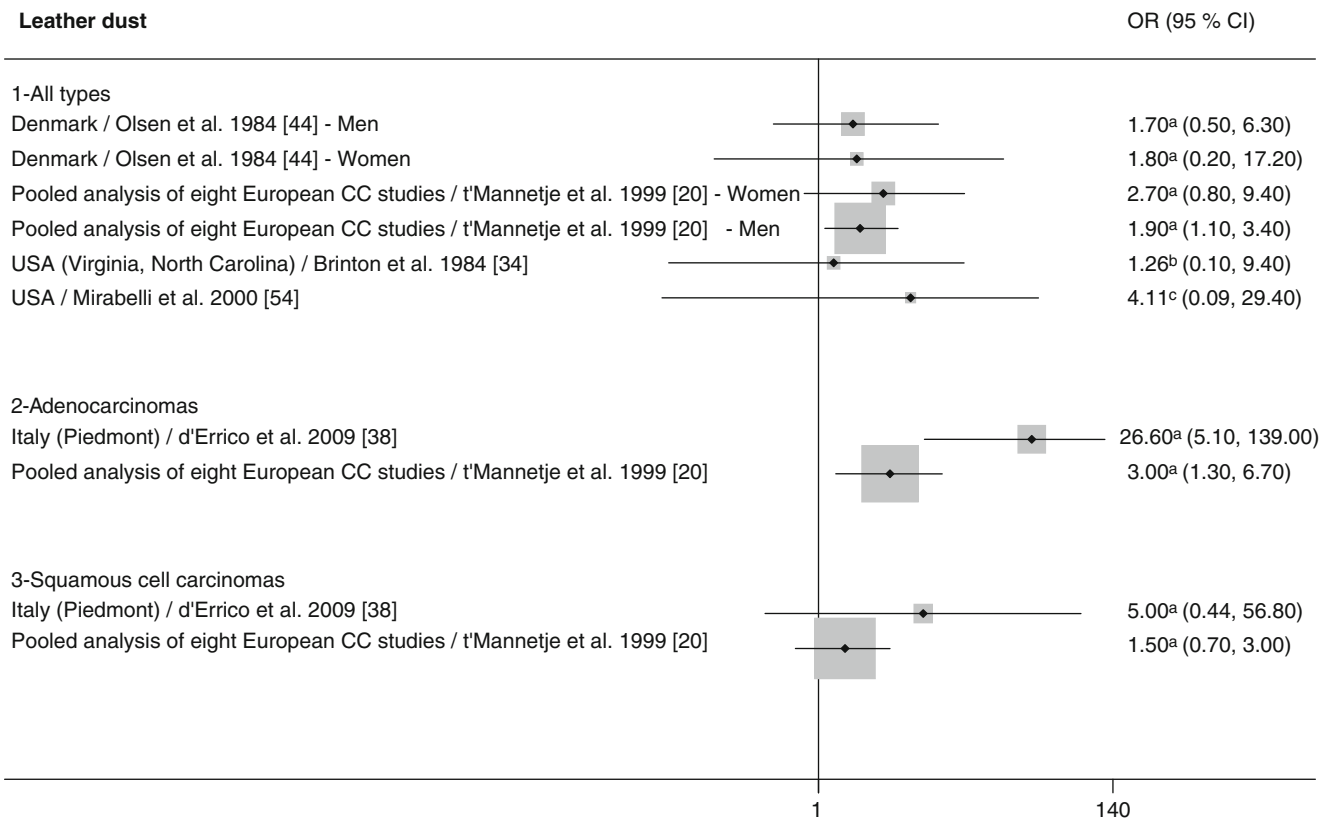
North America and Asia. This difference could be related to the levels of exposure or to the types of wood in use, although no data on the type of wood used were available in the pooled analysis to confirm this hypothesis. However, hardwoods are more widely used in Europe, especially in southern countries, where the proportions of adenocarcinomas among sinonasal cancer cases are higher than in the north.

A large part of the adenocarcinoma cases included in the published studies were related to exposure to hardwood dusts, and the case-control investigations in which the type of wood used was evaluated confirm the suspicion of a stronger association with hardwood dust than with softwood dust [4, 22, 48]. However, it is virtually impossible to distinguish the respective role of each type of wood in the genesis of sinonasal cancer. On the one hand, very few studies have recorded the necessary information, and, on the other, rather often both types of wood are used in furniture factories and also in carpentry and cabinetmaking workshops, the fields of activity in which the risks are highest.

The results of some studies with workers exposed solely or mostly to softwood dusts showed a consistent excess risk, but the magnitude of the excess was small in comparison to hardwood, and the association was primarily with squamous cell carcinoma [4, 57].

Leather Dust

An excess of sinonasal cancers in leather workers, especially in boot and shoe manufacture and repair, has been reported in numerous case-control studies (Fig. 7.3), as well as in cohort or record linkage studies in the United Kingdom [58, 59], the Nordic countries [47, 60], and Italy [61]. The role of leather dust was suggested by the observation of higher risks in jobs exposed to dust and in workers most extensively exposed to leather dust. Leather dust is now considered as a human carcinogen (Group 1) by the IARC [4, 14] with sufficient evidence in humans for the nasal cavity and paranasal sinuses (see also Section on Exposure Characteristics). The association is stronger for



- For each study, when ORs were reported for specific histological types, the OR for the category "All types" is not presented.
- Results from individual studies included in the pooled analysis are not presented.
- Exposure categories: [a]Leather dust, [b]Leather or shoe industries, [c]Leather workers

Fig. 7.3 Exposure to leather dust. Estimated relative risks from case-control (*CC*) studies (Forest plot) for sinonasal cancer associated with occupational exposure, by main histological types. *Diamonds* represent the estimated ORs, *horizontal lines* represent the 95 % CIs, and the size of the *gray squares* indicates the relative size of the study population in each stratum. *OR*, odds ratio; *95 % CI*, 95 % confidence interval

adenocarcinomas, but some results suggest that other histological types could also be involved. Merler and coworkers [30] showed a very clear relationship between the level of exposure to leather dust and the risk of adenocarcinoma, with an OR of 20.4 (95 % CI 2.7–152.0) for moderate exposures and 88.0 [95 % CI 12.1–642.0] for high exposures. For the other histological types, the OR associated with exposure to leather dust was 6.9 (95 % CI 1.4–34.4).

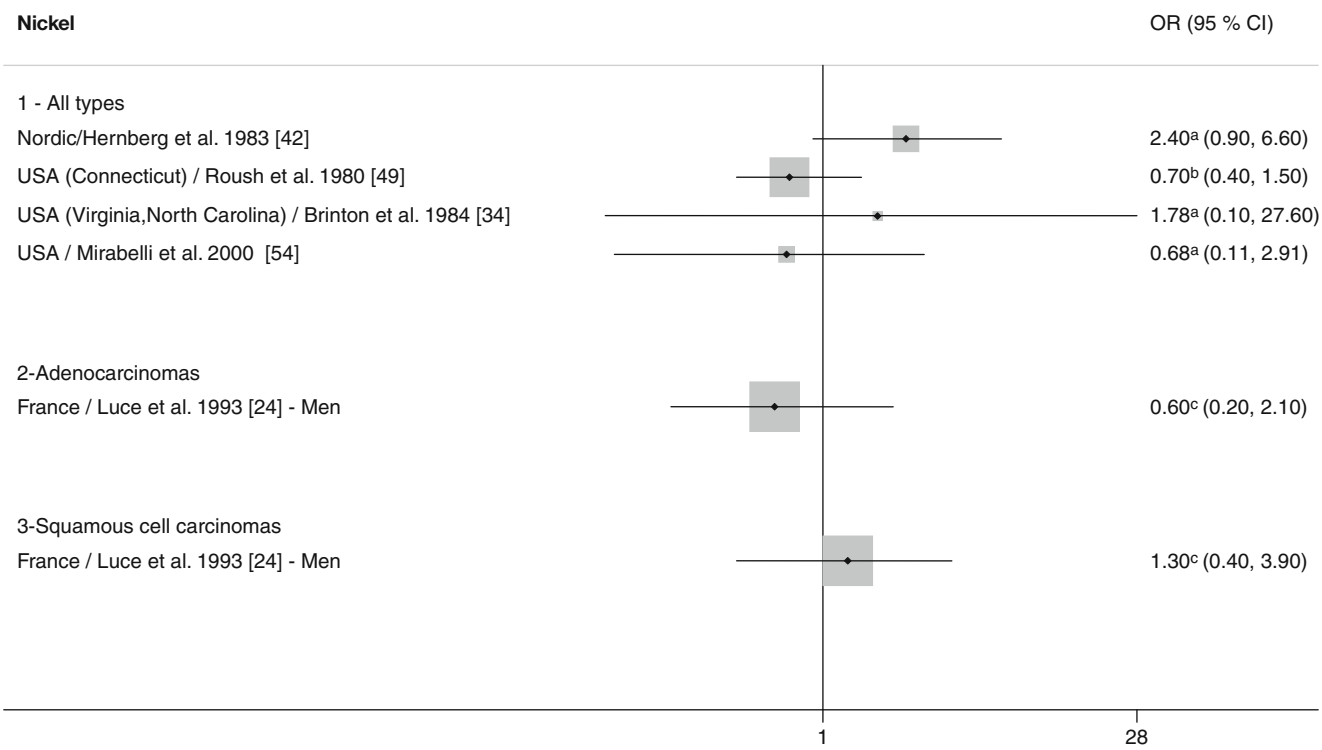
Nickel and Chromium Compounds

The association between the occurrence of sinonasal cancers and exposure to nickel compounds encountered in nickel refining is well recognized. Excesses of sinonasal cancers have also been observed in cohorts of workers exposed to hexavalent chromium [4, 14, 62].

In case-control studies, exposures to nickel and chromium (often simultaneously) have emerged mainly from welding stainless steel, or spray painting, and the levels of exposure were low, which may explain the mainly null results (Figs. 7.4 and 7.5). However, Hernberg and coworkers [42] studying these exposures in these kinds of activities for sinonasal cancer observed an OR of 2.7 (95 % CI 1.1–6.6) for exposure to chromium and of 2.4 (95 % CI 0.9–6.6) for exposure to nickel. Other studies have not confirmed these results. Brinton and coworkers [34] observed a nonsignificantly increased risk of sinonasal cancer in those subjects exposed to chromates (OR 1.49; 95 % CI 0.40–5.60) through the use of these products in construction and painting. Only one male case was exposed to nickel in this study (OR 1.78; 95 % CI 0.10–27.6]. Two studies have examined the histological types separately [24, 38], and no significant association with exposure to chromium and nickel was observed, regardless of histological type. The results with regard to exposure to welding fumes were conflicting [24].

Formaldehyde

Formaldehyde is a probable cause of sinonasal cancer based on sufficient evidence from excess of squamous cell carcinomas in rodents and limited evidence in humans (with an overall evaluation of carcinogenic to humans, Group 1) [13, 63].



- For each study, when ORs were reported for specific histological types, the OR for the category "All types" is not presented.
- Results from individual studies included in the pooled analysis are not presented.
- Exposure categories: [a]Ever exposed, [b]Nickel workers (grinder, filer, turner, molder, welder…), [c]Ever exposed 'Probable or definite'

Fig. 7.4 Exposure to nickel compounds. Estimated relative risks from case-control (*CC*) studies (Forest plot) for sinonasal cancer associated with occupational exposure, by main histological types. *Diamonds* represent the estimated ORs, *horizontal lines* represent the 95 % CIs, and the size of the *gray squares* indicates the relative size of the study population in each stratum. *OR*, odds ratio; *95 % CI*, 95 % confidence interval

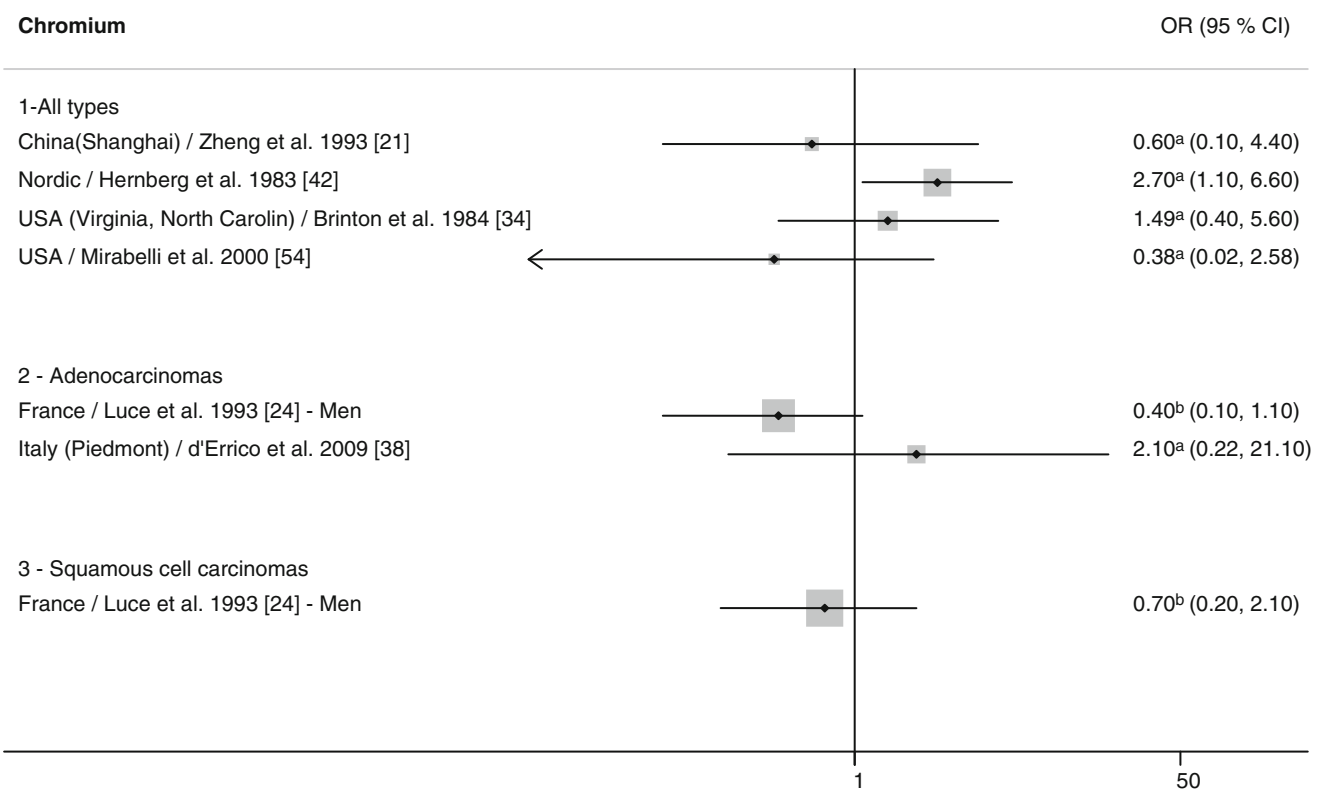


Fig. 7.5 Exposure to chromium compounds. Estimated relative risks from case-control (*CC*) studies (Forest plot) for sinonasal cancer associated with occupational exposure, by main histological types. *Diamonds* represent the estimated ORs, *horizontal lines* represent the 95 % CIs, and the size of the *gray squares* indicates the relative size of the study population in each stratum. *OR*, odds ratio; *95 % CI*, 95 % confidence interval

Following the reporting of nasal squamous cell carcinogenicity in rats exposed to high doses of formaldehyde in the early 1980s [64], several epidemiological studies have been published [2, 63]. Five cohort studies and one study of proportionate morbidity based on industrial formaldehyde exposure [65–73], and five studies based on exposures among pathologists and embalmers [74–78] have examined the association between formaldehyde and sinonasal cancer. The histological subtypes have not been specified in any of the cohorts. Due to the rarity of the disease, the observed and expected numbers in each study have been very small, and the interpretation of risk is therefore uncertain. A study of proportionate morbidity from Denmark, however, included 13 male and 4 female cases on nasal cavity cancer with corresponding estimated relative risks of 2.3 (95 % CI 1.3–1.4) and 2.4 (95 % CI 0.6–6.0) [69, 70].

The pooled data of 12 case-control studies were analyzed with respect to formaldehyde exposure [19] (Fig. 7.6). Significantly elevated relative risks for adenocarcinomas appeared in the groups with the highest cumulative exposure in both men (OR 3.0; 95 % CI 1.5–5.7) and women (OR 6.2; 95 % CI 2.0–19.7), whereas relative risks for squamous cell carcinomas were not significantly increased (OR 1.2; 95 % CI 0.8–1.8 and OR 1.5; 95 % CI 0.6–3.8 in men and women, respectively). However, in the group with highest probability of formaldehyde exposure, an elevated relative risk of squamous cell carcinomas was observed in men (OR 2.5; 95 % CI 0.6–10.1) and women (OR 3.5; 95 % CI 1.2–10.5). Formaldehyde exposure has also been studied in four case-control studies not included in the pooled analysis (Fig. 7.6) and was found to be associated with an increased risk of sinonasal cancer in two of them.

Textile Workers/Textile Dust

Data from the 12 case-control studies presented above and in Table 7.1 were analyzed according to the occupation and industry [18]. This pooled analysis detected an increased risk of sinonasal adenocarcinoma among women employed in the textile industry (OR 2.6; 95 % CI 1.0–6.6), and a high risk of squamous cell carcinoma for men involved in fiber

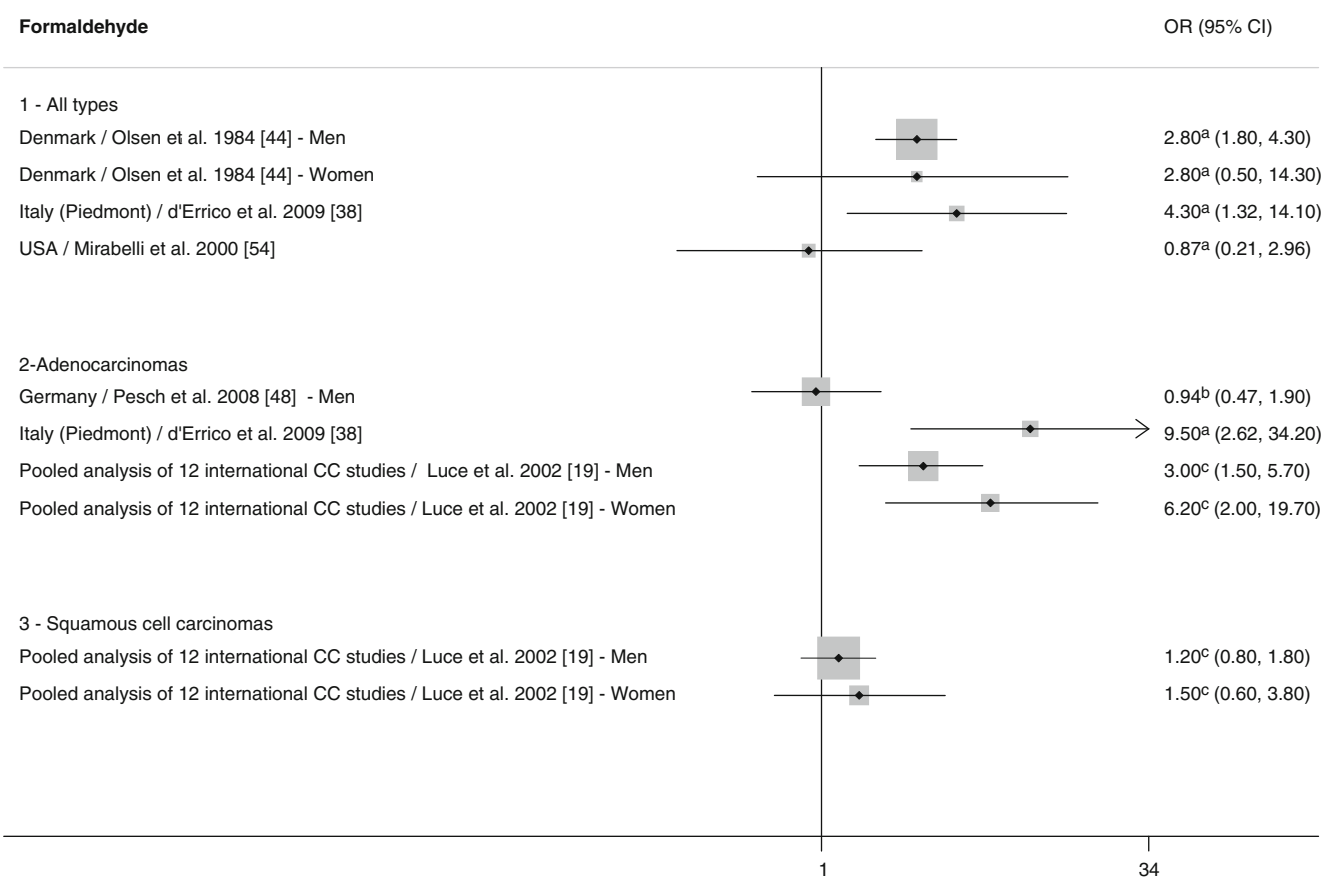


Fig. 7.6 Exposure to formaldehyde. Estimated relative risks from case-control (*CC*) studies (Forest plot) for sinonasal cancer associated with occupational exposure, by main histological types. *Diamonds* represent the estimated ORs, *horizontal lines* represent the 95 % CIs, and the size of the *gray squares* indicates the relative size of the study population in each stratum. *OR*, odds ratio; *95 % CI*, 95 % confidence interval

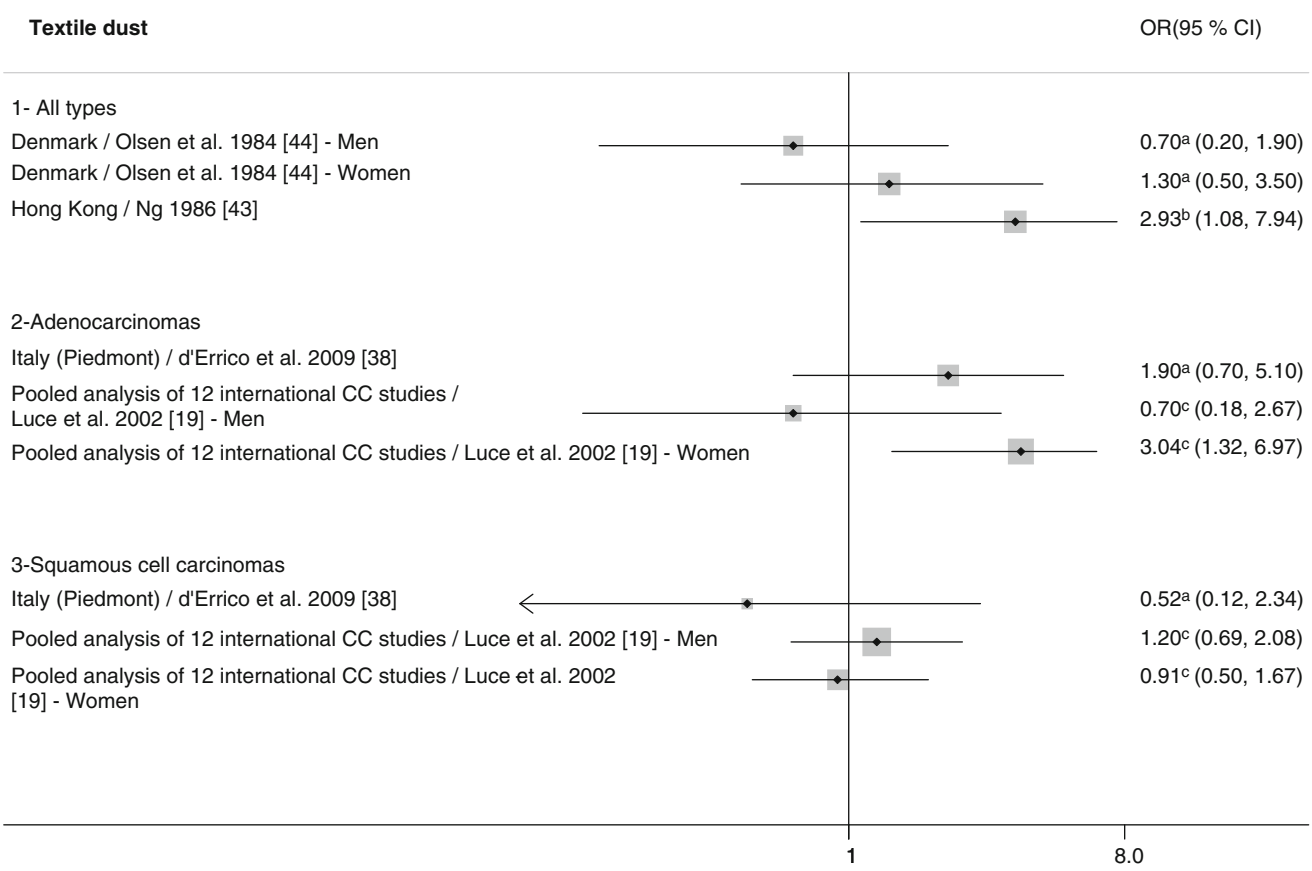
preparation (OR 5.1; 95 % CI 1.3–19.2) or finishing of textile products (OR 3.0; 95 % CI 1.0–9.1).

The same dataset was also analyzed according to exposure to textile dust, which was considered a plausible causal agent [19]. The risk of adenocarcinoma was associated with cumulative exposure to textile dust only in women, with no clear dose-response relationship: the ORs were 1.7, 3.5, and 2.5 for low, medium, and high levels, respectively. No association with the cumulative level, probability, and duration of exposure to textile dust was found among men for both histological types or among women for squamous cell carcinoma. However, a high risk of squamous cell carcinoma (OR 6.6; 95 % CI 1.4–31.8) was observed among men who had been exposed to more than 0.5 mg/m^3. Textile dust or textile work was also associated with elevated risks of sinonasal cancer in several other case-control studies (Fig. 7.7).

A possible role of exposure to formaldehyde has been proposed to explain the observed elevated risk in the textile industry, but in the pooled analysis, adjustment for formaldehyde exposure did not change markedly the ORs associated with textile dust [19]. The difference between men and women might be explained by exposure to different types of textile fibers. The role of cotton dust was postulated by Brinton et al. [35], who reported a high proportion of cases exposed to cotton. The nature of textile fibers (cotton, wool, synthetic fibers) was available in four studies in the pooled analysis, but when the data were combined, no specific effect of a particular type of textile was found [19].

Other Occupational Exposures

An increased risk of carcinomas of the paranasal sinuses and mastoid process was found in radium watch-dial painters, who ingested radium by "pointing" their brush with their lips. This excess risk was associated with internally



• For each study, when ORs were reported for specific histological types, the OR for the category "All types" is not presented.
• Results from individual studies included in the pooled analysis are not presented.
• Exposure categories: [a]Textile dust [b]Textile workers,[c]Level of cumulative exposure : ≥ medium high (recalculated)

Fig. 7.7 Exposure to textile dust. Estimated relative risks from case-control (*CC*) studies (Forest plot) for sinonasal cancer associated with occupational exposure, by main histological types. *Diamonds* represent the estimated ORs, *horizontal lines* represent the 95 % CIs, and the size of the *gray squares* indicates the relative size of the study population in each stratum. *OR*, odds ratio; *95 % CI*, 95 % confidence interval

deposited radium-226 [15]. There is also sufficient evidence that the manufacture of isopropyl alcohol by the strong-acid process causes sinonasal cancer. The evidence is inadequate to draw conclusions on the carcinogenicity of isopropyl alcohol, isopropyl oils, or isopropanol produced using other methods [63].

Other occupational exposures have been associated with the risk of sinonasal cancer, such as paints [42], adhesives [24], cutting oils [49, 50], and chlorophenols [33, 54, 55]. In the pooled analysis [19], an increased risk of squamous cell carcinoma was observed among men with a high cumulative exposure to asbestos (OR 1.6; 95 % CI 1.1–2.3). However, no significant association has been found in the few other case-control studies that have evaluated the risk associated with exposure to asbestos [21, 42], but the level of exposure and the histological type were not taken into account. Associations between exposure to arsenic (OR 5.2; 95 % CI 1.20–22.20) and sinonasal squamous cell carcinoma and between exposure to organic solvents and adenocarcinoma (OR 8.2; 95 % CI 4.32–15.72) have also recently been reported [38] and need to be confirmed.

A high risk of sinonasal cancer has been observed in many other occupations. The pooled analysis of 12 case-control studies highlights several associations [18]. Some results have reinforced the plausibility of associations reported in other studies (not included in the pooled analysis): a significantly elevated risk of sinonasal cancer has been observed in farmers, men employed in the food industry, food preservers, cooks, and vehicle drivers. The high risks reported in some studies for coal miners [79], construction [23, 27, 43], or metalworking [28, 47, 79] were not confirmed in the pooled analysis. However, two new associations emerged with respect to sinonasal squamous cell carcinomas: significant ORs were observed for hairdressers (OR 2.87; 95 % CI 1.03–8.02) and rubber workers (OR 3.17; 95 % CI 1.28–7.86).

Other Risk Factors

There is a causal relationship between tobacco smoking and the risk of cancer of the nasal cavity and the paranasal sinuses [80, 81]. One cohort study and nine case-control studies have examined the risk of tobacco smoking and sinonasal cancer. The association is consistently stronger for sinonasal squamous cell carcinomas than for adenocarcinomas [82]. With an average relative risk of 1.5–2.5, the association is significantly less strong than for many other tobacco-associated cancers, e.g., for lung cancer with an estimated relative risk of 15–30 [82].

No other nonoccupational risk factor has been identified for sinonasal cancer. In particular, with regard to biological agents classified as human carcinogens, nasal cavity and sinuses are not among the cancer sites for which there is sufficient or limited evidence in humans. Although Epstein-Barr virus (EBV) infection is associated with sinonasal lymphomas, no relation was reported with sinonasal carcinomas. Similarly, the detection of human papillomavirus (HPV) was reported in sinonasal cancer cases, but there is a lack of evidence from case-control studies to support these data [83, 84].

Summary and Conclusions

Occupational factors have a predominant role in the etiology of sinonasal cancer, and apart from these exposures, only tobacco smoking has been confirmed as a risk factor. Exposures to wood dust and leather dust are predominantly associated with adenocarcinomas, whereas increased risks for tobacco smoking were mainly found in squamous cell carcinomas. Epidemiological data do not allow determining whether other occupational exposures linked to sinonasal cancer are associated with specific histological types. In addition, no epidemiological studies are available differentiating histological subtypes, such as intestinal-type adenocarcinoma. The very high excess risks associated with wood dust exposure, together with the large number of exposed workers, mean that wood dust is a major cause of sinonasal cancer.

Exposure Characteristics

There is a range of exposures where causality to development of sinonasal cancer has been documented (see Section on Epidemiology and Occupational Risk Factors). This section summarizes and discusses exposure characteristics for commonly used substances evaluated by the International Agency for Research on Cancer (IARC) as being carcinogenic to humans and to which there is sufficient evidence for sinonasal cancer in humans [4]. The work-related substances are wood dust, nickel compounds and nickel metal, and "shoe and leather work" (leather dust). Hexavalent chromium is also included, although in the latest IARC evaluation, it is stated that "the epidemiological evidence remains suggestive but inconclusive regarding the effect of chromium VI on nasal and sinonasal cancers" [4]. In addition to these occupational exposures, tobacco smoking is associated with increased risk of sinonasal cancer [81].

The exposure characteristics for each substance are summarized in Table 7.3. Formaldehyde is not included as there is only limited epidemiological evidence that formaldehyde causes sinonasal cancer, as opposed to nasopharyngeal cancer where the association with formaldehyde exposure is well documented [4, 89] (see Section on Epidemiology and Occupational Risk Factors).

All substances, except for "shoe and leather work," are prevalent exposures all around the world. In 2001–2003, approximately 3.6 million workers in the European Union alone were being exposed to wood dust on a regular basis; worldwide the numbers are hundreds of millions [2, 90]). Similarly, several million workers worldwide are exposed to airborne fumes, dusts, and mists containing nickel and nickel compounds; the same is true for exposure to chromium or its compounds [62]. Smoking is still very prevalent in most countries and is practiced by more than 1,000 million people around the world [80, 81, 88].

Wood Dust

Wood dust exposure is present in many industries; the typical high exposure industries or tasks are furniture industry, cabinetmaking, and joineries [2, 4] (see Section on Epidemiology and Occupational Risk Factors). The wood dust exposure levels in various industries in the past and more recently have been fairly well documented; it is known that dust levels above 5 mg/m^3 were previously common, mainly in sanding operations and similar tasks, for example, during furniture and cabinet manufacturing. However, even today many subjects are exposed to levels above 5 mg/m^3 [90, 91]. In epidemiological studies on wood dust exposure and sinonasal cancer, more exposure-response relations have been revealed, and now there is evidence in the literature that high exposure (>1–5 mg/m^3) for several years may be required in order to develop sinonasal cancer [2, 38, 57, 85, 92] (see Section on Epidemiology and Occupational Risk Factors). Although no threshold value exists, it is likely that health effects at exposure levels below 1 mg/m^3 are clearly less significant as opposed to higher exposure levels [92].

Chromium VI

Exposure to hexavalent chromium is prevalent in a range of industries and chromium compounds have been in widespread commercial use for more than 100 years. High exposure to chromium VI occurs during chromate production,

Table 7.3 Exposure characteristics for agents causally related to sinonasal cancer (SNC). Only agents evaluated as carcinogenic to humans by IARC (Group 1) are included

	Histological type of SNC	Industries/job of relevance	Exposure-response patterns, threshold values	Exposure information sources
Wood dust[a]	Adenocarcinoma. Probably squamous cell carcinoma	High exposed wood industries, e.g., furniture industry, cabinet manufacturing, joinery shops	Exposure-response relationships observed in several studies	IARC [2]
			High exposure (>1–5 mg/m^3) for several years. No confirmed risk for exposures below 1 mg/m^3	IARC [85] Demers et al. [57] d'Errico et al. [38] IARC [4]
Chromium VI	Not specified	Chromium production, chromium pigment production, chromium platers	Exposure-response relationships not reported	IARC [62]
			Airborne chromium VI concentrations >1 mg/m^3 found in past studies, lower in recent years	d'Errico et al. [38] Luippold et al. [86] IARC [4]
Nickel compounds	Not specified	Nickel refining industry	No clear exposure-response relationships reported	IARC [62]
		Hydrometallurgy Electrolysis workers Calcining workers	Airborne nickel concentrations >1 mg/m^3 found in earlier studies, lower in recent years	IARC [4]
"Shoe and leather work" (leather dust)	Mainly adenocarcinoma. Possibly other types	Boot and shoe manufacture	Exposure-response relationships observed in five studies ("leather dust years" or exposure intensity)	IARC [87]
		Boot and shoe repair	Increased for both light and heavy exposure, and increased for 5 and 10 years of exposure	Merler et al. [30] d'Errico et al. [38] Straif et al. [14] IARC [4]
Tobacco smoking	Squamous cell carcinoma	–	Exposure-response relationships observed in several studies (duration, intensity)	IARC [88]
			No clear threshold values	't Mannetje et al. [20] IARC [81]

[a]The evaluation is based on studies including workers predominantly exposed to hardwood dust

chrome pigment manufacturing, chrome plating, spray painting, and during welding [4, 62].

IARC's evaluations are based on the excess cases of sinonasal cancer found in workers in chromium and chromium pigment production and among chromium platers, whereas no consistent relationship has been seen among spray painters and welders (see Section on Epidemiology and Occupational Risk Factors). Airborne chromium VI levels above 1 mg/m^3 have been found in earlier studies, but in general the exposure levels have decreased substantially to below 10 µg/m^3 in the chromium production industry [4, 86]. No epidemiological studies on chromate VI and sinonasal cancer have reported exposure-response relationships, and there is no definitive knowledge of the duration and the intensity of the exposure needed to cause sinonasal cancer.

Nickel Compounds and Nickel Metal

Nickel compounds and nickel metal are used in many industries and have also been in widespread commercial use for more than 100 years. High exposure to airborne nickel occurs in nickel refining, nickel alloy production, welding, electroplating, grinding, and cutting operations [4, 62]. IARC's evaluation is based on excess cases of sinonasal cancer found among workers in the nickel refining industry and employees in hydrometallurgy and electrolysis plants, whereas no consistent relation has been seen in other occupations, e.g., welders. Furthermore, IARC's evaluation is based on exposure to nickel compounds like nickel sulfate and the combination of nickel sulfides and oxides [4, 62] (see Section on Epidemiology and Occupational Risk Factors). For example, airborne nickel levels above 1 mg/m^3 have earlier been found during nickel refining and nickel alloy production. The exposure levels have decreased with time, but are still highly variable with measured levels between 4 and 800 µg/m^3 in different industries and with different production methods [4]. The past concentration levels of individual nickel compounds are not known. A range of epidemiological studies included exposure-response analysis, but no clear exposure-response relationships have been revealed. There is no firm knowledge of the duration and the intensity of the exposure needed to cause sinonasal cancer.

Shoe and Leather Work

Working in the "shoe and leather work" industry is causally related to the development of sinonasal cancer. Excess risks have been observed among workers employed in boot and shoe manufacture and in boot and shoe repair [87]. Shoe and leather work involves a wide variety of different work procedures and exposure to many toxic substances, and in the IARC monograph published in 1981, the occupation "shoe and leather work" was stated as the causal agent. In the following year, an increased body of evidence in both case-control studies and cohort studies revealed leather dust to be causally related to sinonasal cancer in a dose-dependent manner, especially adenocarcinoma (see Section on Epidemiology and Occupational Risk Factors). Leather dust is now considered as a human carcinogen by IARC [4, 14], but there is no firm knowledge of the duration and the intensity of the exposure needed to cause sinonasal cancer.

Tobacco Smoking

Smoking is still very prevalent worldwide and has been a common lifestyle-related exposure for at least subgroups of individuals for several decades [80, 81, 88]. Several studies have analyzed exposure-response relations for sinonasal cancer in terms of intensity (cigarettes/day), duration, or pack-years, and most have revealed a positive exposure-response relationship. No clear threshold limit for intensity or duration has been identified. In general, the associations to cancer of the nose and paranasal sinuses were considerably lower than for wood dust exposure [4, 88].

IARC has also evaluated the effect of involuntary smoking, the type of tobacco smoke exposure related to exposure at work, on the development of sinonasal cancer, and the evaluation concluded that the literature was sparse and with conflicting results [4, 88].

Pathology

General

The WHO Classification of Tumours [6] lists a total of 63 primary tumor types occurring in the nasal cavity and paranasal sinuses, 12 of which are malignant epithelial types of tumor (Table 7.4). The other tumor categories are benign epithelial tumors, soft tissue tumors, tumors of the bone and cartilage, hematolymphoid tumors, neuroectodermal tumors, and germ cell tumors. In addition to a linkage to occupational exposure, some sinonasal tumors are associated with viruses [6]. The lymphoepithelial carcinoma is strongly associated with EBV, and HPV can be identified in some cases of squamous cell carcinomas [6].

The most common location of the sinonasal carcinomas is in the maxillary sinus (55–60 %), 19–35 % occur in the nasal cavity, 9–15 % in the ethmoid sinus, and only 1 % in the sphenoid and frontal sinuses [93, 94] (Fig. 7.1). A staging (T) classification for maxillary and ethmoid carcinomas has been adopted [95]. Occupational exposure is predominantly associated with squamous cell carcinomas and adenocarcinomas (Fig. 7.8) with these two tumor types having somewhat different etiologies as indicated by epidemiological studies [2, 4, 6] (see Section on Epidemiology and Occupational Risk Factors).

In several studies, squamous cell carcinomas have constituted approximately 35–70 % of the malignancies in the sinonasal region [6, 94, 96] (see Section on Epidemiology and Occupational Risk Factors). Squamous cell carcinoma of the vestibule is considered to be a carcinoma of the skin rather than carcinoma of the sinonasal mucous epithelium. Adenocarcinomas account for a variable proportion of sinonasal cancers, varying

Table 7.4 Malignant epithelial tumors of the nasal cavity and paranasal sinuses

Histological type	ICD-O	Histological type	ICD-O
Squamous cell carcinoma	8070/3	**Salivary gland-type carcinomas**	
Verrucous carcinoma	8051/3	Adenoid cystic carcinoma	8200/3
Papillary squamous cell carcinoma	8052/3	Acinic cell carcinoma	8550/3
Basaloid squamous cell carcinoma	8083/3	Mucoepidermoid carcinoma	8430/3
Spindle cell carcinoma	8074/3	Epithelial-myoepithelial carcinoma	8562/3
Adenosquamous carcinoma	8560/3	Clear cell carcinoma NOS	8310/3
Acantholytic squamous cell carcinoma	8075/3	Myoepithelial carcinoma	8982/3
		Carcinoma ex pleomorphic adenoma	8941/3
		Polymorphous low-grade adenocarcinoma	8525/3
Adenocarcinomas		**Neuroendocrine tumors**	
Intestinal-type adenocarcinoma	8144/3	Typical carcinoid	8240/3
Non-intestinal-type adenocarcinoma	8140/3	Atypical carcinoid	8249/3
Lymphoepithelial carcinoma	8082/3	Small cell carcinoma, neuroendocrine type	8041/3
Sinonasal undifferentiated carcinoma	8020/3		

Adapted from WHO Classification of Tumours [6]

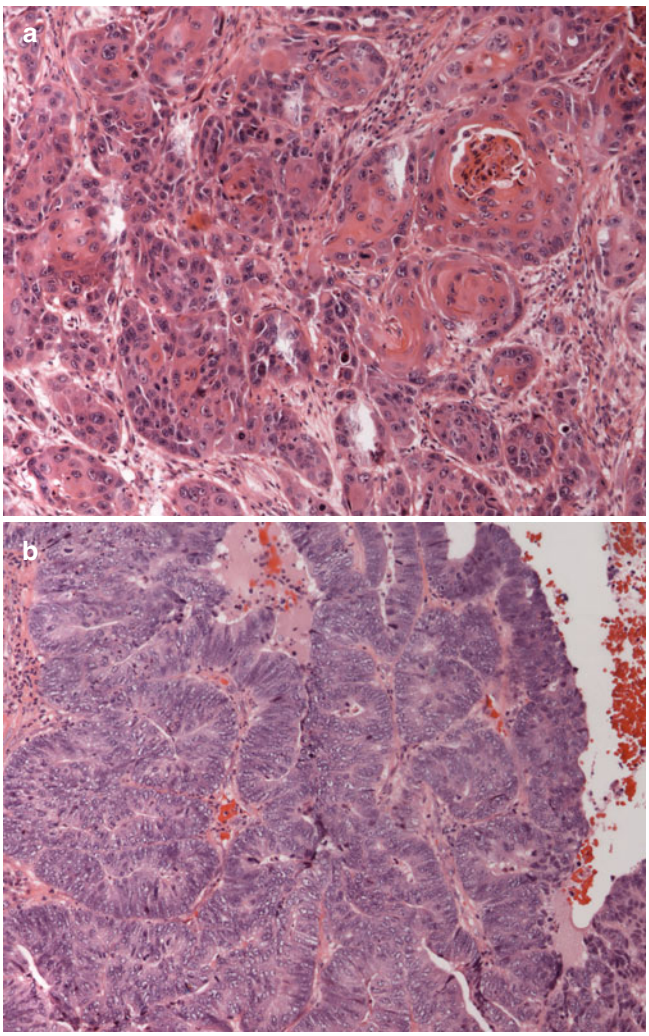


Fig. 7.8 Two main histological types of sinonasal cancer. Squamous cell carcinoma (**a**) and adenocarcinoma (intestinal type) (**b**) are illustrated hematoxylin-eosin staining; 20× objective used

from 10 to 50 %, depending on the country [6] (see Section on Epidemiology and Occupational Risk Factors).

Squamous Cell Carcinoma

Squamous cell carcinomas can be subdivided into distinctive forms including keratinizing, nonkeratinizing, and adenosquamous types (Table 7.4) [6]. An example of a keratinizing squamous cell carcinoma is shown in Fig. 7.8a. The precursor lesions to sinonasal squamous cell carcinomas are poorly known. Sinonasal Schneiderian (inverted) papilloma appears to be a precursor lesion in about 10 % of the cases; the role of squamous metaplasia remains undetermined [6]. There have been no reports describing any specific associations between squamous cell carcinoma subtypes and particular exposures (see Section on Epidemiology and Occupational Risk Factors).

Intestinal-Type Adenocarcinoma

Adenocarcinomas are divided into two groups by WHO, namely, the intestinal-type adenocarcinomas (ITACs) (Figs. 7.8b and 7.9) and the sinonasal non-intestinal type of adenocarcinomas (non-ITACs) [6]. A considerable proportion, 40 % of the sinonasal ITACs, involves the ethmoid sinuses, with the nasal cavities being implicated in 27 % of the cases and the maxillary sinus in 20 % [97, 98]. The distinguishing feature of ITACs is reflected in the name, i.e., they display features of intestinal carcinomas (large intestine or small intestine) morphologically, immunohistochemically, and ultrastructurally. The epidemiological studies on the association between sinonasal cancer and wood dust exposure do not differentiate between adenocarcinoma subtypes. However, the pathology literature associates ITACs with wood dust exposure [6].

Two classifications for ITACs are in use (Table 7.5) [98, 99]. The categories within the classifications are compatible between classifications as shown in the Table 7.5, with the exception that there is no subdivision of mucinous carcinomas in the Barnes classification [6, 98]. In this article, the Barnes classification will be used. Immunohistochemistry for cytokeratin has been routinely used to identify the origin of a tumor; immunostaining for cytokeratin 20 is typically positive in the intestinal epithelium and carcinomas, while cytokeratin 7 is positive in tumors of the respiratory tract. ITACs are usually positive for cytokeratin 20 and less so for cytokeratin 7 (Fig. 7.9b, c). The CDX-2 homeobox gene plays a crucial role in the differentiation of the intestine. CDX-2 is commonly expressed in ITACs (Fig. 7.9d) [100–102].

Precursor lesions to ITACs are of special interest as they could represent a marker which could be used in the early detection and prevention of malignancies in exposed workers. This question has been addressed in three articles [103–105] to some extent. In a cytological study, cuboidal cell metaplasia and goblet cell hyperplasia were observed in wood dust-exposed workers [104]. Histological metaplastic changes have also been associated with wood dust exposure [105]. In a third study examining mucosal lesions adjacent to ITACs, metaplastic and mild dysplastic lesions were found adjacent to the tumors [103]. However, the changes were present whether the patients had been exposed to wood dust or not. Interestingly, in the two later studies, wood dust was associated with increased expression of p53 tumor suppressor protein in epithelial nonmalignant cells.

Non-intestinal-Type Adenocarcinoma

The first description on low-grade sinonasal adenocarcinomas emerged in a study published in early 1980s [106]. In that study, high-grade tumors were also included, and the article

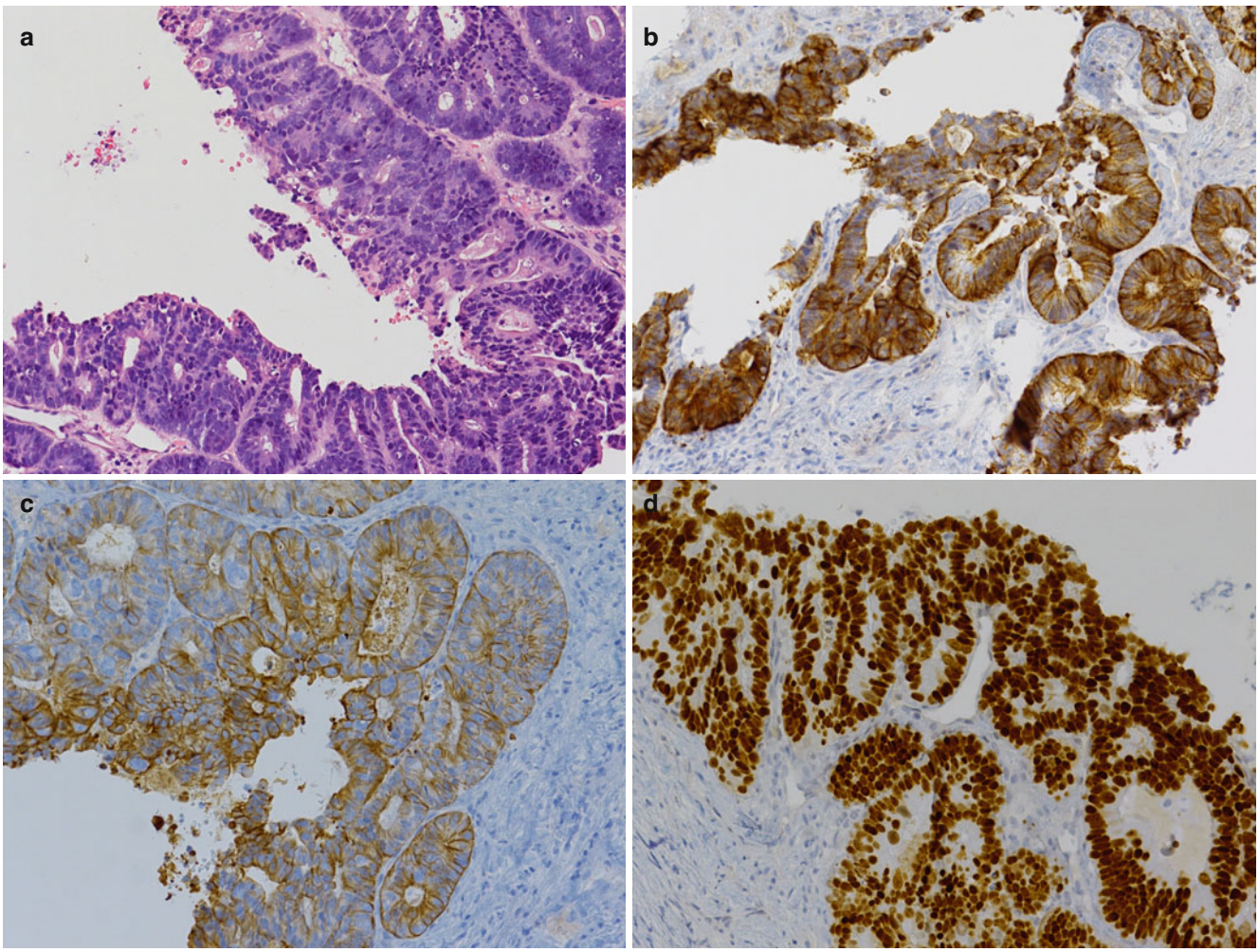


Fig. 7.9 Sinonasal intestinal-type adenocarcinoma (*ITAC*) of colonic type (**a**) hematoxylin-eosin staining, with immunochemistry (**b–d**). Immunohistochemically ITACs are positive for various epithelial markers: positivity for CK20 (**b**), CK7 (**c**), and CDX-2 (**d**) is shown (20× objective used) (Courtesy of Prof. Ilmo Leivo, MD PhD, Dept. Pathology, University of Turku, Turku, Finland)

Table 7.5 Classifications of the sinonasal intestinal-type adenocarcinoma (ITAC). Three-year survival rates from Kleinsasser and Schroeder are also indicated

Barnes and WHO Classification of Tumours [6, 98]	Kleinsasser and Schroeder [99]	3-year cumulative survival [99] (%)
Papillary type	PTCC-I	82
Colonic type	PTCC-II	54
Solid type	PTCC-III	36
Mucinous type	Alveolar goblet	46
	Signet-ring	0
Mixed	Transitional	71

PTCC papillary tubular cylinder cell, *I* well differentiated, *II* moderately differentiated, *III* poorly differentiated

noted that 12 of the 27 high-grade tumors displayed a striking similarity to moderately differentiated colonic adenocarcinomas, with the remainder presumably not exhibiting this feature [106]. The current WHO classification (Table 7.4) recognizes sinonasal non-ITAC tumors as a separate entity which is further divided into low- and high-grade subtypes [5, 6].

The low-grade type is relatively distinctive with numerous fairly uniform small glands or acini arranged in a back-to-back or a coalescent pattern with little or no intervening stroma. The glands are lined by a single layer of various types of fairly bland cells or sometimes by a double layer where the second layer consists of basal/myoepithelial cells. The prognosis of the low-grade non-ITACs is generally good. The high-grade non-ITAC can be described as a high-grade adenocarcinoma with a predominately solid pattern of growth, although glandular or papillary

patterns can be detected [6]. The differential diagnosis between the high-grade non-ITACs and other high-grade adenocarcinomas is challenging [107]. It has been proposed that they form a heterogeneous group of tumors of multiple unknown entities or variants of known entities [107]. The survival rate of subjects with high-grade non-ITACs is dismal; 3-year survival is a mere 20 %.

There is rather limited information available about the immunohistochemistry of non-ITAC tumors. The study of Franchi and coworkers [100] included four low-grade non-ITACs, which in contrast to ITACs did not stain with CDX2 or cytokeratin 20 but stained with cytokeratin 7. In a recent article, high-grade non-ITACS were shown to lack staining for CDX2 and, for the most part, also for cytokeratin 20, whereas cytokeratin 7 staining was relatively common [107].

As mentioned above the epidemiological studies do not differentiate between adenocarcinoma subtypes. In addition, non-ITACs are considered to be rarer than ITACs [107], although there are apparently no studies specifically reporting on the relative frequency of ITACs and non-ITACs. Thus, there is no direct information evaluating the association of non-ITACs to various exposures (see Section on Epidemiology and Occupational Risk Factors).

Summary and Conclusions

The sinonasal area is composed of the centrally located paired nasal cavities surrounded by paired paranasal sinuses (maxillary, frontal, ethmoidal, and sphenoidal). Sinonasal carcinomas are rare. The most important locations of the tumors associated with occupational exposures are the nasal cavity, maxillary sinus, and ethmoid sinus. The two histological types predominantly associated with occupational exposure are adenocarcinoma and squamous cell carcinoma. Squamous cell carcinomas have seven different subtypes; no association has been reported between occupational exposures and the presence of a particular subtype. Adenocarcinomas are divided into intestinal-type adenocarcinomas and non-intestinal-type adenocarcinomas, with some 40 % of the former located in ethmoidal sinuses. The striking feature of the sinonasal ITACs is their close resemblance to adenocarcinomas of the intestine, with similar positivity for various immunohistochemical markers. ITACs presumably represent the majority of sinonasal adenocarcinomas.

There is a strong epidemiological association between wood dust exposure and adenocarcinomas. There is, however, no direct epidemiological information about the association of different adenocarcinoma subtypes to wood dust exposure. In the pathology literature, ITACs are often considered as being associated with occupational exposure to wood dust.

Mechanisms of Carcinogenesis

Relatively little is known about the pathomechanisms involved in the development of sinonasal cancer. However, there is mechanistic information obtained from experimental settings as well as from human biomarker studies on toxicity, inflammatory effects, genotoxicity, and carcinogenicity of wood dust, wood extracts, or chemical constituents of wood. In addition, there are a few studies that have investigated wood dust-related sinonasal cancer in humans providing further molecular and mechanistic data [2, 4].

The mechanisms involved in cancer development have not been investigated to any significant extent for occupational exposures other than wood dust considered to be associated with an increased risk of sinonasal cancer, e.g., exposure to leather dust or textile dusts. However, somewhat more is known about other exposures such as tobacco smoke, nickel and chromium compounds, and formaldehyde, all with evidence for genotoxicity and mechanisms involved [4, 63, 81, 88, 108].

The primary focus of this section will be on reviewing and discussing the data available for cancer mechanisms likely to be involved in the sinonasal cancer related to wood dust exposure. A brief summary of some of the experimental and human evidence published is presented in Table 7.6.

Toxicological Features of Wood Dust Exposure

The chemical composition of wood largely varies according to the species of tree. The wood species used in wood-related industries vary not only from region to region but also by type of product; both hardwoods (gymnosperms, i.e., conifers) and softwoods (angiosperms, i.e., deciduous trees) are widely used. Wood dust, which is generated in processing of wood, is a complex mixture of substances, composed mainly of cellulose (approximately 40–50 %), polyoses and lignin, and a large and variable number of compounds of lower relative molecular masses. The last set of compounds include nonpolar organic extractives (fatty acids, resin acids, waxes, alcohols, terpenes, sterols, steryl esters, and glycerides), polar extractives (tannins, flavonoids, quinones, and lignans), as well as water-soluble extractives. With regard to the inorganic compounds in wood, chromium compounds have been identified although they primarily appear to be present in wood treated with preservatives or stains [2, 4].

A number of biologically active compounds has been identified in both hardwood and softwood species. For example, substances with biological activity belonging to many organic groups have been characterized in wood. These include terpenes, phenols, tannins, flavonoids, quinones, lignans, and stilbenes; wood also contains some alkaloids and

furocoumarins [2]. The various mechanisms through which wood dust may exert its biological activity are not well characterized but are likely to be complex [2, 4].

Some of the compounds identified in wood have been found to exert cellular toxicity (for instance, abeitic acid, plicatic acid) or mutagenicity (Δ^3-carene, quercetin). Furthermore, quinones, present primarily in hardwood species but some also in softwood [2], are recognized as redox-active chemicals that can generate radical oxygen species (ROS) and, ultimately, evoke a toxic response [130]. Wood, nevertheless, also contains compounds that may counteract such toxic effects (e.g., flavonoids and phenolic compounds with antioxidant capacity) [2]. Further adding to the complexity, some compounds or groups of compounds found in wood may exhibit both types of activities, depending on the chemical structure or

Table 7.6 Summary of various molecular mechanisms suggested to be involved in wood dust-related sinonasal carcinogenesis

Mechanism studied/aim	Assay/test system	Exposure/treatment/work environment	Main findings	Reference
Carcinogenicity in animals	Rodent carcinogenicity studies (rats; hamsters; mice)	Beech wood dust by inhalation or intratracheal injection Beech dust extract (solvent) by skin application Oakwood dust (with or without wood preservatives) by inhalation	Inconsistent or inconclusive results from the small number of studies carried out	Reviewed in IARC [2, 4]
Mutagenicity and DNA damage in vitro	Bacterial mutagenicity (*Salmonella*) assay	Solvent or water extracts of beech, oak, and some other woods	Weak mutagenicity for a number of wood species Consistent positive mutagenicity for beech wood extract	Reviewed in detail in IARC [2]
	Comet assay for DNA damage in human cell line	Dusts from beech, birch, oak, pine, spruce, teak, and oak-coated MDF	DNA damage detected for hardwood (beech, teak) and softwood (pine) species, and for oak-coated MDF	Bornholdt et al. [109]
Inflammatory response in experimental systems	Cytokine and chemokine expression (mRNA, protein) in rodent macrophages in vitro	Dusts from hardwood (oak, beech, birch, teak) and softwood (pine, spruce), and oak-coated MDF	Increased expression of various proinflammatory mediators (cytokines and chemokines) following exposure to hardwood and softwood dusts. Generation of ROS by rat alveolar macrophages in response to pine dust	Long et al. [110], Määttä et al. [111, 112], Bornholdt et al. [109]
	A nonallergic in vivo mouse model for pulmonary inflammation	Repeated intranasal instillation of fine (>99 % of particles ≤5 μm) dusts from oak and birch	Elicitation of proinflammatory response (several cytokines and chemokines) by oak and birch dusts in the lungs of the exposed mice	Määttä et al. [113]
	An allergic (ovalbumin sensitized) in vivo mouse model for pulmonary inflammation	Repeated intranasal instillation of fine (>99 % of particles ≤5 μm) dust from oak	Modulation of pulmonary inflammation assessed by cytokine and chemokine expressions (and of asthmatic response) in allergic mice compared to nonallergic mice)	Määttä et al. [114]
Genotoxicity in exposed workers	DNA damage in peripheral blood lymphocytes or WBC DNA by alkaline single-strand breakage or the Comet assay	Wooden furniture manufacturing plant	Elevated DNA damage in exposed versus control workers (both smokers and nonsmokers)	Palus et al. [115], Palus et al. [116]
	Micronuclei in buccal epithelial cells	Furniture workers from a woodworking shop	Increased frequency of micronuclei and other nuclear changes in woodworkers versus controls (both smokers and nonsmokers)	Çelik and Kanik [117]

Table 7.6 (continued)

Mechanism studied/aim	Assay/test system	Exposure/treatment/work environment	Main findings	Reference
Genetic and epigenetic changes in human sinonasal cancer tissue	Various genetic alterations (e.g., chromosomal imbalance [copy number changes], LOH, gene amplification)[a]	Tumor tissue from human SNC Mainly AD, with ITACs examined in many studies	Relatively high frequencies of many of the various types of genetic alterations examined; changes in gene expression	Several studies (reviewed in IARC [4]. E.g., Perrone et al. [131], Korinth et al. [132], Llorente et al. [122], Franchi et al. [133], Perez-Escuredo et al. [135]
	Mutations in *KRAS* gene[a]	Tumor tissue from human SNC (*n* cases = 28 AD). Data available on occupational wood dust and leather dust exposures	*KRAS* mutations observed in 14 % of AD cases, and 9 % of the ITAC cases. A few mutation positive AD cases with occupational exposure to wood dust. Certain types of mutations seen	Saber et al. [130]
		Tumor tissue from human SNC (*n* = 20 ITACs)		Frattini et al. [124]
		Tumor tissue from human SNC (*n* cases = 58 AD, 109 SQ, 7 other carcinomas) from incident cases collected in three European countries. Data available on wood dust and other occupational exposures		Bornholdt et al. [125]
	Mutations in *TP53* tumor suppressor gene[a]	Tumor tissue from human SNC (almost exclusively AD studied). Some studies with tumor tissue from cases with ITAC histology, from compensated cases, or from cases without exposure details	*TP53* mutations found with variable frequencies, ranging between appr. 20 and 60 %	Several studies; e.g., Perrone et al. [118], Perez-Escuredo et al. [122]
		Tumor tissue from human SNC (*n* = 122 AD, 213 SQ, 23 other carcinomas) from incident cases collected in three European countries. Data available on wood dust and other occupational exposures	In the largest single study, high frequency (77 %) of *TP53* mutations in SNC. Risk of mutation increased in association with wood dust exposure at work. Increased risk of mutation associated with long duration of occupational exposure or cumulative level of wood dust exposure	Holmila et al. [127, 128]
	Epigenetic changes[a]	Tumor tissue from human SNC (*n* = 21 ITACs)	High frequency of promoter hypermethylation in tumor suppressor genes *p14ARF* and *p16INK4a*	Perrone et al. [118]
		Inverted sinonasal papillomas (*n* cases = 7); a panel of 35 genes studied	Suggestive data for aberrant methylation	Stephen et al. [145]

WBC white blood cells, *MDF* medium-density fiberboard, *SNC* sinonasal cancer, *AD* adenocarcinoma, *SQ* squamous cell carcinoma, *ITAC* intestinal-type adenocarcinoma, *LOH* loss of heterozygosity
[a]See text for more detail

metabolism in human tissues. One such example is quercetin, as mentioned above, classified as one of the mutagenic compounds [2] but also as a flavonoid known to function as a dietary antioxidant [131].

An essential characteristic of wood dust, in common with many other exposures with a known or putative capacity to increase risk of sinonasal cancer (e.g., leather dust, tobacco smoking, textile dust, welding fumes containing nickel or

chromium; see Sections on Epidemiology and Occupational Risk Factors and Exposure Characterization), is that, in addition to a multitude of various chemical substances, it also contains particulate matter [2]. In wood dust, concentrations and types of particles present in the dust generated largely depend on the type of wood being processed and the methods used in the processing (sawing, sanding, etc.) [2, 4].

Related to its complex nature, wood dust exposure may exert human toxicity at many levels, e.g., through affecting particle deposition in and clearance from the upper respiratory tract. There are many characteristics such as breathing patterns, airflow, and airway epithelium condition of which are known to influence particle deposition in the respiratory tract [4, 132, 133]. Furthermore, there are a multitude of various cellular and molecular mechanisms involved in particle-induced toxicity, including the capacity to evoke DNA damage due to the generation of radical oxygen species (primary genotoxicity) or as a consequence of the inflammatory response elicited (secondary genotoxicity), known or at least suspected to occur in humans [4, 132–134]. It is likely that several of those contribute to wood dust-related toxicity in the epithelia of the nose, sinuses, and other parts of the respiratory tract. It has been suggested that impaired clearance of wood dust leads to prolonged exposure of the upper respiratory epithelium [3, 4].

Finally, in occupational environments where wood is being processed, there may be exposure to other chemicals or agents, such as glues, lacquers, paints, solvents, formaldehyde, wood preservatives, and fungal spores [2, 4].

Animal Carcinogenicity Studies on Wood Dust

Studies with experimental animals exposed to wood dust have so far provided little clarification for processes involved in wood dust-related sinonasal carcinogenesis. The few published studies on rodents (rats or hamsters), conducted mainly in the 1980s and 1990s, utilized inhalation or intratracheal injection as the routes of exposure to investigate carcinogenicity of beech or oakwood dusts. The results obtained from such studies have largely been negative or inconclusive [2, 4], at least partially due to many shortcomings in design and reporting [2, 4]. In addition to testing wood dusts as such in the experiments, the mutagenic fraction of beech dust solvent extract has also been studied for skin cancer (exposure by skin application) in mice. Similarly to the carcinogenicity studies on wood dust, the results reported for beech solvent extracts were somewhat variable [2, 4].

A more recent study on rats investigated the carcinogenicity of oakwood dust administered by inhalation, and in addition to pure oakwood dust, the carcinogenic effects of dust from oakwood treated with preservatives or a chromium-containing stain were examined. The results obtained were, however, inconclusive to some extent [135].

In the most recent evaluation by IARC [4], the evidence for the carcinogenicity of wood dust in experimental animals remained inadequate as few studies additional to those evaluated in the earlier monograph [2] had been published in the interim.

DNA Damage Induced by Wood Dust *In Vitro*

DNA damage following exposure to wood dust has been investigated in a few genotoxicity studies, with some positive results reported. Early work pointed to mainly weak bacterial mutagenicity for solvent or water extracts of oak, ash, obeche, walnut, and limba wood (also particle board) [2]. Consistent mutagenicity in the *Salmonella* assay was observed for beech wood extract (reviewed in detail in [2]). Wood extracts have also been studied in some other experimental systems for their ability to damage DNA, with positive findings [2, 4].

Apart from wood extracts, also dusts from hardwood and softwood species have been studied for their ability to cause DNA damage. Fine dusts from six commonly used wood species, including beech, birch, oak, teak, pine, spruce, plus dust from oak-coated medium-density fiberboard (MDF), were studied for DNA damage in a human lung cell line in a widely used genotoxicity assay (the Comet assay) [109]. The study found that hardwood (beech, teak) and softwood (pine) dusts, plus the MDF dust, induced genotoxicity. Importantly, it was reported that the DNA damage observed was not secondary to the cytokine response [109], pointing to primary genotoxicity.

Inflammatory Response to Wood Dusts Exposure in Experimental Studies

Recent studies have indicated that exposure to wood dust, both hardwood and softwood dusts, has the capacity to trigger a proinflammatory process by modulating the expression of macrophage-derived cytokines and chemokines. A series of *in vitro* studies revealed that fine dusts from hardwood species (oak, beech, birch, and teak) and softwood species (pine and spruce) modulate inflammatory response in rat alveolar macrophages [110], in a mouse macrophage cell line [111, 112], and in a human lung cell line [109]. In these *in vitro* experiments, hardwoods and softwoods have induced the expression of several cytokines (e.g., TNF-α, IL-6, and IL-8) and chemokines [109–112], with some quantitative differences being observed between some of the species [111, 112]. It is likely that the induction of an inflammatory response by wood dusts involves at least in part mechanisms mediated by ROS; reactive nitrogen species are also known to be generated in the inflammatory process [109, 110, 136]. As mentioned above, the timing of DNA damage induction

in human A549 lung cells by hardwood and softwood dusts indicates that inflammatory response is not necessary for genotoxicity of wood dust [109].

The inflammatory effects of wood dust in the lungs were further studied utilizing *in vivo* mouse models. Repeated intranasal instillation of fine dust (particle size of ≤5 μm for >99 % of the particles) from two hardwood species, oak and birch, induced the influx of inflammatory cells (macrophages, neutrophils, lymphocytes, and eosinophils) into the lungs of nonallergic mice [113]. An enhancement of lymphocytes and neutrophils was observed after oak dust exposure, whereas a greater infiltration of eosinophils followed exposure to birch dust. The infiltration of inflammatory cells was associated with an increased level of expression of several cytokines, chemokines, and chemokine receptors in the lung tissue. Overall, oak dust appeared to be a more potent inducer of these inflammatory mediators than birch dust [113]. Finally, findings from an allergic (ovalbumin sensitized) *in vivo* mouse model have indicated that repeated airway exposure to fine oak dust can modulate pulmonary inflammation (and also asthmatic response) [114].

Inflammation has also been postulated to play a role in the development of sinonasal cancer in humans [2, 120]. Recently, increased expression of COX-2, an enzyme involved in prostaglandin synthesis and upregulated by many inflammatory factors, was described in sinonasal adenocarcinoma [137]. COX-2 expression showed a significant association to occupational wood dust exposure, whereas tobacco smoking was not linked with COX-2 expression [137].

Genotoxicity in Wood Dust-Exposed Workers

There are a limited number of studies that have investigated genomic damage in workers occupationally exposed to wood dust. The level of DNA damage (DNA single-strand breaks) in peripheral blood lymphocytes was about twice as high among wooden furniture workers who were smokers, when compared to nonexposed smoking controls [115]. Further, the study also observed significant induction of DNA repair in the exposed workers, both smokers and nonsmokers, working in a wooden furniture plant in Poland [115]. Another study by the same group assessed DNA damage in white blood cells (WBC) from another group of workers from the same wooden furniture manufacture plant. Increased levels of DNA damage were detected by the Comet assay in WBC of these woodworkers, as compared to controls, in both smokers and nonsmokers [116]. The two studies indicated that the elevated DNA damage reflected the genotoxic effects of wood dust exposure; however, the possibility that they may have been at least partially related to other exposures present in the work environment of furniture making could not be totally ruled out [115, 116].

A more recent study observed significantly higher frequencies of micronuclei and other nuclear changes in buccal mucosa cells of furniture workers exposed to high concentrations of mixed hardwood and softwood dust in a woodworking shop, as compared to controls. Smokers had higher micronucleus frequencies in both groups, with the wood-dust-exposed smokers exhibiting the highest frequencies [117].

Genetic and Other Alterations in Human Sinonasal Cancer

Studies on the molecular mechanisms involved in human sinonasal cancer, even though somewhat limited in number due to the rare occurrence of the malignancy, demonstrate a variety of genetic and other molecular alterations in sinonasal tumors, as described in more detail in the following section (see also Section on Molecular Markers). Many of these studies have investigated sinonasal cancer cases with occupational exposure to wood dust. However, very few studies have investigated larger series of cancers and provided detailed data on the exposure characteristics [125, 127]. Some of the molecular alterations, the tumor suppressor gene *TP53* mutations in particular, show association to wood dust exposure [127, 128]. In some studies, adenocarcinomas (typically ITACs) from cases occupationally exposed to wood or leather dust have been investigated, with genetic and other molecular alterations being reported [118, 119, 121–124, 126, 138] (see Section on Molecular Markers) for detail).

Other alterations include a reduction of mucociliary transport and neoplastic lesions (epithelial hyperplasia, metaplasia, and dysplasia) proposed to play a role in the development of wood dust-related sinonasal cancer [2, 4]. It is noteworthy that wood dust particulate matter, as well as the chemical constituents present in wood, is believed either to directly participate in such processes or to be able to enhance them [2, 4, 132].

There are also data suggesting that viral factors (HPV or EBV) and some host factors, such as nasal polyps, sinusitis, or rhinitis, may be involved in sinonasal tumorigenesis but the evidence and suggested contributions have remained open [2–4, 132].

Summary and Conclusions

Experimental *in vitro* and *in vivo* studies on wood dust have described a wide variety of adverse biological effects and molecular changes, including cytotoxicity, oxidative DNA damage, genotoxicity, inflammatory response, and increased cell proliferation. It is believed that particulates, chemical substances, and their combinations present in complex mixture exposures, such as wood dust exposure, are the primary players in evoking these harmful effects

likely acting in concert in the biological and molecular pathways leading to development of sinonasal cancer.

There are also reports, although somewhat limited in number, pointing to the occurrence of wood dust-related genotoxic effects in exposed workers, in line with findings of the DNA damaging capacity of wood dusts as reported in various *in vitro* test systems. Studies carried out on human sinonasal cancer, perhaps not as plentiful as they could be if the cancer type were not so rare, have observed multiple genetic and other molecular alterations in the tumor tissue. These findings are also in good agreement with the experimental data and findings from exposed workers.

Collectively, the various sets of data point to a central role for genomic damage, in particular *TP53* mutations, in the development of sinonasal cancer. The frequent occurrence of *TP53* mutations fit well with data from other human cancers which involve regular, long term-exposure to carcinogens, including head and neck cancer. Inflammation is likely to also play a role in the carcinogenesis process. Much less is, however, known about how cancer susceptibility, other host-related factors, or viruses may contribute to tumorigenesis.

Finally, it appears justified to speculate that similar cancer mechanisms as described in the literature for wood dust-related sinonasal cancer may be involved, at least to some extent, in the sinonasal carcinogenesis associated with some other occupational exposures. There is, however, virtually no data available on mechanisms leading to cancer development in association with occupational exposures other than wood dust.

Molecular Markers

Literature on molecular markers in human sinonasal cancer is limited, as partially summarized and discussed in the previous section (see Section on Mechanisms of Carcinogenesis). Overall, the published findings have mainly been based on a relatively small number of cases, mostly involving adenocarcinomas. The studies published have, for example, described high frequencies of DNA copy number changes as detected by comparative genomic hybridization [119, 129, 139], while the mutation rates reported for the *KRAS* gene [123–126, 140–142] and the *TP53* tumor suppressor gene [118, 122, 127, 143, 144] in general have been lower or variable. Furthermore, a few studies have indicated that epigenetic changes (mainly promoter hypermethylation of certain tumor suppressor genes) play a role in sinonasal cancer as in many other types of human cancer [118, 145].

TP53 and *KRAS* Gene Mutations in Human Sinonasal Cancer

Most of the studies exploring the tumor suppressor gene *TP53* mutations, a hallmark genetic change in human cancer [146, 147] or investigating accumulation of the p53 protein in the cell have focused on intestinal-type adenocarcinomas, and there have been limited numbers of cases. In general, the accumulation of p53 often reflects a *TP53* mutation, but other reasons for p53 accumulation are also known; furthermore, not all mutations induce nuclear accumulation of p53 [148, 149]. The results reported for sinonasal cancer indicate that p53 accumulation is a common feature in the adenocarcinomas, with immunopositivity ranging between 20 and 100 % [118, 122, 141, 142, 150, 151]. In the studies analyzing the *TP53* mutations, a variable occurrence has been reported (18–60 %) [118, 122, 141, 143, 144]. *TP53* gene mutations were investigated in a large series of sinonasal cancers collected in three European countries (Denmark, Finland, and France; $n = 358$ cases), with both adenocarcinoma and squamous cell carcinoma histological types being included [127]. All histological tumor diagnoses were reviewed in consensus by a pathology panel, and data on occupational exposure to wood dust were obtained by interview and assessed by industrial hygienists [127]. The study detected a significantly elevated risk of adenocarcinoma histology as opposed to squamous cell carcinoma among the wood dust exposed cases. Furthermore, an overall high frequency of *TP53* mutations (77 %) was found among all sinonasal cancers. The risk of *TP53* mutations was higher among the adenocarcinomas as compared to the squamous cell carcinomas, but there was no difference between ITACs (86 %, 76 of 88 studied) and non-ITACs (85 %, 29 of 34 studied) [127].

The multicenter study further found that *TP53* mutations increased along with increased duration of occupational wood dust exposure, with a fivefold increased risk seen in association with ≥24 years of exposure (OR 5.1; 95 % CI 1.5–17.1), in comparison to nonexposed cases [127]. In addition, an elevated risk of mutation was significantly related to an average level of wood dust exposure of >2 mg/m^3 (OR 3.6, 95 % CI 1.2–10.8) and to a cumulative level of exposure of 30 mg/m^3 × years (OR 3.5, 95 % CI 1.2–10.7). Neither tobacco smoking nor formaldehyde exposure affected these findings significantly [127]. In a further investigation, some differences between the wood dust-exposed and the nonexposed cases in the *TP53* mutation profiles were discovered (Fig. 7.10) [128].

In a series of 44 sinonasal ITACs from Spain, mostly from cases occupationally exposed to wood dust, *TP53* mutations were also commonly detected (41 %), and they were exclusively found in cases with occupational wood dust exposure [122]. From smokers, only 20 % exhibited *TP53* mutation. The profile of mutations discovered in the study exhibited characteristics supporting wood dust-related etiology [122]. Based on the mutation profiles observed (50 % G to A transitions, almost exclusively detected in nonsmokers; all G to T transversions detected in smokers), the authors proposed that reactive nitrogen species generated via chronic inflammatory

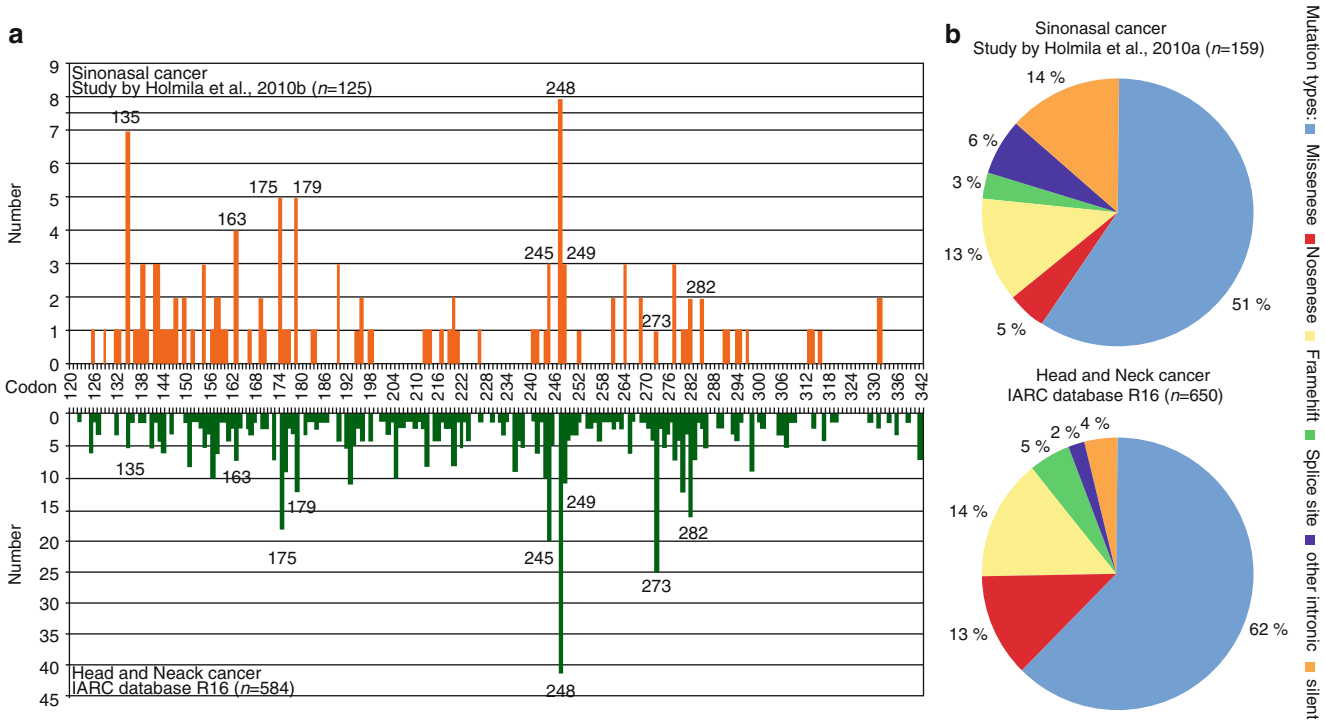


Fig. 7.10 Profile of tumor suppressor gene TP53 mutations in sinonasal cancer and in comparison to head and neck cancer. (**a**) Mutations presented by location (codon number in TP53 gene) in a series of sinonasal cancers studied in a European multicenter study by Holmila et al. [127] (*top*) as compared to similar data for head and neck cancers in IARC mutation database (IARC TP53 Mutation Database, version R16, 2012) (*bottom*). (**b**) Types of mutations detected in the multicenter study by Holmila et al. [128] (*top*) as compared to those included in the IARC mutation database (IARC TP53 Mutation Database, version R16, 2012) (*bottom*). The data for head and neck cancer from IARC database do not include sinonasal cancer cases. Numbers of cancer cases included in the analyses and the various classes of mutations are indicated

process contributed to the *TP53* gene mutagenesis in the exposed cases [122].

Initially, also *KRAS* and *HRAS* mutations were reported to be relatively frequent in sinonasal cancer, with implications for histogenetic and prognostic significance [118, 123, 124, 140–142]. In the large multicenter study of Bornholdt and coworkers [125], the frequency of *KRAS* mutations in adenocarcinoma histology (13 %) was similar to that found in earlier studies. Furthermore, the *KRAS* mutations were found almost exclusively in adenocarcinomas (of which two were ITACs) [125]. The most common type of mutations was G to A substitution; this was also the case among the few wood dust exposed cases [125]. A case series of sinonasal cancers from Spain (57 squamous cell carcinomas and 58 ITACs) were examined for *KRAS* and *BRAF* gene mutations. From these, seven cases (12 %), all ITACs and woodworkers, were positive for *KRAS* mutations but no *BRAF* gene mutations were found [126].

Other Genetic Features

In addition to mutations found in the central cancer-related genes, chromosomal imbalances, loss of heterozygosity (i.e., loss of one of the two alleles or the target gene region due to genetic alterations), gene amplifications, as well as altered gene expression have been discovered in human sinonasal cancer (reviewed in [2, 4, 120]). The pattern of chromosomal abnormalities found in sinonasal adenocarcinomas appears to be different from that of the other tumors of the head and neck region but displays similarities with gastric and colonic adenocarcinomas [121]. On the other hand, DNA copy number analyses and microarray comparative genome hybridization in sinonasal squamous cell carcinoma have shown gene amplifications and similarities with genetic changes found in head and neck squamous cell carcinomas (HNSCC) [152, 153]. In ITACs, comparative genomic hybridization analysis conducted on a limited number of tumors suggests copy number gains and loss throughout the whole genome [120]. In a study reporting on a series of almost 100 ITACs from Spain, *EGFR* (epidermal growth factor receptor) gene copy number changes were detected in 46 % of the cases [138]. All cases were, nevertheless, negative for *EGFR* mutations, while 31 % were positive in immunohistochemistry for EGFR expression [138].

It is well known that even though environmental factors predominantly contribute to the development of most common cancers, heritable factors are also involved [154]. In addition to somatic alterations as reviewed above for sinonasal cancer, genetic susceptibility plays a role in tumorigenesis

[155]. However, only very limited data are available regarding genetic susceptibility in sinonasal cancer. A study of 30 cases of ethmoidal ITAC and 79 noncancer controls suggested an overrepresentation of a certain *CYP1A1* genotype (heterozygotes for codon 46 Thr/Asn) as well as of the combination of this genotype and the deletion (null) genotype of *GSTM1* gene among ITAC cases [156].

Other Molecular and Cellular Changes

The molecular alterations reported for sinonasal cancer have included changes in protein expression as mentioned earlier (see Section on Pathology). Expression of Annexin A1, a member of the annexin family known to be implicated in a broad range of cellular processes, e.g., maintenance of the cytoskeleton, extracellular matrix integrity, tissue growth, and differentiation, was found to be frequently lost in all types of ITACs compared to nonmalignant tissue [157]. The expression of another member of the annexin family, Annexin A2, was also reduced in ITACs; however, this loss was restricted to the less differentiated histopathological types [157]. Another study examined 62 cases of ITACs (most with a history of employment in leather or wood industry) using tissue microarray [158]. Expression of p53 and p16 was the most common alteration observed in ITACs, with mucinous ITACs exhibiting a molecular profile distinct from that of non-mucinous ITACs [158]. Earlier, a difference in the expression pattern of the cell cycle regulators p21, p27, and p53 has been identified between adenocarcinomas and other tumor types of paranasal sinuses, especially the adenoid cystic carcinomas [152].

The expression of COX-2, an enzyme involved in inflammation, has been found to be associated with adenocarcinoma type of tumors, wood dust exposure, and nonsmoking [137]. In another study, EGFR expression was increased among ITAC type of tumors from workers exposed to wood dust [159]. Furthermore, profiling of gene expression in sinonasal adenocarcinomas has led to the identification of the two differentially expressed proteins LGALS4 and CLU [160].

Other types of changes include impaired mucociliary clearance and mucosal alterations that have consistently been reported in sinonasal cancer and associated with chronic wood dust exposure [2]. Mucosal alterations include dysplasia and metaplasia of the columnar epithelium and, to a lesser extent, changes in the squamous epithelium [2, 4, 104].

Summary and Conclusions

Sinonasal cancer exhibits an array of molecular changes, such as DNA copy number changes, allelic imbalance or loss of heterozygosity, gene amplifications, epigenetic changes, and altered gene expression, some of which it apparently shares with head and neck cancer. Mutations of the *TP53* gene frequently occur in sinonasal cancer, and *TP53* mutations have been associated with one of the main occupational risk factors, wood dust exposure. *KRAS* mutations also occur but are clearly less frequent compared to *TP53* mutations. Changes in protein expression profile have also been reported. However, since a distinctive feature of sinonasal cancer is its rare occurrence, more data on molecular markers central to this cancer type are likely to accumulate in the future.

Acknowledgements We thank all our colleagues who participated in the research collaboration in connection with the EU 5 FW project WOODRISK (QLK-2000-00573) and afterwards. Dr. Ewen MacDonald, University of Eastern Finland, Kuopio, is thanked for language revision and Ms. Ritva Järnström, Finnish Institute of Occupational Health, Helsinki, for technical assistance.

References

1. International Agency for Research on Cancer (IARC), Curado MP, Edwards B, Shin HR, et al., editors. Cancer incidence in five continents, IX. IARC Scientific Publications No160. Lyon: IARC; 2007. p. v-897.
2. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, Wood dust and formaldehyde, vol. 62. Lyon: IARC; 1995. p. 1–405.
3. Littman AJ, Vaughan TL. Cancers of the nasal cavity and paranasal sinuses. In: Schottenfield D, Fraumeni Jr JF, editors. Cancer epidemiology and prevention. 3rd ed. New York: Oxford University Press; 2006. p. 603–19.
4. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens: arsenic, metals, fibres, and dusts, vol. 100C. Lyon: IARC; 2012. p. v-499.
5. Gnepp DR. Diagnostic surgical pathology of the head and neck. Philadelphia: Saunders Elsevier; 2009.
6. WHO (World Health Oranization). Classification of tumours. Pathology and genetics of head and neck tumours. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. WHO classification of tumours, vol. 9. 3rd ed. Lyon: International Agency for Research on Cancer (IARC); 2005. p. 12–42.
7. International Agency for Research on Cancer (IARC), Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J, editors. Cancer incidence in five continents, VII. IARC Scientific Publications No 143. Lyon: IARC; 1997. p. v-1274.
8. Bhattacharyya N. Cancer of the nasal cavity: survival and factors influencing prognosis. Arch Otolaryngol Head Neck Surg. 2002;128:1079–83.
9. Hansen J, Olsen JH. Survival of Danish cancer patients 1943–1987. Respiratory system. APMIS Suppl. 1993;33:77–98.
10. Ries LAG, Young JL, Keel GE, Eisner MP, Lin YD, Horner M-J, editors. SEER survival monograph: cancer survival among adults: U.S. SEER program, 1988–2001, patient and tumor characteristics. 2007 National Cancer Institute, SEER Program. NIH Pub. No. 07-6215. Bethesda: NIH; 2007.
11. Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R. EUROCARE-4. Survival of cancer patients

diagnosed in 1995–1999. Results and commentary. Eur J Cancer. 2009;45:931–91.
12. Thorup C, Sebbesen L, Dano H, et al. Carcinoma of the nasal cavity and paranasal sinuses in Denmark 1995–2004. Acta Oncol. 2010;49:389–94.
13. Baan R, Grosse Y, Straif K, et al. A review of human carcinogens–Part F: chemical agents and related occupations. Lancet Oncol. 2009;10:1143–4.
14. Straif K, Benbrahim-Tallaa L, Baan R, et al. A review of human carcinogens–Part C: metals, arsenic, dusts, and fibres. Lancet Oncol. 2009;10:453–4.
15. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens: radiation, vol. 100D. Lyon: IARC; 2012. p. v-341.
16. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, Some flame retardants and textile chemicals, and exposure in the manufacturing industry, vol. 48. Lyon: IARC; 1990. p. v-345.
17. Demers PA, Kogevinas M, Boffetta P, et al. Wood dust and sinonasal cancer: pooled reanalysis of twelve case-control studies. Am J Ind Med. 1995;28:151–66.
18. Leclerc A, Luce D, Demers PA, et al. Sinonasal cancer and occupation. Results from the reanalysis of twelve case-control studies. Am J Ind Med. 1997;31:153–65.
19. Luce D, Leclerc A, Begin D, et al. Sinonasal cancer and occupational exposures: a pooled analysis of 12 case-control studies. Cancer Causes Control. 2002;13:147–57.
20. 't Mannetje A, Kogevinas M, Luce D, et al. Sinonasal cancer, occupation, and tobacco smoking in European women and men. Am J Ind Med. 1999;36:101–7.
21. Zheng W, McLaughlin JK, Chow WH, Chien HT, Blot WJ. Risk factors for cancers of the nasal cavity and paranasal sinuses among white men in the United States. Am J Epidemiol. 1993;138: 965–72.
22. Leclerc A, Martinez CM, Gerin M, Luce D, Brugere J. Sinonasal cancer and wood dust exposure: results from a case-control study. Am J Epidemiol. 1994;140:340–9.
23. Luce D, Leclerc A, Morcet JF, et al. Occupational risk factors for sinonasal cancer: a case-control study in France. Am J Ind Med. 1992;21:163–75.
24. Luce D, Gerin M, Leclerc A, Morcet JF, Brugere J, Goldberg M. Sinonasal cancer and occupational exposure to formaldehyde and other substances. Int J Cancer. 1993;53:224–31.
25. Luce D, Gerin M, Morcet JF, Leclerc A. Sinonasal cancer and occupational exposure to textile dust. Am J Ind Med. 1997;32:205–10.
26. Bolm-Audorff U, Vogel C, Woitowitz H. Occupation and smoking as risk factors of nasal and nasopharyngeal cancer. In: Sakurai H, editor. Occupational epidemiology. New York: Elsevier Science Publishers; 1990. p. 71–4.
27. Comba P, Battista G, Belli S, et al. A case-control study of cancer of the nose and paranasal sinuses and occupational exposures. Am J Ind Med. 1992;22:511–20.
28. Comba P, Barbieri PG, Battista G, et al. Cancer of the nose and paranasal sinuses in the metal industry: a case-control study. Br J Ind Med. 1992;49:193–6.
29. Magnani C, Comba P, Ferraris F, Ivaldi C, Meneghin M, Terracini B. A case-control study of carcinomas of the nose and paranasal sinuses in the woolen textile manufacturing industry. Arch Environ Health. 1993;48:94–7.
30. Merler E, Baldasseroni A, Laria R, et al. On the causal association between exposure to leather dust and nasal cancer: further evidence from a case-control study. Br J Ind Med. 1986;43:91–5.
31. Hayes RB, Gerin M, Raatgever JW, de Bruyn A. Wood-related occupations, wood dust exposure, and sinonasal cancer. Am J Epidemiol. 1986;124:569–77.
32. Hayes RB, Raatgever JW, de Bruyn A, Gerin M. Cancer of the nasal cavity and paranasal sinuses, and formaldehyde exposure. Int J Cancer. 1986;37:487–92.
33. Hardell L, Johansson B, Axelson O. Epidemiological study of nasal and nasopharyngeal cancer and their relation to phenoxy acid or chlorophenol exposure. Am J Ind Med. 1982;3:247–57.
34. Brinton LA, Blot WJ, Becker JA, et al. A case-control study of cancers of the nasal cavity and paranasal sinuses. Am J Epidemiol. 1984;119:896–906.
35. Brinton LA, Blot WJ, Fraumeni Jr JF. Nasal cancer in the textile and clothing industries. Br J Ind Med. 1985;42:469–74.
36. Vaughan TL, Davis S. Wood dust exposure and squamous cell cancers of the upper respiratory tract. Am J Epidemiol. 1991;133:560–4.
37. Battista G, Cavallucci F, Comba P, Quercia A, Vindigni C, Sartorelli E. A case-referent study on nasal cancer and exposure to wood dust in the province of Siena, Italy. Scand J Work Environ Health. 1983;9:25–9.
38. d'Errico A, Pasian S, Baratti A, et al. A case-control study on occupational risk factors for sino-nasal cancer. Occup Environ Med. 2009;66:448–55.
39. Elwood JM. Wood exposure and smoking: association with cancer of the nasal cavity and paranasal sinuses in British Columbia. Can Med Assoc J. 1981;124:1573–7.
40. Fukuda K, Shibata A. A case-control study of past history of nasal diseases and maxillary sinus cancer in Hokkaido, Japan. Cancer Res. 1988;48:1651–2.
41. Fukuda K, Kojiro M, Hirano M, Hyams VJ, Heffner D. Predominance of squamous cell carcinoma and rarity of adenocarcinoma of maxillary sinus among Japanese. Kurume Med J. 1989;36:1–6.
42. Hernberg S, Westerholm P, Schultz-Larsen K, et al. Nasal and sinonasal cancer. Connection with occupational exposures in Denmark, Finland and Sweden. Scand J Work Environ Health. 1983;9:315–26.
43. Ng TP. A case-referent study of cancer of the nasal cavity and sinuses in Hong Kong. Int J Epidemiol. 1986;15:171–5.
44. Olsen JH, Jensen SP, Hink M, Faurbo K, Breum NO, Jensen OM. Occupational formaldehyde exposure and increased nasal cancer risk in man. Int J Cancer. 1984;34:639–44.
45. Olsen JH, Jensen OM. Nasal cancer and chlorophenols. Lancet. 1984;2:47–8.
46. Olsen JH, Asnaes S. Formaldehyde and the risk of squamous cell carcinoma of the sinonasal cavities. Br J Ind Med. 1986;43:769–74.
47. Olsen JH. Occupational risks of sinonasal cancer in Denmark. Br J Ind Med. 1988;45:329–35.
48. Pesch B, Pierl CB, Gebel M, et al. Occupational risks for adenocarcinoma of the nasal cavity and paranasal sinuses in the German wood industry. Occup Environ Med. 2008;65:191–6.
49. Roush GC, Meigs JW, Kelly JA, Flannery JT, Burdo H. Sinonasal cancer and occupation: a case-control study. Am J Epidemiol. 1980;111:183–93.
50. Roush GC, Walrath J, Stayner LT, Kaplan SA, Flannery JT, Blair A. Nasopharyngeal cancer, sinonasal cancer, and occupations related to formaldehyde: a case-control study. J Natl Cancer Inst. 1987;79:1221–4.
51. Shimizu H, Hozawa J, Saito H, et al. Chronic sinusitis and woodworking as risk factors for cancer of the maxillary sinus in Northeast Japan. Laryngoscope. 1989;99:58–61.
52. Takasaka T, Kawamoto K, Nakamura K. A case-control study of nasal cancers. An occupational survey. Acta Otolaryngol. 1987;435(Suppl):136–42.
53. Caplan LS, Hall HI, Levine RS, Zhu K. Preventable risk factors for nasal cancer. Ann Epidemiol. 2000;10:186–91.
54. Mirabelli MC, Hoppin JA, Tolbert PE, Herrick RF, Gnepp DR, Brann EA. Occupational exposure to chlorophenol and the risk of

nasal and nasopharyngeal cancers among U.S. men aged 30 to 60. Am J Ind Med. 2000;37:532–41.
55. Zhu K, Levine RS, Brann EA, Hall HI, Caplan LS, Gnepp DR. Case-control study evaluating the homogeneity and heterogeneity of risk factors between sinonasal and nasopharyngeal cancers. Int J Cancer. 2002;99:119–23.
56. Demers PA, Boffetta P, Kogevinas M, et al. Pooled reanalysis of cancer mortality among five cohorts of workers in wood-related industries. Scand J Work Environ Health. 1995;21:179–90.
57. Demers PA, Teschke K, Kennedy SM. What to do about softwood? A review of respiratory effects and recommendations regarding exposure limits. Am J Ind Med. 1997;31:385–98.
58. Acheson ED, Pippard EC, Winter PD. Nasal cancer in the Northamptonshire boot and shoe industry: is it declining? Br J Cancer. 1982;46:940–6.
59. Pippard EC, Acheson ED. The mortality of boot and shoe makers, with special reference to cancer. Scand J Work Environ Health. 1985;11:249–55.
60. Andersen A, Barlow L, Engeland A, Kjaerheim K, Lynge E, Pukkala E. Work-related cancer in the Nordic countries. Scand J Work Environ Health. 1999;25 Suppl 2:1–116.
61. Cecchi F, Buiatti E, Kriebel D, Nastasi L, Santucci M. Adenocarcinoma of the nose and paranasal sinuses in shoemakers and woodworkers in the province of Florence, Italy (1963–77). Br J Ind Med. 1980;37:222–5.
62. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, Chromium, nickel and welding, vol. 49. Lyon: IARC; 1990. p. v-648.
63. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens: chemical agents and related occupations, vol. 100F. Lyon: IARC; 2012. p. v-499.
64. Swenberg JA, Kerns WD, Mitchell RI, Gralla EJ, Pavkov KL. Induction of squamous cell carcinomas of the rat nasal cavity by inhalation exposure to formaldehyde vapor. Cancer Res. 1980;40:3398–402.
65. Bertazzi PA, Pesatori AC, Radice L, Zocchetti C, Vai T. Exposure to formaldehyde and cancer mortality in a cohort of workers producing resins. Scand J Work Environ Health. 1986;12:461–8.
66. Edling C, Jarvholm B, Andersson L, Axelson O. Mortality and cancer incidence among workers in an abrasive manufacturing industry. Br J Ind Med. 1987;44:57–9.
67. Bertazzi PA, Pesatori A, Guercilena S, Consonni D, Zocchetti C. Carcinogenic risk for resin producers exposed to formaldehyde: extension of follow-up. Med Lav. 1989;80:111–22.
68. Andjelkovich DA, Janszen DB, Brown MH, Richardson RB, Miller FJ. Mortality of iron foundry workers: IV. Analysis of a subcohort exposed to formaldehyde. J Occup Environ Med. 1995;37: 826–37.
69. Hansen J, Olsen JH. Formaldehyde and cancer morbidity among male employees in Denmark. Cancer Causes Control. 1995;6:354–60.
70. Hansen J, Olsen JH. Occupational exposure to formaldehyde and risk of cancer. Ugeskr Laeger. 1996;158:4191–4.
71. Coggon D, Harris EC, Poole J, Palmer KT. Extended follow-up of a cohort of British chemical workers exposed to formaldehyde. J Natl Cancer Inst. 2003;95:1608–15.
72. Hauptmann M, Lubin JH, Stewart PA, Hayes RB, Blair A. Mortality from solid cancers among workers in formaldehyde industries. Am J Epidemiol. 2004;159:1117–30.
73. Pinkerton LE, Hein MJ, Stayner LT. Mortality among a cohort of garment workers exposed to formaldehyde: an update. Occup Environ Med. 2004;61:193–200.
74. Walrath J, Fraumeni Jr JF. Mortality patterns among embalmers. Int J Cancer. 1983;31:407–11.
75. Walrath J, Fraumeni Jr JF. Cancer and other causes of death among embalmers. Cancer Res. 1984;44:4638–41.
76. Levine RJ, Andjelkovich DA, Shaw LK. The mortality of Ontario undertakers and a review of formaldehyde-related mortality studies. J Occup Med. 1984;26:740–6.
77. Stroup NE, Blair A, Erikson GE. Brain cancer and other causes of death in anatomists. J Natl Cancer Inst. 1986;77:1217–24.
78. Hayes RB, Blair A, Stewart PA, Herrick RF, Mahar H. Mortality of U.S. embalmers and funeral directors. Am J Ind Med. 1990;18:641–52.
79. Acheson ED, Cowdell RH, Rang EH. Nasal cancer in England and Wales: an occupational survey. Br J Ind Med. 1981;38:218–24.
80. Secretan B, Straif K, Baan R, et al. A review of human carcinogens–Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol. 2009;10:1033–4.
81. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens: personal habits and indoor combustions, vol. 100E. Lyon: IARC; 2012. p. v-579.
82. Sasco AJ, Secretan MB, Straif K. Tobacco smoking and cancer: a brief review of recent epidemiological evidence. Lung Cancer. 2004;45 Suppl 2:S3–9.
83. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens–Part B: biological agents. Lancet Oncol. 1990;10:321–2.
84. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, A review of human carcinogens: biological agents, vol. 100B. Lyon: IARC; 2012. p. v-475.
85. International Agency for Research on Cancer (IARC), Demers PA, Boffetta P, editors. Cancer risk from occupational exposure to wood dust, A pooled analysis of epidemiological studies. IARC Technical report No. 30. Lyon: IARC; 1998. p. i-97.
86. Luippold RS, Mundt KA, Dell LD, Birk T. Low-level hexavalent chromium exposure and rate of mortality among US chromate production employees. J Occup Environ Med. 2005;47:381–5.
87. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, Wood, leather and some associated industries, vol. 25. Lyon: IARC; 1981. p. v-421.
88. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, Tobacco smoke and involuntary smoking, vol. 83. Lyon: IARC; 2004. p. v-1452.
89. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans, Formaldehyde, 2-Butoxyethanol and 1- tert-Butoxypropan-2-ol, vol. 88. Lyon: IARC; 2006. p. v-478.
90. Kauppinen T, Vincent R, Liukkonen T, et al. Occupational exposure to inhalable wood dust in the member states of the European Union. Ann Occup Hyg. 2006;50(6):549–61.
91. Rongo LM, Msamanga GI, Burstyn I, Barten F, Dolmans WM, Heederik D. Exposure to wood dust and endotoxin in small-scale wood industries in Tanzania. J Expo Anal Environ Epidemiol. 2004;14(7):544–50.
92. Scientific Committee group on Occupational Exposure Limits (SCOEL). Wood dust. Luxembourg: European Commission; 2003. SCOEL/INF/576.
93. Roush GC. Epidemiology of cancer of the nose and paranasal sinuses: current concepts. Head Neck Surg. 1979;2:3–11.
94. Robin PE, Powell DJ, Stansbie JM. Carcinoma of the nasal cavity and paranasal sinuses: incidence and presentation of different histological types. Clin Otolaryngol Allied Sci. 1979;4:431–56.
95. Sobin L, Wittekind C, editors. TNM classification of malignant tumours. 6th ed. New York: Wiley; 2002.
96. Muir C, Weiland L. Upper aerodigestive tract cancers. Cancer. 1995;75:147–53.

97. Klintenberg C, Olofsson J, Hellquist H, Sokjer H. Adenocarcinoma of the ethmoid sinuses. A review of 28 cases with special reference to wood dust exposure. Cancer. 1984;54:482–8.
98. Barnes L. Intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. Am J Surg Pathol. 1986;10:192–202.
99. Kleinsasser O, Schroeder HG. Adenocarcinomas of the inner nose after exposure to wood dust. Morphological findings and relationships between histopathology and clinical behavior in 79 cases. Arch Otorhinolaryngol. 1988;245:1–15.
100. Franchi A, Massi D, Palomba A, Biancalani M, Santucci M. CDX-2, cytokeratin 7 and cytokeratin 20 immunohistochemical expression in the differential diagnosis of primary adenocarcinomas of the sinonasal tract. Virchows Arch. 2004;445:63–7.
101. Kennedy MT, Jordan RC, Berean KW, Perez-Ordonez B. Expression pattern of CK7, CK20, CDX-2, and villin in intestinal-type sinonasal adenocarcinoma. J Clin Pathol. 2004;57:932–7.
102. Resto VA, Krane JF, Faquin WC, Lin DT. Immunohistochemical distinction of intestinal-type sinonasal adenocarcinoma from metastatic adenocarcinoma of intestinal origin. Ann Otol Rhinol Laryngol. 2006;115:59–64.
103. Vivanco B, Llorente JL, Perez-Escuredo J, Alvarez Marcos C, Fresno MF, Hermsen MA. Benign lesions in mucosa adjacent to intestinal-type sinonasal adenocarcinoma. Patholog Res Int. 2011:Article ID 230147; 8 pages. doi:10.4061/2011/230147.
104. Wilhelmsson B, Lundh B. Nasal epithelium in woodworkers in the furniture industry. A histological and cytological study. Acta Otolaryngol. 1984;98:321–34.
105. Valente G, Ferrari L, Kerim S, et al. Evidence of p53 immunohistochemical overexpression in ethmoidal mucosa of woodworkers. Cancer Detect Prev. 2004;28:99–106.
106. Heffner DK, Hyams VJ, Hauck KW, Lingeman C. Low-grade adenocarcinoma of the nasal cavity and paranasal sinuses. Cancer. 1982;50:312–22.
107. Stelow EB, Jo VY, Mills SE, Carlson DL. A histologic and immunohistochemical study describing the diversity of tumors classified as sinonasal high-grade nonintestinal adenocarcinomas. Am J Surg Pathol. 2011;35:971–80.
108. Sunderman FW. Nasal toxicity, carcinogenicity, and olfactory uptake of metals. Ann Clin Lab Sci. 2001;31:3–24.
109. Bornholdt J, Saber AT, Sharma AK, Savolainen K, Vogel U, Wallin H. Inflammatory response and genotoxicity of seven wood dusts in the human epithelial cell line A549. Mutat Res. 2007;632:78–88.
110. Long H, Shi T, Borm PJ, et al. ROS-mediated TNF-α and MIP-2 gene expression in alveolar macrophages exposed to pine dust. Part Fibre Toxicol. 2004;1:3. doi:10.1186/1743-8977-1-3.
111. Määttä J, Majuri M-L, Luukkonen R, et al. Characterization of oak and birch dust-induced expression of cytokines and chemokines in mouse macrophage RAW 264.7 cells. Toxicology. 2005;215:25–36.
112. Määttä J, Luukkonen R, Husgafvel-Pursiainen K, Alenius H, Savolainen K. Comparison of hardwood and softwood dust-induced expression of cytokines and chemokines in mouse macrophage RAW 264.7 cells. Toxicology. 2006;218:13–21.
113. Määttä J, Lehto M, Leino M, et al. Mechanisms of particle-induced pulmonary inflammation in a mouse model: exposure to wood dust. Toxicol Sci. 2006;93:96–104.
114. Määttä J, Haapakoski R, Leino M, et al. Immunomodulatory effects of oak dust exposure in a murine model of allergic asthma. Toxicol Sci. 2007;99:260–6.
115. Palus J, Dziubaltowska E, Rydzynski K. DNA single-strand breaks and DNA repair in the lymphocytes of wooden furniture workers. Mutat Res. 1998;408:91–101.
116. Palus J, Dziubaltowska E, Rydzynski K. DNA damage detected by the comet assay in the white blood cell of workers in a wooden furniture plant. Mutat Res. 1999;444:61–74.
117. Çelik A, Kanik A. Genotoxicity and occupational exposure to wood dust: micronucleus frequency and nuclear changes in exfoliated buccal mucosa cells. Environ Mol Mutagen. 2006;47:693–8.
118. Perrone F, Oggionni M, Birindelli S, et al. TP53, p14ARF, p16INK4a and H-ras gene molecular analysis in intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. Int J Cancer. 2003;105(2):196–203.
119. Korinth D, Pacyna-Gengelbach M, Deutschmann N, et al. Chromosomal imbalances in wood dust-related adenocarcinomas of the inner nose and their associations with pathological parameters. J Pathol. 2005;207(2):207–15.
120. Llorente JL, Perez-Escuredo J, Alvarez-Marcos C, Suarez C, Hermsen M. Genetic and clinical aspects of wood dust related intestinal-type sinonasal adenocarcinoma: a review. Eur Arch Otorhinolaryngol. 2009;266:1–7.
121. Franchi A, Miligi L, Palomba A, Giovannetti L, Santucci M. Sinonasal carcinomas: recent advances in molecular and phenotypic characterization and their clinical implications. Crit Rev Oncol Hematol. 2011;79(3):265–77.
122. Pérez-Escuredo J, Martinez JG, Vivanco B, et al. Wood dust-related mutational profile of TP53 mutations in intestinal-type sinonasal adenocarcinoma. Hum Pathol. 2012;43:1894–901.
123. Saber AT, Nielsen LR, Dictor M, Hagmar L, Mikoczy Z, Wallin H. K-ras mutations in sinonasal adenocarcinomas in patients occupationally exposed to wood or leather dust. Cancer Lett. 1998;126(1):59–65.
124. Frattini M, Perrone F, Suardi S, et al. Phenotype-genotype correlation: challenge of intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. Head Neck. 2006;28(10):909–15.
125. Bornholdt J, Hansen J, Steiniche T, et al. K-ras mutations in sinonasal cancers in relation to wood dust exposure. BMC Cancer. 2008;8:53.
126. López F, García Inlcán C, Pérez-Escuredo J, et al. *KRAS* and *BRAF* mutations in sinonasal cancer. Oral Oncol. 2012;48:629–97.
127. Holmila R, Bornholdt J, Heikkila P, et al. Mutations in TP53 tumor suppressor gene in wood dust-related sinonasal cancer. Int J Cancer. 2010;127:578–88.
128. Holmila R, Bornholdt J, Suitiala T, et al. Profile of TP53 gene mutations in sinonasal cancer. Mutat Res. 2010;686:9–14.
129. Hermsen MA, Llorente JL, Perez-Escuredo J, et al. Genome-wide analysis of genetic changes in intestinal-type sinonasal adenocarcinoma. Head Neck. 2009;31(3):290–7.
130. Monks TJ, Jones DC. The metabolism and toxicity of quinones, quinonimines, quinone methides, quinone-thioethers. Curr Drug Metab. 2002;3:425–38.
131. Boots AW, Haenen GR, Bast A. Health effects of quercetin: from antioxidant to nutraceutical. Eur J Pharmacol. 2008;585:325–37.
132. Feron VJ, Arts JHE, Kuper CF, Slootweg PJ, Woutersen RA. Health risks associated with inhaled nasal toxicants. Crit Rev Toxicol. 2001;31:313–47.
133. Oberdörster G, Oberdörster E, Oberdörster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect. 2005;113:823–39.
134. Kuper CF, Woutersen RA, Slootweg PJ, Feron VJ. Carcinogenic response of the nasal cavity to inhaled chemical mixtures. Mutat Res. 1997;380:19–26.
135. Klein RG, Schmezer P, Amelung F, Schroeder H-G, Woeste W, Wolf J. Carcinogenicity assays of wood dust and wood additives in rats exposed by long-term inhalation. Int Arch Occup Environ Health. 2001;74:109–18.
136. Naarala J, Kasanen J-P, Pasanen P, et al. The effects of wood dusts on the redox status and cell death in mouse macrophages (RAW 264.7) and human leukocytes in vitro. J Toxicol Environ Health. 2003;66(A):1221–35.
137. Holmila R, Cyr D, Luce D, et al. COX-2 and p53 in human sinonasal cancer: COX-2 expression is associated with adenocarcinoma

histology and wood-dust exposure. Int J Cancer. 2008;122: 2154–9.
138. Gárcia-Inclán C, López F, Pérez-Escuredo J, et al. *EGFR* status and *KRAS/BRAF* mutations in intestinal type sinonasal adenocarcinomas. Cell Oncol. 2012;35:443–50.
139. Ariza M, Llorente JL, Alvarez-Marcas C, et al. Comparative genomic hybridization in primary sinonasal adenocarcinomas. Cancer. 2004;100(2):335–41.
140. Perez P, Dominguez O, Gonzalez S, Trivino A, Suarez C. Ras gene mutations in ethmoid sinus adenocarcinoma: prognostic implications. Cancer. 1999;86(2):255–64.
141. Wu TT, Barnes L, Bakker A, Swalsky PA, Finkelstein SD. K-ras-2 and p53 genotyping of intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. Mod Pathol. 1996;9(3): 199–204.
142. Yom SS, Rashid A, Rosenthal DI, et al. Genetic analysis of sinonasal adenocarcinoma phenotypes: distinct alterations of histogenetic significance. Mod Pathol. 2005;18(3):315–9.
143. Bandoh N, Hayashi T, Kishibe K, et al. Prognostic value of p53 mutations, bax, and spontaneous apoptosis in maxillary sinus squamous cell carcinoma. Cancer. 2002;94(7):1968–80.
144. Licitra L, Suardi S, Bossi P, et al. Prediction of TP53 status for primary cisplatin, fluorouracil, and leucovorin chemotherapy in ethmoid sinus intestinal-type adenocarcinoma. J Clin Oncol. 2004;22(24):4901–6.
145. Stephen JK, Vaught LE, Chen KM, et al. Epigenetic events underlie the pathogenesis of sinonasal papillomas. Mod Pathol. 2007;20(10):1019–27.
146. Levine AJ, Oren M. The first 30 years of p53: growing ever more complex. Nat Rev Cancer. 2009;9:749–58.
147. Vousden KH, Prives C. Blinded by the light: the growing complexity of p53. Cell. 2009;137(3):413–31.
148. Partridge M, Costea DE, Huang X. The changing face of p53 in head and neck cancer. Int J Oral Maxillofac Surg. 2007;36(12):1123–38.
149. Goh AM, Coffill CR, Lane DP. The role of mutant p53 in human cancer. J Pathol. 2011;223(2):116–26.
150. Bashir AA, Robinson RA, Benda JA, Smith RB. Sinonasal adenocarcinoma: immunohistochemical marking and expression of oncoproteins. Head Neck. 2003;25(9):763–71.
151. Affolter A, Helmbrecht S, Finger S, Hormann K, Gotte K. Altered expression of cell cycle regulators p21, p27, and p53 in tumors of salivary glands and paranasal sinuses. Oncol Rep. 2005;13(6):1089–94.
152. Lopez F, Llorente JL, Garcia-Inclan C, et al. Genomic profiling of sinonasal squamous cell carcinoma. Head Neck. 2011;33(2): 145–53.
153. Lopez F, Llorente JL, Oviedo CM, et al. Gene amplification and protein overexpression of EGFR and ERBB2 in sinonasal squamous cell carcinoma. Cancer. 2012;118:1818–26.
154. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer–analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med. 2000;343(2):78–85.
155. Fletcher O, Houlston RS. Architecture of inherited susceptibility to common cancer. Nat Rev Cancer. 2010;10(5):353–61.
156. Pastore E, Perrone F, Orsenigo M, et al. Polymorphisms of metabolizing enzymes and susceptibility to ethmoid intestinal-type adenocarcinoma in professionally exposed patients. Transl Oncol. 2009;2(2):84–8.
157. Rodrigo JP, Garcia-Pedrero JM, Llorente JL, et al. Down-regulation of annexin A1 and A2 protein expression in intestinal-type sinonasal adenocarcinomas. Hum Pathol. 2011;42(1):88–94.
158. Franchi A, Palomba A, Fondi C, et al. Immunohistochemical investigation of tumorigenic pathways in sinonasal intestinal-type adenocarcinoma. A tissue array of 62 cases. Histopathology. 2011;59:98–105.
159. Franchi A, Fondi C, Paglierani M, Pepi M, Gallo O, Santucci M. Epidermal growth factor receptor expression and gene copy number in sinonasal intestinal type adenocarcinoma. Oral Oncol. 2009;45(9):835–8.
160. Tripodi D, Quemener S, Renaudin K, et al. Gene expression profiling in sinonasal adenocarcinoma. BMC Med Genomics. 2009;2:65.