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Malignancy of the nose and sinuses. Epidemiological and aetiological considerations

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SUMMARY

Sinonasal malignancy is a rare disease in which a number of aetiological factors have been implicated. Incidence, site and histological type can vary in different geographical areas which may be due to occupational, social and genetic factors. Relative risk rates have been determined for a number of occupations such as workers with wood, nickel, chrome, chemicals, shoes and textiles though the exact causative agents and mode of action is not entirely clarified. Some non-occupational agents and pathological conditions may also play a role in certain cases.

A group of 350 patients with sinonasal malignancy have been reviewed with regard to aetiological factors and more detailed information was obtained in 50 of these patients by questionnaire and interview. Significant exposure to a wide range of known carcinogens was revealed suggesting a possible causative relationship in several unusual histological types.

INTRODUCTION

Malignancy of the nose and paranasal sinuses is relatively uncommon but a great deal has been written concerning epidemiological and aetiological factors. Consideration of this subject necessitates the examination of information derived from around the world which is fraught with all the difficulties of pooled data. Under the International Classification of Disease, rubric ICD160 includes not only nose, nasal cavity and accessory sinuses but also middle ear (WHO, 1967). Whilst this latter category does not constitute a large proportion, it is nevertheless often impossible to disentangle it from the statistics, immediately leading to inaccuracy.

This paper compares published data with that derived from 350 patients with

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sinonasal malignancy treated on the Professorial Unit between 1962 and 1990. More detailed information on possible aetiological factors has been obtained from 50 patients in this group by questionnaire and interview.

INCIDENCE

Nose and sinus malignancy is fortunately a rare condition, constituting approximately 3% of head and neck cancer. One must be cautious that published figures have not included malignancy of the external skin which is covered by a different ICD classification and remember that when dealing with a relatively rare disease, small changes in numbers produce exaggerated fluctuations which can complicate the interpretation of trends.

Less than 1% of cancer deaths in the United States between 1950 and 1969 were attributed to sinonasal tumours (Mason et al., 1974) and a similar picture emerges for England and Wales when considering cancer mortality between 1951 and 1980 (Osmond et al., 1983).

The incidence of the disease around the world, when adjusted for age and sex, occurs in 1/100,000 people/year in most countries but there are considerable geographical differences (Muir et al., 1980). Data from the International Agency for Research on Cancer shows that the incidence is strikingly higher in Japan, where a rate of 2.6/100,000 men between 1969 and 1973 in the Osaka area has been observed and rates of up to 3.6 have been reported in other parts of Japan (Waterhouse et al., 1976).

In Nigeria and Jamaica similar increases have been observed in the black population (2.5 and 2.0/100,000 males respectively) and in Saskatchewan, Canada and Oxford, U.K., two areas with established local risk factors from the wood-working industry, slightly increased rates are seen (1.2 and 1.0/100,000 males) compared to other parts of the respective countries where the overall rate is less than 1/100,000.

Referral patterns to the Professorial Unit result in a wide geographical distribution from both this country and abroad for the 350 patients precluding determination of incidence.

SEX AND AGE DISTRIBUTION

In general the male to female ratio is approximately 2:1 (Muir et al., 1980) which was the finding in the 350 cases though local occupational factors may influence this. A 2:1 ratio has also been observed in the 32 patients aged between 16 and 35 years old at presentation (Lund et al., 1990).

Sinonasal malignancy can occur at any age. In the series of 350 patients the age ranged from 5 to 88, with the majority presenting between 50 and 69 years (47%). In women a slight increase has been noted in association with the menopause, akin to Clemmesen's hook observed in breast cancer (Roush et al., 1987) and may

possibly be related to the presence of oestrogen receptors in the nasal cavity (Wilson et al., 1986). This was not seen in our own patients.

SITE

The distribution by site again demonstrates geographical differences (Muir et al., 1980). In Japan the maxilla is predominantly affected and this is also the commonest site in other countries, though to a lesser extent. However, in figures from the United Kingdom a comparatively larger proportion of nasal and ethmoidal cancer is found (Table 1).

Table 1. Distribution by anatomical site (%).

	maxilla	nose	other sinuses
Japan	93	3	4
Canada	63	26	11
Sweden	48	35	13
United Kingdom			
England and Wales	41	43	16
Oxford	61	13	26
Institute of Laryngology	55	35	10

The ICD classification does not separate ethmoid from sphenoid or frontal disease but the former almost certainly contributes the major part of this group (9:1 ratio). Similarly no allowance is made for those more extensive lesions affecting the antro-ethmoid area where the primary site cannot be determined.

HISTOLOGY (Table 2)

Examination of distribution by histological classification shows squamous cell to be commonest both in our own and pooled IARC data (Muir et al., 1980) but local factors may skew results such as the large number of malignant melanomas in our series and patients referred for craniofacial resection with ethmoidal adenocarcinoma, olfactory neuroblastoma and chondrosarcoma.

All forms of malignancy can occur in the nose and sinuses, probably the area of greatest histological diversity in the head and neck but no tissue diagnosis was checked in IARC material and with new immunocytochemistry techniques it may be that some anaplastic tumours might be reassigned as olfactory neuroblastomas, melanomas or lymphoma. Furthermore lymphoma is frequently allocated to another ICD code which may account for the low numbers encountered in these figures.

There are clear differences in many aspects of this uncommon condition and not only in global distribution but at a regional level with obvious increased in-

Table 2. Range of histology (%).

	IARC (n=3574)	ILO total (n=350)	ILO questionnaire (n=50)
epithelial			
squamous	59	24	16
anaplastic	11	8	8
adenocarcinoma	9	14	20
salivary gland	2	10	6
malignant melanoma	1	15	16
olfactory neuroblastoma	<1	5	12
mesenchymal			
sarcoma	3	10	12
lymphoma	2	9	10
other	12	5	

IARC: International Agency for Research on Cancer
ILO : Institute of Laryngology and Otology

cidence of disease in those areas such as Suffolk and Buckinghamshire with associated wood-working industries (Gardner et al., 1983).

In general terms aetiological factors can be considered as environmentally related, either occupational or non-occupational, or related to other pathological conditions which may predispose or progress to malignancy. The route by which environmental agents have their effect can be three-fold:

a. Airbourne - by direct inhalation of particles whose effect will depend upon their size, density and the breathing pattern of the host (Andersen et al., 1977; Stokinger, 1977; Wilhelmson et al., 1984).
b. Absorption - such as the effect of radium absorbed from the oral mucosa into the facial bones (Rowland, 1975).
c. Parenteral - by experimental administration of toxins such as dioxane, nitrosamines and nickel compounds (Hoch-Ligeti et al., 1970; International Agency for Research on Cancer Working Group, 1975; Sunderman, 1975; Tucker, 1975; Cardesa et al., 1976; Sunderman, 1976; Boysen et al., 1984).

Occupational Risks

With changing patterns of work practise, improved working conditions and a mobile population, the effects of such occupational factors will become increasingly difficult to unravel despite our greater vigilance in this respect.

Reports on the association between adenocarcinoma of the ethmoid and the wood-working trade, in particular hardwood exposure, began in 1965 from the United Kingdom and have subsequently appeared from many other countries

(Macbeth, 1965; Acheson et al., 1968; Hadfield, 1970; Cecchi, 1963; Gignoux et al., 1968; Debois et al., 1969; Delamare et al., 1971; Mosbeck et al., 1971; Ironside et al., 1975; Brinton et al., 1977; Engzell et al., 1978; Tola et al., 1980; Elwood et al., 1981; Hayes et al., 1986). In addition to the association between hard woods and adenocarcinoma, the effects of softwood in the development of squamous and anaplastic carcinoma have been reported (Hernberg et al., 1983; Voss et al., 1985; Boysen et al., 1986). It is, however, noteworthy that Japan which has a large traditional wood-working industry has found no such association in a country where squamous cell carcinoma of the maxilla predominates (Takasaka et al., 1987).

The leather and shoe industry has also been the subject of extensive epidemiological study for squamous and adenocarcinoma since Acheson's report in 1975. Other occupations which are associated with an increased risk of adenocarcinoma are the manufacture of chrome pigment (Heuper, 1966; Enterline, 1974; Levy et al., 1975), isopropyl alcohol (Fraumeni, 1975; International Agency for Research on Cancer Working Group, 1976; National Institute for Occupational Safety and Health, 1976) and the textile and clothing trade, the latter also being associated with malignant melanoma (Acheson et al., 1972). The relative risk and suspected carcinogens, other associated tumours and where calculated the latent period in years are shown in Table 3.

Three occupations are linked with squamous cell carcinoma in the nose and sinuses. Of these radium dial painting has largely disappeared and mustard gas manufacture only occurred in Japan between 1924 and 1945 (Wada et al., 1968). Scintering and roasting processes in nickel refining have been implicated in reports from Russia, Norway, Canada and Wales (Hill, 1939; Morgan, 1958; Sutherland, 1959; Doll et al., 1970; Pederson et al., 1973). There is a high relative risk with a minimum exposure of six months though the majority of those affected had contact in excess of nine years. The risk increased with duration of exposure and the age at first exposure and was probably eliminated before the first epidemiological studies were done.

The literature contains other reports of occupational risks for nose and sinus malignancy, such as asbestos exposure in two documented cases (Bogouski et al., 1973; Stell et al., 1973) and baking (six cases - three squamous cell and three adenocarcinomas) (Roush, 1979).

Non-occupational risks

The situation regarding smoking remains unclair. Smoking has not been implicated in several studies on wood-workers who are largely non-smokers due to safety restrictions at work (Acheson et al., 1968; Tola et al., 1980; Brinton et al., 1983) but conflicting evidence has come from Canada (Elwood, 1981).

Table 3. Occupational agents correlated with sinonasal cancer (After Roush, 1979).

occupation	relative risk	suspended carcinogen	latent period	histology	other associated cancers
wood-workers	70	dust 5 μm diameter tar aldehyde aflatoxin chromium tannins	35 years	adenocarcinoma (hardwood) squamous (softwood)	lung testis brain
leather/shoe	87	dust tar aldehydes aflatoxins tannins	55 years	adenocarcinoma	rectum bladder
chrome pigment manufacturers	>21	calcium chromate zinc potassium chromate	-	adenocarcinoma	lung
isopropyl alcohol manufacturers	>21	isopropyl oil	<20 years	adenocarcinoma	larynx
textile & clothing	5–8	wool dust & dyes	-	adenocarcinoma malignant melanoma	tongue mouth pharynx
nickel refining	>100	nickel subsulphide, oxide, carbonyl	24 years (5–40)	squamous cell anaplastic	lung larynx
dial painting	-	radium	15 years	squamous	osteosarcoma Ca mastoid
mustard gas manufacture	>30	BB dichloroethyl sulphide	25 years	squamous	tongue pharynx larynx lung

A recent Japanese study exonerated both passive and active smoking (Shimizu et al., 1989) but another study from the Netherlands suggested a relative risk of 3.1 in the development of squamous cell carcinoma in this region (Hayes et al., 1987). Snuff usage is common in Africa and has been linked with squamous cell carcinoma of the maxilla. The snuff used by the Bantu may contain trace elements such as nickel and chromium which are known carcinogens (Harrison, 1967; Baumslag et al., 1972; Keen, 1974).

The direct effects of radiation in the development of anaplastic carcinoma is documented in two case reports (Roush, 1979) and up to 1954 thorium dioxide was used as a radiological contrast agent which was injected directly into the antrum. Peak radioactivity is not achieved for 15 years, the active agents being mesothorium α, β, γ and again the association is with squamous cell carcinoma of the maxilla (Rankow et al., 1974).

Of more significant therapeutic importance is a study from the United States suggesting that subjects who reported a history of nasal preparation use were 3.5 times more likely than non-users to develop sinonasal cancer and that the risk increased with duration of use (Strader et al., 1988)!

The relationship between chronic infection and sinonasal malignancy is not as well-established as it is with cancer of the middle ear but a recent report from Japan showed a relative risk of 2.3 for squamous cell cancer (Shimizu et al., 1989) in contradistinction to other studies (Fukuda et al., 1985) though it is noteworthy that both conditions are relatively more common there. This may however, explain the possible increased risk of sinonasal malignancy with the use of nasal medication.

Paget's disease affecting the facial bones can of course occasionally progress to osteosarcoma (Michaels, 1987). The rate of malignant transformation of inverted papilloma varies from 0-53% in the literature (Michaels, 1987). Such high rates are almost certainly cases of initial misdiagnosis and in 86 cases reviewed at the Institute of Laryngology and Otology no such change could be determined. It is likely that benign and malignant pathologies may occur concomitantly and the true rate of transformation is $< 1\%$ if at all.

Questionnaire Results

A questionnaire and where possible a personal interview was conducted on 50 surviving patients out of the cohort of 350, to look in detail at the following areas:

occupation
hobbies
contact with wood-dust – hard
– soft
carbon tetrachloride
chloroform

formaldehyde
methanol
industrial alcohol and petrol
asbestos
tar
radiation/radioactive substances
other chemicals
smoking and/or use of snuff
geographical location during lifetime.

The proportion of females was somewhat higher than normal at 1.2:1 but age distribution was similar to the whole group of 350.
The distribution by histology is shown in comparison with the whole group (Table 2). No significant information emerged regarding hobbies, or geographical location. None of the patients had ever used snuff and 79% either smoked in the past or present though there was a similar distribution of this in the different histological types.
Carcinogen contact was present in a surprisingly large number of respondants (Table 4). Wood-dust exposure was, as expected, one of the main occupational factors though exposure to both hard and softwoods was documented in 5 out of 10 of the adenocarcinoma group with between 7 and 41 years of contact. Wood-dust exposure was also found in 3/8 patients with malignant melanoma, one case of squamous cell carcinoma and one of malignant fibrous histiocytoma.
Adenocarcinoma occurred in 46 patients out of the 350, only 10 of whom were woodworkers so although it is an important definable factor the link is not absolute.
Two patients with anaplastic carcinoma had received significant radiation, one received irradiation for adenoidal hypertrophy as a child, and one had been on Christmas Island shortly after the nuclear tests in 1958.

Table 4. Questionnaire results of carcinogen contact (n=50).

carcinogen	%		%
wood dust		tar	6
- hard	20	radiation	6
- soft	20	benzene	4
industrial alcohol/petrol	16	glues	4
carbon tetrachloride	14	mercury	4
formaldehyde	14	bakelite	4
asbestos	14	ammonia	2
methanol	8	arsenic of lead	2
chloroform	6	xylene	2

Of considerable interest are three patients out of eight respondants with mucosal malignant melanoma who had had significant occupational exposure to formaldehyde, a chemical which has been the focus of considerable attention both in the U.S.A. and Scandinavia (Olsen, 1984; Moran et al., 1986; Holmstrom, 1989). In a rare form of a rare cancer such an apparent association must be worthy of investigation. Similarly of note are two cases of olfactory neuroblastoma occurring in dental nurses.

Inevitably all such studies are reliant upon the memory and knowledge of our patients and defining 'significant' exposure retrospectively is fraught with difficulty though a survey of this sort may provide important clues for further investigation.

As a tertiary referral centre the Professorial Unit deals with rare disease drawn from all over the world, not a localised and settled population which enables an obvious causal relationship to be extablished with relative ease. Furthermore although a cohort of 350 cases is a large personal series, each individual histology is represented by relatively small numbers and this particular investigation was for obvious reasons not case-controlled.

However despite these many drawbacks we should as clinicians be constantly vigilant for such possible aetiological factors as despite newer more successful techniques in their management such as craniofacial resection (Lund et al., 1988), as always in medicine, prevention is better than cure!

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