BMJ 1996;313:615-619 (7 September)

Education and debate

ABC OF Work Related Disorders: OCCUPATIONAL CANCERS

C A Veys

The first report of cancer caused by occupational exposure was in 1775 by Percival Pott, a British surgeon who described scrotal cancer in boy chimney sweeps. A century later, in 1895, Rehn, a German surgeon working in Frankfurt, treated a cluster of three cases of bladder cancer in workers at a local factory producing aniline dyestuffs from coal tar.

Occupational cancer is any malignancy wholly or partly caused by exposures at the workplace or in occupation. Such exposure may be to a particular chemical (such as ß-naphthylamine), a physical agent (such as ionising radiation or a fibre like asbestos), a biological agent (such as hepatitis B virus), or an industrial process in which the specific carcinogen may elude precise definition (such as coke production).

About 4% of all cancer deaths in people aged over 15 years may have an occupational cause. This translates into over 3000 male deaths in England and Wales from potentially preventable malignancies. The proportion occurring in women is probably less because of their lower potential for exposure.

> Of all the occupationally related diseases, cancer evokes particular concern and strong emotions, because of the opportunity afforded for attribution, blame, and compensation. On the other hand, occupational cancers have unique potential for prevention.

Foundry workers may be exposed to a complex mixture of carcinogenic agents in fumes.

View larger version (108K):
[in this window]
[in a new window]

The International Agency for Research on Cancer (IARC) was set up within the World Health Organisation in 1971 to assess whether individual agents, mixtures, and occupational exposures have carcinogenic potential for humans. Since 1972 the agency has published 63 monographs covering more than 700 such evaluations. Today, some 65 agents and occupational environments are regarded by IARC as established human carcinogens. Over 50 are listed as probably carcinogenic, and about 300 are thought to be possibly carcinogenic.

Characteristics of occupational cancer Mechanisms

Cancer induction is a complex multistage process in which nuclear damage occurs at an early stage.

Genotoxic (DNA reactive) carcinogens interact with and alter DNA.

Epigenetic carcinogens act more directly on the cell itself, through hormonal imbalances, immunological effects, or promoter activity, to cause abnormal cell proliferation and chromosomal aberrations that affect gene expression.

Site of cancers

The target organ is usually singular and site specific, but not necessarily so. In Britain the most commonly affected sites are the lung and mesothelium (~75%), bladder (~10%), and skin (<1%), with the haemopoietic system, nasal cavities, larynx, and liver much less affected.

Natural course of cancers

Occupationally related cancers are characterised by a long latent period--that is, the time between first exposure to the causative agent and presentation of the tumour. This latency is not usually less than 10-15 years and can be much longer--40-50 years in the case of some asbestos related mesotheliomas. Thus, presentation can be in retirement rather than while still at work.

An occupationally related tumour does not differ substantially, either pathologically or clinically,

from its "naturally occurring" counterpart.

Thick walled mesothelioma of pleura with haemorrhagic cavitation in a former insulation worker.

View larger version (130K):
[in this window]
[in a new window]

Effective dose of carcinogen

There is probably a minimal threshold dose as well as a clear dose-response relation influencing the occurrence of cancers. For example, all workers involved in distilling ß-naphthylamine eventually developed tumours of the urothelial tract, whereas only 4% of rubber mill workers--who were exposed to ß-naphthylamine contaminating an antioxidant (at 0.25%) used in making tyres and inner tubes-- developed bladder cancer over a 30 year follow up. Studies indicate that susceptibility to occupational carcinogens is greater when the exposure occurs at younger ages.

Recognition and diagnosis

For a group of workers, occupational cancer is evidenced by a clear excess of cancers over what would normally be expected. However, it is not possible to distinguish individual tumours that were actually caused by the occupational exposure from those that would have occurred anyway. Furthermore, some common malignancies that can be work related also have a well recognised and predominant aetiology related to other agents, diet, or lifestyle (for example, lung cancer from smoking). There are, however, some features which may help to distinguish occupational cancers from those not related to work.

```
Diagnosis of work related cancer is
assisted by
* Detailed lifelong occupational history
* Comparison with a check list of recognised
causal associations
* Search for additional clues:
  Shift to a younger age
  Presence of signal tumours
  Other cases and "clusters"
  Long latency
  Absence of anticipated aetiologies
  Unusual histology or site
* Confirmation of requisite exposure
```

Rubber workers in mill room.

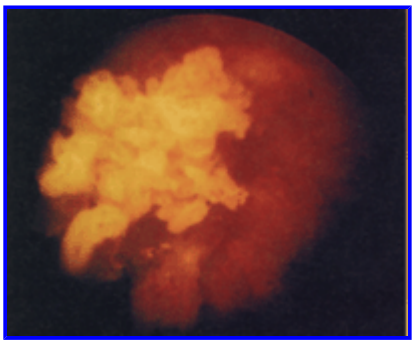
View larger version (144K):
[in this window]
[in a new window]

History taking--Taking a patient's occupational history (that is, since leaving school until retirement or the present) is of paramount importance. It should be defined in detail and sequentially. For example, a holiday job in a factory that lasted only a few months could easily be overlooked, but it may have involved delagging a boiler or handling sacks of asbestos waste.

Signal tumours--Several uncommon cancers are associated with particular occupations. Thus, an angiosarcoma of the liver may indicate past exposure to vinyl chloride monomer in the production of polyvinyl chloride (PVC); a laryngeal tumour may have derived from exposure to the fumes of strong acids as well as from cigarette smoke; a nasal cancer may have resulted from exposure to dusts from hardwood in furniture manufacture. These less common cancers are sometimes called signal tumours because they should always alert a doctor to a possible occupational aetiology.

Age--A younger age at presentation with cancer may suggest an occupational influence. For example, a tumour of the urothelial tract presenting in anyone under the age of 50 years should always arouse suspicion.

Patients' information--Patients may speak of a "cluster" of cancer cases at work or may have worked in an industry or job for which a warning leaflet has been issued.



Cystoscopic view of papillary carcinoma of the bladder in a 47 year old rubber worker.

View larger version (112K):
[in this window]
[in a new window]

Prevention

Primary prevention of occupationally related cancers depends essentially on educating employers and employees--firstly, about recognising that there is a risk, and then about the practical steps that can be taken to eliminate or reduce exposure and to protect operators. Modern legislation now directs these educational and practical measures.

Action for primary prevention of occupational cancers
* Recognising presence of hazards and risks
* Educating management and workforce
* Eliminating exposure by substitution and automation
* Reducing exposure by engineering controls (such as local exhaust ventilation and enclosure), changes in handling, and altering physical form in processing
* Monitoring exposure and maintaining plant
* Protecting workers by means of personal protective equipment
* Limiting access
* Providing adequate facilities for showering, washing, and changing
* Legislative provisions

Secondary prevention of occupational cancer is helped by screening tests and medical surveillance--for example, exfoliative urinary cytology and skin inspections

Secondary prevention--Screening procedures can be used if they might help with earlier diagnosis (for example, exfoliative urinary cytology), but the final outcome may not necessarily be altered. Once initiated, such surveillance must be lifelong or until old age or other serious intercurrent illness intervenes. Routine skin inspections are a very effective method of secondary prevention for

cutaneous cancers of occupational origin because of the excellent prognosis afforded by treatment.

Legislation and statutory compensation

Essential legislative provisions in Britain and the European Community are comprehensive. Ten types of cancer are prescribed diseases, which means that sufferers can claim social security benefits. Some cancers are also notifiable under the RIDDOR regulations. In 1993 the 713 new cases of occupational cancer prescribed under the various industrial injuries benefit schemes (mesothelioma 608 cases, asbestos related lung cancer 72, bladder cancer 26, others 7) almost certainly considerably underrepresented the true picture.

Main legislative provisions in United Kingdom
* Control of Substances Hazardous to Health (COSHH) Regulations 1994 and associated ACOP on the Control of Carcinogens
* European Commission Carcinogens Directive (90/934/EEC)
* Chemicals (Hazard Information and Packaging) Regulations 1993 (CHIP)
* Ionising Radiation Regulations (1985)
* Control of Asbestos at Work Regulations (1988).
* Reporting of Injuries, Diseases and Dangerous Occurrences Regulations 1995 (RIDDOR)

Specific carcinogens Metals and metalliferous compounds

Arsenic, beryllium, cadmium, chromium (VI), nickel, and iron are considered to be proved human carcinogens, either as the metal itself or as a derivative. The risk from iron is related only to mining the base ore and is due to coincidental exposure to radon gas. In foundries, where there is concomitant exposure to several agents in a complex mix of emanating fume, the responsible agents are not clearly defined.

With all the metallic carcinogens, the lung is the main target organ, but other potential sites are the skin (arsenic), prostate gland (cadmium), and nasal sinuses (nickel), indicating the metals' pluripotential nature.

The main occupational exposures occur in the mining, smelting, founding, and refining of these metals, and less commonly in secondary industrial use.

Metalliferous carcinogens

Agent	Target organ
* Arsenic	Lung, skin
* Beryllium	Lung
* Cadmium	Lung, prostate gland
* Chromium (hexavalent)	Lung
* Nickel	Lung, nasal sinuses
* Iron in:	
Haematite mining (radon)	Lung

Iron and steel founding	Lung, digestive tract

Aromatic amines

Aromatic amines are one of the best known and most studied of chemical carcinogens. The bladder is the main target organ, but any site on the urothelial tract comprised of transitional cell epithelium can be affected--that is, from the renal pelvis to the prostatic urethra. Tumours of the upper urothelial tract (renal pelvis or ureter) are very uncommon, and a cluster of these signal tumours usually heralds an underlying risk of occupational cancer. The carcinogenic potential of aromatic amines lies not in the parent compound but in a metabolite formed in the liver and excreted through the urinary system.

Aromatic amine carcinogens

Agent	Target organ
* 4-Aminobiphenyl (xenylamine) and its nitro derivative	Bladder predominantly, but also other parts of the urothelial tract lined by transitional cell epithelium (renal pelvis, ureter, and first part of prostatic urethra)
* ß-naphthylamine	
* Benzidine	
* Auramine and magenta (in manufacture only)	

Recent evidence also implicates the polycyclic aromatic hydrocarbons as probable human urinary tract carcinogens, and the hardener MbOCA (41,4[1]-methylene-bis-(2-chloroaniline)) is suspect

The occupations classically associated with risk from these chemicals were in the industries manufacturing chemicals and dyestuffs--a detailed study of this risk led to occupational bladder cancer becoming a prescribed disease in 1953.

Antioxidants contaminated with ß-naphthylamine were used in the rubber and cable making industries until the end of 1949, when they were universally withdrawn, and they caused an excess of bladder cancer. The level of contamination was only about 0.25%, yet it almost doubled the risk for the workforce so exposed. People who started work in the rubber industry after 1951 seem to have no excess risk.

Although the presenting pathology is often that of a papillary tumour, it can range from carcinoma in situ to an advanced infiltrating lesion. At most, only about 6% of all bladder tumours registered annually are realistically work related. This contrasts with the 30-50% that can probably be attributed to tobacco smoking.

There is now increasing evidence that some polycyclic aromatic hydrocarbons can also act as urinary tract carcinogens. This is reflected in excesses seen in aluminium refiners and in painters exposed to solvents.

```
Occupations causally associated with
urothelial tract cancers
* Dyestuffs and pigment manufacture
* Rubber workers (in tyre, tube, and cable making
before 1950)
* Textile dyeing and printing
* Manufacture of some chemicals (such as
MbOCA)
* Gas workers (in old vertical retort houses)
* Laboratory and testing work (using
chromogens)
* Rodent controllers (formally using ANTU
((alpha)-naphthylthiourea))
* Painters
* Leather workers
* Manufacture of patent fuel (such as coke) and
firelighters
* Tar and pitch workers (roofing and road
maintenance)
* Aluminium refining
```

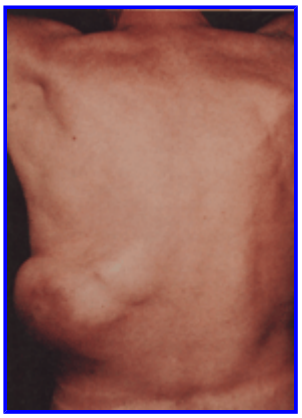
Asbestos

Few natural materials used in industry have been the subject of more epidemiological and pathological research than the asbestos fibre. Its association with lung cancer was finally confirmed in the middle 1950s, and with mesothelioma nearly a decade later.

```
Asbestos related cancers
* Lung
* Malignant mesothelioma--most commonly of
pleura, occasionally peritoneal, and rarely of
pericardium
* Larynx
* Possibly gastrointestinal tract
```


In asbestos workers who have developed asbestosis the risk of lung cancer is increased at least fivefold. Smoking with concomitant exposure to asbestos also greatly increases the risk of developing lung cancer. This synergistic action is multiplicative: compared with nonsmokers not exposed to asbestos, a smoker exposed to asbestos has a 75-100 times greater risk if exposure was sufficient to cause asbestosis, otherwise the risk is about 30-50 times higher. Over 40% of people with asbestosis die of lung cancer, and 10% die of mesothelioma.

Mesotheliomas, which are predominantly of the pleura (ratio of 8:1 with peritoneum), have usually been growing for 10-12 years before becoming clinically evident. This latency can be very long--often 30 years and sometimes up to 50 years. However, median survival from the time of initial diagnosis is usually short, some three to 12 months.



Mesothelioma extending through needle bipsy tract.

View larger version (121K):
[in this window]
[in a new window]

The amphibole fibres in crocidolite (blue asbestos) and amosite (brown asbestos) carry the greatest risk of causing mesothelioma, but the serpentine fibres in chrysotile (white asbestos) can also do so, especially if they contain tremolite.

In about 90% of patients with mesothelioma, close questioning will usually reveal some earlier exposure to asbestos. The prevalence of mesothelioma is increasing; it currently causes more than 1000 deaths annually in Britain, and it is no longer a rare disease. It is predicted that, by the year 2020, there will be up to 3300 deaths annually. The possible risk to neighbourhoods outside asbestos factories from discharged asbestos dust or contaminated clothing brought home should not be forgotten.

Occupations involving exposure to asbestos
* Manufacture of asbestos products
* Thermal and fire insulation (lagging, delagging)
* Construction and demolition work
* Shipbuilding and repair (welders, metal plate workers)
* Building maintenance and repair
* Manufacture of gas masks (in second world war)
* Plumbers and gasfitters
* Vehicle body builders
* Electricians, carpenters, and upholsterers

Tyndall beam photography showing asbestos fibres released by mere handling of asbestos boards (left), emphasising the need for proper protection when dealing with asbestos (right).

View larger version (57K):
[in this window]
[in a new window]

Ultraviolet radiation

Ultraviolet radiation from excessive exposure to sunlight causes both melanotic and non-melanotic skin cancers (basal cell and squamous cell carcinomas).

In Britain few of the 40 000 new cases of skin cancer registered annually are occupationally related. Research shows no consistent increased risk to outdoor workers compared with those of similar socioeconomic status working indoors, but the overall incidence of melanotic skin cancer has almost doubled in 10 years.

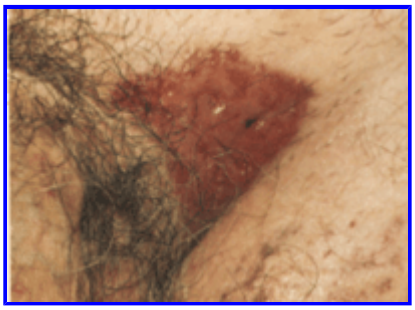
Initial presentation may be that of solar keratoses or a premalignant state. Immunosuppression can increase the risk; other possible additive factors are trauma, heat, and chronic irritation or infection.

Premalignant melanosis (lentigo maligna) in a man retired after a lifetime of working outdoors.

View larger version (148K):
[in this window]
[in a new window]

Mineral oils

The classic epithelioma of the scrotum or groin due to contact with mineral oil is rarely seen today, but these tumours can appear at other sites (such as arms and hands) if contamination with oil persists.



Epithelioma of groin due to past exposure to mineral oil.

View larger version (125K):
[in this window]
[in a new window]

Miscellaneous proved human carcinogens	
Agents and exposures	Target o
* Aluminium production	Skin, lu
* Benzene in petroleum associated industries	Leukaemi
* Bis-(chloromethyl)-ether in production of ion exchange resin	Lung
* Benzene and leather dust in boot and shoe making and repair	Leukaemi
* Polycyclic aromatic hydrocarbons and aromatic amines in coal gasification and coke production	Skin, lu
* Coal tars and pitch in roofing and road maintenance	Skin, lu
* Ethylene oxide as medical steriliser and chemical intermediary	Leukaemi
* Hardwood dust in furniture and cabinet making	Nasal ca
* Isopropyl alcohol manufacture	Nasal ca
* Ionising radiation in nuclear processing, industrial x rays, and medical fields	Various
* Mineral and shale oils in engineering and metal machining, past exposure to mule spinning in cotton industry and jute processing	Skin, sc
* Solvents and pigments in painting and decorating	Various
* Mists of strong inorganic acid (sulphuric acid) in acid pickling and soap making	Larynx
* Soots from chimney sweeping and flue maintenance	Skin, lu
* Vinyl chloride monomer in PVC production	Liver, b

Other occupational carcinogens

Several other agents are proved human carcinogens. Epidemiological studies now suggest that heavy exposure to crystalline silica dust may increase the risk of subsequent lung cancer. The question of a causal link between electromagnetic fields and cancer, whether in the occupational or domestic context, is still unanswered. Similarly, much recent debate, but finally reassurance, has centred on the potential risk of childhood leukaemia after parental exposure to ionising radiation. Barring accidental exposure, any risk to classified workers exposed to ionising radiation is negligible.

Useful references

* British Association of Urological Surgeons (BAUS). Occupational bladder cancer: a guide for clinicians. Br J Urol 1988;61:183-91.
* Duffus JH. Cancer and workplace chemicals: Handbook No 17. Leeds: H and H Scientific Consultants, 1995.
* Section 7: Occupational cancer. In: Hunter's diseases of occupations. 8th ed. London: Edward Arnold, 1994: 623-88.
* Alderson M. Occupational cancer. London: Butterworths, 1986.
* IARC monographs on the evaluation of carcinogenic risks to humans. Volumes 1-63. Lyons: International Agency for Research on Cancer, 1972-1995.

C A Veys is senior research fellow in occupational medicine at School of Postgraduate Medicine, University of Keele.

The ABC of Work related disorders is edited by David Snashall, clinical director of Occupational Health Services, Guy's and St Thomas's Hospitals NHS Trust, London.