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EPIDEMIOLOGY OF OCCUPATIONAL CANCER

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Cancer is a major cause of morbidity and mortality worldwide. Occupational carcinogens were among the first human carcinogens to be identified, and the causal relationship between occupational exposures and some human cancers has been established. Occupational carcinogens include chemical substances, physical agents, and microbiological agents that are present in the workplace. Occupational carcinogens may cause a significant increase in a particular type of cancer in the exposed working population. Although the number of known occupational carcinogens to humans are limited so far, the prevention of occupational cancer and the protection of workers against exposure to carcinogens are needed. This chapter provides an up-to-date review of the occurrence and causes of occupational cancer based on epidemiologic studies in humans, characteristics of occupational cancer, research priorities, and cancer surveillance.

MAGNITUDE OF OCCUPATIONAL CANCER

Cancer is the second leading cause of death in the United States.[94] The American Cancer Society estimated 1,359,000 new cancer cases in 1996 based on data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute.[6] A recent report showed that age-adjusted incidence rates for all cancers combined increased by 18.6% among males and 12.4% among females from 1975–1979 to 1987–1991, due to large increases in prostate cancer incidence rates in men and for breast and lung cancer in women.[17]

More than half of a million deaths due to cancer, with an annual age-adjusted cancer mortality of 133.1 per 100,000 population in 1992, were reported.[94,95] About 30–40% of Americans will develop cancer during their lifetimes.[25] Cancer mortality is increasing, and occupational exposures appear to account for at least part of the pattern.

The proportion of occupational cancer to exposure is difficult to precisely calculate. Adequate data that allow calculations of the number of exposed individuals or levels of exposure are not available. Two possible approaches to calculate the proportion of cancer due to occupation[33] include the following:

1. Calculation based on exposure to occupational factors. In this case, it is necessary to know (a) the total population exposed to the hazard, (b) the duration and level of exposure, (c) confounding variables, and (d) the increased relative risk associated with exposure at different dose levels.

2. Calculation based on evaluating the cause of cancer at each site. It is probably more appropriate to examine cancers at each site and to calculate the proportion due to defined or suspected factors. From such calculations, it may be possible to establish the upper limits of the proportion of cancers that could be predominantly due to occupational factors.

An investigation in the United Kingdom showed that only 6% of cancers might be occupationally related to exposures in the workplace, while 88% are due to other lifestyle factors.[33] In 1991, Vineis and Simonato evaluated the proportion of cancers attributable to occupation.[104] The proportion ranged from 1–5% when considering only exposure to asbestos and 40% for subjects exposed to ionizing radiation. Three quarters of occupational cancers among men are found in the lungs.[18] Between 13–27% of lung cancers are attributable to some form of occupational exposure and, in particular, asbestos exposure.[47] Up to 25% of bladder cancer cases in the general population can be attributed to occupational exposure.[83,103,104] These estimates were determined by the prevalence of exposed individuals within the general population and the proportion of individuals actually exposed within the group under consideration. Doll and Peto have estimated that about 4% of all cancer deaths can be attributed to occupational exposures.[18] Recently, Leigh and coworkers estimated that 6–10% of all cancers have occupational origins.[50] In the United States, this would represent 80,897–134,828 new cancer cases and 33,018–55,030 deaths due to occupational exposures in 1996 (Tables 1 and 2).

TABLE 1. Estimated Incidence of Occupational Cancer, United States, 1996

	Estimated Number of New Cases*			
	All Ages	25 Years & Older	Percentage Due to Occupation†	Estimated Number of Cases Due to Occupation
All sites	1,359,150	1,348,277	6–10	80,897–134,828
Lung	177,000	176,929	10	17,693
Prostate	317,100	314,563	1	3,146
Leukemia	27,600	25,723	7	1,801
Bladder	52,900	52,879	7	3,702
Skin	38,300	37,994	6	2,280

* Estimated by the American Cancer Society, 1996.
† Estimated by Richard Doll and Richard Peto, 1981.

TABLE 2. Estimated Number of Deaths Due to Occupational Cancer, United States, 1996

Cancer Site	Estimated Number of Deaths*		Percentage Due to Occupation†	Estimated Number of Deaths Due to Occupation
	All Ages	25 Years & Older		
All sites	554,740	550,302	6–10	33,018–55,030
Lung	158,700	158,636	10	15,864
Prostate	41,400	41,069	1	411
Leukemia	21,000	19,572	7	1,370
Bladder	11,700	11,606	7	812
Skin	7,300	7,242	6	434

* Estimated by the American Cancer Society, 1996.
† Estimated by Richard Doll and Richard Peto, 1981.

HISTORY OF OCCUPATIONAL CANCER

An occupational carcinogen was first reported more than 200 years ago. In 1775, Sir Percival Pott reported the first occupational cancer, scrotal skin cancer, among chimney sweeps in England who were heavily exposed to soot.[68] In 1822, Paris reported excess scrotal cancer among Cornish smelter workers.[65] Over the years, other chemicals were found to cause cancer after occupational exposures, including aromatic amines, asbestos, arsenic, benzene, vinyl chloride, and various radioactive materials. In 1879, Haerting and Hesse identified cancer of the lung.[31] Prior to 1950, the association between lung cancer and cigarette smoking was not well established. Currently, about 85–90% of all lung cancer cases are estimated to be caused by cigarette smoking.[18] Since 1973, various occupational exposures were reported to be associated with lung cancer. In 1973, Figueroa reported an excess lung cancer among chloromethyl methyl ether workers.[24]

Other occupational cancers recognized before 1950 were bladder cancer in German dyestuff workers,[71] bone cancer in American radium dial painters,[55,56] and leukemia in Italian workers exposed to benzene.[102] Since 1950, various occupations have been evaluated in many case-control and prospective studies. Because of the importance of occupational cancer and the protection of workers against cancer in the workplace, the International Labor Conference in 1973 and 1974 recommended prevention and control methods of occupational hazards caused by carcinogenic substances and agents.[42]

In 1977, a working group of the International Agency for Research on Cancer (IARC) reviewed and standardized the evaluations of evidence for carcinogenic activity from both human and animal studies, and a scheme for categorizing degrees of evidence for carcinogenicity was developed. They categorized the agents as sufficient, limited, inadequate, and lacking evidence for carcinogenicity.[100]

The history of federal regulation of carcinogens has been summarized by Yodaiken et al.[110] A precursor to the National Cancer Institute (NCI) was established in 1937. The National Cancer Act was signed in 1971, and it established the national cancer program. The NCI is responsible for a comprehensive research program that includes prevention, diagnosis, and treatment. The next step was the control of the workplace safety and health. In 1970, the Occupational Safety and Health Act established the Occupational Safety and Health Administration and the National Institute for Occupational Safety and Health. Both NIOSH and the Environmental Protection

TABLE 3. Occupational Carcinogens Regulated by OSHA

Section	Carcinogen
1910.1001	Asbestos
1910.1001	4-Nitrobiphenyl
1910.1004	Alpha-Naphthylamine
1910.1006	Methyl chloromethyl ether
1910.1007	3,3'-Dichlorobenzidine
1910.1008	bis-Chrolomethyl ether
1910.1009	beta-Naphthylamine
1910.1010	Benzidine
1910.1011	4-Aminodiphenyl
1910.1012	Ethyleneimine
1910.1013	beta-Propiolactone
1910.1014	2-Acetylaminofluorene
1910.1015	4-Dimethylaminoazobenzene
1910.1016	N-Nitrosodimethylamine
1910.1017	Vinyl chloride
1910.1018	Inorganic arsenic
1910.1027	Cadmium
1910.1028	Benzene
1910.1029	Coke oven emissions
1910.1044	1,2-dibromo-3-chloropropane
1910.1045	Acrylonitrile
1910.1047	Ethylene oxide
1910.1048	Formaldehyde
1910.1050	Methylenedianline

From 29 CFR, Part 1910—Occupational Safety and Health Standards, July 1995.

Agency prepared publications that provided information on possible carcinogens and methods for controls.[110] NIOSH especially recommended exposure limits and appropriate preventive measures that were designed to reduce adverse health effects of occupational chemicals in accordance with the OSHA rulemaking process.[69] OSHA has issued regulations for occupational carcinogens in the workplace (Table 3).[64]

CHARACTERISTICS OF OCCUPATIONAL CANCER

Latency Period

The latency period is the interval between the first exposure to the responsible agents and the first appearance of the manifestation of the tumor. It is a summation of the times required for the initiation of the malignant change and for the growth of the tumor to a size that permits recognition and diagnosis. Cancer does not usually develop within months after exposure. The minimum latency period is usually 5 years for noncutaneous cancers, with a large proportion of cases appearing 10–30 years after first exposure. For humans, the latency period varies from a minimum of 6 years for radiation-induced leukemia to 40 or more years for some cases of asbestos-induced mesotbelioma. For most tumors, the interval is 12–25 years.[26]

Occupational skin cancers exhibit a wide span of latent periods—from less than 1 year to more than 50 years.[32,82] In general, the higher the dose the more likely the latency will be shorter. The latency period has an important impact on the design of epidemiologic studies of occupational groups exposed to potential or known carcinogens. In a relatively short follow-up study, if the workers are young, the cancer incidence may not occur within the time limitations of the study.

Dose-Response Relationship

Although thresholds may not exist, there is strong evidence for a dose-relationship for most carcinogens that have been adequately studied. The degree of exposure has been used to indicate relative concentrations such as high, medium, and low. An increasing risk with increasing exposures is generally observed. Both experimental studies in animals and epidemiologic reports in humans support this concept. For example, dose-response relationships have been shown for lung cancer associated with asbestos[22,57] and coke oven emissions.[52]

Threshold Limit Values

The threshold limit value is the time-weighted average concentration that may safely be inhaled over an 8-hour working day. However, the TLV is a controversial issue. No one knows if a "safe" level for carcinogens exists. Since a single mutation in a single cell can theoretically give rise to a malignancy, it has been argued that there is no safe level of exposure in terms of cancer development. However, other arguments have shown support for establishing thresholds. Those who favor the threshold theory believe that defense mechanisms operate to inhibit or inactivate carcinogenic agents.[30] The assumption is that as long as a healthy immune defense system exists, there will be a threshold. Still, there is no way of knowing the adequacy of each individual's defense mechanism.

In epidemiologic studies in humans, no safe threshold for carcinogen exposure has been demonstrated with certainty. Currently, there is insufficient evidence to prove the existence of a threshold for carcinogens. While it is impossible to prove the existence of thresholds for carcinogens, some recent studies in animals indicate that a threshold mechanism exists.[21,28] A recent study on the relationship between saccharin and bladder cancer reported that a threshold effect exists in male rats, but a carcinogenic effect on the human urothelium is unlikely at even the highest levels of human consumption of saccharin.[21] If a threshold does exist for saccharin bladder tumor promotion that is above the saccharin consumption level of all humans, the risk is zero.[28] In the absence of a safe dose for a carcinogen, a dose-response curve for each carcinogen can estimate the risk at low levels of exposure. With this information, one can evaluate the risks that are probable in the workplace.[30]

Histologic Types

Cancers developing from the same anatomic site may differ widely in histologic properties and in factors of causation. For some sites, such differences may be associated with well-defined dissimilarities in the microscopic appearance of the neoplasms. For example, patients with varions cell types of leukemia differ in regard to clinical characteristics. Some occupational cancers also show different histologic types. For example, angiosarcoma is the particular cell type of liver cancer associated with vinyl chloride.[86] In primary bronchial carcinoma, a number of microscopic types have been identified; some differ in their clinical characteristics as well as in their association with occupational or environmental factors such

as cigarette smoking. For lung cancer associated with bischloromethyl ether, arsenic, and radiation, the histologic cell types are predominantly small cell, undifferentiated carcinomas.[24,63,76]

Demographic Variables

The age at diagnosis of cancer is related to the age at first exposure. People older than 50 and younger than 15 are more sensitive to carcinogens.[30] Occupational cancers are still manifested after age 65 among individuals who have retired from hazardous industries. For example, increased lung cancer has been observed among retirees who worked at asbestos plants.[22]

Gender is another variable being evaluated to determine cancer frequency. The incidence of lung cancer is generally much higher for males than females due to confounding variables (i.e., smoking) and occupational exposures.[104]

OCCUPATIONAL CARCINOGENS IN HUMANS

The International Agency for Research on Cancer categorizes four groups of carcinogenicity based on the amount of evidence:[40] group 1 is sufficient evidence of carcinogenicity in humans; group 2 is limited evidence, group 3 is insufficient evidence, and group 4 is lack of evidence of carcinogenicity. Group 1 includes chemicals and processes established as human carcinogens based on epidemiologic studies in humans. Table 4 summarizes group 1 occupational carcinogens.

Known lung carcinogens are asbestos, arsenic, chloromethyl ethers, chromium, mustard gas, nickel compounds, radon, and polychlorinated aromatic hydrocarbons including coke production.[4,40] These carcinogens are classified as occupational carcinogens based on sufficient evidence from various human epidemiologic studies.

Skin cancer is associated with arsenic, coal tars, coke production, mineral oils, shale oils, and soots. Mineral oils are a complex class of materials ranging from crude petroleum through various fractions produced at refineries to products used as coolants and lubricants in various industries. But not all mineral oils cause cancer of the skin. Extraction and refining of oil from Scottish shale oil has been associated with skin cancer among workers exposed to certain fractions of unrefined oils.[40]

Liver cancer is associated with aflatoxins and vinyl chloride; bladder cancer is caused by benzidine and beta-naphthylamine.

Occupational cancer epidemiology requires valid research methods depending on the research objectives. The primary objective in epidemiologic studies of occupational cancer is to study cancer morbidity and mortality in working populations and to investigate the distribution of causal factors. The evidence required for establishing carcinogenicity from epidemiologic studies is a positive association between exposure and disease in groups of individuals with known exposures that (1) are not explicable by bias in recording or detection, confounding or chance, (2) vary with dose and time after exposure, and (3) are observed repeatedly in different circumstances. There are two types of epidemiologic studies of cancer: descriptive and analytic studies. Descriptive epidemiologic studies are usually concerned with the collection of cancer incidence, prevalence, and mortality in the working population. These studies are used to test hypotheses that a particular segment of the population, for instance an occupational group or a group of employees in specific work settings, are subject to an increased risk of cancer. In such studies, national or regional rates of cancer mortality or cancer incidence are normally used as reference values. Descriptive cancer epidemiology is of great importance in occupational health. It would be impossible to set up effective

TABLE 4. Occupational Carcinogens in Humans*

Carcinogen	Cancer Site	Exposure	Industry/Occupation
Aflatoxin	Liver, lung	Ingestion of contaminated food	Grains, peanuts
4-Aminobiphenyl	Bladder	Inhalation; skin absorption	Dye manufacture, dye intermediate, rubber antioxidant
Arsenic and arsenic compounds	Lung, skin	Inhalation; skin absorption; ingestion	Copper and cobalt smelters, glass production, wood treatment, pesticides, wool fiber production, mining of gold-bearing ores containing arsenic
Asbestos	Lung, mesothelioma	Inhalation	Asbestos industry, insulation, buildings, brake and shoes workers, shipyard workers, sheet-metal workers, asbestos cement industry, plumbers and pipe-fitters
Benzene	Leukemia	Inhalation; skin absorption	Petroleum, coking industry, rubber and petrochemical workers
Benzidine	Bladder	Skin absorption; inhalation	Dye manufacture, rubber, plastic, cable industries, chemical industries
Bis(chloromethyl) ether	Lung	Inhalation; skin absorption	Ion-exchange resin production, chemical intermediate, contaminant of chloromethyl methyl ether, electronic, chemical, ceramic, mining industries
Chromium	Lung, nasal cavity	Inhalation	Chromium production, plants, chromate pigment industry, plating, painters, jewelers
Coal tar and coal tar pitches	Skin, lung, bladder	Inhalation; skin contact	Paving and roofing, steel industries, patent-fuel workers, coal gasification, coke production, tar-distilling, optical lens workers
Mineral oils	Skin	Inhalation; skin contact	Solvents in printing, lubricant in metal-working
Mustard gas	Lung	Inhalation; skin contact	Manufacture of mustard gas, poison gas manufacture
Beta-naphthylamine	Bladder	Dye industry	(No longer in commercial use)
Nickel compounds	Lung, nasal cavity	Inhalation	Nickel refining and smelting industries
Radon	Lung	Inhalation	Underground miners, uranium mining, iron mining
Shale oils	Skin	Skin contact	Oil shale industry, cotton-textile workers
Soots	Skin, lung	Skin contact	Chimney sweepers
Vinyl chloride	Liver (angiosarcoma)	Inhalation	Polyvinyl plastic production workers, polyvinyl chloride resins production industry

* Sufficient evidence for carcinogenicity to humans, according to evaluation by the International Agency for Research on Cancer.

cancer control programs for working populations in the absence of such data. In analytical epidemiologic studies, specific hypotheses concerning association between factors in the working environment and the occurrence of cancer are examined.

The number of well-established occupational carcinogens and associated cancers are relatively small (see Table 4). Some carcinogens and related cancers that are reviewed using epidemiologic study results are described below.

Asbestos and Respiratory Diseases: Lung Cancer, Mesothelioma, Asbestosis

There is sufficient evidence for the carcinogenicity of asbestos in humans.[40,80,81] Occupational exposure to asbestos has been associated with three important diseases: lung cancer, malignant mesothelioma, and asbestosis. There are four commercially important forms of asbestos: chrysotile, amosite, anthophyllite, and crocidolite. Asbestos is used in roofing products, friction products, asbestos cement, and gaskets.[96] Asbestos, which is not a single mineral, has two natural forms: amphiboles, which are chain silicates and have straight fibers, and serpentine forms, which have a short structure and fibers arranged to produce hollow, tube-like spirals. The two common varieties of the amphiboles are crocidolite (blue asbestos) and amosite (brown asbestos). The serpentine form is known as chrysotile (white asbestos), which is currently used almost exclusively in industry.

The major industrial use of asbestos is restricted to chrysotile in the manufacture of piping, roofing, insulation, and friction materials. The lung cancer mortality of occupationally exposed chrysotile miners in Quebec has been well documented by McDonald.[58] Occupational exposures to chrysotile, amosite, anthophyllite, and mixed fibers containing crocidolite have also resulted in a high incidence of lung cancer.

Malignant mesothelioma is a rare cancer associated with asbestos exposure. In 1960 the first case, which was reported by Wagner, was associated with crocidolite exposure in South Africa.[105] The importance of the amphiboles in pathogenesis was further demonstrated by Newhouse and Thompson in 1965.[62] The incidence of mesothelioma has increased over the years, with an annual incidence for adults in North America of 2–3 cases per million for men and 0.7 per million for women.[25] In 1994, the OSHA permissible exposure limit (PEL) for asbestos fibers in the workplace was changed from an 8-hour time weighted average of 0.2 f/cc to 0.1 f/cc.[99] This exposure standard requires personal protective equipment, training, medical surveillance, and engineering controls.[96]

Aromatic Amines: Bladder Cancer

Several chemicals within aromatic amines, including 2-naphthylamine and 4-aminobiphenyl benzidine, have been reported as the cause of bladder cancer.[43] The first occupational bladder cancer was associated with the German dyestuff industry.[71] 2-naphthylamine was used mainly as an intermediate in the manufacture of dyes and as an antioxidant in the rubber industry. However, it was not produced for commercial use in the United States.[96] Benzidine has been used for more than 60 years as an intermediate in the production of azo dyes, sulfur dyes, fast color salts, naphthols, and other dyeing compounds.[96] The primary routes of potential human exposure to benzidine are inhalation, ingestion, and dermal contact.

A survey of workers with dyestuff intermediates revealed that a large number of bladder cancer cases over 30 years were associated with benzidine and naphthylamines.[79] This result was confirmed in numerous studies.[13,27] In addition to benzidine and 2-naphthylamine, a number of other aromatic amines have been suspected of bladder carcinogenicity. Melick et al. reported that there was an increased risk of bladder cancer associated with exposure to 4-aminobiphenyl, which was used in the North American rubber industry.[58,59] Two other aromatic amines, including N-phenyl-2-naphthylamine and N,N-bis (2-chloroethyl-2-naphthlamine), have been reported as possible human carcinogens.[36]

Alkylating Agents: Lung Cancer and Leukemia

Alkylating agents are of interest from the point of view of cancer induction because the alkylation of nucleic acids is thought to be an important mechanism in carcinogenesis. Of all known alkylating agents, bis-chloromethyl ether is known to be a carcinogen that causes lung cancer in humans. BCME occurs as a contaminant in the production of chloromethyl methyl ether, which is used as a chloromethylating agent in the manufacture of ion exchange resins. BCME also has been used in dental restorative materials. The primary routes of potential human exposure to BCME are inhalation and dermal contact. Evidence for the carcinogenicity of BCME has come from studies conducted in the Federal Republic of Germany,[89] Japan,[77] and the United States.[24] In all cases, BCME was associated with oat-cell carcinomas.

Ethylene oxide is one of the epoxide alkylating agents with a three-numbered ring that readily opens even under mild conditions. Ethylene oxide is primarily used as intermediate in the production of several industrial chemicals, most notably, ethylene glycol. It also has been used as a sterilant and fumigant in health products and flame retardants. Human studies associated with exposure to ethylene oxide have been inconclusive. However, Scandinavian studies have reported increased risk of leukemia in a small group of workers using ethylene oxide as a sterilant.[35] In a study of ethylene oxide in the United States, no excess mortality was found, and a cohort study of the chronic effects of this chemical in the U.S. workers showed no adverse hematologic findings.[16]

Benzene: Myelogenous Leukemia

Benzene is an integral component of petrochemical feed stocks and is present in gasoline in the United States in the range of 1.0–1.5%. Benzene is also formed during coke oven operations. Benzene is a major raw material used extensively as a solvent in the chemical and drug industries. It is a useful intermediate in organic synthesis and is frequently used in research and commercial laboratories. The primary routes of potential human exposure to benzene are inhalation and dermal contact. Benzene is associated with acute and chronic myelogenic leukemia.[1–3,37,38] A causal relationship has been established through epidemiologic research.[48] The form of leukemia associated with benzene is usually myeloid, occasionally monocytic, but never lymphatic. The most recent mortality study of 74,828 benzene-exposed workers in China reported significantly increased risk of myelogenous leukemia.[109]

In 1977, after NIOSH identified a group of rubber workers with a fivefold increased risk of acute myelogenous leukemia, OSHA attempted to lower the workplace standard for benzene to 1 ppm. In 1987, OSHA established the 1 ppm TWA (time-weighted average) standard for benzene based on the rubber workers cohort.[72]

Polycyclic Aromatic Hydrocarbons: Scrotal Cancer and Lung Cancer

Polycyclic aromatic hydrocarbons are a large group of chemicals. In industry, their main sources are soots, tars, and mineral oils, and the primary routes of potential exposure are inhalation, ingestion, and dermal contact. There is sufficient evidence for the carcinogenicity of soots, coal tars, and mineral oils in humans.[40] In the 18th century, Percival Pott reported that scrotal cancer in chimney sweeps was caused by soots. An increased number of skin and scrotal causes have been found in workers operating aromatic lathes who are exposed to the fine mists of cutting oils.[49,106] Although scrotal and skin cancer remain a problem in a number of industries due to the exposure to polycyclic aromatic hydrocarbons, there is an increasing recognition that other sites of cancer are associated with these materials.

Evidence of an increased risk of lung cancer has been found in workers exposed to coal and tar gas.[45] Foundry workers also are at risk from exposure to polycyclic aromatic hydrocarbons; an increased risk of lung cancer was particularly associated with iron and steel foundries.[29,61,88] Several studies in Finland showed a high excess of lung cancers in foundry workers, and molders were the group apparently at highest risk. In these studies, occupations were classified according to their exposure to benzo-(a)-pyrene, and higher exposures were more common among cases than controls, which suggested that exposure to polycyclic compounds may be a causative factor.

Vinyl Chloride: Angiosarcoma

Vinyl chloride is a colorless gas but is usually handled as a liquid under pressure. It is used for production of vinyl chloride resins, production of methyl chloroform, and as a component of propellant mixtures. The primary cancer site associated with human exposure to vinyl chloride is the liver. This association has been confirmed in many studies since 1974.[9,10,27,107] More than 30 cases of angiosarcoma of the liver have been reported among vinyl chloride polymerization workers in the United States and in nine other nations.[14,23] Because this tumor is extremely rare, the occurrence of these cases suggests a causal relationship to a specific phase of vinyl chloride production. However, after reviewing the epidemiologic studies conducted in the United States and United Kingdom, Doll concluded that the evidence that vinyl chloride is a human lung carcinogen is weak.[19]

Although the latency period from first exposure to diagnosis varies considerably, in most cases it is between 15–24 years from first exposure, with a median latency of 15–19 years.[36] In 1994, the Environmental Protection Agency and the Food and Drug Administration banned the use of vinyl chloride as an aerosol propellant, eliminating the potential vinyl chloride exposure of 1 million-5 million people annually.[96] OSHA has adopted a permissible exposure limit of 1 ppm for vinyl chloride as an 8-hr TWA, with a 5-ppm ceiling for any 15-minute period. OSHA also requires medical surveillance and the use of protective clothing and respirators in the workplace.

Metals: Lung Cancer and Skin Cancer

The association between chromates and lung cancer has been confirmed in several studies on the chromate production industry.[5,53] The first report of an increased risk of respiratory cancer among nickel workers came from Wales, and the association was confirmed by studies in other countries.[88] The risk was generally attributed to nickel carbonyl, a gas that is produced when nickel reacts with carbon monoxide. Nickel carbonyl has been found to be carcinogenic in experimental studies in animals, and epidemiologic studies of workers exposed to other nickel compounds have shown an excess of lung and other respiratory tract cancers.[66] In 1987, IARC concluded that long-term occupational exposure to cadmium also may contribute to lung cancer.[40]

Arsenic was widely used as a herbicide and fungicide, and it is still extensively used in wood treatment. The carcinogenic properties of arsenic have been suspected since the 1820s, but the first clear association between arsenic exposure and cancer was demonstrated by Hill and Faming in 1948.[34] There is sufficient evidence for the carcinogenicity of inorganic arsenic compounds in humans.[40] Skin cancer was the original cancer associated with arsenic, and the relationship has been well documented.[7] Epidemiologic studies on smelter workers have indicated a synergistic

effect between arsenic exposure and cigarette smoking in the induction of lung cancer.[12]

Cadmium, which is broadly distributed in the environment, has many industrial applications, including electroplating, pigment production, and additives for plastics, especially polyvinyl chloride.[67] Although information on the carcinogenicity of cadmium is incomplete, recent epidemiologic studies have provided evidence that cadmium is carcinogenic in the lung but not in the prostate. In 1987, IARC concluded that long-term occupational exposures to cadmium may contribute to lung cancer.[40]

Metalworking Fluids: Cancers of the Stomach, Bladder, Pancreas, Larynx, Skin, and Other Sites

Metalworking fluids (MWF) have been used in various industries and encompass a diverse group of agents. Rather than describing a specific chemical composition, the term machine fluids describes a function, that of cooling and lubricating surfaces in machining operations. Suspected carcinogens contained in various types of machining fluid as additives or contaminants include polyaromatic hydrocarbons, nitrosoamines, sulfur-containing compounds, formaldehyde-releasing biocides, and certain metals.[90] The route of exposure to MWFs is generally through dermal contact or inhalation. Large sizes of many airborne particles can lead to gastrointestinal exposure.

Many studies suggest an association between MWF exposure and various cancers, including the stomach, bladder, pancreas, larynx, skin, and esophagus. Specific classes of MWFs may be associated with cancer at certain sites. Straight oil exposure has been associated with an increased risk of laryngeal cancer and rectal cancer, while synthetic oil exposure has been associated with an elevated risk of pancreatic cancer. For stomach cancer, several studies reported that MWF exposure is associated with a significantly elevated risk.[73,84] Soluble oil exposure may be associated with an increased risk of stomach cancer.[84] A number of MWF-exposed cohorts were reported to have an increased risk of bladder cancer.[84,101] Based on case-control studies, other MWF-exposed populations have been found to have an increased risk of bladder cancer. Mortality studies have found an excess of pancreatic cancer among workers exposed to soluble oils.[90] The risk of pancreatic cancer mortality was increased among workers who were employed 10 or more years as grinders at ball bearing manufacturing plants.[84] For laryngeal cancer, several studies of MWF-exposed cohorts reported significantly elevated risk of laryngeal cancer.[90,101] Specifically, study groups were exposed to straight oils. For skin cancer, a cohort study[44] and a population-based case-control study have found an increased risk of skin cancer among MWF-exposed workers.[74] A recent mortality study in England reported that significantly elevated proportional mortality ratios of scrotal cancer were found in metal machinists exposed to cutting oils.[15]

OCCUPATIONAL CANCER SURVEILLANCE

Occupational cancer surveillance monitors cancer incidence, mortality, and exposure to workplace hazards. The ultimate purpose of occupational cancer surveillance is to provide useful information for planning cancer control programs that are directly linked to preventive action. The surveillance efforts include data collection through surveillance systems and surveillance activities such as disease-based surveillance, exposure-based surveillance, and medical screening.

Mortality Data

The National Center for Health Statistic codes each of the 2 million deaths in the United States that are reported to vital registration offices annually. The data for each decedent include underlying and contributing causes of death, age, sex, race, and residence. Since 1985, the usual occupation and industry of each decedent have been available for about 25 states. Since 1985, these mortality data have provided valuable information on relationships between cancer and occupation. In 1976, a comprehensive analysis of occupation and cause of death for the state of Washington was completed.[60] In England and Wales,[70] similar data have been available for analysis every 10 years.

Cancer Survey Data

As part of the Third National Cancer Survey in the United States, occupational histories were obtained on a random sample of incident cases. The data were analyzed to evaluate associations between specific cancer sites and various occupations.[108] The Third National Health and Nutrition Examination Survey (NHANES III) conducted by the National Center for Health Statistics collected information on skin cancer and occupation as a part of its survey components during 1988–1994.[97] The NHANES III is a 6-year survey measuring the health and nutritional status of the civilian noninstitutionalized U.S. population aged 2 months and older. Revision of the Bureau of Labor Statistics Annual Survey beginning in 1992 allowed identification of numbers of specific diseases that were considered serious. According to this 1992 survey, among the serious cases, employers reported 103 employees with occupational cancer.[91]

Cancer Registries

In 1994, the NCI expanded the SEER program, which is a network of nine population-based cancer incidence registries located in selected areas of the country and covering about 10% of the U.S. population. Currently, the cancer files maintain about 1.7 million cancer cases, and about 120,000 are added each year.[17] Unfortunately, this registry does not contain information on occupational history. To be useful for occupational surveillance in the future, it would need to collect the usual occupational information in certain types of cancer on the SEER registry system. In Europe, the European Cancer Registry-Based Study of Survival and Care of Cancer Working Group collected data on cancer survival from 30 cancer registries in 11 countries and established a database that covered about 800,000 cancer patients who were diagnosed in 1978–1985 and followed to the end of 1990.[41]

Type of Occupational Cancer Surveillance

Disease-Based Surveillance

Disease-based surveillance includes case reports on the occurrence of cancer in a person with a specified occupation. Evaluation of routinely collected data on occupation and persons with cancers may lead to the identification of unrecognized occupational hazards. A formalization and generalization of case reports is known as the sentinel health event.[75] The occurrence of diseases known to be associated with occupational exposure can lead to identification of currently uncontrolled exposures. The SEER program is an example of disease-based surveillance, but it does not contain occupational information. The next level of disease-based surveillance is the conduct of formal case-control studies. Case-control studies are useful in finding

new occupational causes of cancer. The advantages of disease-based surveillance of possible occupationally related cancer are that specific cancers can be targeted for evaluation and that a wide variety of occupations can be related to the occurrence of cancer.

EXPOSURE-BASED SURVEILLANCE

Exposure-based surveillance is usually based on cohort or follow-up studies in which persons with an occupation of concern are identified and followed in order to measure the rate of occurrence of cancer. If follow-up is prospective, exposure can be measured with greater accuracy. In a retrospective study, it is difficult to measure the exposure level, and an approximation is possible. Researchers conducting retrospective cohort studies should consider the issues of what, whom, where, and how to study. Levine and Eisenbud have identified more than 20 industrial populations that could potentially be studied retrospectively.[89] Some of these populations include persons with exposure to known human carcinogens, including benzene and chromates.

Through prospective studies, exposure can be quantified with accuracy and exposed persons followed according to adverse health outcomes. A disadvantage of these studies is that many years of follow up are required for appropriate evaluation of possible associations between exposure and the occurrence of cancer.

NIOSH conducted the National Occupational Exposure Survey in 1981–1983.[98] It consisted of an on-site exposure survey in a sample of 4,490 establishments that had been selected to represent most sectors of the American workforce covered by the Occupational Safety and Health Act of 1970.

MEDICAL SCREENING

Medical screening programs are used to detect early signs of disease. In general, ideal programs should be simple, inexpensive, and accurate in testing a population with a high prevalence of a certain disease. Furthermore, intervention should be available for those who are found to have a positive sign of disease. Occupational medical screening is one of the most complex processes in medical practice. In designing a medical screening program, practitioners should be familiar with clinical medicine and toxicology and understand a standardized approach to data collection.[8] Medical surveillance of populations at high risk of cancer is only effective in the following situations: (1) if the screening test is easy to perform and sensitive, (2) if it detects premalignant abnormalities or tumors at an early stage, and (3) if there is an effective intervention that reduces morbidity and mortality when applied to early tumors.[25]

Cancer surveillance in occupational settings has been explored for bladder cancer among workers exposed to beta-naphthylamine and for benzidine exposures and lung cancers. For bladder cancer screening, two methods have been used: urinalysis for microscopic hematuria and urine cytology. Hematuria is relatively sensitive in detecting superficial and invasive bladder cancer, but it may result in a high false-positive rate. Urine cytology has good sensitivity and specificity for invasive bladder cancer, but no survival advantage has been demonstrated with this technique. However, in 1989, the International Conference on Bladder Cancer Screening in High-Risk Groups concluded that urinalysis and cytology might be appropriate.[78]

Lung cancer surveillance includes chest radiography or sputum cytology. These methods have been evaluated at several academic institutions in the 1970s. Medical screening for lung cancer was comprehensively reviewed by Marfin and Schenker

in 1991.[54] The results from these approaches showed a significant increase in lung cancer detection, but there was no significant decrease in lung cancer mortality. With these results and other data, no routine surveillance for lung cancer was recommended, even to high-risk populations.[87] Other medical surveillance for occupational cancers includes Pap tests for cervical cancer, fecal occult blood testing and sigmoidoscopy for colorectal cancer, and mammography for breast cancer. Some form of medical surveillance is required by the OSHA standard for asbestos, arsenic, benzene, and a variety of other carcinogens[85] (see Table 3).

PRIORITIES FOR OCCUPATIONAL CANCER RESEARCH

Priorities for occupational cancer research should be considered in relation to occupational carcinogenic hazards. Several papers have suggested the importance of priorities for future occupational cancer research.[20,39] In 1996, the National Occupational Research Agenda includes occupational cancer research methods as one of the 21 research priorities identified by NIOSH.[93] The NORA emphasizes the importance of molecular biology as a powerful new research tool that may lead to information that could be used to take protective measures before workers suffer the consequences of exposures to various potential carcinogens. Advances in understanding the mechanisms of cancer causation are beginning to improve the ability of scientists to use laboratory research to evaluate the carcinogenic potential of a substance and to describe the hazard to humans with accuracy. More research is needed on comparative mechanisms of toxicity and on the development of rapid and inexpensive tests to complement or modify traditional animal toxicity tests. Advanced techniques of molecular biology are needed to understand interactions of chemicals with critical target genes and to develop more accurate and less expensive methods to estimate worker exposure to potential carcinogens.

Numerous factors need to be considered when hypothesizing that an occupational cancer exists in a given occupation: (1) the level of significance of the possible association between occupation and types of cancers, (2) the possibility of confounding factors such as smoking, (3) the number of cancers sites with which the occupation is associated, (4) the likelihood of occupational exposure levels, (5) the degree to which the occupation-cancer association is supported by other epidemiologic studies, and (6) whether occupations with similar exposures have an excess of the cancer of interest due to known or suspected carcinogenic agents.

Dubrow and Wegman recommended five working groups for further study:[20]

Asbestos Workers. Asbestos is a well-known occupational carcinogen that is associated with cancers of the lung, larynx, esophagus, stomach, and other sites.[40] The association between asbestos exposure and lung cancers or mesotheliomas among asbestos insulation workers and shipyard workers are particularly well established.[11,46,80,81] Additional work is needed to characterize level of exposure and cancer risk and to establish a safe dose level at the workplace. The problem of asbestos exposure has been widely recognized and has occupational and public health significance. Therefore, a national program for prevention of asbestos exposure is needed.

Motor Vehicle Operators. The United States had more than 3.9 million commercial motor vehicle operators in 1995.[92] Cancers of the lung and larynx have been reported among motor vehicle operators. As risk factors for these cancers, smoking, diesel exhaust and gasoline should be studied.

Machinists and Related Occupations. There were more than 2.8 million machinists and related workers in the United States in 1995.[92] In particular, tool makers

were reported to have excess cancers of the large intestine and bladder. Potential carcinogenic agents include synthetic abrasives and cutting fluids.

Electric Workers. The United States had more than a half million electric workers in 1995.[92] Electricians were reported to have an excess of lymphoma and cancers of the bladder and brain. Potential carcinogenic exposure includes nonionizing radiation.

Metal Molders. There were more than 100,000 metal molders in the United States in 1995.[92] Metal molders had a high risk of lung cancer. Potential carcinogenic exposures include polycyclic aromatic hydrocarbons, metal dusts, fumes, and oxides.

A panel from IARC developed 10 criteria for selecting occupational exposures in epidemiologic studies.[39] These criteria, which are related to the issues of potential public health importance, include (1) the number of workers exposed, (2) level of exposure to workers, (3) quality of exposure data, (4) carcinogenic potential, (5) evidence of human carcinogenicity, (6) ongoing exposure to known carcinogens at permissible levels of exposure, (7) trends in exposure, (8) control of confounding factors, (9) cases potentially attributable to exposure, and (10) length of time since first exposure.

For epidemiologic approaches in occupational cancer, the epidemiologist develops hypotheses from clinical observations or from statistical associations between specific forms of cancer and population characteristics that are derived from an analysis of population morbidity or mortality statistics. By means of such statistics, the cancer epidemiologist seeks to discover and to exploit variations in the occurrence of cancer. Such variations are recognized by making comparisons, for example, between different times between groups of people living in different areas, or perhaps between groups of people living closely but who differ in such characteristics as sex, age, occupation, or habits such as smoking. For comparisons of cancer occurrence to be valid, the following requirements must be fulfilled: (1) the diagnosis of cancer must be clearly and uniformly defined, (2) a uniform procedure must exist for selecting the recognized cases of cancer that will be used to obtain an estimate of cancer occurrence; and (3) the population groups themselves and the group characteristics must be adequately defined. All epidemiologic data should be integrated with experimental and clinical data, and the epidemiologist should attempt to derive inferences from these data regarding etiologic factors. The methods have general applications, but each method is not equally applicable to all sites. For example, cancer of the skin, which has a low fatality rate, cannot be studied through mortality data, and prospective inquiries are seldom suitable unless the incidence of the cancer under study is relatively high.

CONCLUSION

Occupational cancer differs from other occupational diseases in several ways: (1) no safe level of exposure to carcinogens has been determined; (2) cancer develops many years after exposure; (3) many different sites of cancer exist; and (4) most cancers are preventable. The risk of cancer in humans is increased by a variety of occupational/environmental factors, ranging from exposure to an identified agent to exposures through lifestyle factors such as smoking or socioeconomic conditions. Occupation may contribute to the development of cancer if there is an exposure to certain carcinogenic agents, such as certain metals, dyes, organic and inorganic dusts, solvents, and pesticides. Since carcinogenesis is a multisequential process, reductions in exposures to carcinogens at the workplace are necessary to maximize the

effectiveness of cancer prevention in the workplace. Prophylactic intervention is also possible for some known risk factors associated with certain cancer sites. Cancer prevention and control intervention in the workplace must include (1) primary prevention programs that emphasize avoiding potential exposures and use of proper education; (2) secondary prevention programs that emphasize increasing medical screening practices; and (3) appropriate surveillance programs. The prevention of occupational cancer requires the participation of various federal and state agencies and the development of good practice. At present, fewer than 20 known carcinogenic agents have been evaluated based on studies in humans and animals. Furthermore, exciting developments in epidemiologic and animal studies will contribute to the identification of additional carcinogenic agents in the workplace. New biologic markers of exposures and cancer-related outcomes need to be identified and integrated into epidemiologic studies. Because epidemiologic data regarding the carcinogenicity of many exposures are not available, research methods to evaluate and improve the predictive value of animal and in vitro systems must be developed. A more complete understanding of occupational cancer trends will require further research on occupational cancer risks and means of prevention. Finally, ultimate prevention of occupational cancer could be effectively accomplished when health administrators, epidemiologists, industrial hygienists, occupational physicians, toxicologists, and safety engineers work together as a team to provide proper guidelines for preventive strategies and controls.

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