Journal of Toxicology and Environmental Health, Part B
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uteb20

Roles of epidemiology, pathology, molecular biology, and biomarkers in the investigation of occupational lung cancer

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Available online: 02 Sep 2009

To cite this article: Val Vallyathan, Francis Green, Barbara Ducatman & Paul Schulte (1998): Roles of epidemiology, pathology, molecular biology, and biomarkers in the investigation of occupational lung cancer, Journal of Toxicology and Environmental Health, Part B, 1:2, 91-116

To link to this article: http://dx.doi.org/10.1080/10937409809524546

ROLES OF EPIDEMIOLOGY, PATHOLOGY, MOLECULAR BIOLOGY, AND BIOMARKERS IN THE INVESTIGATION OF OCCUPATIONAL LUNG CANCER

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The pathology and molecular biology of lung cancer demonstrate that these tumors evolve through a series of mutations, molecular changes, and corresponding morphologic changes. To elucidate how occupational and environmental factors influence lung cancer histogenesis it is important not only to understand epidemiology and the interactions between etiologic agents but also to integrate information from pathology, biochemistry and molecular biology. This review focuses on the range of techniques currently available for characterizing lung cancer and how their prudent use can be beneficial in the identification of occupational carcinogens. Because many occupational and environmental lung cancers are caused by multiple etiologic agents, the integration of histology with cellular, biochemical and molecular biomarker techniques may provide new approaches for understanding the disease process.

The contribution of occupational and environmental factors to the development of lung cancer is well recognized. Lung cancer is the most common cause of cancer mortality among men in the United States and ranks fifth among cancers in women worldwide (Stanley, 1986). Since the 1930s there has been a 15-fold increase in the mortality rate of lung cancer in men in the United States. This profound increase in lung cancer is attributable primarily to tobacco smoking, and to a lesser degree to occupational exposures and environmental factors. In the United States

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Journal of Toxicology and Environmental Health, Part B, 1:91–116, 1998

1093-7404/98 $12.00 + .00

approximately 170,000 new lung cancer cases were diagnosed in 1993 (Boring et al., 1993). Among cancer-related deaths, lung cancer is the leading cause of death of men and women in the United States (Garfinkel & Silverberg, 1991).

The recognition of an occupational exposure to the development of cancer was first reported in 1775 by Percival Pott in chimney sweepers developing an excess of scrotal carcinoma (Pott, 1775). Several occupational and environmental factors have since been implicated as contributing factors in the development of lung cancer. Agents associated with lung cancer include air pollution, arsenic, asbestos, beryllium, cadmium, chloromethyl ether, hexavalent chromium, coke oven emissions, diesel exhaust, fluorospar, mustard gas, nickel, radon, and radon daughters. In addition, in the past 15 years an excess lung cancer risk has been reported from occupational exposure to crystalline silica and in persons with silicosis (IARC, 1987). Although the relationship is still debated, the International Agency for Research on Cancer recently concluded that there is sufficient evidence in humans for the carcinogenicity of inhaled crystalline silica in the forms of quartz or crystobalite from occupational sources (IARC, 1997). The proportion of lung cancer associated with occupational and environmental factors is uncertain and approximations are often based on estimates involving unproven assumptions about numbers of individuals exposed, duration of exposure, and the dose-response relationship. For example, the amount of exposure extrapolated from historical studies of smoking, air pollution, and other risk factors may be inaccurate in relation to current actual exposures. Furthermore, several risk factors are often involved, complicating the risk assessment because of their interactive effects. Traditionally such studies have been handicapped by a long latency period of the cancer, inadequate exposure data, and the inability of some study designs to detect modest increases in cancers. Analyses of histologic cell type, sites of origin, molecular alterations, and biomarkers may provide valuable information in evaluating the true contribution of independent risk factors.

Cigarette smoking is the most important etiologic agent for lung cancer in the United States, and approximately 80–85% of all lung cancers are attributable to smoking (Garfinkel & Silverberg, 1991). Cigarette smoking in synergy with occupational factors may account for as much as 40% of lung cancers. Characteristically, cigarette smoking-associated cancers appear to originate in central rather than peripheral regions of the lungs. On the other hand, Doll and Peto (1981) estimated that 15% of the lung cancer in men and 5% in women could be attributed to occupational exposures. Vineis and Simonato (1986) attributed from 4 to 40% of all lung cancers in males to occupation. In the United States, Perera and Boffetta (1988) estimated 4–20% or 20,000–100,000 excess lung cancer deaths per year due to occupational exposures, whereas Landrigan and Markowitz (1995) estimated a lower bound percent incidence. Occupa-

tionally induced lung cancers may have a higher frequency of certain cell patterns and are more likely to have a peripheral origin, rather than a central origin in the lung.

This review summarizes epidemiologic, pathologic, molecular, and biomarker studies to demonstrate how occupational and environmental factors influence lung cancer histogenesis. Preliminary information on oncogenes and tumor suppressor genes and their correlation with known risk factors are also discussed. We further speculate on how a functional understanding of oncogenes and tumor suppressor genes may provide a better understanding of the mechanisms involved in tumor induction.

EPIDEMIOLOGIC STUDIES

Epidemiology focuses on the categorization of individuals into diseased and nondiseased status in carefully defined populations. The individuals for occupational epidemiologic studies are often drawn from occupational cohorts, and the data on disease status is usually gleaned from summary documents such as death certificates. Epidemiology has been useful in describing exposure-response relations, in identifying sources of variability of occurrence of disease, and in detecting hazardous environmental conditions that can be a target of preventive action (Valleron et al., 1992). The initial study of carcinogenesis in occupationally exposed populations is often descriptive in nature and does not account for all other possible influences. Epidemiological studies are generally observational, and rarely experimental. Consequently, the demonstration of an association between occupational exposure can never prove causality, although the weight of evidence from multiple epidemiological studies can contribute to an understanding of the causes of cancer and identify causal associations.

The major types of epidemiologic studies in populations of exposed workers include cohort studies, case-control studies, cross-sectional studies, and case-control within cohort studies. Although cohort studies more closely model experimental science, these tend to be prospective, costly, and time-consuming. In contrast, case-control studies are retrospective, but their results are highly dependent upon the selection of populations from which the samples are drawn, the criteria for case inclusion, the matching process, and the validity of risk factor ascertainment. Case-control studies are particularly useful for the study of cancer when the occurrence of disease in the exposed is uncommon. These studies are often used in preliminary, exploratory investigations.

Epidemiologic studies are useful public health tools because they provide a systematized approach for identifying risks in human populations. They are valuable for assessing causation, although many studies may be necessary to sort out the effects of confounding or interacting influences. Confounding factors for socioeconomic factors, for example, may be very

important when the demonstrated increase in risk is small, leading to a strong possibility of reaching the wrong conclusions (Taubes, 1995). Historically, epidemiologic studies do not account for mechanisms of carcinogenesis and it is often difficult to assess the complex interactions of multiple carcinogens. The inclusion of biomarkers may offer the opportunity to remediate these limitations.

HOW PATHOLOGIC TECHNIQUES COMPLEMENT EPIDEMIOLOGIC DATA

Epidemiologic approaches have been very successful in identifying potential carcinogens in the workplace. They have considerable power to detect an effect when the population of exposed individuals is large, the exposures are pure, and the exposures occur over a range of concentrations. It is likely that some occupational/environmental carcinogens are missed because the exposed populations are small and workers are exposed to many agents in the workplace. Pathologic techniques, including molecular biology and biomarkers, can be used to bridge the gap between epidemiology and bioassays. There are many specific areas where pathology and bioassays can complement epidemiology.

Confirmation of Diagnosis

Cohort mortality studies, for the most part, have relied on ascertainment of cause of death from death certificates. Many studies over the years have shown that agreement between death certificate diagnosis and autopsy diagnosis is variable (Selikoff, 1992; Feinstein et al., 1989). For major diagnostic categories, the overall agreement between death certificate and autopsy diagnosis is approximately 70% (Selikoff, 1992; Feinstein et al., 1989). Furthermore, agreement varies by specific diagnostic category. For example, agreements are usually high for conditions such as homicide, accidental death, and suicide, but notoriously poor for diagnostic categories such as emphysema and hypertension. Information from autopsies can therefore be used to increase the quality of the epidemiologic data and to obtain some idea of the uncertainty in categorization by diagnosis. Pathology also can be valuable when an etiologic agent may induce a distinct lung tumor, as asbestos is known to cause mesotheliomas. Because the number of mesotheliomas is small in relation to other lung cancers, the inclusion of these tumors with lung or pleura may provide only an insignificant elevation of cancer. In this instance the specific pathologic information of the mesothelial tumor was useful to define the outcome variable for epidemiologic studies. Therefore, such studies have great potential to offer more definitive proof of causation. Besides confirming the presence or absence of a lung neoplasm, pathology can be used to characterize the tumor further by criteria such as benign or malignant, and by cell type. Furthermore, pathology can be used to detect

the exact site of origin within the lung, the extent of its spread, and whether it was the attributable cause of death.

CYTOPATHOLOGY IN EARLY DETECTION AND DIAGNOSIS

Cytopathology is a frequently used, minimally invasive method valuable in the detection and diagnosis of early occult lung cancers without any clinical or radiological signs. Sputum cytopathology is the easiest and most common method of choice. Unfortunately, the sensitivity of sputum cytology when lung cancers are present ranges from 27% when only a single sample is examined to 89% with 3 samples (Johnston & Elson, 1991). This method is most sensitive for centrally located carcinomas, such as centrally placed squamous-cell and small-cell carcinomas. The use of bronchoscopy with bronchial washings, brushings, and biopsy can improve the detection of more peripheral tumors. However, in order for a tumor to be sampled by any of these techniques, it must communicate directly with the bronchial tree. Carcinomas that are not growing within the bronchial system will not be accessible by these techniques. The advent of fine-needle aspiration has proven to be sensitive with very specific diagnostic value to pulmonary neoplasms. By using this technique, tumors can be sampled with a minimal invasion percutaneously, most commonly via fluoroscopic or computed tomography (CT) imaging or via the bronchoscope with a Wang needle.

From the perspective of occupational medicine, it would be worthwhile to have a screening test available for high-risk workers prone to develop lung cancer. The two suggested methods include chest radiographs and sputum cytology, either alone or in combination with each other. Three large-scale screening projects of male smokers 45 yr and older have been conducted by Johns Hopkins Hospital, Baltimore, MD, Memorial Sloan-Kettering Hospital, New York, NY, and the Mayo Clinic, Rochester, MN. However, the effectiveness of these screening programs on lung cancer mortality was not demonstrated, and large-scale population screening was not advocated (Johnston & Elson, 1991). Although these studies do not conclusively support screening of all smokers, surveillance programs might be more useful in those workers exposed to known carcinogens, particularly if they smoke.

Identification of Preneoplastic Conditions

Malignant tumors develop slowly through a series of steps that have been well studied in colon cancer, the carcinoma of the cervix, and to some extent in the lung. The latency period of most occupational and environmental lung cancers is in the order of decades, and it is thought that these tumors evolve through a series of mutations with corresponding morphologic attributes. Standard histologic techniques readily detect these premalignant changes and involve hyperplasia (increase in cell numbers), metaplasia (change of one mature cell type to another mature

cell type), and dysplasia (abnormal development). Dysplasia occasionally progresses to carcinoma in situ and eventually to invasive carcinoma. Dysplastic lesions involve changes in the structure of the nuclear material, alterations in the nucleo-cytoplasmic ratio, disorganization of the cell layers, and increased and abnormal mitotic activity. These changes are often multifocal and can be mapped by severity and extent within autopsy and surgically resected lungs. Work in this regard has identified bifurcation of large airways as susceptible sites for malignant transformation (Cagle, 1995). Identification of preneoplastic changes in exposed working populations can also be used to develop early intervention and tumor prevention programs.

Serum Tumor Markers

In clinical laboratories serum oncofetal proteins and other tumor markers are frequently used as a diagnostic aid in confirming the presence of a neoplasm. Although these tumor markers play an important role in tumor staging, monitoring therapeutic response, and detecting cancer recurrence, their value in establishing a diagnosis is minimal.

Food and Drug Administration-approved and most commonly used tumor markers are alpha fetoprotein (AFP), B-human chorionic gonadotropin (BHCG), carcinoembryonic antigen (CEA), cancer antigen 125 (CA-125), prostatic acid phosphatase (PAP), and prostate-specific antigen (PSA).

Telomerase

Telomerase is a ribonucleoprotein enzyme that adds TTAGGG repeats onto telomeres to compensate for the shortening and stability of desmosomes. Telomerase is detected in most cancers and immortal cell lines, whereas it is absent in most somatic cells. Telomerase activation and telomerase-dependent immortalization of cells are considered to be an essential feature of the immortality of cancer cells (Sharma et al., 1996; Nouso et al., 1996).

Molecular Markers

Pathologic materials can be used to study the tumor and the surrounding normal lung parenchyma. Oncogene expression, tumor suppressor gene inactivation, formation of DNA and protein adducts, and endogenous productions of paraneoplastic hormones by the tumor are all potentially useful tools for studying the way in which specific agents interact with cells to produce tumors. The more normal tissue adjacent to the tumors can be used to identify genetic changes associated with risk; for example, a profile of P-450 isoenzymes (P-4501A1 and -1A2) has been identified as mainly involved in the metabolic activation of precarcinogens (Newaz et al., 1983).

CONFIRMATION OF EXPOSURE AND ESTIMATION OF DOSE

Many techniques exist for the identification of potentially carcinogenic agents within lung tissue, body fluids, and urine. Many techniques are available for the qualitative and quantitative determinations of mineral dusts such as asbestos, silica, and coal, and other inorganic minerals, chemicals, and pesticides in the lung and body fluids. In addition, investigations are being expanded to confirm or refute exposure to cigarette smoke. Past cigarette smoke exposure is assessed by the measurement of smoke-related mineral particulates in the lung tissue (Churg & Stevens, 1992), and current smoking status can be determined through the measurement of short-lived derivatives of organic materials of cigarette smoke in body fluids, such as cotinine and nicotine (Jarvis & Russell, 1984). The presence of DNA adducts can also be used to establish exposure. These techniques may play a major role in future studies to identify potentially confounding exposures and to resolve such difficult questions as the role of silica as a carcinogen. DNA adducts, however, are limited by the life span of the cells in which they are detected, and generally they represent exposures from the recent past.

OCCUPATIONAL AND ENVIRONMENTAL RISK FACTORS

Cigarette Smoke

An overwhelming majority of lung cancers in the United States occur in smokers (Garfinkel & Silverberg, 1991). Cigarette smoke contains tar, nicotine, several carcinogens, and other biologically active components (Stelman, 1968; Burns, 1991). In addition, cigarette smoking induces an inflammatory cellular influx into the lung including alveolar macrophages and neutrophils, whose products can induce mutations (Weitzman & Stossel, 1981; Heppner et al., 1989). Cigarette smoking is known to induce lung cancer with a dose-response relationship up to a 25-fold increased risk (Department of Health and Human Services, 1989). Cigarette smoking-induced neoplasms commonly occur in the central regions of the lungs. Kreyberg (1955, 1962) proposed that squamous-cell, small-cell, and large-cell carcinomas are etiologically associated with cigarette smoking, while the adenocarcinomas and bronchoalveolar carcinomas are unrelated to smoking. Further studies by Doll et al. (1957) demonstrated this relationship between the amount of cigarettes smoked and the development of squamous cancer. Subsequent histopathologic studies with a significant cigarette smoke exposure history have shown most squamous-cell carcinomas have no correlation to cigarette amount and cell type (Weiss et al., 1972). Yesner et al. (1973) observed good positive correlation between cigarette smoking and both small-cell carcinoma and squamous-cell carcinoma.

Asbestos

Commercial mining and large-scale industrial use of asbestos started in North America during the early 19th century. Asbestos was suspected as a carcinogen in 1935 by Lynch and Smith (1935) in North America and by Gloyne (1935) in the United Kingdom. Several case studies of asbestos-associated lung tumors with an exposure history to asbestos have appeared in the literature. These sporadic case reports were confirmed conclusively by epidemiologic studies in different asbestos-exposed populations showing a dose-response relationship between asbestos exposure and lung cancer mortality (Doll, 1955; Berry et al., 1972; Selikoff et al., 1968; Hammond et al., 1979; McDonald et al., 1974). It is estimated by the National Institutes of Health that over the next decades, roughly 13–18% of the total cancer mortality in the United States will be due to occupational exposure to asbestos (Bridport et al., 1978). We know that all types of asbestos increase the risk of developing bronchogenic carcinomas. However, the relative risk of developing a lung carcinoma may be greater among individuals exposed to amphiboles than to serpentine asbestos. The risk of developing a neoplasm is cumulative and increases with severity of exposure. Asbestos-associated lung cancer usually occurs at an earlier age than lung cancer in the general population and has a latency period of 20–30 yr.

Cigarette smoking increases the risk of developing bronchogenic carcinomas in asbestos-exposed workers (Selikoff et al., 1968; Hammond et al., 1979) by up to 50-fold when compared with a nonsmoking/non-asbestos control population. In contrast, presumed nonsmokers exposed to asbestos had an approximate fivefold increase in the risk for lung cancer compared with a nonsmoking population (Selikoff, 1992; Feinstein et al., 1989). From these studies, the synergistic and multiplicative effects of cigarette smoke and asbestos exposure were evident.

Although it is generally accepted that all types of asbestos are carcinogenic, it was at one time proposed that chrysotile asbestos may pose a decreased risk for developing lung cancer (Enterline & Henderson, 1973). However, subsequent studies have refuted this hypothesis. An increased fivefold risk of lung cancer between heavily exposed chrysotile mine and mill workers in Quebec, Canada, was reported by McDonald et al. (1974). In a population of predominantly nonsmoking Amish chrysotile workers, Wagoner et al. (1973) reported an increase in lung cancer with all durations of employment up to 9 yr. A prospective follow-up study of an additional 385 deaths further confirmed these studies in 8 yr resulting from exposure to chrysotile asbestos (Robinson et al., 1979). In addition, an increased two- to fourfold risk for respiratory cancer was observed in retired chrysotile workers (McDonald et al., 1980). Dement et al. (1982) presented further data linking chrysotile asbestos exposure to lung cancer.

Asbestos-associated lung tumors often arise from the lower lobes of

the lung, whereas smoking-related tumors tend to have a more central origin (Kannerstein & Churg, 1972; Whitwell et al., 1974; Hueper, 1966). The predisposition of asbestos-related tumors to develop in the lower lobes may be due to the increased retention of long asbestos fibers and the resulting pulmonary fibrosis in the lower zones of the lung. However, fibrosis may not be a prerequisite, as in a recent study it was reported that in asbestos-exposed workers with and without diffuse interstitial pulmonary fibrosis, tumors predominated in the lower lobes (Karjalainen et al., 1993).

Several studies have reported the relative frequencies of histological types of lung cancer in asbestos-exposed workers (Kannerstein & Churg, 1972; Whitwell et al., 1974; Hueper, 1966; Karjalainen et al., 1993; Weiss, 1988; Johansson et al., 1992; Muscat et al., 1995; Mollo et al., 1990, 1995; Churg, 1993; Raffin et al., 1993; Anttila et al., 1993; Imbernon et al., 1995). A relative risk of 3.3:1 was reported for adenocarcinoma by type among asbestos cement workers in Denmark from 1928 to 1984 (Raffin et al., 1993). Although in autopsy series a trend toward an association of adenocarcinoma was present in many of these studies, there was no significant relationship between cell types and lung cancer in surgical series. Furthermore, in a case-control study of workers in the electricity and gas industry Imbernon et al. (1995) observed a predominance of squamous-cell carcinoma in association with asbestos exposure. However, in many of these studies the effect of asbestos may be difficult to measure in relation to other factors, such as cigarette smoke exposure and age. In a case-control study considering various risk factors Brownson et al. (1987) found cigarette smoking to be the most significant predictor for lung cancer. Most of these studies suggest a relative increase in the number of adenocarcinomas in the lower lung zones in asbestos-exposed workers. Furthermore, in recent years higher proportions of adenocarcinomas have been reported in women smokers and unexposed workers, so it is possible the increase in adenocarcinomas seen in asbestos workers is artifactual. Despite the apparent associations between adenocarcinoma and asbestos-associated lung cancers, most studies have been on relatively small numbers and were uncontrolled for many factors associated with cell type. These include gender, smoking, unreviewed histology reports, changing underlying patterns of cancer type, and geographical factors. When all these are considered, Churg (1994) in a recent review concluded that there was insufficient evidence to link asbestos-associated cancers to any specific cell type and that asbestos exposure is associated with all major types of lung cancer.

Arsenic

A relationship between arsenic exposure and subsequent development of lung cancer was first suspected in miners in Schneeberg, Germany, in early 1879 (Henry, 1934). This excess mortality was later

confirmed through studies of workers exposed to arsenic compounds (Hill & Fanning, 1948) and grape workers exposed to insecticides containing arsenic (Roth, 1957). In the United States, copper smelter workers exposed to arsenic trioxides were found to have a threefold increase in respiratory cancer (Lee & Fraumeni, 1969). The respiratory cancer was eightfold higher among workers who were heavily exposed to arsenic for more than 15 years. Several other epidemiologic studies of arsenic workers have established a dose-response relationship between arsenic exposure and lung cancer. The National Institute for Occupational Safety and Health in 1973 estimated that approximately 1.5 million workers are potentially exposed to inorganic arsenic at industrial operations (Department of Health, Education, and Welfare, 1973). In copper-mining and smelting workers exposed to arsenic, squamous-cell carcinomas were the predominant cell type, followed by adenocarcinoma (Newman et al., 1976). On the other hand, Wicks et al. (1981) reported adenocarcinoma as the predominant cell type in arsenic exposure.

Bis(chloromethyl) Ether

Chloromethyl ether was first shown to be carcinogenic in animals. This finding led to extensive epidemiologic studies in workers exposed to the chemical. Several European and American epidemiologic studies in the 1970s conclusively established an increased risk of lung cancer among workers exposed to chloromethyl ethers (Theiss et al., 1973), including a significant increase in lung cancer among workers exposed to bis(chloromethyl) ether (BCME) in a dyestuff factory (Sakabe, 1973).

In four of the five studies of histologic cell type in BCME-exposed workers, small-cell carcinomas were the predominant lung cancer (Sakabe, 1973; Lemen et al., 1976; Weiss & Figueroa, 1976). Age has been suggested as having a confounding influence on histologic cell types in these studies (Weiss et al., 1979). However, a similar preponderance of small-cell carcinomas has also been associated with exposure to radon (Saccomanno et al., 1971) and mustard gas (Yamada, 1963).

Chromate

Alwens and Jonas (1938) demonstrated an increased incidence of lung cancer in German workers exposed to chromium. These observations were confirmed in the United States by a study of 6 chromate industries, which showed a 25% elevated risk of lung cancer above the general population (Machle & Gregorius, 1948). Evidence has continued to accumulate from several International and American epidemiologic studies that workers exposed to various chromium compounds in the pigment manufacture, plating, ferro-chromium, and other industries are at increased risk for bronchogenic cancer (Baetjer, 1950; Mancuso & Hueper, 1951; Enterline, 1974; Tsuneta et al., 1980; Davies et al., 1991).

The National Academy of Sciences (1974) concluded that lung can-

cers in chromate workers do not show a predominant cell type. This conclusion was based on a study by Hueper (1966). In a more recent study of 20 lung cancer cases in Japan, 65% were squamous-cell carcinomas and 25% were small-cell carcinomas (Abe et al., 1982). Increased carcinogenic risk is common with hexavalent chromium compounds, and the proportion of small-cell carcinomas was increased at higher doses (Abe et al., 1982).

Coke Oven Emissions

Recognition that an occupational exposure could lead to human cancer was first reported by Percival Pott in 1775 in chimney sweep workers exposed to carcinogenic agents produced by the combustion and carbonization of coal (Pott, 1775). Kennaway and Kennaway (1947) reported excess lung cancer mortality in workers exposed to coke oven emissions in several industries in England and Wales. A detailed prospective mortality study of gas and coke oven workers in 1972 further linked the strong excess lung cancer risk among workers to the coal combustion and carbonization industry in the United Kingdom (Doll et al., 1972). In the United States, the Public Health Service initiated long-term mortality studies in the steel industries and in workers employed in specific trades to determine the mortality patterns and specific causative agents involved in coke oven emissions (Lloyd, 1971). These studies showed a 10-fold higher risk for lung cancer in coke plant workers exposed for 5 or more years (Rockette & Redmond, 1985), and confirmed that lung cancer mortality among coke oven workers was related to dose and severity of exposure.

Crystalline Silica

Despite several decades of research, the carcinogenic, cocarcinogenic, or cancer-promoting potential of crystalline silica and silicosis is still being debated (IARC, 1987). Goldsmith et al. (1982) reviewed the literature in 1982 and concluded that the available human and experimental evidence strongly supported a carcinogenic potential for crystalline silica. Epidemiologic studies have reported inconsistent results about a possible association between crystalline silica exposure, silicosis, and the potential for developing bronchogenic cancer in humans (IARC, 1987; Goldsmith et al., 1982; Amandus & Costello, 1991; Infante-Rivard et al., 1989; Finkelstein et al., 1985; Merlo et al., 1991; McDonald, 1989; Hnizdo & Sluis-Cremer, 1991; Ng et al., 1990; Amandus et al., 1991). An autopsy study of South African gold miners with silicosis in the lymph nodes, rather than in the lung parenchyma, showed an increased prevalence of lung cancer (Hnizdo & Sluis-Cremer, 1991). The study suggested that impeded lymphatic clearance of inhaled carcinogens led to increased availability for DNA damage and mutations. Although evidence presented by the IARC (1987) and Goldsmith et al. (1982) has provided substantial support to indicate a role of silica in the carcinogenesis of lung

cancer, when other risk factors were factored in results were inconclusive (Merlo et al., 1991; McDonald, 1989; Hnizdo & Sluis-Cremer, 1991; Ng et al., 1990; Hessel et al., 1990). The confounding influences of other exposures and early death have not been considered in many analyses. Although the relationship is still inconclusive, the International Agency for Research on Cancer recently concluded that crystalline silica is carcinogenic in humans (IARC, 1997).

Diesel Exhaust

Diesel emissions are highly complex and contain gases such as nitrogen dioxide, carbon monoxide and sulfur dioxide, organic hydrocarbons, aldehydes, and fine particulate matter. Compared to gasoline-powered engines, the emissions from diesel engines are enriched in particulates and nitrogen dioxide. The carbon particles are very small (0.01–0.08 μm diameter) and tend to agglomerate. Vapor-phase hydrocarbons and liquid condensed hydrocarbon particles are readily adsorbed to the particle agglomerates. Estimates of workplace exposures to the particulate fractions vary from 1–100 $\mu g/m^3$ in trucking and transportation to 100–1700 $\mu g/m^3$ in underground mines (Health Effects Institute, 1995).

The International Agency for Research on Cancer, after evaluation of the limited epidemiologic data available, concluded in 1989 that diesel exhaust is probably carcinogenic to humans (IARC, 1989). A more recent review monograph from the Health Effects Institute (1995) concluded that the epidemiologic data were consistent with a weak association between diesel exhaust and lung cancer, with a 1.2- to 1.5-fold increase in relative risk compared to unexposed workers. This was also found for those epidemiologic studies that had adequately controlled for cigarette smoking. Although many evaluated studies showed an elevated risk, no quantitative measures were used to show an exposure dose-dependent risk increase with the information on smoking (Steenland, 1986). In a recently reported case-referent study of Swedish dock workers, Emmelin et al. (1993) showed an independent effect of diesel exhaust exposure but not significant interaction between smoking and diesel exhaust exposure.

Nickel

Although a relationship between occupational exposure to nickel and development of nasal cancer among workers was reported in 1932 (Chief Inspector of Factories, 1933), it was not until 1950 that a published report identified 93 cases of nickel exposure-related lung cancer (Chief Inspector of Factories, 1952). Further studies by Doll et al. (1970) and Kreyberg (1978) confirmed the increased risk of lung cancer in nickel workers compared with an unexposed reference population. Although all types of nickel compounds are considered carcinogenic to humans, a recent international review committee report based on 10 cohort studies stated that excess cancer risk was related to exposure to soluble nickel (Report of the ICNC, 1990).

Kreyberg (1978) showed that lung cancers in nickel-exposed workers were predominantly small-cell anaplastic carcinomas and squamous-cell carcinomas. Further studies of histologic cell types in nickel workers revealed a predominance of squamous cancers (Sunderman, 1973). Histologic studies of nickel refinery workers in Norway confirmed this association with squamous-cell cancer (Kreyburg, 1978). Unfortunately the influence of smoking was not determined in these studies, due to the lack of adequate smoking histories.

Nickel ions can enhance the oxidation, hydroxylation, and deglycosylation of DNA bases in the presence of reactive oxygen species and may also bind to histones in the cell nucleus. Exposure to nickel compounds is associated with chromosomal aberrations and sister chromatid exchanges, DNA strand breaks and inhibition of DNA repair (Shen & Zhang, 1994).

Fluorospar

Fluorospar is used as a flux in the industrial production of steel, aluminum, and ceramics. It is also used as a source of fluorine in several chemical industries and dental products. The National Academy of Sciences estimated that approximately 118 thousand tons of fluoride emissions occur in a year from various industrial sources. NIOSH recognizes more than 92 occupations with potential exposure to fluoride, including approximately 350,000 workers.

A study of fluoride mine workers in Newfoundland, Canada, showed an increased lung cancer risk 29 times greater than the unexposed population (de Villiers & Windish, 1964). However, this increased risk was partially attributed to radon exposure, and the independent effect of fluoride exposure could not be ascertained. Excess lung cancer has also been identified in workers exposed to fluoride in the aluminum industry, where fluoride was used as an electrolyte or flux (Gibbs & Horowitz, 1979).

Beryllium

In a study of beryllium production workers employed between 1942 and 1948, Mancuso (1979) observed an excess of lung cancer. A follow-up study of 3685 workers who were employed between 1937 and 1948 showed a statistically significant excess of lung cancer. Another retrospective study of 3055 beryllium workers employed between 1942 and 1948 and followed from 1968 through 1975 also showed an overall statistically significant 40% excess cancer rate (Mancuso, 1980). Further studies established these increased mortality patterns in beryllium processing and other industrial workers exposed to beryllium (MacMahon, 1994; Ward et al., 1992; Wagoner et al., 1980). In a histologic study of beryllium-associated lung cancer Smith and Suzuki (1980) found small-cell carcinomas to be the predominant cell type in biopsies and adenocarcinoma in autopsy studies.

Mustard Gas

Exposure during World War I between 1914 and 1918 to mustard gas has been implicated as a cause of lung cancer in soldiers (Beebe, 1960; Case & Lea, 1955). A study of mustard gas production workers substantiated these early observations (Wada et al., 1968). An excessive number of lung cancer cases among mustard gas workers exposed in World War II further supported these findings (Easton et al., 1988). In histologic studies of lung cancers in mustard gas workers, small-cell carcinoma and squamous-cell carcinoma were most frequently observed (Yamada, 1963; Easton et al., 1988).

Radon and Radon Daughters

Uranium is a rare element and represents less than 1% of ore containing uranium. Uranium-238 decays to radium-226 and then to radon-222. Radon gas emits alpha radiation. Polonium-218, -214 and -210 are three progenies of radon commonly known as radon daughters. Radon and its daughters diffuse into the ambient air and become attached to particles in the uranium mines. Inhaled particles emit alpha radiation for distances of 40–70 μm. This can penetrate and damage the bronchial epithelial cell nuclei, leading to malignant transformation of cells, presumably due to initiation of DNA mutations.

Miners in the Erz mountains of Bohemia were first reported to develop fatal lung disease in 1557 (Agricola, 1557/1950). The mine ore in the Saxony (Erzgeberge) mountains contains uranium, among other known and suspected carcinogens including arsenic and silica. Harting and Heese in 1879 identified Schneeberg lung disease as a malignancy (Agricola, 1557/1950). In a study of Schneeberg miners Arnstein reported that 40% of deaths in miners were due to lung cancer (Arnstein, 1913). Further studies in Jachymov and Joachimsthal mines in Europe confirmed an increased rate of lung cancers occurring in uranium miners (Pirchan & Sill, 1932; Peller, 1939; Lundin et al., 1969; Wagoner et al., 1964; Saccomanno et al., 1971; Archer et al., 1973).

In the United States, extensive studies were undertaken to evaluate the effects of uranium mining between 1950 and 1967 (Horacek et al., 1977). A sixfold increase in the mortality from lung cancer was evident from the cumulative, dose-dependent exposure to radon. The study also showed that exposure at a low 4 "working level months" (WLM) per year for 30 yr could be expected to double the respiratory cancer risk over a 40-yr period. This excess in respiratory cancer mortality in underground uranium workers could not be attributed to age, cigarette smoking, heredity, self-selection, diagnostic accuracy, prior hard-rock mining, or nonradioactive ore constituents, including silica (Tomasek et al., 1994).

A high frequency of small-cell carcinomas in the United States uranium miners was reported by Saccomanno et al. (1971). Increasing doses of radiation resulted in an increased proportion of small-cell carci-

nomas, suggesting a dose-response relationship in the histogenesis of this lung cancer (Archer et al., 1974). In another report of uranium miners Archer et al. (1973) observed considerable differences in the proportion of lung cancer cell types in different age groups. Small-cell carcinomas remained the largest proportion of cancer, but declined by 10% in the miners aged 70 to 79 yr. These findings were further confirmed by a study of lung cancers in 115 uranium miners in Czechoslovakia, which showed 54% small-cell carcinomas and 35% squamous-cell carcinomas (Horacek et al., 1977; Tomasek et al., 1994; Schuttmann, 1993).

MOLECULAR BIOLOGY

Environmental and occupational carcinogens may initiate and/or promote the development of cancer through many biochemical pathways and micromolecular alterations in the cellular constituents. The most common defects observed in lung cancers with an occupational exposure history in humans are loss of control of cellular differentiation and proliferation due to activation of oncogenes and/or mutations of tumor suppressor genes, such as p53 (Harris, 1993; Harris & Hollstein, 1993; Rodenhuis & Slebus, 1990; Vahakangas et al., 1992; Taylor et al., 1994; Kriek et al., 1993; Brandt-Rauf, 1992; Westra et al., 1993; Nuorva et al., 1994; Perera, 1993; Luo et al., 1994; Goldstein et al., 1985; Roth, 1995). In addition, activated oncoproteins, mutated oncogenes, tumor suppressor genes, and DNA adducts in the extracellular fluids may reflect toxins to which one was exposed, and can be used as biomarkers for exposure risk assessment and surveillance (Miyamoto et al., 1991; Duffy, 1995). Serum tumor markers may also be of value in identifying and monitoring patients with lung cancer (Ferrigno et al., 1994; Johnson, 1995).

Studies of cigarette smokers, asbestos workers, polycyclic aromatic hydrocarbon-exposed populations, vinyl chloride-exposed workers, and uranium miners have documented the value of molecular biomarkers in fingerprinting the toxin-specific changes in exposed populations (Vahakangas et al., 1992; Nuorva et al., 1994).

In a simplified sense, the development of cancer results from a loss of control, with subsequent unchecked proliferation and lack of differentiation. Mutation of DNA and an additional stimulus to proliferation have long been hypothesized as a basic mechanism. Newer advances in molecular pathology, biomarkers, and immunohistochemical techniques have further elucidated these theories. Those genes most often associated with cancer, that is, oncogenes and tumor suppressor genes, are ultimately involved in stimulus and control of cellular proliferation.

Oncogenes and tumor suppressor genes play a central role in carcinogenesis. Among the activated oncogenes, *ras, jun, fos,* and *myc* are the most important ones associated with lung cancer (Sabichi & Birrer, 1996). The *myc* oncogenes code for nuclear regulatory proteins. The *myc* muta-

tions cause continuous cell division resulting in immortality. The *jun* and *fos* gene families are early-response genes that code for transcription factors involved in cell growth signals originating at the cell membrane. H-*ras*, K-*ras*, and N-*ras* oncogenes elaborate p21 proteins involved in the signal transduction of mitogenesis in response to growth factors (Harris, 1993; Harris & Hollstein, 1993). Activation of K-*ras* oncogenes is a frequent phenomena in a large proportion of lung cancers (National Research Council, 1989). The *ras* oncogene activation appears to be present in non-small-cell carcinomas of cigarette smokers (Luo et al., 1994), but not in non-smokers. The presence of *ras* oncogenes is associated with a poor prognosis (Rodenhuis & Slebus, 1990; van Zandwijk et al., 1995). Mutations in *ras* are associated with development of adenocarcinomas; however, the effect of occupational exposure in relation to specific mutations in lung cancer has been less frequently studied. No mutations in K-*ras* were observed in 19 lung cancers from uranium miners (Vahakangas et al., 1992).

Mutations of the tumor suppressor gene p53 are the most common genetic changes seen in lung cancer. About 50–60% of human lung cancers contain a mutated form of tumor suppressor gene p53. They have a longer half-life compared to wild-type p53 and are found in higher concentrations in cancer cells, preneoplastic cells, and dysplastic cells. The p53 protein is involved in transcription, DNA synthesis and repair, cell cycle, growth, metabolism and inhibition of abnormal growth in normal cells. The p53 protein is also important in programmed cell death (apoptosis) (Harris, 1993; Harris & Hollstein, 1993). Tumor suppressor genes normally serve to control cell division by acting at various checkpoints in the cell cycle. This is particularly true with p53, which normally functions to suppress cellular division when DNA damage is present. Loss of function in these genes allows for uncontrolled growth. Other factors, such as hormones and cytokines, may also stimulate cellular proliferation. Mutations in p53 and *ras* genes may be shed by malignant and premalignant cells (Duffy, 1995). Their detection may be useful in the early diagnosis of malignancy. Mao et al. (1994) have shown mutant forms of p53 and *ras* genes in the sputum of patients before a clinical diagnosis of lung cancer could be made. The p53 is involved in transcription, DNA synthesis and repair, cell cycle, growth, metabolism, and inhibition of abnormal growth in normal cells.

An international database of human p53 gene point mutations includes over 5000 cancers, of which 552 are lung cancer. This database can be accessed through a file server at the EMBL Data Library (Hollstein et al., 1996). Some risk factor information is available in the data set, including the observation that tobacco smoking is associated with G → T transversions (Ruggeri et al., 1993). Such mutations are associated with exposure to polycyclic aromatic hydrocarbons including the ultimate carcinogenic metabolite of benzo[a]pyrene, the diol epoxide (BPDE; Denissenko et al., 1996).

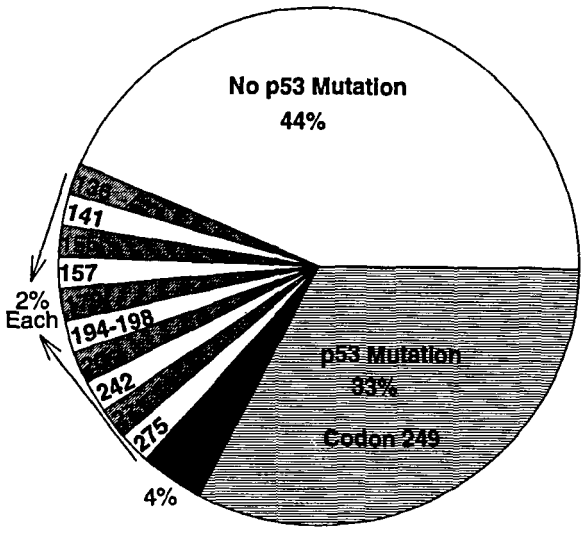
Although there are more than 250 codons at the p53 gene, mutations at five of these (273, 248, 175, 249, and 245) account for 25% of the total. The lung cancer subset showed mutational hot spots at codons 157, 248, and 273 (Denissenko et al., 1996). A mutation at codon 157 is relatively specific for lung cancer. The majority of mutations at these sites also involve G → T transversions (Hollstein et al., 1996), indicating weak spots that are vulnerable to mutagenic agents.

Denissenko et al. (1996) mapped the distribution of BPDE adducts along the exons of the p53 gene in BPDE-treated bronchial epithelial cells and showed selective strong adduct formation at codon positions 157, 248, and 273. The affinity of BPDE adducts for these mutational hot spots suggests a mechanism whereby metabolites of benzo[a]pyrene are involved in malignant transformation (Eisenstadt et al., 1982). The linking of specific adducts to sites of tumor suppressor genes and oncogenes provides exciting new possibilities for identifying occupational carcinogens and for identifying the "culprit" in exposures involving multiple agents.

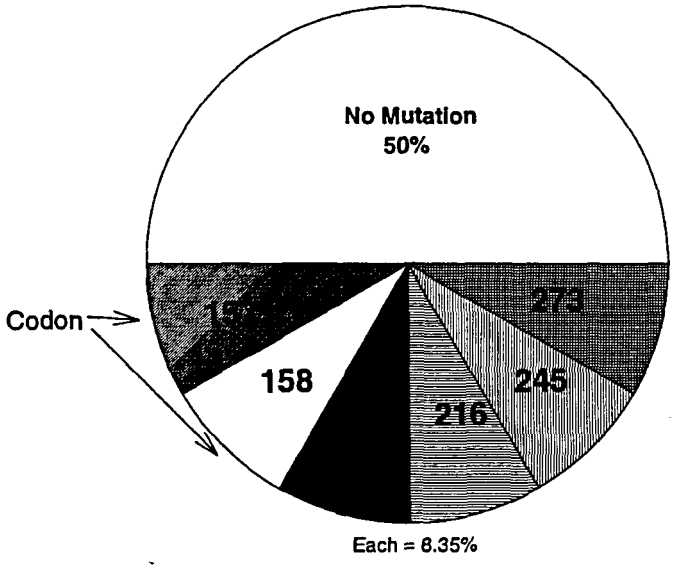
Recent studies in the field have demonstrated unique p53 mutations in uranium miners that differed from those associated with cigarette smoking (Vahakangas et al., 1992; Taylor et al., 1994; Reynolds et al., 1991). These include a variety of mutations in exons 5–9 not usually associated either with cigarette smoking or lung cancer. Taylor et al. (1994) showed a unique G → T transversion in the base pair of codon 249 resulting in amino acid substitution from arginine to methionine (AGG → ATG). This specific substitution was rarely seen in lung cancers caused by other agents (Figure 1). The histologic cell type was also different in the two studies, with small-cell anaplastic tumor predominating.

Abnormal p53 protein accumulation was demonstrated in 36 of 70 (51%) primary lung cancers from patients with and without asbestos exposure (Nuorva et al., 1994). Significant associations were noted between asbestos exposure and asbestos bodies in lung tissue and p53 expression. Although it is intriguing to postulate that unique molecular signatures may be associated with specific carcinogens, further studies will be necessary to confirm this hypothesis. Oncogene expression may vary by histologic type of lung cancer. Among oncogenes *bcl*-2 is unique in that it blocks apoptosis in addition to synergizing with classical oncogenes. A study of *bcl*-2 oncogene protein in human lung cancer showed a high incidence in small-cell carcinomas and other lung cancers expressing neuroendocrine markers (Jiang et al., 1996). There have been no studies to date to associate it with specific carcinogens; however, its expression would be of interest in radon-associated lung cancers in view of their association with the small-cell phenotype (Taylor et al., 1994).

Indicators or markers of events at the molecular and genetic levels can be used in various ways in the study of occupational lung cancer. These markers can be of three types: those indicative of exposures to a lung carcinogen, those indicative of biologic effects of a carcinogen, and



(a) p53 mutations in 52 large cell and squamous cell lung cancers from uranium miners



(b) p53 mutations in non-miners

FIGURE 1. (a) Distribution of p53 mutations in 52 non-small-cell lung cancers from uranium miners (Taylor et al., 1994). (b) Distribution of p53 mutations in 12 non-small-cell cancers from nonminers (Taylor et al., 1994). Mutation at base pair codon 249 appears to be a distinguishing feature of radiation exposure. This particular mutation is not seen in the nonminer controls and is rare (0.4%) in smoking-associated lung cancers (Harris & Hollstein, 1993).

those indicative of susceptibility to preclinical biologic effects or lung cancer. These markers taken together can also depict a continuum of events between exposure to a lung carcinogen and resultant lung cancer. This continuum includes markers of internal dose (e.g., concentration of dust in lungs); biologically effective dose (DNA adducts); early biologic effects (e.g., mutated oncogenes); altered structure and function (e.g., p53 base change); and susceptibility (e.g., CYP2D6 polymorphism).

These markers can be used in epidemiologic studies to reduce misclassification of exposure or disease; indicate mechanisms by which an exposure or disease are related; and provide better accounts of variability and effect modification. They can also be used to relate animal and human studies and to assess the nature of effects in humans at levels below which there are actual exposure and disease data. Thus, if exposure to a low level of lung carcinogens, such as polycyclic aromatic hydrocarbons (PAHs), is found to result in more PAH–DNA adducts and cytogenetic changes than in "nonexposed" persons, this would be indicative of risk for disease in the exposed group. Molecular markers are therefore tools that should be used in conjunction with the other approaches described herein for investigating occupational lung cancer (Schulte & Perera, 1993).

CONCLUSIONS

The prevention of occupational lung diseases is a national goal because large numbers of workers are still exposed to carcinogenic agents. Despite more stringent engineering controls and lower exposures, we will continue to see cases of occupational lung cancer because of its relatively long latency period and difficulty in proving the association for new agents that are weakly carcinogenic (Taubes, 1995). Their recognition will become easier as the complex pathologic and molecular processes involved in carcinogenesis are elucidated. Future research in occupational lung cancer should be directed toward the identification of etiologic agents, early detection, and prevention. Currently, there is concern about the potential carcinogenicity of such agents as asphalt fume, refractive ceramic fibers, and fibrous glass. The use of molecular tools, biomarkers, and pathology to detect presymptomatic alterations would be an important advance, because most patients with lung cancer are diagnosed at the late stages of disease when the prognosis is dismal. Early detection of the carcinogenic process at least offers the possibility of intervention and a decrease in mortality.

A final challenge for future studies is to differentiate the effects of multiple etiologic agents using pathologic, cellular, biochemical, and molecular markers. Because cigarette smoking is the most important etiologic agent of lung cancer, knowledge of its independent and synergistic effects is important in differentiating its signal from the weaker signals of occupational carcinogens. These integrated studies could contribute to the prevention of occupational lung cancers and a decrease in mortality.

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