

Massachusetts mortality survey (Dubrow and Wegman 1984), it must be concluded that to the extent smoking effects were adequately controlled by statistical design, certain occupations appear to be associated with significant risks of cancer, independent of the role of smoking. Unavoidably, the occupational classes used for this kind of study are broad: the actual exposure circumstances within these classes that might be conducive to cancer can only be speculated.

Viadana and colleagues (1976) studied 11,591 white male cancer patients and controls who were hospitalized at Roswell Park Memorial Institute between 1956 and 1965. They used occupational histories to classify cases and controls as being exposed to "chemicals" and "combustion products," and into specific groups within these broad classifications, e.g., operatives in the chemical industry or bus, cab, or taxi drivers. Operatives in the chemical industry had an increased relative risk of having cancer of the stomach (RR 4.25,  $p < 0.05$ ). The relative risks for lung and laryngeal cancer were slightly, but not significantly, increased.

Relative risks for larynx (RR 3.63,  $p < 0.05$ ), pharynx (RR 3.38,  $p < 0.05$ ), and bladder (RR 6.77,  $p < 0.05$ ) cancers were significantly elevated for operatives in the leather industry. Relative risks were altered after controlling for smoking, but the risks associated with occupation appeared to be independent of smoking. The influence of smoking on the risks associated with occupation were difficult to assess, because the relative risks adjusted for age and smoking were not tabulated. Instead, these results were discussed selectively. Although the information needed to investigate the interaction between smoking and occupation was available, this report did not discuss this issue.

### **Lung Cancer**

Stayner and Wegman (1983) used a case-control design to study the relationship between smoking, lung cancer, and occupation, based on a portion of the data from the Third National Cancer Survey. The analysis was limited to men aged 30 to 84 when diagnosed as having lung cancer who had responded to an interview that included occupational and smoking histories. Occupation was coded in broad categories defined for the 1970 census. Cases and controls were grouped as "ever" or "never" users of tobacco to control for smoking exposure. Controls were selected from survey participants with other types of cancer, excluding those individuals with the types of cancer that have been associated with occupation or smoking (e.g., lip, mouth, pharynx, larynx, esophagus, pancreas, bladder, liver, skin, brain, and blood and bone marrow). These exclusions left 900 controls to be compared with 420 cases. Blue-collar workers had an odds ratio (OR) of 1.24 ( $p < 0.05$ ) for developing lung cancer after adjustment for smoking status and age. This

difference was due in part to the increased odds for developing squamous cell carcinoma (OR 2.11,  $p < 0.05$ ) compared with average odds for developing adenocarcinoma (OR 0.97) and small cell carcinoma (OR 1.22). When the data were analyzed using more narrowly defined occupational groups, no statistically significant associations were found. However, when histologic types were considered separately, laborers had higher odds ratios for small-cell carcinoma (OR 2.47,  $p < 0.05$ ) and squamous cell carcinoma (OR 1.97,  $p < 0.05$ ) after adjustment for smoking.

Stayner and Wegman reported positive associations between smoking and all three histologic types of lung cancer. They did not consider the potential interactions between smoking and occupation in discussing their data. Their report did illustrate the importance of considering histologic type when conducting etiologic studies of lung cancer.

Few studies of occupational risk focus on women. Leung (1977) reported an association between cooking with a kerosene stove and lung cancer in Chinese women living in Hong Kong. This case-control study was conducted to identify factors that might account for the relatively high mortality rates for lung cancer experienced by women in Hong Kong. In 260 consecutive cases of histologically proven lung cancer, 92 percent (166/180) of the men and 56 percent (45/80) of the women smoked cigarettes compared with 59 percent of the male smokers and 11 percent of the female smokers in a "nonrandom" population sample. In a second series of 44 lung cancer cases in women, 91 percent (40/44) used a kerosene stove daily for over 2 years compared with 36 percent of the families sampled in seven areas of Hong Kong.

The sampling schemes used in this study could easily produce biased results. Smoking prevalence in the community was based on a convenience sample and might have underestimated the prevalence of smoking by women. Kerosene stove usage could be associated with many other environmental exposures that might be related to lung cancer. Nevertheless, strong associations between smoking and kerosene stove use and lung cancer were found among women. The author concluded that the question of synergy between stove usage and smoking requires further study.

In a case-control study of lung cancer, Pastorino and colleagues (1984) estimated the proportions of lung cancer attributable to smoking and occupational exposure to known or suspected carcinogens. Lung cancer cases were drawn from a well-defined geographic area in northern Italy where a large proportion (74 percent) of employed men work in industry. In this area, 240 incident cases of lung cancer in men occurred between 1976 and 1979. Twenty-nine cases were excluded because diagnostic criteria were not met and 7 cases could not be reached for interview, leaving 204 cases (85

percent of total) for analysis. Controls were selected at random from the electoral rolls of men living in the same region and matched with cases for age within 2 years. Of the 366 controls enrolled, 15 could not be reached for interview. Interviews were conducted by two occupational physicians and two public health nurses. Occupational histories focused on specific exposure to asbestos, tars and mineral oil, chromium, nickel, arsenic, bis-chloromethyl ether, chloromethyl methyl ether, vinyl chloride, and polycyclic aromatic hydrocarbons as contained in soot. "No exposure" was defined strictly as a work situation where the subject could not have been exposed to these materials. "Possible" and "probable" exposures were defined on the basis of descriptions of specific job tasks. Ten percent of the control interviews and 50 percent of the case interviews were with next of kin.

The relative risk for lung cancer was strongly related to cigarette smoking in a dose-related way. Relative risk ranged from 2.3 for smokers of 1 to 9 cigarettes per day to 9.0 for smokers of 30 or more cigarettes per day. Occupational exposures were also positively associated with lung cancer. The relative risk for possible exposure was 1.6, and for probable exposure, 2.7. The authors estimated that 81 percent of lung cancers could be attributed to smoking (95 percent confidence interval, 69 to 93) and that 33 percent could be attributed to occupational exposure to known carcinogens (95 percent confidence interval, 19 to 47).

Pastorino and colleagues (1984) illustrated how relative risk varies positively with occupational exposure and cigarette smoking. The relative risk increased in men without occupational exposure from 1.0 in nonsmokers to 2.7, 6.2, 9, and 11 in men who smoked 1 to 9, 10 to 19, 20 to 29, and 30 or more cigarettes per day, respectively. In men with possible and probable occupational exposure, the relative risk increased from 2.5 in nonsmokers to 3.8, 14, 19, and 20 in men who smoked 1 to 9, 10 to 19, 20 to 29, and 30 or more cigarettes a day, respectively. Occupational exposure was subcategorized by exposure to asbestos and PAH, the most common occupational exposures in this study. Both were independently associated with lung cancer risk. The relative risks associated with asbestos and PAH exposures in combination with smoking were more consistent with additive effects, but a specific analysis of the possible interactions was not discussed.

### **Bladder Cancer**

In the last 15 years, many case-control studies and analyses of mortality statistics have been used to examine relationships between occupation and bladder cancer. In only a few has enough historical information been aggregated in detail sufficient to permit exploration of interactive effects between occupation and smoking.

A case-control study of bladder cancer patients in the hospitals of Leeds, England, failed to show that smoking was a risk factor for bladder cancer, but did indicate that the prognosis was worse in patients who continued to smoke (Anthony and Thomas 1970a). Controls for this study were lung cancer patients and surgical cases interviewed 5 years previously at the same hospital. They were not matched to cases by age. In an expansion of this study, Anthony and Thomas (1970b) matched cases to controls (again using previously interviewed patients) with respect to age, sex, residence, and smoking habit (never smoked, greatest amount ever smoked, cessation of smoking). They then calculated risk ratios for aggregates of cases according to their "predominant occupations" and "employment in suspect environments." They identified significantly elevated risks of bladder cancer among workers in the chemical dye industry, textile workers, tailors, engineering workers, and hairdressers. Because cases and controls were matched for smoking habit, risks were presumably attributable only to occupation.

In an extensive case-control study of bladder cancer in the Boston-Brockton, Massachusetts, area in 1967-1968, Cole and colleagues (1971, 1972) examined occupation and smoking information obtained by interviewing 470 incident cases and 500 age- and sex-matched controls. Controls were selected at random from published "resident lists." Smoking was taken into account with respect to intensity (cigarettes per day) and also estimated total dose (pack-years). Thirteen occupational exposure categories were used in classifying patients and controls: dyestuffs, rubber, leather, printing, paint, petroleum, other organic chemicals, other chemicals, fumes and dust, manufacturing (not elsewhere classified), farming, service, and office. From this study the authors calculated mean relative risk ratios of 1.89 and 2.00 for bladder cancer in male and female smokers, respectively, and demonstrated gradients of risk in both sexes, based on numbers of cigarettes smoked per day. The maximum mean relative risk ratio (3.8) was for women who smoked more than one and one-half packs per day. Standardization by occupational categories did not alter the relative risk estimates for smoking.

When risks were analyzed by occupational categories (ever employed), significantly elevated ratios were found in only two categories: those working with rubber and rubber products (1.57) and those working with leather and leather products (2.00). People exposed to dyestuffs, paint, and other organic chemicals exhibited apparent elevations of risk, but the number of cases available for study was too small to yield statistically significant increases. Relative risks were very similar whether or not controlled for smoking. Examined in terms of "usual occupation" instead of "ever employed," risk associations with occupation tended to be weaker, but rubber and leather industries were again identified as those most likely to

involve an occupational hazard of bladder cancer, even when controlled for smoking. Risk attributable to hazardous occupation (work in industries involving exposure to chemicals) was estimated to be 7 to 18 percent of the total bladder cancer risk, depending on the basis used for specifying occupation. Relative risk ratios ranged from 1.21 to 1.75.

The epidemiology of bladder cancer with respect to beverage habits as well as smoking and occupation was addressed in three Canadian studies. Miller (1977) conducted a case-control study of 349 bladder cancer cases from British Columbia, Nova Scotia, and Newfoundland, matching each case to controls by age, sex, and residence (but not by smoking). Control subjects were recruited from the residential neighborhoods of the subjects. Questionnaires administered in the homes inquired into the occupations of the respondents, as well as their smoking and coffee-consuming habits. Significant relative risk ratios (2.0 to 10.5) were found for cigarette smoking, and showed a substantial dependence on estimated lifetime consumption of cigarettes. Occupational risks were evaluated only with respect to seven categories: chemical, rubber, photography, spray painting, petroleum, medicine, and "other." Risk ratios were 2.0 or more in all categories, and were statistically significant in two: "chemical" (12.0) and "other" (2.1). No details of the nature of chemical exposures were offered, and no analysis of smoking habit within occupational categories was presented. The number of case-control pairs within the six specific categories was small (total 78), and no occupation-based risk ratios for nonsmokers were stated explicitly. Population-attributable risk percentages calculated by the authors for men were occupation (known and suspect), 35 percent; cigarette smoking, 56 percent; coffee drinking, 27 percent; and total, 118 percent. For women the percentages were 1, 29, and 13 percent, respectively; the total was 43 percent.

An extension of this study on bladder cancer published in 1980 (Howe et al. 1980) included 632 case-control pairs from the same Canadian provinces. Strong relative risks for smoking were confirmed in men and women, the magnitudes depending on daily usage, duration, and estimated lifetime consumption. Associated with significantly elevated bladder cancer risk in men were workers in the chemical, rubber, petroleum, welding, and railroad industries, guards and watchmen, nurserymen, metal machinists, material recorders, and military personnel. Risk ratios for military personnel and clerical workers declined when smoking was controlled for; other risk ratios reportedly did not. This analysis was based on responses to a query as to whether subjects had ever worked in the specified jobs, not on usual occupation. Despite the size of the study, the number of discordant matched pairs was relatively small: fewer than 50 in all occupational categories except agriculture, military,

and mechanics. No excess risk was indicated for people engaged in the dyeing of cloth or tanning, but the number of pairs available for analysis was not sufficient to provide reliable estimates. Discordant pair ratios of 4/3 and 5/1 were recorded for past contacts with benzidine and bis-chloromethyl ether, respectively, on the part of male respondents. The numbers were too small to permit an examination for the confounding effects of smoking. Very few women were employed in the suspect industries, and no significant risk elevations associated with occupation were identified among women.

Miller and colleagues (1978) matched each of 265 incident bladder tumor patients diagnosed at the Ottawa Civic Hospital Urology Clinic to two control patients treated at the clinic who did not have bladder tumors. Administered questionnaires inquired into previous disease in self and family, occupational exposures, use of coffee, tobacco, and sweeteners, exposure to radiation, and prior treatment with antituberculosis drugs. Relative risk calculations and discriminant analysis identified the following significant risks, in apparent order of importance: in men, a family history of allergy (1.8), occupational exposure to radiation (1.6), occupational exposure to chemicals (1.5), cigarette smoking (1.6), and a history of gout (1.7). In women, coffee drinking (1.6) and a history of tuberculosis (2.0) were identified as risks; a history of allergy in the patient appeared to be protective (0.3). Chemical exposures were identified tentatively as paints, varnishes, lacquers, gum and wood chemicals, and industrial chemicals. Risk ratios derived from this study are uniformly low, and those for factors traditionally regarded as important for bladder cancer (smoking and occupation) are lower than a risk ratio having no previously recognized association with the disease (family history of allergy, in men only). This aspect of the findings casts a degree of doubt on the soundness of the study design, particularly the use of patients with urologic disease other than bladder cancer as controls. Discriminant function analysis presumably identified both smoking and occupational exposure to chemicals and radiation as independent risk factors for bladder cancer. No data were offered from which to determine whether these risks are additive or synergistic.

Calculating proportionate incidence ratios for bladder cancer within broad occupational categories used by the Los Angeles County/University of Southern California Cancer Surveillance Program, Weinberg and colleagues (1983) examined incidence data for Los Angeles County over the period 1972–1976. They found higher relative risks of bladder cancer among managers and salesmen (high on the socioeconomic scale) than among service workers, laborers, and transportation workers (low on the socioeconomic scale). The latter group have been reported to be the heavier smokers (CDC 1976; Bonham and Leaverton 1976). The authors argued that, at

least in the Los Angeles area, the occurrence of bladder cancer in relation to social class corresponds more closely with coffee-drinking habits (greater in the upper classes) than with smoking or occupation. The social class distribution of bladder cancer incidence in Los Angeles contrasts sharply with the report of Adelstein (1980) in England, who found from analysis of death certificate and census data for 1970–1972 that cancer in general and bladder cancer in particular were afflictions primarily of the lower socioeconomic classes. The discrepant relationships to social class categories may be attributable to the different parameters used in the two studies (incidence versus mortality), to the disparate cultural and economic circumstances of the populations examined, or specifically, to different spectra of environmental carcinogens in the two regions. Interestingly, the two studies are in essential agreement with respect to lung cancer but not bladder cancer.

Glashan and Cartwright (1981) and colleagues (Cartwright et al. 1981), in a case-control study, matched 991 incident cases of bladder cancer treated at three West Yorkshire clinics over 3 years to age- and sex-matched controls "without malignant disease." The source of the controls was not mentioned, but presumably they were clinic patients. Elevated relative risk ratios for smoking (not quantitatively defined) were found in men (1.8) and women (1.6). Significantly elevated relative risks were found for chemical industry workers and printers, but not for leather workers, hairdressers, or dye users. Nonsmoking dye manufacture process workers experienced an apparent increase in risk of bladder cancer (RR 1.9, not statistically significant), but dye process workers who smoked were at highly significant risk (RR 4.6). A similar relationship was found among printers. The risk ratios for nonsmokers were admittedly based on few subjects. Risk ratios for dye process workers increased strikingly with duration of employment (>29 years, RR 10.5). The chemical nature of the dyes to which workers were actually exposed was not discussed.

A case-control study of 212 cases of bladder cancer in rural Denmark drew upon general population controls matched to cases by sex, age, and region of residence (Mommensen et al. 1982, 1983). Multivariate logistic regression was used to identify factors (evaluated by questionnaire) associated statistically with the malignancy. Significant relative risk ratios were found for tobacco use (1.6–2.1), work with petroleum, asphalt, oil, or gasoline (2.9–3.8), industrial work (2.2), work with chemical materials (2.0), alcohol use (2.3), and previous venereal disease (2.9). Farmers, who were presumably exposed to pesticides, were at less than average risk of developing bladder cancer. The report did not explore the interactive effects of occupation and tobacco use.

A case-control study in the greater New Orleans area, wherein 82 patients with bladder cancer and 169 matched general population controls were interviewed by telephone, was used to identify smoking of filter cigarettes (but not of unfiltered cigarettes or other tobacco products) as a risk factor for bladder cancer (Sullivan 1982). Matching criteria were not specified. A large number of employment categories and chemical exposures appeared to involve risks, most prominently mechanical engineers and people exposed to paint thinners, coal, petroleum, metals, welding materials, office supplies, and industrial equipment.

In a study in northern New Jersey (Najem et al. 1982), 75 cases were compared with 150 patient controls, matched by age, sex, race, place of birth (in New Jersey or elsewhere), current residence, and the clinic providing care. Occupations were recorded only when job tenure was more than 1 year. Smoking habits were characterized as never smoked, former smoker, or current smoker. Several criteria were used to test the significance of associations, and significant risks were analyzed to test for the confounding effects of smoking. Significant risk ratios were identified for cigarette smoking (2.0) and work in dye (3.1), petroleum (2.5), and plastics (3.4) industries, but not for employment in rubber, textile, printing, rodenticide, or cable industries, although some ratios did exceed 1. When the significant occupational risk ratios were analyzed within the three strata of smoking status, ratios for current smokers were essentially the same as those calculated without controlling for smoking. Curiously, the occupational risk ratios for nonsmokers in the dye, plastics, and petroleum industries consistently exceeded the ratios for current smokers, but the ratios for ex-smokers were consistently lower (1.3 to 1.5). Some ratios were based on only a single case in a smoking-occupation cell.

In a recently reported case-control study at Turin, Italy, 512 male bladder cancer patients diagnosed from 1978 to 1983 were compared with 596 patient controls (225 urologic, 371 surgical) (Vineis et al. 1984). Smoking and occupational information was assembled by interview. Highly significant relative risk ratios were found for cigarette smoking, the magnitude depending on smoking intensity, on age when smoking started, and possibly on brand of cigarettes smoked. Occupational risk analysis was based on 64 patients classified as "exposed": 14 cases and 2 controls employed more than 6 months in dye production (said to include exposure to benzidine and betanaphthylamine), plus 28 cases and 20 controls employed in the rubber industry. From this, the authors calculated risk ratios strongly suggesting interactive effects of occupational exposure and smoking, most striking in workers less than 50 years of age, and dependent on smoking intensity (relative risk was 144.0 for hazardously employed workers who smoked). The relative risk for

hazardous occupation among nonsmokers of all ages (there were only five chemically exposed: two cases, three controls) was 3.7. The relative risk for smoking among the nonexposed of all ages was 5.2. The risk for the occupationally exposed who smoked was 11.6 relative to nonexposed nonsmokers. The risk ratio relationships based on all age groups are more suggestive of an additive overall effect than of synergy. The small number of occupationally exposed nonsmokers in the study limits the confidence that can be placed in the analysis.

Smith and colleagues (1985) recently examined relationships of occupational solvent exposure and smoking to incident cases of bladder cancer in regions of the United States served by the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program and included in the National Bladder Cancer Study (NBCS) of 1978. Controls selected from the NBCS study were frequency-matched to the cases by age and sex. Among nonsmokers reporting at least 6 month's exposure to chlorinated and simple hydrocarbon solvents used in dry cleaning and in other industries, the relative risk of bladder cancer was significantly elevated only in women (RR 1.38), and this was not significantly related to duration of exposure. In both men and women chemically exposed, however, the risk of bladder cancer increased progressively and significantly from nonsmokers to former smokers to current smokers. There was no evidence of interaction between the effects of occupation and smoking. The evidence of a smoking effect was consistent and substantial in this study (highest RR 4.68), but indications of a solvent exposure effect were weak and of borderline statistical significance.

Inhalation of combustion effluents is thought to pose a risk of cancer at various sites, including the bladder. For a case-control study of 81 male bladder cancer patients in Quebec (1970-1975), age- and sex-matched individuals living in the patients' neighborhoods were recruited to serve as controls (Theriault et al. 1981). Detailed histories were taken covering lifetime employment and residence, medications, personal habits, and water supply. Smoking habit was characterized qualitatively and quantitatively. Information on deceased cases was received from next of kin. These authors calculated a mean relative risk of bladder cancer of 5.70 among currently smoking workers in the electrolysis department of an aluminum reduction plant. Relative risk for smoking among other workers was 1.82, and risk associated with electrolysis department employment alone was 1.90. (It was necessary to base the latter estimate on ex-smokers because there were no nonsmokers so employed.) The independent risk ratios are not statistically significant, but the range of values for electrolysis workers who smoked extended from 2.0 to 12.30. To the extent that the ratio estimates can be relied

upon, they suggest a strong interaction between smoking and occupational exposure.

Silverman and colleagues (1983), in a population-based case-control study of 303 white male bladder cancer cases in Detroit (1977-1978), explored occupational, dietary, and personal habit associations. Controls under 65 years of age were chosen from the Detroit population by random digit dialing, operating with a pool of 2,110 households. Controls of retirement age were selected at random from Health Care Financing Administration lists. A total of 296 controls were recruited for home interviews. Analysis of occupational associations relied on an "ever employed" query, and responses were classified according to the industry identified and by occupation. An apparent strong interaction involved truck driving as an occupation and cigarette smoking. Among people who had never been truck drivers, smoking one or two packs of cigarettes per day increased the risk of bladder cancer by a factor of 1.6; smoking more than two packs increased the risk ratio to 2.1. The ratio for truck drivers smoking less than one pack per day was 1.3; for smokers of one or two packs per day, the ratio was 6.8. The risk ratio for heavy smokers could not be calculated because none of the controls reported smoking more than two packs per day. A relationship with the inhalation of diesel exhaust was suspected, but could not be confirmed from the data.

Not unexpectedly, the case-control studies used to test a relationship of pesticide exposure to urinary tract cancer are inconclusive. Pesticides are chemically and toxicologically diverse; worker exposures to them are equally varied. It is unlikely that in epidemiologic studies based on broad occupational categories carcinogenic risk would be detected, if indeed it exists. Several case-control studies of bladder cancer have indicated that as an occupational group, people "working in agriculture" are at no more than average risk of urinary tract cancer, or are actually at less than average risk (Anthony and Thomas 1970b; Cole et al. 1972; Howe et al. 1980). In some studies of exposures to pesticides, specifically, nonsignificantly elevated risk ratios have been shown (Najem et al. 1982; McLaughlin et al. 1983). In Canada, bladder cancer was found to be significantly associated with crop spraying and nursery work as occupations (Howe et al. 1980). These associations were said to be unaffected by controlling for smoking.

### **Other Specific Cancer Sites**

Cancer of the kidney and upper urinary tract has received less attention than bladder cancer. In a nationwide case-control study of 202 patients with renal adenocarcinoma (Wynder et al. 1974), the past personal and occupational histories of the patients were examined in relation to histories from other hospitalized patients.

Relative risk among heavy smokers (more than one pack per day) under 50 years of age was 8.0, but only 2.1 in patients over age 50. Moderate smokers (up to one pack per day) were at intermediate risk. Except for a tentative identification of employment in textiles as a risk factor, no associations with occupational exposures to metals, dyes, or other organic chemicals were found.

In the Boston area, 43 cases of cancer of the renal pelvis and ureter were studied in relation to bladder cancer cases and randomly chosen general population controls (Schmauz and Cole 1974). Only among smokers of more than two and one-half packs of cigarettes per day did a significant risk appear (RR 10.0). Of the occupational categories identified, only leather working exhibited a suspect relationship to cancer at these sites.

Occurrences of renal cell carcinoma (495) and cancer of the renal pelvis (74) in the Minneapolis-St. Paul area from 1974 to 1979 were studied for heritable and environmental risk factors (McLaughlin et al. 1983, 1984). Controls were chosen randomly from the metropolitan area population. Because half of the cases were already deceased, background data had to be obtained through next-of-kin interviews. With respect to cancer of the renal pelvis, the risk of disease increased steadily in both men and women in relation to smoking intensity (maximum RR 10.7 in men, 11.1 in women). The only links to occupation appeared in relation to exposures to hydrocarbons: coal, natural gas, and mineral and cutting oils. There were not enough cases to permit analyses for smoking risk within occupations. Renal cell carcinoma also appeared to be related to cigarette smoking, but relative risk ratios were much lower (2.3 in male, 2.1 in female heavy smokers), and the dose-response relationship was not as consistent as in the case of renal pelvis or bladder cancer. Analysis for "usual industry of employment" failed to identify any significant occupational associations.

Musicco and colleagues (1982), in a case-control study of brain neoplasms in Italy, sought to associate the occurrence of gliomas (various types and grades) with occupations of victims prior to diagnosis during 1979 and 1980. Forty-two cases were matched with nonglioma patients at the Neurological Institute C. Besta of Milan. The controls were matched by age, sex, and area of residence. They suffered from a variety of chronic diseases, some probably characterized by physical and or mental disability from a relatively early age. Smoking was defined as a minimum 1-year usage, and total lifetime usage was estimated. More than 20 pack-years was considered heavy smoking. The authors found a significantly elevated risk ratio (5.0) for "agricultural work after 1960" when the data were analyzed without stratification. When stratified by sex, age, and residence, the ratio was 1.9 (not significant). The relative risk was 1.3 for smoking and 1.5 for heavy smoking, neither statistically significant. No

occupational risk ratios for nonsmokers were calculated. Particularly with respect to occupational risk calculations, the appropriateness of neurologically afflicted patients as controls must be questioned. Nonetheless, the authors were inclined to indict modern pesticides and fertilizers as causal factors for gliomas.

Austin and Schnatter (1983), in a followup case-control study of 21 patients dying from a brain tumor in a Texas petrochemical worker cohort, indicated that the tumors were of several different types. Efforts to identify unique past chemical exposures of brain tumor victims were not successful.

Using case-control methodology in reviewing 142 cases of pancreatic adenocarcinoma in several large U.S. clinical centers, Wynder and colleagues (1973) demonstrated that cigarette smokers were at increased risk of developing this disease. Risk ratios increased progressively with the number of cigarettes smoked per day. Controls for this study were patients in the same hospitals who had been interviewed for other epidemiologic studies. Controls did not include patients suffering from tobacco-related cancers (mouth, larynx, lung, esophagus, bladder, kidney) or other tobacco-related diseases (bronchitis, emphysema, coronary heart disease). Fifteen male cancer patients reported having been occupationally exposed to "dyes, chemicals, metal dust, saw dust, grease, oil, or gas fumes," but there was no difference between cases and controls with respect to the frequency with which this exposure was reported.

A case-control study in New Jersey (Stemhagen et al. 1983) of 265 victims of primary liver cancer occurring from 1975 to 1980 was conducted by interview of family members. Controls were selected from hospital records and death certificates, and were matched by age, sex, race, and county of residence. No evidence was adduced to indict smoking as a factor in causing this disease. Significantly elevated risk ratios were derived for farm laborers but not for farm owners or farm managers or for people engaged in manufacturing pesticides. Other people apparently at risk were gasoline service station employees, those employed at eating and drinking establishments, and those providing laundry and dry cleaning services. It was not possible to identify specific past chemical exposures that might have contributed to the risk.

A recent study of 102 cases of primary liver cancer in Sweden utilized controls matched by age, sex, race, year of death, and municipality where the decedent had lived (Hardell et al. 1984). No association with smoking history was found. Occupational exposure to solvents appeared to double the risk of liver cancer. No other occupations or chemical exposures were identified as risk factors, although a strong association with alcoholism was indicated.

Investigation of 207 cases of large bowel cancer in a Quebec community explored several risk factors in cases and controls, the

latter selected from the communities where the cases resided, and matched by age and sex (Vobecky et al. 1983). Smoking was not identified as a significant risk factor, although a slightly elevated risk ratio (1.2) for smoking (alone) was calculated. Industrial exposure at a local synthetic fiber factory did appear to be a significant association (RR 2.2). When the risk of industrial exposure and smoking were considered in combination, a higher risk was evident (2.8), at a stronger level of significance. A moderate degree of smoking-occupation interaction is suggested.

### **Chronic Lung Disease**

The likelihood that exposure to dusts and fumes in rubber product manufacture plays a causative role in the chronic obstructive lung disease encountered in this industry was examined in two studies. Fine and Peters (1976) assessed symptomatology and pulmonary function in 65 white male workers engaged an average of 7 years in rubber processing at three Akron tire plants. Air sampling showed 1 to 3 mg/m<sup>3</sup> of respirable dust in the work environments. Smoking habits were classified as never smoker, former smoker, current cigarette smoker, and current and former pipe and cigar smoker. Controls (189) were chosen from plant workers not exposed to polluted air. Processing workers reported a much higher prevalence of cough and phlegm than controls; this was true among nonsmokers as well as smokers in the various categories. Smoking nearly doubled the frequency of this symptom complex in the processing workers. However, dyspnea and wheeze, generally considered indicative of chronic obstructive lung disease, were no more prevalent among processing workers than among controls. Reported frequencies of bronchitis, pneumonia, asthma, and winter colds were not significantly greater among these workers than among controls. Pulmonary function testing yielded important findings. In comparing all workers with all controls, only the ratio of forced expiratory volume in 1 second to forced vital capacity (FEV<sub>1</sub>/FVC) was significantly lower in the particulate-exposed workers. However, the exposed group and the control group were subdivided according to whether they had been employed in their respective jobs for more or less than 10 years. Although the long-term processing workers were older and had smoked longer than the controls, decrements in flow rates and FEV<sub>1</sub>/FVC were not significantly correlated with years of cigarette smoking. Using appropriate adjustments for age, the long-term-exposed employees exhibited significant deficits in FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, and flow rates at 50 and 25 percent of FVC. Multiple regression analysis confirmed that duration of employment in rubber processing was a significant predictor of reduced FEV<sub>1</sub> and FVC. Employment for more than 10 years appeared to cause a significant decline in FEV<sub>1</sub>/FVC and the FVC-standardized flow rate

at 50 percent FVC. These results were independent of smoking variables, ethnicity, socioeconomic status, and age. The absence of a correlation between decrement in lung function and cigarette smoking and the small number of workers in this study raise questions about the generalizability of the data in this study.

Lednar and colleagues (1977) examined the work history and smoking habit backgrounds of 73 former rubber workers who were retired prematurely between 1964 and 1973 with medically documented, disabling pulmonary disease. They were members of a cohort of 4,302 workers employed in 1964 at an Akron plant. Thirty-nine were retired with emphysema, 10 with lung cancer, 8 with asthma, and 16 with other pulmonary conditions. Work background and likely exposure to dusts and fumes were determined from company records; smoking histories were obtained from questionnaires mailed to retirees or relatives. The investigators utilized two control groups, the first consisting of disabled employees retired because of diseases other than pulmonary (disabled controls) and the second of currently employed workers and early retirees free of acknowledged pulmonary disease (nondisabled controls). Relative risk ratios were calculated for smoking and for occupational exposures to dusts and fumes. Relative risks for pulmonary disability retirement in relation to smoking and various occupational titles were also calculated. Risk ratios for smoking alone (based on smokers and nonsmokers at worksites not otherwise contaminated) were consistently greater than 1.0, but they were significant only in the case of maintenance workers. For all workers combined, the smoking risk ratio was 2.95 ( $p < 0.05$ ). Ratios for occupational exposure alone were remarkably elevated in some job classifications, but none were significant. When the combination of smoking and occupational exposure was considered, however, substantially and significantly elevated risk ratios were found for workers engaged in extrusion (15.8), finishing and inspection (7.8), curing (6.7), and other tasks. Furthermore, combined exposure to dust and cigarette smoke appeared to increase by tenfold to twelvefold the risk of pulmonary disability. The data suggested interactive effects between smoking and occupational pollutants, more in the range of potentiation than simple addition.

Another suggestion of enhanced adverse effects from cigarette smoke and irritating air pollutants has come from examination of workers exposed to airborne contaminants from the milling of rubber (Sparks et al. 1982). For the factory worker population as a whole, productive cough was definitely more common among current smokers than among nonsmokers: 35.5 percent of the smokers versus 6.5 percent of the nonsmokers in parts of the plant where dust concentrations were minimal. Among workers exposed to irritating dust, 8 percent of the nonsmokers experienced a productive cough

and 42.5 percent of the smokers were so affected. In a work area where dust concentrations were highest, but did not generate complaints of upper respiratory tract irritation, 3.3 of the nonsmokers and 29.3 of the smokers reported productive cough. The combination of irritating fumes or particles with cigarette smoke may stimulate bronchial mucus secretion more than either factor acting alone.

In a recent longitudinal study of 3,799 male coke oven workers, Madison and colleagues (1984) examined relationships between a series of risk variables (age, current smoking status, job location) and indices of pulmonary function ( $FEV_1$ , FVC, and detailed exfoliative cytology of sputum). Covariance and multiple logistic regression analyses were done to identify the principal factors predicting  $FEV_1$  and  $FEV_1/FVC$ . Measurements were done in 1978 and in 1982. Appropriate adjustments were made for height, weight, and years at the coke oven. Data from Caucasians and blacks were analyzed separately. Both smoking and job location (six categories) had significant detrimental effects on  $FEV_1$  and  $FEV_1/FVC$  in Caucasian workers. In blacks, smoking adversely affected  $FEV_1$  and  $FEV_1/FVC$  but job location did not.

Sputum cytology included examination for various cells (reactive bronchial epithelial cells, metaplastic epithelium, histiocytes, polymorphonuclear leukocytes); prominence in each specimen was graded on a scale of 0 to 4, and atypical metaplasia was rated as mild, moderate, or severe. The investigators found excessive prominence of certain exfoliated cells well correlated with reduced  $FEV_1$  and  $FEV_1/FVC$ , a result apparently not caused by smoking, because the percentage of workers showing cells was equivalent in both smoking categories. Multiple logistic regression was done to identify factors principally responsible for metaplasia in Caucasians: age and smoking were the strongest predictors, but job location was also a significant factor. Among blacks, only smoking and age were significantly predictive.

Madison and colleagues (1984) believe that their use of data from two examinations, plus sputum cytology, identified work-related pulmonary injury not demonstrated in earlier cross-sectional studies and that the findings may portend pulmonary disability in some workers. The interval between examinations was not considered long enough to permit time trend analysis. These authors reported no measurement of airborne particulate or fumes at the six job locations.

### **Research Recommendations**

1. Efforts to minimize workplace exposure to known and suspected carcinogens should continue and not be delayed in anticipa-

tion of definitive evidence of hazard from occupational or environmental studies in humans.

2. Efforts to assist smokers in their efforts to quit smoking must continue in all sectors of the population. Blue-collar workers have a higher prevalence of smoking and a higher exposure to materials that might interact with cigarette smoke to increase disease risk. Because of these dual exposures, an intensive effort should be made to reduce the smoking rates of these workers.
3. Epidemiologic studies to assess the health impacts of smoking or work exposures to noxious substances should take both factors into account as potentially causative. Additionally, the possibility of interaction should be kept in mind, and whenever possible, tested for.
4. Laboratory animal studies designed to explore the health-damaging effects of tobacco smoke should include experiments capable of identifying interactions with major industrial pollutants.
5. There should be continuing research aimed at identifying the principal constituents of common industrial pollutants that act as cancer initiators and promoters. There should also be continuing efforts to demonstrate the mechanism of tissue damage caused by cigarette smoke and various industrial pollutants, alone and in combination.
6. Modern tissue culture techniques employed to identify carcinogens should be exploited as test systems for interactive effects between tobacco smoke constituents and industrial pollutants.

## **Summary and Conclusions**

1. The biotransformation of industrial toxicants can be modified at least to some extent by the constituents of tobacco smoke through enzyme induction or possibly inhibition. Both tobacco smoke and some industrial pollutants contain substances capable of initiating and promoting cancer and damaging the airways and lung parenchyma. There is, therefore, an ample biologic basis for suspecting that important interactive effects between some workplace pollutants and tobacco smoke exist.
2. In mortality studies of coke oven workers and gas workers, convincing evidence has indicated that work exposures to oven effluents are causing an excess risk of lung cancer in spite of the lack of adequate information on smoking. Other mortality studies that suggest small increases in smoking-related diseases, such as pancreatic cancer in refinery workers, cannot be interpreted without more information on smoking.

3. For bladder cancer, the interactions between smoking and occupational exposure are unclear, with both additive and antagonistic interactions having been demonstrated.
4. The risk of pulmonary disability in rubber workers was increased when smoking and occupational exposure to particulates were combined. There are few empirical animal experiments that demonstrate interactive effects between cigarette smoking and various industrial chemicals for lung disease.

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## **CHAPTER 10**

### **COTTON DUST EXPOSURE AND CIGARETTE SMOKING**