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CANCER MORBIDITY AND MORTALITY: THE IMPORTANCE OF OCCUPATIONAL EXPOSURES

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Environmental factors--specifically, cigarette smoking, diet, naturally occurring and synthetic chemicals, radiation and all other factors which are not purely genetic--together are responsible for most human cancers.

First, we will review the general evidence on the importance of environment; next, the extent to which industrial chemicals may contribute to the cancer load and the types of cancer of greatest concern; and finally, using several examples, interactions of industrial and other carcinogens and methodologic problems in studying occupation and cancer.

Comparisons of incidence rates show striking differences in the frequency of cancer in different countries. These vary for the different types of cancer. Where large population groups have migrated, the frequency of cancer in these populations has changed (Haenszel 1961). The tendency is for migrating populations to take on the cancer risk of the place to which they move. Thus, for example, when the Japanese moved from Japan to California, their risk for stomach cancer (high in Japan) has fallen while their risks for colon and breast cancers (low in Japan) have increased. Foreign-born in New York State have higher risks for cancers common in Central Europe than do native-born descendants from these same populations. Systematic analysis of these international differences in cancer incidence have yielded estimates that 90 percent of cancer may be environmentally determined

(Higginson 1969). Note that this neither means that the causes are known nor that the cancers are due to industrial chemicals. It merely refers to environment in the general sense, encompassing all influences, including genetic and environmental interactions, and excluding only cancers that may be purely genetic.

In support of the major influence of environment are socioeconomic differences in cancer incidence. Stomach and cervical cancers are more common among poor people while brain tumors, breast and prostate cancers, and leukemia are more common in upper income groups. Furthermore, known carcinogens such as cigarette smoke, several recognized industrial carcinogens and radiation have been shown to induce cancer in every ethnic and nationality group studied. On a population basis for these known carcinogens, environment has a predominant influence on cancer risk.

Proportion Due to Occupation

Industrial chemicals first come to mind when talking about occupation and cancer. Yet many people spend 20 percent or more of their time working. They eat at work; they may smoke at work, and taking these factors into account it would not be surprising if as much as one-fifth or more of cancer is related to the work place. This, of course, only means that the cigarette is the most common carcinogen in the work place, and that other dietary and life-style factors pertain to the work as well as the home environment. Furthermore, certain occupations have a

carcinogenic risk unrelated to industrial chemicals. For example, farmers get more skin cancer from working in the sun, nuns have high breast cancer risk because of the absence of the protective effect of pregnancy, prostitutes more cervical cancer because of their trade, and there are selected occupational groups which smoke or drink more than do others. These types of life-style factors, however, will not be considered in the rest of the discussion, since our focus shall be the chemical environment.

Doll and Peto in the June 1981 Journal of the National Cancer Institute estimate the proportion of cancers related to occupation. Their method was to examine the occupational risks for each cancer site and assess the proportion of cancers due to known or suspected occupational exposures. An alternative approach of estimating the number of exposed workers and the level of exposures, then multiplying by estimated risk levels is not feasible at this time, because we lack crucial data on the number of exposed persons and their level of exposure. Problems of interaction of carcinogens complicate both methods.

Table 1 gives a rough estimate of the number of cancers in the United States that might be attributable to occupational hazards. The percents attributable are taken from Doll and Peto and the incidence rates from American Cancer Society (1981) estimates. Lung cancer is the major site thought to be related to occupation. Doll and Peto judge that perhaps 5 percent of male

lung cancers could be related to asbestos, 5 percent to combustion products of fossil fuel and 5 percent to other occupational hazards. The uncertainty of these estimates should be stressed. The lung cancer estimates are particularly uncertain because of insufficient attention to the strong impact of cigarettes in many occupational studies.

Recognized occupational carcinogens for lung and bladder cancers and leukemia, as reviewed by Cole and Goldman (1975), are shown in Table 2. Many carcinogens have been related to these cancer sites. Even though the risk to exposed individuals may be very high, the proportion of cancers nationwide due to many of these factors may be very small.

Automation and other industrial advances, improvements in worker safety and changes in the use of industrial chemicals undoubtedly will have major effects on future occupational cancer risks. Thus, no attempt is made to estimate these future risks.

Cancer Trends

If occupational exposures contribute substantially to the total cancer load, because of the huge post-World War II industrial expansion, this should be reflected in cancer trends over time. Since men have had more years of work exposure, the increases over time should be greater for men. Table 3 shows age-adjusted cancer mortality rates since 1950 for leading causes of cancer deaths in men and in women. (Shown are cancers which

are in the top five for any time period.) The major rises in lung cancer deaths obviously are chiefly related to cigarette smoking. Trends in nonsmokers are discussed below.

Colon cancer has increased for men, but not for women, and rectal cancer has declined for both. Although diet is the most suspect etiologic factor, the sex difference in trends might make one wonder about occupation and colon cancer. Pancreatic cancer has increased for both sexes, partially as a result of increased smoking. The other common cancers have not changed much or have declined. Improvements in treatment also would impact on these mortality rates.

A rising lung cancer mortality among nonsmokers was described by Enstrom (1979). Using national mortality surveys of informants listed on death certificates of lung cancer patients in 1958-59 and 1966-68, Enstrom estimated a doubling of the lung cancer death rate for nonsmoking men in the intervening decade (see Table 4). The rates for nonsmoking women stayed level. To our knowledge, no other data on trends among nonsmokers have been published; thus, no direct information exists about this trend since 1968.

Enstrom's data have been challenged by Doll and Peto (1981) on the basis that former smokers may be misclassified as nonsmokers in questionnaire studies. This is particularly true when informants rather than patients themselves are questioned. Since with men the number of former smokers has increased over time, the apparent increase in lung cancer among men who never

smoked could result from misclassifying former smokers as nonsmokers. Since there were fewer former smoking women in the time period studied by Enstrom, such an artifact might not be seen for women.

Dr. Marvin Schneiderman, during his Keynote Address to the Society for Occupational and Environmental Health (1979), stated that "nonsmoking-related lung cancers have probably doubled in the 1970s (and probably also in the decade before)". His estimate was based on an assumption that relative risks from cigarette smoking declined because of a lower average number of cigarettes smoked by men and the proportionately greater use by women of filter cigarettes, and low tar and nicotine cigarettes. He attributed .85 and .70 of lung cancer in men and women respectively to smoking in 1969-71 and .75 and .60 in men and women respectively in 1976. Consistent with this assumption is the report by Auerbach et al (1979) of fewer bronchial epithelial changes in 1970-77 male cigarette smokers than in 1955-60 men who smoked equivalent amounts. Factoring in this assumption, Dr. Schneiderman calculated a doubling in the nonsmoking related cancers. He acknowledged the uncertainty about these assumptions but emphasized the need to look further into the industrial component.

We added smoking status to New York State Cancer Registry Reports in 1978. Excluding unknown smoking status (unfortunately still substantial), Cancer Registry data indicate that never-smoked

represent about 7 percent of lung cancer cases in males and 18 percent in females. This percent of nonsmokers is somewhat higher than seen in past epidemiological studies of males but far lower than past data on females (National Clearinghouse, 1976). Since lung cancer among men is rising and the percentage of nonsmokers among male cases also appears to be rising slightly, one many infer that there is a rise in lung cancer among male nonsmokers. Since the female lung cancer rate is rising rapidly but the percentage of nonsmokers is falling, it is not possible to draw an inference about the lung cancer trends among nonsmoking women.

Thus, there are hints of an increase in lung cancer among nonsmokers which might suggest an impact of occupation, but we lack the crucial data to be sure of these trends.

Mesothelioma as a Marker

Asbestos and cigarette smoking interact to greatly multiply lung cancer risk (Saracci 1977). It is for this reason and widespread asbestos contamination of the environment that asbestos is thought of as a major lung carcinogen. Because of the cigarette interaction and the difficulty in demonstrating asbestos exposure to individuals, it has been difficult to document the degree to which asbestos contributes to the lung cancer load.

Mesothelioma is known to result from asbestos exposure and does not require cigarette interaction. It is about .01 as frequent as lung cancer. Mesothelioma incidence or mortality rates might be used as a marker of the carcinogenic impact of asbestos.

The rates of mesotheliomas for the past five years, as reported to the New York State Cancer Registry are shown in Table 5. Pleural rates are probably a better marker than peritoneal rates, since there is less chance for error in pathological or clinical diagnosis. This is a difficult tumor to diagnose accurately, which could bias these statistics. While mesothelioma may have increased slightly, there is not the major shift that might be expected if asbestos were contributing to a rapidly growing proportion of cancer. There also may be a slight increase in the male:female ratio, but numbers are too small to be certain. The ratio of pleural to peritoneal mesotheliomas is greater for men than for women.

Halogenated Ethers as an Example

Bis (chloromethyl) ether and chloromethyl methyl ether are particularly interesting as lung carcinogens because:

1. Laboratory carcinogenesis testing preceded documentation of a carcinogenic effect in humans. This differs from most proven human carcinogens, which were first discovered through observations on humans.

2. There is a possibility that the cigarette interaction is one of lessening rather than increasing the risk.

In 1968, Van Duuren et al reported that Bis (chloromethyl) ether was a potent carcinogen for mouse skin and that chloromethyl methyl ether might have weak carcinogenic activity. They had studied these compounds because of their high reactivity and wide laboratory and industrial utility as intermediates in organic synthesis, in the treatment of textiles, for the manufacture of polymers, insecticides, the preparation of ion exchange resins, and as solvents for industrial polymerization reactions.

In 1973, Figueroa et al reported lung cancer in 14 chloromethyl methyl ether workers. Men at a chemical manufacturing plant had been studied because of a suspected high lung cancer incidence noted during the previous 10 years. A later report by Weiss (1980) who had followed 51 men with moderate to heavy cumulative exposures to chloromethyl ethers revealed 11 to have developed lung cancer. The risk was higher in men not smoking cigarettes at the start of the observation period than in smokers. Weiss speculated that the heavy bronchial secretions induced by smoking might hydrolyze halo ethers or separate them from the bronchial epithelium, thus, accounting for the greater risk in nonsmokers. It must be realized, however, that the entire study involves only 11 lung cancer patients.

Sensitivity of Current Methods

Rapid advances are being made in the use of epidemiological methods to identify occupational cancers. Still we have a need for further improving these methods. Two examples will be used to illustrate limitations of surveillance techniques requiring attention. In the first, a known occupational cancer epidemic could not be detected through Cancer Registry surveillance. In the second, an apparent cancer excess at a company was explained by better medical diagnosis for workers, and no true excess was found.

The first example involves 96 bladder cancer patients who were reported from among 366 male employees of a coal tar and dye factory in Western New York State (Goldwater et al 1965). These men had been exposed to ß-naphthylamine, benzidine and other chemicals. Thus, in New York State we had a known epidemic of bladder cancer--at least, 96 cases--clearly resulting from chemical exposures in one plant. Company employment and medical records had been used for case ascertainment in the initial study.

The New York State Cancer Registry has been in existence since 1940. It is population-based and covers the entire State. A number of years after Goldwater et al's report, Cancer Registry data were examined to see if the known epidemic was detectable by looking for time or geographic clustering. It was not. Detection apparently was obscured by bladder cancer with

its long induction period being diagnosed over a period of many years, by registration of home address of the cancer patients rather than place of work, and by dilution of these cases by other cancer patients from the large population of the Buffalo area. This assessment was one of the factors which led us to add occupation and industry to the New York State Cancer Registry. We think that occupation and industry coding may help us to detect this type of episode in the future.

The second example is a recently completed study in which we initially had examined death certificates of adult male brain tumor patients to see if any occupation or industry appeared as unusually frequent. One company was more commonly listed on death certificates of brain tumor patients than on control certificates. In collaboration with the company this question was studied in great detail. We found that rather than an excess, workers diagnosed with brain tumors had more complete medical diagnostic evaluation than other brain tumor patients in the State not working at the company. This could account for the initially observed difference. In the general population many brain tumors apparently are misdiagnosed as strokes or other medical problems. This is what epidemiologists would refer to as a sensitivity/specificity problem. In general, epidemiologists take great pains to be sure the individuals under study actually have the disease -- i.e., the diagnosis is specific. In occupational studies, it also is essential to assure case-control

comparability in detecting the disease -- i.e., equal sensitivity for making the diagnosis.

Conclusion

The epidemiologic method has a great deal to offer in identifying specific occupational carcinogens and the extent to which human cancer results from these occupational exposures. These methods require careful documentation of the actual exposure by individuals who later develop cancer, the extent of exposure in the general population and in selective subgroups that may be at high risk, and assurance that the diagnosis is being made with equal sensitivity in case-control comparisons.

Available data do not allow a precise estimate of the extent to which occupational exposures contribute to human cancer. Lung cancer appears to be the site most related to occupational exposures, but the contribution of cigarette smoking must be taken into account as this is studied further. Identification of occupational carcinogens offers potential for prevention that may be more immediate than identifying other cancer causes. Epidemiological studies should proceed in parallel with efforts to lessen human contact with active chemicals suspected of being hazardous on the basis of animal or other laboratory testing.