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# OCCUPATIONAL CANCER: CLINICAL INTERPRETATION AND APPLICATION OF SCIENTIFIC EVIDENCE

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## ABSTRACT

Haintaining an awareness that workplace factors may contribute to occupational cancer is one of the most formidable obstacles in early clinical recognition. This early recognition provides an opportunity for a practicing physician to make an important contribution to new knowledge in the field. Another important reason for the physician to have a high index of suspicion of cancers being related to workplace exposures has to do with compensation benefits which may accrue to the injured worker. The physician's role in the compensation system is critical both in providing medical opinion, which is material to the final decision, and because in many states it is the physician who starts the time clock for the statute of limitations. Three case examples are used to illustrate the importance of clinical recognition by an alert physician: 1) mesothelioma and labor; 2) lung cancer in a plumber who smokes and one who does not smoke; 3) leukemia in a rubber industry worker. Given the inherent preventable nature of occupational cancers, it is hoped that society will assist in searching for these important links.

## INTRODUCTION

Despite the accumulation of knowledge about and tools to assess known and suspected occupational carcinogens, the task remains a difficult one for the physician faced with determining the work-relatedness of cancer in any individual patient. Perhaps the





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most formidable obstacle in this determination is the first step which the physician must take in evaluating any patient who may have an occupational disease, namely, maintaining awareness that workplace factors may be of importance. Only then can the other important steps follow of diagnosing, treating, and notifying the appropriate parties of the presence of a known or suspected occupational disease. That the physician usually fails to obtain even the most rudimentary information necessary to initiate this sequence has by now been commented upon by many (1,2). Alice Hamilton's comments of over 50 years ago, following similar comments by Ramazzini of 200 years earlier, are, unfortunately, still too apt. She said, "If the recording interne would only treat the poison from which the man is suffering with as much interest as he gives to the coffee the patient has drunk and the tobacco he has smoked, if he would ask as carefully about the length of time he was exposed to the poison as about the age at which he had measles, the taste of the searcher for the truth about industrial poisons would be made so very much easier (3)."

## Reasons to Consider the Work-relatedness of Cancer

There are many potential benefits that derive from the clinician's consideration of the work-relatedness of cancer. The first is to help arrive at the correct diagnosis and in turn design appropriate treatment. A new pleural effusion in an asbestos-exposed worker should call for placing mesothelioma higher on the list of differential diagnoses than it otherwise would be. Primary lung carcinoma, particularly if that worker

is also a smoker, is, of course, also a strong consideration. And knowing of the asbestos exposure and its many sequelae should add another entity to the list, that of a benign asbestotic effusion. The second reason to consider workplace factors is to find new associations between hazards and disease. Perhaps in no other area than occupational health is there as much opportunity for the practicing physician to make important contributions to new knowledge. The instances are multiple of the physician who, sometimes after the problem is first brought to his or her attention by workers, established a new link between an exposure and an adverse health outcome. This was the case when only a few years ago Dr. Keogh identified the neurotoxic properties of dimethylaminopropionitrile, a chemical used in plastics manufacturing *(4)*. The history of identification by physicians of occupational carcinogens is a long one, starting with Percival Pott who in 1775 reported scrotal carcinoma among London chimney sweeps (5). That this same class of substances, coal combustion by-products, which caused the rare scrotal tumor continues to cause lung cancer in coke-oven workers is a clear and sorry statement that identification alone is not enough. A more recent example of identification of a human carcinogen by a physician, in this case a part-time plant physician, is the report in 1974 by Dr. Creech of three cases of hepatic angiosarcoma among workers in a single polyvinyl chloride manufacturing facility (6). In this instance, the car-

cinogenic properties of vinyl chloride had been well-predicted by earlier animal studies (7).

Other reasons for considering workplace factors in clinical practice include being better able to educate and counsel workers. The role of smoking cessation, which is a primary, but also a secondary preventive intervention, insofar as it relates to asbestos-related lung cancer risk, is but one example. Consideration of exposure to occupational carcinogens is an important component of designing effective Screening or surveillance programs for individuals or groups of workers. One important factor in this regard is the appreciation of the effect of population prevalence of the abnormality, or the pretest risk of the disease in any individual, on the diagnostic efficacy of the screening test. This aspect of Bayes's theorum has received increased attention, in general, in the clinical literature, for example, as noted in the marked variation in the ability of ST segment depression in exercise treadmill testing to predict the presence of coronary artery disease (8). For example, assuming a sensitivity and specificity of 90% of the chest x-ray to detect a lung abnormality such as cancer, then 90% of those with the abnormality will have an abnormal chest x-ray and 90% of those without abnormalities will have a normal chest x-ray.

If one then evaluates patients from a population where the lung abnormality has a prevalence of 1 in 100, the positive predictive value of the chest x-ray, that is how many with the abnormal

chest x-ray are going to have the abnormality, is quite low at roughly 8%. This is contrasted with the use of the chest x-ray to screen patients with a higher prevalence of the abnormality, 1 in 10, where the test characteristics of 90% sensitivity and specificity have not changed, but the positive predictive value of an abnormal chest x-ray has increased to 50%. It is important, formally or informally, to incorporate this concept of pretest probabilities into clinical practice when screening for health problems among those occupationally exposed. Chest x-rays have not been shown to be cost-effective as routine screening tests in part because of this effect of population prevalence. In addition, if early detection does not alter significantly the course of identified abnormalities, then one of the main principles of usefulness of screening tests is violated. This appear6 to be the case with screening chest x-rays. For this reason, theoretical calculations of the cost-effectiveness of screening for lung cancer among asbestos workers do not support its use, despite the profoundly increased risk for lung cancer among this population (9). These same calculations, not surprisingly, support the cost-effectiveness of screening for colon cancer among asbestos-exposed individuals because of their increased risk for these cancers at about 1 1/2 to 3-fold and because early detection can alter the natural history of these tumors. Further work clearly needs to be done in this area, however, given the potential that among this exceptionally high-risk group, other surveillance strategies may turn out to

have individual health benefit. This brings us to the last reason to assess the work-relatedness of cancer, namely, for the non-medical or quasimedical benefits, of which workers' compensation is but one, albeit, important component. Mesothelioma can be used as an example; that the course of this tumor cannot, at this point in time, be altered, despite occasional spurts of enthusiasm for single or combined intervention modalities, is unfortunately all too clear (10). Yet, making the diagnosis in an individual patient has significance in and of itself. One clear reason is the large number of patients who would prefer a definite diagnosis rather than an uncertain one, particularly in such a highly-malignant process which has a mean survival of about 18 months from the onset of symptoms and only about 12 months from time of diagnosis (11). A second reason is that for those occupationally exposed, compensation benefits, even independent from litigation under third party product liability, may be significant and can be established in the setting of definite occupational exposure and a pathologic diagnosis. A third reason is that mesothelioma is a signal neoplasm of asbestos exposure so that monitoring the incidence of this tumor provides one means to evaluate the overall burden of asbestos-induced disease.

## The Physician and Workers' Compensation

The physician's role in the workers' compensation system is critical, both in providing the medical opinion which is material to the final decision, and because in many states it

is the physician who starts the time clock of the statute of limitations. In the State of Washington, for example, the worker has only one year to file from the time first notified by a physician of the presence of a work-related problem. It has been interpreted that this same notification will start a three year statute of limitations on litigation under third party product liability. The physician is also legally bound to inform the worker of his or her rights under the compensation system, including the right to be represented by an attorney and to pursue third party liability (12).

The judgment by the physician of the probability of the work-relatedness of the medical condition is key in compensation and related situations. The workers' compensation forms in moat states demand that the physician indicate the degree of certainty of work-relatedness. The workers' compensation form in the State of Washington is the same for accidents and diseases. The physician must reply to the question, "is the condition diagnosed the result of the incident described?" by marking one of four categories: definitely, probably, possibly, no. Despite the yearning to treat this as a Likert scale, placing a large X somewhere between possibly and probably, the physician must effectively make, with important implications, what is ultimately a yes or no answer. "Yes", by answering definitely or probably, and "No" by answering possibly or no. If the decision is no, the patient will almost never receive cornpensation and if it is yes, the patient will sometimes

receive compensation.

The effective dichotomization of the physician's determination stems in part from the legal definition that the criterion for work-relatedness is met if the condition arose out of or was aggravated by exposures at work on a more probable than not basis. It is no easy task, even in the simplest of circumstances, to ask physicians to make a definite statement about probability. "Probable" invokes in most physicians a sense of a degree of certainty that is greater than its actual definition, which is that the event, or in this case the relations of the problem to work is more likely than not or has a greater than 50% chance of being the case. Black's Law Dictionary defines probability as "a condition or state created when there is more evidence in favor of the existence of a given proposition than there is against it". The physician often intuits some degree of certainty beyong this legal one, perhaps more like 80% probability. This is not surprising given Webster's first definition of probable which is "likely to occur or be; that can reasonably but not certainly be expected". Webster's second definition would be more in line with the legal definition, also "reasonably so, as on the basis of evidence but not proved (the probable cause of disease)".

Clinical Situations

12 A number of clinical situations will be presented in order to explore how to interpret available scientific data on occupational cancer and apply this evidence to practice and judgments

of causation. These are: mesothelioma in a laborer; lung cancer in a plumber who smokes and in one who does not smoke, and leukemia in a rubber industry worker.

Case Number 1

The patient is a 60-year-old man with a thirty-five year history of unprotected asbestos exposure while employed doing general labor and demolition work in the costruction trades. He had several months of malaise, a 10 pound weight loss and constant, dull, right-sided chest pain. Chest x-rays showed a right-sided pleural-based mass with freely-layering fluid. Pleural plaques were present in the left hemithorax. A diagnosis of mesothelioma was made from biopsy material obtained at limited open thoractomy.

The relationship of the diagnosis of mesothelioma to this patient's occupational asbestos expsure, would probably be unquestioned even by the most skeptical. This is a situation where most who are informed would not hestitate at responding even with a 'definite' to the question of the probability of the work-relatedness of this patient's tumor. In the case of mesothelioma, the smoking status of the patient appears to have no relation to risk such that an individual's smoking status is not relevant to the determination of cause. Evidence for the relationship between mesothelioma and asbestos exposure is derived from animal studies but more importantly from epidemiologic studies. Mesothelioma has been identified as a signal neoplasm of asbestos exposure, with a history of asbestos

exposure found in anywhere from 50% to nearly 100% of those with mesothelioma. While asbestos may not be the only cause, it is certainly the most significant one in risk for mesothelioma, such that relative risk has virtually no meaning, as there are no expected cases in the absence of exposure. Absolute risk is used to develop dose–response relationships.

Before examining the evidence about the dose–response relationship between asbestos and mesothelioma, it is worth reviewing some of the reasons why the practicing physician should be concerned with such relationships. Few would question the importance of recognizing aplastic anemia as an idiosyncratic response to chloramphenicol, distinct from that drug's predictable myelosuppressive activity. In the same way, understanding dose–response relationships in occupationally-related diseases allows the physician to understand better why and to what degree the individual patient is at risk for an adverse outcome and to anticipate, and if possible prevent, this outcome in the individual or other exposed workers. It also may be helpful in determining prognosis and treatment (13).

Although mesothelioma may result from brief and sometimes casual asbestos exposure, there is convincing evidence that the occurrence of mesothelioma has a consistent relationship to increasing dose, although not a linear one (14). Risk does not appear to be related to age at first exposure, but time from first exposure, with a dramatic increase in risk with time. This relationship of risk is as a function of the 4th or 5th

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power of time from first exposure (15). This phenomenon raises concerns about even low-dose childhood exposures, as these confer the greatest risk of developing mesotheliomna at an age when there are fewer other competing causes of death. But, clearly, the greatest burden of this consequence of exposure is borne by those occupationally exposed. Berry's review of the mortality pattern of British workers certified with asbestosis by pneumoconiosis panels found mesothelioma to be the cause of death in 9% (16). He also examined loss of longevity, finding that the extent of disability and time of certification by the pneumoconiosis panel was a potent predictor of survival. Compared to the expected survival of 75% of the cohort at 10 years from certification, had the death rates of England and **Wales** been applied, those with disabilities at certification of 10 or 20% had only **50%** survival, only about one-third survived at 10 years if initial disability was 30 or 40%, and only one-sixth were alive at 10 years if initial disability was 50% or more. For a man aged 55 at time of certification and awarded 10% disability benefits, longevity would be reduced by 3 years; if Initial disability was 20%, then longevity would be reduced by 5 years, if 30 or 40%, then by 8 years, and if at least 50% disability, then reduction would be by 12 years. Goldsmith's analysis of mortality of 11 cohorts of about 32,000 asbestos-exposed workers provided good evidence that at non-pulmonary sites asbestos acts as a systemic carcinogen, but he also showed the significant risk of those exposed for developing mesothelio-

ma (17). In his calculations, he considered all deaths from asbestosis or mesothelioma as excess asbestos-related deaths and calculated other excess asbestos-related deaths by determining the differences of observed minus expected for each cause. In this manner, he found 1845 excess deaths from asbestos-related cancers, 20 or more years after exposure. Among these, about 45% were due to lung cancer, 20% to asbestosis and 15% to mesothelioma.

Case Number 2

The patient is a 50-year-old plumber and pipefitter, employed in his trade in the construction industry for 30 years. He had been exposed, without any respiratory protection, to significant amounts of asbestos, particularly in the early years. The patient had never smoked cigarettes and presented with a 6-month history of cough. His chest radiograph showed a right-sided irregular mass about 4 cm in diameter. The mass was subsequently diagnosed as adenocarcinoma. There was no other radiographic evidence of asbestos-related sequelae.

How should the physician interpret available evidence in considering the relation of this patient's cancer to his work exposures? The relation between asbestos exposure and lung carcinoma was first suggested by Lynch and Smith in 1935 and further supported in 1955 by epidemiologic studes (18). Selikoff's studies in the early 60s further characterized the strength of the association. His important publication in 1964 in which he reported the high rates of neoplasms among insula-

tion workers, closed with this prophetic comment, pertinent to the case under discussion, "Asbestos exposure in industry will not be limited to the particular craft that utilizes the material. The floating fibers do not respect job classification ... insulation workers undoubtedly share their exposures with their workmates in other trades; intimate contact with asbestos is possible for electricians, plumbers, sheet-metal workers, steam fitters, laborers, carpenters, boilermakers, and foremen... (18). In 1968, Selikoff reported the remarkably increased rate of about 92-fold for smoking asbestos workers of dying from bronchogenic carcinoma (19). Subsequent analyses supported the absolute increased risk for bronchogenic carcinoma, even among non-smokers exposed to asbestos and the profound synergism in risk for those who smoked and were exposed (20).

Henderson and Enteline have studies the mortality experience after the age of 65 of a cohort of about 1,000 employees working in a U.S. asbestos company and retiring with a company pension (21). Cumulative asbestos dust exposure was calculated for each individula, based on personnel records and dust level estimates for each job and time period. Plotting the data of the relation between total dose and mortality from respiratory cancer yields a strong linear relationship with a correlation of .98; the predicted line has the formula of $SMR = 100 + 0.658$ (cumulative exposure). The relative risk of developing lung cancer appears to be independent of age at first exposure. And although the mean latency for lung cancer from time of first

exposure is about 25 years, there is a linear increase in excess risk of death from lung cancer which occurs very close to the onset of exposure and certainly at no more than 10 years (15).

Identification of tumor type is probably of little benefit in assigning cause to lung cancer in the individual patient. Squamous and adenocarcinoma are the predominant types of asbestos-related cancers, but this reflects the pattern of lung cancer seen in the general population (22). One difference between lung cancer in those with asbestos exposure compared to unexposed individuals is the location of the tumor; in the general population, about 2/3 of lung cancers are found in the upper lung fields, whereas lower lobe tumors are more likely in asbestos-related lung cancer (23). The reasons for this are unclear, but perhaps include the predominance of asbestos-induced fibrosis in these same areas. Although some investigators have reported a greater number of peripheral tumors in those exposed, this was not found in one case-control study which addressed this issue (23).

In the case presented here, the relationship of the tumor to his work exposures, while not as clear-cut as if he had mesothelioma, meets almost all criteria which can be employed by the physician in determining the work-relatedness of a condition. It is biologically plausible, the time course is appropriate, and there is lack of exposure to known agents outside the workplace which can cause the same process. The presence of other manifestations of asbestos exposure would

have provided more evidence to support the nature and extent of exposure. Two studies have reported that pleural plaques alone, even with the same degree of exposure, may confer a doubling of risk for carcinoma *(24)*. The absence of these other radiographic manifestations, however, does not alter the correctness of stating his tumor is probably work-related. He has, after all, just on the basis of his exposure, multiplied his risk for lung cancer by 5-fold (20).

But what if this patient were a smoker? A similar decision to state that this patient's tumor was more probably than not work-related can be soundly based on available scientific evidence, with the smoking asbestos-exposed worker having a five- to ten-fold increased risk for lung cancer than if he or she did not have the asbestos exposure. This decision will, however, be met with far more argument and controversy. Less so because of the statistics, or so-called science, but because of the implications. Smoking is common, lung cancer is common, and asbestos exposure is common. If the same rules of evidence were to apply for all smokers who got lung cancer who had asbestos exposure, the cost implications for many industries in terms of industrial insurance, not to mention those for a few industries in terms of third-party product liability, are enormous. The cost implications of the added risk posed by the asbestos exposure do not, of course, disappear with the judgment that these tumors are not work-related; they are just shifted away from or externalized by industry, with the greatest burden

borne by the affected patient and his/her family. In-depth analyses of compensation for asbestos-related disability have shown the same trend previously found, namely, that workers' compensation pays only a small share of the bill for disabilities arising from occupational disease *(25)*. Compensation for occupational disease in general, and in particular for those situations of multifactoral origin and less well-characterized risk goes well beyond evidence and physician assessment of individual cases.

Under the British system, asbestosis and mesothelioma are prescribed diseases, entitling the patient or his or her dependents to compensation. Decisions about compensation are made by a pneumoconiosis panel, and certification has recently been expanded to include pleural thickening, if extensive. Under their system, cancer of the lung has been compensable only if it occurs in association with asbestosis, so that claims rejected during life may be accepted after death if post mortem examination reveals asbestosis which had been not radiographically detectable. Recent recommendations from the British Industrial Injuries Council, using the relative risk estimates previously discussed, are that smoking status should be disregarded in determining compensation as should tumor type **(26).** Moreover, it was recommended that lung cancer be compensated if it ocurrs not only in association with parenchymal asbestosis but with bilateral pleural plaques or diffuse thickening. The aim of these recommendations is to compensate those with suf-

ficient asbestos exposure who get afflicted with lung cancer. Although this can be applauded as a more rational and consistent approach to both the legal and medical interpretation of the scientific evidence, it does not address the circumstance of the worker who, for unknown reasons, faced with the same amount of exposure as a fellow-worker who develops pleural or parenchymal fibrosis, is spared from these sequalae but develops lung cancer. This circumstance of asbestos-related carcinoma in the absence of other radiographic abnormalities, will continue, particularly as the risk for fibrosis decreases with decreasing exposures. At current allowable levels, depending on the risk assessment model used, it is estimated that there will be at least 5,000 excess lung cancer deaths for each million workers exposed (27).

The interaction between smoking and workplace hazards has been unusually well-defined for asbestos. It is not so much data which are lacking but an economic, philosophical and ethical consensus in order to answer the question which was posed by Sterling several years ago: "Does smoking kill workers or working kill smokers?" (28). It is not sufficient to pursue only one approach, namely, individual smoking cessation programs, particularly when this approach is associated with such low success rates. Institutional interventions, such as eliminating tobacco subsidization and occupational carcinogens, are ones likely to be associated with far more achievable results.

Case 3

The patient is a 45-year-old worker exposed for the past 15 years to benzene in a chemical manufacturing process, at levels that were determined to be at around the current standard of 10 parts per million. He had been in generally good health, without any medical evaluation in the 10 years previous to this presentation and diagnosis of acute myelogenous leukemia.

The question, then, is whether the patient's benzene exposure on a more probable-than-not basis is related to his leukemia. There have been multiple clinical reports of benzene-induced leukemia since the association was first reported in 1928, so that in the last 20 years, reports of leukemia have outnumbered those of fatal pancytopenias (29). Only recently has benzene been shown to be carcinogenic in animals, leaving arsenic and hematitite the only known human carcinogens without demonstrated animal carcinogenicity. Two cohort studies have demonstrated an increased leukemia risk of up to 20-fold, particularly of the myelogenous form, from benzene exposure (30, 31). Excess chromosomal aberrations have been demostrated in workers exposed to current allowable levels of benzene at 10 parts per million (32).

Risk assessment analysis of benzene exposure, based on these and other studies, has been performed. The most conservative risk assessment has projected, at the minimum, an excess of 140 to 170 leukemia deaths per 1,000 lifetime exposed workers at 100 ppm, translating to a range of 14 to 170 excess deaths as

low and high estimates for exposures at 10 ppm (33).

Given the available data, how should the physician respond to the question of the probablitity of the relation of this patient's leukemia to his work exposures? The answer, I think, should be yes, on a more probable-than-not basis. Using an approximate lifetime risk of 7/1000 of developing leukemia, the more conservative estimates would indicate a relative risk of 3 for developing leukemia as a result of this individual's benzene exposures at current allowable levels. In other words, since the background rate of leukemia is at least doubled, any exposed individualwould on a more probable than not basis have gotten that leukemia because of the benzene exposure.

It is because of these and many other situations that we need to do better with collecting, interpreting and analyzing evidence about occupational carcinogens. But it should also be clear that it is often not lack of available data that limits our conclusions or causes disagreement, but the values and interests which we bring to bear individually and collectively in Interpreting the data. As physicians, it is our obligation to protect the interests of our worker-patients. I would argue that this would be best achieved, when in doubt about the causality of a problem, by erring on the side of assuming it is work-related. Given the inherently preventable nature of occupational cancers, I would hope that as a society we would do the same.

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