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Cancer epidemiology and the workplace

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Abstract

Occupational exposure occurs most frequently through direct contact with carcinogenic agents, with any of their active metabolites during absorption (skin, respiratory tract); or during excretion (urinary tract). In the USA, from 2-8% of cancer are attributed to this circumstance. In developing countries emphasis should be made on prevention measures of possible carcinogenic exposure factors, with three basic premises: a) identify exposure markers (biological monitoring); b) identification of high risk subjects, presumable before exposure occurs, and c) early identification of signs of sickness (medical surveillance). This article proposes that, in theory, all occupational cancer can be prevented.

Key words: neoplasms/working risks; review

Frumkin H.
La epidemiología del cáncer y el ámbito de trabajo.
Salud Publica Mex 1997;39:356-369.

Resumen

La exposición ocupacional ocurre más frecuentemente por contacto directo con agentes carcinogénicos, con cualquiera de sus metabolitos activos durante su absorción (piel, tracto respiratorio); o durante su excreción (tracto urinario). A esta circunstancia, en los Estados Unidos de América se le atribuye de 2 a 8% de los cánceres. En países en desarrollo se debe hacer énfasis en medidas de prevención de posibles factores de exposición carcinogénica, con tres premisas básicas: a) identificar marcadores de exposición (monitoreo biológico); b) identificación de sujetos de alto riesgo, presumiblemente antes que suceda la exposición, y c) identificación temprana de signos de enfermedad (vigilancia médica). En este artículo se establece que, en teoría, todos los cánceres ocupacionales pueden ser prevenibles.

Palabras clave: neoplasmas/riesgos laborales; revisión

Work is a central part of the human experience, an activity that occupies a large part of our waking hours. Work can influence health in many ways, both positive and negative. Exposure to carcinogens, resulting in an increased risk of occupational cancers, is an important example of the adverse effects of work.

Workplace exposures have great significance to the cancer epidemiologist, for scientific, social, and public health reasons.

- As a scientific issue, the workplace offers unique possibilities for epidemiologic study. The exposed

population is defined and can be enumerated and followed. Exposures are more intense than in other environments, and can often be identified and measured. Health data may be accessible through employment-linked health care systems, and may be able to be linked to exposure data. It is therefore no surprise that the workplace has been a fertile setting for demonstrating the effects of carcinogens.

- As a social issue, work has special place in most cultures and political systems. One result is that occupational illnesses, including cancer, merit spe-

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cial compensation –creating legal as well as scientific reasons to explore the links between exposure and disease.

- Finally, as a public health issue, occupational cancer is theoretically preventable, so it offers a crucial opportunity for intervention.

How much cancer is occupational? This has been a matter of considerable debate. Doll and Peto, in a widely cited 1981 estimate,¹ attributed between two and eight percent of cancers in the United States to workplace exposures, representing between 25 000 and 100 000 new cases of cancer each year. Other estimates have been several times higher.² It is important to recall that these estimates pertain to the entire population. Within high-risk groups such as chemical workers, the proportion of cancers related to work may be substantially higher. Similarly, for those cancers most closely associated with workplace exposures, the proportion that is occupational may be markedly elevated. These include common types such as lung cancer and skin cancer, and less common types such as bladder cancer, leukemia, and brain cancer.

The process of carcinogenesis: Implications for epidemiology

Cancer encompasses dozens of distinct diseases that share several characteristics: rapid, relatively unrestrained growth by a population of cells; failure of these cells to differentiate and function normally; and survival and propagation of these cells for abnormally long times.

A carcinogen is a substance that causes cancer. Carcinogens can be chemicals, physical agents such as ionizing radiation, or biologic agents such as viruses or aflatoxin. In some cases, such as in parts of the rubber industry, elevated rates of cancer have been detected but a specific carcinogen has not been identified.

Carcinogenesis at the cellular level

Current knowledge of the mechanisms of carcinogenesis remains incomplete. Based on experimental work with mouse skin in the 1940's, two stages in carcinogenesis were identified, initiation and promotion. Initiation was defined as the critical event, when an irreversible change occurred to the cell's genetic material. Promotion consisted of one or more subsequent steps, when intra and extracellular factors allowed the transformed cell to develop into a focal proliferation such as a nodule, then to a malignant tumor, and finally to metastases.

When DNA was identified as the genetic material of cells, initiation was recognized as an alteration of the DNA, or a mutation. In fact, in the 1970's laboratory tests of mutagenicity were introduced as a marker of carcinogenicity. Promoters, on the other hand, were viewed not as mutagens, but as epigenetic factors that enhanced cell proliferation, interfered with normal control and regulation of cell processes, and/or increased the probability of further genetic damage.³ Further experimental observations suggested that successive steps were necessary to induce a neoplasm, leading to multistep theories of carcinogenesis.^{4,5}

Rapid developments in molecular biology have further clarified the events of carcinogenesis.⁶ In the 1980s, studies revealed that some RNA viruses coded for genetic sequences that caused malignant transformation when inserted into host genomes. These were called oncogenes. It soon became clear that nascent forms of oncogenes, called proto-oncogenes, were common in many human and animal cells, and often played an important role in normal cell function. However, if transformed into oncogenes, their products code for oncoproteins that in turn act as growth factors, membrane receptors, protein kinases, or in other ways, resulting in rapid cell growth and dedifferentiation. One of the best studied examples is the *ras* oncogene, which was first identified in rat sarcomas. The *ras* oncogene can be activated by polycyclic aromatic hydrocarbons (PAH), N-nitroso compounds, and ionizing radiation, and has been found in a wide variety of human cancers including bladder cancer, lung cancer, and others of occupational and environmental importance.⁷

A second kind of gene important in carcinogenesis is the tumor suppressor gene, or anti-oncogene. Tumor suppressor genes function normally to regulate cell growth and stimulate terminal differentiation. When inactivated, they fail to perform those functions, and increase the probability of neoplastic transformation. The most commonly identified example is the *p53* gene, located on chromosome 17.⁸ *p53* mutations have been identified in approximately half of human cancers, including those of the colon, lung, liver, esophagus, breast, and reticuloendothelial and hematopoietic tissues, and in the Li-Fraumeni syndrome of familial multiple cancer susceptibility. Of special interest, carcinogenic exposures such as aflatoxin and hepatitis B virus have been associated with specific mutations on the *p53* gene, suggesting that each carcinogen may leave a unique genomic "signature".⁹

These findings have several implications for epidemiology. First, the fact that alterations in specific genes confer an increased risk of cancer, and that these genes vary among individuals, implies population heterogeneity in cancer susceptibility. Second,

the fact that some carcinogens induce specific genetic lesions permits epidemiologic study based on specific biomarkers of exposure. Third, the sequence of events in carcinogenesis occurs over time, corresponding to the latency period.

Latency

Latency refers to the period of time between the onset of exposure to a carcinogen and the clinical detection of resulting cancers. The latency period for hematologic malignancies is in the range of 4 or 5 years, while the latency period for solid tumors is at least 10 or 20 and possibly as long as 50 years. For the epidemiologist, latency implies that person-time at risk does not begin with the onset of exposure, but at some later time. Studies must be designed and analyzed accordingly, with adequate duration of follow-up and with careful definition of person-time at risk, to avoid bias toward the null.

Carcinogen metabolism and individual susceptibility

Individuals differ not only in oncogenes and tumor suppressor genes, but also in the genes that code for various metabolic enzymes. This is important because some chemicals require activation by enzymes before they become carcinogenic. Therefore, the enzymes may help determine carcinogenic risk.

The enzymes primarily responsible for chemical activation are those of the cytochrome P450 system.¹⁰ Others include N-acetyltransferase, epoxide hydrolase, and glutathione S-transferase. The primary function of these enzymes is to render xenobiotics more polar and therefore more readily excretable. However, their products are often reactive electrophiles, which can bond with DNA to cause adducts, and result in mutations.

Considerable variation in these metabolic functions has been noted among species, and among different people.¹¹ For example, people vary several thousand-fold in their levels of aryl hydrocarbon hydroxylase (AHH), an enzyme of the cytochrome P450 system that helps metabolize PAH. High levels of AHH have been associated with increased risk of lung cancer. Another example is the cytochrome P450 enzyme responsible for hydroxylating the antihypertensive drug debrisoquine. So-called extensive hydroxylators have several thousand times more enzyme activity than poor hydroxylators. The extensive hydroxylator phenotype has also been associated with a markedly increased risk of lung cancer. These variations may reflect not only genetic factors, but also environmental

exposures such as cigarette smoking and diet that induce enzyme activity.

These insights into gene expression and enzyme activity are important to epidemiologists for several reasons. First, as noted above with regard to oncogenes, inter-individual differences in metabolic enzymes imply variable susceptibility to carcinogenic exposures. Second, metabolic differences may have implications for epidemiologic study. For example, knowledge of different metabolic states may enable the epidemiologist to measure them in subjects and control for possible confounding.

Threshold levels

A threshold is a safe level of exposure to a carcinogen, below which carcinogenesis does not occur. Whether thresholds exist has been a controversial question.¹² Definitive evidence on this point is elusive, since both epidemiologic and experimental data are inherently uninformative at very low exposure levels. In theory, a single molecule of a carcinogen may be sufficient to initiate carcinogenic transformation, albeit with low probability. By this argument, there is no level of exposure to a carcinogen that is without risk. However, several arguments in support of thresholds have been advanced. First, there are known repair mechanisms that correct DNA damage, at least at low levels of exposure. Second, certain carcinogens, such as trace elements and hormones, are ubiquitous and even essential at low doses; it is argued that these substances are carcinogenic only at higher doses. Third, factors that act epigenetically, such as promoters that stimulate cell division, often have reversible effects, implying a threshold phenomenon. Finally, certain empirical data have been interpreted to be consistent with the existence of thresholds.

Endocrine mechanisms

In recent years, environmental and occupational health researchers have increasingly focused on the health effects of hormonally active compounds. An environmental endocrine disrupter is defined as "an exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body".¹³ This concept is relevant to cancer since hormonal action, especially that of the sex hormones, plays a role in several common cancers. An early example of such an extrinsic estrogen was diethylstilbesterol, or DES, which caused vaginal carcinomas in the daughters of women who took the drug during pregnancy. According to the endocrine dis-

rupter hypothesis, other compounds –including many that are encountered in the workplace such as polycyclic aromatic hydrocarbons; chlorinated organics such as polychlorinated biphenyls (PCB), dioxins, and furans; phthalates; and some pesticides –may exert estrogenic effects. These may be direct hormonal effects on such outcomes as fertility, sperm production, and endometriosis. They may also extend to the development of cancers, including those of the breast,¹⁴ testicles,¹⁵ endometrium¹⁶ and perhaps prostate. One case-control study showed an association between breast cancer and DDE, a metabolite of DDT,¹⁷ while another did not.¹⁸ Some but not all studies of farmers show an increase in prostate cancer¹⁹ which may be related to pesticide exposure. Of note, a number of hormonally active compounds, especially phytoestrogens that occur naturally in some plants, may reduce cancer risk.²⁰ Much remains to be learned about possible hormonally mediated environmental and occupational carcinogenesis.

Which chemicals are carcinogenic?

Approaches to identifying carcinogens

Epidemiology has made critical contributions to the identification of carcinogens. However, epidemiology has important limitations. It is expensive, time-consuming, subject to important biases, and insensitive to many associations. Perhaps most importantly, positive epidemiologic results come too late; people are already ill or dead by the time an epidemiologic association is described. Accordingly, other methods of detecting carcinogens have been developed, including animal studies, in vitro test systems, and structure-activity relationship analysis. Epidemiologic findings must be understood as part of a continuum of evidence used in identifying carcinogens and in setting prevention policy.

Types of epidemiologic studies

The kinds of epidemiologic study designs applied to occupational cancer are no different than those used in cancer epidemiology more generally. These include cross-sectional studies, cohort studies, and case-control studies. A full review of these designs is beyond the scope of this article, and the reader is referred to standard texts, including both general epidemiology texts^{21,22} and texts of occupational epidemiology.^{23,24} However, several methodological issues that are especially salient in occupational cancer epidemiology are reviewed below.

Methodological challenges in occupational cancer epidemiology

Exposure assessment is the Achilles heel of occupational epidemiology. In many situations that merit study, precise, accurate knowledge of individual workers' exposure is unavailable or limited. Exposure misclassification limits the accuracy with which cancer, or any other health outcome, can be associated with exposures of interest.

What is exposure? The phenomenon of primary biological interest is the arrival of a quantity of potential carcinogen at the target, presumably the DNA in cells of a target organ. This is what toxicologists refer to as dose –and it is different than exposure. Two people who work side by side in the same factory may have similar exposures, breathing the same air and working the same hours. But their doses may differ for many reasons –one may have a higher respiratory rate or minute volume than the other, causing him to inhale more; one may use protective equipment more diligently or with a better fit than the other, causing him to inhale less; one may have more skin contact than the other, causing him to absorb more; one may metabolize the carcinogen more than the other, modifying his dose either up or down, depending upon the individual carcinogen.

An occupational exposure, and its resulting target organ dose, can be approximated in many ways, depending upon the investigator's a priori belief regarding the biological mechanism of action. For example, a simple approximation is to count the duration of exposure; this approach is frequently used in occupational studies when quantitative exposure information is unavailable. The cumulative exposure, the product of the duration and intensity, may be defined as the exposure, implying that total exposure is the biologically important phenomenon. A third approach is the cumulative exposure above a certain level, reflecting a belief that what matters biologically is supra-threshold exposures that overwhelm repair mechanisms. Finally, one may build a time dimension into the exposure measure, considering only exposures that occurred during a certain time interval or weighting different time intervals differently.

The ideal approach to exposure assessment in occupational epidemiology is prospective. The epidemiologist, together with an industrial hygienist, identifies the exposure of interest, selects the optimal means of measuring it, designs a measurement protocol, and collects measurements prospectively. However, this ideal scenario is almost never available in occupational cancer studies, since the outcome of interest follows

the exposure by many years. Therefore, exposure assessment in occupational cancer epidemiology is generally retrospective, in both case-control studies and in retrospective cohort studies.

For this reason, efforts at quantifying exposure have traditionally focused on "exposure reconstruction". Interviews with subjects or proxies may be used, but these are expensive, time-consuming, logistically difficult, and limited by low validity when administered either to study subjects^{25,26} or, as is often necessary, to spouses.^{27,28} Expert assessment based on occupational histories is an alternative, but it is expensive, time-consuming, and limited by the scarcity of qualified experts.^{29,30}

To address these problems, the concept of the job-exposure matrix (JEM) emerged in the early 1980s.^{31,32} A job-exposure matrix is a cross-classification of job titles and exposures, which allows exposure to be imputed on the basis of the job title³³ (or, in more complex JEMs, on the basis of job title, industry, and/or calendar times of employment). A large number of JEMs have been described, some designed for population-based studies (e.g.,^{31, 34-37}), others designed for use in specific industries such as electric utilities,³⁸ paint manufacturing,³⁹ or hard metals,⁴⁰ and still others designed to study specific chemicals.⁴¹

The advantages and disadvantages of JEMs have been extensively discussed and evaluated in recent years.^{30,32,42-48} While JEMs are relatively inexpensive, especially for use on large data sets, their use may entail considerable misclassification, leading to biased risk estimates. Validity is thought to improve if a JEM is based on empirical data, if it uses probabilities and/or scales of exposure rather than dichotomous designations, if it is confined to specific exposures, plants, industries or worker populations rather than broadly inclusive, if exposures are imputed based on specific time periods, and if appropriate statistical analytical techniques are used. Interestingly, there is evidence that the same job title may imply different exposures in male or female workers,⁴⁹ suggesting that gender correction might improve the performance of JEMs.

An alternative to historical reconstruction of exposure is the use of biomarkers.⁵⁰⁻⁵¹ In the context of occupational cancer, biomarkers are indicators, from biological specimens, of events on the continuum from exposure to carcinogenic transformation. Biomarkers are commonly divided into three types: markers of exposure, markers of effect, and markers of susceptibility.⁵² Markers of exposure are well established. For many years carcinogens or their metabolites have been directly measured in biological media such as

blood and urine. For example, benzene exposure can be monitored through expired air and blood benzene levels and through urinary phenol levels, and exposure to the aromatic amine 4,4'-methylenebis(2-chloroaniline) (MBOCA) can be monitored through urinary MBOCA levels.

A newer approach, developed over the last two decades, has been called "molecular dosimetry". It involves measuring the "biologically effective dose" at the ultimate target, DNA.⁵³⁻⁵⁵ Here the biomarker is DNA adducts, which are measured by sensitive methods such as ³²P-postlabeling and immunoassay. As a proxy, RNA adducts and protein adducts may also be studied.⁵⁶ This approach has been used to assess exposure among smokers, and among occupational groups such as ethylene oxide workers, welders, and hazardous waste workers. It has important advantages, such as integrating multiple routes of exposure, partially controlling for differences in metabolic enzymes such as glutathione-S-transferase, and providing an innovative approach studying mixed exposures.⁵⁷ However, molecular dosimetry also has limitations, including the absence of DNA in the most readily available tissue, red blood cells, the instability and unknown clearance rates of DNA adducts, and the lack of good dose-response data. Overall, it remains a promising approach to exposure assessment.

Markers of effect are increasingly available. These signal that a carcinogen has reached a target tissue and caused changes in genetic material, changes that may presage the development of cancer. Cytogenetic abnormalities such as sister chromatid exchanges and micronuclei have been measured since the 1970's, and have been found to be elevated in many working populations, including those exposed to benzene, epichlorhydrin, styrene, vinyl chloride, asbestos, and ethylene oxide. Specific DNA mutations can be assessed using polymerase chain reaction (PCR) amplification and oligonucleotide hybridization, or immunocytochemical staining.⁵⁸ Similarly, the protein products of mutated genes can be detected using such techniques as enzyme-linked immunosorbent assay (ELISA). These approaches have been used in various occupational settings, such as among vinyl chloride workers,^{59,60} foundry workers⁶¹ and workers exposed to PCBs.⁶² While some carcinogenic exposures are associated with increased prevalence of abnormal genes or gene products, precise dose-response relationships have not been established, and the predictive power of these findings remains generally unknown.

Finally, markers of risk are also emerging from molecular biology advances.⁶³ These fall into at least three general categories: markers of unusually high or

low ability to metabolize carcinogens, markers of low ability to repair damaged DNA, and markers of other cancer-prone states. Examples of risky metabolic profiles include high levels of aryl hydrocarbon hydroxylase (AHH), the extensive debrisoquine hydroxylator phenotype, and the rapid acetylator phenotype, which are thought to signal increased risks of lung and skin cancer, lung and liver cancer, and bladder cancer respectively.⁵⁸ An example of repair deficiencies is O⁶-methyltransferase deficiency, which increases the risk of liver and intestinal cancers. Finally, the p53 mutations discussed above exemplify other cancer-prone states. Even when such markers of risk can be reliably identified, they seem more promising in etiologic research than in occupational health practice. Stratifying workers on risk raises profound ethical questions. What should workers be told if they have a high-risk profile? Should they be prohibited from some exposures, or does that entail job discrimination? The social impact of advances in molecular epidemiology are complex and troubling.

Outcome assessment is the counterpart of exposure assessment, and is generally a more manageable challenge in occupational cancer epidemiology. Cancer registries are maintained in many jurisdictions, and in some, notably the Nordic countries, they can be linked with population data bases that include occupation. The accuracy of cancer diagnoses on death certificates and in clinical records is beyond the scope of this paper, but is well reviewed elsewhere.^{64,65}

Confounding is a critical concept throughout epidemiology. In occupational cancer epidemiology, several confounders bear special mention. Age is important, since cancer varies greatly with age during and after the working years. Occupational cancer studies are no different than other cancer studies in the need to control for confounding by age. However, occupational mortality studies often involve relatively small cohorts, in which observed stratum-specific death counts would be relatively small and death rates relatively unstable. As a result occupational epidemiologists have long preferred indirect standardization to direct standardization. The corresponding summary measure is the Standardized Mortality Ratio, or SMR.²³ Gender and race may be important; studies of occupational cancer routinely control for these factors.

Another important confounder in occupational epidemiology is social class. Workers who experience carcinogenic exposures belong to the working class, or are sometimes poor. There is a complex relationship between social class and cancer,⁶⁶ one that, at least in the United States, is further entangled with racial disparities in social class.⁶⁷⁻⁶⁹ Social class is itself a surro-

gate for a range of other behaviors and exposures, including the most ubiquitous environmental carcinogen, smoking. In fact, smoking prevalence has long been known to vary by occupational category and social class.⁷⁰ Occupational cancer epidemiology studies often do not control for social class or smoking, because information is not available on these factors. However, there is some evidence that major confounding by either social class or smoking, in studies of occupational cancer, is unlikely.⁷¹

The healthy worker effect is an interesting phenomenon that, although not unique to occupational epidemiology, is better appreciated in this field than in others. Simply stated, it refers to the fact that working people are healthier than the general population, since the general population includes persons who are unable to work. Therefore, in simple comparisons with the general population, an occupational group will appear to be healthier, masking some or all of any work-related adverse health outcomes. It is not unusual for mortality in a working population to amount to 80 or 90 per cent that of the general population.

The healthy worker effect is dynamic, manifesting itself in several ways over the course of a worker's life.^{72,73} First, there is a "healthy hire" effect; a person must be healthy enough to be hired in the first place. Second, there is the "healthy survivor" effect; a person must maintain a certain level of health to remain in the workforce, and workers who are least healthy are most likely to leave work.⁷⁴ In fact, the healthy survivor effect may represent more than a selective departure of less health workers. If working is in general healthier than not working, then remaining at work may enhance the baseline health of the actively employed. Third, there are time-related factors, since time since first employment is associated with both cumulative exposure and mortality.⁷⁵ Other more subtle factors may operate. For example, actively employed workers may have better access to medical services than the general population, and incomplete followup of an occupational cohort (in cohort or cross-sectional studies) may occur, both resulting in an underestimate of the effects of work.⁷⁶

The healthy worker effect was originally thought to center more on cardiovascular and musculoskeletal diseases than on cancer. However, it has been empirically demonstrated to affect cancer results in several occupational studies.⁷⁷ Several methods have been proposed to control the healthy worker effect, including careful selection of the comparison group, restriction of analysis to long-term survivors, control for time-related factors such as duration of exposure, exposure lagging, and control for employment status.⁷⁶⁻⁷⁸

Interaction

Interaction is another important concept in occupational cancer epidemiology. This phenomenon occurs when the joint effect of two or more carcinogens is different than what would have been predicted based on the individual effects. Synergy, in which joint effects exceed the combined individual effects, and antagonism, in which joint effects are less than combined individual effects, are two examples of interaction. The best known example in occupational epidemiology is the combined effect of asbestos exposure and cigarette smoking; the two exposures combine in a manner that is more than additive⁷⁹ and possibly multiplicative.⁸⁰ In some cases, interaction may be nothing more than the combined effects of two carcinogens acting through distinct mechanisms, such as an initiator and a promoter. Individually these substances may be predicted to have a certain magnitude of effect, but in sequence they may be far more potent. The statistical and epidemiologic expression of interaction is complex and varies based on whether additive or multiplicative models are selected and other considerations.⁸¹

The IARC classification of carcinogens

Based on epidemiologic and other data, regulatory and research agencies have developed standardized ways to classify chemical carcinogenicity. The most widely recognized classification is that of the International Agency for Research on Cancer (IARC). IARC designates three categories.^{82,83} Group 1 includes chemicals and processes established as human carcinogens, based on "sufficient evidence," usually epidemiologic data. Group 2 includes chemicals and processes that are "probably" (Group 2A) or "possibly" (Group 2B) carcinogenic to humans. Group 2A reflects limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals, while Group 2B reflects limited evidence in humans without sufficient evidence in animals, or sufficient evidence in animals without any human data. IARC policy has been to recommend treating Group 2 chemicals as if they presented a carcinogenic risk to humans. Group 3 includes agents that are not classified, and Group 4 includes agents that are probably not carcinogenic to humans. Using this classification, IARC has evaluated over 750 chemicals, industrial processes, and personal habits. More than 50 have been placed in Group 1, and almost 250 have been placed in Group 2. Other national regulatory bodies have adopted similar schemes.

The Group 1 carcinogens are shown on Table I, and the Group 2A carcinogens are shown on Table II.

Occupational cancer in developing nations

Developing countries face special challenges in confronting occupational cancer, as summarized in an excellent monograph from the International Agency for Research on Cancer⁸⁴ and elsewhere.⁸⁵

The profile of carcinogenic exposures is different than in industrialized countries. Carcinogens that have been greatly restricted in wealthy countries may still be used, as has been documented for asbestos,⁸⁶⁻⁸⁸ pesticides,⁸⁹ and other workplace exposures.^{90,91} The intensity of exposures may be higher due to inadequate controls. The duration of exposure may also be longer, on a weekly basis because of longer work schedules, and over a lifetime because of the prevalence of child labor. Workplaces may be adjacent to residential areas, even within the same structures, increasing the opportunities for exposure and extending exposures from the workforce to family members and others. Control is difficult because much of the workforce in developing nations is in small firms. These firms have few technical and financial resources to reduce exposures, and are beyond the reach of labor inspectors.

Occupational epidemiology faces considerable challenges in developing nations.^{92,93} Working populations are difficult to enumerate, given the large informal sector and the absence of universal registration or enumeration of workforces. Exposure information is often inaccessible, and health information may be equally elusive, especially in settings where health services are not widely available. In addition to the usual confounders, such factors as dietary deficiencies and infectious diseases may challenge the epidemiologist. Resources for research—trained epidemiologists and data managers, software, and even computers, and research funds—are scarce.

Despite these challenges, occupational cancer epidemiology is nowhere more important than in developing nations. With exposures high and prolonged, and with the epidemiologic transition giving progressively more importance to workplace and environmental exposures,⁹⁴ research on workplace carcinogens remains a high priority.

From epidemiology to practice: The control of occupational cancer

Public health practice: Primary prevention

Primary prevention of occupational cancer involves removing or greatly reducing carcinogenic exposures. In some cases a carcinogen may be replaced with a noncarcinogen, as in the substitution of toluene for benzene. In other cases the carcinogen may be enclosed,

Table I
ESTABLISHED HUMAN OCCUPATIONAL CARCINOGENS (IARC GROUP I)*
BASED ON IARC MONOGRAPHS 1-69 (THROUGH 1997)

<i>Industrial processes</i>		
Aluminum production	Inorganic acid mists, strong, containing sulfuric acid	
Auramine manufacturing	Iron and steel founding	
Boot and shoe manufacturing and repair	Isopropyl alcohol manufacturing (strong acid process)	
Coal gasification	Magenta manufacturing	
Coke production	Painting	
Furniture and cabinet making	Rubber industry	
Hematite mining (with radon exposure)		
<i>Chemicals and mixtures *</i>		
<i>Exposures [CAS number]</i>	<i>Examples of occurrence</i>	<i>Target organ / comment</i>
Aflatoxins [1402-68-2]	Grains, peanuts	Liver. Agricultural workers may be at risk
4-Aminobiphenyl [92-67-1]	Rubber industry	Bladder
Arsenic and arsenic compounds [7740-38-2]	Insecticides	Lung, skin, hemangiosarcoma
Asbestos [1332-21-4]	Insulation, friction products	Lung, mesothelioma, respiratory tract, gastrointestinal system
Benzene [71-43-2]	Chemical industry	Leukemia, Hodgkin's disease
Benzidine [92-87-5]	Rubber and dye industries	Bladder
Beryllium and beryllium compounds [7440-41-7]	Aerospace, nuclear, electric and electronics industries	Lung
Bis(chloromethyl)ether and chloromethyl methyl ether [542-88-1 and 107-30-2]	Chemical industry	Lung
Cadmium and cadmium compounds [7440-43-9]	Metalworking industry, batteries, soldering, coatings	Prostate
Chromium (VI) compounds	Metal plating, pigments	Lung
Coal tar pitches 65996-93-2]	Coal distillation	Skin, scrotum, lung, bladder
Coal tars [8007-45-2]	Coal distillation	Skin, lung
Dioxin, 2,3,7,8-tetrachlorodibenzo-	Herbicide production and application	All sites combined, lung
Erionite [66733-21-9]	Environmental (Turkey)	See asbestos
Melphalan (nitrogen mustard gas) [148-82-3]	Antineoplastic agent.	Lung. Risk for exposed health care workers
Mineral oils	Machining, jute processing	Skin
Mustard gas [505-60-2]	Production, war gas	Lung
2-Naphthylamine [91-59-8]	Rubber and dye industries	Bladder
Nickel compounds	Nickel refining and smelting	Nose, lung
Radon and its decay products [10043-92-2]	Indoor environments, mining	Lung
Schistosoma hematobium infection	Outdoor work in endemic areas	Bladder. An occupational carcinogen of farmers and other outdoor workers
Shale oils [63808-34-9]	Energy production	Skin
Silica, crystalline [14808-60-7]	Hard rock mining, sandblasting, glass & porcelain manufacturing	Lung
Soots	Chimneys, furnaces	Skin, lung
Talc containing asbestiform fibers	Talc mining, pottery manufacturing	See asbestos
Vinyl chloride [75-01-4]	Plastic industry	Hemangiosarcoma
Wood dust	Wood and furniture industries	Nose, sinuses

* Other carcinogens, including medications, tobacco, and viruses, have been classified in Group I

Source: Adapted from Stellman JM⁸³

Table II
PROBABLE HUMAN OCCUPATIONAL CARCINOGENS (IARC GROUP 2A)
BASED ON IARC MONOGRAPHS I-69 (THOUGH 1997)

<i>Industrial processes</i>		
Glass manufacturing		Insecticide application (non-arsenicals)
Hairdressing/barbering		Petroleum refining (certain exposures)
<i>Exposures</i>	<i>Chemicals and mixtures *</i>	<i>Examples of occurrence</i>
Acrylamide [79-06-1]		Polyacrylamide manufacturing
Acrylonitrile [107-13-1]		Plastics industry
Benz[a]anthracene [56-55-3]		Coal distillation
Benzidine-based dyes		Dye industry
Benzo[a]pyrene [50-32-8]		Coal and petroleum-derived products
1,30Butadiene [106-99-0]		Polymer and latex production
Captfol [2425-06-1]		Fungicide
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosurea (CCNU) [13010-47-4]		Antineoplastic agent
Cis-platin [15663-27-1]		Antineoplastic agent
Creosotes [8001-58-9]		Wood preservatives
Dibenz[a,h]anthracene [53-70-3]		Coal distillation
Diesel exhaust		Motor vehicles
Diethyl sulfate [64-67-5]		Petrochemical industry
Dimethylcarbamoyl chloride [79-44-7]		Chemical manufacturing
Dimethyl sulfate [77-78-1]		Former war gas, now used in chemical industry
Epichlorhydrin [106-89-8]		Resin manufacturing, solvent
Ethylene dibromide [106-93-4]		Fumigant, gasoline additive
Ethylene oxide [75-21-8] SEE v 60		Sterilizing agent, in health care facilities
4,4'-methylene bis(2-chloroaniline) (MOCA) [1010-14-14]		Resin manufacturing
N-nitrosodiethylamine [55-18-5]		Solvent
N-nitrosodimethylamine [662-75-9]		Solvent
Polychlorinated biphenyls		Electrical equipment
Propylene oxide [75-56-9]		Chemical industry
Styrene oxide [96-09-3]		Chemical industry
Tetrachlorethylene		Dry cleaning
Toluidine, para-chloro-ortho and its strong acid salts [95-69-2]		Diazo dye manufacturing
1,2,3-Trichloropropane [96-18-4]		Pesticide and rubber manufacturing; solvent
Tris(2,3-dibromopropyl)phosphate [126-72-7]		Flame retardant, polystyrene foam manufacturing
Vinyl bromide [593-60-2]		Plastic industry
Vinyl fluoride [72-02-5]		Chemical industry

* Other probable carcinogens, including medications and foodstuffs, have been classified in Group 2A

Source: Adapted from Stellman JM⁸³

as has occurred in polyvinyl chloride manufacturing. In general, such interventions are guided, and their success monitored, by reference to some permissible level of exposure, set by government and/or industry standards.

Permissible levels are often set through a process of risk assessment. Risk assessment has been defined as a four-part process: hazard identification, expo-

sure assessment, dose-response assessment, and risk characterization.⁹⁵ Hazard identification asks whether a chemical is carcinogenic to humans, based on data from epidemiologic studies, animal studies, short-term bioassays, and structure-activity relationships. Exposure assessment asks how many people are exposed, for how long, and through what routes. Dose-response assessment combines data from the first

two steps to estimate quantitatively the magnitude of human cancers at specific dose levels, generally below the epidemiologically observable range. This involves extrapolation across species and down the dose-response curve, and often relies on complex mathematical models. Finally, risk characterization provides the "bottom line": a quantitative estimate of human cancer risk at known exposure levels. This step can lead, in turn, to standard-setting and regulation.

Risk assessment has been widely debated. It represents a methodical approach to quantifying risks, and it is especially useful in comparing risks between or among different exposures. However, many argue that available data are rarely adequate to support quantitative estimates of human risk. Extrapolation from high exposures to low exposures is based on a number of assumptions, most of which are unverifiable. The same is true of extrapolation from animal tests to human experience. Moreover, risk is generally calculated based on a single chemical exposure, while exposures are more often to mixtures of chemicals. However, at present risk assessment is a key component of carcinogen regulation by many government agencies.

Public Health Practice: Secondary Prevention

Secondary prevention involves the early detection of disease through screening. With regard to cancer, screening programs have three goals: (a) identifying markers of exposure (biological monitoring); (b) identifying susceptible or high-risk individuals, presumably before exposure, and (c) identifying early signs of disease (medical surveillance). Some screening tests fall between biological monitoring and medical surveillance, since they identify physiological changes related to exposure but of uncertain pathological significance. Each of these initiatives may rely on the use of biomarkers, as discussed above. The focus of this discussion will be medical surveillance.

Medical surveillance aims to detect early signs of disease. In general, a successful medical surveillance program offers a simple, inexpensive, and accurate test of a population with sufficiently high disease prevalence to confer on the test a high predictive value.⁹⁶ Moreover, there should be an intervention available for those who test positive that will favorably alter the course of disease. In the occupational setting, conventional principles of medical surveillance may be modified, permitting screening to benefit an exposed population even if no effective treatment can be offered to individual cases and permitting screening programs

that might not be cost-effective in the community setting.⁹⁷

Cancer surveillance in occupational settings has been best explored with regard to bladder cancer and lung cancer. Among workers exposed to beta-naphthylamine, benzidine, and/or benzidine congeners such as o-tolidine, two methods have been primarily used: urinalysis for microscopic hematuria and urine cytology. Hematuria is relatively sensitive in detecting both superficial and invasive bladder cancer, but its low specificity results in a high false-positive rate, requiring a large number of invasive studies on healthy individuals. Urine cytology has good sensitivity and specificity for invasive bladder cancer, but it has lower sensitivity for early bladder cancer. Moreover, no firm evidence demonstrates a survival advantage for patients whose disease is detected through such screening.⁹⁸ More advanced techniques such as flow cytometry, quantitative fluorescence image analysis, and urinary mutagen screening^{99,100} remain unvalidated, but appear to have suboptimal sensitivity and/or specificity. The International Conference on Bladder Cancer Screening in High-Risk Groups, sponsored by NIOSH in 1989, concluded that urinalysis and cytology might be appropriate, especially following high exposure to known or suspected bladder carcinogens, but that further data were necessary.⁹⁸ Ongoing studies of high-risk groups such as the Drake Health Registry¹⁰¹ should support further recommendations in the near future.

Lung cancer surveillance consists of interval chest radiography and/or sputum cytology. These approaches were evaluated in a series of trials at the Mayo Clinic, Johns Hopkins University, and the Memorial Sloan-Kettering Cancer Center in the 1970s. The combination of chest x-rays and sputum cytology tests three times a year yielded a significant increase in lung cancer detection and resectability compared to controls (who were merely advised to be tested once a year). However, there was no significant decrease in lung cancer mortality. These results, in combination with other data, have supported the recommendation that no routine surveillance for lung cancer be offered, even to high-risk populations.^{102, 103} Further research is underway, through the National Cancer Institute's Prostate, Lung, Colon and Ovary Cancer Screening Trial. This very large randomized trial of men and women aged 60 to 74 will evaluate the utility of annual chest x-rays in reducing lung cancer mortality. Results should be available during the first decade of the 21st century. In addition, there is considerable interest in augmenting sputum cytology with detection of tumor mark-

ers,^{104,105} which may lead to increased sensitivity and specificity of lung cancer screening.

Other kinds of medical surveillance for occupational cancer are also not recommended. Most approaches carry a high risk of false-positives, a low positive predictive value, high cost, worker unacceptability, and/or morbidity. The major exceptions are tests that are generally recommended for the larger population, and that might be easily provided in the workplace setting; these include Pap smears for cervical cancer, stool guaiac testing and sigmoidoscopy for colorectal cancer, physical examination and mammography for breast cancer, and possibly digital examination and prostate-specific antigen for prostate cancer.

Clinical practice: Applying epidemiology to individual patients

Epidemiologic results, derived from the study of populations and based on probabilistic thinking, are difficult to apply in individual cases.¹⁰⁶ However, patients with cancer who have been exposed to carcinogens often inquire about the possibility that the exposures were causal. The question sometimes arises when a patient seeks compensation or insurance coverage, or may simply reflect a patient's psychological need to explain a catastrophic life event. Applying epidemiologic data in this situation is as much philosophical as scientific.

Certain requirements must be met before it may be said that an exposure has "causally contributed" to a cancer. There must be evidence that the exposure has indeed occurred. The tumor type in question must be associated with the exposure, based on prior studies. Finally, the appropriate temporal relationship must hold; in particular, a sufficiently long latency period must have elapsed between the onset of exposure and the diagnosis of cancer.

When these requirements have been met, additional issues should be considered. Suppose that the baseline incidence of lung cancer in unexposed adult men is 80 cases per 100 000 per year. Suppose further that a particular occupational exposure has been associated with a relative risk of lung cancer of 1.8. Therefore, the incidence among exposed men would be 144 cases per 100 000 per year. If an exposed man develops lung cancer and wonders whether his exposure caused his cancer, what should he be told?

The simplest analysis is qualitative. Any exposure that substantially increases risk may be considered to contribute to the development of cancer in an exposed individual. A "substantial" increase has no firm definition; relative risks as low as 1.3 have been consid-

ered in this category. By this analysis, the patient could be told that his exposure contributed to his cancer.

A second qualitative approach is to ask whether the patient's cancer would have occurred "but for" the exposure. In the numerical example above, over half the cases of lung cancer in the exposed population would occur even without the exposure. It might then be concluded that any individual case is "more likely than not" to have occurred irrespective of exposure. Similarly, a relative risk of 2.2 would lead to the conclusion that any individual case of cancer would not have occurred "but for" exposure. This approach is obviously unsatisfactory. It accounts for no cancer causation when the relative risk is below 2.0, and it accounts for all cancer causation when the relative risk exceeds 2.0. This violates common-sense notions of causation, and it depends excessively on the precision of the relative risk estimate.

Finally, in the quantitative approach, causation is allocated to various causes, including occupational exposures. In the above example, the patient might be told that the occupational exposure was "responsible" for 44% (0.8/1.8) of his lung cancer. On the other hand, if he were a smoker, with a consequent tenfold increase in lung cancer risk, he might be told that smoking accounted for 83% (9/10.8) of his cancer, that the job exposure accounted for 7% (0.8/10.8), and that baseline population risk factors accounted for 9% (1/10.8). This approach has intuitive appeal, since it confronts the multiplicity of exposures and attempts to quantify the relative importance of each. However, the data needed for this approach are rarely available. Interaction of multiple exposures, such as synergy, often occurs but is rarely quantitated. Consequently, even if a population relative risk can be estimated for an occupational exposure, the relative causal contribution of several factors in an individual is usually impossible to quantitate.

The choice among these approaches depends upon local medicolegal requirements, and upon the philosophical preferences of the individual deciding.

Summary and conclusion

This paper has reviewed several of the major issues in occupational cancer epidemiology. Controversy exists about the magnitude of the problem. In developed countries, it is likely that well under 10 per cent of cancers are occupational in origin. In developing countries, given more severe exposure conditions and different competing diseases, it is possible that the workplace plays a greater relative role in cancer causation.

Increased understanding of the mechanisms of carcinogenesis, and increased ability to recognize transformed genes and their products, promise new tools for both the epidemiologist and the clinician, including biomarkers that can detect carcinogenic exposures, early precancerous changes, and high-risk states. Increasing attention is focused on the cancers that are mediated by hormonal changes, since there is growing evidence that synthetic chemicals may have hormonal effects.

Occupational cancer epidemiology faces interesting methodological challenges, including the difficulty of exposure assessment and the complexity of the healthy worker effect. However, a large body of epidemiologic evidence has evolved. In combination with other kinds of evidence, it has permitted the identification of several dozen workplace carcinogens. Epidemiologic techniques can be applied to primary prevention, secondary prevention, and the management of individual patients. The preventive interventions are especially important, since in theory nearly all occupational cancers should be preventable.

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