The use of job exposure matrices for cancer epidemiology research and surveillance

by

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Abstract

The epidemiologic investigation of occupational cancers is intended to identify new pathogenic agents or to analyse the effects of occupational hazards. The workplace today is characterised by lower levels of exposure than in the past, and these exposures tend to induce common cancers for which there are other occupational and non-occupational causal agents.

Confronted with the difficulties of studying low risks, epidemiologic research is currently developing along several pathways. One of these involves the development of methods of retrospective assessment of occupational exposures that might have taken place several decades before the onset of the disease. These methods can be applied to very large samples of subjects and make it possible to assess the multiple concomitant exposures that are common in occupational settings.

The principle of job-exposure matrices is to associate exposure data with occupations, jobs, or workstations, making it possible to attribute...
exposure to subjects “automatically” by linking the exposure data with individual work histories. Despite some limitations, its automatic nature presents decisive advantages in very large surveys.

Multi-hazard matrices have been developed, as well as matrices specific for a given agent. Both may be applicable in population-based or in industry-based studies. They are used for etiological research, to describe exposures in a population, or to help ensure individual follow-up of workers. They will surely make important progress possible in the years to come; they should also become common industrial hygiene tools for prevention purposes.

Keywords

Occupational epidemiology, Cancer, Job Exposure Matrix.

Résumé

L’investigation épidémiologique concernant les cancers professionnels a pour buts de définir les effets pathogènes éventuels de certaines nuisances professionnelles, ou d’identifier de nouveaux risques. La situation se caractérise aujourd’hui par des niveaux d’exposition plus faibles que dans le passé, susceptibles d’induire des cancers fréquents pour lesquels existent d’autres agents caustiques.

Devant la difficulté d’étude des risques faibles, la recherche épidémiologique se développe actuellement selon plusieurs voies, dont l’une concerne les méthodes d’évaluation rétrospective des expositions professionnelles survenues parfois plusieurs décennies avant l’occurrence de la maladie, pouvant être appliquées sur de très grands échantillons de sujets et permettant l’évaluation des expositions concomitantes multiples qui sont la règle en milieu professionnel.

Les «matrices emplois-expositions», dont le principe est d’associer à des professions ou des postes de travail des données d’exposition, permettent par croisement avec des données individuelles de carrière professionnelle, d’attribuer «automatiquement» des expositions à des sujets. Malgré certaines limites, elles présentent de ce fait des avantages décisifs dans les enquêtes à très large échelle.

Occupational Cancers: the Epidemiologic Context

In the industrialised countries, occupational factors play an important part in the etiology of cancers: according to the most recent estimates, it is in the order of 5% of all cancer deaths (1). These estimates, of course, are based on our knowledge of the carcinogenic factors now known. It is clear, however, that we have not yet identified, let alone assessed, all the carcinogenic factors in the workplace. Almost every type of cancer may be involved. Cancers of the respiratory tract are the most frequent for several reasons: many environmental toxic agents enter the body through inhalation; some of them interact with tobacco; and lung cancers are relatively common (2). Numerous factors in occupational settings are carcinogenic to humans. Indeed, by far the largest number of the human carcinogens so far identified come from the workplace: they represent approximately half the chemical and physical agents, compounds and industrial processes listed among the 75 factors currently classified in Group 1 (known carcinogens) by the International Agency for Research on Cancer (IARC), and more than two thirds of those listed in Group 2 (probable carcinogens) (3). Men are most affected by the occupational factors that cause cancers. Women are also affected, however, especially in some occupational sectors where they work in large numbers (4).

Epidemiologic research into occupational cancers

Vigorous epidemiologic research on an international scale is currently underway in the field of occupational cancers. From a scientific point of view, these cancers are especially interesting for our knowledge of carcinogenesis, for we know that environmental factors play a major role in the onset of most cancers (5). Epidemiologic research has a preeminent and vital place in the identification of environmental carcinogens, because of the limitations of animal experiments. IARC, for example, requires as an essential criterion for classifying a factor as a known human carcinogen (Group 1) the existence of “sufficient epidemiologic evidence”.

Briefly, the principal objectives of epidemiologic research into the risks associated with environmental exposures are: (i) identification of a risk associated with exposure to an environmental factor; (ii) specification of the relation between exposure and effect; (iii) identification of the exposed populations and assessment of the specific risks; (iv) estimation of the impact of exposures in the population; (v) study of interactions (joint exposures, individual sensitivity factors).
Current Research

Whether the aim is to keep control of situations that we theoretically can contain, to better define the possible pathogenic effects of some occupational hazards in order to set up effective prevention, or to identify new risks attached to the use of new products, epidemiologic investigation of occupational cancers remains critically important today.

Etiological research in this domain has stagnated somewhat, as shown by Figure 1, a summary of major publications about occupational carcinogens according to the decade in which they first were published. We see that after a particularly fruitful period in the 1950s and 60s, new carcinogens are now uncovered less frequently.

![Figure 1: Number of major publications about new occupational carcinogens by decade.](Source: P. Boffetta, personal communication)

It is probably not because unknown carcinogens are encountered in the workplace at a lower rate that there has been a relative decline in research productivity. The reasons are more likely related to the increasing difficulties in demonstrating these carcinogens. In the past, occupational carcinogens were characterised by powerful carcinogenicity (relative risks on the order of tens or even hundreds), very elevated exposures, an almost specific association with some occupations or activities, a small number of multiple concomitant exposures, and induction of tumours which are rare in the industrialised nations (cancers of the paranasal sinus and nasal cavity, angiosarcoma of the liver, etc.). Workers today are better protected...
and exposed to lower levels of hazards, which thus induce lower effects. The greater occupational mobility of today also contributes to reducing cumulative exposure. Although the duration of employment in exposed jobs might thus be shorter, it nonetheless leads to frequent and multiple exposures that can induce frequent cancers for which other occupational and non-occupational causal agents exist. Moreover, the strongest carcinogens have most likely been detected already.

These reasons explain the current interest in the study of low expected effects, either because of lower exposure or because the intrinsic carcinogenic power of the agents considered is lower than in the past. Confronted with the inherent difficulties of demonstrating low risks, epidemiologic research is currently developing along several complementary routes.

Very large epidemiologic studies, which increase the chances of demonstrating low-level risks. Case-control studies today sometimes include several thousand subjects, and cohorts studies, several hundred thousand workers in an industrial sector. Examples of very large studies are a study of cancer risks associated with occupational exposure to magnetic fields among electric utility workers in Ontario and Quebec (Canada), and France where a cohort of about 220,000 men was established in three companies; during the observation period (1970-1989), 4,151 new cases of cancer occurred (6). The effects of low doses of ionizing radiation on cancer among nuclear industry workers were already analysed in a cohort of about 100,000 workers in three countries (7), and an extension of this project, coordinated by the International Agency for Cancer Research, including a total cohort of about 700,000 workers in more than ten countries, is currently in progress.

Consideration of early and more common events: cancers are relatively rare diseases on the scale of a population, and they have long latency periods. This presents methodological problems, because it is difficult to bring together large enough samples and to set up long-term follow-up. Thus, it might be useful to study the effects of occupational exposures on events which take place earlier and which are less rare than clinical cancer, such as chromosomal alterations.

The selection of more “sensitive” populations: genetic factors affect sensitivity to cancer. The demonstration of differential sensitivity to some cancers would enable populations to be better stratified, and this could improve the precision and power of epidemiologic studies examining the carcinogenic role of an occupational factor.
Biomarkers: exposure biomarkers signal exposure to a given environmental agent in the days, weeks or months before the sampling. Early effect biomarkers concern more specifically biological or biochemical events that represent either a subclinical stage or a manifestation of the disease itself. Markers of individual sensitivity make it possible to identify interindividual differences in susceptibility in developing a given disease; they most often involve genetic polymorphisms or differences in enzyme activities.

The development of methods for the retrospective assessment of occupational exposures: in the field of cancer epidemiology, the long latency periods (which can reach 30 or 40 years) mean that the exposures that must be considered are those that took place in the past, sometimes several decades before the onset of the disease. It is thus necessary to develop methods for reconstructing past exposures that can be applied to very large samples and that enable the assessment of the multiple concomitant exposures that are common in occupational settings (8). Several approaches are used. The most common are those of case-by-case expert assessment by industrial hygienists and of “job-exposure matrices” for general populations (9) or populations specific to a company or industrial sector (10).

Methods for retrospective assessment of occupational exposures

Among the various approaches intended to increase the power and sensitivity of epidemiologic studies for occupational cancers, improving the methods for assessing occupational exposures is particularly important.

The possibility of detecting an association between exposure to a given factor and a disease is closely related to the quality of the exposure assessment, and a poor exposure assessment hurts the quality of the study (11). Imprecision in the quantification induces a dilution of the effect and reduces the study power, whereas misclassification can bias the estimate of the association between exposure and disease (12). In the case of non-differential misclassification (the most frequent type of misclassification), this estimate is biased towards unity and thereby reduces the possibility of observing associations between exposure and cancer. To illustrate this phenomenon, Table 1 shows the extent of this reduction in observed odds ratios according to different hypotheses of the real relative risk associated with an exposure, and according to the proportion of subjects actually exposed in the study population and subjects incorrectly classified. One
see that the diminution in the odds ratios observed can be very substantial, especially when only a small proportion of subjects is exposed, as it is the case for most occupational exposures studied in the general population. That is, the consequences are particularly harmful when the real association is weak, as it is for most current potential carcinogens.

### TABLE 1

*Reduction in odds-ratios according to the value of the true odds-ratio and to the proportion of exposed in the population when 60% of the subjects are accurately classified*

<table>
<thead>
<tr>
<th>% of misclassification</th>
<th>True odds-ratio</th>
<th>1.0</th>
<th>2.0</th>
<th>4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE = 0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of misclassification</td>
<td>0.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE = 0.8</td>
<td></td>
<td>1.0</td>
<td>1.30</td>
<td>1.68</td>
</tr>
<tr>
<td>PE = 0.1</td>
<td>1.0</td>
<td>1.0</td>
<td>1.14</td>
<td>1.24</td>
</tr>
<tr>
<td>% of misclassification</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE = 0.8</td>
<td></td>
<td>1.0</td>
<td>1.56</td>
<td>2.41</td>
</tr>
<tr>
<td>PE = 0.1</td>
<td>1.0</td>
<td>1.0</td>
<td>1.26</td>
<td>1.53</td>
</tr>
<tr>
<td>% of misclassification</td>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE = 0.8</td>
<td></td>
<td>1.0</td>
<td>1.74</td>
<td>2.99</td>
</tr>
<tr>
<td>PE = 0.1</td>
<td>1.0</td>
<td>1.0</td>
<td>1.38</td>
<td>1.78</td>
</tr>
</tbody>
</table>

PE = proportion of exposed subjects in the population.

Recall that for cancer the relevant exposures have already occurred, sometimes several decades before the onset of the disease. It is thus necessary to reconstruct past exposures to many different agents, in a context where the subjects do not have a very precise (or indeed any) knowledge of them and the exposures were not measured, let alone recorded.

Various methods of retrospective exposure assessment for epidemiologic purposes have been proposed to overcome these difficulties. It is important to underline that some of these methods were developed because of the lack of recording of accurate exposure data in the past: today, epidemiologist must try to reconstruct past exposures. Hopefully, better measurement methods and continuous registration of individual as well as environmental exposure data will facilitate future epidemiologic research.

**Biological exposure indicators**

As we have pointed out, almost all current biomarkers of exposure are valid only for exposure to environmental agents in the days, weeks or months that precede the sampling.
Sensors for the workplace environment or for the individual

Old measurements being nearly systematically missing, only recent and isolated exposures can be considered by these sensors.

“Ad hoc” Questionnaires

This method relies on questionnaires specifically designed to assess exposure to a given agent; they usually include mainly closed items for the characterization of the exposure of interest. It is especially used when considering isolated hazards; it is very cumbersome to use and allows only very few factors to be taken into account.

General Questionnaire with Experts

This method combines the administration by a specialized interviewer of a general open questionnaire (to reconstruct for the subject’s lifetime and for each occupational episode, operating procedures, materials used, etc., described in full details without an a priori codification) and a subsequent analysis of the questionnaire by industrial hygiene experts who can then code many exposures over a long period; it is currently considered as the reference method. It is nonetheless cumbersome, and industrial hygiene experts are rare: this limiting factor can be quite important for large-scale epidemiologic studies that include several hundreds or even several thousands subjects, each of whom might have had several different jobs or trades throughout their career.

Job-exposure matrices

Job-exposure matrices are fairly recent tools. Their general principle is based on the construction of a database that associates occupations, jobs or workstations with data about exposures to various hazards (13). Linking the individual work history data with a job-exposure matrix enables exposures to be attributed “automatically” to the subjects. Depending on the context, one might then have individual exposure data (which can be retrospective) that make it possible to perform analytic (case-control or cohort surveys) or descriptive (exposure mapping, when the individual occupational data come from a representative population sample) epidemiologic studies. Despite some methodological limitations (14), the job-exposure matrix has decisive advantages, because it can be used in
circumstances in which the traditional methods for assessing occupational exposures may be impossible to implement (in particular, very large-scale cross-sectional or retrospective surveys). One can also use the two methods together: the matrix allows an initial screening for various hazards, and case-by-case expert assessment is used to complete the exposure assessment. This approach yields valid results, as shown by some formal comparisons of the two methods on the same data set (15).

Current use of job-exposure matrices in occupational cancer epidemiology

Some job-exposure matrices are specific for a given hazard of particular interest, while others are broader and include many hazards (9). Some job-exposure matrices are applicable for the general population (population-based case-control studies, where cases are selected from cancer registers or hospitals and controls from various sources such as electoral rolls or phone books; descriptive studies of the distribution of exposure from representative samples of the population of a region or a country), or in specific industrial sectors (10).

Job-exposure matrices for the general population

“Multi-hazard matrices” may cover a broad spectrum of exposures. They have been specifically developed in a national context, as in Finland (16), and are based on occupational classifications and activity sectors in the country concerned. This allows to perform more specific exposure assessment and to link the matrix with data already collected in various contexts. These matrices are used in applications involving epidemiologic research (case-control studies where they allow individual exposure assessment by linking them with the subjects’ job histories) or surveillance, in particular for describing the distribution of exposure in a population. Thus, the CAREX project made it possible to describe exposure to a number of carcinogens in different European countries, by linking national data with the Finnish and American matrices (17). In France, the SUMEX matrix was developed during the SUMER study, which was carried out by the Ministry of Labor to examine working conditions and occupational exposures in a large multi-sector sample of workers in France. In its current phase, it concerns only the exposures to chemical factors that were contemporaneous with the SUMER study (18). It is now distributed as a CD-ROM and used
by occupational physicians to facilitate the medical surveillance and control of the workplace.

Despite some problems, it is also possible in some cases to use matrices from one country for an epidemiologic survey in another country, as shown by several French works on paranasal sinus and nasal cavity cancers (19) or respiratory function (20). However, such use is only possible if these matrices are based on international classifications (ILO ISCO classification of occupations (21); UN ISIC classification of economic activities (22)). This is, however, the case for most job-exposure matrices developed by researchers, because they want to compare their results with those from colleagues in other countries.

Various job-exposure matrices for specific hazards have also been constructed; they are easier to develop and to validate than a general matrix. Thus, in France we have a specific matrix for asbestos exposure (23), which has already been used in various different epidemiologic studies. One example of its use was in the analysis of a population-based case-control study of pleural mesothelioma, where its epidemiologic performance was comparable to that of the traditional methods of case-by-case assessment by expert hygienists (24). In another study, a description of the evolution of asbestos exposure in the French population since the beginning of the last century was obtained by linking the matrix with the work history of a large sample of people included in case-control studies in France (25). It was also used to identify retired subjects who had been exposed to asbestos during their working life, in order to offer them post-retirement medical follow-up (26).

Company or activity sector specific matrices

Job-exposure matrices specific to a company or an economic sector have the advantage of being able to be much more detailed and specific than those for the general population (10). Moreover, they can often be combined with other data available within the company, such as personnel files including detailed work history of the workers.

Today, the development of a job-exposure matrix for a specific hazard has become the favored method for assessing occupational exposures in industrial cohort studies of cancer. The epidemiologic literature provides numerous illustrations, including, for example, the hard metal industry (27) and the nuclear sector (28).
“Multi-hazard” matrices in companies are less common, despite their utility for systematic epidemiologic surveillance. Some work has shown the feasibility and validity of such an approach, notably at Électricité de France-Gaz de France (EDF-GDF), where the MATEX matrix (31, 32), associated with other databases (epidemiologic database, employee cohort) was used in many studies, both descriptive and etiological (33). EDF-GDF is the French national utility company: it produces electricity, and transports and distributes both electricity and gas. It employs approximately 145,000 workers. As part of the development of a programme of epidemiologic surveillance of EDF-GDF employees by the occupational medicine department, a job-exposure matrix was set up from 1988 to deal with about 30 potentially carcinogenic hazards, most of them from IARC groups 1, 2A and 2B, who constitute the exposure axis of the matrix. The job axis of the matrix lists 403 jobs, consolidated from personnel department codes that characterise the tasks in the company, combined with information about the sector and branch of activity. Changes in job tasks over time, as reflected in the operating procedures, made it possible to identify 45 different periods, depending on the hazards considered. MATEX thus includes approximately 2,000 “job-periods”. For each job-period, its cells contain information on the probability of exposure to each substance and an assessment of the level of exposure. This level was quantified whenever possible (asbestos, toluylene-diisocyanate, benzene) or, most often, semi-quantified and expressed as a proportion of working time; in some cases, only the dichotomous variables of presence or absence of exposure could be assessed. This matrix has been used in several epidemiologic surveys about specific cancers (lung, leukemia (32)) or particular hazards, such as asbestos (31) or electromagnetic fields (34). MATEX has also been used as an industrial hygiene tool to describe the distribution of occupational exposures in the company and its change over time, and to help in reconstructing individual exposures to facilitate medical follow-up of employees once they retire.

Conclusion

Job-exposure matrices are an exposure assessment tool whose development and use require expertise in epidemiology and industrial hygiene. They have progressively become an essential tool in the epidemiologic study of occupational cancers, despite some disadvantages due to their inevitable imprecision. They will contribute to a large extent to epidemiologic research about occupational risks in the years to come; they will also be used as common industrial hygiene tools for prevention purposes.
References