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Commentary

Confounders and Confusion: Dealing With Cancer Cases of Occupational Origin

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Background *The recognition of occupational cancers is often hampered by confusion between the individual determinants of the disease and effects at the group level.*
Methods *Here we propose an approach, based on the evaluation of the attributable risk at the group level, that provides quantitative estimates of the roles of multiple causes in individuals affected of cancer within a population exposed to occupational risk.*
Results *The estimate of individual probability can be easily obtained computing the attributable risk. This can be often achieved by using the existing information available in the literature.*
Conclusions *Dismissing the occupation as a cause of a cancer in an exposed subject on the sole basis of potential confounding is erroneous and should be withdrawn from medical practice.* Am. J. Ind. Med. 53:1002–1005, 2010. © *2010 Wiley-Liss, Inc.*

KEY WORDS: causes; attributable risk; occupational cancer; confounders

INTRODUCTION

When a patient is diagnosed with cancer of the pleura or cancer of the nose, one immediately suspects an occupational origin for the disease. Why? Because these cancers are rare and their occupational etiologic fraction (proportion of cases found to be attributable to occupational exposure) is high. However, for cancers like those of lung, larynx, or bladder—which may also have an occupational origin—the possibility of an occupational cause is often not fully explored. Why? Because (a) the occupational etiologic fraction of these diseases is low in the general population; (b) these cancers are common; and (c) other factors such as smoking are considered sufficient per se to explain disease occurrence in any individual.

This article provides a framework for deciding the extent to which cancers are occupational in exposed individuals, also taking into account non-occupational etiologic factors, to provide a simple means of recognizing victims of occupational cancers.

RELATIVE RISK: AN EXAMPLE

Of the male workers at a conventional oil-fired power station in service on January 1, 1960, or employed over the next decade (to December 31, 1969), a total of five had died of lung cancer by December 31, 1985. All the workers were exposed in the workplace to asbestos, polycyclic aromatic

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Note: The example was taken from the article: Cammarano G, Crosignani P, Berrino F, Berra G. Cancer mortality among workers in a thermoelectric power plant. Scand J Work Environ Health 1984; 10:259–261 and from the article: Cammarano G, Crosignani P, Berrino F, Berra G. Additional follow-up of cancer mortality among workers in a thermoelectric power plant. Scand J Work Environ Health 1986; 12:631–632. The number of expected cases was changed from 2.83 to 2.50 for the sake of simplicity.

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hydrocarbons, and heavy metals (chrome, nickel, and beryllium), all of which are established causes of lung cancer [IARC, 1987]. In an age-matched sample of men from a comparable population, not occupationally exposed to carcinogens, 2.5 cases of lung cancer would have occurred over the same period. These observations can be summarized by stating that the power station workers had a relative risk of dying from lung cancer of 2, where relative risk is defined as the number of lung cancer deaths observed (over a given period) in the exposed population divided by the number of lung cancer deaths expected, that is, observed in the age-matched reference population considered not exposed to carcinogens at work. All five workers who died for lung cancer were smokers.

The main question that arises is: was it the smoking or the occupational exposure that caused these deaths?

THE CONFOUNDER

Cigarette smoking is the main cause of lung cancer. Careful studies have established that the relative risk of smokers developing lung cancer compared to non-smokers is about 10-fold, and that 90% of lung cancers are directly attributable to smoking [IARC, 2004]. In fact, almost all cases of lung cancer in a population occur in smokers.

Let us suppose that 50% of the male reference population are smokers. It is evident that in order to explain the excess cancers among the power station workforce as due only to smoking, *all the workers* would have to be smokers, as illustrated in Figure 1. To put it another way: assuming that 50% of our power station workers were also smokers, smoking cannot be invoked as the cause of the excess of lung cancers among them. The fact, therefore, that all the lung cancer deaths in the workforce occurred in smokers does not mean that the excess was due to smoking: essentially all the lung cancer deaths in the reference population also occurred in smokers, but there were only 2.5 of these, compared to 5 in the power station workforce.

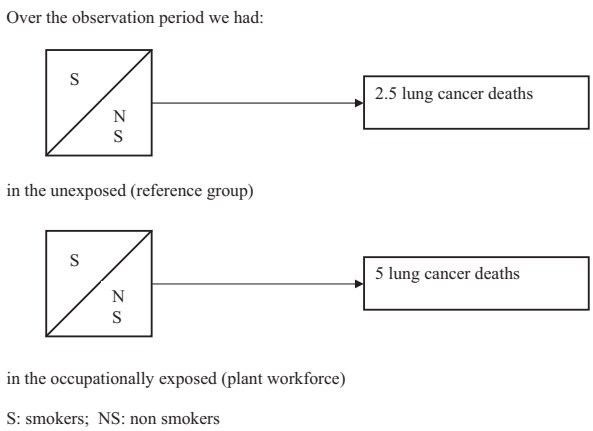

FIGURE 1. Lung cancer mortality in two cohorts with same prevalence of smoking.

THE CONFUSION

In evaluating the relation between occupational exposure and risk of lung cancer, smoking is almost always considered a potential confounder. Formally a confounder is an exposure that (a) can cause the disease being studied and (b) is present to different extents in the populations being compared [Rothman and Greenland, 2008]. If a such a confounder is present, the risk estimated to be associated with the exposure of interest (in the present case workplace carcinogens) will be increased or reduced according to the extents to which the confounder (smoking) is present in the studied and the reference populations and the risk level it confers to the outcome. Thus, if there were many more smokers in the workforce than the general population, the excess risk associated with the exposure of interest would be overestimated if smoking were not considered.

However, it is rare that the difference in smoking prevalence (or in any other confounding factor) between the studied and reference populations is so great that it can, on its own, account for an observed excess risk. A recent article [Blair et al., 2007] which examined the role of smoking as a confounder in epidemiological studies on occupational exposure concluded that smoking very rarely has been able to completely explain the excess risks found. Furthermore, when the estimated risk associated with occupational exposure is above 1.5, it is extremely unlikely that this excess can be explained by a difference in smoking prevalence between the two groups, since such a difference would have to be very large indeed [Axelson, 1989]. To emphasize: in order to demonstrate that the strongly increased risk of lung cancer among our power plant workers is due to smoking as a confounder, one would have to show a much greater smoking prevalence in this group compared to the reference population. Yet it remains the case that smoking (and other potential confounders such as diet) are very commonly invoked as alternative (and often more likely) explanations of increased risks. The error is simple: the theoretical possibility of a confounder effect is not backed up by an estimate of its likely size.

One consequence of such an error is that it can discourage interventions to reduce occupational exposures. In the present article, however, we are concerned with the consequence that cases due to occupational exposure are ''dismissed'' as due to smoking. Such dismissal may occur for any cancer (classically lung cancer, bladder cancer, and leukemia) that is attributable to occupational exposure but also has other causes, that is, cancers of low occupational etiologic fraction.

THE ATTRIBUTABLE CASES

Returning to our example, we expect 2.5 lung cancer deaths in our workforce since that is the risk in the reference

population. But we have 5 cases—2.5 cases in excess, which would not have occurred if the workers had not been exposed to workplace carcinogens. These excess cases are the *attributable cases* due to workplace exposure and the proportion of attributable to total cases is $2.5/5 = 0.5$. *Thus 50% of the lung cancer deaths in the power plant are due to occupational exposure*. This result could also be obtained from the relative risk (equal to 2 for the workforce) using the formula [Rothman and Greenland, 2008]:

$$\text{Proportion of attributable cases among exposed cases} = \frac{\text{relative risk} - 1}{\text{relative risk}}$$

$$\text{or} \quad \text{AR(attributable risk)} = \frac{2-1}{2} = 0.5$$

Let us suppose that smoking and occupational exposures act independently, that is, that factor-specific relative risks are independent of other factors. In our example, the relative risk due to smoking is equal in occupationally and non-occupationally exposed persons, and the risk due to occupational exposure is the same for smokers and non-smokers. Table I outlines the situation: the relative risk associated due to smoking is 9 among both occupationally exposed and occupationally non-exposed peoples compared to reference, the relative risk due to occupation is 2—and the same for smokers and non-smokers. Hence, for the 5 cases observed in the power plant workforce:

4.5/5 (90%) are *attributable* to smoking.
2.5/5 (50%) are *attributable* to carcinogenic exposure in the workplace.

Since all five cases were both smokers and occupationally exposed, it is impossible to sustain that they would *not* have developed cancer if they had *not* worked in the power plant. So, in terms of *attributable* cases, both smoking and occupational exposure conspired to cause the excess cases observed. It follows that the effect of occupational exposure can be assessed only on the entire workforce, not on individual workers (irrespective of whether or not they smoke) and that it does not make sense to ask, for any individual lung cancer victim, whether the disease was caused exclusively by smoking or exclusively by occupational exposure.

Even though smoking is the main cause of lung cancer, invoking it as the cause of the excess cases is not correct, since, as we have seen, only a much greater proportion of smokers in the workforce, compared to the reference population, could explain the excess. Furthermore, the fact that all five lung cancer deaths occurred in smokers tells us nothing of the role of smoking in the excess deaths, and again does not allow us sustain that smoking is the sole cause of the observed excess.

THE CAUSAL RELATION BETWEEN EXPOSURE AND DAMAGE

From the above considerations it is evident that we must distinguish between attributing the cause of health damage in a group of workers and identifying cause of health damage in an individual case.

To establish causality the existence of a risk excess should be evaluated considering the whole group of exposed workers and the potential for confounding. In the example we have been considering, an excess of lung cancers has been established, exposure to carcinogens in the workplace has been established as well, and confounding has been shown to be unable to explain the excess. This should be sufficient to attribute the excess 2.5 cases to occupational exposure.

Although it is possible to attribute a causal connection to a population of workers, it is not possible to attribute an occupational cause to a given individual within that population. This is the reason why companies are acquitted when taken to court. For any individual, the illness could have been caused by factors other than occupational exposure, yet the defense asks for proof that for *this particular* worker that the disease was caused by occupational exposure. Such proof cannot be given.

ESTIMATING THE INDIVIDUAL PROBABILITY THAT OCCUPATIONAL EXPOSURE WAS THE CAUSE

As we have seen therefore, and as also noted by Checkoway et al. [1982] it is the *attributable risk* that indicates the individual probability of developing lung cancer due to occupational exposure. In our example, for each of the five cases the attributable risk is 50%; or in other words the probability that each cancer was caused by occupational exposure is 50%, irrespective of whether or not the person smoked.

TABLE I. Numbers of Lung Cancer Deaths in Different Exposure Categories

	Relative risk	Non-smokers (1, reference)	Smokers (9)	Total deaths	No. of deaths attributable to smoking
Reference group (not exposed)	1 (reference)	0.25	2.25	2.5	2.25/2.5 (90% of total)
Occupationally exposed	2	0.5	4.5	5	4.5/5 (90% of total)
Deaths attributable to occupation				5/2.5 (50% of total)	

It is not always necessary to perform a specific epidemiological study to estimate the attributable risk for an occupationally exposed cancer case. In many cases it is appropriate to use relative risk estimates obtained from past studies of similar situations to arrive at an estimate based on the quantification of exposure and the exposure-response data available in the literature.

We do not express an opinion here as to whether each victim or his family should receive only the attributable fraction of the allotted compensation, or whether all should be fully compensated, knowing that only a proportion are entitled—but knowing also that the individual cases due to exposure cannot be identified. It may be possible to attribute individual cause considering characteristics such as latency, and relation to cumulative dose.

CONCLUSIONS

There are numerous industrial sectors for which an excess cancer risk is well documented in the scientific literature and for which the exposure conditions responsible to the increased risk are well known. If a worker in such a sector develops a cancer, it is not necessary to investigate individual exposure to confounders such as smoking, in order to attribute an occupational origin to the cancer. All that should be required is the demonstration that the worker has been exposed to the conditions characteristic of the sector. An extended inventory of occupational cancer literature arranged by cancer site and economic sector is available on our web site (www.occam.it) under the header ''matrix.''

The scientific literature is always highly cautious when assessing the consequences of workplace exposure: the fear of publishing false positive results [Boffetta et al., 2008] is much stronger than the fear of publishing false negatives [Blair et al., 2009; Crosignani, 2009]. In addition, the reference population used for comparison is almost always the general population, which is decidedly less healthy than the population of workers most of whom are selected for good health at the start of employment, and must remain healthy in order to continue working. This selection process gives rise to the well-documented *healthy worker effect* [Li and Sung, 1999] such that only *very* high occupational risks become evident in a working population. It is also true that many ''scientific'' studies are sponsored by companies in (or organizations representing) the industrial sector responsible for the exposure; in many cases too, negative findings are due to incorrect methods [Gennaro and Tomatis, 2005]. We may conclude that the scientific literature reveals only the tip of the iceberg when it comes to the damage to health and loss of life caused by occupational exposure, and that risk estimates are systematically over-conservative. In fact, many occupational cancers are never identified or acknowledged, and many victims and their families never receive compensation.

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