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Opportunities for the development and use of biomarkers

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Abstract

Limitations in understanding the relationship between occupational and environmental exposures and disease present opportunities for using biological markers to fill gaps in knowledge. Three situations can be identified that could foster the development and use of biomarkers, where epidemiological evidence is (1) definitive, (2) equivocal, and (3) lacking. When there is clear epidemiological evidence of disease risk given an exposure, biomarkers could be used to identify high- and low-risk subsets of a cohort that might benefit from differential practices such as counseling about job risks, varying frequency and intensity of medical surveillance, and using protective equipment. Biomarkers could also be used to test the effectiveness of environmental controls. Assessment of blood lead in bridge workers and purified protein derivative (PPD) testing in health care workers illustrates biomarkers that have been used to evaluate control efforts. When epidemiological evidence is equivocal, a broad and consistent database on intermediate biomarkers in the path between exposure and disease could provide a compelling case as to whether a substance should be treated as hazardous. The case of ethylene oxide illustrates this situation: the epidemiological evidence of risk of lymphohematopoietic cancer is equivocal but there is an informative database on genetic and cytogenetic changes in various species consistent with carcinogenicity. Biomarker data also can be used to assist in the interpretation of inconclusive epidemiological information as is illustrated in the case of styrene where markers provide a mechanistic rationale for the epidemiologic findings. When there is little or no epidemiological evidence of risk in an exposure situation, such as around hazardous waste operations or with new technologies, biological markers can serve as early warning indicators of exposure or risk. In such cases it is important to have an underlying biological theory and an appropriate epidemiological study design if the principal results are to be of value in indicating risk and preventing disease.

Keywords: Biomarkers; Epidemiology; Biological monitoring; Study design

1. Introduction

A biological marker is a biological indicator that can be used to represent exogenous exposure, effects of exposures, early or frank disease, or susceptibility to any of these [1]. The utility of a biomarker is derived from its potential to provide information with regard to hazard or risk and ultimately to the prevention of disease. Where there are gaps in the scientific knowledge base concerning exposure-disease relationships or characteristics, human studies using biomarkers can provide useful information to scientists and decision makers.

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The premise of this paper is that the complete development of biomarkers requires demonstration of their utility in resolving uncertainties of exposure-disease relationships. Three situations can be envisioned that will foster the development of biological markers. These involve where epidemiological evidence is (1) definitive, (2) equivocal, and (3) lacking. Each of these will be discussed and illustrated with examples. Some criteria for using biomarkers in these situations will be suggested. Overall, the utility of a biomarker will be influenced by the degree to which it is validated [2,3]. Validation has many meanings, but generally it pertains to the extent to which a biomarker is related to the event for which it is used. A biomarker can be valid for more than one event. For example, DNA adducts can be markers both of exposure to a carcinogen and of risk of cancer. Validation for each of these uses involve 2 different types of study. A marker can also be useful even if it is not validated. For example, the predictive value for cancer of cytogenetic changes has not been determined, yet there is enough information about the role of genotoxicity in cancer to make the assumption that the risk of cancer is increased with increasing frequencies of cytogenetic changes [4–6]. Thus by reducing population levels of these changes by controlling exposures may reduce the risk of cancer. In this paper a biomarker will be considered developed if it is useful in resolving uncertainty in the 3 situations where epidemiological evidence is definite, equivocal, or lacking.

1.1. Definitive evidence

Where there is definitive epidemiological evidence that an exposure causes a particular disease biomarkers can serve various purposes. Once the exposure-disease relationship has been established and replicated, it does not need to be re-established in every population with that exposure, although questions of intensity and timing of exposure may still be issues. In such an exposure situation, it may be enough to measure a marker to know if there has been exposure and hence risk. For example, blood lead can be measured in bridge workers [7] and purified protein derivative (PPD) in hospital workers to assess whether controls are effective [8]. The presence of increased concentration above background of lead blood or the increased frequency of PPD positive can indicate that the control procedures are not working. In these types of case it is necessary to have accurate information on baseline background levels or have a comparison group. Control for confounding is also important in such assessments. The use of markers to test the effectiveness of controls also requires that the marker be specific to exposures and show a dose-response relationship since the level of the marker response is generally more of interest than whether or not there is such a response.

Another use of biomarkers is to assess subgroups within a population. For example, beryllium exposure may cause beryllium disease and lung cancer. The Lymphocyte Transformation Test (LTT) and the genetic marker HLA-DPB1 Glutamate 69 are candidate biomarkers that could indicate subsets of exposed workers at risk of these diseases [9,10]. These workers could be counseled about different job placement or the need for more intensive medical surveillance. Critical in this use is that effect modification has been investigated and the markers have been validated to be linked with disease risk. This has not yet occurred. Prior to use, ethical, legal and social aspects of using these types of markers should be addressed.

Another type of biomarker that is useful where a known exposure-disease relationship exists is a marker of early disease. Blood in urine or exfoliated bladder cells with morphological or molecular changes are routinely used to screen workers at risk of developing bladder cancer [11]. Key to utilizing markers to screen is the need to demonstrate that screening will reduce morbidity and mortality. Hematuria and Papanicolaou cytology of exfoliated cells have been shown to reduce morbidity but these changes occur relatively late in the natural history of bladder cancer. Markers, such as DNA-ploidy and F-actin, that occur earlier in the natural history of bladder cancer are now being used to screen workers [12,13]. These markers can also be used in intervention trials, such as in testing the effectiveness of chemopreventive agents. Groups with and without chemoprevention would be expected to differ in

levels of a marker that was intermediate in the cancer process.

1.2. Equivocal evidence

When epidemiological evidence is inconclusive about the relationship between an exposure and a disease, biomarkers may be used to inform a decision about whether an exposure-disease relationship exists. For example, epidemiological evidence for the carcinogenicity of ethylene oxide in humans is not conclusive; there are positive and negative studies of adequate quality [14–18]. In one study where the risk for lymphohematopoietic (LH) cancer was not statistically significant for the cohort as a whole it was significant for workers stratified by cumulative exposure [18]. On balance, with the other negative studies of ethylene oxide this may not be enough evidence to conclude that ethylene oxide is a carcinogen. However, the expansive database of genetic and cytogenetic effects in various species and in humans, and the fact that these changes are consistent with a genotoxic mechanism for cancer could serve as the basis to characterize ethylene oxide as a human carcinogen [19–22]. Critical in this regard is how to assess the biomarker data. In this case, it is quite consistent, but in cases where it is not there needs to be criteria for how to weigh positive and negative studies in different species or within a species. For example, in humans a negative study with poor statistical power to detect a difference in marker frequencies between exposed and nonexposed groups should not be given the same weight as a positive study. Moreover, multiple negative studies with poor power or other methodological defects should not be considered to outweigh a single positive study with no major flaws.

Biological markers could also be used to assist in the interpretation of inconclusive epidemiological evidence. For example, a number of studies have found no elevated risk of LH cancer in worker populations exposed to styrene [23] but a few larger studies in the glass fibre reinforced plastics industry are suggestive of a risk [24,25]. In the multinational study by Kogevinas et al. [24], despite no overall risks for LH cancer, risks were found in those workers in the highest styrene exposure category, but only related to intensity of exposure, and not to cumulative exposure [25]. Can biological information provide an explanation for these results? These characteristics of styrene could be illuminating. First, styrene is probably a weak carcinogen because it and its reactive metabolite, styrene-7,8-oxide bind relatively weakly to DNA. Second, styrene-7,8-oxide only has a half-life in the body of 30 min. Third, at higher levels of exposure detoxification pathways for styrene become saturated. Taken together these characteristics could explain why there is no overall LH cancer excess and why the statistically significant excesses were confined to the high exposure subset. No overall excess was observed possibly because styrene and its oxides are weak, short-lived carcinogens. The explanation for a finding of statistically significant risk only with intensity of exposure rather than cumulative exposure could also be explained by the short half-life of styrene 7,8-oxide and that at high levels of exposure detoxication pathways could be saturated thus, risk would only be associated with the highest exposure level prior to saturation and a cumulative effect would not be likely to result in further risk. Clearly these explanations are speculative, but they do demonstrate how using biological marker data could be useful in interpreting epidemiological findings.

1.3. Lack of evidence

When there is no epidemiological data of an exposure-disease relationship biomarker studies can be of particular use. The absence of epidemiological information could be for a number of reasons: an exposure is new or recent, not enough people have been exposed or exposed for a long enough time, or exposure is to a mixture of substances. Epidemiologic methods are generally insensitive under these conditions. However, in all of these situations assessment of biomarkers in exposed populations can contribute information about risk and serve as potential early warning indicators [26]. For example, when little is known of the human cancer risk of a substance or technology newly introduced into commerce or used in new ways that result in worker exposure, the ability to find it binding to DNA or producing cytogenetic changes could be reason to take action

and institute controls. When workers are exposed to a mixture of substances such as in hazardous waste operations, it might be useful to determine whether group changes in a nonspecific cytogenetic marker, indicative of recent exposure to genotoxicants, are associated with occupational exposures or occupational characteristics.

2. Organizational scheme

Too often considerations of the use of biomarkers are hampered by imprecise discussion and consideration about the type of marker or its intended use. Investigators need to consider biomarkers in light of the scientific questions they are asking. To help foster better thinking and communication about biomarkers my colleague Nat Rothman and I have been using a matrix to organize biomarker types and study designs (Fig. 1) [27]. The matrix presents along the horizontal axis the continuum of biomarkers between exposure and disease as well as biomarkers of susceptibility. Along the vertical axis is a continuum of study designs and uses that reflects the development and validity of the marker. In laboratory studies the marker is developed and the assay tested for sensitivity and reliability. Transitional studies involve taking the marker from the laboratory to the field and determining its prevalence and variability in healthy populations with various demographic characteristics. Finally, when the marker is validated for exposure, disease or susceptibility, it can be used as dependent or independent variables in etiological studies or in applied situations such as biological monitoring and medical screening. Key in considering biomarkers is to be clear on which cell in the matrix characterizes a particular biomarker.

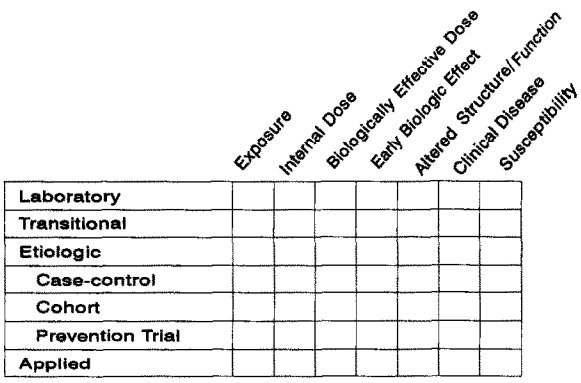

Fig. 1. Matrix of biomarker combinations and study designs. (Schulte and Rothman, 1994).

3. Conclusion

In all of these examples where biomarker studies might be conducted it is necessary to adhere to good epidemiological principles for study design, sample selection, control for confounding and effect modification [2,3]. There is also need for specifying the underlying biological assumptions that support the choice of a particular marker and the biological and environmental sampling time frame in relation to the marker. When a situation is unclear about the health risks of a particular substance, agent or process, studies using biological markers that are poorly described or not based on a biological hypothesis should be avoided. The selection of a single biological marker for use in the situations described in this paper is generally not the best approach. A battery of markers selected to address different aspects of the natural history of disease or to represent different parts of the exposure-disease continuum is likely to provide the most useful information [21].

The selection and the use of biomarkers to resolve uncertainties or explain epidemiological findings should be considered as part of a process. The pace of scientific research in this area is very fast. The biomarkers of today might easily be replaced in the future by ones that explain better the events of interest [28]. Efforts to use biomarkers to monitor workers or exposed populations or make decisions need to be updated in light of new knowledge. Only when the use of biomarkers is seen as part of a dynamic process of scientific exploration will they be of utmost value in preventing disease.

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