INTRODUCTORY NOTES

Environmental Epidemiology, Present Chances and Challenges for Future

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A short 14 years have elapsed since the 1993 ISEE annual conference in Stockholm where we founded our Central and Eastern European Chapter (CEEC) approved by the ISSE Executive Council. It was headed at that time by Wieslaw Jedrychowski from Jagelonian University in Krakov, Poland (1993 − 1995) followed consecutively by Ildikó Farkas from National Institute of Environmental Health in Budapest, Hungary (1995 – 1998), Ivan Čižnár, Slovakia (1998–2000), Vladimír Bencko − Charles University in Prague, Czech Republic (2000 – 2002), Bogdan Wojtyniak − National Institute of Hygiene, Warsaw, Poland (2002 – 2003), Anna Páldy − National Institute of Environmental Health, Budapest, Hungary (2003 – 2006) and Hana Šlachtová − Institute of Public Health in Ostrava, Czech Republic (2006 – to present).

These 14 years have been marked with major developments in the field of our research. There have been remarkable advances in the broad area of environmental epidemiology. These include research not only of human exposures to major risk factors in environmental and occupational settings but also to lifestyle and nutrition related risks. What remarkable problems, changes and challenges lie ahead in environmental epidemiology which are conceived in broad concepts covering not only human exposure to xenobiotics but also settings in environmental and occupational risk, lifestyle risks and nutrition related risks and/or benefits.

Environmental epidemiology aims at identifying risk and/or potential protective factors in broadly conceived environmental settings and at evaluating associated risks and benefits. Ultimately, this aims for a safe environment. In the past, environmental epidemiology has been successful in approximating this goal in occupational settings. This is because of human exposure to xenobiotics and other risk factors in occupational settings were and to some extent still are by one or more orders of magnitude higher compared with the general environment. For example, many chemicals classified as carcinogens by the International Agency for Research on Cancer (IARC), were first evaluated in the workplace. In previous decades, occupational exposure to established carcinogens has actually diminished in many countries and awareness of their hazard has increased (e.g. 1, 2).

However, in recent years the field of environmental epidemiology has been balancing on a turning point. On the one hand, it seems that most major occupational carcinogens have already been identified. On the other hand, we are left with a long list of substances for which epidemiological data are inconclusive. There is evidence that many occupational carcinogens remain to be identified. This is illustrated by the numerous associations between cancer and individual occupations for which the specific agents have not been identified, and the large number of established animal carcinogens that have not been well investigated in humans. The above data suggest that workers continue to be exposed to substances that may be hazardous but are not yet recognized as such. In principle the same holds true for the general environmental settings and for much risk, as well as, protective factors of life style including nutrition.

The classical approaches and study designs in environmental epidemiology have, however, not been able to identify and evaluate these possible risks and protective factors adequately. The two main reasons for this are thought to be inadequate exposure assessment and insufficient study size. In the last decade, the field of epidemiology has therefore advanced in these two directions.

Increasing study size: An important characteristic of research in the last decade is the increasing number of collaborative studies involving various countries. By increasing the sample size, the power of a study to identify significant associations is augmented. Considering for example that lifetime prevalence of occupational exposures in the general population are low (typically below 5 to 10%), and associated risk can be small (e.g. relative risk of 2), the study sample size of a community-based study needs to be large to identify statistically significant associations. This is even more crucial if exposure or outcome is misclassified in the study population. A sample size of at least 1000 cases and controls have been recommended for future community-based case-control studies on cancer. Given that one centre or one country can often not provide such numbers within a reasonable amount of time, multi-centre studies are the obvious solution. Besides increased power, multi-centre studies can provide additional advantages, including a greater exposure contrast in the study population. These are advantageous for exposure-response analysis, and the opportunity to study differences in exposure and disease patterns between countries.

Multi-centre studies can be realized in two different ways. Collaboration between the centres can be initiated after completion of each individual study (retrospectively planned multi-centre studies), or before the studies have actually started (prospectively planned multi-centre studies). Meta- and pooled analyses are examples of retrospectively planned multi-centre studies, and have been performed in many areas of epidemiology.

Prospectively planned multi-centre studies have only recently become possible since international organizations and institutions such as the European Commission have started to offer funding for these costly operations. They offer the advantage of identical protocol data collection in each centre that are involved. Which, avoid loss of information at the stage of data pooling. From the CEEC perspective, an important example of this approach serves the CEEC Multi-centre Lung Cancer Study organized by IARC/WHO/ Lyon, France which started 10 years ago and was supported by EC Inco Copernicus 4thFP. It represents collaboration of centres in the Czech Republic, Hungary, Poland, Rumania, the Russian Federation, and Slovakia (e.g. 3, 4). Later on the same organization principle was applied in the Kidney Cancer Study supported by NCI/Bethesda, USA (e.g. 5).

Improving exposure assessment: Optimizing methods for exposure assessment and reducing exposure misclassification represent the most difficult components of environmental epidemiology studies. A perfect exposure assessment for long latency diseases such as cancer would consist of quantitative measurements of internal dose, over the whole exposure period, for each subject in the study. However, this is a utopia not likely to be attained in the near future. The availability of group based external exposure measurements in some points in time, are already a luxurious position for the epidemiologist trying to estimate the exposure of the study subjects. More often one has to fall back on subjective methods of exposure assessment. The possibilities for exposure assessment largely depend on the design of the epidemiological study, with community-based and industry based studies imposing their own specific limitations.

In community-based case-control studies, the exposures of interest can often not be measured and have to be estimated entirely retrospectively. Consequently, risk estimates are often directly based on the job-information provided by the study subjects (or proxies), or exposure is inferred from the job-information through job-exposure matrices or case-by-case expert assessment. The subjecti-vity and the limited use of data-driven quantitative estimates of exposure of the methods used in case-control studies are considered important shortcomings that can lead to substantial exposure misclassification.

How to improve retrospective exposure assessment methods has been of frequent debate. The difficulty in evaluating the validity of all retrospective exposure assessment methods in the absence of a gold standard is considered a major shortcoming. Reliability studies indicate that in all retrospective methods a considerable amount of misclassification can occur. There is, however, an urgent need for the quantification of the levels of misclassification that can be expected from each method in order to anticipate the attenuation of the odds ratio (OR) that results.

One major field of improvement is the departure from crude exposure indicators such as never/ever exposed towards a more quantitative exposure assessment covering the whole exposure period. Quantitative exposure data enable the investigation of an exposure − response relation, an important criteria for causation. The availability of quantitative exposure data also facilitates valid comparison of risk and exposure-response relations between studies, countries and industries. It also provides a solid base for risk assessment and standard setting.

Risk assessment: Risk assessment is a new and evolving science, and methods for conducting risk assessment are still at an embryonic stage, although undergoing rapid development. Controversies still abound concerning the appropriate methods and data to use and are likely to persist given the great uncertainties involved in extrapolating beyond the range of available data, the underlying biases and other limitations of observational data, and the political and societal implications of these analyses (2). Skeptics have argued that risk assessment, at least as it is currently practiced, has not been a useful tool for addressing societal concerns about exposures to environmental and occupational hazards (e.g. 6). Their primary concern is that the increasingly intense debates concerning risk assessments may come to be used as an excuse for delay in the development of appropriate regulatory and other responses to environmental and occupational hazards. For example, it has taken the U.S. EPA more than 20 years to finalize its risk assessment for exposure to diesel exhaust particulates (7). A spirited debate has emerged over the use of the “precautionary principle” as an alternative basis for public health decision-making. This approach has recently been embodied in some environmental legislation of the European Union (8). The precautionary principle has been defined as the need to take some precautionary measures to prevent threats to human health even when a cause-and-effect relation has not been fully established (9) This is not a new principle for epidemiologists. We all know the story of how John Snow convinced the authorities to remove the Broad Street pump well before the cause of the cholera epidemic in London was understood (2).

In our view, risk assessment and the precautionary principle should not be viewed as conflicting paradigms but rather, as complementary approaches for developing appropriate policies to address risks posed by exposure to carcinogens and other risk factors like e.g. obesity (10) or particulate air pollution (11). Identification and quantification of risk are clearly a useful tool for informed decision-making. Risk assessments are inherently uncertain and should, as the NAS (1996) suggested, be viewed as an iterative process in need of continual improvements through research targeted to fill the gaps in our knowledge.

Tremendous advances in our understanding of basic epigenetic mechanisms and rapid progress that are being made in developing new powerful technologies, such as those for sensitive and quantitative detection of epigenetic changes, as well as, for genome-wide analysis (epigenomics), hold great promise that these issues may be addressed in the near future (12).

Epigenomics - one of the future challenges: While the field of cancer genetics has enjoyed a great deal of attention among cancer researchers in the last few decades, the appreciation of cancer epigenetics is more recent.

The study of the role of epigenetic changes induced by environmental, dietary and lifestyle factors is in its infancy. Furthermore, little is known of the precise contribution of epigenetic mechanisms to different types of human health alterations induced by adverse stimuli in the environment and diet. While there is accumulating evidence showing that aberrant DNA methylation may result from adverse exposures to epimutagens, there is a paucity of evidence regarding the effects of stimuli causing heritable changes in epigenetic information stored in histones, owing to the fact that this is a new and largely unexplored field. Although it seems inevitable that perturbations in histone modifications are induced by dietary and environmental factors that contribute to the development of, for example human cancer. A formal proof of such a relationship remains to be established (12).

Large cohort and case–control studies offer some of the most exciting opportunities to study the contribution of epigenetic events induced by the diet and environment to human cancer. Such examples are the European Prospective Investigation into Cancer and Nutrition, a large prospective cohort study designated to investigate the relationship between diet, various lifestyles and the incidence of cancer in 10 European countries (13), and the case–control study on lung and upper-aerodigestive tract cancers in Central and Eastern Europe (14-16).

These multi-centre studies, boast a large sample size of several thousand subjects and represent unique possibilities to identify which dietary and environment stimuli and lifestyle practices may exert risk and/or benefit effects through epigenetic changes.

Epigenetic alterations in comparison with genetic changes are reversible and are typically acquired in a gradual manner. These features offer an important potential for prevention strategies (9).

Conclusion: Therefore, there is a real hope that the foreseeable future is likely to bring long awaited answers on the impact of aberrant genetic and epigenetic information caused by environment and diet. These also provide important information for the discovery of new biomarkers and the development of novel strategies for prevention – a major public health priority in the 21st century.

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