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Epidemiology

Non-Hodgkin lymphoma and occupational exposures: multiple exposures $\neq$ multiple papers

H Kromhout, R Vermeulen

Commentary on the paper by Karipidis *et al* (see page 25)

In this issue, Karipidis and colleagues report the interesting finding of a possible association between non-Hodgkin lymphoma and occupational exposure to power-frequency magnetic fields.¹ Their results are important given that existing studies on this topic are few, with conflicting results.^{2–3} As in any other community-based case-control study their subjects have been exposed to a variety of chemical and physical agents. The authors, like many others, have published associations between various occupational exposures and non-Hodgkin lymphoma in separate papers.^{4–6} Every researcher ever involved in large and expensive community-based case-control studies focusing on an adverse outcome and occupational exposures will be aware of the factors increasing the likelihood of publication of the results of positive and negative exposure-response relations in multiple papers. These include a general trend towards shorter papers in journals, but an expectation that assessment methods are specifically tailored to the exposure in question and that other aspects of methodology are described in sufficient detail.

This example, however, highlights an increasingly important issue in occupational epidemiology—how to assess a series of related publications. With the use of job exposure matrices (JEMs) or experts to assign occupational exposure to cases and controls, it is possible to relate many occupational exposures to the studied health effect in the absence of

clear a priori hypotheses. The risk of finding several positive associations simply by chance may thus be substantial. Where such findings are spread across several publications, there may not be full recognition of the problem of multiple comparisons or the often complex relationship between different occupational exposures included in different papers.

Moreover, later analyses may raise questions about confounding by factors that were less completely considered in papers of earlier and different focus.

The paper by Karipidis *et al* follows two previous publications concerning the association of lymphoma with chemical exposures like solvents, metals, organic dust and PCBs and exposure to pesticides.^{5–6} A third paper was published on the protective effects of sun exposure in the same population.⁴ In the earlier papers, not all of the estimated exposures included in later analyses could be described and so adjusted for. However, when we look at the exposures considered: sunlight, pesticides, solvents, metals, organic dust and PCBs, one can safely assume that exposures to these agents did not occur independently. For instance, utility personnel clearing the undergrowth of power lines will be exposed to power-frequency magnetic fields, pesticides (herbicides) and sunlight at the same time. Also, a subset of metal workers may have been exposed to solvents and metals simultaneously. From the four papers one can derive a picture of overlapping (occupational)

exposures in this population of cases and controls (see table 1).

Analyses of occupational exposures often start with looking for increased risks in certain jobs. Most case-control studies, however, are too small to come up with conclusive results when analysing at job level. The consequent use of JEMs and case-by-case expert assessment enables more powerful analyses since exposures to single (groups of) agents are combined across industries and jobs. At the same time the intrinsic and complex underlying exposure profiles are often not fully considered. With prevalence of exposure as high as those shown above and a considerable potential of strong correlations between agents in subsets of the study population, a more elaborate statistical analysis is warranted (see for instance De Roos *et al*).⁷ Simple statistical adjustment for other exposures might often not be sufficient, given different type 1 error structures for the different exposures and possible complex correlation structures.

An analogy can be made with the field of genetics where enormous amounts of data on genetic variants are being assembled that have to be correlated with outcome parameters. The huge number of comparisons (up to thousands or even hundreds of thousands) in the genetic studies gives rise to a substantial chance that an initial “statistically significant” finding will turn out to be a false-positive finding. Therefore, several techniques have been developed to account for multiple comparisons, including false

Table 1 Overlapping (occupational) exposures among cases and controls

Exposure	Cases	Controls
Sunlight	100%	100%
ELF-EMF	100%	100%
Pesticides	11%	11%
Solvents	33%	29%
Metals	13%	14%
Organic dust	20%	17%
PCB	2%	2%

discovery rate procedures,⁸ or more Bayesian approaches like false positive report probability (FPRP), in which the prior probability of a true association of the gene (exposure) with a disease is specified a priori.⁹ Although the number of comparisons in occupational studies is very much lower than in genetics, it is our opinion that such approaches should start to find their way into case-control studies that focus on multiple occupational exposures. At a minimum, authors should make clear how many exposures were considered at that time, justifying their inclusion in the study hypotheses. Furthermore, presenting initial observations together in one paper, and applying state-of-the-art statistical analyses accounting for multiple exposures (e.g. hierarchical regression) would be extremely helpful for the readership and would better reflect the complexity in which occupational exposures occur.

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COMMENTARY

Cancer risk in the semiconductor industry: responding to the call for action

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Commentary on the paper by Bender *et al* (see page 30)

In a 2002 editorial, an international group of occupational physicians and health scientists issued a “call for action”, specifically raising concerns about cancer risk in the semiconductor industry.¹ Citing the small number of published papers available at that time,^{2,3} and some unpublished and anecdotal reports, the authors of the editorial highlighted ways in which “some real elevation in the cancer risks” might remain unascertained. They noted, “Though the [earlier] findings are not conclusive, it is clear that more detailed studies are urgently needed to determine whether or not there is a workplace risk, and if so to determine its specific nature and size”.¹ Subsequent epidemiological investigations of cancer risk in the semiconductor industry have been limited to two cohorts of about 1800 and 4900 employees in the semiconductor industry in the UK.^{4–6} These studies identified increased risks

for a few cancer sites; however, the numbers of cases were small and it could not be determined whether occupational exposures played any part.

In this issue of *Occupational and Environmental Medicine*, Bender *et al*⁷ respond to the “call for action” with a large, detailed cohort study of cancer risk in nearly 90 000 semiconductor workers in the semiconductor and storage device sectors employed at two IBM facilities between 1965 and 1999. Although the median follow-up was modest—16 years for semiconductor manufacturers and 11 years for storage device manufacturers—more than 17 000 cohort members were first employed before 1974. Results of thorough, systematic analyses of site-specific cancer risks are reported by industry sector, years of employment and potential for exposure to non-office workplaces (but not specific chemicals), as well as for specific job activities.

Observed incidence rates for all cancers combined were 81% and 87% of the local state rates for workers in semiconductor and storage device sectors, respectively. Nearly all cancer-specific relative risk estimates were near or below unity, some (including colorectal and lung cancers) indicating significant deficits. Even when cancers related to smoking and other lifestyle factors were excluded from the analyses, no excess risks were seen. Cancers of the prostate and the female breast were observed in excess, with prostate cancer being the only significant excess. Such patterns of cancers detected through screening are not unusual in employed populations that are generally healthy and medically well served.⁸

Analyses stratified by work group generated a handful of increased relative risk estimates. However, most of these estimates were based on small numbers of cases, and only soft tissue sarcomas (based on six cases) generated a relative risk estimate >2.5.

Although reporting a few excesses of specific cancers, some of which may be expected owing to random error, the study offers some reassurance that at this stage of follow-up no noteworthy increases in cancer risk are seen among employees in the semiconductor production and storage device sectors. Results may differ for those employed in the earliest years or outside Europe or North America because of differences in workplace conditions or cancer screening and