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Commentary: Observational studies may conceal a weakly elevated risk under the appearance of consistently reduced risks

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The paper by Lahkola *et al.*¹ is interesting in two respects. First, the issue of possible health effects, in particular cancers, of mobile phones is of obvious public health importance given the wide extent of the exposure. Second, the paper raises several noteworthy methodological issues of general import.

The study of meningiomas in five countries reported in the paper adds two countries to previous articles

covering three countries^{2–4} and is an integral part of a larger multinational study on meningiomas, gliomas, acoustic neurinoma and parotid gland tumours in 13 countries ('Interphone')⁵ whose findings are as yet unpublished. Multi-centric international studies originate and develop within a variety of contexts and constraints, ranging from the degree of urgency of the question under study to the investigators' research and career interests to conditions posed by funding bodies. Given this spectrum of circumstances, each study will necessarily have its own criteria for the publication of results, and a variety of criteria are justifiable provided they are explicitly agreed upon beforehand by the participating investigators.

From a research viewpoint, however, the rationale for multi-centric studies largely rests on the potential

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for: (i) improving inferences on the validity of the findings through the simultaneous replication of the study in different populations and (ii) increasing the precision of the effect estimates through large sample sizes. However, each centre also has its own ethical and funding pressures with regard to the rapid publication of its findings, and there is a danger that the publication of important findings may be delayed while the 'last centre' finishes its work. For example, the 'Phase one manual of the International Study of Asthma and Allergies in Childhood (ISAAC)',⁶ which includes a large numbers of centres (155 in Phase One), states that 'Each centre may publish its own data without the approval of ISAAC. All publications and communications arising from comparisons of more than five international centres require the approval of ISAAC and will be authored by ISAAC whose participants will be identified.' Such restrictions recognize the importance of rapid publication of findings from specific centres and regions, but that international comparisons (particularly comparisons across regions) should be collectively authored by the entire collaboration.

The publication of results from some, but not all, centres of an international collaborative study may undermine the very rationale for a multi-centric study, and reduces its potential advantages. This may be particularly the case if the first published results from an arbitrary subgroup of centres turn out to be discrepant from those of the overall study. The interpretation of results, which should be primarily based on the overall findings, may become controversial and lead to endless debate. Thus, publishing first the results for the whole study, rather than for a subgroup of centres, should remain the rule for multi-centric studies, with exceptions to be agreed upon at the planning stage.

The Lakhola *et al.* paper¹ abstract states that the 'risk of meningioma among regular users of mobile phones was apparently lower than among never or non-regular users (OR = 0.76, 95% CI = 0.65–0.89)'. In fact inspection of Tables 3–5 shows a constant pattern of the risks for regular mobile phone users falling below the level for never or non-regular users (reference category), whatever exposure variable is considered (frequency of use, years of use, etc.). This decreased risk is usually more marked for the lowest category of exposure, and tends to be less marked as exposure increases, but in only two of the multiple comparisons does it go above 1. A key finding is that risk is decreased in all five countries: OR 0.87 (95% CI 0.60–1.27) for Denmark, 0.75 (0.56–1.01) for Finland, 0.85 (0.57–1.29) for Norway, 0.68 (0.49–0.94) for Sweden and 0.72 (0.51–1.01) for Southeast England. Can these findings be due to chance? On the null hypothesis of no effect of mobile phone use the probability of a country-specific OR below 1.0 is 50% and the probability of all five OR's being below 1.0 by chance is only 3%. Also one would expect zero or one

OR's to be statistically significant at $P < 0.10$ whereas three are observed. In addition, the already noted systematic pattern of decreased risk in the aggregate data indicates that these findings are unlikely to be due to chance. If chance is an implausible explanation consideration must shift to uncontrolled confounding and/or biasing factors. The authors pertinently discuss the latter issues, stating, with the support of some empirical evidence, that 'at least' some of the reduction in risk estimates is likely to be due to selection bias deriving from a differential participation into the study of exposed and non-exposed people among cases and controls (in particular controls who are not regular mobile phone users may be less likely to participate than controls who are regular mobile phone users). The less immediately evident consequence of this explanation is that, unless data are at hand to quantify how much 'at least' can be, the observed reduced risk becomes compatible with three different inferences: (i) that there is no association between mobile phone use and meningioma occurrence if all the observed reduction in risk were due to bias; (ii) that there is a positive association if the observed reduction would result from a larger reduction due to bias masking an increased risk associated, possibly causally, with the exposure; and (iii) that there is a negative association, if the observed reduction would result in part from bias and in part from a negative association, possibly causal, with the exposure.

Such an indecisive three-pronged conclusion is not unique to this study. The investigations of silicone implants for breast augmentation and breast cancer offer a similar example. Most observational studies consistently show a decreased risk of breast cancer among women^{7–9} with implants with respect to women without implants. Here the biasing factor, which introduces a non-comparability between the pre-implant rates of breast cancer in women undergoing and not-undergoing an implant, is likely to be the smaller mass (number) of cells at risk of malignancy in women who demand a breast augmentation (an hypothesis that finds some support from the reduced risk of breast cancer in women undergoing a cosmetic reduction of breast mass).¹⁰ In this case, as in the case of mobile phones the reduction in risk becomes compatible with different and contrasting inferences, making it impossible to reach clear conclusions—at least solely on the evidence of the specific studies—about the existence or not of a hazard from mobile phone use or from silicone implants.

These examples remind us that two points should not be forgotten when interpreting the results of observational studies, particularly those conducted for detection of environmental hazards. First, when several replicated observational investigations consistently show a decreased risk chance may be an unlikely explanation. Second, while the decreased risk speaks 'prima facie' against a risk increase in fact it

implies that, unless data are available to substantiate the likely size of the bias inducing the reduction in the risk estimates, the data do not support *any* inference in particular, whether of no association or of a negative or positive association. If the latter was the central question addressed by the study, it remains unanswered—the most that can be said is that the possibility of a strong positive association can perhaps be ruled out, but the possibility of a weak positive association cannot be.

Conflict of interest: Neil Pearce is a Co-investigator of the Interphone study.

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