Global health BSC

Module 2 In-Course Assessment

Format: **Data Interpretation**

Date: **15th December 2010**

Time allowed: **90 minutes**

Instructions: please examine the data on the attached sheet before answering the questions below. The table comes from the Interphone study on brain cancer and exposure to electromagnetic fields from mobile phones. It shows the associations between meningioma or glioma, respectively, and the cumulative number of hours of calls from mobiles.

Questions

1. **Describe the table attached and formulate hypotheses on potential interpretations, commenting on the different histological (brain tumour) types. (4 marks)**

The table shows the results of a case control study. The exposure/predictor under investigation is mobile phone use. The condition (outcome) is brain tumour and is further classified under meningioma and glioma. (both of these are rare conditions with long latent periods, hence the choice of study design). Mobile phone use is stratified into different categories and the odds ratios relating to exposure for meningioma and glioma respectively. These represent:

(N cases using mobile phones/N cases not using mobile phones)
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(N controls using mobile phones/N controls not using mobile phones)

Data was collected (retrospectively) for 2409 meningioma cases and 2708 glioma cases with their controls. Exposure was quantified by categories under the following: Regular use in the last year, Time since the start of use, Cumulative call time and Cumulative number of calls The null hypothesis of this study is likely to have been that there is no association between mobile phone use and the outcome of meningioma or glioma. An association would be indicated by an odds ratio > 1 in the categories with high exposure (ie. Regular use in the last year, longer time since the start of use, higher cumulative call time and number of calls) with a confidence interval not including 1. The results shown do not strongly suggest that mobile phone use and intensity of its use predict risk of meningioma and glioma. A dose-response relationship would be an indication of causality (although, being a case-control study, this would not be conclusive as such). In this study, there is no strong dose-response relationship (in fact, there is a reduced odds ratio in some categories with high exposure) except for a significantly raised OR for cumulative call time >1640 hours in glioma.

As indicated below, there may have been limitations to this study, and therefore another study would be needed to generate hypotheses about this association. Furthermore, even in the presence of a strong association, a case-

control study is not conclusive about causality. A further multi-centre case control study or a cohort study would be appriopriate, as experimental studies would be unethical to conduct on a question like this.

2. **Comment on the statistical stability of the data. How was the data relating to the length of mobile phone use stratified? Discuss this briefly. (4 marks)**

There is a reduced odds ratio for a majority of the categories of mobile phone use both in glioma and meningioma. Some of these reduced odds ratios have a confidence interval which includes 1. In these cases the data does not suggest an association between that particular category and the outcome (meningioma or glioma). Other reduced ORs have a confidence interval which does not include 1. This suggests an association between that particular category and brain tumour.

Interestingly however, the data indicates a significantly reduced OR for regular use of mobile phones in the past year for both meningioma and glioma. It is not plausible that a decreased risk of brain tumour is associated with mobile phone exposure, if all other variables are accounted for (this is discussed below).

ORs above 1 are seen with the cumulative call time category >1640 for glioma and meningioma and with 13-30.9 for glioma. These however are not statistically significant except for >1640 cumulative call time in glioma. It may be useful to further stratify this group to investigate whether there is a stronger association in extremely high usage groups.

The data was stratified according to:

a. the presence or absence of regular mobile phone use in the past: binary (2 categories)

b. time since start of use in years – 5 categories

c. cumulative call time with no hands-free devices in hours: 11 categories

d. cumulative number of calls: 11 categories

Extra note: The ordinal categories (b, c and d) appear to be skewed towards low usage: ie. heavy users could all end up falling into the >10 years of regular use, >1640 hrs cumulative call time and >2700 number of calls categories.

3. **Why did the authors choose to adjust for confounding variables and why do you think they chose this particular set of confounders? (4 marks)**

The authors adjusted for sex, age, study centre, ethnicity in Israel and education. They will have chosen these because they know that:

- certain categories under sex, age, study centre, ethnicity in Israel and education are more at risk of glioma and meningioma
- each of these categories could be associated with different levels of mobile phone use
- sex, age, study centre, ethnicity in Israel and educational attainment are not a consequence of mobile phone use

The effect of confounding variables can be dealt with in the study design by matching or stratifying sampling of the study subjects, or in the data analysis by stratified or multivariate analyses. If there is a

systematic error in the estimate of the effect of mobile phone use on the risk of brain tumour, then bias would result. An example would be: old age is associated with a higher risk of meningioma and glioma. Participants who are older may have a lower use of mobile phones than younger participants. Not adjusting for age could in this case underestimate the association between mobile phone use and brain tumours.

In more details:

- **sex**: male or female sex could be an independent risk factor for brain tumour. Alternatively, female or male sex could be associated with a higher exposure to carcinogens (eg. Occupational or smoking) according to the area.
- **age**: age and the risk of brain tumour could be linked (Note: indeed they are positively related)
- **study centre**: there may be other environmental exposures locally which add to (or even modify) the putative risk of mobile phone use for brain tumour
- **ethnicity**: genetic risk factors could exist for brain tumours in certain ethnic groups. Also ethnicity and educational attainment may both be linked with socioeconomic status in Israel, and in turn, this could be associated with different environmental/occupational risk factors.

4. **Which categories have Odds Ratios below 1 that are statistically significant? How do you interpret these? (4 marks)**

   For Gliomas a reduced odds ratio related to the following categories of exposure was seen with:

   - Regular use in the past ≥1 year
   - Time since start of use (years): 1-1.9 and 5-9
   - Cumulative call time (in hours): <5h, 5-12.9, 31-60.9, 115-199.9, 735-1639.9
   - Cumulative number of calls (in hundreds): <1.5, 1.5-3.4, 41.5-67.9

   For Meningiomas a reduced odds ratio related to the following categories of exposure was seen:

   - Regular use in the past ≥1 year
   - Time since start of use (years): 2-4 and 5-9
   - Cumulative call time (in hours): 13-30.9, 31-60.9, 115-199.9, 200-359.9
   - Cumulative number of calls (in hundreds): 1.5-3.4, 14-25.4

   A reduced odds ratio for high usage categories would suggest that mobile phone use has a protective effect for brain tumours. There is no biological plausibility for this.

   Furthermore, the results include a disproportionately high number of ORs <1, and only a few elevated ORs. This could indicate a number of situations including: the null hypothesis is true (ie no association – although such a large proportion of reduced ORs in this case would still imply some bias) or systematic bias from one or more sources.

A reduced odds ratio (OR) related to ever having been a regular mobile phone user was seen for glioma [OR 0.81; 95% confidence interval (CI) 0.70–0.94] and meningioma (OR 0.79; 95% CI 0.68–0.91). This could reflect participation bias or other methodological limitations

5. **How would you improve the study? Which additional information would you like to collect? (4 marks)**

It would be useful to read the Methods section of the paper, including:

- How were the cases and controls selected? The selection of controls for instance, could be done from the population or from the hospital population, with different implications. (eg. hospital patients may have a history of chronic illness which for example could influence rates of history of regular mobile phone use). Bias could be reduced by choosing cases representative of the population suffering from glioma/meningioma and controls representative of the rest of the population.

- What was the percentage of individuals who declined enrolling on the study? A reduced odds ratio (OR) related to ever having been a regular mobile phone user was seen for glioma [OR 0.81; 95% confidence interval (CI) 0.70–0.94] and meningioma (OR 0.79; 95% CI 0.68–0.91), suggesting a possibility of participation/self-selection bias. This could be improved with measures to facilitate participation if not already in place – refund of transport expenses for participants, improved information about the process, shortening of the interview time. Alternatively, at the analysis stage, any information on these individuals (study centre, age etc..) could be compared with participants' details to detect any source of bias.

- How was the data collected? Was it by interview or proxy interview? This could determine whether there is a risk of recall bias (especially for cases with cognitive problems). This could be improved by collecting data from a variety of sources (the participant, relatives. mobile phone bills)

- How were the categories defined? What does "regular use" mean?

- The majority of subjects in the study were not heavy mobile phone users. It would be helpful to further stratify mobile phone use in the heavy users categories, to see whether an association with very heavy use can be detected. Indeed, an association between mobile phone use and brain tumour may only be present above a certain threshold of exposure.

- Are there any other sources of downward bias which could account for the disproportionate number of low ORs?

For interest: The authors of the study also decided to collect data on preferred side of use of mobile phone and the side of the tumour occurrence. This would be useful if we suspect that the effect of mobile phone use is related with the distance between human tissue and handset.