Reviewer's report

Title: Meningioma patients diagnosed 2007-2009 and the association with use of mobile and cordless phones

Version: 1 Date: 6 June 2013

Reviewer: Michael Kundi

Reviewer's report:

This manuscript reports about a very important investigation that would for the first time allow a meaningful analysis of the potential association between mobile and cordless phone use and meningioma. Earlier studies were compromised by two short periods of use of these devices. Due to the long latencies of meningioma and the slow growth an effect could only be detected, if it exists, if a substantial proportion of cases have used a wireless phone for 15 years or longer. In this study more than 20% of cases had usage durations exceeding 15 years. However, there are some problems with the analysis that make it difficult to decide whether or not there is an association. Detailed comments are given below.

Page 3, second paragraph: The study by Korhonen et al. (2006) has been mentioned as indicating that sex hormones cannot fully explain the differences in incidence between males and females. However, what the study actually shows is that the hormone receptor status does not differ between male and female meningioma. The interpretation by Korhonen et al. is not in line with the evidence. Obviously, since women have higher levels of circulating estrogen this will cause a larger growth rate and consequently a higher incidence of meningioma.

Page 7, last paragraph: The method used for selection of controls should be described in greater detail. 1. Because cases were reported in different intervals for the regions of Sweden at which time the population register was contacted to provide controls? 2. It is stated that cases were recruited from the same population source; does this mean that they were obtained from the same region? This should be clarified. 3. As it would take time to contact the physician once a case is reported, was the population registry contacted before or after eligibility of the case was established? A table, similar to Table 1 or included in Table 1, with participation of controls should be provided with details of contacted controls and refusals (if possible also reason for refusal). There is also another issue that needs to be addressed in this section or in statistical analysis section: Since controls were selected matched to cases according to gender, age (and region?) it is stated that they were assigned year of diagnosis as cutoff for assessment of exposure. But because controls for malignant brain tumors were included in this analysis as well this is insufficiently correcting for time of diagnosis. I suggest performing a re-matching. This will consist of a selection of all suitable controls for each case (that could be more than one) and assigning all
controls the same cutoff date as the case. A conditional logistic regression analysis should then be conducted with varying sizes of matched sets (which is actually no big problem).

Page 8, first paragraph: Please specify how many cases and controls needed to be contacted over the phone for supplementary information. Also explain how interviews were done to keep case status blinded.

Page 8, 2nd paragraph: Has ear mostly been used during calls been inquired separately for mobile and cordless phones? Please clarify!

Page 8, last paragraph: It would be interesting to specify (maybe by expanding Table 1) participating cases by diagnosis (if this is available from cancer registry).

Page 9: There is a fundamental problem with the analysis related to the different type of age-incidence function for meningioma. In contrast to that for glioma, it is a power function of age. If we assume, as authors mention on page 10 (2nd paragraph), there is an effect of mobile phone use on promotion then, necessarily, the odds ratio for mobile phone use must depend on age! Of course this effect cannot be removed by including age as a covariate in the analysis. The expected odds ratio for an effect on growth rate resulting in an earlier diagnosis is \(((\text{age}+m)/\text{age})^b\), where \(m\) is the shift in years due to earlier diagnosis and \(b\) is the exponent of the power function (a value between 2 and 3). For a sample with an equal number of years of mobile phone use the logistic regression with mobile phone use as the predictor variable will result in a parameter estimate \(\beta=b\ln(1+m/\text{age})\). Since \(m\) will be much smaller than \(\text{age}\) we can approximate the logarithm by \(m/\text{age}\) yielding \(\beta\approx b\cdot m/\text{age}\).

Hence the effect of mobile phone use is biased depending on age. This bias cannot be removed unless the shift parameter \(m\) is known. It can be shown that this bias is always towards the null.

There is another problem related to the development of mobile phone technology. As the figures in Table 3 demonstrate, almost all analogue phone users have later used a 2G or 3G phone and likewise 3G phone users have previously used 2G and/or analogue phones. Cordless phones have mostly been used concomitantly with mobile phones. Hence the analyses of amount and duration of use of these types of phones are not independent and the analyses presented are therefore misleading. For hours of use, which is additive, a multivariate approach would be possible \((\beta_{\text{analogue}}\cdot d_{\text{analogue}}+\beta_{2G}\cdot d_{2G}+\beta_{3G}\cdot d_{3G}+\beta_{\text{DECT}}\cdot d_{\text{DECT}}\), with \(d_x\) hours of use of phone type \(x\)). But years of use (‘latency’) is not additive due to overlapping periods of use (especially of mobile and cordless phones) and hence cannot be modeled in the same way. However, in separate analyses of the different phone types years of use of any mobile or cordless phone prior to using the respective type can be used as a covariate.

Page 11, 1st paragraph: SEI has been categorized into 4 groups. It is unclear whether ‘no work’ indicates unemployment, retirement, living on returns etc. It can thus indicate a very high or very low SEI. Clarify!
Page 11, 2nd paragraph: Analysis of tumor volume is not a very good idea without referring to the location. Meningiomas grow to a size that depends on the location. If pressure of the tumor induces symptoms (e.g. seizures) it might soon be detected and at a smaller volume than in areas where symptoms might easily remain unnoticed or not being related to a tumor for a long time (e.g. headaches). It has also to be noted that if mobile phone use increases tumor growth rate this will not be associated with a larger volume but with earlier diagnosis. However, it is possible that mobile phone use increases the area occupied by the tumor which would not necessarily result in an earlier diagnosis. Therefore, I suggest adding an analysis of the tumor area (i.e. omitting the third axis).

Page 13, 2nd paragraph: In the legend to Table 4 it is stated that ipsilateral was assigned if >50% of the time the phone was held to the side where the tumor occurred while in the methods section it is stated the both side users were included among ipsilateral users (as would be reasonable). It seems, comparing figures for ‘All’ that both side users were omitted. I suggest including them among ipsilateral users as stated in the methods section. Furthermore, due to a possible effect of symptoms on side of use it would be important to clarify whether change of the side of use was addressed in the questionnaire. I also suggest to do the laterality analysis only for latencies above 5 years to overcome this problem (if laterality was specified separately for the current and earlier use).

Page 14, 3rd paragraph: The smaller tumor volume in wireless phone users could be due to an awareness bias or a consequence of the different tumor locations. Meningioma in the temporal lobe are often associated with memory loss and also with problem of coordination that are quite distinct and often lead to an early diagnosis with volumes of 10 cm³ or less. Therefore, as mentioned above location must be considered.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests