# PEER REVIEW HISTORY

## ARTICLE DETAILS

| TITLE (PROVISIONAL) | Mobile phone use and incidence of brain tumour histological types, grading or anatomical location: A population-based ecological study |
|---|---|
| AUTHORS | Karipidis, Ken; Elwood, JM; Benke, Geza; Sanagou, Masoumeh; Tjong, Lydiawati; Croft, Rodney |

## VERSION 1 – REVIEW

| REVIEWER | Simon Chapman<br>School of Public Health, University of Sydney, Australia |
|---|---|
| REVIEW RETURNED | 06-Jun-2018 |

| GENERAL COMMENTS | This is an excellent and very important paper that will deservedly receive global attention. It adds considerable value to our 2016 highly publicised paper (Altmetric score:901) in Cancer Epidemiology by testing observed v expected incidence data on a range of RRs and latency periods; by considering (as far has been possible) all v heavy v regular mobile phone users; histological types; and the data relevant to the hypothesis that apparent increases in the brain cancer incidence have been associated with the uptake of CT & MRI diagnostics.<br><br>In addressing each of these variables, the main "yes, but.." objections of intransigent opponents of mobile phones and RFR phobics have been anticipated and the debate should move to a higher standard.<br><br>The reclassification described for cases with unspecified grade and location is defensible.<br><br>I make only minor suggestions:<br><br>Page 4: ideally, you should reference the claim that the brain receives higher RFR exposure than other body parts. Some will argue that areas like chests, thighs and groins adjacent to pockets where cell phones are often carried get considerable exposure Line 16, same page – suggest you add "very large" or "great" in front of "majority" – call phone use is all but universal today.<br><br>I think it would help readers if you noted the year when mobile telephony first commenced in Australia. You provide data from 1987, but unless I missed it, don't actually say when it started. |
|---|---|

| REVIEWER | Yasuto Sato<br>Tokyo Women's Medical University, School of Medicine, Department of Public Health, Japan |
|---|---|

| REVIEW RETURNED | 09-Jul-2018 |

| GENERAL COMMENTS | Australia. In addition, this study estimates annual percent change of brain tumor incidence when assuming the risk of mobile phone use under some conditions.

This paper is well written and I think that no major change is necessary. As a minor point, the following can be considered.

The data used in this study is the data from cancer registration in Australia. Although the mandatory cancer registration started from 1982, is registration accuracy sufficient even in the 1980s when registration was started? If the data has a limit point, you should mention the limit in the discussion.

In the analysis the period is divided in three parts (1982-1992, 1993-2002, 2003-2013). Have you analyzed throughout the whole period for 30 years? Since the observation points increases, I think that a significant difference is observed. If you conducted an analysis throughout the whole period for 30 years, I think it would be better to add that information.

Page 7 line 27, and page 19 line 5
1982-1982
The year is incorrect. |

| REVIEWER | Fabbro-Peray Pascale
Nimes University Hospital; Montpellier University, France |
| REVIEW RETURNED | 17-Jul-2018 |

| GENERAL COMMENTS | 1 Is the research question or study objective clearly defined? Complete the objective to: "We examined the incidence time trends of brain tumour in Australia for three distinct time-periods to ascertain the influence of improved diagnostic technologies and increase in mobile phone use on the incidence of brain tumours"

2. Is the abstract accurate, balanced and complete?
Setting: add "national Australian incidence registration…
Replace "Participants" with "Population" in the abstract and define geographical location (nb of brain tumors and target population)
3. Is the study design appropriate to answer the research question?
This is an ecological observational study, not based on individual data thus it is not possible to account for confounding factors. This study cannot provide a high level of evidence but the design is appropriate to define global trends.
4. Are the methods described sufficiently to allow the study to be repeated?
Add a section: "mobile phone use data sources" before "Statistical analysis of observed incidence" and extract corresponding information from "Statistical analysis of predicted incidence".
7. If statistics are used are they appropriate and described fully?
In the section "Statistical analysis of observed incidence", please justify the choice of a Poisson regression model (assumptions, etc.)

In the section "Statistical analysis of predicted incidence", please explain the method to calculate confidence intervals and statistical significance of observed and expected incidence rates: Ulm (17) |

| | provided a method to calculate the confidence interval of a standardized mortality (or incidence) ratio, not incidence rates. |
| | 10. Are they presented clearly? |
| | Please indicate in the tables that observed incidence rates are age standardized |
| | Page 6 line 30, you say: "it was not possible to stratify prevalence of use by age and gender; thus an overall estimate of prevalence is provided across the 20-59 age range and for both males and females": in this case, how do you provide estimated incidence rates limited to 20-59 years, knowing that older and younger participants do not show the same mobile phone use behavior? |
| | Figure 3 is not very legible |
| | 11. Are the discussion and conclusions justified by the results |
| | Page 10, lines 37-43, it's not exact that there was an increase in the glioblastoma rates in the earlier periods: 1982- 1992, which saw increased use of CT and MRI |
| | Page 11, lines 10-12 "The results on anatomical location showed that there was a strong increase in gliomas located in the temporal and parietal lobes prior to the period of substantial mobile phone use, but not during it". It's not a "strong" increase because it's not statistically significant after redistribution of many unclassified tumors |
| | Please |
| | The originality of your study compared to that of Chapman, based on the same source data, is related to the longest latency considered. I find that you do not highlight this result, nor discuss it. |
| | Please, do it. |
| | 13. Is the supplementary reporting complete (e.g. trial registration; funding details; CONSORT, STROBE or PRISMA checklist)? |
| | Trial registration: not relevant |
| | Funding details: not relevant |
| | STROBE checklist reported but some items are not relevant for ecological studies |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer 1

1. "Page 4: ideally, you should reference the claim that the brain receives higher RFR exposure than other body parts. Some will argue that areas like chests, thighs and groins adjacent to pockets where cell phones are often carried get considerable exposure"

We have included a reference (Cardis et al, 2008) indicating that the brain receives higher RF exposure compared to the rest of the body when using a mobile phone against the head

2. "Line 16, same page – suggest you add "very large" or "great" in front of "majority" – call phone use is all but universal today."

We have included "great majority" as suggested.

3. "I think it would help readers if you noted the year when mobile telephony first commenced in Australia. You provide data from 1987, but unless I missed it, don't actually say when it started."

In the new section titled "Mobile Phone Use Data Sources" we now mention: "Data on the annual number of mobile phone accounts from 1987, when mobile telephony first commenced in Australia,…"

Reviewer 2

1. "The data used in this study is the data from cancer registration in Australia. Although the mandatory cancer registration started from 1982, is registration accuracy sufficient even in the 1980s when registration was started? If the data has a limit point, you should mention the limit in the discussion."

We have now included in the Discussion the following: "The accuracy of the Australian cancer registration system in the early periods when it began in the 80s is unknown for all the states and territories. In Northern Territory mandatory notification of cancer cases by pathology laboratories was introduced in 1991. Case ascertainment was found to be approximately 40% incomplete for the period 1981-1986 and approximately 10% incomplete for the period 1987-1990. However the Northern Territory makes up a very small proportion of Australia's population (~ 1%).(Condon et al, 2004) All Australian state and territory registries conform to the International Agency for Research on Cancer's criteria for population based cancer registration, are "A" rated and have their data published in the "Cancer Incidence in Five Continents" series. (Chapman, 2016; IARC, 2016)".

2. "In the analysis the period is divided in three parts (1982-1992, 1993-2002, 2003-2013). Have you analyzed throughout the whole period for 30 years? Since the observation points increases, I think that a significant difference is observed. If you conducted an analysis throughout the whole period for 30 years, I think it would be better to add that information."

We have now included results in the text looking at the entire observation period (1982-2013) and these are also now mentioned in the Discussion section.

3. "Page 7 line 27, and page 19 line 5, 1982-1982, the year is incorrect."

We have corrected the year in both instances.

Reviewer 3

1. "Complete the objective to: "We examined the incidence time trends of brain tumour in Australia for three distinct time-periods to ascertain the influence of improved diagnostic technologies and increase in mobile phone use on the incidence of brain tumours""

We have made the change in the abstract as suggested by the reviewer.

2. "Setting: add "national Australian incidence registration… Replace "Participants" with "Population" in the abstract and define geographical location (nb of brain tumors and target population)"

We have made the changes in the abstract as suggested by the reviewer.

3. "This is an ecological observational study, not based on individual data thus it is not possible to account for confounding factors. This study cannot provide a high level of evidence but the design is appropriate to define global trends."

In the second last paragraph of the Discussion section we have added: "Finally this is an ecological observational study, not based on individual data thus it is not possible to account for confounding factors. This study design is appropriate to define global trends."

4. Add a section: "mobile phone use data sources" before "Statistical analysis of observed incidence" and extract corresponding information from "Statistical analysis of predicted incidence".

We have made the change as suggested by the reviewer.

5. "In the section "Statistical analysis of observed incidence", please justify the choice of a Poisson regression model (assumptions, etc.)"

The following justification was added: "The incidence rates were low compared to the population at risk so the variability in the observed cases was assumed to follow a Poisson distribution (Jensen et al 1991). Analyses of incidence time trends were carried out using Poisson regression to estimate the annual percent change (APC) in the incidence,…"

6. "In the section "Statistical analysis of predicted incidence", please explain the method to calculate confidence intervals and statistical significance of observed and expected incidence rates: Ulm (17) provided a method to calculate the confidence interval of a standardized mortality (or incidence) ratio, not incidence rates."

Although Ulm (1990) provided a method to calculate the confidence interval of a standardized mortality (or incidence) ratio as pointed out by the reviewer, Ulm also describes how to obtain confidence intervals for incidence rates by relating the chi-square and Poisson distributions. We have revised the text to mention: "Confidence intervals and statistical significance of observed and expected incidence rates were calculated using Poisson confidence intervals as described in Ulm (1990)".

7. "Please indicate in the tables that observed incidence rates are age standardized"

We have now indicated in the tables that the observed incidence rates are age standardized as suggested by the reviewer.

8. "Page 6 line 30, you say: "it was not possible to stratify prevalence of use by age and gender; thus an overall estimate of prevalence is provided across the 20-59 age range and for both males and females": in this case, how do you provide estimated incidence rates limited to 20-59 years, knowing that older and younger participants do not show the same mobile phone use behavior?"

We have revised the text to read: "It was not possible to stratify prevalence of use by age or gender; thus an overall estimate of prevalence is provided equally for all ages across the 20-59 age range and for both males and females."

9. "Figure 3 is not very legible."

We have now split the figures to make them more legible into Figure 3 for a 10 year latency and Supplementary Figure B for 1, 5, 15 and 20 year latencies.

10. "Page 10, lines 37-43, it's not exact that there was an increase in the glioblastoma rates in the earlier periods: 1982- 1992, which saw increased use of CT and MRI."

We have corrected the sentence to read: "…there was an increase in the glioblastoma rates in the earlier periods: 1982-1992 (non-statistically significant increase), which saw increased use of CT and MRI…"

11. "Page 11, lines 10-12 "The results on anatomical location showed that there was a strong increase in gliomas located in the temporal and parietal lobes prior to the period of substantial mobile phone use, but not during it". It's not a "strong" increase because it's not statistically significant after redistribution of many unclassified tumors."

We have omitted the word "strong" so the sentence now reads: "The results on anatomical location showed that there was a increase in gliomas located…."

12. "The originality of your study compared to that of Chapman, based on the same source data, is related to the longest latency considered. I find that you do not highlight this result, nor discuss it."

We have highlighted the longer latency more in the Discussion as suggested by the reviewer. Specifically we have included the following: "We modelled predicted incidence rates for a variety of latency periods up to 20 years whereas previous studies only included latencies up to 10 years (Little et al, 2012; Chapman et al, 2016).

13. "STROBE checklist reported but some items are not relevant for ecological studies"

The STROBE checklist has been revised to indicate that this was an ecological study.

## VERSION 2 – REVIEW

| REVIEWER | Pascale FABBRO-PERAY<br>Nimes University Hospital, Montpellier University, France |
| --- | --- |
| REVIEW RETURNED | 04-Oct-2018 |

| GENERAL COMMENTS | The authors answered clearly to the issues raised.<br>I have no other comments and I am in favor of the publication of this study, which provides additional epidemiological data. |
| --- | --- |