

Journal Pre-proofs

Correspondence

Letter to the editor

Michael Kundi

PII: S0160-4120(24)00251-4

DOI: <https://doi.org/10.1016/j.envint.2024.108665>

Reference: EI 108665

To appear in: *Environment International*

Received Date: 4 March 2024

Accepted Date: 15 April 2024



Please cite this article as: M. Kundi, Letter to the editor, *Environment International* (2024), doi: <https://doi.org/10.1016/j.envint.2024.108665>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2024 The Author(s). Published by Elsevier Ltd.

Letter to the editor

Michael Kundi, Medical University Vienna, Center for Public Health, Vienna, Austria

Some have looked forward to the publication of the results of the COSMOS study on brain tumors, because the potential biases from retrospective investigations predominating the search for brain tumor risks of mobile phone use since the late 1990s were deemed unresolvable by further investigations of that type. Indeed, prospective cohort studies typically have the advantage of being not or less affected by differential exposure misclassification, recall and selection bias, and, as they proceed in the direction of the time arrow, results are more easily interpreted in terms of causation. However, results of the COSMOS study¹ published now in this journal are not of help for the risk assessment of mobile phone use and do not support the conclusions of the authors that their findings “suggest that the cumulative amount of mobile phone use is not associated with the risk of developing glioma, meningioma, or acoustic neuroma”.

First of all, the study can never be one that assesses the risk of developing (!) brain tumors because brain tumors have average latencies much longer than the median follow-up of 7.12 years (e.g. for glioma: from tinea capitis x-ray treatment studies 28 years², atomic bomb survivors 38 years³, or from population incidence estimates 22 years⁴). Virtually all participants that were diagnosed with a brain tumor during follow-up must have had the tumor already covertly growing at time of enrollment. Second, at the time of enrollment (between 2007 and 2012) participants had accumulated a certain amount of exposure to mobile phone frequencies that was used to stratify the sample; however, they have unlikely stopped usage at that time but accumulated further amounts that could have levelled off the differences at baseline.

But even if we take the duration of use that increases linearly during follow-up, the study has no chance to detect a relevant effect of mobile phone use. If we exclude the risk to develop a brain tumor as a potential aim of the COSMOS trial, what else can be an adverse effect of mobile phone use? Theoretically, three adverse effects may occur as a consequence of the exposure in individuals that covertly harbor a brain tumor: 1) exposure may lead to regrowth of a regressive or dormant tumor; 2) exposure may lead to higher malignancy of the tumor; and 3) exposure may increase the tumor growth rate. The first of these possibilities will (slightly) increase the incidence because such dormant or regressive tumors may never be detected without them restarting to grow. The second possibility will not increase the incidence at all but only shifts the distribution of brain tumor types to higher grades. The third one will lead to earlier diagnosis because the tumor will reach the size earlier when it is causing symptoms and is detectable. This is noticeable by a shift of the age-incidence function to younger age in the exposed compared to the non-exposed.

Malignant central nervous system (CNS) tumors display a special shape of the age-incidence function that has a peak in early childhood decreasing until about 20 years of life and then starts to increase exponentially until about 70 years levelling off afterwards and strongly declining at advanced age (see Fig.1).

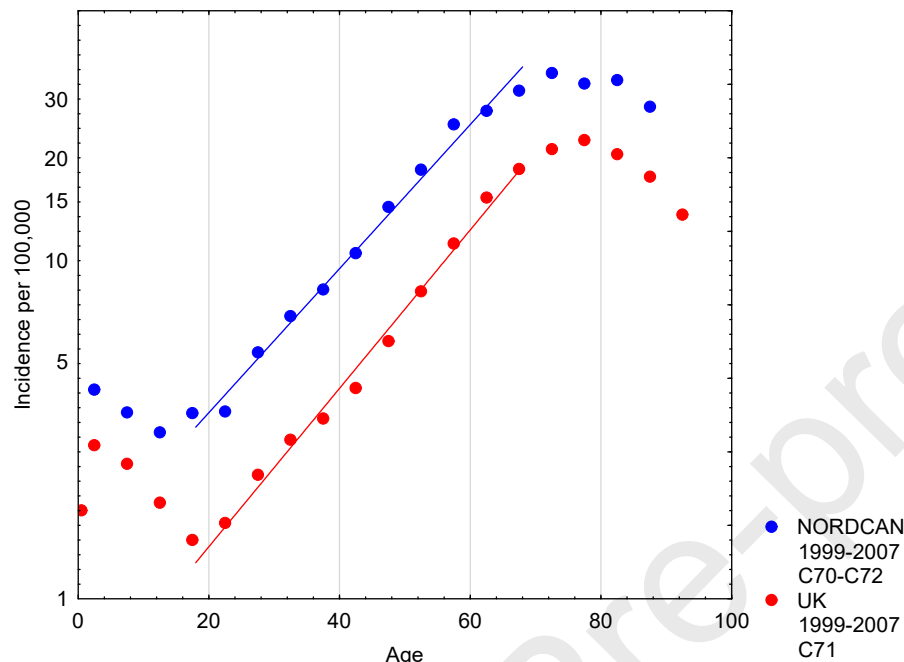


Fig 1. Age-log Incidence function for the Nordic Countries (<https://nordcan.iarc.fr/en/dataviz/>) and the UK (<https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/>). The lines show the linear relationship between 20 and 70 years of age.

The first type of an adverse effect of mobile phone use mentioned above can hardly be detected by a cohort study of the size of the COSMOS investigation because dormant or regressive tumors are likely very rare⁵. Since the second possibility does not change the incidence but the distribution of tumor types only, it may be detected by analysis of the grading, however, it seems that the number of cases (overall 149 glioma) is too small to allow such differentiation.

Finally, the third possibility, an increase of tumor growth rate due to mobile phone use, may in principle be detected by a cohort study. Since the age-incidence relationship in the age-range covered by the COSMOS study is of a simple type, it is easy to calculate an expected hazard ratio for the average follow-up duration of 7.12 years, taking into account that cases occurring during the first 6 months were excluded. Within the age range 20 to 70 years the age-incidence function is given by $\alpha \cdot \exp(\beta A)$, with A the age in years. β is for different countries between 0.04 and 0.06. For the Nordic countries (however including C70 and C72, because no separate data for C71 are publicly available) β was found to be 0.049, and for UK $\beta=0.054$ (C71, glioma). I calculated the hazard ratios for the average age at enrollment (47 years, obtained from the reported age distribution, Table 1¹) and a follow up of 7 years for the groups with 10-15 and >15 years of mobile phone use relative to the

reference category of 0-9 years use at entry by assuming arbitrarily that mobile phone use shifts the age-incidence function by 20% of the usage duration. Confidence intervals were calculated based on the person-years of follow-up.

As shown in Table 1, not only are the values obtained in the COSMOS study well within the confidence limits of the estimates but despite the assumed pronounced effect of a 20% shift of the age-incidence function the HRs are small and statistically far from being significant.

Table 1: Hazard ratios (HR) and 95% confidence intervals (CI) for the association between time since start of regular mobile phone use and glioma form the COSMOS cohort¹ and calculated assuming a shift of the age-incidence function of 20% of mobile phone use

Years of use	No of cases	HR (95% CI) COSMOS	HR (05% CI) Estimate
0-9	47	1 (Ref)	1 (Ref)
10-14	39	0.81 (0.51-1.28)	1.04 (0.66-1.65)
≥15	58	0.97 (0.62-1.52)	1.06 (0.68-1.66)

Hence we must conclude that COSMOS not only cannot find a risk for developing brain tumors but can also not find an effect on tumor growth since a reasonable shift of the age-incidence function leads to too small hazard ratios to become significant after such a short follow up.

References

1. Feychting M, Schüz J, Toledano MB, et al. Mobile phone use and brain tumour risk – COSMOS, a prospective cohort study. *Environment International* 2024;108552.
2. Sadetzki S, Chetrit A, Freedman L, Stovall M, Modan B, Novikov I. Long-term follow-up for brain tumor development after childhood exposure to ionizing radiation for tinea capitis. *Radiation research* 2005;163:424-32.
3. Brenner AV, Sugiyama H, Preston DL, et al. Radiation risk of central nervous system tumors in the Life Span Study of atomic bomb survivors, 1958–2009. *European journal of epidemiology* 2020;35:591-600.
4. Nadler DL, Zurbenko IG. Estimating cancer latency times using a Weibull model. *Advances in Epidemiology* 2014;2014.
5. Mohyuddin A, Vokurka EA, Evans DG, Ramsden RT, Jackson A. Is clinical growth index a reliable predictor of tumour growth in vestibular schwannomas? *Clinical otolaryngology and allied sciences* 2003;28:85-90.