Article:
Grell, K, Frederiksen, K, Schüz, J et al. (2016) The Intracranial Distribution of Gliomas in Relation to Exposure From Mobile Phones: Analyses From the INTERPHONE Study. American Journal of Epidemiology, 184 (11). pp. 818-828. ISSN: 0002-9262

https://doi.org/10.1093/aje/kww082

This is a pre-copyedited, author-produced version of an article accepted for publication in American Journal of Epidemiology following peer review. The version of record is "The Intracranial Distribution of Gliomas in Relation to Exposure From Mobile Phones: Analyses From the INTERPHONE Study. Grell K, Frederiksen K, Schüz J, Cardis E, Armstrong B, Siemiatycki J, Krewski DR, McBride ML, Johansen C, Auvinen A, Hours M, Blettner M, Sadetzki S, Lagorio S, Yamaguchi N, Woodward A, Tynes T, Feychting M, Fleming SJ, Swerdlow AJ, Andersen PK. Am J Epidemiol. 2016 Dec 1;184(11):818-828."
It is available online at: http://aje.oxfordjournals.org/content/184/11/818
Doi: 10.1093/aje/kww082

The spatial distribution of gliomas in relation to exposure from mobile phones: analyses from the Interphone Study

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When investigating the association between brain tumors and mobile phone use, accurate data on tumor position is essential, due to the highly localized absorption of energy in the human brain from the radiofrequency fields emitted. We used a point process model to investigate this association using data that included tumor localization from the multinational Interphone Study. Our main analysis included 792 regular mobile phone users diagnosed with a glioma between 2000–2004. Similar to earlier results, we found a statistically significant association between the spatial distribution of gliomas and the self-reported location of the phone. When accounting for preferred side not being exclusively used for all mobile phone calls, the results were similar. The association was independent of the cumulative call time or cumulative number of calls. We also observed a significant association between tumor distribution and total cumulative specific energy absorbed at the tumor's center of gravity, which had been calculated for a subset of the data. However, our model uses reported side of mobile phone use, which is potentially influenced by recall bias. The point process method provides an alternative to previously used epidemiological designs when including localization in the investigation of brain tumors and mobile phone use.

Abbreviations: CT, Computerized tomography; IARC, International Agency for Research on Cancer; MRI, Magnetic resonance image; RF, Radio frequency; RF-EMF, Radio frequency electromagnetic fields; SAR, Specific absorption rate; TCSE, Total cumulative specific energy; WHO, World Health Organization

Mobile phone use has increased dramatically within the last three decades in most countries (1). The extensive use of mobile phones has been followed by concerns about potential adverse health effects of exposure to radio frequency electromagnetic fields (RF-EMF) emitted by mobile phones (2). RF-EMF were classified as group 2B 'possibly carcinogenic to humans' in May 2011 by the International Agency for Research on Cancer (IARC) (3, 4). The IARC monograph's working group considered that the most informative epidemiological evidence came from the Swedish case-control studies by Hardell et al. (5) and the multinational case-control "Interphone" study coordinated by IARC (6). The latter is the largest investigation of mobile phone use and brain tumors to date. Interphone observed no increased glioma risk except for the decile with the highest reported cumulative call-time (>1640 hours) and with uncertain interpretation. The national publications on the Interphone data (7–13) and other studies on the association between RF radiation from mobile phones and brain tumors (14–23) have shown mixed results. When interpreting these findings, the timing of the study, the exposure variables of relevance, and methodological limitations have to be considered (24, 25).

The absorption of energy from RF-EMF in human tissue greatly depends on distance from the source in addition to factors such as frequency band, network characteristics, and conditions of use (26). Consequently, increased occurrence of tumors in the part of the brain closest to the phone would be expected if there were a causal association. Analyses of all brain tumors together without localization are likely to dilute a risk if present, hence it is crucial to include localization. Some studies divided the participants into ipsilateral phone users (participants reporting preferential use of the phone on the same side of the head as the tumor was localized) and contralateral phone users (the opposite) (6, 9–12, 16, 20–22). Others investigated the risk of brain tumors separately in the different anatomical lobes of the brain (6, 12, 14, 16, 19, 21). Some studies estimated the distance between the brain tumor and the mobile phone and divided cases into those close to the phone where most energy from RF-EMF is absorbed versus further away (27, 28). Additionally,

both the specific absorption rate of energy (SAR) inside the tumor (29) and the total cumulative specific energy (TCSE) for each tumor (30) have been estimated for use as exposure measures.

Our aim is to use the three-dimensional point process model described in Grell et al. (31) to analyze the Interphone localization data for glioma and thereby further investigate the association between glioma and mobile phone use. A case-only approach removes possible differential bias between cases and controls, and the specific tumor localizations collected in the Interphone study allow detailed analysis of spatial relations. Moreover, we added a mixing proportion to our model to take into account that self-reported preferred side of use did not mean exclusive use on that side.

METHODS

The Interphone study included participants from 13 countries (Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, and the United Kingdom) and cases were between 30 and 59 years of age when diagnosed with a first primary glioma, meningioma or acoustic neuroma during study periods of 2–4 years between 2000 and 2004. The study has been described in detail elsewhere (32). We included only gliomas in our analyses as their putative origin is less spatially confined compared to those of meningiomas and acoustic neuromas. The Interphone data comprise 2700 glioma cases and tumor localization was performed by neuroradiologists on 1530 of these cases. The localization could not be determined for all cases due to difficulties in retrieving appropriate scans. The computer program GridMaster was created specifically for recording localizations in the Interphone study and consisted of a three-dimensional grid map of the human head and brain made up of 1 cm cubes (voxels) (33). Neuroradiologists recorded the tumor contours and their best estimate of the tumor origin in GridMaster using radiological images (preferably MRI, otherwise CT) when available (92.2%) or radiology reports otherwise (7.8%); hence, they scaled each brain to match the GridMaster

brain. Of the 1530 tumors with localization data, 906 had a single voxel marked as the putative origin, 383 had no putative origin marked, and 241 had several voxels marked as the putative origin.

Detailed information on past mobile phone use was collected by interview, including number of calls, duration of calls, use of a hands-free device, preferred side of the head for mobile phone use, and time since start of use. A regular phone user was defined as a person who made at least one call per week for a period of 6 months or more. Among the 1530 glioma cases with recorded localization, 933 were regular phone users. The 597 non-regular phone users and non-users were defined as not exposed and are not included in our analyses. The lifetime cumulative call time and number of calls excluding use with hands-free devices were calculated in the Interphone study (32, 34). Absorbed RF energy is widely used as a quantity of RF exposure in tissue and the TCSE was calculated based on an algorithm which included, among other things, self-reported call time, laterality of use, hands-free devices, frequency band, communication system, phone class, and network characteristics (35) at each location in the GridMaster brain for the 372 Interphone study subjects with tumor localization from five countries (Australia, Canada, France, Israel, and New Zealand).

The Interphone interview had a question about which side of the head mobile phones were generally used with 'generally' meaning more than 50% of the time. Of the 933 regular phone users 265 (28.4%) reported left side, 527 (56.5%) reported right side, 110 (11.8%) reported both sides and for the remaining 31 (3.3%) the preferred side was unknown.

All diagnoses were histologically confirmed or based on unequivocal diagnostic imaging. From the morphology codes the tumors were assigned a grade as defined by WHO (36) but this was only possible for 880 (94.3%) of the regular phone users.

Exposure localization. The ear canals were fully contained within 48 voxels on each side of the GridMaster head and we defined the location of the exposure source as the geometric midpoint of the outer area of these voxels. We will refer to this point as the ear. For the

GridMaster head, the nearest brain tissue is 15 mm and the midline of the brain is 85 mm in horizontal distance from the ear. We assumed that the energy was emitted at the ear on the side of the head where the mobile phone was self-reported as generally used.

Tumor localization. We condensed the tumor localization for each of the 792 regular mobile phone users with self-reported preferred side into a single point. Ideally, this point would represent the origin of the tumor. However, a glioma can grow diffusely and does not necessarily form a single, consolidated mass. Actually, 36 of the 1530 tumors comprised more than one patch of contiguous (i.e., sharing either a vertex, edge or face) voxels. We reviewed a plot of these tumors and decided to include them with all tumor voxels when calculating a tumor central point. We calculated the tumor localization point as the 'center of gravity', which has previously been used in analyses of Interphone data (30). It is the midpoint of the voxel at the shortest distance from the other voxels in the tumor. In the 906 cases with a single voxel marked by the neuroradiologists as the putative origin, the latter had a mean distance of 4.1 mm from the center of gravity (median 0 mm, 75th centile 10.0 mm, maximum 51 mm). We also calculated the geometric midpoint of the tumor as an alternative to the center of gravity. The results were similar, see the Web Appendix.

Statistical analyses

The main point process analysis included all 792 subjects with a self-reported preferred side of use. Each tumor was identified with a single reference location $\mathbf{x} = (x_1, x_2, x_3)$ chosen as the gravity center of the whole tumor. The ears were identified with locations $\mathbf{x}_L$ and $\mathbf{x}_R$. We assume the spatial distribution of tumors in the two brain halves to be symmetrical and that the susceptibility of the brain tissue is uniform across each hemisphere.

The point process model is described in further detail in Grell et al. (31). Briefly, we assumed that the left-sided users's and right-sided users's centers of gravity form independent Poisson processes with the intensities

$$\lambda_L(\mathbf{x}) = \lambda_0(\mathbf{x}) g(\mathbf{x} - \mathbf{x}_L, z; \boldsymbol{\alpha}) \text{ and } \lambda_R(\mathbf{x}) = \rho \lambda_0(\mathbf{x}) g(\mathbf{x} - \mathbf{x}_R, z; \boldsymbol{\alpha}) \quad (1)$$

where ρ is a nuisance parameter related to the relative number of left-sided and right-sided users and the baseline intensity $\lambda_0(\mathbf{x})$ reflects the intensity for non-users. The function g describes the distance relation between tumor and preferred ear. We modeled g as a piecewise constant decreasing function of the distance in millimeters $d_L = ||\mathbf{x} - \mathbf{x}_L||$

$$g(d_L; \boldsymbol{\alpha}) = \begin{cases} \alpha_1 & if \quad 0 < d_L \leq 55 \\ \alpha_2 & if \quad 55 < d_L \leq 75 \\ \alpha_3 & if \quad 75 < d_L \leq 95 \\ \alpha_4 & if \quad 95 < d_L \leq 115 \\ 1 & if \quad d_L > 115 \end{cases} \tag{2}$$

with the added constraint $\alpha_1 \geq \alpha_2 \geq \alpha_3 \geq \alpha_4 \geq 1$ to ensure a decreasing distance relation. This was supported by the data subset analyzed in Grell et al. (31). The α-values represent the change in risk of observing a tumor within the given interval compared to the baseline intensity. We assume that a possible effect of mobile phone use will not affect the contralateral hemisphere; consequently, we have fixed $g = 1$ for distances larger than 115 mm. The null hypothesis ($g = 1$ or $\boldsymbol{\alpha} = 1$) is that occurrence of tumors across each hemisphere for both the left- and right-sided phone users is similar to the occurrence of tumors for persons not using mobile phones. If $\boldsymbol{\alpha}$ is significantly higher than 1, the tumor intensity is significantly higher for the users than the non-users. Note that the approach does not require the baseline intensity $\lambda_0(\mathbf{x})$ to be estimated (31); hence, the non-users are not included in the analyses even though they appear in the phrasing of the null hypothesis. The significance testing was done by simulating 1000 test statistics under the null hypothesis and calculating the empirical p-value (31). The reported confidence intervals are the Monte Carlo confidence intervals calculated by bootstrapping. The change points in equation 2 were chosen using the actual distances to preferred ear in the data (39.0–147.7 mm) such that the first four intervals were of approximately equal length starting from the shortest distance. Figure 1 is a naive two-dimensional representation of the GridMaster head and the intervals. The data are from a three-dimensional model so

α_1 covers part of a ball with a radius of 55 mm, α_2 a 20 mm layer outside that ball, etc.

We dichotomized each of the seven variables: sex, tumor grade, age, tumor size, time since start of mobile phone use, lifetime cumulative phone use, and lifetime cumulative number of calls using the median for the last four variables. Years of phone use and length and number of calls are related to the exposure, whereas tumor grade and size are related to the outcome, but they all entered the model similarly. We stratified our model for each of these variables z and estimated the eight parameters $\boldsymbol{\alpha}^j = (\alpha_1^j, \alpha_2^j, \alpha_3^j, \alpha_4^j)$, $j \in \{0, 1\}$ corresponding to the model with

$$g(d_L, z; \boldsymbol{\alpha}^0, \boldsymbol{\alpha}^1) = \begin{cases} \alpha_1^j & if \quad 0 < d_L \leq 55 \text{ and } z = j \\ \alpha_2^j & if \quad 55 < d_L \leq 75 \text{ and } z = j \\ \alpha_3^j & if \quad 75 < d_L \leq 95 \text{ and } z = j \\ \alpha_4^j & if \quad 95 < d_L \leq 115 \text{ and } z = j \\ 1 & if \quad d_L > 115 \text{ and } z = j. \end{cases} \tag{3}$$

We cannot estimate the absolute difference between $\boldsymbol{\alpha}^0$ and $\boldsymbol{\alpha}^1$. Consequently, we cannot assess whether the tumor intensity is higher for one level of the covariate than the other. However, the model enables us to investigate whether the covariate alters the distance relation such that the shape of the function g differs between the two covariate levels.

The preferred side of the head for phone use did not imply exclusive use at the preferred side; consequently, we redefined our model writing the intensities for left- and right-sided users as mixtures of the distance relation to the left ear and to the right ear:

$$\begin{aligned} \lambda_L(\mathbf{x}) &= \lambda_0(\mathbf{x}) \left(w_{pref} g(\mathbf{x} - \mathbf{x}_L, z; \boldsymbol{\alpha}) + w_{nonpref} g(\mathbf{x} - \mathbf{x}_R, z; \boldsymbol{\alpha}) \right), \\ \lambda_R(\mathbf{x}) &= \rho \lambda_0(\mathbf{x}) \left(w_{pref} g(\mathbf{x} - \mathbf{x}_R, z; \boldsymbol{\alpha}) + w_{nonpref} g(\mathbf{x} - \mathbf{x}_L, z; \boldsymbol{\alpha}) \right). \end{aligned}$$

We chose the mixing proportions $w_{pref} = 0.75$ and $w_{nonpref} = 0.25$.

We conducted several sensitivity analyses. We changed the exposure variable to the distance to the point with the highest SAR instead of the preferred ear. The former is 15 mm in horizontal distance from the latter and coincident with the location of the nearest

brain tissue. In this analysis, we redefined the change points in equation 2 by subtracting 15 mm from each of them. Moreover, we changed the exposure variable to the TCSE at the tumor point $\mathbf{x}$, $E(\mathbf{x})$, in a model with

$$g(E(\mathbf{x});\boldsymbol{\beta}) = \begin{cases} 1 & if \quad 0 < E(\mathbf{x}) \leq 43 \\ \beta_4 & if \quad 43 < E(\mathbf{x}) \leq 186 \\ \beta_3 & if \quad 186 < E(\mathbf{x}) \leq 771 \\ \beta_2 & if \quad 771 < E(\mathbf{x}) \leq 3514 \\ \beta_1 & if \quad E(\mathbf{x}) > 3514 \end{cases} \tag{4}$$

where the change points are the quintiles of TCSE. The interpretation of $\boldsymbol{\beta}$ is the same as for $\boldsymbol{\alpha}$: the change in risk of observing a tumor within the given interval compared to the (not estimated) risk in non-users. We estimated the model with and without the decreasing constraint $\beta_1 \geq \beta_2 \geq \beta_3 \geq \beta_4 \geq 1$. These analyses included the 324 cases with preferred laterality of the 372 cases with TCSE.

We estimated the model with smaller steps than in equation 2 and we estimated the standard model for the subsets used in previous case-only analyses: Denmark; Finland; Germany; Italy; Norway; Sweden; and UK (N=428 with preferred laterality of 515 in original paper) (28) and: Australia; Canada; France; Israel; and New Zealand (N=332 of 380) (30).

Because of the uncertainty in the assessment of tumor origin, we conducted the same analyses as in Grell et al. (31) with the same data subset but using the center of gravity to see whether the choice of either point was crucial for these results.

The analyses were carried out using R software (37).

RESULTS

Descriptive characteristics of the regular users with a self-reported side of use are presented in Table 1 and a flow chart is presented in Figure 2.

Figure 3 shows histograms of the distances from tumor center of gravity to closest ear for all regular users and the non-users with no marked difference between the two.

Table 2 shows the estimates and 95% confidence intervals for the model with piecewise constant decreasing distance relation (shown in Figure 4), with exposure variable 'point with highest SAR', and with mixing proportions $w_{pref} = 0.75$ and $w_{nonpref} = 0.25$. The hypothesis of no association with the mobile phone is rejected for all three models with $P < 0.01$. The estimates for the first two models are similar. For the model with mixing proportions, the estimates are higher but the confidence intervals are also wider.

Table 3 shows the results for the standard model with the dichotomized covariates included one at a time. Moreover, the P-value from the test of no difference in the distance relation for the two groups is included. The distance relation was unrelated to levels of sex, age, tumor grade, tumor size, years of mobile phone use and amount of mobile phone use, whether measured as cumulative call time or cumulative number of calls. The test of no association with the distance to mobile phone yielded $P < 0.01$ for each strata (not shown).

The results with TCSE instead of distance are shown in Table 4 and the relation concurs with the relation for distance with $P < 0.01$ when testing $g = 1$. The association between TCSE and tumor distribution is close to constant after the first interval with the highest TCSE.

In Table 5 the results from the sensitivity analysis comparing the center of gravity with the results from Grell et al. (31) are shown (reported with standard errors as (31)) and the estimates are similar for both types of tumor points. The results from further sensitivity analyses are found in the Web Appendix and are similar to those presented in Table 2. This includes the piecewise constant model with smaller intervals and the results for the subsamples from Larjavaara et al. (28) and Cardis et al. (30).

DISCUSSION

This is the first analysis that has modeled the spatial distribution of gliomas in relation to mobile phone use by using the exact localization data from the full Interphone study. Our results show that the three-dimensional distribution of gliomas within the brain is skewed towards the ear self-reported to be preferred for mobile phone use. This applies also when considering that the preferred side of the head was not used for all mobile phone calls by assuming all study participants used the preferred side for 75% and the non-preferred side for 25% of the calls. However, we did not find a difference in distance relation for different levels of lifelong cumulative phone use and for the persons who had used their mobile phone less than 200 hours there was still a relation with distance. Neither did we observe any difference in distance relation for age, sex, tumor grade, tumor size, time since start of mobile phone use, or cumulative number of phone calls. We found a significant association between tumor intensity and TCSE, though with lower estimates than for distance alone.

Our results concur with the observation of a statistically significant excess of gliomas on the self-reported side of mobile phone use (28). However, Larjavaara et al. (28) did not observe significantly higher odds for a short distance between glioma and mobile phone for cases than for speculars (a hypothetical control location). Contrary to our method, they considered exposure on the same side of the head as the glioma, irrespective of the reported preferred side of mobile phone use. This avoids potential recall bias but may attenuate any possible association. Our results contrast with the finding in another study of an increase of gliomas for persons with the highest level of TCSE applied only for mobile phone use more than 7 years (30). Restricting our analysis to the subsets used in the two studies did not markedly change our results.

Studies on the SAR distribution in the human head have shown that the energy absorption drops considerably after 5 cm with almost all energy being absorbed within the brain hemisphere closest to the phone (26). Our data had only a small proportion of tumor points closer than 5 cm to the ear which could be related to our use of the three-dimensional

gravity point of the glioma. This point has limitations for large, irregular shaped tumors close to the edge of the brain because these may grow towards the center of the brain resulting in the gravity point being further from the edge and hence the exposure. For most of the models, $\hat{\alpha}_4$ is close to 1 indicating that the size of association with the phone use is small further than 95 mm away from the phone, in agreement with almost all energy being absorbed within the ipsilateral hemisphere.

The strengths of this paper include the large number of cases with localization data and that the localization is used as a continuous measure. Moreover, because our analysis includes only cases, the findings are not affected by differential bias between cases and controls (38–41). A limitation is uncertainty about the tumor origin and that the self-reported side of use may be influenced by systematic and recall bias. Our method necessitates inclusion of side of mobile phone use. Frequently, cases were aware where their tumor was located when asked about preferred side of the head for mobile phone use, which could have caused a systematic over-reporting of ipsilateral use. A recent study with healthy volunteers reported considerable disagreement between self-reported preferred side for mobile phone use with a 10–12 months recall, and that measured by a software modified phone (42). This indicates that our data on self-reported side of phone use might be influenced by random recall bias. Moreover, the cases reporting a preferred side might not have used the phone exclusively on that side but occasionally used it on the non-preferred side. We dealt with the latter by introducing mixing proportions with 75% of use assigned to the preferred side and 25% assigned to the not preferred side. This could not eliminate systematic recall bias but it could ameliorate the parameter estimates by not assuming preferred use to be exclusive use.

Figure 3 shows that the distance to closest ear is similarly distributed for regular users and for non-users, indicating that mobile phone use does not overall result in tumours being located closer to the ears. Together with the no relation with phone use, this suggests that our finding could be a result of recall bias.

The main exposure measure in our model was distance between tumor and phone but this is a simplification because the spatial distribution of SAR within the head also depends on the frequency band and other characteristics (26, 43). Further, the exposure source was modelled as a single point, though in reality it is mainly the antenna of the phone, which is frequently embedded in the body of the phone. We modeled the distance relation as a simple piecewise constant function and it would have been preferable to use also a model with a continuous distance function, but the data did not support this (31). The model relies on the assumptions that the tumor baseline intensity in the two brain halves is symmetrical and is uniform across each hemisphere. This is a simplification because gliomas occur more frequently in some lobes than others (44) and the susceptibility of the brain tissue is very likely not completely uniform across each hemisphere because the cells that gliomas arise from are not uniformly distributed in the brain (45).

Taken together, our results suggest that ever using a mobile phone regularly is associated with glioma localization in the sense that more gliomas occurred closer to the ear on the side of the head where the mobile phone was self-reported to be used the most; however, this trend was not related to amount of mobile phone use making it less likely that the association observed is caused by a relation between mobile phone use and cancer risk. We cannot draw firm conclusions about cause and effect, but our approach shows several strengths compared with traditional epidemiological approaches though the results may be affected by recall bias in reported side of phone use. Nevertheless, it provides an alternative in future mobile phone related research.

ACKNOWLEDGMENTS

This work was supported by funding from the Danish Cancer Society's scientific committee (KBVU), grant R20-A897. The Interphone study was supported by funding from the European Fifth Framework Program, 'Quality of Life and Management of Living Resources' (contract QLK4-CT-1999901563) and the International Union Against Cancer (UICC).

The UICC received funds for this purpose from the Mobile Manufacturers' Forum and GSM Association. Provision of funds to the Interphone study investigators via the UICC was governed by agreements that guaranteed Interphone's complete scientific independence. The terms of these agreements are publicly available at http://www.iarc.fr/en/research-groups/RAD/RCAd.html. The Australian centre was supported by the Australian National Health and Medical Research Council (EME Grant 219129) with funds originally derived from mobile phone service licence fees; Bruce Armstrong was supported by a University of Sydney Medical Foundation Program Grant and Julianne Brown by an Australian Postgraduate Award. The Cancer Council NSW and The Cancer Council Victoria provided most of the infrastructure for the project in Australia. The Canada-Montréal study was primarily funded by a grant from the Canadian Institutes of Health Research (project MOP-42525). Additionally, Dr Siemiatycki's research team was partly funded by the Canada Research Chair programme and by the Guzzo-CRS Chair in Environment and Cancer. Dr Parent had a salary award from the Fonds de la Recherche en Santé du Québec. The other Canadian centres were supported by a university-industry partnership grant from the Canadian Institutes of Health Research (CIHR), the latter including partial support from the Canadian Wireless Telecommunications Association. The CIHR university-industry partnerships program also includes provisions that ensure complete scientific independence of the investigators. D. Krewski is the NSERC/SSHRC/McLaughlin Chair in Population Health Risk Assessment at the University of Ottawa. The Danish centre was supported by the Danish Cancer Society and the Finnish centre by the Emil Aaltonen Foundation and the Academy of Finland. Additional funding for the study in France was provided by l'Association pour la Recherche sur le Cancer (ARC)(Contrat No 5142) and three network operators (Orange, SFR, Bouygues Télécom). The funds provided by the operators represented 5% of the total cost of the French study and were governed by contracts guaranteeing the complete scientific independence of the investigators. In Germany, additional funds were received from the German Mobile Phone Research Program

(Deutsches Mobilfunkforschungsprogramm) of the German Federal Ministry for the Environment, Nuclear Safety, and Nature Protection; the Ministry for the Environment and Traffic of the state of Baden-Württemberg; the Ministry for the Environment of the state of North Rhine-Westphalia; the MAIFOR Program (Mainzer Forschungsforderungsprogramm) of the University of Mainz. The study conducted in Japan was fully funded by the Ministry of Internal Affairs and Communications of Japan. In New Zealand, funding was provided by the Health Research Council, Hawkes Bay Medical Research Foundation, the Wellington Medical Research Foundation, the Waikato Medical Research Foundation and the Cancer Society of New Zealand. The Swedish centre was also supported by the Swedish Research Council and the Swedish Cancer Society. Additional funding for the UK North and UK South studies was received from the Mobile Telecommunications, Health and Research (MTHR) program, and the UK North study received funding from the Health and Safety Executive, the Department of Health, the UK Network Operators (O2, Orange, T-Mobile, Vodafone, '3') and the Scottish Executive. The Institute of Cancer Research acknowledges National Health Service (NHS) funding to the NIHR Biomedical Research Centre.

The authors thank Mrs. Monika Moissonier (IARC) for extracting the data used for this work from the Interphone database, and Mr. Jordi Figuerola (CREAL) for extracting the TCSE data for five Interphone countries. The authors also thank the IARC team coordinating the study during its fieldwork: Dr Isabelle Deltour, Dr Lesley Richardson, Dr Martine Vrijheid, Mrs. Monika Moissonnier, Mrs. Emilie Combalot and Mrs. Helen Tardy. Moreover, the authors thank Dr Johanna Vompras, who programmed the GridMaster program under the supervision of the German Interphone team and the IARC coordinators, and all neuroradiologists of the centers for mapping the gliomas in the GridMaster. Finally, the authors thank all the neuroradiologists from the study centers who mapped the tumours in the Gridmaster as well as Dr Graham Giles, Dr Julianne Brown, Dr Marie-Élise Parent, Dr Louise Nadon, Dr Helle Collatz Christensen, Dr Päivi Kurttio, Dr Anna Lahkola,

Dr Tiina Salminen, Dr Marlène Bernard, Dr Lucile Montestrucq, Dr Juliet Britton, Dr Gabriele Berg-Beckhoff, Dr Birgitte Schlehofer, Dr Angela Chetrit, Dr Avital Jarus-Hakak, Dr Ivano Iavarone, Dr Toru Takebayashi, Dr Angus Cook, Dr Neil Pearce, Dr Karl G Blaasaas, Dr Lars Klaeboe, Dr Stefan Lönn, Dr Anders Ahlbom, Dr Patricia A McKinney, Dr Sarah J Hepworth, Dr Kenneth R Muir, Dr Minouk J Schoemaker, and Dr Juliet Britton.

Conflicts of interest: none declared.

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Table 1: Characteristics of the Regular Mobile Phone Users With Preferred Side of Use From the Interphone Grid Data, N=792

	No.	%
Sex		
Male	508	64.1
female	284	35.9
Age, years		
30–39	224	28.3
40–49	257	32.4
50–59	311	39.3
Grade		
I	16	2.0
II	315	39.8
III	114	14.4
IV	303	38.3
missing	44	5.6
Tumor size, no. of voxels		
1–10	240	30.3
11–20	201	25.4
21–30	138	17.4
31–187	213	26.9
Time since start of use, years		
1–3.99	273	34.5
4–6.99	253	31.9
7–9.99	145	19.3
10–22.8	121	15.3
Cum. phone use, hours		
0–29.9	207	26.1
30–149.9	191	24.1
150–649.9	196	24.7
650–211,000	198	25.0
Cum. number of calls		
0–999	235	29.7
1,000–2,999	145	18.3
3,000–11,900	209	26.4
12,000–506,000	203	25.6

Table 2: Estimates and 95% Confidence Intervals for the Interphone Grid Data With Preferred Side of use, N=792. The $\hat{\alpha}$s Represent the Elevation in Risk of Observing a Tumor Within a Given Interval Compared to the Assumed Baseline Risk. The Intervals are Distances From the Ear Preferred for Mobile Phone Use. The Numbers are Number of Tumors Within a Given Interval.

	0–55 mm			55–75 mm			75–95 mm			95–115 mm			>115 mm		
Model	No.	$\hat{\alpha}_1$	95% CI	No.	$\hat{\alpha}_2$	95% CI	No.	$\hat{\alpha}_3$	95% CI	No.	$\hat{\alpha}_4$	95% CI	No.	-	95% CI
Standard	45	2.37	1.66, 4.56	159	1.75	1.38, 2.34	220	1.42	1.14, 1.81	166	1.10	1.00, 1.49	202	1.00	-
Highest SAR[a]	25	2.62	1.70, 6.33	150	1.92	1.47, 2.60	210	1.38	1.11, 1.80	173	1.10	1.00, 1.45	234	1.00	-
Mixing prop. (0.75/0.25)[b]	45	9.66	2.84, 39.3	159	3.50	1.96, 8.78	220	2.09	1.36, 3.76	166	1.28	1.00, 2.52	202	1.00	-

Abbreviations: CI, confidence interval.

[a] The intervals are: 0–40 mm, 40–60 mm, 60–80 mm, 80–100 mm, >100 mm.

Table 3: Estimates and 95% Confidence Intervals for the Stratified Models for the Interphone Grid Data With Preferred Side of Use. The $\hat{\alpha}$s Represent the Elevation in Risk of Observing a Tumor Within a Given Interval Compared to the Assumed Baseline Risk. The Model Cannot Estimate Absolute Differences in α-values Between Covariate-groups but the Test can Detect if the Distance Relation Differs Between the two Groups. The Intervals are Distances From the Ear Preferred for Mobile Phone Use. The Numbers are Number of Tumors Within the Covariate Group.

		0–55 mm		55–75 mm		75–95 mm		95–115 mm		>115 mm		
Covariate	No.	$\hat{\alpha}_1$	95% CI	$\hat{\alpha}_2$	95% CI	$\hat{\alpha}_3$	95% CI	$\hat{\alpha}_4$	95% CI	-	95% CI	P value[a]
Female	284	1.85	1.41, 4.04	1.85	1.36, 2.96	1.71	1.17, 2.44	1.00	1.00, 1.41	1.00	-	0.26
Male	508	3.04	1.63, 7.54	1.68	1.26, 2.33	1.31	1.00, 1.78	1.21	1.00, 1.64	1.00	-	
Age $\leq$ 46 years	379	1.86	1.45, 4.37	1.86	1.38, 2.76	1.54	1.10, 2.09	1.00	1.00, 1.34	1.00	-	0.39
Age $>$ 46 years	413	3.06	1.63, 7.29	1.69	1.25, 2.51	1.40	1.03, 1.98	1.36	1.00, 1.91	1.00	-	
Grade 1 and 2	331	2.59	1.45, 6.61	1.82	1.25, 2.75	1.15	1.00, 1.76	1.15	1.00, 1.68	1.00	-	0.54
Grade 3 and 4	417	2.16	1.46, 5.01	1.64	1.34, 2.39	1.64	1.23, 2.13	1.08	1.00, 1.62	1.00	-	
Tumor size $\leq$ 18 cm^3	401	1.96	1.51, 3.66	1.96	1.48, 2.97	1.70	1.21, 2.28	1.25	1.00, 1.85	1.00	-	0.19
Tumor size $>$ 18 cm^3	391	4.09	1.90, 12.0	1.51	1.17, 2.25	1.23	1.00, 1.64	1.00	1.00, 1.40	1.00	-	
Years of use $<$ 6 years	461	2.02	1.31, 4.28	1.39	1.13, 1.99	1.39	1.06, 1.81	1.00	1.00, 1.43	1.00	-	0.38
Years of use $\geq$ 6 years	331	3.27	1.92, 11.3	2.32	1.57, 3.57	1.41	1.00, 2.12	1.24	1.00, 1.85	1.00	-	
Cum. phone use $<$ 200 hours	435	1.57	1.29, 3.36	1.57	1.27, 2.22	1.48	1.10, 1.95	1.07	1.00, 1.55	1.00	-	0.37
Cum. phone use $\geq$ 200 hours	357	4.06	2.03, 11.6	1.94	1.32, 3.02	1.34	1.00, 1.97	1.13	1.00, 1.71	1.00	-	
Cum. no. of calls $<$ 4,000	420	1.55	1.25, 3.42	1.44	1.19, 2.02	1.44	1.10, 1.84	1.00	1.00, 1.37	1.00	-	0.16
Cum. no. of calls $\geq$ 4,000	372	3.56	2.05, 9.88	2.26	1.51, 3.38	1.39	1.03, 2.08	1.29	1.00, 1.92	1.00	-	

Abbreviations: CI, confidence interval.

[a] Test of no difference in distance relation between levels of the covariate.

Table 4: Estimates and 95% Confidence Intervals for the Interphone Grid Data With Preferred Side of Use from Australia, Canada, France, Israel and New Zealand using Total Cumulative Specific Energy Instead of Distance, N=324. The $\hat{\beta}$s Represent the Elevation in Risk of Observing a Tumor Within a Given Interval Compared to the Assumed Baseline Risk. The Intervals are TCSE-values Calculated Using Distance to the Ear Preferred for Mobile Phone Use. The Numbers are Number of Tumors Within a Given Interval.

	>3514 J/kg			771–3514 J/kg			186–771 J/kg			43–186 J/kg			0–43 J/kg		
Model	No.	$\hat{\beta}_1$	95% CI	No.	$\hat{\beta}_2$	95% CI	No.	$\hat{\beta}_3$	95% CI	No.	$\hat{\beta}_4$	95% CI	No.	-	95% CI
Piec. constant	82	2.38	1.33, 5.03	57	1.03	0.58, 1.91	58	1.02	0.57, 1.79	66	1.10	0.66, 1.81	61	1.00	-
Decreasing[a]	82	2.43	1.65, 1.57	57	1.06	1.00, 1.96	58	1.06	1.00, 1.70	66	1.06	1.00, 1.64	61	1.00	-

[a] Constraint added to the piecewise constant model to ensure decreasing βs.

Table 5: Comparison of Tumor Points for the Interphone Grid Data With Single Voxel Origin Recorded by Neuroradiologists or Calculated Center of Gravity, N=478

	0–55 mm			55–75 mm			75–95 mm			95–115 mm			>115 mm		
Model	No.	$\hat{\alpha}_1$	SE	No.	$\hat{\alpha}_2$	SE	No.	$\hat{\alpha}_3$	SE	No.	$\hat{\alpha}_4$	SE	No.	-	SE
Origin point[a]	25	1.82	0.32	100	1.82	0.28	127	1.48	0.22	105	1.09	0.18	121	1.00	-
Gravity center	24	1.75	0.58	105	1.68	0.24	126	1.52	0.22	95	1.00	0.13	128	1.00	-

Abbreviations: SE, standard error.

[a] Result from Grell et al. (31)

Figure legends

Figure 1

Naive representation of the head with the intervals from the point process model. The radius of α_1 is 55 mm, of α_2 75 mm, of α_3 95 mm, and of α_4 115 mm; the short radius of the ellipse is 85 mm.

Figure 2

Study Subjects

Figure 3

A) Density Histogram for Distance to Closest Ear for all Regular Users, N=933. B) Distance to Closest Ear for all Non-users, N=597

Figure 4

Results from the model with piecewise constant decreasing distance relation for the Interphone Grid Data With Preferred Side of Use. Step function, $\hat{\alpha}$-values representing the elevation in risk of observing a tumor within a given interval compared to the assumed baseline risk; Vertical bars, 95% confidence intervals.

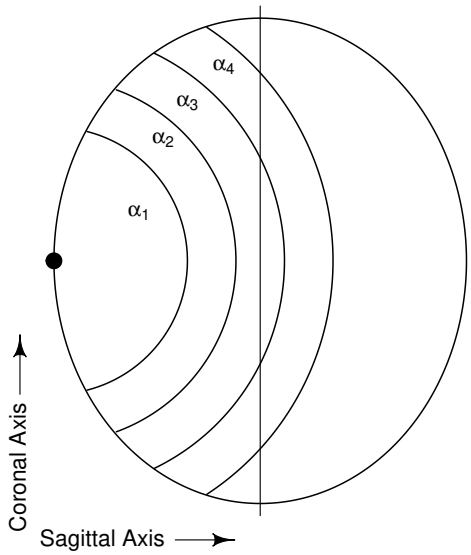

Figure 1

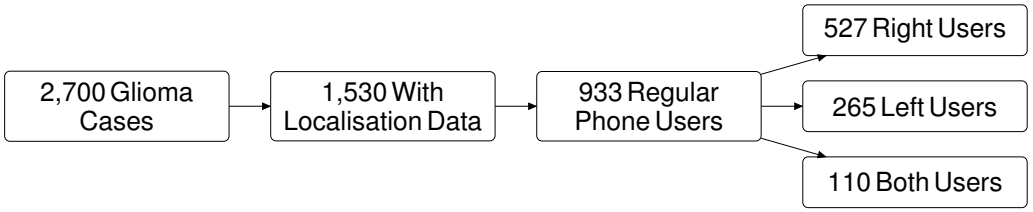

Figure 2

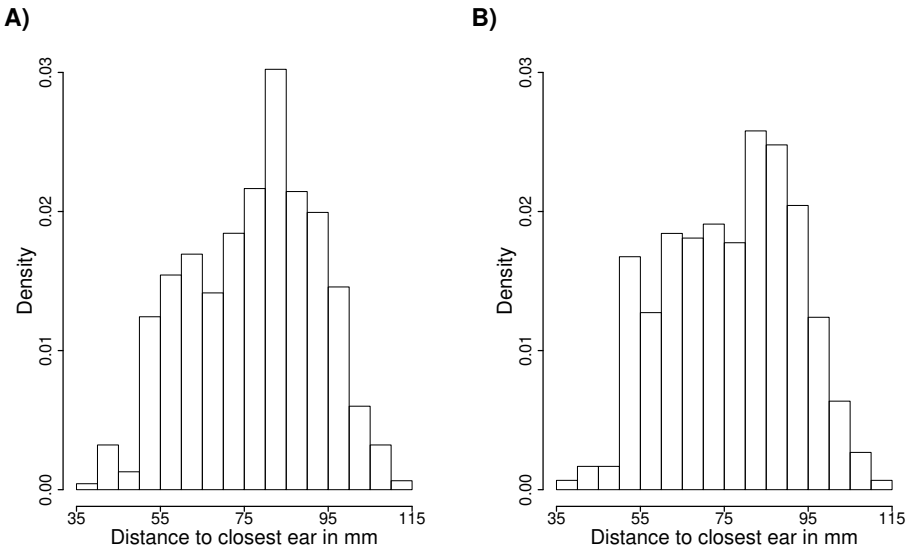

Figure 3

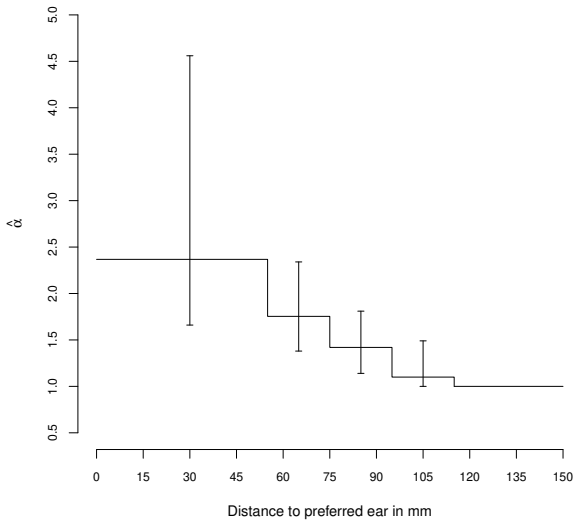

Figure 4

Web Appendix

EXTRA SENSITIVITY ANALYSES

Here follow the results from the extra sensitivity analyses mentioned but not shown in the article: in Table 6 the subsets in Cardis et al. 2011 (30) and Larjavaara et al. 2011 (28); in Table 7 the standard model with smaller intervals and thus 9 $\hat{\alpha}$-parameters instead of 4.

Table 6: Estimates and 95% Confidence Intervals for the standard model for the Interphone Grid Data With Preferred Side of Use. The $\hat{\alpha}$s Represent the Elevation in Risk of Observing a Tumor Within a Given Interval Compared to the Assumed Baseline Risk. The Intervals are Distances From the Ear Preferred for Mobile Phone Use.

	0–55 mm			55–75 mm			75–95 mm			95–115 mm			>115 mm		
Model	No.	$\hat{\alpha}_1$	95% CI	No.	$\hat{\alpha}_2$	95% CI	No.	$\hat{\alpha}_3$	95% CI	No.	$\hat{\alpha}_4$	95% CI	No.	-	95% CI
Cardis et al., N=332	18	1.87	1.34, 4.67	66	1.87	1.21, 2.73	96	1.19	1.00, 1.74	65	1.19	1.00, 1.67	87	1.00	-
Larjavaara et al. N=428	16	2.44	1.58, 5.86	78	1.73	1.40, 2.49	93	1.73	1.29, 2.24	99	1.04	1.00, 1.56	142	1.00	-

Abbreviations: CI, confidence interval.

Table 7: Estimates and 95% Confidence Intervals for the standard model with smaller intervals for the Interphone Grid Data With Preferred Side of Use, N=792. The $\hat{\alpha}$s Represent the Elevation in Risk of Observing a Tumor Within a Given Interval Compared to the Assumed Baseline Risk. The Intervals are Distances From the Ear Preferred for Mobile Phone Use.

	0–50 mm			50–60 mm			60–70 mm			70–80 mm			80–90 mm		
Model	No.	$\hat{\alpha}_1$	95% CI	No.	$\hat{\alpha}_2$	95% CI	No.	$\hat{\alpha}_3$	95% CI	No.	$\hat{\alpha}_4$	95% CI	No.	$\hat{\alpha}_5$	95% CI
Standard model	13	4.22	1.88, 29.2	69	1.86	1.50, 2.87	83	1.86	1.45, 2.65	81	1.47	1.23, 1.95	117	1.47	1.22, 1.95
	90–100 mm			100–110 mm			110–120 mm			120–130 mm			>130 mm		
Model	No.	$\hat{\alpha}_6$	95% CI	No.	$\hat{\alpha}_7$	95% CI	No.	$\hat{\alpha}_8$	95% CI	No.	$\hat{\alpha}_9$	95% CI	No.	-	95% CI
	111	1.47	1.20, 1.93	58	1.02	1.00, 1.64	102	1.00	1.00, 1.33	104	1.00	1.00, 1.31	54	1.00	-

Abbreviations: CI, confidence interval.

ALTERNATIVE TUMOR POINT: THE GEOMETRIC MIDPOINT

As an alternative to the tumor's center of gravity, we calculated also the geometric mean of each tumor. We compared the geometric midpoint and the single voxel marked by neuroradiologists as the origin and in these 906 subjects, the geometric midpoint was a mean distance of 5.4mm from the origin, with median 4.9, 75th centile 7.3mm and maximum 44mm. The medians of the distance from the ear point to the single voxel marked as the origin and from the ear point to the geometric midpoint differ less than 2mm. Using this geometric midpoint instead of the center of gravity does not change any of the results markedly. In Table 8 are shown the results from the standard model. This is similar to the corresponding result in Table 2 in the article. In Table 9 is shown a comparison of a result from Grell et al. (31) with the result using the same data subset but the geometric midpoint instead of the recorded origin. The two sets of estimated αs are similar.

Table 8: Estimates and 95% Confidence Intervals for the standard model for the Interphone Grid Data With Preferred Side of Use, N=792. The $\hat{\alpha}$s Represent the Elevation in Risk of Observing a Tumor Within a Given Interval Compared to the Assumed Baseline Risk. The Intervals are Distances From the Ear Preferred for Mobile Phone Use.

	0–55 mm			55–75 mm			75–95 mm			95–115 mm			>115 mm		
Model	No.	$\hat{\alpha}_1$	95% CI	No.	$\hat{\alpha}_2$	95% CI	No.	$\hat{\alpha}_3$	95% CI	No.	$\hat{\alpha}_4$	95% CI	No.	-	95% CI
Geometric mean	47	2.09	1.60, 3.80	159	1.88	1.48, 2.45	224	1.40	1.15, 1.81	153	1.04	1.00, 1.43	209	1.00	-

Abbreviations: CI, confidence interval.

Table 9: Comparison of Tumor Points for the Interphone Grid Data With Single Voxel Origin Recorded by Neuroradiologists or Calculated Geometric Midpoint, N=478

	0–55 mm			55–75 mm			75–95 mm			95–115 mm			>115 mm		
Tumor points	No.	$\hat{\alpha}_1$	SE	No.	$\hat{\alpha}_2$	SE	No.	$\hat{\alpha}_3$	SE	No.	$\hat{\alpha}_4$	SE	No.	-	SE
Origin point[a]	25	1.82	0.32	100	1.82	0.28	127	1.48	0.22	105	1.09	0.18	121	1.00	-
Geometric mean	24	1.70	0.56	105	1.70	0.30	126	1.70	0.30	95	1.00	0.23	128	1.00	-

Abbreviations: SE, standard error.

[a] Result from Grell et al. (31)