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

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Running Head: Intracranial Glioma Distribution and Mobile Phones

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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 Interphone Study (Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, UK). 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 intracranial 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 and cumulative number of calls. 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.

Interphone; glioma; mobile phones; radio frequency fields, intracranial distribution; spatial point pattern

Abbreviations: RF, radio frequency; RF-EMF, radio frequency electromagnetic fields; SAR, specific absorption rate; TCSE, total cumulative specific energy;

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 2011 in a monograph by the International Agency for Research on Cancer (IARC) (3, 4). The 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 (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 was 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 (phone used on the same side of the head as the tumor) 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 of 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 intracranial relations.

METHODS

The Interphone study included participants from 13 countries (Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, UK). 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 (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 of whom tumor localization was performed by neuroradiologists in 1530. 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 magnetic resonance imaging, otherwise computerized tomography) when available (92.2%) or radiology reports otherwise (7.8%), scaling 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 origin marked, and 241 had several voxels marked as the 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 (∼50% were interviewed within three months from diagnosis and ∼90% within a year). 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 (32, 34). Overall, the levels of use are low compared to today due to the period of data collection, 2000–2004, where mobile phones were less common. 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, 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 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 the World Health Organization (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 ('the ear') as the geometric midpoint of the outer area of these voxels. 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 (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 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 (Web Appendix 1).

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 tumor. The ears were identified with locations $\mathbf{x}_L$ and $\mathbf{x}_R$. We assumed the intracranial distribution of tumors in the two brain halves to be symmetrical and that the susceptibility of the brain tissue was 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' and right-sided users' centers of gravity form independent Poisson processes with intensities

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

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 (31). The α-values represent the change in risk of observing a tumor within the given interval compared to the baseline intensity. We assumed that a possible association with mobile phone use will not affect the contralateral hemisphere; consequently, we fixed $g = 1$ for distances >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. Significance testing was done by simulating 1000 test statistics under the null hypothesis and calculating the empirical P-value (31). The reported Monte Carlo confidence intervals are 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. 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; 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 $\boldsymbol{\alpha}^j = (\alpha_1^j, \alpha_2^j, \alpha_3^j, \alpha_4^j)$, $j = 0, 1$, 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:

$$\begin{aligned} \lambda_L(\mathbf{x}) &= \lambda_0(\mathbf{x}) \left(w_{pref} g(\mathbf{x} - \mathbf{x}_L; \boldsymbol{\alpha}) + (1 - w_{pref}) g(\mathbf{x} - \mathbf{x}_R; \boldsymbol{\alpha}) \right), \\ \lambda_R(\mathbf{x}) &= \rho \lambda_0(\mathbf{x}) \left(w_{pref} g(\mathbf{x} - \mathbf{x}_R; \boldsymbol{\alpha}) + (1 - w_{pref}) g(\mathbf{x} - \mathbf{x}_L; \boldsymbol{\alpha}) \right). \end{aligned}$$

We chose the mixing proportion $w_{pref} = 0.75$ inspired by the findings in (37).

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, the model with mixing proportion $w_{pref} = 0.85$; and the standard model for the subsets used in previous case-only analyses: Denmark; Finland; Germany; Italy; Norway; Sweden; UK (N=428 with preferred laterality of 515 in (28)) and: Australia; Canada; France; Israel; New Zealand (N=332 of 380) (30). Because of the uncertainty in the assessment of tumor origin, we conducted the analyses as in (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 (38).

RESULTS

Descriptive characteristics of the regular users with a self-reported side of use are presented in Table 1 and a flow chart 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 (Figure 4), with exposure variable 'point with highest SAR', and with mixing proportion $w_{pref} = 0.75$. The P-value for the hypothesis of no association with the mobile phone was <0.01 for all three models. The estimates for the first two models are similar. For the model with mixing proportion, 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 including P-values from the test of no difference in the distance relation for the two covariate levels. 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 stratum (not shown).

The results with TCSE instead of distance are shown in Table 4 and concurs with those 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.

Table 5 shows the results from the sensitivity analysis comparing the center of gravity with the results from (31) (reported with standard errors as in (31)), and the estimates are similar for both types of tumor points. The results from further sensitivity analyses; using the geometric mean, the model with mixing proportion $w_{pref} = 0.85$, restricting data to the subsamples from (28) and (30), and the model with smaller intervals are similar to those presented in Table 2 and 5 (Web Table 1–4).

DISCUSSION

This is the first analysis modeling the intracranial distribution of gliomas in relation to mobile phone use by using the exact localization data from the full Interphone study. The three-dimensional distribution of gliomas within the brain was skewed towards the self-reported preferred ear 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 that 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). For most of the models, there was a drop after 5.5 cm (between $\hat{\alpha}_1$ and $\hat{\alpha}_2$); however, this is not as substantial as observed in the studies on SAR. 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, irregularly 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. Using point process modeling is also a strength; thus, a paired t-test comparing distance from tumor to preferred ear to distance to opposite ear was insignificant (P=0.17). Moreover, because our analysis includes only cases, the findings are not affected by differential bias between cases and controls (39–42). A limitation is uncertainty about the tumor origin and that the self-reported side of use may be influenced by recall bias. Our method necessitates inclusion of side of mobile phone use. Frequently, cases were aware of their tumor location 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 (37). This indicates that our data on self-reported side of phone use might be influenced by random recall bias. The proportion of preferred left- versus right-sided users 0.50 (265/527) was slightly lower than for the controls from the Interphone Study who were regular mobile phone users 0.58 (630/1082) (6). Moreover, the cases reporting a preferred side might not have used the phone exclusively on that side. We dealt with the latter by introducing mixing proportions. 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 tumors 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 intracranial distribution of SAR also depends on the frequency band and other characteristics (26, 43). Further, the exposure source was modeled 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.

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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 in the Interphone grid data, 2000–2004. Of the 933 regular phone users, 31 had no information on side of use.

Figure 3: A) Density histogram for distance between gravity center of the tumor and closest ear for all regular users in the Interphone grid data, 2000–2004, N=933. B) Distance between gravity center of the tumor and 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, 2000–2004, 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.

Table 1: Characteristics of the Regular Mobile Phone Users With Preferred Side of Use From the Interphone Grid Data, 2000–2004, 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
Tumor 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, 2000–2004, With Preferred Side of use, N=792

	0–55 mm[a]			55.01–75 mm			75.01–95 mm			95.01–115 mm			>115.01 mm		
Model	No.[b]	$\hat{\alpha}_1$[c]	95% CI	No.	$\hat{\alpha}_2$	95% CI	No.	$\hat{\alpha}_3$	95% CI	No.	$\hat{\alpha}_4$	95% CI	No.	REF	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[d]	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 w_{pref}=0.75[e]	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; REF, referent.

[a] Distance from the ear preferred for mobile phone use to the gravity center of the tumor.

[b] Number of tumors within a given interval.

[c] The $\hat{\alpha}$s represent the elevation in risk of observing a tumor within a given interval compared to the assumed baseline risk.

[d] The intervals are: 0–40 mm, 40.01–60 mm, 60.01–80 mm, 80.01–100 mm, >100.01 mm.

[e] The model with mixing proportion: 75% assigned to the preferred side of use and 25% to the non-preferred side of use.

Table 3: Estimates and 95% Confidence Intervals for the Stratified Models for the Interphone Grid Data, 2000–2004, With Preferred Side of Use, N=792

		0–55 mm[a]		55.01–75 mm		75.01–95 mm		95.01–115 mm		>115.01 mm		
Covariate	No.[b]	$\hat{\alpha}_1$[c]	95% CI	$\hat{\alpha}_2$	95% CI	$\hat{\alpha}_3$	95% CI	$\hat{\alpha}_4$	95% CI	REF	95% CI	*P* value[d]
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 ≤ 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[e]	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 ≤ 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 ≥ 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 ≥ 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 ≥ 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; REF, referent.

[a] Distance from the ear preferred for mobile phone use to the gravity center of the tumor.

[b] Number of tumors within the covariate level within a given interval.

[c] The $\hat{\alpha}$s represent the elevation in risk of observing a tumor within a given interval compared to the assumed baseline risk.

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

[e] It was possible to assign tumor grade for only 748 of the 792 regular phone users with preferred side of use.

Table 4: Estimates and 95% Confidence Intervals for the Interphone Grid Data, 2000–2004, With Preferred Side of Use from Australia, Canada, France, Israel and New Zealand using Total Cumulative Specific Energy Instead of Distance, N=324

	>3514.01 J/kg[a]			771.01–3514 J/kg			186.01–771 J/kg			43.01–186 J/kg			0–43 J/kg		
Model	No.[b]	$\hat{\beta}_1$[c]	95% CI	No.	$\hat{\beta}_2$	95% CI	No.	$\hat{\beta}_3$	95% CI	No.	$\hat{\beta}_4$	95% CI	No.	REF	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[d]	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	-

Abbreviations: CI, confidence interval; REF, referent.

[a] TCSE-values calculated using distance from the ear preferred for mobile phone use to the gravity center of the tumor.

[b] Number of tumors within a given interval.

[c] The $\hat{\alpha}$s represent the elevation in risk of observing a tumor within a given interval compared to the assumed baseline risk.

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

Table 5: Comparison of Tumor Points for the Interphone Grid Data, 2000–2004, With Single Voxel Origin Recorded by Neuroradiologists or Calculated Gravity Center of the Tumor, N=478

	0–55 mm[a]			55.01–75 mm			75.01–95 mm			95.01–115 mm			>115.01 mm		
Model	No.[b]	$\hat{\alpha}_1$[c]	SE	No.	$\hat{\alpha}_2$	SE	No.	$\hat{\alpha}_3$	SE	No.	$\hat{\alpha}_4$	SE	No.	REF	SE
Origin point[d]	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: REF, referent; SE, standard error.

[a] Distance from the ear preferred for mobile phone use to the gravity center of the tumor.

[b] Number of tumors within a given interval.

[c] The $\hat{\alpha}$s represent the elevation in risk of observing a tumor within a given interval compared to the assumed baseline risk.

[d] Result from Grell et al. [31]