Location of glioma in relation to mobile phone use: a case-case and case-specular analysis.

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ABSTRACT

The energy absorbed from the radiofrequency (RF) fields of mobile phones depends strongly on distance from the source. The objective of the study was to evaluate whether gliomas among phone users occur preferentially in the areas of the brain having the highest RF exposure from the handset. We used two approaches: in a case-case analysis, tumor location within 5 cm of the putative position of the mobile phone was compared between glioma cases with varying exposure levels; in a case-specular analysis, a hypothetical reference location was assigned for each glioma and the distance from the actual and specular location to the source of exposure was compared. The study included 888 gliomas from seven European countries with tumor mid-points defined on a three-dimensional grid based on radiologic images. The case-case analyses were carried out using unconditional logistic regression, whereas in the case-specular analysis, conditional logistic regression was used. In the case-case analyses, tumors were located closest to the source of exposure among never-regular and contralateral users, but not statistically significantly. In the case-specular analysis, the mean distances between exposure source and location were similar for cases and speculars. Our results do not suggest gliomas in phone users being preferentially located in the parts of the brain with the highest RF fields from mobile phones.
Mobile phone use has become common worldwide since the beginning of the 1990’s (1). Mobile phones emit radiofrequency (RF) electromagnetic fields; those fields have not been shown to be tumorigenic (2), but research is still ongoing to investigate whether low-level RF fields have adverse health effects.

Several studies have been conducted on the association between mobile phone use and brain tumors, with unclear results. There is no clear evidence for increased risk of gliomas related to use of mobile phones, but the exposure and latency times analyzed have been limited (3-5). However, recent reviews have concluded that, to date, there was no consistent support for a causal effect of mobile phone use on glioma risk even with use of over 10 years (2,6).

Two previous studies have evaluated the location of glioma in relation to mobile phone use (7,8), but with very small sample sizes (approximately 100 cases). Because the RF field emitted by the phones penetrates the brain in a highly localized fashion, occurrence of tumors in the part of the brain closest to the handset would be expected if there is an etiological effect. The absorbed RF energy transmitted to the tissue from a mobile phone depends primarily on the distance from the source, decreasing to one tenth in 5 cm (9).

The current analysis is based on data from seven European centers within the Interphone study, an international collaborative case-control study whose main objective was assessing whether mobile phones increase the risk of brain tumors (10).

The aim of this analysis was to investigate whether gliomas among mobile phone users are located closer to the presumed position of the mobile phone handsets (the source of the RF field) than gliomas among non-users.
MATERIALS AND METHODS

MATERIALS

Eligible cases were all glioma cases diagnosed in seven countries (or areas within the country) (Denmark, Finland, Germany, Italy, Norway, Sweden and the Southeast of England) between September 2000 and January 2004 (the study periods varied between countries), with mid-point(s) of the tumor in three dimensions defined by neuroradiologists based on computerized tomography (CT) or magnetic resonance imaging (MRI) images. A specific location (mid-point(s)) was assigned to 912 cases, i.e. 63% of all glioma cases diagnosed during the study period that fulfilled the study inclusion criteria. The inclusion criteria were age at diagnosis between 18-69 years (with some variation between countries), no prior diagnosis of brain tumor and a histological confirmation (N=910) or diagnostic imaging allowing unambiguous classification of the tumor type (N=2). The case selection is described in further detail elsewhere (10).

All gliomas were assigned a mid-point(s) by neuroradiologists, blind to the data on mobile phone use, in each center. The coordinates for the mid-point were recorded using a software program (GridMaster) designed for the Interphone study. In GridMaster, three projections (axial, sagittal, and coronal) form a three-dimensional (3D) grid (1 x 1 x 1 cm). Cases with no clear single mid-point (i.e. irregularly shaped tumors, N=116) were assigned several mid-points (thus also several sets of coordinates). Multifocal cases (with non-adjacent mid-points) were excluded from the study (N=24). For each case with multiple mid-points, the mean of the tumor mid-points was defined (for calculating the distance to the exposure source).
All cases were interviewed (83% personally, 17% via proxies) about their mobile phone use and other potential risk factors. Phone use in the eighteen months prior to glioma diagnosis was excluded from the analyses, as well as use of hands-free-devices. Use of cordless phones (DECT) was not included. Regular use was defined as at least one call per week for a period of six months or more.

The study protocols were approved by local ethical review boards in each center.

STATISTICAL METHODS

Two types of analyses were used to evaluate the anatomic distribution of gliomas within the brain in relation to mobile phone use. A case-case analysis was based on comparing exposed and unexposed cases using dichotomous exposure indicators. A case-specular analysis contrasted the actual location of the case with a hypothetical (specular) assigned for each case as a mirror image on the opposite side of the same hemisphere in terms of axial and coronal axes (Figure 1).

The main exposure indicator in the analyses was the shortest estimated distance from the mid-point of the glioma to the putative source of exposure, i.e. typical location of the phone. A line from the external orifice of the ear canal to the corner of the mouth was assigned to represent the likely position of the phone. The entire phone was regarded as the source of exposure, as most GSM phones have an integrated antenna with the whole body of the phone emitting an RF field.
The exposure line (approximately 6.7 cm) was divided into a hundred segments of similar length. The distance from the mid-point of the glioma was calculated separately to each of the 101 points and the shortest was used as the main exposure indicator.

To avoid potential recall bias, distance was calculated to the nearest source of exposure on the same side as the glioma was located, irrespective of the patient’s reported typical side of use.

In the case-specular analysis, 3D coordinates were defined for the specular cases representing a hypothetical control location (point of reference) symmetrically reflecting the location of the actual case across the mid-point of the axial and coronal planes. In accordance with the rationale of the case-specular study design, the specular location was taken to represent what the exposure would have been if the tumor had been located in another location (11). This counterfactual ‘control’ was contrasted in the analysis with the actual case. Given that the hypothetical locations are assigned systematically and symmetrically in relation to the exposure parameter (in this case distance to the source of exposure), a greater exposure to the actual sites would support the study hypothesis (an effect of RF exposure on case occurrence).

We constructed the specular locations (from which the distance was calculated in a similar fashion as for the actual cases) using a geometrical ‘mirror reflection’ through a center-point. This center-point was defined as the point that resulted in a similar distance from the exposure line for unexposed cases (i.e. never-regular users) and their specular controls. The anatomical center-point of the brain could not be used, because the gliomas are not evenly or symmetrically distributed within the brain and therefore using the zero point of the anatomic coordinate axes (origo) would have led to an asymmetrical distribution.
of the specular locations (and hence bias). Thus, the center-point used was based on the mean coordinates of cases among never-regular users (the unexposed group), which corresponds to the observed median coordinate of all cases (independent of mobile phone use) moved 5 mm to the posterior (coronally) and 5 mm to the inferior (axially) direction. If for instance, a case was located 3 cm anterior from the assigned center-point on the coronal axis, a specular coordinate was computed as 3 cm posterior from the assigned center-point, and vice versa. The axial coordinate was obtained in a similar fashion. For the sagittal projection, an identical coordinate on the sagittal axis was used (i.e. the specular location had identical distance to the falx cerebri as the actual case). The procedure for the axial coordinate is illustrated in Figure 1.

The specific locations of gliomas are presented in four projections to demonstrate the heterogeneous distribution of gliomas, which restricted the use of the anatomic mid-point of the brain as the origo. These figures are shown using an axial projection of the brain, a coronal projection, and right and left sagittal projections (Figure 2).

In the analyses of differences in distances of glioma from the exposure line, the statistical significances were evaluated using the Mann-Whitney test. When analyzing differences of glioma distribution by lobe and by increasing level of intensity or duration of mobile phone use, chi-square tests were used.

In the case-case analysis, unconditional logistic regression was used with distance between the mid-point of the glioma and the presumed source of exposure (location of the mobile phone) as a binary outcome (≤5 cm, >5 cm). The cut-point was chosen because the energy from RF field is predominantly absorbed by the tissue within 5 cm of the phone (9). Exposure indicators analyzed included regular use of mobile phone,
cumulative call-time, laterality (preferred side of use) and duration of use (years). Never regular use of a mobile phone was considered as the unexposed reference category in all analyses. Phone users were divided into tertiles by cumulative call-time (0.001-46 hours, 47-339 h and >339 h, with a median of 133 hours and maximum of 20,000 hours). Similarly, duration of use was categorized into three groups, with cut-points chosen to correspond to those in previous studies (1.5 years to 4 years, 5 to 9 years and 10 or more years of use). All analyses were adjusted for country, sex, age group and socioeconomic status.

Case-specular analyses were conducted using conditional logistic regression. The odds ratios (OR) were calculated with distance as the exposure variable and case/specular status as the outcome. The explanatory variables included regular phone use, cumulative call-time and duration of use in years.

The statistical software Stata 8.2 (StataCorp, Texas, USA) was used in all analyses.

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RESULTS

A total of 912 cases fulfilled the inclusion criteria, with one or more mid-points of glioma recorded. Of these, 24 cases (3%) were excluded as they had several non-adjacent mid-points. Of the remaining 888 cases, 116 (13%) had two or more mid-points (range 2 to 21, mean 3.6, median 2).

Altogether 518 (58%) gliomas were in men and 370 (42%) in women.

Information on mobile phone use was obtained from 873 cases (98%), with 57% regular mobile phone users and 43% reporting no regular use. The median cumulative call-time among regular users was 133 hours, while the mean call-time was 917 hours.

Preferred laterality of use was known for 490 cases (99% of all regular users). Of these, 59% were using the phone on the right side, 28% on the left side and 13% on both sides. The reported side of use and the brain hemisphere where the glioma was located are presented in Table 1.

Regular mobile phone use was most common in the youngest ages, among men and subjects with the highest level of education (Table 2).

There were no differences in phone use (regular vs. never-regular) among cases with only one glioma mid-point and those with several (14% of never-regular users had several mid-points vs. 12% of regular users, p=0.65).

Tumors were located in the right hemisphere in 49% of cases, in the left in 49% of cases and in a central location in 1.4% of cases. Glioma cases included in the present study were most frequently located in the frontal lobe (40% of 733 gliomas with a cerebral lobe assigned), followed by the temporal (30%). There were no major differences in the
distribution of gliomas by cerebral lobes between regular phone users and never-regular users (Table 3). The distribution by lobe was also comparable between regular and never-regular users when gliomas were subdivided into glioblastomas and other gliomas.

The mean distance did not vary substantially by the indicators of mobile phone use being somewhat shorter among cases who had never used phone regularly or reported a preferred side of use as contralateral to the tumor (in comparison to regular or ipsilateral users) (Table 4). The mean distance was slightly longer for those with the highest cumulative call-time and for those having used a mobile phone for more than ten years, but the differences were not significant.

In the case-case analysis, non-significantly decreased ORs for gliomas located within 5 cm of the presumed phone location were found in regular users compared with never-regular users (Table 5). All the ORs for the higher categories of intensity or duration of mobile phone use were below unity in these analyses, indicating no excess risk in the highly exposed parts among regular vs. never-regular users, although all the upper confidence limits were above one.

In the case-specular analysis, the average distance from the source of exposure was comparable for actual and specular glioma cases (6.25 vs. 6.24 cm, p=0.49 with medians 6.34 cm (SD 1.60, range 2.42-10.7) and 6.26 cm (SD 1.38, range 2.98-11.0), respectively). The distribution of the distances of the actual glioma cases showed more kurtosis (p<0.001, with a peak at 6-7 cm) than for the specular gliomas. The specular cases on the other hand, showed some evidence for skewness (p=0.002, two cases exceeding the expected range, i.e. μ + 3 x 6) not observed among the actual cases.
In the case-specular analyses with distance as a categorical variable, a slightly larger proportion of glioma cases than speculars were within 5 cm of the presumed typical phone location (Table 6). However, the confidence intervals covered unity. In addition, no significantly increased OR was found among regular users or those with highest exposure; on the contrary, highest ORs were observed among never-regular users and among regular users with the lowest call-time. A two-fold OR was found in those having used mobile phone over ten years, but with a confidence interval including unity. With distance as a categorical variable, all ORs were above unity, also for the unexposed. In the analyses of distance as a linear variable, no increased ORs were observed.

Analyses of digital and analogue phones separately did not show substantially different results from the main analyses, nor did analyses by histological sub-groups of gliomas (glioblastomas and other gliomas separately).
DISCUSSION

Our results do not support the hypothesis of gliomas among users of mobile phones being preferentially located in the parts of the brain with the highest exposure. In the case-case analyses, gliomas among contralateral and never-regular users, representing lower RF exposures, had a shorter mean distance between tumor mid-point and the presumed source of exposure than ipsilateral and regular users. In the case-specular analysis, both exposed and unexposed glioma cases were non-significantly located within 5 cm from the typical position of a phone more frequently than the hypothetical locations assigned for speculars, but no such pattern was found in analyses by amount of phone use. In both models glioma cases were closer to the exposure line in long-term users, but the differences remained non-significant.

We applied a novel approach for studying focal effects of RF fields emitted by mobile phones in the etiology of gliomas. Instead of concentrating on crude indicators of phone use as in most previous studies, the method utilizing tumor location enabled us to focus on risk in relation to the postulated distribution of the RF field within the brain. This offers a biologically and physically more meaningful and more specific measure of RF exposure compared with phone usage pattern.

The case-specular method has not been previously used in brain tumor studies, but was developed for studies on residential (extremely low frequency) electromagnetic fields from power lines and childhood cancer (12,13). In those analyses, the residential location was the exposure indicator, for which specular indices were obtained. In our case, hypothetical tumor locations were generated following the same principles. The analysis resembles a case-case study, but with the advantage of avoiding potential confounding.
The RF field decreases sharply in the brain tissue, with 90% of the energy to the head absorbed in the tissue within 5 cm range of the handset. Nearly all (97-99%) of the energy from a mobile phone is absorbed to the hemisphere on the side of the phone, with the highest exposure to the temporal lobe (50-60%) (9). In our study, gliomas among regular users were more frequently self-reported as ipsilateral (49% of those with known laterality) than contralateral (34%), but the distance to the hypothetical closest source of exposure among contralateral users was shorter. This may indicate that even if the side of reported use and affected hemisphere are correlated, the tumor location within the brain does not differ between phone users and non-users.

The discrepancy in our results pertaining to laterality and location within the hemisphere could be explained by a positive recall bias (cases over-reporting phone use on the side of the tumor) without a relation between absorbed energy and risk of gliomas. The analysis of location has the advantage of avoiding the distortion due to recall bias, as location was evaluated objectively based on radiological imaging. Theoretically, our findings are also consistent with mobile phone use affecting laterality, but without an effect of field strength (or location within the hemisphere). This could be the case if, implausibly, the effect is not related at all to field strength, but another exposure characteristic (e.g. frequency, modulation).

Side of use was ignored in the case-specular analyses, and glioma cases were overall, both among regular mobile phone users and never-users, slightly closer to the postulated source exposure than the hypothetical locations assigned for speculars, but the differences were not significant, and disappeared when exposure was analyzed in more detail (e.g. cumulative call-time). Yet, the only suggestion of an increased risk was related to
long-term use in this analysis, but with a wide confidence interval. The ORs for different exposure indicators showed hardly any departure from unity, when distance was considered as a continuous variable, and in analyses among users, the point estimates for the higher exposure groups never exceeded those for less mobile phone usage.

In our study, no excess of gliomas was found in the temporal lobe among regular users compared with never-users (28% vs. 33% of the locations in the cerebral lobes). Overall, the distribution of anatomic locations in our study was similar to previously reported findings (14-17), with somewhat lower relative frequency of gliomas in the frontal lobe in our data (35% of all brain vs. previously reported 40-53%) and a higher frequency in the occipital lobe (6% vs. 2-3%).

Our localization approach was based on the 3D mid-point(s) of the glioma, as defined by neuroradiologists, for its unequivocal nature compared with the theoretically relevant, but in practice equivocal point of origin, which is no longer identifiable at the time of diagnosis. The mid-point is a crude but robust measure. It has limitations particularly for large, irregularly shaped tumors close to the margin of the brain tissue. The size of gliomas has been reported being smaller in regular mobile phone users in one study, but with a relatively small number of glioma cases (18). However, vestibular schwannomas have been reported to be larger among regular than never-regular users, though no association with amount of use was reported (19). If a similar (unknown) mechanism was to influence also gliomas, they may be larger among phone users. Larger gliomas may not grow symmetrically around their point of origin, but e.g. towards the center of the brain, resulting in the mid-point being further from the cortex and thus the exposure. Larger tumor size among users could therefore potentially cause a bias towards the null. In our study gliomas with several
mid-points were slightly further away from the exposure line than those with only one mid-point (6.44 cm vs. 6.22, p=0.15).

In the case-specular analysis, the hypothetical alternative location in the coronal and axial axes of the 3D brain model was assigned symmetrically across the mid-point of the plane to reflect the location of the case. The center-points of the axes (in relation to which the specular coordinates were obtained) were chosen based on the medians observed among never mobile phone users, in accordance with the null hypothesis. Minor correction to the anatomic center-point was applied to create a symmetric distribution corresponding to the unexposed cases. The number of such cases was substantial (more than 370) and the precision should be adequate.

However, in the case-specular analyses the ORs are slightly above unity also for never-regular phone users (Table 6). This indicates that the reference is not necessarily located on an exact basis rendering the results of the case-specular analysis somewhat difficult to interpret.

Never-users were on average older and more commonly women and if these features affect the tumor location, bias could be introduced. Nevertheless, in our data, the average distances from the exposure line did not differ significantly between age groups (ranging from 6.14 cm in those aged 50-59 years to 6.43 in those aged 40-49 years, p=0.32), whereas there was a borderline significant difference between the sexes (6.16 cm in men vs. 6.37 in women, p=0.051). This higher proportion of women among the unexposed may have driven the center-point somewhat further from the exposure line (as gliomas among women are located further from the line), which may accentuate the differences in distances when comparing all cases and all speculars.
Due to the short penetrance of the RF field into the head, exposure emitted by a mobile phone is virtually confined to the brain hemisphere at the side of the phone. However, most people do not use the phone exclusively on one side. Several earlier studies have found an increased risk on the side of head where the user reported that the phone had predominantly been used (2). Frequently, however, this has been accompanied by a deficit on the contralateral side, giving rise to suspicion of recall bias (overestimation of use on the side of the tumor by the cases, with corresponding underreporting on the other side). Case-case analysis overcomes the discrepancy of information between cases and controls. However, self-reported preferred side of use is a crude indicator of exposure compared with distance from the putative source of exposure, and can be affected by recall-bias. The results of our case-case analysis did not show differences by laterality of use in relation to tumor location.

As only cases were included in our study, selection bias arising from lower participation among controls, in particular non-users of mobile phones, was avoided (20,21).

Still, even if only cases were included, reported usage may be inaccurate. Slight underestimation of the number of calls and substantial overestimation of call duration have been demonstrated in short-term recall (22). Regular users with the lowest amount of use tend to underestimate their call-time and heaviest users tend to overestimate it relative to the recorded amount. Such overestimation would, however, distort the current results only if it were related to the location of the tumor. In addition, information on usage may not be accurate as particularly gliomas in the temporal and frontal lobes can affect cognition and complex memory tasks, leading to problems in accurate recall of previous phone usage. These areas are also the most heavily exposed parts of the brain and this could therefore
induce differential misclassification (larger uncertainty in the group with the heaviest exposure), but it is unclear whether this would lead to over- or under-estimation of risk.

The main limitation of the study is the relatively short time since first exposure. While a fifth of the cases (N=184) had used phones for at least five years, only 5% (N=42) had used phone for ten or more years, which adds considerable uncertainty to our results on long-term exposure. No statistically significant difference was found for gliomas among cases with five to nine years or over ten years of use in terms of mean distance to the typical phone location in our case-case or case-specular analyses. Even if in the case-specular analysis the OR was twofold for cases with over ten years of use, the confidence intervals of the risk estimates for the increasing categories of duration of use remained wide.

This is the largest study on detailed glioma localization published to date, with 888 glioma cases from seven countries. Further research with similar methods, but a larger number of long-term users is warranted.

To conclude, the results do not indicate that gliomas are located in excess in the brain tissue presumably receiving the highest intensity electromagnetic field among regular mobile phone users. Cumulative call-time, duration of use and laterality were not consistently associated with the location of the gliomas.
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REFERENCES


Figure 1. A schematic representation of the assignment of the coronal coordinates for the specular analysis. In the axial projection, x-axis sagittal and y-axis coronal the mid-point for a case is indicated with a solid circle and the corresponding specular location with an open circle. The distance from the source of exposure (exp) is denoted by d separately for the case \( d_{\text{case}} \) and for the specular location \( d_{\text{spec}} \). Axial coordinates were obtained in a similar fashion using a coronal projection. R = right, L = left.

Figure 2. The anatomic distribution of gliomas in different projections of the brain (from left to right, top to bottom): the axial projection (frontal part at top), the coronal projection (facing the front) and the sagittal projections, sagittal right and sagittal left. The colors represent the number of gliomas in each 1 x 1-cm square, smoothing based on adjacent squares.
Table 6. Case-specular analysis: OR (95% confidence interval) for distance between glioma mid-point and typical position of mobile phone as a categorical (≤5 cm) and a continuous by exposure characteristics, all compared with speculars (case vs. specular).

<table>
<thead>
<tr>
<th></th>
<th>OR for case ≤5 cm (95% CI)</th>
<th>OR for case with increasing distance (cm) from exposure (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case vs. specular</strong></td>
<td>1.22 (0.99-1.51)</td>
<td>1.00 (0.95-1.07)</td>
</tr>
<tr>
<td><strong>Never-regular users</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>1.19 (0.89-1.59)</td>
<td>0.99 (0.92-1.08)</td>
</tr>
<tr>
<td>Never-regular</td>
<td>1.30 (0.95-1.80)</td>
<td>1.01 (0.92-1.11)</td>
</tr>
<tr>
<td><strong>Cumulative call time (hours)</strong></td>
<td></td>
<td></td>
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<tr>
<td>0.001-46</td>
<td>1.39 (0.81-2.38)</td>
<td>1.00 (0.87-1.16)</td>
</tr>
<tr>
<td>47-339</td>
<td>1.21 (0.74-1.97)</td>
<td>0.99 (0.86-1.13)</td>
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<tr>
<td>&gt;339</td>
<td>1.00 (0.59-1.69)</td>
<td>1.01 (0.88-1.16)</td>
</tr>
<tr>
<td><strong>Duration of use (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5-4</td>
<td>1.15 (0.80-1.66)</td>
<td>0.98 (0.89-1.09)</td>
</tr>
<tr>
<td>5-9</td>
<td>1.04 (0.61-1.76)</td>
<td>1.02 (0.89-1.18)</td>
</tr>
<tr>
<td>≥10</td>
<td>2.00 (0.68-5.85)</td>
<td>1.08 (0.82-1.42)</td>
</tr>
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