

Re-evaluation of the Interphone Study

Application of a Correction Factor

L. Lloyd Morgan, ^{1*} Michael Kundi, ² and Michael Carlberg, ³

¹Senior Research Fellow, Environmental Health Trust, P.O. Box 58, Teton Village, WY 83025, USA; ²Associate Professor Occupational Health & Epidemiology, Medical University of Vienna, Vienna, Austria; and ³MSc, Department of Oncology, University Hospital, SE-701 85, Örebro, Sweden.

* Corresponding author. 2022 Francisco Street, Berkeley, CA 94709, USA. E-mail: bilovsky@aol.com.

Aim of Work: Previously it has been shown that the 11 single country Interphone studies ^[1-11] on the risk of brain tumors have a systemic underestimation of risk ($p = 6.2 \times 10^{-20}$). ^[12] This study calculates the value of the systemic underestimation. With this value, every Odds Ratio (OR) can be corrected thereby correcting for the systemic underestimation.

Materials and Methods Each of the 11 studies is a statistically independent study, based on a common protocol. Each study examines the risk of from 1 to 3 brain tumors types resulting in a total of up to 20 statistically independent studies of brain tumors depending on the category chosen. If there was no risk of brain tumors from cellphone use then about the same number of Odds Ratios (ORs) would be below one as above one. Several commonly reported minimal exposure categories were selected as candidates for calculating the correction factor. Using published ORs for these minimal exposure categories, the geometric mean value of these ORs was calculated. Dividing a published OR by this median OR value provides a correction to the systemic underestimation of risk, in effect, readjusting the set of ORs such that they are roughly symmetrical above and below 1.0. Several low exposure categories were selected as potential candidates. These were the lowest exposures reported in the 11 single-country studies for minimum

cumulative hours, min. years of use, min. number of calls, “regular use,” and min. years of contralateral use. Table 1 shows the median OR, the number of ORs used to calculate the median, and the associate binomial p-value.

Examining these results, whatever exposure category was chosen, it is demonstrated that the magnitude of the geometric mean is almost equal. However, maybe due to a variable amount of cases with long duration of use in the categories “cumulative hours of use”, “cumulative number of calls”, and “regular use,” the variance of the average is greater for these categories than for duration of use. Therefore, we chose the category “Min. Years of Use” for selection of the correction factor. It should also be noted that this is the same median OR for “regular” use reported for the 14 Interphone study centers.^[13]

The p-value for the OR testing the hypothesis 50% were below and above 1 was calculated in Stata/SE 10.1^[14] using a binomial distribution. In order to calculate the corrected ORs the reported ORs were divided by the bias (OR=0.80). The variance of the logarithm of the corrected OR is given as the sum of the variance of the original biased log-OR and the variance of the log-correction factor. The confidence interval and p-values for the corrected ORs were based on this variance estimate.

The p-value for the median minimum years of use OR was calculated in Stata/SE 10.1^[14] using a binomial method that makes no assumptions about the underlying distribution. By testing for decreasing alpha values, the p-value was found to be between p=0.0001 and p=0.0002. Rather than using the conservative, p=0.0002 (identical to the binomial p-value) to calculate confidence intervals we chose the even more conservative p-value=0.00145 found for the p-value from the 95% confidence intervals found by the Stata/SE 10.1 program. Because this calculation method for the p-value assumes a normal distribution, which is not the case here, it is incorrect, but such an error is conservative, because a larger p-value increases the conservative approach we have used.

Table 1 Median Odds Ratio for minimum exposure categories.

Category Min Exposure Reported in Each Study	No. of Results	Geo Mean OR	Binomial p-value
Min. Number of Calls, 11 single countries	16	0.88	0.011
Min. Cum. Hours, 11 single countries	20	0.83	0.058
Min. Years Contralateral Use, 11 single countries	12	0.83	0.073
“Regular” Use, 11 single countries	19	0.82	0.0022
“Regular” Use, 14 centers, glioma (median OR)	13*	0.80	0.011
Min. Years of Use, 11 single countries	20	0.80	0.00020

France OR=1.00, not counted

Bold indicates statistically significant OR. Font size increases by one for every order of magnitude decrease in p-value.

Discussion The 11 single country Interphone study has a systemic-protective-skew. Out of the 284 statistically independent ORs in the 11 studies, 217 ORs were <1.0 and 67 ORs were >1.0 . ($p=6.2 \times 10^{-20}$).^[12] The median OR=0.80 describes the systemic underestimation of risk in these studies. Applying this value to all published Odds Ratios in the 11 studies will result in a 25% increase in every OR. In aggregate, the 11 Interphone studies contain design flaws in the Protocol, thereby creating a systemic-protective-skew. Two of the Interphone Principal Investigators, have stated that one of these potential flaws, selection bias (non-participation bias), could account for about a 10% underestimation of risk.^[15,16] In the pooled 13-country Interphone there is a recognition of the systemic bias. The authors estimate, “...non-participation bias may have led to a reduction in the ORs for regular use of 5–15%, which is less than the observed reductions below the null in the ORs in ever regular mobile phone users for meningioma (21%, 95% CI 32–9) and glioma (19%, 95% CI 30–6; Table 2).” Because “regular” users include a proportion of users with ≥ 10 years of use, even this under estimation, is under-estimated. This suggests that our yet larger under-estimation of risk by 25% is closer to a correct value.

Though the possibility of a real protective effect cannot be excluded, we conclude, as did The Interphone Study Group, the protective effect is an artifact of the Interphone Protocol, and thus the median OR=0.80 calculated above can be used to correct this systemic problem.

Applying this correction factor to published ORs <1.0 while increasing the OR, decreases the confidence level; applying it to ORs >1.0 increases both the OR and the confidence level.

Results Table 2 shows selected results from previously published Interphone studies and the effect of applying the correction factor. Pooled results from the 5-country meningioma study^[17] shows how three seemingly meaningless findings for risk per year, per 100 hours of use, and per 10,000 calls, when corrected for the systemic underestimation of risk, becomes an alarming and statistically significant risk.

The 13-country pooled laterality results for risk of meningioma from Table 2,^[13] we see the published OR for ipsilateral use was a non-statistically significant protective result, but when corrected becomes a non-statistically significant risk result. Similarly for contralateral results we see the non-significant protective result, when corrected, the protective effect is reduced while the p-value is increased (confidence reduction). For brain cancer (glioma), there is a more dramatic change when the results are corrected. The non-significant ipsilateral 21% increased risk becomes a significant 51% increase risk, while the non-significant contralateral protective results are further reduced and the p-value has increased to even less significance.

It is interesting to note the UK study on the risk of glioma, when corrected becomes a very similar 55% increased risk from ≥ 10 years of ipsilateral use.^[8]

When we examine the effects of correcting acoustic neuroma results an interesting picture emerges. The 390% increased risk reported in Sweden increases to 490% and the p-value decreases by close to an order of magnitude.^[3] The same effect on p-value is seen in the 5-country study of acoustic neuroma.^[16]

Citation	Exposure Description	Published				Corrected			
		OR	CI	Calculated p-value	OR	CI	Calculated p-value		
Lahkola et al. 2008 [14]	Risk of meningioma per years of use	0.99	0.96	1.01	0.43	1.24	1.07	1.43	0.0033
	Risk of meningioma per 100 hours of use	1.005	1.001	1.010	0.026	1.26	1.09	1.45	0.0014
	Risk of meningioma per 10,000 calls	1.00	0.96	1.05	1.00	1.25	1.08	1.45	0.0029
Interphone Study Group 2010 [13]	Risk of meningioma for ≥ 10 years of ipsilateral use	0.88	0.52	1.47	0.62	1.10	0.65	1.87	0.72
	Risk of meningioma for ≥ 10 years of contralateral use	0.58	0.29	1.16	0.12	0.73	0.36	1.45	0.36
	Risk of glioma for ≥ 10 years of ipsilateral use	1.21	0.82	1.80	0.33	1.51	1.00	2.3	0.05
	Risk of glioma for ≥ 10 years of contralateral use	0.70	0.42	1.15	0.16	0.88	0.22	3.48	0.85
Hepworth et al. 2006 [8]	Risk of glioma for "regular" ipsilateral use	1.24	1.02	1.52	0.031	1.55	1.22	1.97	0.00036
	Risk of glioma for ≥ 10 years of ipsilateral use	1.60	0.92	2.76	0.27	2.00	1.15	3.49	0.015
Lahkola et al. 2007 [15]	Risk of glioma for 5 to 9 years of ipsilateral use	1.10	0.89	1.35	0.36	1.38	1.07	2.45	0.012
	Risk of glioma for 5 to 9 years of contralateral use	0.74	0.59	0.92	0.0067	0.88	0.68	1.12	0.30
Löon et al. 2004 [3]	>10 years since first ipsilateral use for acoustic neuroma	3.9	1.6	9.5	0.0027	4.9	2.0	12	0.00057
	>10 years since first contralateral use for acoustic neuroma	0.9	0.2	3.1	0.88	1.1	0.3	4.5	0.87
Schoemaker et al. 2008 [19]	Risk of acoustic neuroma for ≥ 10 years of ipsilateral use	1.8	1.1	3.1	0.023	2.25	1.33	3.81	0.0025
	Risk of acoustic neuroma for ≥ 10 years of contralateral use	0.9	0.5	1.8	0.74	1.13	0.6	2.1	0.72

Bold indicates statistically significant OR. Font size increases by one for every order of magnitude decrease in p-value.

Table 2. Selected Interphone study results as published and as corrected.

Conclusions: For the selected results from the various Interphone studies, the corrected results remove the systemic underestimation of risk and become closer to what has been found in the other major case-control studies by a Swedish team led by Dr. Lennart Hardell.

In some cases exceeding the risk of found by the Hardell team's results. For example, this Swedish team reported an increased risk of meningioma per year of cellphone use was 5% for analog cellphone use (OR=1.05, CI: 1.02-1.09), and 2% risk per year for

digital cellphone use (OR=1.02, CI: 0.98-1.06).^[20] While the corrected results from the Interphone's 5-country meningioma study show a far larger increased risk per year of 24% (OR=1.24, CI: 1.07-1.43).

In some cases the results, when corrected for the systemic underestimation of risk, the results were similar. For example when ≥ 10 years of ipsilateral use, the UK Interphone study corrected risk of glioma increased by 100% (OR=2.00, CI: 1.15-3.49).^[8] The Swedish team reported an 80% increased risk of brain cancer from ipsilateral digital cellphone use (OR=1.8, CI: 1.4-2.4).^[21]

The 13-country Interphone study^[13] spends some 4 pages discussing possible sources of the underestimation of risk, the only large contributor they discussed was selection bias (AKA non-participation bias) which they estimate contributes between 5% and 15%. Yet they estimate the total underestimation could be 19% for glioma and 21% for meningioma.

Twelve design flaws have been identified, 11 by one of us (LLM),^[12] the twelfth by a meta-analysis examining the quality of all studies on the risk of tumors from cellphone use,^[22] and in another review by one of us (MK).

The 12 design flaws identified are:

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| 1 Selection bias (participation bias) | 7 Insufficient rural users (cellphones radiate greater power in rural areas) |
| 2 Exposure bias (treating cordless phone use as a non-exposure) | 8 Exclusion of brain tumor types (only acoustic neuroma, glioma and meningioma were included) |
| 3 Treating tumors outside the cellphone's radiation plume as exposed | 9 Exclusion of cases due to death or being too ill |
| 4 Insufficient latency time, | 10 Recall accuracy of cellphone use |
| 5 Definition of "regular user," | 11 Funding bias |
| 6 Exclusion of young adults and children | 12 Lack of double blinding. |

Their 4-page discussion of the sources of bias never mentions their treating cordless phone use as a non-exposure (Flaw 6 above). During the time of the Interphone studies' data collection (2000 to 2004), the prevalence of cordless phone use was typically higher than cellphone use.^[5] Perhaps this is the single largest contributor to the Interphone studies' underestimation of risk?

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