Interphone's Provocative Analysis of the Brain Tumor Risks

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An essential part of the Interphone story is Appendix 2. Although not included in the paper, it offers a way to look at the risks free of some of the bias that so muddled the published results. It also provides a window on the controversy that deadlocked the Interphone group for four years.

There is a general consensus that the large number of abnormally low risks observed in Interphone is a sign of a systematic problem —selection bias— in the way that the study was carried out. As the Interphone group acknowledges, it is "unlikely" that cell phones could immediately provide protection against brain tumors (see main Interphone Story).

When the Interphone team analyzed the data in a way to compensate for selection bias, they saw a much more provocative picture of the risks associated with long-term use of cell phones.

Those who used a mobile phone for ten or more years were found to be twice as likely to develop a brain tumor. This increased risk is statistically significant. Indeed, the risk is higher for all three indices of exposure —years of use, total talk time and total number of calls. There even appears to be a dose-response relationship, with the highest risk among the heaviest users. This is all clearly shown in the table below taken from Appendix 2.

Brain Tumor Risks Corrected for Selection Bias

Appendix 2 Table – ORs between mobile phone use and brain tumours (meningioma and glioma separately) by time since start of regular use, cumulative call time and cumulative number of calls, excluding use with hands-free devices; analyses restricted to ever regular-users

	Meningioma					Glioma				
	Cases	Controls	OR	95 % CI		Cases	Controls	OR	95 % CI	
Time since start of regular use (years)										
1-1.9 years	116	112	1.00			93	159	1.00		
2-4	362	367	0.90	0.62	1.31	460	451	1.68	1.16	2.41
5-9	288	308	0.75	0.51	1.10	468	491	1.54	1.06	2.22
10+	76	67	0.86	0.51	1.43	190	150	2.18	1.43	3.31
Cumulative call time with no hands-free devices (hours)[1]										
<5 hours	113	88	1.00			90	114	1.00		
5.0-12.9	83	88	0.79	0.48	1.29	92	124	0.88	0.56	1.39
13-30.9	95	107	0.72	0.45	1.15	127	118	1.37	0.87	2.14
31-60.9	70	87	0.59	0.35	0.99	108	126	1.13	0.72	1.77
61-114.9	74	88	0.58	0.35	0.97	121	135	1.06	0.68	1.67
115-199.9	69	95	0.64	0.39	1.06	129	119	1.13	0.71	1.78
200-359.9	74	81	0.58	0.35	0.96	116	138	1.00	0.63	1.58
360-734.9	83	80	0.85	0.51	1.41	142	139	1.17	0.74	1.84
735-1639.9	85	69	0.81	0.49	1.36	126	125	1.09	0.69	1.72
1640+	96	71	1.10	0.65	1.85	160	113	1.82	1.15	2.89
Cumulative number of calls with no hands-free devices (in hundreds)[1]										
<1.5 x 100 calls	109	81	1.00			92	102	1.00		
1.5-3.4	86	98	0.54	0.32	0.90	91	123	0.95	0.59	1.52
3.5-7.4	92	97	0.76	0.46	1.27	108	148	0.85	0.55	1.32
7.5-13.9	88	91	0.76	0.45	1.26	121	111	1.19	0.74	1.89
14-25.4	75	107	0.56	0.34	0.92	133	134	1.10	0.70	1.73
25.5-41.4	71	72	0.60	0.35	1.02	121	124	1.19	0.75	1.88
41.5-67.9	85	94	0.63	0.38	1.05	126	122	1.02	0.64	1.62
68-127.9	102	89	0.79	0.49	1.29	136	147	1.13	0.73	1.77
128-269.9	79	63	0.76	0.44	1.32	154	120	1.49	0.94	2.36
270+	55	62	0.66	0.37	1.17	129	120	1.31	0.82	2.11

[1] ORs adjusted for sex, age, study centre, ethnicity in Israel, and education.

Note: OR stands for odds ratio; an OR of 2 indicates a doubling of the risk;

Source: Appendix 2 of Interphone paper

Microwave News has learned that this table was originally part of the Interphone paper. It was later removed during negotiations to achieve consensus within the research group.

The peer reviewers then asked that the table be included. In a compromise, it ended up as an appendix that was relegated to the Internet. Appendix 2 must now be downloaded separately from the paper. Even so, the published paper does not explicitly refer to the findings of the analysis in Appendix 2. There is just one passing reference to Appendix 2 in the text.

Appendix 2 might never have attracted much notice had it not been a major focus of the commentary by Rodolfo Saracci and Jonathan Samet, which accompanies the Interphone paper. IARC did not distribute the commentary with the press release and the paper when they were sent out under embargo last week.

Is the Analysis in Appendix 2 Appropriate?

The brain tumor risks emerge so much more clearly in the alternate analysis that it begs the question as to whether it is an appropriate way to look at the data.

But first, some first context is needed in order to explain the difference between the analysis in the paper and the one in the appendix. Interphone is a case-control study, in which those with brain tumors are compared with a reference group. In the paper, the members of the reference group are those who *never* used mobile phones. Members of the reference group for the analysis in the appendix are the *lightest users*: those who used cell phones for less than two years. The reason for this substitution is that the non-users were not properly matched to the users: This is the selection bias or participation bias, which distorted the results. (For more on this, see the analysis by Martine Vriheid and other members of the Interphone group.)

“I myself think [the table in Appendix 2] is an appropriate way to look at the data,” Elisabeth Cardis, the head of the Interphone project, said in an interview from Barcelona. “This technique is commonly used in occupational epidemiology.” She noted that, “There were differences in opinion [within Interphone]; Others did not think it was appropriate,” but, she added, “I totally agree that it is important for the overall interpretation of the results.”

“It’s definitely legitimate,” Ken Rothman said in an interview, cautioning that he had not yet had a chance to read the Interphone paper. “It’s quite conceivable that this would be a good idea.” Rothman, a leading epidemiologist, is a member of the International Scientific Oversight Committee of the Interphone project.

Indeed, Siegal Sadetzki, who led the Israeli Interphone team, used the same technique in her Interphone study of parotid gland tumors, which was published in the *American Journal of Epidemiology,* a leading journal, in 2008. In her paper, the table with the alternative analysis, is also in an appendix, but remained part of the published paper.

“The results in Appendix 2 support the idea that there is an indication of an association,” Sadetzki said.

Appendix 2 is an "entirely reasonable way to look at the data,” said Bruce Armstrong who led the Australian Interphone group. “I am completely comfortable with the argument and the conclusion reached in Appendix 2.”

Jack Siemiatycki of the University of Montreal, a member of the Canadian Interphone team, cautioned that, while selection or participation bias is a plausible explanation for the deficits in the odds ratios, the risks in Appendix 2 would only be true *if* the deficits are in fact due to selection bias.

Interphone outsiders offered varying views. “The importance of the additional analysis in Appendix 2 cannot be overestimated,” said Michael Kundi of the Medical University of Vienna. Kundi, the author of “The Controversy About a Possible Relationship Between

Mobile Phone Use and Cancer," said that excluding those who never used phones removes part, but not all, of the selection bias and provides a clearer view of the risk.

But Martin Röösli of the Swiss Tropical and Public Health Institute in Basel. "It's not necessarily a valid analysis," he said. Röösli is working on a study of cell phone risks to children, known as CEFALO, which should be completed next year.

The ipsilateral risks —for tumors on the same side of the head as the phone was used— for the alternative analysis in Appendix 2 have not been published. Cardis said that she could not remember what they are, but added that even if she could, she would not feel free to respond. In general, the ipsilateral brain tumor risks are higher than the general tumor risk. For instance, in the analysis in the published paper, the ipsilateral glioma risk among those who used a mobile phone for ten or more years is 20% higher than the overall risk.

Kundi said that a "crude" estimate of the ipsilateral risk would show a tripling of the rate of gliomas among those most heavily exposed with the reference group of light users.

Sam Milham, an epidemiologist in Olympia, WA, argued that using a reference group that is also exposed, "will always take the odds ratios down—so, what you see is always lower than what really is." When asked about this, Armstrong replied, "Strictly speaking, that's true."

Why wasn't Appendix 2 part of the paper? Siemiatycki said that, "A lot of things came in and out." He pointed out that, "There were 200-to-300 pages of tables."

"I'm very satisfied with the way we present this additional analysis," said Joachim Schüz of the Danish Cancer Society, a member of Interphone. "I think it is appropriate to have the appendix, because this allowed a thorough discussion of the approach with advantages and disadvantages and the presentation of the full scope of results."

Cardis confirmed that the presentation of the results in Appendix 2 were a bone of contention between the two camps within Interphone. "We tried to reach a consensus," she said.

"There was a range of views," said Armstrong. "This was the best compromise that could be reached."

Interphone, cell phones, brain tumors, cancer, Ken Rothman, parotid gland tumors, Martin Röösli, Joachim Schüz, Danish Cancer Society, Michael Kundi, Bruce Armstrong,

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