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Interphone Points to Long-Term Brain Tumor Risks

Interpretation Under Dispute

There's an old saying that a camel is a horse designed by a committee. Welcome to Interphone.

The good news is that the Interphone paper has finally been made public after a four-year stalemate within the 13-country research team. But it comes at a price. A series of compromises over how to interpret the results of the largest and most expensive study of cell phones and brain tumors ever attempted has left the paper with no clear conclusions other than more research is needed.

Everyone anticipated that Interphone wouldn't offer any definitive findings, and they were right. "An increased risk of brain cancer [has not been] established," said Christopher Wild, the director of the International Agency for Research on Cancer (**IARC**) in Lyon, which coordinated the study.

But, there are "suggestions of an increased risk" at "the highest exposure levels," according to the **abstract of the paper** published by the *International Journal of Epidemiology.*

How should those "suggestions" be interpreted?

(continued on p.2)

Interphone's Provocative Analysis Of the Brain Tumor Risks

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 above).

When the Interphone team analyzed the data in a way to compen-

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At the very least, the risks are greater than many believed only a few years ago. In a series of interviews, a number of the members of the Interphone project told Microwave News that they now see the risk among long-term users as being larger than when the study began. Some think the risk warrants serious attention.

"To me, there's certainly smoke there," said **Elisabeth Cardis**, who leads the Interphone project. "Overall, my opinion is that the results show a real effect." Cardis is with the Center for Research in Environmental Epidemiology (**CREAL**) in Barcelona. She moved there two years ago after working on Interphone at IARC for close to a decade.

"There is evidence that there may be a risk; Interphone has made that a little stronger," said **Bruce Armstrong** of the University of Sydney, another member of Interphone. "It shows some indication of an increased risk of gliomas, but I cannot say this with certainty." (A glioma is a type of brain tumor.)

Siegal Sadetzki, the Israeli member of Interphone, goes further. She pointed out that while the risks are inconclusive, a number of the results show some consistency. These include increased risks among the heaviest users, the fact that the risks were highest on the side of the head the phone was usually used and that the tumors were in the temporal lobe of the brain, which is closest to the ear. Sadetzki is with the Gertner Institute outside Tel-Aviv. "The data are not strong enough for a causal interpretation, but they are sufficient to support precautionary policies," she said.

One strong dissenting voice is that of Interphone's **Maria Feychting** of the Karolinska Institute in Stockholm. "The use of mobile phones for over ten years shows no increased risk of brain tumors," stated a **press release** issued by the Karolinska. Feychting declined to be interviewed for this article.

The Interphone study included 2,708 cases of glioma and 2,409 of meningioma, another type of brain tumor, with a total of over 5,634 controls—from 13 countries. Eligible cases were patients diagnosed between 2000 and 2004. (Meningioma was not linked to cell phone use.) It is the largest study of cell phone and tumors ever done. The total budget of the study, which got underway in 2000, was 19.2 million (~US$25 million). Funding came from the European Commission (€3.74 million) and the cell phone industry (€5.5 million), as well as other sources.

Bias, Bias, Bias

Jack Siemiatycki of the University of Montreal, a member of the Canadian Interphone group, called the Interphone "genuinely perplexing, enigmatic and paradoxical" because, as he put it, "the data were dirty." (Siemiatycki said his perception of the risk has gone "from implausible to something higher.")

Part of the problem is the way the data were collected. Epidemiology is imperfect at best, and biased data are hardly uncommon. **Martin Röösli** of the Swiss Tropical and Public Health Institute in Basel, who is in the midst of his own cell phone study, summed up this way: "You can see patterns in the data that show some risk, but the issues of selection and recall bias make me concerned." This reflects the consensus view of Interphone.

The problem with selection bias —also called participation bias— became apparent after the brain tumor risks observed throughout the study were so low as to defy reason. If they reflect reality, they would indicate that cell phones confer immediate protection against tumors. All sides agree that this is extremely unlikely. Further analysis pointed to unanticipated differences between the cases (those with brain tumors) and the controls (the reference group).

The second problem concerns how accurately study participants could recall the amount of time and on which side of the head they used their phones. This is called recall bias.

The published paper addresses these biases, but not completely. One notable omission is a discussion of an analysis carried by the Interphone group to correct for selection bias. The tumor risks were recalculated with a different reference group —light users instead of non-users. The new set of risks presents a totally different picture: They are higher and significant. "The results are important and very suggestive," Cardis told *Microwave News* . (See our related story: "Interphone's Provocative Analysis of the Brain Tumor Risks".)

The potential influence of recall bias is harder to estimate. In an **analysis** published last year, the Interphone team reported that there was "little evidence" that recall bias is non-differential. That's a fancy way of saying that it would

not be expected to substantially change the observed tumor risks.

Nevertheless, **Joachim Schüz**, who led the German Interphone group, told Microwave News that he is "very confident" that recall bias affected the study. "We have identified implausible values of use in the main data set," he said. Schüz is now with the **Danish Cancer Society**. Christoffer Johansen, a member of the Danish Interphone team who is also at the cancer society, noted that the possible role of recall bias is "difficult to quantify."

On the other hand, Michael Kundi of the **Medical University of Vienna**, questioned the influence of recall bias. "There are no facts that support the assumption of a distorting recall bias," he said in an interview.

What About the Earlier Studies?

Another telling indication of the tensions within the Interphone group is the extremely brief discussion of previous epidemiological studies. It would appear that they could not agree on how to describe them.

The earlier studies are reviewed in one paragraph. The work of the Swedish team lead by Lennart Hardell, which has attracted worldwide attention, is dismissed in a single sentence: "However, the methods of these studies have been questioned." This is in fact an opinion of some members of the Interphone group, sometimes known as the **ICNIRP** contingent. The **critical review** was written by ICNIRP's committee on epidemiology. Three Interphone members were on that panel: **Anders Ahlbom**, **Maria Feychting** and **Tony Swerdlow**.

In an interview, Hardell, who is with **Örebrö University**, challenged this criticism. "I cannot understand their statements, either they do not understand or have not read my papers," he said. In a statement, Hardell stated that he sees the Interphone study as supporting his own work, which shows that "the continuing use of a mobile phone increases risk of brain cancer."

David Carpenter, the director of the Institute for Health and Environment in Albany, NY, was even harsher in his criticism: "It's unprofessional to ignore some of the strongest evidence that shows a risk." Carpenter and Hardell, as well as Michael Kundi, are members of the **BioInitiative Working Group**, which has called for precautionary policies for the use of cell phones.

When asked about this omission, Elisabeth Cardis said, "It was not an easy decision," adding that, "We would have needed a significant amount of text." Cardis agreed that the Hardell results are "not inconsistent with those of Interphone."

The Interphone paper fails to cite any meta-analyses of the past epidemiological studies. (A meta-analysis is a way of combining past studies to determine if they show a consistent pattern of results.) One such **meta-analysis**, carried out by a Korean-U.S. team and published last year, concluded that, "There is possible evidence linking mobile phone use to an increased risk of tumors."

Joel Moskowitz of the University of California, Berkeley, a coauthor of the meta-analysis told Microwave News that he was "surprised" that there was no discussion of his and other meta-analyses in the Interphone paper.

sate 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 on the table on p.5 taken from Appendix 2.

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 nonusers 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."

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.

Brain Tumor Risks Corrected for Selection Bias

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

Source: **Appendix 2** of **Interphone Paper**