Interphone Points to Long-Term Brain Tumor Risks; Interpretation Under Dispute

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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.

See also: Interphone's Provocative Analysis of the Brain Tumor Risks and Interphone Resources

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?

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.

Interphone, Christopher Wild, IARC, Elisabeth Cardis, CREAL, Bruce Armstrong, Siegal Sadetzki, Maria Feychting, Jack Siemiatycki, Martin Röösli, David Carpenter,

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