One Conclusion Emerges From Interphone Study: Controversy Will Continue

By Judy Peres

The 13-nation Interphone study was supposed to establish, once and for all, whether a link between cell phone use and brain tumors exists. But after 10 years and more than $25 million, the only clear message to emerge was that more research was needed.

The study, which the International Agency for Research on Cancer sponsored and the *International Journal of Epidemiology* reported last month, spawned confusing press reports. The *Evening Times* (Glasgow) trumpeted, “Phones not linked to cancer,” while the *Sunday Times* (London) declared, “Heavy mobile users risk cancer”—and other headline writers tried to take positions between the extremes.

If the lay press didn’t know what to make of the results, the Interphone researchers also seemed to have trouble agreeing on what the study showed.

Maria Feychting, M.D., Ph.D., of the Karolinska Institute in Stockholm, an Interphone study group member, said in a press release, “The use of mobile phones for over 10 years shows no increased risk of brain tumors.” But principal investigator Elisabeth Cardis, Ph.D., of the Centre for Research in Environmental Epidemiology in Barcelona, told Microwave News, “To me, there’s certainly smoke here. Overall, my opinion is that the results show a real effect.”

In an interview with JNCI 2 weeks later, Cardis was more careful: “We have not demonstrated an increased risk of brain cancer, but I think it’s important to point out that we also have not demonstrated that there’s no risk.”

**Range of Interpretation**

Cardis acknowledged “a range of interpretation among the investigators about whether there is an effect [of cell phone use on the risk of brain tumors] or whether the results are related to bias. . . . Some investigators think there is probably no risk, and the increased odds ratios are just artifacts. Others, on the contrary, think many of the odds ratios may be underestimated. All of these interpretations are legitimate.”

Jack Siemiatycki, Ph.D., of the University of Montreal, who directed one of the Canadian Interphone centers, concluded, “For the great majority of users—about 90%—the message is rather encouraging. There was absolutely no evidence of any risk. There is some doubt in the top 10% of usage, which corresponds to more than 100,000 minutes of cell phone use. If a
person has used it for 10 years, that would correspond to 30 minutes a day, every day.”

But he added, “The level of excess risk that we may be detecting—and I stress may be
detecting—is not a very high risk. Brain cancer
is already a relatively rare type of tumor. In this
subpopulation (the high-level users), we may be
detecting an excess risk of 40% or 80%,
depending on how you look at the data.”

The American Cancer Society estimates
that about 22,000 cancers of the brain and
nervous system will be diagnosed in the
U.S. this year.

Both Cardis and Siegal Sadetzki, M.D., of
the Gertner Institute at Sheba Medical
Center near Tel Aviv, said that limiting one’s
exposure to cell phone radiofrequency en-
ergy would be reasonable until we know the
effects. “Although the risk is not established,”
said Sadetzki, the principal Israeli investiga-
tor, “we have enough indications, and
there are so many users, that we should adopt
the precautionary principle—especially since
it’s so easy to implement. All we need to do
is keep the phone away from the body” by
using a wired earpiece or a speakerphone.

While the members of the Interphone
study group were careful not to disagree
too much with one another publicly, experts
who did not take part in the research were
blunter in their evaluations.

Joel Moskowitz, Ph.D., director of the
Center for Family and Community Health
at the University of California, Berkeley,
School of Public Health, said that the
Interphone study “increases our basis for
believing there is a long-term risk for mo-
bile phone use . . . . The risk is likely to
increase over time. And there is good rea-
son to believe younger people are likely to
suffer greater long-term consequences.”

David Carpenter, M.D., director of the
Institute for Health and the Environment
at the University of Albany, agreed: “I see
this study as adding to the concern that cell
phones cause brain cancer—but only on the
side of the head where the phone is regu-
larly used.” As for precautionary measures,
Carpenter said, “Children should not use a
cell phone except in emergencies.”

But Donald Berry, Ph.D., chair of bio-
statistics at the University of Texas M. D.
Anderson Cancer Center in Houston, said

Devilish Details

The Interphone study has neither reassured the concerned nor convinced skeptics of a link
between cell phone use and risk of brain cancer. The two sides interpret the findings differently,
pointing to details of study design, statistical analysis, and trends in cell phone usage. Among
the arguments on each side:

Those who think the study supports a link argue that:

• The study found several odds ratios of less than 1 (meaning that cell phone users had
fewer brain tumors than nonusers). Most analyses of the data concluded that assuming
that cell phones are actually protective was implausible and, therefore, attributed the
results to one or more sources of bias. That assumption implied that the few findings
of excess risk could be underestimated. “The increased risk is all the more significant
against the background that the study is affected by downward bias,” said Rodolfo
Saracci, M.D., of the National Research Council in Pisa, who cowrote a commentary

• Several previous studies, especially by the Swedish research group led by Lennart
Hardell, M.D., found that cell phone users did have a higher risk of malignant brain
tumors. The risk was greatest for tumors on the same side of the head where the phone
was typically held and was especially high for those who had started using their cell
phones when they were younger than 20 years.

• Typical cell phone use today is much greater than 10 years ago, when the Interphone
cases were recruited. “The average user today would fall into the high-use, high-risk
group in about 13 years,” said Berkeley’s Joel Moskowitz, Ph.D.

• Prevalence of cell phone use has increased explosively, with many people using them
instead of land lines. An estimated 5 billion cell phones are in use worldwide. So, if cell
phone use were carcinogenic, it could reach pandemic proportions.

• The effect of a carcinogen can take 20–30 years of exposure to show up, making even
some skeptics admit that more substantial evidence might yet emerge.

• The increased risk that the Interphone study found was greater for tumors on the same
side of the head (although laterality was established by self-report, which allows for
another source of bias).

• Perhaps most important, “You can’t prove a negative,” as Robert Tarone, Ph.D., of the
International Epidemiology Institute put it.

Those who don’t think the study supports a link argue that:

• The only statistically significantly increased risk estimate (odds ratio [OR] = 1.40) in the main
analysis showed up in the top decile of cumulative cell phone use. But data of reported use in
this group included some implausible values: 10 case patients (and no control subjects) said
that they used their cell phones for 12 or more hours per day. The first nine deciles showed
no upward trend. The odds ratio was significantly decreased (OR = 0.71) in the ninth decile.
And, even in the top decile, the increased risk was not in the longest-use group but in the
short-term users: those who had started using a cell phone 1–4 years before their recruitment.

• “This looks more like random variation than like a dose–response effect,” said Tarone. “If
you had a carcinogen, you’d expect to see increasing risk with increasing exposure.”

• No known biological mechanism to explain any increased risk is evident.

• The subset analysis that showed the biggest odds ratios was arguably inappropriate. In this
analysis, reported not in the main study but in an appendix, the researchers compared more-
frequent cell phone users to minimal users (rather than to nonusers). Saracci believes that
this analysis was “logically justified,” of the type that occupational epidemiology often uses
to eliminate a source of bias. But Berry was skeptical. “This is the kind of thing people do
when they don’t have a positive study—they look for things that are positive. But it raises
the bar. If you now show an effect, the results have to be really compelling, and they’re not.”
flatly, “We don’t have a study here that implicates cell phones. It may be uninformative, but it can never be interpreted to implicate cell phones.”

Robert Tarone, Ph.D., of the International Epidemiology Institute, was equally dismissive. “This was basically a negative study,” he said. “It was so negative that they spent a considerable amount of time in their discussion talking about the problems of doing this type of study and how many ways you can get the wrong answer.”

Tarone, who was involved in the National Cancer Institute’s study of cell phones and brain cancer a decade ago, added, “There’s a ton of research, both in humans and in the lab, and there’s no consistent evidence of harm from radiofrequency energy at exposure levels associated with cell phones.”

**More To Come**
Nevertheless, the concern is not likely to go away. It has persisted since the 1993 lawsuit that launched the cell phone scare in the U.S. That was when a Florida businessman, David Reynard, announced on CNN’s *Larry King Live* that he was suing the manufacturer of his wife’s cell phone. Reynard believed that the phone, which his wife had used for less than a year, had caused her fatal brain cancer. The evidence, he said, was that magnetic resonance imaging showed that her tumor was “directly next to the antenna and seemed to be growing inward from that direction.”
A judge dismissed the case on the grounds of insufficient scientific evidence. Seven years later, Baltimore neurologist Christopher Newman, M.D., brought a similar suit, blaming his 6 years of cell phone use for his brain tumor. That suit, too, was summarily dismissed.

In 2000, the International Agency for Research on Cancer in Lyon, France, part of the World Health Organization, launched the Interphone study, which included more than 5,000 patients with either glioblastoma or meningioma. The agency said in a press release that it will continue to analyze the Interphone data on mobile phone use and tumors of the acoustic nerve and parotid gland.

At least two more international studies are under way. One is the UK’s prospective cohort study, called Cosmos, that is now recruiting up to 250,000 participants to be monitored for at least 20 years. The Department of Epidemiology and Biostatistics at Imperial College London is conducting the study. The other is MobiKids, a case-control study using essentially the same design as Interphone, which the Interphone study group is conducting in children and adolescents. Cardis said that MobiKids would attempt to remedy some of the flaws of the Interphone study. For example, MobiKids, like Cosmos, will use phone company billing records where possible to establish use patterns rather than relying on the users’ recall.

Meanwhile, other researchers are monitoring brain cancer incidence and mortality rates (see Statbite).

“If cell phones are a risk,” said Tarone, “the first definitive evidence we’re going to see will be in trends in brain cancer rates published by NCI or the Scandinavian countries, which saw even earlier cell phone use.” He recently ran the latest U.S. SEER (Surveillance, Epidemiology, and End Results) data for brain cancer incidence rates in the 30–59 age group and found no increase in the last 15 years. But, because of the prevalence of cell phone use, he said, “I’m confident we’ll be able to detect it in our population cancer rates in the near future if cell phones do indeed cause cancer.”

Stay tuned.