# Mobile Phones and Cancer

## *Next Steps After the 2011 IARC Review*

*Jonathan M. Samet,*[a,b] *Kurt Straif,*[c] *Joachim Schüz,*[d] *and Rodolfo Saracci*[e]

Do mobile phones cause cancer? If the answer were to prove to be "yes," then more than half of the world's population is already at risk.[1] Mobile phone use increasingly begins in childhood and will likely extend across the full life span, if this technology is not surpassed by another mode of communication. From the public health viewpoint, the introduction of mobile phones, now used by some 5.5 billion people, represents a massive new exposure for which safety information is needed.

A review carried out at the end of May 2011 by the World Health Organization's International Agency for Research on Cancer (IARC) and published as an IARC Monograph[2,3] gave a first answer to the question. This review classified radiofrequency electromagnetic fields—the type emitted by mobile phones—as "possibly carcinogenic to humans." Corresponding to Group 2B in the agency's four-level system, this expresses an inherent uncertainty based on evidence in humans of a positive association between exposure to an agent and cancer "for which a causal interpretation is considered by the Working Group as credible, but bias and confounding could not be ruled out with reasonable confidence." This classification signals a warning, but without enough evidence to move radiofrequency electromagnetic fields to a higher level of concern (Group 2A-Probable or Group 1-Carcinogenic to Humans).

The 2B classification was driven largely by the epidemiologic findings, particularly a set of case-control studies carried out in Sweden by Hardell and colleagues[4] and the multicountry INTERPHONE study.[5] Difficult methodological problems cloud interpretation of these observational studies,[6] and the IARC Working Group concluded that the human studies provided "limited evidence" for carcinogenicity.

The 2B classification for radiofrequency electromagnetic fields by IARC continues to receive worldwide media attention, and it remains of great interest to the public, reflecting the increasing use of mobile phones in our lives. There are diverse opinions about this classification, with deep skepticism from those who see no possibility of carcinogenesis by radiofrequency electromagnetic fields based on biophysical principles or from those who find the epidemiologic findings less convincing. For instance, an article by a panel of the International Commission on Non-Ionizing Radiation Protection (submitted in March 2011) had concluded that the evidence weighed against causation.[7] An editorial accompanying a case-control study of childhood brain cancer published after the meeting of the IARC Working Group and interpreted as "negative" offered a similar view.[8] At variance with this interpretation, another group of scientists regarded the available data as simply "insufficient to make any determinations" about use longer than 10 years.[9]

From the [a]Department of Preventive Medicine, Keck School of Medicine of USC, Los Angeles, CA; [b]Institute for Global Health, University of Southern California, Los Angeles, CA; [c]Section of IARC Monographs, International Agency for Research on Cancer, Lyon, France; [d]Section of Environment and Radiations, International Agency for Research on Cancer, Lyon, France; and [e]International Agency for Research on Cancer, Lyon, France.
Correspondence: Jonathan M. Samet, 2001 North Soto Street, Suite 330A, Los Angeles, CA 90089-9239. E-mail: jsamet@med.usc.edu.


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Here, we offer our views on these studies and the next steps after the IARC classification. This commentary is based on our knowledge of the epidemiologic evidence and our participation (J.M.S. as Chair and R.S., K.S., and J.S. as members of the IARC secretariat) in the IARC Working Group. We make the inevitable call for "more research" but propose an integrated and strategic agenda that will target key uncertainties, well highlighted by the IARC review.

## THE CURRENT EVIDENCE

The IARC Working Group reviewed most of the literature available on radiofrequency electromagnetic fields up to May 2011. The studies date back decades, reflecting various eras of heightened concern about the consequences of electromagnetic fields—for example, worker exposures to radar, and mobile phones and brain cancer dating from the 1990s. Epidemiologic studies have addressed worker populations with higher whole body exposures than the general population, as well as exposures to the general population. Parallel mechanistic studies have been carried out, largely using in vitro methods. Substantial effort has also been directed toward characterizing human exposures to electromagnetic fields. Even though the Working Group considered about 900 publications, much of the evidence had limitations and was collectively found not to be very informative.

Given the uncertainty about possible underlying mechanisms for carcinogenesis, characterization of hazard has largely been driven by epidemiologic studies. Most have been case-control studies, comparing mobile phone use as reported by people with brain cancer and by controls—comparable people without brain cancer. Studies of this design, including the Swedish and INTERPHONE studies previously mentioned,[4,5] are potentially affected by multiple sources of bias, particularly because of reliance on self-reported mobile phone use as a surrogate for exposure to radiofrequency electromagnetic fields. The INTERPHONE study was carefully executed, including a number of validation studies to estimate magnitude and direction of bias.[10] This endeavor demonstrated the clear limits of case-control studies of the design of INTERPHONE or the Swedish studies, restricted by both information bias coming from inherently limited recall of mobile phone use and selection bias coming from patterns of differential participation by potential cases and controls. Since the May 2011 Working Group meeting, further relevant articles have been published.

In the INTERPHONE study, an elevated risk of glioma was observed only among the 10% of heaviest regular users, measured as cumulative time of mobile phone use (ie, among those who have used the mobile phone for 1,640 hours or more). Alternative metrics of exposure were subsequently explored: in five of the 13 participating countries, exposure was also estimated as cumulative energy absorbed by the brain tissue, finding an increased risk of glioma among the 20% of the subjects with the highest cumulative energy dose.[11] However, an approach followed in most of the remaining countries was to investigate the distance of the origin of the glioma from the exposure source. These did not show associations with several analytic approaches.[12]

Results on 1105 acoustic neuroma cases and 2145 controls in the INTERPHONE study have also been presented, again observing increased risk only in the 10% of subjects with the highest exposure (1,640 hours of cumulative call time).[13] A multicentric case-control study of brain tumors in children (n = 352) and adolescents (n = 646)[14] was published after the IARC meeting and had not been available to the Working Group. Almost all odds ratios were slightly elevated (eg, the odds ratio for regular users vs. nonusers was 1.36, with 95% confidence interval [CI] = 0.92–2.02), although not statistically significant in any of the analyses relating various measures of exposure to brain tumor risk. Overall, the results were inconsistent.[14]

Four cohort studies complete the set of investigations published after the IARC meeting. First, the follow-up of a Danish cohort of mobile phone subscribers (a study considered by the IARC Working Group) was updated and restricted to a large subcohort of >3.21 million people with information on socioeconomic status. These were subdivided into approximately 360,000 mobile phone subscribers between 1982 and 1995 and the rest nonsubscribers.[15] The incidence ratios for brain tumors in subscribers compared with nonsubscribers were 1.02 in both men and women. When analysis was restricted to those with 13 or more years of subscription, the ratios were 1.03 (95% CI = 0.83–1.27) in men and 0.91 (0.41–2.04) in women.[15] The prospective design of the study avoids sources of bias specific to case-control studies; however, exposure misclassification may have arisen from using mobile phone subscription as a proxy for actual phone use, with no information on the amount of use to specifically investigate heavy users.[15]

The second cohort study comprises 791,710 participants in the UK Million Women Study who reported on their use of mobile phones.[16] Incident cancers were tracked over 7 years of follow-up, with no increased risk for glioma or meningioma. For acoustic neuroma, ever-use of a mobile phone was associated with increased risk (relative risk = 1.44 [95% CI = 0.91–2.28]) and the risk was greater for those with 10 or more years of use (2.46 [1.07–5.64]).[16]

The remaining two cohorts comprise populations being followed through cancer registries. One cohort involves the populations monitored for incident cancer during the period 1992–2008 by 12 cancer registries in the US Surveillance, Epidemiology, and End Results Program.[17] During this period, use of mobile phones in the United States went from close-to-none to nearly universal, while age-specific incidence rates of glioma remained nearly constant in the 12 registries, which captured 24,183 cases over the 17 years. This finding is not what would be anticipated based on the patterns of risk observed in relation to time since exposure and cumulative

use in the studies of Hardell and colleagues.[3] The near-stability of the rates is compatible with the risks as estimated from the small proportion (10%) of highly exposed people in the INTERPHONE study.[17]

The final study, an analysis of data from the cancer registries of the Nordic countries, supports a similar null conclusion.[18] This finding is noteworthy because it includes incidence data from populations of some INTERPHONE study centers and the Hardell studies. Overall these newer results do not remove the uncertainty inherent in the "possibly carcinogenic" (2B) IARC classification.

## WAYS FORWARD

Given the IARC classification and the rapidly rising number of people exposed to radiofrequency electromagnetic fields, a precautionary call for more research is warranted. However, more research should not be implemented without a coordinated plan that would strategically address the most critical uncertainties. The IARC Monograph[3] represents a starting point for identifying those uncertainties, and there are useful references for constructing such research strategic agendas. In 2010, the World Health Organization issued a general research agenda for radiofrequency fields[19] (now being updated), and the same topic had been considered by the European Union in 2009.[20] There are models in other public health research areas as well; for example, a US National Research Council Committee developed a 13-year research portfolio for addressing uncertainties related to the risks for human health of airborne particles.[21] The committee developed principles for assigning priorities related to feasibility, timing, and decision-making value, and then evaluated progress with the agenda on a 6-year time frame. Multiple research agendas have also been developed for engineered nanomaterials—a parallel example of exposure to an emerging technology with a highly uncertain evidence base.[22,23] In our opinion, the research agenda for mobile phones and cancer include specific components that are given below.

### Epidemiologic Studies: Analytic

#### Cohort Studies

Prospective approaches are needed that are based on access to industry records of calls, essential for a valid assessment of exposure. We have mentioned one cohort (longitudinal) study in Denmark that used industry records for exposure and record linkage for outcomes.[15] Although the lack of information on amount of use is a major problem in interpreting the findings, this study exemplifies the general approach of using industry records linked to registries to carry out a cohort study. A prospective cohort study, COSMOS ("Cohort Study of Mobile Phone Use and Health"), is underway in five European countries. This study of ~290,000 men and women 18 years and over is obtaining permission to prospectively access and archive records of mobile phone use.[24] Although the study has been launched, the follow-up of the study population is not yet secured. Unfortunately, COSMOS could become a great missed opportunity to obtain insight into possible cancer risks associated with long-term mobile phone use.

#### Reanalysis of the Main Case-control Studies

We have doubts about the value of embarking in new case-control studies with design similar to those already reported, given the inherent limitations of their design for research on mobile phone use and cancer. Questions persist about the two studies that were most critical to the IARC classification. Given the importance of these two studies and pending the results—still several years away—of new prospective studies, reanalysis using individual data and improved analytic methods could be valuable. This would include (1) further development of methods to model radiofrequency exposure and take precise tumor localization into account, investigating whether tumors "cluster" in the most exposed areas of the brain; (2) further modeling of bias, in particular simultaneously taking into account competing upward and downward biases; and (3) parallel reanalyses of the INTERPHONE study and the Hardell studies to better describe consistencies and inconsistencies.

The international context of the INTERPHONE and Swedish studies, involving many different centers, would add complexity to an endeavor of this type. Yet, if technically and financially feasible, such an approach would augment the information that had been available for the Monograph assessment.

### Epidemiologic Studies: Descriptive

Ongoing tracking of patterns of brain cancer incidence is an essential component of any future research. Fortunately, there are many population-based cancer registries that collect data of sufficient quality for such surveillance. The data considered by the IARC Working Group did not show any indication of a recent rise in brain cancer rates. However, the time period covered by most reports had ended 5 or more years earlier, and the small increase in glioma risk in the INTERPHONE study was observed only in 10% of regular users (corresponding to <5% of the total population), making it difficult to detect such an increase (if true) in national registry data.

In the meantime, as mentioned above, further follow-ups of incidence-rate time trends in the Nordic countries[14,17] and the United States[17] have been published,[15,18] still showing no increase—particularly in the relevant subgroup of middle-aged men who were among the first to use mobile phones. These trends have provided consistency checks of the relative risk estimates reported from the analytic studies, showing inconsistency with the Hardell results but not with those of INTERPHONE. These trend analyses have to be continued to address even longer latency periods. In addition, more information on the precise localization of the tumor should

be obtained for reliable trend analysis, for instance in tumors located in the temporal lobes.

### Experimental Studies

Animal bioassays, a standard for toxicologic testing, should be included in the research plan, although such studies should be delayed while awaiting the results of the large bioassay just initiated by the US National Toxicology Program (NTP).[25] Short- and long-term bioassays are planned by the NTP that involve whole body exposure of mice (short-term) and rats (short-term and long-term). Further mechanistic studies may also be warranted, as the IARC Working Group took note of some "positive" mechanistic data.[26]

## KEEPING PEOPLE WELL-INFORMED

Finally, we turn to the furor that immediately followed the IARC classification and the lessons learned for risk communication and management. As with many potentially harmful environmental agents, even before the IARC classification, there was already a range of viewpoints in the face of scientific uncertainty, some strongly held. The classification as possibly carcinogenic to humans was trivialized by some who compared it with other agents having a 2B classification and acclaimed by others who found justification for their opinion that mobile phones present a danger. The subtlety of the 2B classification—that there is some, albeit uncertain evidence of risk, precluding classification as conveying no risk (Group 4)—proved difficult to communicate and did not fit well with media seeking a more definitive position.

Communication was further complicated by the restriction of the IARC Monograph Program to hazard identification because IARC does not quantify risk. A classification as possibly carcinogenic to humans may be misinterpreted by a lay person, meaning that there is indeed an increase in risk, but it is small. Although an underlying "weak association" may reduce the certainty with which a hazard identification is made, the "possible" categorization does not refer at all to the size of risk, but only to the strength of evidence.

Furthermore, as a scientific research institution within the broader World Health Organization structure, IARC is not mandated to propose risk management strategies, and the Working Groups do not consider risk management at all. Consequently, the IARC press release based on the Working Group's review of exposure could offer only reasonable precautionary strategies for reducing exposure to radiofrequency electromagnetic fields from mobile phones.

In this case, as with some other carcinogens, IARC faces two main challenges in communicating about carcinogenicity for agents of general concern. The first challenge is to combine the need for rapid notification of categorization of an agent (which becomes publicly known as soon as a Working Group meeting ends) with provision of a complete, accurate, double-checked Monograph publication presenting the arguments buttressing the Working Group evaluation. Although this cannot be an "instant" operation, any delay is now being minimized through fast online reporting of the principal findings in *Lancet Oncology*. Second, a strategy is needed to combine risk evaluation with comprehensive recommendations for risk control—an objective being pursued through a timely coordination with the World Health Organization to which the latter task institutionally belongs.

It is a long established practice of the IARC Monographs Program to reconsider an exposure when important new evidence has accumulated. The Preamble to the IARC Monographs provides the principles and procedures by which IARC Working Groups evaluate evidence for human carcinogenicity.[27] Within this framework, the classification could be upgraded based on either further epidemiologic studies (finding an association of mobile phone use with brain cancer risk that can be shown not to reflect bias) or sufficiently convincing evidence from experimental studies. A downward classification could result if new and consistent studies, covering the full range of levels of exposure, were published that offered precise estimates around the null and were demonstrably free of bias. In addition, sustained investigative efforts will be needed to set aside the possibility that brain cancer risk from mobile phones will manifest only after substantial latency.

Hence, we are hopeful that responsible stakeholders in the mobile phone issue will develop and implement a strategic research agenda as we suggest. Questions will inevitably persist about the risks of mobile phones, and these questions should be answered with credible research. The IARC 2B classification implies an assurance of safety that cannot be offered—a particular concern, given the prospect that most of the world's population will have lifelong exposure to radiofrequency electromagnetic fields.

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