The JNCI Study by Aydin et al on Risk of Childhood Brain Cancer from Cellphone Use Reveals Serious Health Problems

L. Lloyd Morgan, Sr. Research Fellow Environmental Health Trust,
Devra Davis, PhD, MPH, President Environmental Health Trust
Dr. Ronald B. Herberman, Chairman of the Board Environmental Health Trust
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Introduction

Contrary to the accompanying Guest Editorial, the widely circulated "media spin," and a Journal of the National Cancer Institute Press Release the just released study in the JNCI[1] by Aydin et al[1] raises major concerns about cellphone safety despite the authors interpretation as showing no increased risk of brain cancer in children and adolescents from cellphone use.

The Conclusion and the Results of the abstract, "The absence of an exposure–response relationship either in terms of the amount of mobile phone use or by localization of the brain tumor argues against a causal association," and "No increased risk of brain tumors was observed for brain areas receiving the highest amount of exposure," are contradicted by the data within the paper.

Further the study's introduction states, "The lack of genotoxicity of mobile phone radiation has been confirmed by experimental animal and laboratory studies [citing 2 papers from 1999 and 2001]." The authors are, or should be, well aware of a multiplicity of papers showing genotoxicity published in the last decade [e.g. 2-4].

Results

Contradicting the abstract's conclusion, Table 4 found a statistically significant greater than doubled risk of brain cancer, 2.8 years after the first subscription for a cellphone began (OR=2.15, 95% CI=1.07 to 4.29) along with a 99.9% confidence of a trend that the longer the subscription the higher the risk. Thus, this report found a classic example of what is termed an "exposure-response relationship," with longer time since exposure signaling a greater risk of disease.

Contradicting the abstract, Table 5 showed that when the duration of cellphone subscription was more than 4 years (the highest exposure) from ipsilateral use greater than a 3-fold risk of brain cancer (OR=3.74, 95% CI=1.19 to 6.71), and close to a 3-fold risk when the number of cellphone calls was greater than 2,638, the highest exposure (OR=2.91, 95% CI=1.09 to 7.76).

[1] "Children and adolescents who use mobile phones are not at a statistically significant increased risk of brain cancer compared to their peers who do not use mobile phones, according to a study published July 27 in the Journal of The National Cancer Institute."

While the Results section discussed the lack of consistent results at substantial length, it never discussed the fact that the study design had limited statistical power to find consistent results due to the relative small number of cases in each category.

Ipsilateral/Contralateral Data (tumor same side/opposite from where cellphone was held, Table 5)
Many other studies have found a clear association between side of head on which phone use was generally reported and location of brain tumor, referred to as ipsilateral association. Analysis of the reported data in this study found an increased ipsilateral or contralateral risk of brain tumors in most cases and nearly half (46%) of these results that were statistically significant or borderline statistically significant. Eight data trends were reported, and seven of these showed increasing risk with increasing exposure and were either statistically significant or borderline significant. With a five-fold increased risk of brain cancer in children contained within these trends, it is hard to imagine how this did not grab the attention of the authors and the editors of the JNCI.

At first glance, because the ipsilateral risks found in this study are smaller than the contralateral risks, there appears to be something wrong. The most likely explanation is that the reported laterality was not consistent with the use. Nevertheless these results indicating increased risk for brain cancer are of *major concern*.

Among the possible explanations for why holding a phone on the opposite side of the head from the tumor, where very little cellphone radiation was absorbed results in a greater risk compared to holding the cellphone on the same side of the head where almost all of the cellphone radiation was absorbed, are:

1. There are more brain tumor cases (215in the “Central or unknown location” than in either the ipsilateral (208) or contralateral (190) results. The lack of tumor location data is a major flaw in this report, and such key data should have been available from hospital records.
2. Ipsilateral use is defined in the study as “predominately on same side of head, or both sides of head.” Strangely a footnote implies all of these data should have been excluded.[2]
3. Contralateral use is defined in the study as “mostly on side opposite the tumor.”[2]
4. Ipsilateral, contralateral and central or unknown locations are mutually exclusive categories, yet when the cases in each category are summed, the total is substantially larger than the number of cases (613 compared to 352). No explanation is provided.

The study’s definitions of ipsilateral and contralateral use differ from dictionary definitions,[3] and from those employed in all previous cellphone studies.

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[2] “All matched sets in which the case patient and/or the control subject was a regular contralateral user were *excluded* from the ipsilateral analyses; similarly, sets in which the case patient and/or the control subject was a regular ipsilateral user were excluded from the contralateral analyses.” [Emphasis added]
[3] Ipsilateral: “situated or appearing on or affecting the same side of the body;” Contralateral: “occurring on or acting in conjunction with a part on the opposite side of the body.” [5]

This suggests that this anomaly may be the combined result of unknown locations, and the unprecedented and overlapping definitions of laterality in this study. It also suggests that children and adolescents may in fact have a shorter latency time for the development of brain cancer than adults. Given the large significant increases in brain cancer in children found from both reported ipsilateral and contralateral use, and the inconsistent definitions of these terms in this study, such data should be taken seriously.

Data Discrepancies

In examining the detailed data within the text in comparison to the summary data we find the following discrepancies:

1. The study reports 423 eligible cases and 909 eligible controls, with participation by 352 cases (83.2%) and 646 controls (71.0%) resulting in exclusion of 71 cases and 263 controls. Yet when the reasons for exclusion are summed, the number of cases excluded were 121 (50 more than stated), and the number of controls excluded were 280 (17 more than stated. This would result in case participation of 60% and control participation of 69%, which in turn would likely increase various biases.
2. The text reports that 35% of cases and 34% of controls had operator data for length of time since prescriptions began. Calculating the number of cases and controls this would mean that there would be 123 cases and 200 controls with this information. Yet, Table 4 reports 196 cases and 360 controls. The reason for this discrepancy is unclear, but it would likely make a large difference in the associated risks as there would be 37% fewer cases and 39% fewer controls.
3. As noted above, the number of cases in Table 5 sums to 613, when the total number of cases were 352.

Missing data

Table 6 reports the risk from cordless phone use. However, for 33% of the cases, the data are "missing," as well as for 35% of the controls. This major data gap for cordless phones, which also generate radiofrequency emissions, is striking in contrast to the detailed data for cellphones. Yet other than reporting the missing data in Table 6, there is no mention of such a glaring problem.

Table 6 reports two identical P-trend values (0.20 or 80% confidence that there is a trend for increasing risk with increasing exposure). Certainly, removing the missing data from the trend analysis would result in a lower P-trend, and it might have resulted in a statistically significant trend.

Choice of Cutoffs Used in Exposure Ranges

In the Statistical Analysis section the choice of cutoffs used for exposure ranges is stated, "… the 50th and 75th percentiles were chosen as cutoffs to allow for the skewed data distribution." Also in Table 6 where cordless phone data is presented a footnote stated, "The 75th and 90th percentiles served as cutoffs because of broad categories." Nothing is said about what these "broad categories" are, or how using different cutoffs would affect the reported results.

Journal of the National Cancer Institute's Invited Editorial
The JNCI invited Editorial, written by two principals of the International Epidemiology Institute (IEI), John Boice and Robert Tarone, who are former NCI employees, ignores these numerous methodological problems. The editorial describe the "Implications" of this study as, "The authors found little or no evidence that mobile phones increase brain tumor risk, and the single positive association could be explained by bias or chance."

Numerous data discrepancies and other problems can be found with this paper that makes its publication in a peer-reviewed journal like the JNCI quite surprising. In fact there are multiple positive association in Tables 4 and 5 as indicated above. It appears that this paper was rushed to publication in order to offset the impact of the World Health Organization's declaration that cellphones are "possible human carcinogen." based on an expert review for the International Agency for Research on Cancer, by 30 experts from 14 nations [6].

According to David Michaels who heads the Federal Occupational Safety and Health Agency (OSHA), IEI is one of many "product protection firms" [personal communication] hired by corporations to create doubt about products that may cause harm. For more information see: http://www.cspinet.org/integrity/nonprofits/international_epidemiology_institute.html.
In *Disconnect—the truth about cell phone radiation*, Davis reports that IEI engaged in this work with the Danish Cancer Society as part of a business development strategy [7].

IEI designed the Danish cellphone cohort study. This study was 100% funded by industry and by IEI, and examined the risk of cancers and neurological diseases from over 400,000 subscribers (85% were men, and over 200,000 corporate users were excluded).

Three Danish cellphone cohort studies have been published (2 by JNCI) over a period of 8 years [8-10]. They found being a cellphone subscriber *protects* cellphone subscribers from the following cancers:[4] All cancers, cancer of the buccal cavity/pharynx, esophageal cancer, stomach cancer, liver cancer, all smoking related cancers, lung cancer, cancer of the larynx, kidney cancer, pancreatic cancer, brain cancer of the parietal lobe (men & women), brain cancer of the cerebellum (men & women), and brain cancer with ≥10 year cellphone subscription (men & women). Additionally, for neurological diseases they found statistically significant *protection* for men & women for: Alzheimer's disease, vascular dementia, other dementia, Parkinson's disease, and male epilepsy.

These statistically significant *protective* effects in adult cellphone users were reported by the authors as finding "no risk" from being a cellphone subscriber. In fact, epidemiologists understand that cohorts cannot be studied to determine the risks of rare diseases such as brain cancer. With an expected rate of about 6 per 100,000 in persons of all ages, in order to detect a change in brain tumors risk in a cohort, one would have to study a cohort that would be several

[4] Men, unless otherwise noted.

million in size, Since being a cellphone subscriber cannot conceivably protect the subscriber from all these cancers and neurological disorders, these studies appear to be designed to create doubt that cellphones are a health hazard.

Conclusions

Both the Results and Conclusion of the abstract are contradicted by the reported results. Contrary to the commentary, this paper presents evidence for a shorter latency of brain cancer tied with cellphone use in children—a finding that is consistent with studies of other environmental carcinogens in children.

The inconsistent results reported for ipsilateral and contralateral use of cellphone and location of brain tumor are likely to reflect the failure to use standardized definitions for these terms and/or the far greater number of cases in Table 5 than the actual cases in the study. Whatever the problem, the ipsilateral/contralateral risks should be taken as a serious indication of potential risk.

The statement in the Guest as JNCI Editorial in JNC, "Children and adolescents who use mobile phones are not at a statistically significant increased risk of brain cancer compared to their peers," is a gross misrepresentation of what this paper actually reports.

The contradictory data between the table and the text or within the text itself speaks of a rushed effort to publish and/or a poor peer-review process.

Lastly, several cellphone companies provided funding for this study. The problem of financial bias has been well documented [11]. Conspicuously missing from the Funding and Notes section are individual conflicts of interests among the authors (e.g., consulting, stock ownership, director status, etc.).

Commonly science journals report the funding sources for the research paper. Less frequently they report funding provided to individual authors. For individual authors they rarely report such conflicts-of-interest as consulting arrangements, stock ownership (for authors and spouses), directorships, etc. The recent dismissal from the IARC Monograph meeting of Professor Anders Ahlbom of the Karolinska Institute because of his individual conflicts of interest, speaks of the essential need for this to be standard practice in all journals and, in particular, the JNCI, both for original articles and for invited commentaries.

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