Commentary

Evaluation of the Validity of a Nonlinear J-Shaped Dose-Response Relationship in Cancers Induced by Exposure to Radiofrequency Electromagnetic Fields

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ABSTRACT

The radiofrequency electromagnetic fields (RF-EMFs) produced by widely used mobile phones are classified as possibly carcinogenic to humans by International Agency for Research on Cancer (IARC). Current data on the relationship between exposure to RF-EMFs generated by commercial mobile phones and brain cancer are controversial. Our studies show that this controversy may be caused by several parameters. However, it seems that the magnitude of exposure to RF-EMFs plays a basic role in RF-induced carcinogenesis. There is some evidence indicating that, in a similar pattern with ionizing radiation, the carcinogenesis of non-ionizing RF-EMF may have a nonlinear dose-response relationship. In this paper, the evidence which supports a nonlinear J-shaped dose-response relationship is discussed.

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Keywords

Dose-Response Relationship, Radiation ● Cell Phone ● Electromagnetic Fields

Nonlinear Dose-Response Relationship

X-ray discovery by Roentgen in the fall of 1895, and the discovery of radioactivity by Becquerel in early 1896 opened new horizons in science and medicine. In spite of this great revolution in science, these discoveries gradually led to irrational use of radiation for treatment of a wide spectrum of diseases such as impotence and blindness as well as non-medical applications (e.g. shoe-fitting fluoroscopes [1]. Therefore, now there is a growing concern about the health effects of human exposure to ionizing radiation. Although the so called linear non-threshold (LNT) hypothesis is widely accepted by regulatory authorities, substantial evidence indicates that exposure to low doses of ionizing radiation, based on a nonlinear dose-response relationship, and only within a specific window of dose and dose rate, can reduce the incidence of the adverse health effects.

Non-detrimental Effects of RF-EMFs

Nowadays, due to rapid advances in telecommunication technology, humans are continuously exposed to nonionizing electromagnetic fields (EMFs). World Health Organization (WHO) estimates that the number

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of mobile phone subscriptions is about 7 billion globally [2]. Increased risk of brain cancer after heavy or long term mobile phone use has been reported by different researchers [3]. Mortazavi et al. have previously tried to answer this question if there are radiofrequency-induced stimulating effects in living organisms [4]. They introduced this hypothesis that in special circumstances, exposures to Radiofrequency Electromagnetic Fields (RF-EMFs) can lead to better responses of animals or humans to different environmental hazards. For example, some evidence supporting the induction of RF-induced cognitive benefits of RF-EMFs has been previously discussed [5]. It has also been reported that exposure to RF-EMFs may cause stimulatory or inhibitory effects on the proliferation and differentiation of stem cells (being stimulatory or inhibitory depends on several factors such as the biological system, experiment conditions, RF-EMF frequency, duration and intensity) [6]. Furthermore, the adaptive response induced by RF-EMF was firstly reported by Sannino et al. [7] and later confirmed by our team [8] and different researchers around the world [9-12].

Can Electromagnetic Fields Cause Cancer?

Currently, International Agency for Research on Cancer (IARC) classifies the EMFs produced by mobile phones as possibly carcinogenic to humans [2]. In this light, numerous studies are being conducted around the world to better evaluate the potential long-term risks associated with mobile phone use. It was previously believed that as RF-EMFs do not have enough energy to remove electrons (producing an ion pair), they are unable to cause cancer. However, considering the evidence of free-radical damage which has been confirmed in studies on humans, animals, plants and microorganisms, some scientists now believe that EMF-induced oxidative stress can cause damage to cellular targets such as DNA and trigger processes which lead to cancer [13].

Studies Showed no Link to Cancer

On the other hand, there are both case control [14] and cohort [15-17] studies which could not link the RF-EMF exposure to cancer. For example, The Interphone Study Group has previously investigated the relationship between brain tumor (glioma and meningioma) risk and mobile phone use [18, 19]. In this study, no elevated odds ratio (OR) for glioma or meningioma was observed ≥10 years after first phone use. This study that was coordinated by the International Agency for Research on Cancer (IARC); a part of WHO, conducted as a joint project between some partner institutions. Furthermore, in Australia, a country in which mobile phone use was started in 1987, it has been reported that despite the steep increase in mobile phone use, no compatible increase in brain cancer incidence has been found [20]. Moreover, a recent study conducted in the Nordic countries (Denmark, Finland, Norway, and Sweden) could not show any association between increased mobile phone use and glioma. This study revealed that while the mobile phone use was increased dramatically, the incidence of glioma remained almost constant from 1979 to 2008 in all these Nordic countries".

Mortazavi et al. have recently reviewed currently published papers claiming no link between exposure to RF and brain cancer. They found that in many cases there were large errors and/or major shortcomings in these papers [21-24]. For example, in one of the papers reviewed by this research group (Analysis of Mobile Phone Use Among Young Patients with Brain Tumors in Japan), a 400% difference in brain tumors was masked by statistics! [24] Considering the controversies exist today, they reported that these controversies may be caused by several key parameters, especially the large difference in the magnitude of exposures to RF-EMFs in different studies.

Studies Showed a Link to Cancer

A recent 25 million USD large-scale ani-

mal study conducted by the U.S. National Toxicology Program (NTP) showed statistically significant increases in cancer in rodents exposed to GSM or CDMA signals for two-years [25]. This study showed that malignant gliomas in the brain and schwannomas of the heart could be linked to mobile phone exposures. Hardell and Carlberg in 2015 performed a pooled analysis of two case-control studies on malignant brain tumors and showed that mobile phone use was linked to increased risk of glioma (OR=1.3, 95% CI=1.1-1.6 overall) [26]. Moreover, based on the findings of a case-control study on brain tumors, a significant association was found between mobile and cordless phone use and malignant brain tumors. The authors reported that their findings support the hypothesis that exposure to RF-EMFs generated by wireless phones can play a key role in the initiation and promotion phases of carcinogenesis [27]. Bortkiewicz et al. have recently performed a meta-analysis of twenty four studies (26 846 cases, 50 013 controls) and reported that their findings supported this hypothesis that long-term use of mobile phones is linked to increased risk of intracranial tumors [28]. They reported that mobile phone use over 10 years was significantly associated with higher risk of intracranial tumors (all types). Another meta-analysis performed recently by Wang and Guo showed a significant association between mobile phone use (> 5 years use) and the risk of glioma [29].

The Confounding Factor of Advanced Diagnosis

It is worth mentioning that some of current studies have introduced the improvements in diagnostic procedures as the reason for increased cancer incidence. For example, increased brain cancer incidence in Australia has been reported to be linked to advances in diagnostic procedures such as computed tomography and other modern diagnostic imaging technologies [20]. In New Zealand has also been reported that the increased glioma rate at ages >70 years can be due to improvements in diagnostic procedures [30]. However, researchers in other countries reported that the increased cancer rate cannot be attributed to better diagnostic procedures and suggested that the role of exposure to both ionizing (e.g. rapidly increased number of CT scans) and non-ionizing radiation should be further studied [31].

Evidence Supporting a Nonlinear Dose-Response Relationship

Belyaev has previously reported that the combination of exposure duration with power flux density can be regarded as the most appropriate value for setting the safety standards for exposure to RF-EMFs [32]. He has also reviewed the data which showed a S-shaped or sigmoid dose-response relationship for microwave effects [33]. Although the current controversy about the role of exposure to RF-EMFs on cancer incidence may be due to several parameters but it seems that the level of exposure plays a basic role in this issue. For example, although the Interphone study could not find elevated odds ratio (OR) for glioma or meningioma ≥10 years after first mobile phone use, an increased risk of glioma and much less so meningioma, in the highest decile of cumulative call time was suggested (an increased risk of glioma could be suggested at the highest exposure levels but biases and error prevented a causal interpretation) [18]. Furthermore, in a study performed in France on a possible relationship between mobile phone exposure and primary central nervous system tumors (gliomas and meningiomas) in adults, it was found that heavy mobile phone use could be linked to brain tumors [34]. Moreover, a case-control study in Finland found no excess risk associated with self-reported short term and medium term use of mobile phones. However, the authors claimed that there are uncertainties for long term use (only a small proportion of participants were long term users in their study) [14]. The meta-analysis conducted by Bortkie-

wicz et al. also showed that long-term use of mobile phone could be linked to intracranial tumors [28]. Prasad et al. have also provided evidence which proves an association between mobile phone use and brain tumors especially in people who used their mobile phones ≥10 years [35]. Yakymenko et al. have also reviewed the published data on carcinogenic effects of long term exposure to low intensity microwave radiation [36]. They reported that the carcinogenic effect of radiofrequency radiation should typically be manifested after long term exposures (durations > 10 years). In addition, Alexiou and Sioka have reported that although long-term mobile phone use can possibly be associated with increased risk of intracranial tumors, more data is needed to draw firm conclusions [37].

Is there a J-Shaped Dose-Response Relationship?

In this light, it can be postulated that in a similar pattern with ionizing radiation, the carcinogenesis of non-ionizing RF-EMF may have a nonlinear dose-response relationship. There are published reports which their findings support the possible validity of a J-shaped nonlinear dose-response relationship. However, the authors usually only reported that they could not find any excess risk linked to mobile phone use. For example Shresta et al. found an odds ratio (OR) of 0.39 (95% confidence interval 0.21, 0.72) for pituitary tumors in regular mobile phone users [14]. INTERPOHNE study also showed a reduced OR for glioma for ever having been a regular user of mobile phones (OR 0.81, 95% confidence interval 0.70, 0.94). In this study there was also a reduced OR for meningioma (OR 0.79, 95% confidence interval 0.68, 0.91) [19]. The findings of a systematic review and meta-analysis recently published by Yang et al. could not find a link between mobile phone use of any duration and the odds of high-grade glioma (OR = 0.81, 95% CI = 0.72–0.92). However, these researchers found a significant positive association between long-term mobile phone use (> 10 years) and glioma (OR = 1.44, 95% CI = 1.08–1.91) as well as long-term ipsilateral mobile phone use and the risk of glioma (OR = 1.46, 95% CI = 1.12–1.92). In their study, there was a 2.22 times greater odds of the occurrence of low-grade glioma for long-term mobile phone use (OR = 2.22, 95% CI = 1.69–2.92) [38].

There are also reports that their data clearly show a J-shaped nonlinear response for RF-induced cancers. However, the authors did not pay any attention to their findings. For example Morgan et al. in 2015 published a review on the findings of CERENAT and INTERPHONE studies [39]. In this review, they reported results obtained by Coureau (2014, 2015) for cumulative hours of use and the ORs for glioma and meningioma. We plotted these findings to better show the J-shaped dose response relationship (Figures 1 and 2).

It is worth noting that recently Momoli et al.

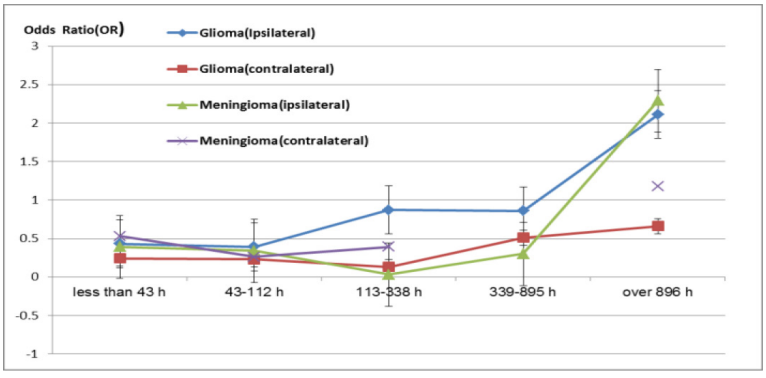

Figure 1: Results for cumulative hours of use [34].

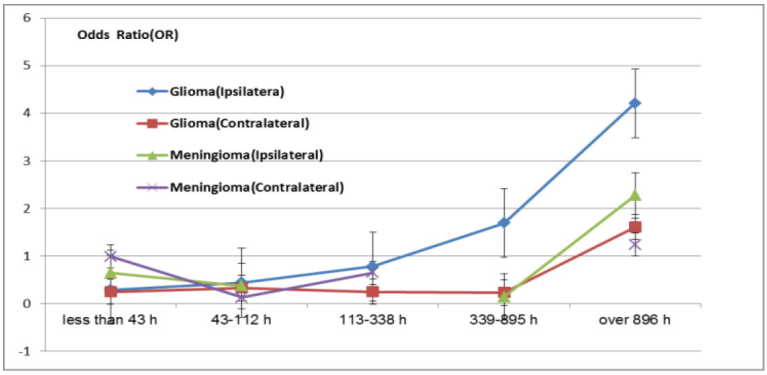

Figure 2: Corrected results for cumulative hours of use [40].

have re-analyzed the Canadian data from the thirteen-country INTERPHONE case-control study [41]. These authors applied a probabilistic multiple-bias model to address possible biases simultaneously. As shown in Figure 3, results of this study, after adjustment for bias

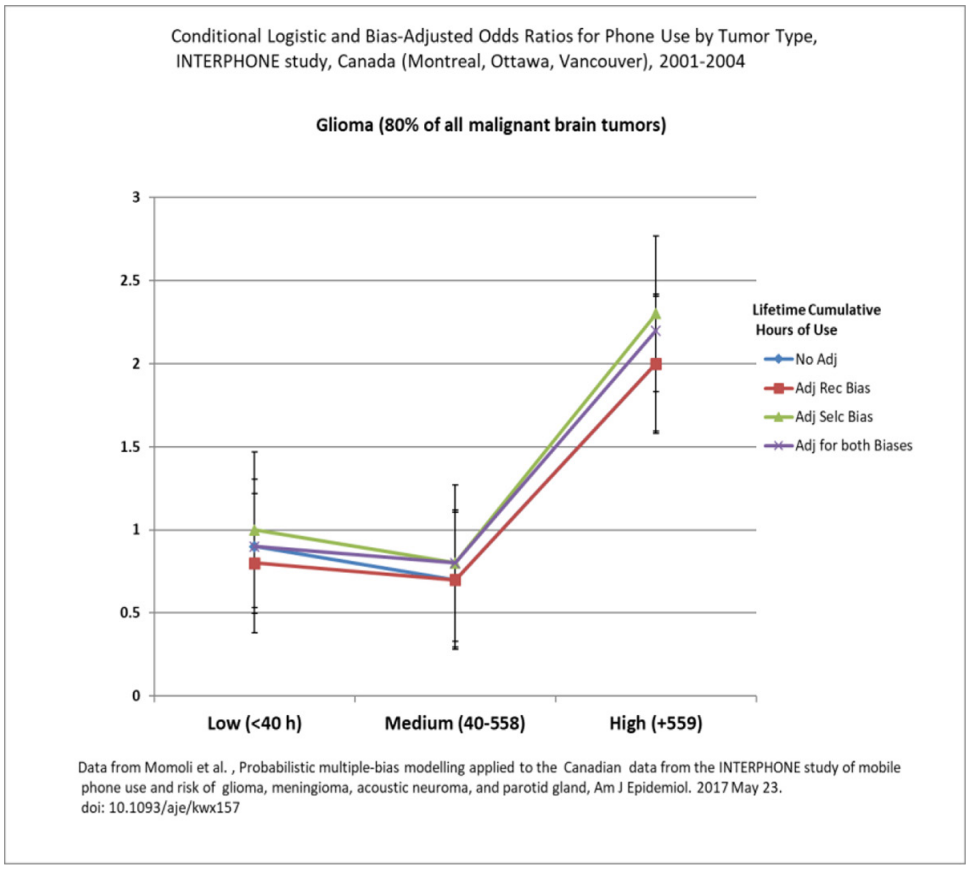

Figure 3: Conditional logistic and bias adjusted Odds Ratios for phone use in glioma [41].
No Adj: No Adjustment for Biases
Adj Rec Bias: Adjustment for bias due to recall error
Adj Selec Bias: Adjustment for selection bias
Adj for both Biases: Adjustment for recall and selection biases, with random error

due to recall error, nearly shows a J-shaped dose response relationship for cumulative hours of mobile phone use and gliomas which make-up 80% of all malignant brain tumors, (< 40 hours, OR = 0.8, 95% CI = 0.7–0.9 and for 40-558 hours, OR = 0.7, 95% CI = 0.6–0.8, while for >559 hours, OR = 2.0, 95% CI = 1.8–2.1).

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Conflict of Interest

None

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