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## LETTER TO THE EDITOR

### MOBILE PHONES, NON-IONIZING RADIOFREQUENCY FIELDS AND BRAIN CANCER: IS THERE AN ADAPTIVE RESPONSE?

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□ There is widespread concern among the general public regarding the ever increasing use of mobile phones. The concern is mainly because the antenna which transmits non-ionizing radiofrequency fields is held close to the head during use and thus might cause brain cancer. By far, the largest epidemiological study was conducted by the INTERPHONE study group and the results were published in 2011. The author's conclusions were (i) no increased risk of meningioma and glioma in mobile phone users and (ii) there were suggestions of an increased risk for glioma at the highest exposure levels but, bias and error prevented a causal interpretation. We have carefully examined all of the odd ratios presented in the INTERPHONE study publication: our results showed 24.3% decreased and 0.7% increased risk for meningioma and 22.1% decreased and 6.6% increased risk for glioma. Hence, we hypothesize that the overwhelming evidence for the decreased risk for both diseases may be due to the induction of 'adaptive response' which is well-documented in scientific literature

*Key Words: Mobile Phones; Radiofrequency fields; Brain Cancer; Adaptive Response*

Non-ionizing radiofrequency fields (RF) are ubiquitous in our environment, especially after the introduction of wireless communications devices which deliver voice, data and images. The widespread use of mobile phones has led to increased concern in the general public regarding potential adverse health effects, especially brain cancer since the antenna which transmit RF is held close to the head during use. During the last several decades, researchers have been examining the extent of genetic damage in human and animal cells exposed *in vivo* and *in vitro* to RF since significant increase in such damage in somatic cells can lead to the development of cancer and/or cell death while such damage in germ cells can be transmitted to subsequent generations. The conclusions from peer-reviewed scientific publications and reviews, expert scientific adviso-

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ry committees in several countries and international organizations were similar: the currently available data did not provide sufficient evidence that RF exposure *per se* is genotoxic (reviewed in Verschaeve *et al.* 2010; Verchaeve 2012). The issue related to RF emitted from mobile phone use and the development of brain cancer was examined in several epidemiological investigations. The data were controversial: some suggested increased incidence of brain and other types of cancers while the others did not (reviewed in Repacholi *et al.* 2012).

By far, the largest investigation was conducted by the INTERPHONE study group using a common protocol in 13 countries with 16 study centers. It was interview-based case-control study with its main analyses involving 2409 meningioma and 2708 glioma cases, i.e., individuals using mobile phone regularly (without hands-free device, cumulative call time of <5 to >1640 hours and cumulative number of calls of <1.5x100 to <270x100) and, 2662 and 2972 controls matched for age, gender and area of residence, respectively. The detailed odd ratios (ORs) and 95% confidence limits (CI) for meningioma and glioma were presented in Tables 2-6 in the publication (The INTERPHONE study group 2010). We have carefully examined all ORs (<1.0 for decreased and >1.0 for increased risk) and CIs (<1.0 for decreased and >1.0 for increased risk) presented in each of these tables and our results for meningioma and glioma separately as well as together for both diseases were summarized in Table 1. There was a consistent and inter-country replication pattern of reduced risk for both meningioma and glioma in mobile phone users. (1) For meningioma, there were a total of 33 ORs which were <1.0 (CI <1.0) and only 1 OR which was >1.0 (CI >1.0) in a total of 136 ORs: the highest OR of 4.80 (1.49-15.4 CI) for >1640 hours of cumulative call time was based on small number of cases (Table 3 in the INTERPHONE

**TABLE 1.** Summary of odd ratios (ORs) and 95% confidence limits (CI) for meningioma and glioma presented in Tables 2-6 by the INTERPHONE STUDY group (2010)\*.

	Meningioma			Glioma			Meningioma + glioma		
	↓Risk p<0.05	↑Risk p<0-05	Total ORs	↓Risk p<0.05	↑Risk p<0-05	Total ORs	↓Risk p<0.05	↑Risk p<0-05	Total ORs
Table 2	9	0	25	11	1	25	20	1	50
Table 3	3	1	15	4	1	15	7	2	30
Table 4	13	0	45	5	1	45	18	1	90
Table 5	8	0	30	10	1	30	18	1	60
Table 6	0	0	21	0	5	21	0	5	42
Total ORs	33	1	136	30	9	136	63	10	272
% ORs	24.3	0.7		22.1	6.6		23.2	3.7	

\*International Journal of Epidemiology. 39, 675-694, 2010.

↑Risk: Odd ratios >1.0 with 95% confidence limits >1.0

↓Risk: Odd ratios <1.0 with 95% confidence limits <1.0

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study group 2010). Thus, the overall ORs indicated 24.3% reduced and 0.7% increased risk for meningioma. (2) For glioma, there were a total of 30 ORs which were  $<1.0$  (CI  $<1.0$ ) and 9 ORs which were  $>1.0$  (CI  $>1.0$ ) in a total of 136 ORs: the highest OR of 3.77 (1.25-11.4 CI) reported for  $>1640$  hours of cumulative call time was based on small number of cases (Table 3 in the INTERPHONE study group 2010). Thus, the overall ORs indicated 22.1% reduced and 6.6% increased risk for glioma. As the authors of the INTERPHONE study group pointed out (see below) the 6.6 % risk for glioma ( $p<0.05$ ) may be due to ‘bias’ and ‘error’ in mobile phone use reported by the participants in the interphone study (see below). When the ORs and CIs for meningioma and glioma were considered together, there were 63 ORs which were  $<1.0$  (CI  $<1.0$ ) and 10 ORs which were  $>1.0$  (CI  $>1.0$ ) among the total of 272 ORs. Thus, the overall ORs indicated 23.2% decreased and 3.7% increased risk for brain cancer.

Nonetheless, the conclusions of the INTERPHONE study group (2010): (a) there was no increased risk of meningioma and glioma with the use of mobile phones and, (b) there were suggestions of an increased risk for glioma at the highest exposure levels, but, bias and error prevented a causal interpretation. Considering the null hypothesis of no association between mobile phone use and brain cancer, the ORs of  $>1.0$  and  $<1.0$  would be expected. However, the observed consistent and replicated pattern of reduced risk would have very small probability of occurring just by chance (Saracci and Samet 2010). Our observations of 24.3% ‘reduced’ risk for meningioma and 22.1% ‘reduced’ risk for glioma (overall 23.2% reduced risk) were more than that expected by chance occurrence ( $p<0.05$ ). In May 2011, the International Agency for Research on Cancer had invited an expert working group of scientists to assess the carcinogenicity of RF; the group reviewed all relevant peer-reviewed publications, considered the ‘limited’ evidence from human and long-term carcinogenicity studies in experimental animals and, classified RF as a possible carcinogen in group 2B (Baan *et al.* 2011). Such classification was not supported, at least, by genotoxicity-based mechanism (Vijayalaxmi and Prihoda 2012). Furthermore, the overall brain cancer indices among the general population did not suggest an increasing trend after the introduction of mobile phones (Roosli *et al.* 2007; Inskip *et al.* 2010; de Vocht *et al.* 2011; Deltour *et al.* 2012). A more recent prospective study also revealed significantly decreased risk for glioma in mobile phone users (Benson *et al.* 2013).

In this context, it is relevant to discuss the phenomenon of adaptive response (AR) which was originally described by Samson and Crains (1977): cells which were exposed to a very low, nontoxic dose (adaptive dose, AD) of a mutagen become resistant to the damage induced by subsequent exposure to high dose (challenge dose, CD) of the same or similar mutagens. Subsequent studies confirmed the induction of AR (espe-

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cially, by low dose ionizing radiation) in several different organisms including human cells and, some underlying mechanisms were investigated and discussed (Dimova *et al.* 2008). The data in some studies also suggested variability/heterogeneity in the induction of AR, i.e. cells from some blood donors exhibited AR while others did not: the suggestion was that such variability might be, at least in part, genetically determined (Bosi and Olivieri 1989; Vijayalaxmi *et al.* 1995; Krishnaja and Sharma 2008). Several recent reports published in peer reviewed scientific journals indicated that non-ionizing RF exposure was capable of inducing AR: (i) human blood lymphocytes exposed *in vitro* to RF (AD) and then treated with a high dose of a chemical mutagen or ionizing radiation (CD) exhibited significantly decreased genetic damage (Sannino *et al.* 2009; Sannino *et al.* 2011; Zeni *et al.* 2012; Sannino *et al.* 2013), (ii) continuously growing human tumor cells exposed to RF and then treated with a chemotherapeutic drug showed significantly increased viability, decreased apoptosis, and several other biological endpoints indicating protective influence of RF exposure (Jin *et al.* 2012) and (iii) mice and rats exposed (whole body) to RF and subsequently subjected to sub-lethal and lethal doses of ionizing radiation showed significant survival advantage, less severe hematopoietic tissue damage, decreased genetic damage in blood and bone marrow cells, increased levels of colony stimulating factor and interleukin-3 in the serum and increased expression of genes related to cell cycle, etc. (Cao *et al.* 2010, 2011; Jiang *et al.* 2012, 2013; Mortazavi *et al.* 2011, 2012, 2013; Haghani *et al.* 2013). Thus, the results in these reports also provided some mechanistic evidence for RF-induced AR and several others were proposed (Vijayalaxmi *et al.* 2014). In view of the above observations, we hypothesize that RF-induced AR may play a role in reducing carcinogenesis, at least, in some individuals. The hypothesis may be far-fetched and perhaps unconvincing but, stimulating for further investigation(s).

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