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Lennart Hardell* and Michael Carlberg

Using the Hill viewpoints from 1965 for evaluating strengths of evidence of the risk for brain tumors associated with use of mobile and cordless phones[1)]

Abstract

Background: Wireless phones, i.e., mobile phones and cordless phones, emit radiofrequency electromagnetic fields (RF-EMF) when used. An increased risk of brain tumors is a major concern. The International Agency for Research on Cancer (IARC) at the World Health Organization (WHO) evaluated the carcinogenic effect to humans from RF-EMF in May 2011. It was concluded that RF-EMF is a group 2B, i.e., a "possible", human carcinogen. Bradford Hill gave a presidential address at the British Royal Society of Medicine in 1965 on the association or causation that provides a helpful framework for evaluation of the brain tumor risk from RF-EMF.

Methods: All nine issues on causation according to Hill were evaluated. Regarding wireless phones, only studies with long-term use were included. In addition, laboratory studies and data on the incidence of brain tumors were considered.

Results: The criteria on strength, consistency, specificity, temporality, and biologic gradient for evidence of increased risk for glioma and acoustic neuroma were fulfilled. Additional evidence came from plausibility and analogy based on laboratory studies. Regarding coherence, several studies show increasing incidence of brain tumors, especially in the most exposed area. Support for the experiment came from antioxidants that can alleviate the generation of reactive oxygen species involved in biologic effects, although a direct mechanism for brain tumor carcinogenesis has not been shown. In addition, the finding of no increased risk for brain tumors in subjects using the mobile phone only in a car with an external antenna is supportive evidence. Hill did not consider all the needed nine viewpoints to be essential requirements.

Conclusion: Based on the Hill criteria, glioma and acoustic neuroma should be considered to be caused by RF-EMF emissions from wireless phones and regarded as carcinogenic to humans, classifying it as group 1 according to the IARC classification. Current guidelines for exposure need to be urgently revised.

Keywords: acoustic neuroma; causation; glioma; Hill criteria; wireless phones.

[1)]Based on a presentation at the Corporate Interference with Science and Health: Fracking, Food and Wireless, Scandinavia House, New York City, March 13 and 14, 2013.

***Corresponding author: Lennart Hardell,** MD, PhD, Department of Oncology, University Hospital, SE-701 85 Örebro, Sweden, Phone: +46-19-6021000, Fax: +46-19-101768, E-mail: lennart.hardell@orebroll.se

Michael Carlberg: Department of Oncology, University Hospital, Örebro, Sweden

Background

Mobile phones have been used since the early 1980s, and the Scandinavian countries were among the first in the world to adopt this technology. At first, analog phones [Nordic Mobile Telephone System (NMT)] were used, but in the early 1990s, the digital system [Global System for Mobile Communication (GSM)] was introduced. The analog system was definitely closed down in Sweden on December 31, 2007. Nowadays, mobile phones are used more than landline phones in Sweden (1). Worldwide, estimates of 5.9 billion mobile phone subscriptions were reported at the end of 2011 by the International Telecommunication Union (2).

Desktop cordless telephones have been used in Sweden since the end of the 1980s, first using the analog system, but since the 1990s, the digital variant was used. They are very common both in homes and at workplaces, overtaking telephones connected to landlines.

Wireless phones, i.e., mobile phones and cordless phones, emit radiofrequency electromagnetic fields (RF-EMF) when used. Cordless phones should be given an equal consideration as mobile phones when this type of exposure is assessed. In fact, this has not been the case except for the Hardell group studies in Sweden (3–8). When used, the handheld mobile phones gives exposure

to RF-EMF to the brain, especially to the temporal lobe on the same side where the phone is used, i.e., ipsilateral exposure (9, 10). This has given concern of an increased risk of brain tumors, although other potential health effects from RF-EMF cannot be excluded.

Few studies exist with data on long-term (i.e., >10 years) use of wireless phones and health risks. Regarding brain tumors, only case-control studies from the Hardell group in Sweden (3–8) and the Interphone Study Group (11, 12) give such results. However, Interphone presented results only for mobile phone use. The cases in the Hardell group studies were diagnosed during 1997–2003, whereas Interphone included 16 research centers in 13 countries during varying periods between 2000 and 2004. There was no overlap of included subjects in the Hardell group studies and the Swedish part of Interphone. A Danish cohort study on mobile users (13) has been evaluated to be inconclusive due to serious methodologic problems (14–16).

Because of the widespread use of wireless technology, even a small risk increase would have serious public health consequences. In May 2011, the International Agency for Research on Cancer (IARC) at the World Health Organization (WHO) evaluated the carcinogenic effect of RF-EMF to humans. It included radiation from mobile phones and from other devices that emit similar nonionizing EMFs in the frequency range 30 kHz–300 GHz. It was concluded that RF-EMF is a group 2B, i.e., a "possible", human carcinogen (14, 16).

This conclusion was mainly based on epidemiologic studies from the Hardell group in Sweden and the IARC Interphone study. These studies showed an association between two types of brain tumors, glioma and acoustic neuroma, and exposure to RF-EMF from wireless phones. There was no consistent pattern of an association within the studied latency period (time since first exposure), with the most common benign brain tumor, meningioma, suggesting specificity for these other tumor types.

To further evaluate strengths of evidence, Bradford Hill gave a presidential address at the British Royal Society of Medicine in 1965 that appeared afterward as an article in the *Proceedings of the Royal Society of Medicine* at the height of the tobacco and lung cancer controversy (17). That article on causation provides a helpful framework for assessing the brain tumor risk from wireless phones and offers some very insightful comments that are useful in this context. In the article "The environment and disease: association or causation", Hill offered a list of nine aspects of an association to be considered when deciding if an association is causal. He did not intend to give a list of necessary conditions but warned that he did not believe "that we can usefully lay down some – hard-and-fast rules of evidence that *must* be obeyed before we can accept cause and effect". He wrote, "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non* (essential requirement)". In fact, temporality (no. 4 in his list) is required for, e.g., infectious diseases; a cause must precede an effect, as noted later (18). However, Hill was correct that in many cases, it is impossible to define the point in time when the disease covertly started. This holds for virtually all chronic diseases and especially for cancer. Meanwhile, an agent may act as a promoter and an existing tumor is stimulated to grow. Tumor promoters are not able to cause a tumor.

Methods

We used the Hill viewpoints to evaluate the causality on brain tumor risk from RF-EMF emitted from wireless phones. The evaluation was based on studies from the Hardell group (3–8) and Interphone (11, 12), the only studies with results on phone use for more than one decade. Other investigations with relevant data on, e.g., laboratory studies, and the incidence of brain tumors were included. More recent comprehensive reviews on this field of research than the IARC evaluation were also considered (8, 19, 20). Furthermore, some data are presented from a new case-control study on brain tumors by the Hardell group, including the time period 2007–2009 (21–23). For statistical methods used to calculate odds ratios (OR) and 95% confidence intervals (CIs), see previous publications from the Hardell group (3–8, 21–23) and Interphone (11, 12). Random-effects model was used for all meta-analyses using StataSE 12.1 (Stata/SE 12.1 for Windows; Stata Corp., College Station, TX, USA). Restricted cubic splines were used to visualize the relationship between latency and cumulative use of wireless phones and the risk of acoustic neuroma and malignant brain tumors, respectively. Adjustment was made for the same variables as in the logistic regression analysis. Four knots were used at the 5th, 35th, 65th, and 95th percentiles.

Results

Strength

The first criterion discussed by Hill is the strength of the association. The highest risk was found for ipsilateral glioma and acoustic neuroma in the highest exposure category based on cumulative use of mobile phones both in Hardell et al. (7, 8) and Interphone (11, 12) (Table 1). Thus, the meta-analysis yielded in total for ipsilateral glioma OR=1.22, 95% CI=0.58–2.55, which increases with cumulative mobile phone use of >1640 h to OR=2.29, 95% CI=1.56–3.37. In addition, regarding acoustic neuroma, the OR was highest for ipsilateral mobile phone use.

Table 1 OR and 95% CI for glioma and acoustic neuroma based on publications from the Hardell group (7, 8) and Interphone (11, 12).

	Hardell et al.		Interphone		Meta-analysis	
	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)
Glioma						
Ipsilateral						
All	279/374	1.78 (1.40–2.25)	677/753	0.84 (0.69–1.04)	956/1127	1.22 (0.58–2.55)
≥1640 h	29/21	2.94 (1.60–5.41)	100/62	1.96 (1.22–3.16)	129/83	2.29 (1.56–3.37)
Acoustic neuroma						
Ipsilateral						
All	80/374	1.78 (1.23–2.59)	271/471	0.77 (0.59–1.02)	351/845	1.16 (0.51–2.64)
≥1640 h	7/21	3.10 (1.21–7.95)	47/46	2.33 (1.23–4.40)	54/67	2.55 (1.50–4.40)

The numbers of exposed cases (Ca) and controls (Co) are given. The use of mobile phones and the risk for glioma and acoustic neuroma are localized on the same side of the brain (ipsilateral) where the mobile phone was mostly used. Results are presented for all use and cumulative use ≥1640 h.

Consistency

Similar results have been found in different studies. As can be seen in Table 2, the results for glioma are similar in Hardell et al. (7) and Interphone (11) when the same inclusion criteria were used. The results by Hardell et al. (4) were recalculated using the same age group, 30–59 years, as in the Interphone study. Cordless phone use was excluded, and such use was included in the "unexposed" group as in the Interphone study. Note that the handheld

Table 2 OR and 95% CI for glioma in the Interphone study (11) compared with the Hardell group (4, 7).

			Hardell group		Interphone	
	20–80 (All)	20–59	30–59	30–59, Cordless among unexposed	30–59	30–59, Appendix 2
Latency ≥10 years						
Ca/Co	88/99	57/74	56/74	56/74	252/232	190/150
OR	2.26	2.15	1.96	1.79	0.98	2.18
95% CI	1.60–3.19	1.41–3.29	1.27–3.01	1.19–2.70	0.76–1.26	1.43–3.31
Latency ≥10 years, ipsilateral						
Ca/Co	57/45	36/30	35/30	35/30	108/82	NR
OR	2.84	2.70	2.48	2.29	1.21	
95% CI	1.82–4.44	1.54–4.73	1.40–4.38	1.33–3.97	0.82–1.80	
Latency ≥10 years, contralateral						
Ca/Co	29/29	20/24	20/24	20/24	49/56	NR
OR	2.18	2.04	1.96	1.71	0.70	
95% CI	1.24–3.85	1.04–4.00	0.995–3.87	0.89–3.28	0.42–1.15	
Cumulative use ≥1640 h						
Ca/Co	42/43	32/37	29/37	29/37	210/154	160/113
OR	2.31	2.23	1.89	1.75	1.40	1.82
95% CI	1.44–3.70	1.30–3.82	1.08–3.30	1.02–3.00	1.03–1.89	1.15–2.89
Cumulative use ≥1640 h, ipsilateral						
Ca/Co	29/21	22/18	20/18	20/18	100/62	NR
OR	2.94	2.71	2.32	2.18	1.96	
95% CI	1.60–5.41	1.36–5.42	1.14–4.73	1.09–4.35	1.22–3.16	
Cumulative use ≥1640 h, contralateral						
Ca/Co	12/12	9/11	8/11	8/11	39/31	NR
OR	2.10	1.99	1.73	1.48	1.25	
95% CI	0.90–4.90	0.77–5.16	0.65–4.63	0.57–3.87	0.64–2.42	

The numbers of cases (Ca) and controls (Co) are given. NR, not reported. Note that >10-year latency were used in the Hardell group studies and contralateral was defined as <50% use of tumor side. Unexposed in the Interphone study (Appendix 2): latency 1–1.9 years; unexposed in Hardell et al.: no use or latency ≤1 year.

cordless phone emits RF-EMF when used, which cannot be neglected (24). The risk would be biased toward unity by including the use of cordless phones in the "unexposed" category. Also excluding the youngest and oldest age groups, as in the Interphone study, may preclude the possibility to find an increased risk (8). The youngest persons may be more sensitive than older ones; in fact, we found the highest risk for glioma and acoustic neuroma in cases with first use of a wireless phone before 20 years old (8). The prevalence of mobile phone use is highest in the age group 30–59 years according to our findings. Excluding older cases diminishes the possibility to find an increased risk, assuming a reasonable latency time. The peak incidence of most brain tumors is at an older age, between 45 and 75 years of age, with median survival of <1 year for glioblastoma (25). In a case series from Canada, all brain tumors showed a bimodal age distribution with one peak in the 0–4 age group and the other in the 60–69 age group (26). It is concluded that, using the same criteria, there is consistency between the Hardell group and Interphone results.

Specificity

The anatomic areas of the brain that absorb the highest wireless phone radiation, e.g., the temporal lobe (9, 10), have the highest risk. Thus, in the latency group ≥10 years, the meta-analyses of Hardell et al. (5, 7) and Interphone (11, 12) gave in total OR=1.48, 95% CI=0.65–3.35, increasing to OR=1.71, 95% CI=1.04–2.26, for glioma in the temporal lobe (Table 3). The meta-analysis gave for acoustic neuroma with latency ≥10 years OR=1.46, 95% CI=0.39–5.47, in total and OR=1.81, 95% CI=0.73–4.45, for ipsilateral use of mobile phones. For ipsilateral acoustic neuroma and cumulative use of mobile phones ≥1640 h, the meta-analysis gave OR=2.55, 95% CI=1.50–4.40 [data not in table, see Hardell et al. (8)]. Regarding acoustic neuroma, reversed causality might be possible. In some of the earlier Interphone studies of the relationship between mobile phone use and acoustic neuroma, there were some indications that because of hearing problems, there is a switching of the ear usually used, thus reducing ipsilateral risk.

Furthermore, there is specificity regarding tumor type. Both the Hardell group and Interphone found increased risk for glioma and acoustic neuroma but not for meningioma in the same sets of studies (3, 4, 11, 12, 21–23).

Temporality

Those with most years since first use have the highest risk, i.e., an effect of time since first use (latency). This is illustrated in Table 4 in studies from the Hardell group. For the study period 2007–2009, OR=1.7, 95% CI=1.04–2.8, was calculated in total for malignant brain tumors, increasing to OR=2.2, 95% CI=1.3–3.8 with latency >20 years (see also Figure 1) (21). The results for acoustic neuroma were based on the study periods 1997–2003 and 2007–2009 (22). Highest risk was calculated in the >20-year-latency group, yielding OR=4.4, 95% CI=2.2–9.0 (see Figure 2). An increased risk with increasing latency may support temporality. It should

Table 3 OR and 95% CI for glioma and acoustic neuroma and mobile phone use in Hardell et al. (5, 7) and Interphone (11, 12).

	Hardell et al.		Interphone		Meta-analysis	
	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)
Glioma						
Latency ≥1 year						
All	432/900	1.32 (1.09–1.61)	1666/1894	0.81 (0.70–0.94)	2098/2794	1.03 (0.64–1.66)
Temporal lobe	116/900	1.30 (0.92–1.83)	509/568	0.86 (0.66–1.13)	625/1468	1.04 (0.70–1.56)
Latency ≥10 years						
All	88/99	2.26 (1.60–3.19)	252/232	0.98 (0.76–1.26)	340/331	1.48 (0.65–3.35)
Temporal lobe	28/99	2.26 (1.32–3.86)	94/69	1.36 (0.88–2.11)	122/168	1.71 (1.04–2.81)
Acoustic neuroma						
Latency ≥1 year						
All	130/900	1.66 (1.20–2.28)	643/1308	0.85 (0.69–1.04)	773/2208	1.17 (0.61–2.26)
Ipsilateral	80/374	1.78 (1.23–2.59)	271/471	0.77 (0.59–1.02)	351/845	1.16 (0.51–2.64)
Latency ≥10 years						
All	20/99	2.93 (1.57–5.46)	68/141	0.76 (0.52–1.11)	88/240	1.46 (0.39–5.47)
Ipsilateral	13/45	2.97 (1.42–6.21)	44/52	1.18 (0.69–2.04)	57/97	1.81 (0.73–4.45)

The numbers of cases (Ca) and controls (Co) are given.

Table 4 OR and 95% CI for malignant brain tumors (n=593; 1368 controls) and acoustic neuroma (n=316; 3530 controls): Hardell group studies (21, 22).

Wireless phones	All		>20-Year latency	
	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)
Malignant brain tumors	571/1261	1.7 (1.04–2.8)	82/125	2.2 (1.3–3.8)
Acoustic neuroma	227/2472	1.5 (1.1–2.0)	14/126	4.4 (2.2–9.0)

The numbers of cases (Ca) and controls (Co) are given.

be noted that Interphone did find only weak evidence for increased risks with increased latency.

Biologic gradient

There is a clear dose-response effect, i.e., higher cumulative use in hours of wireless phones gives a higher risk with statistically significant trend in the Hardell group studies. In the recent study on malignant brain tumors (21), the highest risk was calculated in the fourth quartile, >2376 h, of mobile phone and cordless phone use (Table 5). This amount of time corresponds to about 40 min of wireless phone use per day for 10 years. For mobile phone use, OR=2.8, 95% CI=1.6–4.8 (p, trend=0.0001), and for cordless phone use, OR=3.1, 95% CI=1.8–5.5 (p, trend <0.0001) were calculated in the forth quartile. Figure 3 illustrates the dose-response effect. Also, for acoustic neuroma, the highest risk was found in the fourth quartile of cumulative use (>1486 h), yielding OR=2.2, 95% CI=1.5–3.4 in total (p, trend=0.03) [see Hardell et al. (22) and Figure 4].

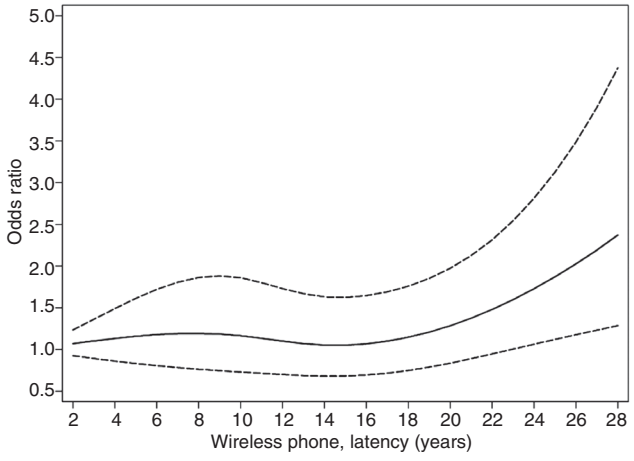

Figure 1 Restricted cubic spline plot of the relationship between latency of wireless phone use and malignant brain tumors (21). The solid line indicates the OR estimate, and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI code (four categories: blue-collar worker, white-collar worker, self-employed, and no work), and year of diagnosis.

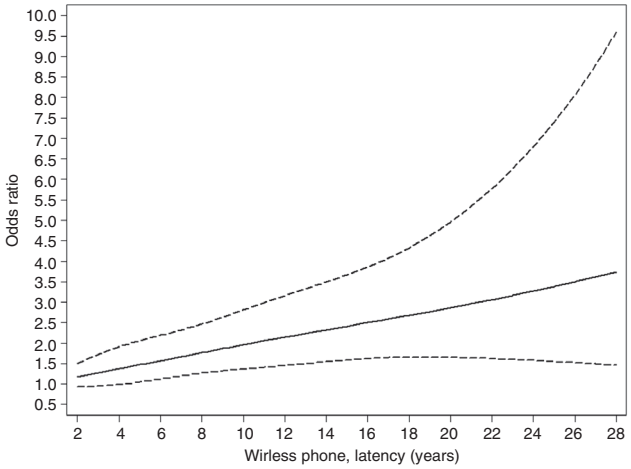

Figure 2 Restricted cubic spline plot of the relationship between latency of wireless phone use and acoustic neuroma (22). The solid line indicates the OR estimate, and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI code (four categories: blue-collar worker, white-collar worker, self-employed, and no work), and year of diagnosis.

In contrast, Interphone, although reporting a significant OR for the highest decile of hours of use, did not find a dose-response relationship for glioma (11). However, it should be noted that according to Appendix 2, with few exceptions, all ORs were >1.0 for glioma in contrast to meningioma. The highest ORs for glioma were found in one of the two highest exposure categories for time since the start of regular use, cumulative call time, and cumulative number of calls. The greatest increase was with increasing time since the start of use of mobile phone. A risk of brain tumors in relation to estimated RF dose from mobile phones in joules per kilogram was reported from five Interphone countries (27). A dose-response relationship for exposure 7+ years ago was reported.

Plausibility

An increase in both single- and/or double-strand breaks of DNA has been detected in humans (28), animal models (29–31), and cell cultures (32, 33). RF-EMF may stimulate reactive oxygen species (ROS) generation both in vivo (34) and in vitro (35). The formation of ROS is considered to be one of the primary mechanisms that are involved in the bio-effects that are mediated by RF-EMF exposure (36).

In a study using a mouse spermatocyte-derived cell line, it was demonstrated that RF-EMF exposure can

Table 5 OR and 95% CI for malignant brain tumors (n=593, 1368 controls) based on Hardell et al. (21).

Quartile	Mobile phone, total			Cordless phone			Wireless phone		
	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co
First quartile	1.4	0.8–2.3	190/587	1.3	0.8–2.2	164/434	1.5	0.9–2.5	108/317
Second quartile	1.7	1.02–3.0	126/261	1.7	1.01–3.0	120/278	1.4	0.8–2.4	110/314
Third quartile	1.5	0.9–2.7	95/210	2.1	1.2–3.7	98/194	1.7	1.003–2.9	137/315
Fourth quartile	2.8	1.6–4.8	137/159	3.1	1.8–5.5	79/109	2.5	1.5–4.2	216/315
p, Trend	0.0001			<0.0001			0.0001		

The numbers of exposed cases (Ca) and controls (Co) are given. First quartile, >39–405 h; second quartile, 406–1091 h; third quartile, 1092–2376 h; fourth quartile, >2376 h according to cumulative use among controls.

increase ROS production and subsequently induce the formation of oxidative base damage as evaluated by FPG-comet assay and 8-oxoG formation (37). To further elucidate the central role of ROS in RF-EMF exposure-induced DNA base damage, the authors used α-tocopherol pretreatment to antagonize the oxidation of ROS; α-tocopherol is an important lipophilic antioxidant that can inactivate harmful ROS. The protective role of α-tocopherol pretreatment confirmed that ROS are involved in RF exposure-induced DNA base damage (37).

However, these studies do not provide a biologic mechanism behind the influence of RF-EMF on brain tumors. Hill pointed out that biologic plausibility cannot be demanded because of the dependency on the limited knowledge of the day. Causality would be strongly supported if rather specific mutations should be demonstrated. Unfortunately, there are currently no studies that address this issue.

Coherence

Brain and nervous system cancer rates, potential confounders, and environmental risk factors were studied in 165 of 208 countries using ecologic data (38). The only exogenous risk factor consistently associated with higher incidence was the penetration of rate of mobile/cellular telecommunication subscriptions. According to these ecologic results, the latency period is at least 11–12 years but probably more than 20 years.

The incidence of brain tumor has been studied in different countries. An increasing incidence of brain tumors, especially of the type that would be expected based on epidemiologic results (glioblastoma multiforme), in the most exposed parts of the brain (temporal and adjacent lobes) has been shown. Such studies are listed below and are more discussed elsewhere (8).

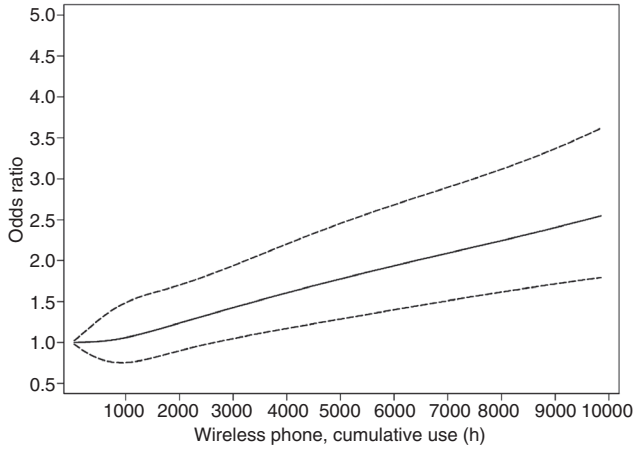

Figure 3 Restricted cubic spline plot of the relationship between cumulative use of wireless phones and malignant brain tumors (21). The solid line indicates the OR estimate, and the broken lines represents the 95% CI. Adjustment was made for age at diagnosis, gender, SEI code (four categories: blue-collar worker, white-collar worker, self-employed, and no work), and year of diagnosis.

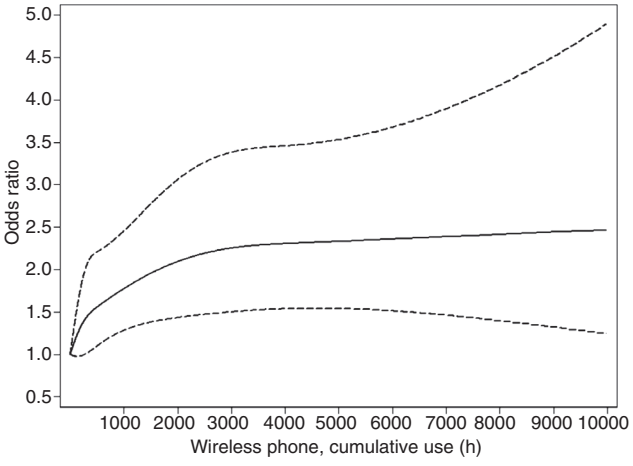

Figure 4 Restricted cubic spline plot of the relationship between cumulative use of wireless phones and acoustic neuroma (22). The solid line indicates the OR estimate, and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI code (four categories: blue-collar worker, white-collar worker, self-employed, and no work), and year of diagnosis.

- United States: High-grade glioma (1992–2008): SEER annual percentage change (APC), +0.64%, 95% CI=+0.33 to +0.95% (39) Microscopically confirmed glioblastoma multiforme (1992–2006): SEER APC, +2.4% to +3.0% ($p \leq 0.001$) (frontal lobe), +1.3% to +2.3% ($p \leq 0.027$) (temporal lobe), across all registries (40). In the parietal and occipital lobes or in overlapping lobes, no statistically significant changes in incidence were seen.
- England: Brain tumors (majority, glioma; 1998–2007): increasing incidence in the temporal lobe for men and women ($p<0.01$) (41) Malignant brain tumors (1998–2011): the age-standardized incidence rates for frontal and temporal lobe tumors in England rose at an average annual percentage change (AAPC) of +3.7%, 95% CI=+2.9% to +4.6% ($p<0.0001$). The overall rates for all (C71) malignant tumors increased slightly. The results show that the pattern of change in incidence over time is statistically significant different for frontal and temporal lobe tumors compared with all other brain tumors (Alasdair Philips, Powerwatch, UK, personal communication, to be published).
- Australia: Malignant brain tumors (2000–2008): APC, +3.9%, 95% CI=+2.4% to +5.4% (42).
- Denmark: Brain and central nervous system tumors (2000–2009): men: APC, +2.7%, 95% CI=+1.1% to +4.3%; women: APC, +2.9%, 95% CI=+0.7% to +5.2% (15).
- Sweden: Astrocytoma (glioma; 2000–2007): age group >19 years: APC, +2.16%, 95% CI=+0.25% to +4.10% (5).

Experiment

The RF-EMF toxic effects on DNA mediated by ROS can be prevented by antioxidants, as shown in several studies. Antioxidants like melatonin and vitamins C and E can alleviate the ROS oxidation and apoptosis that are induced by RF-EMF in an animal model (43, 44). The protective role of α-tocopherol pretreatment in RF exposure-induced DNA base damage was recently demonstrated by Liu et al. (37). However, there is no direct relationship between these findings and brain tumor development because no useful animal model has been investigated so far that shows an increased brain tumor incidence after RF-EMF exposure that could be inhibited by antioxidants.

No studies exist on the risk for brain tumors among subjects that have used a wireless phone previously but are current nonusers. However, especially in the 1980s, mobile phone use was common in cars, with a fixed external antenna as the only mode of use. Such use has been assessed in the Hardell group studies and considered to be no exposure to RF-EMF. For the study period 1 January 1997–30 June 2000, among 1429 responding cases and 1470 controls, 73 cases and 90 controls had always used the mobile phone with fixed external antenna and 1 additional control had always used a hands-free device (45). This yielded crude OR=0.8, 95% CI=0.6–1.1. Thus, this "experiment" showed that if the RF-EMF exposure from the mobile phone was protected, no increased risk was found.

Analogy

Animal carcinogenicity of RF-EMF was evaluated by the IARC Working Group in May 2011 (14, 16). There was limited evidence of carcinogenicity in experimental animals. Four classes of cancer bioassays in animals were reviewed. Although an increased cancer risk was found in some studies, it was concluded that there was no consistent pattern of increased risk in seven 2-year cancer bioassays, 12 studies that used different tumor-prone animal models and 16 studies of promotion and initiation. Of six co-carcinogenesis studies involving five different animal models, four responses were reported (16). It should be mentioned that, for example, increased risk (initiation) or earlier development (promotion) of total cancer including malignant lymphoma (46), mammary tumors (47), skin cancer (48), and lymphoma (49) has been reported from RF-EMF exposure.

Discussion

Bradford Hill warned against the misuse of tests of statistical significance. He noted, "We must not be too ready to dismiss a cause-and-effect hypothesis merely on the ground that the observed association appears to be slight". As noted by Kundi (50), the nine issues discussed by Hill were not intended to dismiss a factor as potentially causing a disease. However, the Hill criteria were used in an overall assessment of mobile phone use and brain cancer and other tumors by Repacholi et al. (51). The authors concluded, "In summary, none of the Hill criteria support a causal relationship between wireless phone use and brain cancer or other tumors in the areas of the head that most absorb the RF energy from wireless phones". This conclusion goes far beyond what the authors studied using less reliable methods. For example, they claimed that the use of "wireless phones" was assessed, although only mobile phones were considered and not cordless desktop phones. There are several other reasons to regard this article as less

informative. For example, the Interphone study on acoustic neuroma (12) was not included, although it was available at that time, with partly the same authors. In addition, the article by Cardis et al. (27) on risk of brain tumors in relation to estimated RF dose from mobile phones was omitted despite being available on line (27). Furthermore, no analyses were performed on ipsilateral or contralateral mobile phone use. The authors used the Interphone exposure criteria for effect estimates without considering our definition that was readily available in our publications and also discussed in detail elsewhere (7, 52). The Danish cohort study on mobile phone subscribers (13) was included, although several methodologic shortcomings including the lack of individual exposure data were inherent (15).

Regarding the strength of evidence, there is clearly an increased risk for glioma and acoustic neuroma in the highest exposure category of cumulative use of mobile phones both in the Hardell group studies and Interphone.

Consistency can only be answered by a repetition of the circumstances and observations both by the same research group and other investigators. According to Table 2 and the IARC evaluation (14, 16), the results of increased risk regarding mobile phone use and risk of glioma and acoustic neuroma are similar in the Hardell group and Interphone studies. Unfortunately, Interphone has not published data on cordless phone use, although the Hardell group has published similar results as for mobile phones. Hill also gives an interesting remark that is an answer to those scientists who insist that every positive study must be replicated, "Once again looking at the obverse of the coin there will be occasions when repetition is absent or impossible and yet we should not hesitate to draw conclusions". However, in this case, results have been repeated and we are beyond that comment.

Hill writes, "if *specificity* exists we may be able to draw conclusions without hesitation". Table 3 presents increased risk for glioma in the temporal lobe with highest risk in the ≥10-year latency group. For acoustic neuroma, the ipsilateral use of the mobile phone gives the highest risk. Moreover, the increased risk is specific for glioma and acoustic neuroma, whereas no increased risk was found for meningioma in the same studies (3, 8, 11, 23).

The fourth issue discussed by Hill deals with temporality. As exemplified in Table 4 and Figures 1 and 2, the risk increases with latency with highest OR for both malignant brain tumors and acoustic neuroma in the >20-year-latency group. This is by far the longest latency (time from first use to diagnosis) that has been published.

With a biologic gradient or a dose-response curve, "then we should look most carefully for such evidence". Clearly, in Table 5, a statistically significant biologic gradient is demonstrated for malignant brain tumors and the use of both mobile phones and cordless phones. This is visualized for wireless phone use in Figures 3 and 4.

Regarding plausability, Hill states to those who insist that we wait until the exact causal mechanism is established: "It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day". To those who insist on more in vivo or in vitro evidence, he states: "Nevertheless, while such laboratory evidence can enormously strengthen the hypothesis and, indeed, may determine the actual causative agents, the lack of such evidence cannot nullify the epidemiological observations in man". Regarding plausibility, as reviewed, oxidative stress is one important mechanism for adverse health effects from RF-EMF emissions. However, it should be pointed out that the exact mechanism for RF-EMF initiation of brain tumors has not been identified.

Bradford Hill discusses coherence among cigarette smoking, lung cancer, and the temporal rise in the two variables over the last generation. No doubt, there are now studies that show an increasing incidence of brain tumors. However, considering the long latency periods of decades in brain tumor genesis, it is currently too early to predict the real incidence increase. By now, there are also studies that show different patterns of incidence for malignant brain tumors in the frontal and temporal lobes compared with the other lobes. This highlights the need of improved data quality in the cancer registries on anatomic localization of the tumors.

Experiment with prevention is one option, especially in industry. Exposure to vinyl chloride and the increased risk of angiosarcoma in the liver is one example of prevention that gave a reduced number of victims (53). Antioxidants like melatonin and vitamins C and E can alleviate the ROS oxidation and apoptosis that are induced by RF-EMF in an animal model (37, 43, 44). No risk increase for brain tumors was found in subjects using external antenna in a car during mobile phone calls without any other wireless phone use (45).

As to the ninth point, analogy, Hill wrote, "In some circumstances it would be fair to judge by analogy". Although he does not discuss this in depth, animal studies may be useful. As stated by IARC, the evidence is limited in experimental animals for carcinogenesis.

Hill noted that, "However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances.... If we are wrong in

deducing causation from associations no great harm will be done… All scientific work is incomplete… That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time". These wise rules should also be considered when RF-EMF from wireless phones is evaluated as a human carcinogen.

Conclusions

Based on Hill's viewpoints and his discussion on how these issues should be used, the conclusion of this review is that glioma and acoustic neuroma are caused by RF-EMF emissions from wireless phones. According to the IARC Preamble (54), the classification should be group 1, i.e., "the agent is carcinogenic to humans", and urgent revision of current guidelines for exposure is needed.

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