Brain Tumour Risk Associated with Use of Mobile and Cordless Phones

Lennart Hardell, MD, PhD, Professor & Michael Carlberg, MSc

The use of both mobile and cordless phones has increased rapidly during the last decade. When used they emit radiofrequency electromagnetic fields (RF-EMF)[1,2] and also extremely low frequency electromagnetic fields (ELF-EMF) from the battery.[3] The brain is the primary target organ for exposure to electromagnetic fields during the use of the handheld phone. This has given concern of an increased risk for brain tumours, although also other health effects are discussed. Worldwide, an estimate of 6.8 billion mobile phone subscriptions was reported at the end of 2013 by the International Telecommunication Union (ITU; http://www.itu.int/en/ITU-D/Statistics/Documents/facts/ICTFactsFigures2013-e.pdf).

Many users are children and adolescents, which is of special concern regarding potential health effects.

On 31 May 2011 IARC categorised RF-EMFs from mobile phones, and from other devices that emit similar non-ionising electromagnetic fields, as a Group 2B, i.e. a 'possible', human carcinogen.[4,5] Nine years earlier IARC had also classified extremely low frequency (ELF) magnetic field as Group 2B carcinogen.[6]

The IARC decision on mobile phones was based mainly on two sets of case-control human studies on brain tumour risk; our studies from Sweden (the Hardell group)[7-9] and the IARC Interphone study (also preprint studies available).[10-12] Both provided complementary and supportive results on positive associations between two types of brain tumours; glioma and acoustic neuroma, and exposure to RF-EMF from wireless phones.

Some technical aspects

The Nordic countries were among the first countries in the world to widely adopt wireless telecommunications technology. Analogue phones (NMT; Nordic Mobile Telephone System) were introduced in the early 1980s using both 450 and 900 Megahertz (MHz) frequencies. NMT 450 was used in Sweden from 1981 to 2007, NMT 900 operated during 1986-2000.

The digital system (GSM; Global System for Mobile Communication) using dual band, 900 and 1,800 MHz, started to operate in 1991 and now dominates the market. The third generation of mobile phones, 3G or UMTS (Universal Mobile Telecommunication System), using 1,900/2,100 MHz has been introduced worldwide in recent years, in Sweden in 2003. Currently the fourth generation, 4G (Terrestrial 3G), operating at 800/2,600 MHz and Trunked Radio Communication (TETRA 380-400 MHz) are being established in Sweden and elsewhere and the fifth (5G) generation is under development. One of the aims is to be possible to transmit large amounts of data in a short time. Nowadays mobile phones are used more than landline phones in Sweden (http://www.pts.se/upload/Rapporter/Tele/2011/sv-telemarknad-halvar-2011-pts-er-2011-21.pdf).

Desktop cordless phones (DECT) have been used in Sweden since 1988, first using analogue 800-900 MHz RF fields, but since early 1990s using a digital 1,900 MHz system. The cordless phones are becoming more common than traditional telephones connected to landlines. Also these phones emit RF-EMF radiation similar to that of mobile phones. Thus, it is necessary to consider the usage of cordless phones along with mobile phones, when human health risks are evaluated.

Further studies on brain tumours

After the IARC evaluation we have published results from our new case-control study including brain tumour patients in Sweden diagnosed during 2007-2009. Results have been published for malignant brain tumours,[13] meningioma,[14] and acoustic neuroma.[15] All of our studies were approved by the Ethical Committee. Further details can be found in the different publications. In the following we present separate analysis for the time period 2007-2009, and also pooled results for 1997-2003 and 2007-2009. In a meta-analysis we combine our results with Interphone.

1. MALIGNANT BRAIN TUMOURS

Glioma is the most common malignant brain tumour and represents about 60 % of all central nervous system tumours. The most common glioma subtype is astrocytoma. Astrocytic tumours are divided in two groups depending on the malignant potential; low-grade (WHO grades I-II) and high-grade (WHO grades III-IV). Low-grade astrocytoma has a relatively favourable prognosis, whereas survival is shorter for patients with high-grade glioma. Glioblastoma multiforme (WHO grade IV) accounts for 60-75 % of all astrocytoma. The peak incidence of this tumour type is between 45-75 years of age with median survival less than one year.

In Table 1 results are displayed for use of different phone types and the risk for malignant brain tumours for our Swedish study period 2007-2009.[13] Mobile phone use increased the risk with highest OR in the >25 years latency group, OR = 2.9, 95 % CI = 1.4-5.8. Cordless phone use gave highest risk in the latency group >15-20 years, OR = 2.1, 95% CI = 1.2-3.8. Only 6 cases and 13 controls reported use of cordless phone with latency >20-25 years, so these results are less reliable.

Table 1. *Odds ratio (OR) and 95 % confidence interval (CI) for malignant brain tumours (N= 593); controls (N = 1,368). Numbers of exposed cases (Ca) and controls (Co) is given; Study period 2007-2009.[13]*

Latency period	Mobile phone	Cordless phone	Wireless phone, total
	OR, CI (Ca/Co)	OR, CI (Ca/Co)	OR, CI (Ca/Co)
Total, > 1 year	1.6 0.99-2.7 (548/1217)	1.7 1.1-2.9 (461/1015)	1.7 1.04-2.8 (571/1261)
>15-20 years	1.5 0.8-2.6 (76/174)	2.1 1.2-3.8 (57/109)	1.7 1.02-3.0 (110/231)
>20-25 years	1.9 1.1-3.5 (48/80)	1.5 0.5-4.6 (6/13)	1.9 1.04-3.4 (52/92)
>25 years	2.9 1.4-5.8 (30/33)	- (0/0)	3.0 1.5-6.0 (30/33)

We further show results for all wireless phones use combined. An increased risk was found overall with an OR = 1.7, 95% CI = 1.04-2.8, increasing in the shortest latency period > 1-5 years to an OR = 2.6, 95% CI = 1.4-5.0 (not in Table), then decreasing somewhat with increasing latency; but with the highest risk is in the longest latency period > 25 years with an OR = 3.0, 95% CI = 1.5-6.0.

Ipsilateral use (use on the same side as brain tumour location) of both mobile phones and cordless phones gave highest risks, OR = 1.7, 95 % CI = 1.01-2.9 and OR = 1.9, 95 % CI = 1.1-3.2, respectively, Table 2. Lower risks were found for contralateral use (use on the opposite side of brain tumour location), OR = 1.4, 95 % CI = 0.8-2.5 for mobile phone use and OR = 1.6, 95 % CI = 0.9-2.8 for cordless phone use.

Table 2. *Odds ratio (OR) and 95 % confidence interval (CI) for malignant brain tumours (N= 593); controls (N = 1,368). Numbers of exposed cases (Ca) and controls (Co) is given; Study period 2007-2009. Ipsilateral (same side), contralateral (opposite side).[13]*

	All			Ipsilateral			Contralateral		
	Ca/Co	OR	95 % CI	Ca/Co	OR	95 % CI	Ca/Co	OR	95 % CI
Mobile phone	548/1217	1.6	0.99–2.7	324/534	1.7	1.01-2.9	190/407	1.4	0.8–2.5
Cordless phone	461/1015	1.7	1.1–2.9	272/454	1.9	1.1–3.2	156/327	1.6	0.9–2.8

In Table 3 results are shown for mobile phone use and glioma risk for the study periods 1997-2003[7] and 2007-2009.[13] Table 4 gives the results for cordless phone use. Highest risk was found for persons with their first ipsilateral use of both phone types before the age of 20 years; mobile phone OR = 2.3, 95 % CI = 1.3-4.2 and cordless phone OR = 3.1, 95 % CI = 1.6-6.3.

Table 3. *Odds ratio (OR) and 95 % confidence interval (CI) for glioma in different age groups for first use of mobile phone. Study periods 1997-2003 and 2007-2009.*[7,13]

	All			**Ipsilateral**		
	Ca/Co	OR	95 % CI	Ca/Co	OR	95 % CI
Mobile phone, total	945/2148	1.3	1.1 – 1.6	592/920	1.8	1.4 – 2.2
< 20 years old	69/93	1.8	1.2 – 2.8	39/38	2.3	1.3 – 4.2
20-49 years old	605/1337	1.3	1.1 – 1.6	384/573	1.8	1.4 – 2.3
≥50 years old	271/718	1.3	1.1 – 1.6	169/309	1.7	1.3 – 2.2

Table 4. *Odds ratio (OR) and 95 % confidence interval (CI) for glioma in different age groups for first use of cordless phone. Study periods 1997-2003 and 2007-2009.*[7,13]

	All			**Ipsilateral**		
	Ca/Co	OR	95 % CI	Ca/Co	OR	95 % CI
Cordless phone	752/1724	1.4	1.1 – 1.7	461/766	1.7	1.3 – 2.1
< 20 years old	46/48	2.3	1.4 – 3.9	28/19	3.1	1.6 – 6.3
20-49 years old	436/1022	1.3	1.02 – 1.6	265/458	1.5	1.2 – 2.0
≥ 50 years old	270/654	1.4	1.2 – 1.8	168/289	1.8	1.4 – 2.3

Both our research group,[7,13] and Interphone[10] have published results for use of mobile phones using > 10 years latency time (≥ 10 years in Interphone). We made a meta-analysis of these results, Table 5. Furthermore we adopted in our studies the same cut-off for highest cumulative use, ≥ 1,640 hours, as in Interphone, Table 6. This meta-analysis gave for ipsilateral mobile phone use, in the ≥10 years latency group OR = 1.55, 95 % CI = 0.99-2.42, Table 5. Regarding anatomical localisation the highest exposure is in the temporal lobe. The risk was statistically significant for glioma in the temporal lobe with OR = 1.45, 95 % CI = 1.07-1.97. Cumulative mobile phone use ≥ 1,640 hours gave increased risk for ipsilateral glioma in total, OR = 2.54, 95 % CI = 1.62-3.98, and also glioma located in the temporal lobe, OR = 1.95, 95 % CI = 1.37-2.78, Table 6.

Table 5. *Use of mobile phones and glioma risk, meta-analysis of study periods 1997-2003 and 2007-2009,*[7,13] *and Interphone.*[10] *- Random-effects model used for all meta-analyses, based on test for heterogeneity in the overall (≥10 years and ≥1,640 hours) groups.*

	Hardell et al. 1997-2009		**Interphone 2000-2004**		**Meta-analysis**	
	Ca/Co	OR, CI	Ca/Co	Ca/Co	OR, CI	Ca/Co
Latency ≥ 10 years						
-all	382/786	1.55 (1.21-1.99)	252/232	0.98 (0.76-1.26)	634/1018	1.23 (0.79-1.93)
-ipsilateral	238/360	1.91 (1.40-2.60)	108/82	1.21 (0.82-1.80)	346/442	1.55 (0.99-2.42)
-contralateral	130/257	1.34 (0.93-1.94)	49/56	0.70 (0.42-1.15)	179/313	0.99 (0.53-1.87)
-temporal lobe	113/786	1.54 (1.01-2.35)	94/69	1.36 (0.88-2.11)	207/855	1.45 (1.07-1.97)
-≥ 1640 h	175/232	3.72 (2.54-5.45)	93/73	1.34 (0.90-2.01)	268/305	2.24 (0.82-6.09)

Table 6. *Use of mobile phones and glioma risk, meta-analysis of study periods 1997-2003 and 2007-2009,[7,13] and Interphone.[10] - Random-effects model used for all meta-analyses, based on test for heterogeneity in the overall (≥10 years and ≥1,640 hours) groups.*

	Hardell et al. 1997-2009		**Interphone 2000-2004**		**Meta-analysis**	
	Ca/Co	OR, CI	Ca/Co	Ca/Co	OR, CI	Ca/Co
Cumulative use ≥ 1640 h						
-all	211/301	2.13 (1.61-2.82)	210/154	1.40 (1.03-1.89)	421/455	1.73 (1.15-2.62)
-ipsilateral	138/133	3.11 (2.18-4.44)	100/62	1.96 (1.22-3.16)	238/195	2.54 (1.62-3.98)
-contralateral	66/105	1.56 (1.01-2.40)	39/31	1.25 (0.64-2.42)	105/136	1.46 (1.02-2.10)
-temporal lobe	59/301	2.01 (1.25-3.21)	78/47	1.87 (1.09-3.22)	137/348	1.95 (1.37-2.78)

Restricted cubic spline plots

Figure 1 illustrates the results for cumulative use of wireless phones using the restricted cubic splines method.[13] There was a linear increasing trend of the risk up to 10,000 h (p, nonlinearity=0.52). Figure 2 demonstrates a borderline statistically significant non-linear relationship for the risk and latency using data up to 28 years from first use of a wireless phone before tumour diagnosis (p, nonlinearity=0.05). Highest risk was found with longest latency. This finding gives support for RF-EMFs to play a role in the initiation and promotion stages of carcinogenesis.

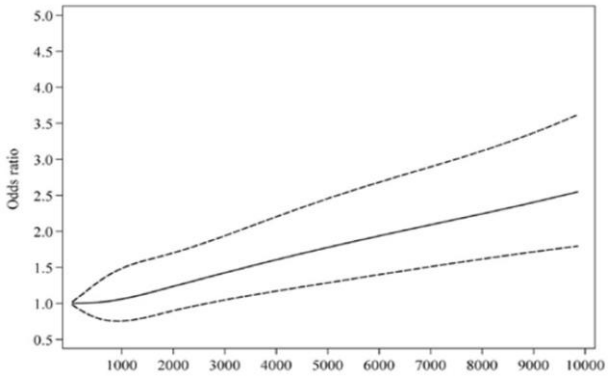

Figure 1. Cumulative use of wireless phone and malignant brain tumours. Number of hours is given. The solid line indicates odds ratio and broken lines 95 % confidence limits.[13]

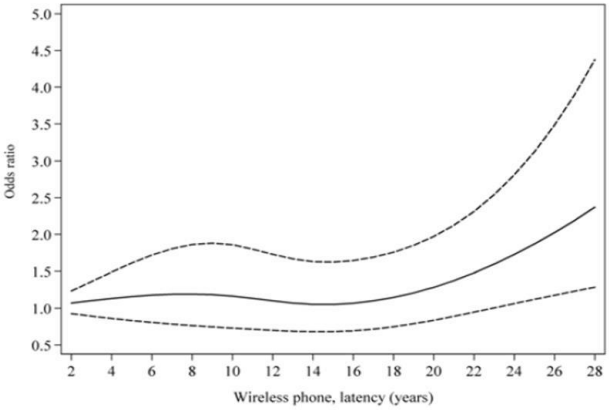

Figure 2. Time from first use of wireless phone and malignant brain tumours. Number of years is given. The solid line indicates odds ratio and broken lines 95 % confidence limits.[13]

Hazard ratio (HR) for survival of patients with glioma

A carcinogenic effect of RF-EMF emissions would be strengthened if exposure correlates with survival of glioma patients. To further elucidate that possibility we analysed survival of all cases with glioma (n=1,498) in our case-control studies for the time periods 1997-2003 and 2007-2009, Table 7.[7,13] Hazard ratio (HR) for survival was elevated both for cases exposed to mobile phones and cordless phones in the > 20 years latency group. Higher HR was found for astrocytoma grade IV (glioblastoma multiforme) than for all glioma. Thus, mobile phone use yielded OR = 2.0, 95 % CI = 1.4-2.9 and cordless phone use gave OR = 3.4, 95% CI = 1.04-11. The results demonstrate a decreased survival for glioma cases with long-term use of wireless phones. These effects show a biological effect from RF-EMF exposure indicating progression to a more aggressive tumour.[16]

Table 7. *Hazard ratio (HR) for survival of patients with glioma. Study periods 1997-2003 and 2007-2009.*[7,9,13]

Latency >20 years	**Glioma**	**Astrocytoma grade IV**
	OR, CI	OR, CI
Wireless phone	1.7 1.2-2.3	2.1 1.5-3.0
Mobile phone	1.8 1.3-2.5	2.0 1.4-2.9
Cordless phone	1.3 0.5-3.7	3.4 1.04-11

Conclusion

The results clearly show that use of mobile phones increases the risk of glioma. We have shown that also use of cordless phones increases the risk. Unfortunately other studies have not assessed use of cordless phones. Excluding such use as in Interphone would bias risk estimated towards unity, as we have shown in one publication. [17] Since Interphone did not assess such use our meta-analysis could only be made for mobile phone use. Excluding cordless phones did thus give conservative risk estimates.

2. MENINGIOMA

Meningioma is the most common benign brain tumour and accounts for about 30 % of intracranial tumours. It develops from the pia and arachnoid membrane that cover the central nervous system. Meningioma is an encapsulated, well-demarked and rarely malignant tumour. It is slowly growing and gives neurological symptoms by compression of adjacent structures. This tumour type is most common among middle-aged and elderly persons. There are more women than men that develop meningioma and the incidence is about two fold higher in women than men. Ionizing radiation is a well-established risk factor with time interval to tumour development of decades.

The meta-analysis of our studies,[8,14] and Interphone[10] gave in the $\geq$ 10 years latency group OR = 0.97, 95 % CI = 0.80-1.18, see Table 8. Similar results were found in that latency group for ipsilateral and contralateral mobile phone use. The risk was not statistically significant increased for meningioma in the temporal lobe. With cumulative mobile phone use $\geq$ 1,640 hours ipsilateral use gave OR = 1.46, 95 % CI = 1.05–2.03, Table 9. Contralateral use produced OR = 0.94, 95 % CI = 0.64-1.37.

Table 8. *Use of mobile phones and meningioma risk, meta-analysis of study periods 1997-2003 and 2007-2009,[8,14] and Interphone.[10] - Fixed-effects model used for all meta-analyses, based on test for heterogeneity in the overall (≥10 years and ≥1,640 hours) groups.*

	Hardell et al 1997-2009		**Interphone 2000-2004**		**Meta-analysis**	
	Ca/Co	OR, CI	Ca/Co	Ca/Co	OR, CI	Ca/Co
Latency ≥ 10 years						
-all	346/786	1.07 (0.84-1.36)	110/112	0.83 (0.61-1.14)	456/898	0.97 (0.80-1.18)
-ipsilateral	161/360	1.05 (0.76-1.44)	40/42	0.88 (0.52-1.47)	201/402	1.00 (0.76-1.31)
-contralateral	126/257	1.20 (0.84-1.71)	20/25	0.58 (0.29-1.16)	146/282	1.03 (0.75-1.42)
-temporal lobe	82/786	1.25 (0.81-1.95)	12/12	0.60 (0.22-1.62)	94/798	1.11 (0.74-1.66)
-≥ 1640 h	109/232	1.28 (0.88-1.88)	44/40	0.95 (0.56-1.63)	153/272	1.16 (0.85-1.58)

Table 9. *Use of mobile phones and meningioma risk, meta-analysis of study periods 1997-2003 and 2007-2009,[8,14] and Interphone.[10] - Fixed-effects model used for all meta-analyses, based on test for heterogeneity in the overall (≥10 years and ≥1,640 hours) groups.*

	Hardell et al 1997-2009		**Interphone 2000-2004**		**Meta-analysis**	
	Ca/Co	OR, CI	Ca/Co	Ca/Co	OR, CI	Ca/Co
Cumulative use ≥ 1640 h						
-all	141/301	1.24 (0.93-1.66)	130/107	1.15 (0.81-1.62)	271/408	1.20 (0.96-1.50)
-ipsilateral	67/133	1.46 (0.98-2.17)	46/35	1.45 (0.80-2.61)	113/168	1.46 (1.05-2.03)
-contralateral	51/105	1.11 (0.71-1.73)	28/28	0.62 (0.31-1.25)	79/133	0.94 (0.64-1.37)
-temporal lobe	32/301	1.37 (0.80-2.34)	21/14	0.94 (0.31-2.86)	53/315	1.28 (0.79-2.07)

Restricted cubic spline plots

Figure 3 demonstrates no relationship for the risk and latency using data up to 28 years from first use of a wireless phone before tumour diagnosis (p, nonlinearity=0.44).[8,14] This finding gives no support for RF-EMFs to play a role in the initiation stages of carcinogenesis during the study period.

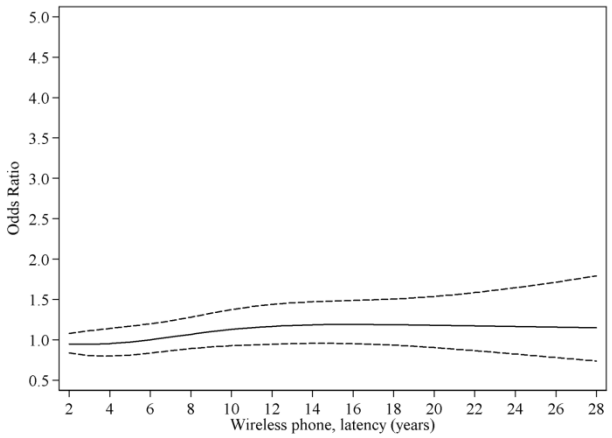

Figure 3. Time from first use of wireless phone and meningioma risk. Number of years is given. The solid line indicates odds ratio and broken lines 95 % confidence limits.[8,14]

Conclusion

There was no statistically significant increased risk for ipsilateral use or localisation in the temporal lobe in the >10 years latency group. With cumulative use ≥1,640 hours a statistically significant increased risk was found for ipsilateral use. In summary the results do not show a clear pattern of an association, and there is no consistent association between use of wireless phones and meningioma. Meningioma is a slowly growing tumour. Thus an increased risk for longer latency period than so far studied cannot be excluded.

3. ACOUSTIC NEUROMA

Acoustic neuroma or Vestibular Schwannoma is a benign tumour that is located in the eighth cranial nerve that leads from the inner ear to the brain. This tumour type does not undergo malignant transformation. It tends to be encapsulated and grows in relation to the auditory and vestibular portions of the nerve. It is a slow growing tumour in the auditory canal but grows gradually out into the cerebellopontine angle with potential compression of vital brain stem centres. Tinnitus and hearing problems are usual first symptoms of acoustic neuroma. Although acoustic neuroma is a benign tumour it causes persistent disabling symptoms after treatment such as loss of hearing and tinnitus that severely affect the daily life. The eighth cranial nerve is located close to the handheld wireless phone when used, so there is particular concern of an increased risk for neuroma development due to exposure to RF-EMF emissions during use of these devices. In fact, acoustic neuroma might be the 'signal tumour' for the carcinogenic effect from RF-EMF emissions.

In our studies we found similar results for both use of mobile phones and cordless phones with increasing risk with latency and cumulative use (data not in Table). In the meta-analysis of our results,[8,15] and Interphone[18] ipsilateral mobile phone use increased the risk for acoustic neuroma. We show the results in the ≥ 10 years latency group in Table 10. Ipsilateral mobile phone use gave somewhat higher risk than contralateral. Cumulative use ≥ 1,640 hours gave OR = 2.60, 95 % CI = 1.32-5.10. In Table 11 results are given in total for ≥ 1,640 hours use yielding OR = 2.71, 95 % CI = 1.72-4.28 in the ipsilateral group whereas contralateral use gave OR = 0.99, 95 % CI = 0.56-1.75.

Table 10. *Use of mobile phones and acoustic neuroma risk, meta-analysis of study periods 1997-2003 and 2007-2009,[8,15] and Interphone.[18] -- Random-effects model used for all meta-analyses of latency ≥ 10 years and fixed-effects model used for all meta-analyses of cumulative use ≥ 1640 h, based on test for heterogeneity in the overall (≥10 years and ≥1,640 hours) groups.*

	Hardell et al 1997-2009		**Interphone 2000-2004**		**Meta-analysis**	
	Ca/Co	OR, CI	Ca/Co	Ca/Co	OR, CI	Ca/Co
Latency ≥ 10 years						
-all	58/786	2.26 (1.43-3.58)	68/141	0.76 (0.52-1.11)	126/927	1.30 (0.45-3.78)
-ipsilateral	34/360	2.10 (1.20-3.67)	44/52	1.18 (0.69-2.04)	78/412	1.57 (0.89-2.76)
-contralateral	22/257	2.41 (1.20-4.84)	17/30	0.69 (0.33-1.42)	39/287	1.30 (0.38-4.41)
-≥ 1640 h	18/232	3.87 (1.80-8.30)	37/37	1.93 (1.10-3.38)	55/269	2.60 (1.32-5.10)

Table 11. *Use of mobile phones and acoustic neuroma risk, meta-analysis of study periods 1997-2003 and 2007-2009,[8,15] and Interphone.[18] - Random-effects model used for all meta-analyses of latency ≥ 10 years and fixed-effects model used for all meta-analyses of cumulative use ≥ 1,640 h, based on test for heterogeneity in the overall (≥10 years and ≥1640 hours) groups.*

	Hardell et al 1997-2003, 2007-2009		**Interphone 2000-2004**		**Meta-analysis**	
	Ca/Co	OR, CI	Ca/Co	Ca/Co	OR, CI	Ca/Co
Cumulative use ≥ 1640 h						
-all	27/301	2.40 (1.39-4.16)	77/107	1.32 (0.88-1.97)	104/408	1.63 (1.18-2.25)
-ipsilateral	19/133	3.18 (1.65-6.12)	47/46	2.33 (1.23-4.40)	66/179	2.71 (1.72-4.28)
-contralateral	8/105	1.54 (0.63-3.76)	16/26	0.72 (0.34-1.53)	24/131	0.99 (0.56-1.75)

Restricted cubic spline plots

Figure 4 demonstrates a linear relationship (p, nonlinearity=0.60) between increasing risk and latency using data up to 28 years from first use of a wireless phone before tumour diagnosis in our studies 1997-2003 and 2007-2009.[8,15]

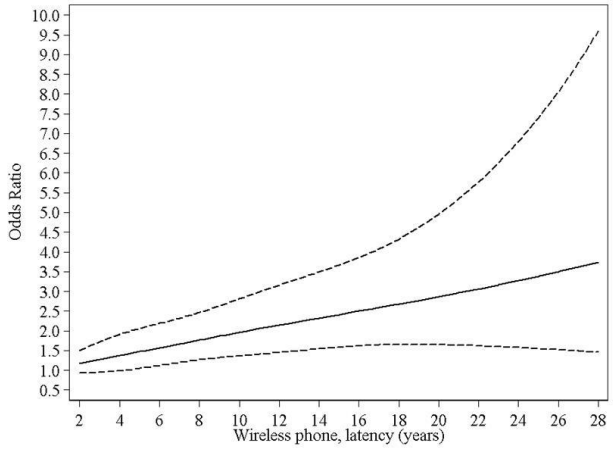

Figure 4. Time from first use of wireless phone and acoustic neuroma risk. Number of years is given. The solid line indicates odds ratio and broken lines 95 % confidence limits.[15]

Conclusion

We conclude that the findings are consistent with an increased risk for acoustic neuroma associated with use of wireless phones.

4. OTHER RECENT STUDIES

After the IARC evaluation in May 2011 some additional studies other than our recent publications have been published.

In the US study by Han et al[19] regular mobile phone use was statistically significant more common among the cases (p = 0.006). The adjusted OR for ≥ 10 years' mobile phone use was 1.29, 95 % CI = 0.69-2.43 (crude OR = 2.20, 95 % CI = 1.43-3.39). Regarding cordless phone use the adjusted OR for ≥ 10 years use was 1.07, 95 % CI = 0.51-2.24 (crude OR = 1.40, 95 % CI =0.84-2.35). However, not all statistically significant confounders were included in the adjusted model (residency excluded) and no results were given for wireless phone use in total.

The authors noted that they had insufficient information on mobile phone use. The results for cordless phones were not discussed in detail.

An increased risk for acoustic neuroma associated with reported use of mobile phone was found in a study from UK.[20] Ever use gave in the 10+ years group RR = 2.46, 95 % CI = 1.07-5.64 with increasing risk with duration of use (p trend = 0.03). The study was limited by e.g. mobile phone use only at baseline, no details on handedness use, no information on tumour laterality and no assessment of use of cordless phones.

Another Swedish study group than our published recently results on acoustic neuroma diagnosed during 2002-2007.[21] Regular mobile phone use produced OR = 1.18, 95 % CI = 0.88-1.59 increasing to OR = 1.51, 95 % CI = 0.92-2.49 in the highest cumulative exposure group $\geq$ 1,640 hours. Higher risk estimates were found for latency < 10 years than for longer time; latency $\geq$ 13 years the longest time period. Regarding analogue phones highest risk was seen in the < 5 years latency group, OR = 2.85, 95 % CI = 0.70-11.6. Use of digital mobile phone gave highest risk in the 5-9 years latency group with OR = 1.53, 95 % CI = 1.02-2.32. No clear pattern of an association was found in the laterality analysis. Contralateral use yielded in general higher risks than ipsilateral casting doubts on the methods used. Deficient or loss of hearing is an early sign of acoustic neuroma and of course an outcome after surgery. Use of cordless phone gave overall OR = 1.41, 95 % CI = 1.07-1.86 increasing to OR = 1.74, 95 % CI = 1.22-2.46 in the 5-9 years latency group. No laterality analysis was published for cordless phone use. In contrast to our studies no category of 'wireless phone use' was presented. That means that when analysing mobile phone use some individuals in the 'unexposed' group might have used a cordless phone and in the analysis of use of cordless phones, users of mobile phone could have been included in the 'unexposed' group.

Associations between the estimated amount of mobile phone use and acoustic neuroma and between the laterality of phone use and tumour location were analysed in a case–control study from South Korea.[22] No increased risk was found for acoustic neuroma but the methods used seem to be less reliable, e.g. time at diagnosis for cases but time at interview of controls were used as cut-off for exposure. In the case–case part of the study, tumour volume and estimated cumulative hours showed a strong correlation (r^2=0.144, p = 0.002), and regular mobile phone users showed tumours of a markedly larger volume than those of non-regular users (p <0.001). When the analysis was limited to regular users who had serviceable hearing, laterality showed a strong correlation with tumour side (OR=4.5, 95 % CI = 0.585-34.608). The authors concluded that acoustic neuroma tumours may coincide with the more frequently used ear of mobile phones and that tumour volume showed strong correlation with amount of mobile phone use.[22]

CERENAT is a multicenter case-control study carried out in four areas in France in 2004-2006 and included in total 253 glioma, 194 meningioma and 892 matched controls.[23] No association with brain tumours was observed when comparing regular mobile phone users with non-users; OR = 1.24, 95% CI = 0.86-1.77 for glioma, OR = 0.90, 95% CI = 0.61-1.34 for meningioma. However, a statistically significant positive association was found in the heaviest users when considering life-long cumulative duration; ≥896 h, OR = 2.89, 95% CI = 1.41-5.93 for glioma; OR = 2.57, 95% CI = 1.02-6.44 for meningioma. Number of calls gave an increased risk for glioma; ≥18,360 calls, OR = 2.10, 95% CI = 1.03-4.31. We conclude that these additional data in the CERENAT study support previous findings concerning a possible association between heavy mobile phone use and brain tumours, especially glioma.

Conclusion

Additional studies from USA, UK, South Korea, France and Sweden strengthen the association between mobile phone use and glioma and acoustic neuroma. Only the US[19] and the Swedish study[21] (other than from our research group) assessed use of cordless phones. An association between such use and acoustic neuroma was reported in the latter.

5. INCIDENCE OF BRAIN TUMOURS

It has been suggested that overall incidence data on brain tumours for countries may be used to qualify or disqualify the association between mobile phone use and brain tumours observed in the case-control studies. It has been claimed that there is no increasing incidence of brain tumours, and thus an association between mobile phone use and glioma has been weakened. [24,25] In fact, that notion is based on wrong data. Moreover most studies neglect to study and discuss RF-EMF exposure from use of cordless phones.

The age-standardized incidence of brain tumours increased in Denmark with +41.2 % among men and +46.1 % among women during 2003-2012, compare Figure 5 (http://www.ssi.dk/Aktuelt/Nyheder/2_013/~/media/Indhold/DK - dansk/Sundhedsdata og it/NSF/Registre/Cancerregisteret/Cancerregisteret 2012.ashx).

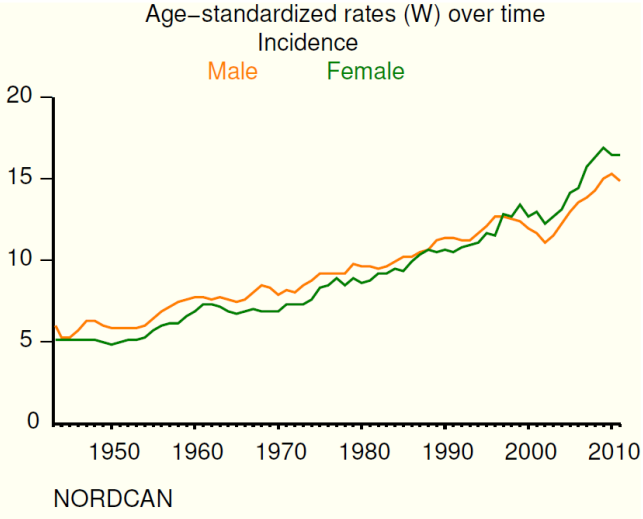

Figure 5. Age-standardized incidence rates per 100,000 person-years of brain tumours over time in Denmark according to NORDCAN (http://www-dep.iarc.fr/NORDCAN/english/StatsFact_asp?cancer=320&country=208).
Male and female rates are shown.

A news release based on the Danish Cancer Register stated that during the last 10 years there has been an almost 2-fold increase in the incidence of the most malignant glioma type, glioblastoma multiforme (https://web.archive.org/web/20121128153253/http://www.cancer.dk/Nyheder/nyhedsartikler/2012kv4/Kraftig+stigning+i+hjernesvulster.htm)

Deltour et al[26] reported increasing glioma incidence rates in Denmark, Finland, Norway, and Sweden for the time period 1979-2008. Annual Percentage Change (APC) increased for men with +0.4 %, 95 % CI +0.1 to 0.6 % and for women with +0.3 %, 95 % CI +0.1 to 0.5 %. Unfortunately no data were given for subtypes of glioma and anatomical sites of the tumours, which would certainly have been informative. The authors did not consider these and other limitations when they conclude that "*Our data indicate that, so far, no risk associated with mobile phone use has manifested in adult glioma incidence trends...many increased or decreased risks reported in case-control studies are implausible, implying that biases and errors in the self-reported use of mobile phone have likely distorted the findings.*"

It should be noted that regarding Sweden we reported increasing incidence of astrocytoma WHO grades I-IV during 1970-2007. In the age group > 19 years the annual percent change was +2.16 %, 95 % CI +0.25 to 4.10 % during 2000-2007.[27] It should be noted that the quality of the Swedish Cancer Registry for reporting central nervous system tumours, particularly high-grade glioma, has been seriously questioned.[28] From county hospitals more than half of the patients with nervous system tumours were never reported to the Cancer Registry during the studied year, 1998. This is a worrying finding which casts doubt on the quality of the Swedish Cancer Registry.

Little et al[29] studied the incidence rates of glioma during 1992-2008 in the United States. They reported statistically significant yearly increasing incidence of high-grade glioma in the SEER data for 1992-2008, +0.64%, 95% CI +0.33 to 0.95 %. On the contrary, the incidence of low-grade glioma decreased with –3.02 %, 95 % CI -3.49 to –2.54 %. They reported also increasing yearly trend for glioma in the temporal lobe, +0.73 %, 95 % CI

+0.23 to 1.23 %, as would be expected based on anatomical distribution of RF-EMF emissions from the handheld wireless phone. However, Little et al concluded that "*Raised risk of glioma with mobile phone use, as reported by one (Swedish) study...are not consistent with observed incidence trends in the US population data...*" which is a conclusion that goes far beyond scientific evidence and what would be possible to show with the faulty methods used in the study. In fact, the observed rates were based on men aged 60-64 years from the Los Angeles SEER registry as the baseline category. These data were used to estimate rates in the entire dataset, men and women aged $\geq$ 18 years and all 12 SEER registries. Thereby numerous assumptions were made. There were many shortcomings in the study but our response to the journal (BMJ) was never accepted for publication in paper version and cannot be found via PubMed, only on the web (http://www.bmj.com/content/344/bmj.e1147/rr/578564).

An increasing incidence of brain tumours was reported from Australia.[30] APC for malignant tumours increased statistically significant +3.9 %, 95 % CI +2.4 to 5.4 %. The increase was seen among both men and women. The APC for benign tumours increased with +1.7 %, 95 % CI -1.4 to +4.9 %, thus not statistically significant.

From urban Shanghai an increasing incidence of brain and nervous system tumours for the time period 1983-2007 was reported with APC +1.2 %, 95 % CI +0.4 to 1.9 % in males and APC +2.8 %, 95 % CI +2.1 to 3.4 % in females.[31]

Certainly it is more informative to analyse incidence trends by anatomical site and histology of the tumour. de Vocht et al reported in England for the time period 1998 to 2007 a statistically significant increasing incidence of brain tumours, the majority glioma, in the temporal lobe for men ($p < 0.01$) and women ($p < 0.01$), and frontal lobe for men ($p < 0.01$). [32] The incidence increased in the frontal lobe also in women, although not statistically significant ($p = 0.07$). The incidence decreased in other parts of the brain.

Zada et al[33] studied incidence trends of primary malignant brain tumours in the Los Angeles area during 1992-2006. APC was calculated for microscopically confirmed histological subtypes and anatomic sub sites. The overall incidence of primary malignant brain tumours decreased over the time period with the exception of glioblastoma multiforme (astrocytoma grade IV). The annual age adjusted incidence rate of that tumour type increased statistically significant in the frontal lobe with APC +2.4 % to +3.0 % ($p \leq 0.001$) and temporal lobe APC +1.3 % to +2.3 % ($p \leq 0.027$) across all registries. In the California Cancer Registry the incidence of glioblastoma multiforme increased also in cerebellum, APC +11.9 % ($p < 0.001$). The authors concluded that there was a real increase in the incidence of glioblastoma multiforme in frontal and temporal lobes and cerebellum. These results are of interest since the highest absorbed dose of RF-EMF emissions from mobile phones has been calculated to occur in these parts of the brain.

de Vocht et al[34] used ecological data to generate hypotheses on environmental risk factors for cancers of the brain and nervous tissue. National age-adjusted cancer incidence rates were obtained from the GLOBOCAN 2008 resource and combined with data from the United Nations Development Report and the World Bank list of development indicators. Cancer rates, potential confounders and environmental risk factors were available for 165 of 208 countries. National incidences of brain and nervous system cancers were associated with continent, gross national income in 2008 and Human Development Index Score. The only exogenous risk factor consistently associated with higher incidence was the penetration rate of mobile/cellular telecommunications subscriptions. According to these ecological results the latency period would be at least 11–12 years, but probably more than 20 years. This is in agreement with the latency period for malignant brain tumours that we have published; see Figure 2.

Conclusion

By now an increasing incidence of brain tumours has been reported from many countries. Certain authors have claimed that the Swedish Cancer Registry has a very high standard in the reporting of incident brain tumour cases.[26] As has been shown this is not the case.[28] Furthermore, one should be careful about using data on the incidence of brain tumours to dismiss results in analytical epidemiology. There might be other factors that influence the incidence rate like changes in exposure to other risk factors for brain tumours that are not assessed in descriptive studies. Cancer incidence depends on initiation, promotion and progression of the disease. The mechanism for RF-EMF carcinogenesis is unclear which adds to the view that descriptive data on brain tumour incidence are of limited value.

DISCUSSION

We know little about the earliest events in the genesis of glioma in humans for obvious reasons. However, progression of glioma has been studied in a large series of tumours of different malignancy grades. Patients with low-grade glioma have been followed with later progression to high-grade glioma.[35] Thus, since the natural history of most glioma cases, from earliest events to clinical manifestation, is unknown, but most likely requires several decades, the exposure duration has in most studies been incompatible with a tumour initiating effect. Our latest study is the first with long-term use of wireless phones.[13] Interestingly, the most elevated OR was found in the latency group > 25 years use. We also found results indicating a late effect on tumour development (promotion).

Initiation and promotion have different effects on the incidence of brain tumours. An initiating effect would have the most direct effect on the incidence. Our results indicate that such an effect would be apparent after more than 20 years use of mobile phones, and thus be too early to be found in cancer registries. On the other hand, if the exposure acts as a promoter, this would decrease latency time for already existing tumours, giving a temporary, but not a continuous, increase in incidence. In addition, it must be noted that any such effect on tumour development is limited by the magnitude of the shift of the age-incidence function and its slope for the respective tumour type.[36]

Sir Austin Bradford Hill gave a presidential address at the British Royal Society of Medicine in 1965 on association or causation that provides a helpful framework for evaluation of the brain tumour risk from RF-EMF.[37] We used his viewpoints to evaluate association *versus* causation on RF-EMF and brain tumour risk.[38] All nine issues on causation according to Hill were evaluated. Regarding wireless phones only studies with long-term use were included. Also laboratory studies and data on the incidence of brain tumours were considered. The criteria on *strength, consistency, specificity, temporality* and *biological 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 tumours, especially in the most exposed area. Support for *experiment* came from antioxidants that can alleviate the generation of reactive oxygen species (ROS) involved in biological effects, although a direct mechanism for brain tumour carcinogenesis has not been shown. Also our finding of no increased risk for brain tumours in subjects using the mobile phone only in a car with an external antenna is supportive evidence. Hill did not consider that all nine viewpoints needed to be essential requirements.

FINAL CONCLUSION

Based on our own research and literature review RF-EMF emissions from wireless phones should be regarded as human carcinogens. Supportive evidence comes from using the Hill criteria. Glioma and acoustic neuroma should be considered to be caused by RF-EMF emissions. Current guidelines for exposure need to be urgently revised.

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