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Brain tumour risk in relation to mobile telephone use: results of the Interphone international case-control study

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The long awaited Interphone study on use of mobile phones and the risk of brain tumour was recently published.¹ It was coordinated by International Agency for Research on Cancer (IARC) and included 16 research centres from 13 countries. Results for cases aged 30-59 years of age diagnosed during study periods of 2-4 years between 2000-2004 were presented. The results were scheduled to be published in years 5 to 6 (2005-2006)² but for unclear and not published reasons they have been delayed for many years.

So far the overall results were published for glioma and meningioma, but the final findings for acoustic neuroma and tumours of the parotid gland are still to be presented.

Other than the Interphone, our research group is the only one that has published results for brain tumour risk and long-term use of mobile phones. In contrast to Interphone, we also included use of cordless phones. Radiofrequency emissions from a cordless phone are in the same magnitude as from a digital mobile phone, as discussed in our publications and recently shown also by Redmayne et al.³ Moreover cordless phones are used for longer calls. Including such use in the 'unexposed' group as in the Interphone study would bias the odds ratio (OR) towards unity.

The Interphone publication has an extremely meager discussion of their findings in relation to current knowledge from other publications. Our results of a consistent pattern of an association between long-term use of wireless phones and ipsilateral glioma⁴⁻⁶ are dismissed in two sentences stating that 'However, the methods of these studies have been questionned.' with reference to another publication by some members of the Interphone group.⁷ No stringent discussion of *pros* and *cons* in our studies are presented and these *ad hoc* statements are made without a thorough review.⁷ This is in contrast to a balanced commentary in the

same issue of Epidemiology⁸ and other independent authors who concluded that our studies have less bias than the Interphone studies.⁹ We have previously compared study methods and results in our investigations with those in the Interphone group.¹⁰

The research budget for Interphone totalled over 19 million euro (\pounds) and a substanial part, 5.5 million \pounds , came from industry.¹¹ Additional funding was provided by industry in some countries. Furthermore, according to the study protocol "Other parties may also be involved in the Study Group as observers or consultants. These may include representatives of industry, other concerned organisations..." In addition, "representatives of industry and other concerned organisations... shall be informed shortly (maximum of seven days) before publication," that is before the scientific community and the laymen have access to the study results.²

Due to the lack of information and any discussion of the Interphone findings in relation to our results it is pertinent to use the same criteria as in Interphone for our case-control studies on glioma.⁴ Our inclusion period was 1997-2003 and we give results for all glioma for the same age group, 30-59 years as in Interphone, (Table 1) and glioma located in the temporal lobe (Table 2). Overall results are also presented for our studies as well as inclusion of the youngest subjects 20-29 years, and in one analysis including use of cordless phone among the unexposed.

In Appendix 2 in the Interphone analysis was restricted to ever users with lowest category of use as reference. There might be a 'healthy mobile phone user' effect among the controls that participated,¹ similar to a 'healthy worker effect' in occupational studies. Thus, the analysis in Appendix 2 would be justified to correct for the lower prevalence of mobile phone use among controls that refused to participate than among included controls in Interphone.¹

As can be seen in Table 1 our results in the same age group as in Interphone, 30-59 years, are similar as in Appendix 2 for latency ≥ 10 years and cumulative use ≥ 1640 h. Unfortunately Interphone did not give results for laterality analysis in Appendix 2.

Interestingly our results for cumulative use in the age group 30-59 years are similar to Interphone results. Furthermore, in both studies highest ORs were found for ipsilateral use.

We found higher risks if the age group 20-29 years was included. This is in agreement with our previous publication showing highest risk for persons that started use of mobile or cordless phone before the age of 20 years.⁶ Thus excluding that age group from the final Interphone seems to have biased the risk towards unity. We examined the results if we considered use of cordless phone as no exposure to microwaves, which yielded lower ORs indicating that excluding such use, as in Interphone, would also bias the risk towards unity.

Table 2 gives the results for glioma in the temporal lobe. Similarly as for overall findings risk estimates were lower in our studies when we restricted the age group to 30-59 years and considered use of cordless phone as no expsosure. No results were given in Appendix 2 for glioma in the temporal lobe.

As has been pointed out elsewhere a probable explanation for the different results in our studies compared with Interphone is bias in the Interphone study.⁹ This is also discussed in a commentary to the Interphone article.¹² Thus, of 50 ORs in Table 2 in the article only 3 ORs were above 1. For no association ORs would vary randomly above and below 1, and not even

the Interphone authors favour the idea that mobile phone use would protect against brain tumours.

The definition of exposure, at least one call per week for 6 months, seems to be vague and arbitary chosen. Taking the fact that 13 countries with 16 study centres were included must have entailed many interviewers, especially since vast geographical areas needed to be covered in many countries. It is not explained how these interviews were performed in e.g. Sweden with large sparsely populated areas, or from what areas controls were recruited, e.g. excluding some geographical areas with low population.

The participation rate was only 64 % for glioma cases and 53 % for controls, i.e. much lower than in the studies from the Hardell group, 90 % of cases with malignant brain tumor and 89 % of the controls.⁴ Furthermore, we used a self-administered questionnaire that was supplemented over the phone. This was done without knowledge if it was a case or a control.

Low participation rate may create selection bias and not blinding as to case or control status may give observational bias, especially in a study with such vague definition of cut-off for exposure. Especially worrying as to observational bias are bed-side interviews of such a mentally ill patient group as with brain tumour. They may even have been newly operated before the interview. In fact patients scored significantly lower than controls due to recalling of words (aphasia), problems with writing and drawing due to paralysis in the Danish part of Interphone.¹³

It is unclear why younger cases were excluded from the final Interphone report, especially since our results indicate highest risk in the youngest age group.⁶ Thus, Denmark and Sweden

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included the age group 20-29 years, Norway 19-29 and UK 18-29, and the age groups are unclear for the countries that have not published individual results.¹⁴

There are several other methodological issues in Interphone that would be pertinent to discuss, e.g. how was use of mobile phone in a car with external antenna judged. Several factors may explain the seemingly discrepancy between our results and those in Interphone. These include in Interphone e.g. proxy interviews among cases (13 % versus 1% among controls), restricting age group to 30-59 years, including use of cordless phone among the unexposed, vague definition of exposure categories, low participation rates for cases and controls, selection bias of controls, bedside interviews of cases, not blinding as to case or controls status and a multitude of research centres and interviewers with potential for observational bias.

We urge Interphone to fill in the gaps in our Tables 1 and 2, so as to make full comparison with our data possible. Currently we present results on the association of use of wireless phones and malignant brain tumours among deceased cases, that were excluded from our study, using deceased controls. These results confirm our previous findings of an increased risk for malignant brain tumour among mobile phone users. ¹⁵

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Table 1. Odds ratio (OR) and 95 % confidence interval (CI) for glioma in Interphone compared with the Hardell group. Numbers of cases (Ca) and controls (Co) are given. N.R. = not reported. All glioma. Note that > 10 y latency was used in the Hardell group studies and contralateral was defined as < 50% use on tumour side.

	Hardell	Hardell	Hardell	Hardell group,	Interphone,	Interphone,
	group,	group,	group,	30-59, cordless	30-59	30-59,
	20-80	20-59	30-59	among		appendix 2
	(all)			unexposed		
Latency ≥ 10 y	(88/99)	(57/74)	(56/74)	(56/74)	(252/232)	(190/150)
	2.26	2.15	1.96	1.79	0.98	2.18
	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 y, ipsilateral	(57/45)	(36/30)	(35/30)	(35/30)	(108/82)	N.R.
	2.84	2.70	2.48	2.29	1.21	
	1.82-4.44	1.54-4.73	1.40-4.38	1.33-3.97	0.82-1.80	
Latency ≥ 10 y, contralateral	(29/29)	(20/24)	(20/24)	(20/24)	(49/56)	N.R.
	2.18	2.04	1.96	1.71	0.70	
	1.24-3.85	1.04-4.00	0.995-3.87	0.89-3.28	0.42-1.15	
Cumulative use > 1640 h	(42/43)	(32/37)	(29/37)	(29/37)	(210/154)	(160/113)
	2.31	2.23	1.89	1.75	1.40	1.82
	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,	(29/21)	(22/18)	(20/18)	(20/18)	(100/62)	N.R.
ipsilateral	2.94	2.71	2.32	2.18	1.96	
-	1.60-5.41	1.36-5.42	1.14-4.73	1.09-4.35	1.22-3.16	
Cumulative use ≥1640 h,	(12/12)	(9/11)	(8/11)	(8/11)	(39/31)	N.R.
contralateral	2.10	1.99	1.73	1.48	1.25	
	0 90-4 90	077-516	0 65-4 63	0 57-3 87	0 64-2 42	

Table 2. Odds ratio (OR) and 95 % confidence interval (CI) for glioma in Interphone compared with the Hardell group. Numbers of cases (Ca) and controls (Co) are given. N.R. = not reported. Glioma, temporal lobe. Note that > 10 y latency was used in the Hardell group studies and contralateral was defined as < 50% use on tumour side.

	Hardell, 20-80 (all)	Hardell, 20-59	Hardell, 30-59	Hardell, 30-59, cordless among unexposed	Interphone, 30-59	Interphone, 30-59, appendix 2
Latency ≥ 10 y	(28/99)	(15/74)	(14/74)	(14/74)	(94/69)	N.R.
	2.26	1.74	1.48	1.40	1.36	
	1.32-3.86	0.85-3.56	0.71-3.10	0.70-2.81	0.88-2.11	
Latency ≥ 10 y, ipsilateral	(18/45)	(10/30)	(9/30)	(9/30)	N.R.	N.R.
	2.49	1.94	1.73	1.69		
	1.29-4.81	0.81-4.63	0.70-4.26	0.71-4.02		
Latency ≥ 10 y,	(9/29)	(4/24)	(4/24)	(4/24)	N.R.	N.R.
contralateral	2.08	1.35	1.28	1.21		
	0.89-4.87	0.41-4.49	0.38-4.28	0.37-3.90		
Cumulative use <u>> 1640 h</u>	(14/43)	(9/37)	(7/37)	(7/37)	(78/47)	N.R.
	2.44	1.96	1.53	1.46	1.87	
	1.21-4.95	0.82-4.66	0.60-3.94	0.59-3.63	1.09-3.22	
Cumulative use <u>> 1640 h</u> ,	(11/21)	(7/18)	(5/18)	(5/18)	N.R.	N.R.
ipsilateral	3.08	2.18	1.68	1.82		
	1.32-7.19	0.77-6.24	0.52-5.41	0.59-5.60		
Cumulative use \geq 1640 h,	(2/12)	(1/11)	(1/11)	(1/11)	N.R.	N.R.
contralateral	1.04	0.72	0.72	0.64		
	0.22-5.00	0.08-6.11	0.08-6.12	0.08-5.33		

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Letter to the Editor

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Due to the lack of information and any discussion of the Interphone findings in relation to our results it is pertinent to use the same criteria as in Interphone for our case-control studies on glioma.⁴ Our inclusion period was 1997-2003 and we give results for all glioma for the same age group, 30-59 years as in Interphone, (Table 1) and glioma located in the temporal lobe (Table 2). Overall results are also presented for our studies as well as inclusion of the youngest subjects 20-29 years and in one analysis including use of cordless phone among the unexposed. We have also re-analysed our material with the same cumulative exposure time as in the Interphone study, i.e. >1640 h, since we before had >2000 h.

In Appendix 2 in the Interphone paper analysis was restricted to ever users with lowest category of use as reference in each category. There might be a 'healthy mobile phone user' effect among the controls that participated,¹ similar to a 'healthy worker effect' in occupational studies. Thus, the analysis in Appendix 2 would be justified to correct for the

lower prevalence of mobile phone use among controls that refused to participate than among included controls in Interphone.¹

As can be seen in Table 1 our results in the same age group as in Interphone, 30-59 years, are similar as in Appendix 2 for latency ≥ 10 years and cumulative use ≥ 1640 h. Unfortunately Interphone did not give results for laterality analysis in Appendix 2.

Interestingly our results for cumulative use in the age group 30-59 years are similar to Interphone results. Furthermore, in both studies highest ORs were found for ipsilateral use.

We found higher risks if the age group 20-29 years was included. This is in agreement with our previous publication showing highest risk for persons that started use of mobile or cordless phone before the age of 20 years.⁵ Thus excluding that age group from the final Interphone seems to have biased the risk towards unity. We examined the results if we considered use of cordless phone as no exposure to microwaves, which yielded lower ORs indicating that excluding such use, as in Interphone, would also bias the risk towards unity.

Table 2 gives the results for glioma in the temporal lobe. Similarly as for overall findings risk estimates were lower in our studies when we restricted the age group to 30-59 years and considered use of cordless phone as no exposure. No results were given in Appendix 2 for glioma in the temporal lobe.

The interview rate was only 64 % for glioma cases and 53 % for controls, i.e. much lower than in the studies from the Hardell group, 90 % of cases with malignant brain tumour and 89

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% of the controls.⁴ Furthermore, we used a self-administered questionnaire that was supplemented over the phone. This was done without knowledge if it was a case or a control.

Low participation rate may create selection bias and not blinding as to case or control status may give observational bias, especially in a study with such vague definition of cut-off for exposure. Especially worrying as to observational bias are bed-side interviews of such a mentally ill patient group with brain tumour. They may even have been newly operated before the interview. In fact patients scored significantly lower than controls due to recalling of words (aphasia), problems with writing and drawing due to paralysis in the Danish part of Interphone.⁶

It is unclear why younger cases were excluded from the final Interphone report, especially since our results indicate highest risk in the youngest age group.⁵ Thus, Denmark and Sweden included the age group 20-29 years, Norway 19-29 and UK 18-29, and the age groups are unclear for the countries that have not published individual results.⁷

We urge Interphone to fill in the gaps in our Tables 1 and 2, so as to make full comparison with our data possible. Currently we have presented results on the association of use of wireless phones and malignant brain tumours among deceased cases, that were excluded from our study, using deceased controls. These results confirm our previous findings of an increased risk for malignant brain tumour among mobile phone users. ⁸

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	Hardell group, 20-80 (all)	Hardell group, 20-59	Hardell group, 30-59	Hardell group, 30-59, cordless among unexposed	Interphone, 30-59	Interphone, 30-59, according to published appendix 2
Latency ≥ 10 y	(88/99)	(57/74)	(56/74)	(56/74)	(252/232)	(190/150)
	2.26	2.15	1.96	1.79	0.98	2.18
	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 y, ipsilateral	(57/45)	(36/30)	(35/30)	(35/30)	(108/82)	N.R.
	2.84	2.70	2.48	2.29	1.21	
	1.82-4.44	1.54-4.73	1.40-4.38	1.33-3.97	0.82-1.80	
Latency ≥10 y, contralateral	(29/29)	(20/24)	(20/24)	(20/24)	(49/56)	N.R.
	2.18	2.04	1.96	1.71	0.70	
	1.24-3.85	1.04-4.00	0.995-3.87	0.89-3.28	0.42-1.15	
Cumulative use > 1640 h	(42/43)	(32/37)	(29/37)	(29/37)	(210/154)	(160/113)
	2.31	2.23	1.89	1.75	1.40	1.82
	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 <a>1640 h,	(29/21)	(22/18)	(20/18)	(20/18)	(100/62)	N.R.
ipsilateral	2.94	2.71	2.32	2.18	1.96	
	1.60-5.41	1.36-5.42	1.14-4.73	1.09-4.35	1.22-3.16	
Cumulative use <a>1640 h,	(12/12)	(9/11)	(8/11)	(8/11)	(39/31)	N.R.
contralateral	2.10	1.99	1.73	1.48	1.25	
	0.90-4.90	0.77-5.16	0.65-4.63	0.57-3.87	0.64-2.42	



Table 2. Odds ratio (OR) and 95 % confidence interval (CI) for glioma in Interphone compared with the Hardell group. Numbers of cases (Ca) and controls (Co) are given. N.R. = not reported. Glioma, temporal lobe. Note that > 10 y latency were used in the Hardell group studies and contralateral was defined as < 50% use of tumour side.

	Hardell, 20-80	Hardell, 20-59	Hardell, 30-59	Hardell, 30-59. cordless	Interphone, 30-59	Interphone, 30-59.
	(all)			among		appendix 2
				unexposed		
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	1.29-4.81	0.81-4.63	0.70-4.26	0.71-4.02		
Latency ≥ 10 y,	(9/29)	(4/24)	(4/24)	(4/24)	N.R.	N.R.
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-	1.32-7.19	0.77-6.24	0.52-5.41	0.59-5.60		
Cumulative use \geq 1640 h,	(2/12)	(1/11)	(1/11)	(1/11)	N.R.	N.R.
contralateral	1.04	0.72	0.72	0.64		
	0.22-5.00	0.08-6.11	0.08-6.12	0.08-5.33		