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ASSOCIATION QUEBECOISE DE LUTTE CONTRE LA POLLUTION ATMOSPHERIQUE (AQLPA) / QUEBEC ASSOCIATION TO FIGHT AGAINST AIR POLLUTION

Interveners

INTERPHONE STUDY GROUP

Interpretation of results of Interphone Study Group by **WORLD HEALTH ORGANIZATION (WHO), INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC).** Carcinogenicity of radiofrequency electromagnetic fields. The Lancet Oncology, Early Online Publication, 22 June 2011. http://www.wirelesswatchblog.org/wp-content/uploads/2011/06/Lancet-June-2011-11.pdf

Interpretation of results of Interphone Study Group by **BIOINITIATIVE WORKING GROUP.** *Ten-Year INTERPHONE Cell Phone Study Reports Increased Risk for Brain Cancer Experts call for changes in cell phone design, warnings, ban on use by children*. May 18, 2010. http://www.bioinitiative.org/freeaccess/press_release/docs/Interphone.pdf

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THE LANCET Oncology

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Carcinogenicity of radiofrequency electromagnetic fields

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In May, 2011, 30 scientists from 14 countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to assess the carcinogenicity of radiofrequency electromagnetic fields (RF-EMF). These assessments will be published as Volume 102 of the IARC Monographs.[1]

Human exposures to RF-EMF (frequency range 30 kHz—300 GHz) can occur from use of personal devices (eg, mobile telephones, cordless phones, Bluetooth, and amateur radios), from occupational sources (eg, high-frequency dielectric and induction heaters, and high-powered pulsed radars), and from environmental sources such as mobile-phone base stations, broadcast antennas, and medical applications. For workers, most exposure to RF-EMF comes from near-field sources, whereas the general population receives the highest exposure from transmitters close to the body, such as handheld devices like mobile telephones. Exposure to high-power sources at work might involve higher cumulative RF energy deposited into the body than exposure to mobile phones, but the local energy deposited in the brain is generally less. Typical exposures to the brain from rooftop or tower-mounted mobile-phone base stations and from TV and radio stations are several orders of magnitude lower than those from global system for mobile communications (GSM) handsets. The average exposure from use of digital enhanced cordless telecommunications (DECT) phones is around five times lower than that measured for GSM phones, and third-generation (3G) phones em it, on average, about 100 times less RF energy than GSM phones, when signals are strong. Similarly, the average output power of Bluetooth wireless hands-free kits is estimated to be around 100 times lower than that of mobile phones.

EMFs generated by RF sources couple with the body, resulting in induced electric and magnetic fields and associated currents inside tissues. The most important factors that determine the induced fields are the distance of the source from the body and the output power level. Additionally, the efficiency of coupling and resulting field distribution inside the body strongly depend on the frequency, polarisation, and direction of wave incidence on the body, and anatomical features of the exposed person, including height, body-mass index, posture, and dielectric properties of the tissues. Induced fields within the body are highly non-uniform, varying over several orders of magnitude, with local hotspots.

Holding a mobile phone to the ear to make a voice call can result in high specific RF energy absorption-rate (SAR) values in the brain, depending on the design and position of the phone and its antenna in relation to the head, how the phone is held, the anatomy of the head, and the quality of the link between the base station and phone. When used by children, the average RF energy deposition is two times higher in the brain and up to ten times higher in the bone marrow of the skull, compared with mobile phone use by adults.[2] Use of hands-free kits lowers exposure to the brain to below 10% of the exposure from use at the ear, but it might increase exposure to other parts of the body.[3]

Epidemiological evidence for an association between RF-EMF and cancer comes from cohort, case-control, and time-trend studies. The populations in these studies were exposed to RF-EMF in occupational settings, from sources in the general environment, and from use of wireless (mobile and cordless) telephones, which is the most extensively studied exposure source. One cohort study[4] and five case-control studies[5—9] were judged by the Working Group to offer

potentially useful information regarding associations between use of wireless phones and glioma.

The cohort study[4] included 257 cases of glioma among 420 095 subscribers to two Danish mobile phone companies between 1982 and 1995. Glioma incidence was near the national average for the subscribers. In this study, reliance on subscription to a mobile phone provider, as a surrogate for mobile phone use, could have resulted in considerable misclassification in exposure assessment. Three early case-control studies[5–7] encompassed a period when mobile phone use was low, users typically had low cumulative exposures, time since first use of a mobile phone was short, and effect estimates were generally imprecise; the Working Group considered these studies less informative. Time-trend analyses did not show an increased rate of brain tumours after the increase in mobile phone use. However, these studies have substantial limitations because most of the analyses examined trends until the early 2000s only. Such analyses are uninformative if excess risk only manifests more than a decade after phone use begins, or if phone use only affects a small proportion of cases—eg, the most heavily exposed, or a subset of brain tumours.

The INTERPHONE study,[8] a multicentre case-control study, is the largest investigation so far of mobile phone use and brain tumours, including glioma, acoustic neuroma, and meningioma. The pooled analysis included 2708 glioma cases and 2972 controls (participation rates 64% and 53%, respectively). Comparing those who ever used mobile phones with those who never did yielded an odds ratio (OR) of 0·81 (95% CI 0·70–0·94). In terms of cumulative call time, ORs were uniformly below or close to unity for all deciles of exposure except the highest decile (>1640 h of use), for which the OR for glioma was 1·40 (95% CI 1·03–1·89). There was suggestion of an increased risk for ipsilateral exposure (on the same side of the head as the tumour) and for tumours in the temporal lobe, where RF exposure is highest. Associations between glioma and cumulative specific energy absorbed at the tumour location were examined in a subset of 553 cases that had estimated RF doses.[10] The OR for glioma increased with increasing RF dose for exposures 7 years or more before diagnosis, whereas there was no association with estimated dose for exposures less than 7 years before diagnosis.

A Swedish research group did a pooled analysis of two very similar studies of associations between mobile and cordless phone use and glioma, acoustic neuroma, and meningioma.[9] The analysis included 1148 glioma cases (ascertained 1997–2003) and 2438 controls, obtained through cancer and population registries, respectively. Self-administered mailed questionnaires were followed by telephone interviews to obtain information on the exposures and covariates of interest, including use of mobile and cordless phones (response rates 85% and 84%, respectively). Participants who had used a mobile phone for more than 1 year had an OR for glioma of 1·3 (95% CI 1·1–1·6). The OR increased with increasing time since first use and with total call time, reaching 3·2 (2·0–5·1) for more than 2000 h of use. Ipsilateral use of the mobile phone was associated with higher risk. Similar findings were reported for use of cordless phones.

Although both the INTERPHONE study and the Swedish pooled analysis are susceptible to bias—due to recall error and selection for participation—the Working Group concluded that the findings could not be dismissed as reflecting bias alone, and that a causal interpretation between mobile phone RF-EMF exposure and glioma is possible. A similar conclusion was drawn from these two studies for acoustic neuroma, although the case numbers were substantially smaller than for glioma. Additionally, a study from Japan[11] found some evidence of an increased risk for acoustic neuroma associated with ipsilateral mobile phone use.

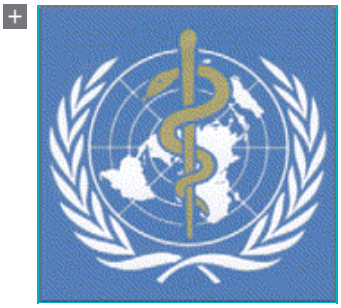
For meningioma, parotid-gland tumours, leukaemia, lymphoma, and other tumour types, the Working Group found the available evidence insufficient to reach a conclusion on the potential association with mobile phone use. Epidemiological studies of individuals with potential occupational exposure to RF-EMF have investigated brain tumours, leukaemia, lymphoma, and other types of malignancy including uveal melanoma, and cancers of the testis, breast, lung, and skin. The Working Group noted that the studies had methodological limitations and the results were inconsistent. In reviewing studies that addressed the possible association between environmental exposure to RF-EMF and cancer, the Working Group found the available evidence insufficient for any conclusion.

The Working Group concluded that there is “limited evidence in humans” for the carcinogenicity of RF-EMF, based on positive associations between glioma and acoustic neuroma and exposure to RF-EMF from wireless phones. A few members of the Working Group considered the current evidence in humans “inadequate”. In their opinion there was inconsistency between the two case-control studies and a lack of an exposure-response relationship in the INTERPHONE study results; no increase in rates of glioma or acoustic neuroma was seen in the Danish cohort study,[4] and up to now, reported time trends in incidence rates of glioma have not shown a parallel to temporal trends in mobile phone use.

The Working Group reviewed more than 40 studies that assessed the carcinogenicity of RF-EMF in rodents, including seven 2-year cancer bioassays. Exposures included 2450 MHz RF-EMF and various RF-EMF that simulated emissions from mobile phones. None of the chronic bioassays showed an increased incidence of any tumour type in tissues or organs of animals exposed to RF-EMF for 2 years. An increased total number of malignant tumours was found in RF-EMF-exposed animals in one of the seven chronic bioassays. Increased cancer incidence in exposed animals was noted in two of 12 studies with tumour-prone animals[12], [13] and in one of 18 studies using initiation-promotion protocols.[14] Four of six co-carcinogenesis studies showed increased cancer incidence after exposure to RF-EMF in combination with a known carcinogen; however, the predictive value of this type of study for human cancer is unknown. Overall, the Working Group concluded that there is “limited evidence” in experimental animals for the carcinogenicity of RF-EMF.

The Working Group also reviewed many studies with endpoints relevant to mechanisms of carcinogenesis, including genotoxicity, effects on immune function, gene and protein expression, cell signalling, oxidative stress, and apoptosis. Studies of the possible effects of RF-EMF on the blood-brain barrier and on a variety of effects in the brain were also considered. Although there was evidence of an effect of RF-EMF on some of these endpoints, the Working Group reached the overall conclusion that these results provided only weak mechanistic evidence relevant to RF-EMF-induced cancer in humans.

In view of the limited evidence in humans and in experimental animals, the Working Group classified RF-EMF as “possibly carcinogenic to humans” (Group 2B). This evaluation was supported by a large majority of Working Group members.



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Upcoming meetings

Oct 11—18, 2011

Bitumen and bitumen fumes, and some heterocyclic polycyclic aromatic hydrocarbons

Feb 7—14, 2012

Polyomaviruses (SV40, BK, JC, and Merkel cell viruses) and malaria

June 5—12, 2012

Diesel and gasoline engine exhausts and some nitroarenes

Monograph Working Group Members

J Samet—Chair (USA); B Armstrong, M Sim (Australia); E Degrave [not present during evaluations], L Verschaeve (Belgium); J Siemiatycki, J McNamee (Canada); D Leszczynski, J Juutilainen (Finland); R de Seze, J-F Doré (France); M Blettner, C Dasenbrock (Germany); J Miyakoshi, T Shirai (Japan); S Szmigielski ([unable to attend] Poland); N Kim (Republic of Korea); I Belyaev (Slovak Republic); E Cardis (Spain); L Hardell (Sweden); M Mevissen, M Röösli (Switzerland); S Mann (United Kingdom); C Blackman, P Inskip [not present during final evaluation], D McCormick, R Melnick, C Portier, D Richardson, Vijayalaxmi (USA)

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Conflicts of interest

MS's spouse owns shares (worth €1350) in Telstra, a telecommunications company in Australia. BA has received travel and accommodation expenses for presentations on mobile phone use and brain tumours, from various Australian organisations and government groups. EC has received travel and accommodation expenses for presentations organised by France Telecom. RdS has received research support from Fondation Santé et Radiofréquences, and was a paid advisor (<€1000) for the plaintiff's lawyer on a lawsuit involving radiofrequency exposure. NK is director and board member of the non-profit IT'IS foundation that performs exposure assessments for industry and governments, and is president of the board and shareholder of Near-Field Technology AG, which controls two companies that develop near-field measurement instruments, simulation software, and medical test equipment. All other Working Group members, specialists, representatives, and secretariat declared no conflicts of interest.

We declare that we have no conflicts of interest.

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Ten-Year INTERPHONE Cell Phone Study Reports Increased Risk for Brain Cancer

Experts call for changes in cell phone design, warnings, ban on use by children.

May 18, 2010: Today's release of the final results of the ten-year long World Health Organization *INTERPHONE Study* confirms previous reports showing what many experts have warned – that regular use of a cell phone by adults can significantly increase the risk of glioma by 40% with 1640 hours or more of use (this is about one-half hour per day over ten years). Tumors were more likely to occur on the side of the head most used for calling. David Carpenter MD MPH, *BioInitiative Report* co-editor and Director of the Institute for Health and the Environment at University at Albany, Rensselaer, NY says that *"While this study is not perfect, the risks documented in it must be taken seriously as a warning to limit cell phone use, to restrict the use of cell phones, especially by children, and to call on manufacturers for redesign of cell phones and PDAs. It should also serve as a warning to governments that the deployment of new wireless technologies may bring risks to the public that are widespread, involuntary and increase long-term health care costs."*

The study appears in the International Journal of Epidemiology. Thirteen teams from countries around the world combined their results.

Michael Kundi, head of the Institute of Environmental Health, Medical University of Vienna says of the study "*Authors emphasize that no increased risk was detected overall. But this is not unexpected. No exposures to carcinogens that cause solid tumors like brain cancer or lung cancers, for example from tobacco and asbestos have ever been shown to significantly increase cancer risk in people with such short duration of exposure. The latency period for brain cancer is 15-30 years."*

The INTERPHONE findings lend support to previous studies from Sweden's Orebro University Hospital, University of Utah and UC Berkeley where meta-analyses have all reported increased risk of glioma when combining results of brain tumor studies.

Lennart Hardell, Orebro University, Sweden concludes *"The final INTERPHONE results support findings of several research groups, including our own, that continuing use of a mobile phone increases risk of brain cancer. We would not expect to see substantially increased brain tumor risk for most cancer-causing agents except in the longer term (10 year and longer) as is the case here in the population of regular cell phone users."*

"The patients included in this study were 30-59 years old, excluding younger and older users. Use of cordless phones was neglected in the analysis. Radiofrequency radiation from some cordless phones can be as high as mobile phones in some countries, so excluding such use would underestimate the risk."

With more than four billion cell phone users around the world, the potential for a brain cancer epidemic leads experts to call for changes in cell phone design, warnings, and a ban on use by children. Children are more at risk than adults from the effects of most toxic exposures in life, including both chemicals and radiofrequency radiation from cell phones. Experts are worried about the effects of radiofrequency radiation on the developing brain and nervous system of children.

Public health warnings were raised in the BioInitiative Report on possible risks from cell phones and other exposures to electromagnetic fields (EMF) in 2007. It advised against the continuing deployment of sources of EMF and radiofrequency radiation from wireless technologies in advance of health studies, and argued for new biologically-based public safety limits to deal with emerging risks from new technologies. Results of the INTERPHONE study provide strong confirmation of the importance of these warnings.

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Reports: Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study, The INTERPHONE Study Group, May 2010, International Journal of Epidemiology, 1-20.doi:10.1093/ije/dyq079

December 3, 2008

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We understand that each of you has participated in the Interphone Study Group on various aspects (brain tumors, acoustic neurinoma, parotid gland tumors) and cell phone use, and that your study results remain unpublished. After four years, results have been published from eight different countries but some results remain unpublished (see Exhibit 1).

We ask for your cooperation in publishing your study results in the very near future. We have been in recent contact with Dr. Elizabeth Cardis. She has provided contact information for each of you so we can directly obtain these results through your publication of them in the peer-reviewed literature.

This will enable scientists and other experts not directly involved in the Interphone studies to get the whole pattern of results without further delay. Thank you for your kind support.

With best personal regards,

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Exhibit 1

Interphone studies from 13 different countries.

No = results have not been published, Yes = results have been published

Country	Glioma	Acoustic neuroma	Meningioma
Australia	No	No	No
Canada	No	No	No
Japan	Yes	Yes	Yes
New Zealand	No	No	No
Israel	No	No	No
Italy	No	No	No
France	Yes	Yes	Yes
Germany	Yes	Yes	Yes
UK	Yes	Yes	Yes
Denmark	Yes	Yes	Yes
Finland	Yes	Yes	Yes
Norway	Yes	Yes	Yes
Sweden	Yes	Yes	Yes

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Appendix Table 1 – Outcome of fieldwork: ascertainment and interviewing by country

a) Meningioma cases

	Overall		Country												
														UK	
Data collection outcome	Number of cases	%	Australia	Canada	Denmark	Finland	France	Germany	Israel	Italy	Japan	New Zealand	Norway	Sweden	*North*	*South*
Number of cases ascertained	3115		413	134	155	252	190	275	390	124	102	72	191	205	222	390
Outcome of attempt to interview																
% refused	339	11	17	13	14	7	9	3	8	8	5	15	1	6	10	24
% MD refused	69	2	4	7	0	0	5	0	0	1	15	3	0	2	0	3
% died or too ill	66	2	1	2	6	0	2	4	1	2	0	3	0	2	4	4
% untraced or other reasons[1]	216	7	16	7	0	2	8	3	1	0	0	7	22	0	5	13
% interviewed	2425	78	62	70	81	92	76	91	90	89	80	72	77	90	81	56
Interview																
% self respondent	2383	98	100	96	98	99	99	98	97	92	100	98	99	98	99	100
% face-to-face	2294	95	100	100	100	99	95	100	100	65	100	100	53	93	100	100
Delay between diagnosis and interview[2] (months)																
median	3.4		3.9	7.7	3.2	1.3	3.4	0.0	4.1	8.2	1.8	4.1	15.4	5.7	2.3	5.6
5-95 percentiles	0.0 /21.9		1.4 /17.7	2.5 /22.9	0.8 /13.7	0.0 /8.4	0.2 /27.9	-0.4 /9.5	0.2 /24.2	0.9 /19.7	0.4 /12.8	1.8 /9.0	-0.1 /29.9	0.3 /15.7	1.0 /11.4	1.8 /23.9
Delay between case and control interviews[3] (months)																
median	-2.1		-0.3	-0.3	-0.5	-0.5	-4.1	-3.1	-9.3	-3.2	-5.1	-4.1	-0.4	-0.5	-2.9	0.0
5-95 percentiles	-16.1 /6.3		-9.2 /10.6	-3.6 /7.8	-5.2 /2.0	-6.2 /2.0	-14.1 /-0.8	-11.1 /6.5	-33.0 /6.5	-15.0 /5.5	-14.4 /-1.3	-29.2/11.7	-14.9 /11.4	-8.1 /6.6	-9.4 /-0.9	-8.4 /8.7

[1] This includes 7 cases who were interviewed but for whom data were lost (these are included as non-interviewed subjects in the current paper, unlike in Cardis et al 2007 (26)).
[2]Date of interview – date of diagnosis
[3] Date of case interview – date of control interview

b) Glioma cases

Data collection outcome	Overall		Country													
															UK	
	Number of cases	%	Australia	Canada	Denmark	Finland	France	Germany	Israel	Italy	Japan	New Zealand	Norway	Sweden	*North*	*South*
Number of cases ascertained	4301	100	536	273	248	211	155	312	206	128	90	132	236	298	628	848
Outcome of attempt to interview																
% refused	470	11	16	7	16	12	19	5	6	1	4	10	1	8	10	15
% MD refused	198	5	4	7	0	0	7	0	0	1	26	4	0	9	2	8
% died or too ill	637	15	14	18	10	1	6	11	6	6	3	14	0	5	16	33
% untraced or other reasons[2]	231	5	9	6	1	2	6	1	0	0	0	9	22	1	3	7
% interviewed	2765	64	56	62	73	84	61	82	87	92	67	64	76	76	68	36
Interview																
% self respondent	2416	87	86	82	94	97	89	90	81	56	98	80	69	93	92	95
% face-to-face	2606	94	99	97	100	99	97	100	99	61	100	100	52	94	100	100
Delay between diagnosis and interview (months)																
median	2.9		3.5	6.1	2.2	0.5	1.9	0.1	3.5	6.2	1.4	3.8	15.0	2.7	2.1	4.4
5-95 percentiles	0.0 / 18.8		1.3 / 18.8	2.9 /12.2	0.5 / 11.2	0.0 / 5.0	0.3 /24.1	-0.3 / 15.1	0.2 / 20.6	0.4 / 17.5	0.3 / 6.5	1.8 / 8.5	-0.1 / 33.2	0.5 / 12.4	1.0 / 8.5	1.4 / 19.8
Delay between case and control interviews (months)																
median	-2.3		-0.5	-1.2	-0.5	-0.9	-4.5	-3.0	-8.1	-4.6	-6.0	-4.6	0.1	-1.2	-2.9	-0.6
5-95 percentiles	-13.9 /7.1		-11.2 /10.8	-8.6 /5.8	-7.2 /2.2	-7.8 /2.1	-11.4 /-0.9	-11.6 /13.0	-32.8 /4.0	-17.2 /13.5	-16.3 /-1.3	-38.3 /3.0	-10.9/17.0	-12.0 /3.6	-10.4 /-0.9	-13.5 /7.4

[2]This includes 12 cases who were interviewed but for whom data were lost **(**these are included as non-interviewed subjects in the current paper, unlike in Cardis et al 2007 (26))

c) Controls (all)

Data collection outcome	Overall		Country												
														UK	
	Number of controls	%	Australia	Canada	Denmark	Finland	France	Germany	Israel	Italy	Japan	New Zealand	Norway	Sweden	*North*	*South*
Number of controls sampled	14354		1608	1330	1277	1337	639	1869	911	486	568	350	404	617	1747	1211
Outcome of attempt to interview																
% refused	4303	30	37	32	32	42	21	29	25	13	25	16	21	22	20	47
% MD refused	126	1	0	0	0	0	0	0	0	0	0	0	0	0	7	0
% died or too ill	49	0	0	0	1	0	0	1	0	0	0	0	0	1	0	0
% untraced or other reasons[1]	2218	15	21	18	16	16	5	6	9	17	25	35	10	12	27	5
% interviewed	7658	53	42	49	52	42	74	64	66	70	51	49	69	66	45	48
Interview																
% self respondent	7615	99	100	99	100	100	100	100	100	95	100	88	100	100	100	100
% face-to-face	7179	94	98	98	100	99	88	100	99	35	100	100	54	94	100	100

[1]This includes 38 controls who were interviewed but for whom data were lost

Appendix Table 2 – ORs between mobile phone use and brain tumours (meningioma and glioma separately) using the "Inskip method" for comparing side of use with side of tumour, by different windows of time before the reference date – excludes use with hands-free devices

a) Meningioma

Time window/ Side of use	Overall					Highest decile of cumulative call time only				
	Left sided tumours	Right sided tumours	OR[1]	95% CI		Left sided tumours	Right sided tumours	OR[1]	95% CI	
Overall										
Left	185	153	1.00			21	13	1.00		
Right	255	278	1.07	1.00	1.16	25	32	1.22	0.96	1.62
Regular users 1-4 years before reference date										
Left	111	86	1.00			5	2	1.00		
Right	147	163	1.10	1.00	1.22	3	5	1.52	0.81	3.88
Regular users 5-9 years before reference date										
Left	58	54	1.00			8	9	1.00		
Right	91	86	1.00	0.90	1.14	15	15	0.97	0.76	1.36
Regular users 10 years or more before reference date										
Left	16	13	1.00			8	2	1.00		
Right	17	29	1.22	0.95	1.68	7	12	1.81	0.98	4.09

b) Glioma

Time window/ Side of use	Overall					Highest decile of cumulative call time only				
	Left sided tumours	Right sided tumours	OR[1]	95% CI		Left sided tumours	Right sided tumours	OR[1]	95% CI	
Overall										
Left	281	170	1.00			48	20	1.00		
Right	345	499	1.27	1.19	1.37	37	68	1.55	1.24	1.99
Regular users 1-4 years before reference date										
Left	125	86	1.00			8	1	1.00		
Right	167	247	1.23	1.12	1.37	4	7	2.37	0.93	8.59
Regular users 5-9 years before reference date										
Left	116	54	1.00			21	9	1.00		
Right	128	169	1.34	1.19	1.53	18	25	1.40	1.04	2.01
Regular users 10 years or more before reference date										
Left	40	30	1.00			19	10	1.00		
Right	50	83	1.24	1.05	1.50	15	36	1.57	1.13	2.30

[1] ORs adjusted for sex, age, study centre, ethnicity in Israel, and education.

Appendix Table 3 – ORs between mobile phone use and brain tumours (meningioma and glioma separately); joint analyses of effects of phone technology (analogue and digital) and phone use – excludes use with hands-free devices

Type of phone signal	Exposure category	Meningioma					Glioma				
		Cases	Controls	OR[1]	95% CI		Cases	Controls	OR[1]	95% CI	
Analogue	Never regular user or non analogue user	2182	2392	1.00			2283	2518	1.00		
	Ever regular analogue user	227	270	0.81	0.65	1.03	425	454	1.00	0.83	1.21
	Cumulative call time (hours) of exclusive analogue use										
	<5 hours	14	21	0.63	0.29	1.37	30	26	1.34	0.66	2.72
	5 h - 114.9	84	111	0.72	0.51	1.01	161	188	0.92	0.70	1.22
	115-359.9	59	55	1.13	0.71	1.80	85	103	0.93	0.65	1.33
	360-1639.9	48	49	0.84	0.51	1.39	91	108	0.86	0.60	1.24
	1640 +	22	34	0.50	0.25	0.99	58	29	1.95	1.08	3.54
Digital	Never regular user or non digital user	1266	1306	1.00			1252	1276	1.00		
	Ever regular digital user	1143	1356	0.79	0.68	0.92	1456	1696	0.76	0.66	0.88
	Cumulative call time (hours) of exclusive digital use										
	<5 hours	160	209	0.86	0.65	1.12	156	202	0.69	0.52	0.92
	5 h - 114.9	511	642	0.72	0.60	0.86	639	764	0.80	0.68	0.96
	115-359.9	194	259	0.81	0.63	1.05	266	332	0.71	0.56	0.89
	360-1639.9	182	189	0.80	0.60	1.06	267	320	0.65	0.51	0.83
	1640 +	96	57	1.84	1.17	2.88	128	78	1.46	0.98	2.17
Unknown or both	Never regular user or only analogue or only digital user	2174	2395	1.00			2292	2574	1.00		
	Ever regular user of unknown signal type or both analogue and digital phones	235	267	1.05	0.84	1.32	416	398	1.13	0.93	1.38
	Cumulative call time (hours) of exclusive unknown or both use										
	<5 hours	27	30	1.19	0.64	2.22	30	36	1.10	0.60	2.02
	5 h - 114.9	106	124	1.08	0.78	1.51	177	179	1.03	0.78	1.35
	115-359.9	40	54	0.81	0.49	1.34	88	82	1.12	0.76	1.66
	360-1639.9	44	49	0.95	0.56	1.61	81	74	1.46	0.95	2.26
	1640 +	18	10	4.43	1.42	13.9	40	27	1.37	0.69	2.70

[1] ORs adjusted for sex, age, study centre, ethnicity in Israel, and education.

Appendix Table 4 – Results of additional sensitivity analyses on ORs between mobile phone use and brain tumours (meningioma and glioma separately) for the highest decile of cumulative call time, covering method of analysis, adjustment for confounders and influence of individual study centres

	Meningioma					Glioma				
	Cases	Controls	OR[1]	95 % CI		Cases	Controls	OR[1]	95 % CI	
Main analysis (baseline for comparison)	130	107	1.15	0.81	1.62	210	154	1.40	1.03	1.89
Method of analysis										
Stratified analysis	130	107	1.10	0.82	1.48	207	154	1.39	1.08	1.77
Adjustment for confounders										
Epilepsy	130	107	1.16	0.82	1.63	210	154	1.44	1.07	1.96
Skull x-rays 5 years prior to reference date	130	107	1.17	0.83	1.66	210	154	1.49	1.09	2.03
Neck x-rays 5 years prior to reference date	na[2]					210	154	1.43	1.05	1.94
Full mouth x-rays 2 years prior to reference date	na					210	154	1.40	1.03	1.90
Regular smoking	na					210	154	1.41	1.04	1.90
Industrial work involving heating of food or other materials	na					210	154	1.42	1.04	1.92
Working with electrical motors	na					210	154	1.39	1.03	1.88
Working with ionising radiation	na					210	154	1.41	1.04	1.91
Use of portable or non-portable transmitters	130	107	1.18	0.83	1.66	210	154	1.44	1.06	1.95
Impact of individual countries										
Exclude Australia	114	95	1.16	0.80	1.69	176	132	1.39	0.99	1.95
Exclude Canada	125	101	1.15	0.81	1.64	196	147	1.41	1.03	1.93
Exclude Denmark	125	106	1.07	0.76	1.52	201	147	1.40	1.02	1.92
Exclude Finland	103	88	1.13	0.77	1.66	182	135	1.34	0.97	1.85
Exclude France	126	102	1.13	0.80	1.60	202	151	1.38	1.02	1.88
Excluding Germany	126	98	1.17	0.81	1.67	202	146	1.35	0.98	1.85
Excluding Israel	109	76	1.30	0.90	1.88	196	130	1.47	1.08	2.02
Excluding Italy	122	104	1.08	0.76	1.54	205	151	1.40	1.03	1.90
Excluding Japan	127	104	1.15	0.81	1.62	204	150	1.40	1.03	1.90
Excluding New Zealand	127	107	1.14	0.81	1.62	202	148	1.39	1.02	1.89
Excluding Norway	122	105	1.08	0.76	1.54	197	149	1.38	1.01	1.89
Excluding Sweden	124	99	1.28	0.89	1.84	198	148	1.36	0.99	1.85
Excluding UK-North	123	106	1.15	0.81	1.62	185	135	1.42	1.05	1.93
Excluding UK-South	117	100	1.12	0.78	1.62	184	133	1.46	1.04	2.03

[1] ORs adjusted for sex, age, study centre, ethnicity in Israel, and education.

[2] na: this factor was not related to mobile phone use in controls or to risk of disease in non mobile phone users and was therefore not considered as a potential confounder for meningioma

Appendix Table 5 – Results of sensitivity analyses on ORs between mobile phone use and brain tumours (meningioma and glioma separately) for regular use, covering possible indicators of sample representativeness and response quality

Factors included in sensitivity analyses	Meningioma					Glioma				
	Cases	Controls	OR[1]	95 % CI		Cases	Controls	OR[1]	95 % CI	
Main analysis (baseline for comparison)	1262	1488	0.79	0.68	0.91	1666	1894	0.81	0.70	0.94
Presentation of the study										
Explicit mention of mobile phones	634	737	0.67	0.55	0.82	827	878	0.87	0.71	1.07
Mobile phones mentioned, but not stressed	502	619	0.86	0.68	1.08	710	888	0.72	0.57	0.91
No mention of mobile phones	126	132	1.54	0.74	3.23	129	128	0.85	0.46	1.58
Participation rates										
Study centres with control participation rates < 60%	634	692	0.78	0.63	0.97	1015	1062	0.91	0.74	1.12
Study centres with control participation rates ≥ 60%	628	796	0.79	0.64	0.96	651	832	0.70	0.56	0.86
Excluding study centres with hospital based case ascertainment[2]	1175	1395	0.79	0.68	0.91	1584	1815	0.81	0.69	0.94
Quality and timing of interview										
Excluding proxy interviews	1241	1462	0.79	0.68	0.92	1480	1666	0.84	0.71	0.99
Excluding telephone interviews	1128	1351	0.77	0.65	0.89	1509	1737	0.82	0.70	0.96
With experienced interviewers only[3]	1190	1388	0.77	0.66	0.90	1551	1751	0.82	0.70	0.96
Balanced interviewer workload[4]	984	1138	0.78	0.66	0.93	1321	1490	0.79	0.66	0.93
Control interviews within 1 month of case interview	321	360	0.74	0.56	0.97	375	393	0.84	0.63	1.11
Interviewer judgement of quality of response[5]										
Excluding non-responsive study subjects or subjects with poor memory	952	1141	0.79	0.67	0.93	1117	1282	0.81	0.67	0.97
Duration of call time										
When answered by day/week/month	84	84	1.29	0.84	1.99	83	95	0.84	0.48	1.47
When answered by call	1054	1273	0.73	0.63	0.86	1304	1527	0.77	0.66	0.91
Exclusion of subjects who reported more than 5 hours per day[6]	1221	1452	0.78	0.67	0.90	1611	1844	0.80	0.69	0.93
Use of imputation and ranges										
Excluding responses with imputed items	1082	1298	0.77	0.66	0.90	1301	1555	0.73	0.63	0.86
Using minimum rather than median when range given	1260	1483	0.79	0.69	0.92	1659	1889	0.80	0.69	0.93

[1] ORs adjusted for sex, age, study centre, ethnicity in Israel, and education.
[2] Japan and France-Paris excluded
[3] Included only interviewers who conducted at least 20 interviews
[4] Included only interviewers' whose case/control interview ratio was between 1/4 and 3/4 (between 1/6 and 5/6 in Germany where 2 controls were matched to each case)
[5] Restricted to study subjects who the interviewers judged to be fairly or very cooperative and responsive and who were judged to remember fairly well, well or very well both their current and past mobile phone use history.
[6] Exclusion was based on all use of a mobile phone; that is, including use with hands-free devices

Appendix Table 6 – Distribution of Regular User OR for meningioma and glioma by ratio of case to control participation rates

	Menigioma				Glioma			
	Participation rate (%)			OR[2] for regular use 1 year or more in the past	Participation rate (%)			OR[2] for regular use 1 year or more in the past
	Cases	Controls	Ratio[1]		Cases	Controls	Ratio[1]	
Australia	62	42	1.48	0.71	56	42	1.33	1.05
Canada	70	49	1.43	2.03	62	49	1.27	0.74
Denmark	81	52	1.56	1.10	73	52	1.40	0.8
Finland	92	42	2.19	0.68	84	42	2.00	0.85
France	76	74	1.03	0.77	61	74	0.82	1.00
Germany	91	64	1.42	1.04	82	64	1.28	0.83
Israel	90	66	1.36	0.50	87	66	1.32	0.96
Italy	89	70	1.27	1.02	92	70	1.31	0.62
Japan	80	51	1.57	0.91	67	51	1.31	0.58
New Zealand	72	49	1.47	0.65	64	49	1.31	1.12
Norway	77	69	1.12	0.80	76	69	1.10	0.39
Sweden	90	66	1.36	0.48	76	66	1.15	0.74
UK North	81	45	1.80	0.67	68	45	1.51	0.66
UK South	56	48	1.17	0.71	36	48	0.75	0.80

[1] Ratio of case to control participation rates
[2] ORs adjusted for sex, age, study centre, ethnicity in Israel, and education.

Appendix 2

We observed an overall decrease in risk of glioma and of meningioma with any regular use of a mobile phone (main text Table 2). One means of correcting, at least crudely, for downward bias in the risk estimates for mobile phone use might be to undertake analyses using the lowest category of users as the reference category for risk estimates in higher categories. We present here INTERPHONE results obtained using this approach and discuss their justification and issues in their interpretation.

Material and Methods

These analyses were confined to INTERPHONE participants who were ever regular users of a mobile phone and were done using as reference categories the lowest categories of time (years) since first regular use, cumulative number of calls and cumulative duration of calls (see main text Table 2). They included only matched sets where both the case and the control(s) were regular users. As in the main analyses, we estimated odds ratios (OR) and their respective 95% confidence intervals (CI) using conditional logistic regression for matched sets.

Results

The total study base for these analyses was 1211 glioma cases (44.7% of subjects used in the main analysis), 1251 glioma controls (42.1%), 842 meningioma cases (35.0%) and 854 meningioma controls (32.1%). For meningioma, the ORs for each category of each variable remained below 1.0 except in the highest category of cumulative call time (see Table). In contrast, the ORs for glioma were, with few exceptions, all above 1.0 and the highest odds ratios were found in one of the two highest exposure categories for each variable. The greatest increase was with increasing time since start of use of a mobile phone.

Discussion

In assessing the effects of environmental exposures in epidemiological studies, the estimated risk in a given exposure category is generally evaluated relative to the risk in unexposed people. This approach is clearly appropriate when exposed and unexposed subjects are similar in all respects except the exposure of interest; bias can occur, however, when this is not the case (1). Dissimilarity between exposed and unexposed subjects can result from differences in selection factors, such as a higher refusal rate among unexposed than exposed subjects, or from the presence of an important confounder distinguishing exposed from unexposed subjects that has not been measured or not controlled. In such situations, analyses excluding unexposed subjects have been recommended (1;2).

Analyses of the INTERPHONE non-response questionnaire suggest the presence of participation bias: less participation of non-users of mobile phones than users (3). In addition, controls were less likely to participate than cases. A simulation study taking these biases into account has shown that they could lead to a J-shaped exposure-response relationship (4). Given the penetration of mobile phone technology at the time of the INTERPHONE study it is also reasonable to speculate that non-regular mobile phone users differed from regular users with respect to a number of unmeasured factors, some of which might have been confounding. If the most appropriate reference group is unclear a priori, as these considerations suggest it might reasonably have been, it has been recommended that analyses are done using both reference groups (unexposed and lowest exposed) to see if the results depend on inclusion of the

unexposed group and, if so, this fact should be reported (2). The use of the lowest exposed as a reference group was not an a priori decision in this case, however.

Restricting analyses to regular users to correct for apparent downward bias in risk estimates caused by participation bias assumes that this bias (less frequent participation by non-users) is the main reason for the bias in risk estimates. It assumes also that participation bias affects comparisons of non-users with users but not comparisons of different times since start of use or levels of cumulative use *in users*. Neither of these assumptions is necessarily correct.

If participation bias were the main reason for reduced odds ratios in recent or light users relative to non-users, the reduction would be expected to be less in study centres with higher participation rates. There is, however, no clear trend in this direction. ORs well below unity were observed in the lowest regular use category as much in centres with the highest participation rates as in centres with the lowest (Appendix Table 6); and there are centres with high and with low participation rates among the few in which ORs in this exposure category were close to or above unity.

There is also evidence in our data that participation bias may affect the distributions of time since start of use of a mobile phone. In analyses of the INTERPHONE non-responder questionnaire, not only did we observe a higher proportion of regular mobile phone users among participants but we also observed, in regular users, that participants tended to be earlier regular users than non-participants (Table 4 in (3)). If this observation reflects a general pattern, it provides evidence for greater participation bias in recent regular users than in longer-term regular users. Failure to take account of this pattern when correcting for bias could lead to overestimation of ORs in longer-term users, because their OR which is less affected by bias would be "corrected" with the same factor as the OR for the recent regular users, which was more affected by bias.

There is another observation that suggests that participation bias may not be the main reason for the observed low odds ratios. In Table 2 of the main text, the reductions in the ORs for glioma in the lowest exposure categories are much greater than those for meningioma. For example, the OR for glioma at 1-1.9 years since first use is 0.62 (95% CI 0.46-0.81) while that for meningioma is 0.90 (95% CI 0.68-1.18); each point estimate is not within the 95% confidence interval of the other. The contrast is similar but not as great for the lowest categories of cumulative call-time and number of calls.

Prodromal symptoms could, perhaps, explain this greater risk reduction in the lowest exposure categories for glioma than for meningioma by making cases less likely to take up regular mobile phone use close to the time of diagnosis of the glioma (reverse causation). While little has been published on the duration and effects of prodromal symptoms of brain tumours, there is evidence that epilepsy is strongly associated with and can precede subsequent glioma by up to 10 years (5). There is a similar but much weaker association of epilepsy with subsequent meningioma. Thus an impact of prodromal symptoms on uptake of mobile phones that is greater for glioma than for meningioma is plausible. If prodromal symptoms rather than participation bias explained the low relative risks in short-term users, then restricting analyses to regular users would introduce upward bias in odds ratios for the higher exposure categories.

Disregarding the issues raised above, the Table could be taken to suggest that mobile phones increase risk of glioma but not of meningioma; but there are some discordant patterns in these

results. First, ORs for meningioma that are well below unity persist in lower levels of cumulative use of mobile phones. It seems implausible that mobile phone use would increase the risk of glioma but decrease the risk of meningioma, particularly at low levels of exposure. Second, the OR for glioma increases more strongly with time since start of use than with cumulative use. While it could be argued that this stronger increase is due to more accurate recall of the date of first regular use than the amount of use, an OR of 1.68 (95% CI 1.16-2.41) 2-4 years after use began seems implausible, given a very high prevalence of mobile phone use in recent years and the absence of reports of increasing incidence of malignant brain tumours (mainly gliomas) in people under 65 years of age, where use is greatest (6-8). Third, in the results using never regular users as the reference category (main text Table 2) and the results presented here, there is little or no upward trend in ORs for glioma across the first eight or nine deciles of cumulative call time and cumulative number of calls; and the only materially increased OR was in the highest exposure category (the tenth decile) for cumulative call time. This exposure category includes some highly implausible reported values of mobile phone use (e.g., 12+ reported hours of use per day), which were more common in glioma cases than in controls. This possible differential recall bias is not removed by changing the reference category.

Conclusion

Analyses excluding never regular users of mobile phones may have reduced downward bias in ORs for menigioma and glioma due to selective non-participation of people who were never regular users. There is evidence, however, of persisting bias in the results of these analyses and it is possible that the exclusion of never regular users has produced upward bias in the ORs, particularly for glioma. Thus biases and error prevent a causal interpretation of these results.

Appendix 2 Table – ORs between mobile phone use and brain tumours (meningioma and glioma separately) by time since start of regular use, cumulative call time and cumulative number of calls, excluding use with hands-free devices; analyses restricted to ever regular-users

	Meningioma					Glioma				
	Cases	Controls	OR	95 % CI		Cases	Controls	OR	95 % CI	
Time since start of regular use (years)										
1-1.9 years	116	112	1.00			93	159	1.00		
2-4	362	367	0.90	0.62	1.31	460	451	1.68	1.16	2.41
5-9	288	308	0.75	0.51	1.10	468	491	1.54	1.06	2.22
10+	76	67	0.86	0.51	1.43	190	150	2.18	1.43	3.31
Cumulative call time with no hands-free devices (hours)[1]										
<5 hours	113	88	1.00			90	114	1.00		
5.0-12.9	83	88	0.79	0.48	1.29	92	124	0.88	0.56	1.39
13-30.9	95	107	0.72	0.45	1.15	127	118	1.37	0.87	2.14
31-60.9	70	87	0.59	0.35	0.99	108	126	1.13	0.72	1.77
61-114.9	74	88	0.58	0.35	0.97	121	135	1.06	0.68	1.67
115-199.9	69	95	0.64	0.39	1.06	129	119	1.13	0.71	1.78
200-359.9	74	81	0.58	0.35	0.96	116	138	1.00	0.63	1.58
360-734.9	83	80	0.85	0.51	1.41	142	139	1.17	0.74	1.84
735-1639.9	85	69	0.81	0.49	1.36	126	125	1.09	0.69	1.72
1640+	96	71	1.10	0.65	1.85	160	113	1.82	1.15	2.89
Cumulative number of calls with no hands-free devices (in hundreds)[1]										
<1.5 x 100 calls	109	81	1.00			92	102	1.00		
1.5-3.4	86	98	0.54	0.32	0.90	91	123	0.95	0.59	1.52
3.5-7.4	92	97	0.76	0.46	1.27	108	148	0.85	0.55	1.32
7.5-13.9	88	91	0.76	0.45	1.26	121	111	1.19	0.74	1.89
14-25.4	75	107	0.56	0.34	0.92	133	134	1.10	0.70	1.73
25.5-41.4	71	72	0.60	0.35	1.02	121	124	1.19	0.75	1.88
41.5-67.9	85	94	0.63	0.38	1.05	126	122	1.02	0.64	1.62
68-127.9	102	89	0.79	0.49	1.29	136	147	1.13	0.73	1.77
128-269.9	79	63	0.76	0.44	1.32	154	120	1.49	0.94	2.36
270+	55	62	0.66	0.37	1.17	129	120	1.31	0.82	2.11

[1] ORs adjusted for sex, age, study centre, ethnicity in Israel, and education.

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THEME: CANCER

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

The INTERPHONE Study Group*

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Background The rapid increase in mobile telephone use has generated concern about possible health risks related to radiofrequency electromagnetic fields from this technology.

Methods An interview-based case–control study with 2708 glioma and 2409 meningioma cases and matched controls was conducted in 13 countries using a common protocol.

Results A reduced odds ratio (OR) related to ever having been a regular mobile phone user was seen for glioma [OR 0.81; 95% confidence interval (CI) 0.70–0.94] and meningioma (OR 0.79; 95% CI 0.68–0.91), possibly reflecting participation bias or other methodological limitations. No elevated OR was observed $\geqslant$10 years after first phone use (glioma: OR 0.98; 95% CI 0.76–1.26; meningioma: OR 0.83; 95% CI 0.61–1.14). ORs were $<$1.0 for all deciles of lifetime number of phone calls and nine deciles of cumulative call time. In the 10th decile of recalled cumulative call time, $\geqslant$1640 h, the OR was 1.40 (95% CI 1.03–1.89) for glioma, and 1.15 (95% CI 0.81–1.62) for meningioma; but there are implausible values of reported use in this group. ORs for glioma tended to be greater in the temporal lobe than in other lobes of the brain, but the CIs around the lobe-specific estimates were wide. ORs for glioma tended to be greater in subjects who reported usual phone use on the same side of the head as their tumour than on the opposite side.

Conclusions Overall, no increase in risk of glioma or meningioma was observed with use of mobile phones. There were suggestions of an increased risk of glioma at the highest exposure levels, but biases and error prevent a causal interpretation. The possible effects of long-term heavy use of mobile phones require further investigation.

Keywords Brain tumours, mobile phones, radiofrequency fields

Introduction

Mobile phone use has increased dramatically in many countries since its introduction in the early-to-mid 1980s. The expanding use of this technology has been accompanied by concerns about health and safety. In the late 1990s, several expert groups critically reviewed the evidence on health effects of low-level exposure to radiofrequency (RF)

electromagnetic fields, and recommended research into the possible adverse health effects of mobile telephony.[1–4] As a result, the International Agency for Research on Cancer (IARC) coordinated a feasibility study in 1998 and 1999, which concluded that an international study of the relationship between mobile phone use and brain tumour risk would be feasible and informative.[5,6]

INTERPHONE was therefore initiated as an international set of case–control studies focussing on four types of tumours in tissues that most absorb RF energy emitted by mobile phones: tumours of the brain (glioma and meningioma), acoustic nerve (schwannoma) and parotid gland. The objective was to determine whether mobile phone use increases the risk of these tumours and, specifically, whether RF energy emitted by mobile phones is tumourigenic.

This article presents the results of analyses of brain tumour risk in relation to mobile phone use in all INTERPHONE study centres combined. Analyses of brain tumours in relation to mobile phone use have been reported from a number of cohort[7–9] and case–control studies, including several of the national components of INTERPHONE.[10–25] No studies, however, have included as many exposed cases, particularly long-term and heavy users of mobile phones, as this study.

Methods

Study design

The INTERPHONE study is an international, largely population-based case–control study. The common core study protocol is described in detail elsewhere.[5,26] Sixteen study centres from 13 countries (Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden and the UK) were included. To maximize statistical power, the INTERPHONE study focussed on tumours in younger people, 30–59 years of age, as they were expected to have had the highest prevalence of mobile phone use in the previous 5–10 years, and on regions likely to have the longest and highest use of mobile phones (mainly large urban areas).

Eligible cases were all patients with a glioma or meningioma of the brain diagnosed in the study regions during study periods of 2–4 years between 2000 and 2004. Cases were ascertained from all neurological and neurosurgical facilities in the study regions (except in Paris and Tokyo where some did not agree to participate), and in some centres also from cancer registries. All diagnoses were histologically confirmed or based on unequivocal diagnostic imaging. To facilitate interviews soon after diagnosis, cases were ascertained actively within treatment facilities wherever possible. Completeness of ascertainment was checked through secondary sources, such as population- or hospital-based cancer registries, medical archives and hospital discharge or billing files.[26]

One control was selected for each case from a locally appropriate population-based sampling frame, except in Germany where two controls were chosen. The sampling procedure involved individual matching in seven centres (Canada – Ottawa, Canada – Vancouver, France, Israel, Japan, New Zealand and UK North) and frequency matching elsewhere. The matching variables were age (within 5 years), sex and region of residence within each study centre. In Israel, the subjects were also matched on ethnic origin. Where stratified matching had been used, individual matching was conducted *post hoc*, with cases being assigned one control (two in Germany), interviewed as close as possible in time to the case, from those who fitted the matching criteria.

Detailed information on past mobile phone use was collected during face-to-face interviews with the study subject, or a proxy, if the subject had ever been a regular user of a mobile phone (had an average of at least one call per week for a period of $\geqslant$6 months).[26] A proxy was sought when the study subject had died or was too ill to be interviewed. The interviews were conducted by a trained interviewer using a computer-assisted questionnaire, except in Finland where a paper version was used. The questionnaire also included sections on socio-demographic factors, occupational exposure to electromagnetic fields and ionizing radiation, medical history (subject's and family), medical ionizing and non-ionizing radiation exposure and smoking. For cases, information was also collected on the anatomic location and histological type of the tumours. Where possible, location data were obtained from magnetic resonance imaging (MRI) reports or images; they were otherwise obtained from surgical records or clinical notes. Details of the specific source for each case were not recorded in the INTERPHONE database. Those collecting the data did not know the reported mobile phone use of individual cases.

Statistical methods

Data from countries with multiple centres were combined for the analyses, except in the UK where the UK South and UK North, each with large numbers of subjects, were kept separate. The word 'centre' in the remainder of this article is used to refer to the 14 analytic entities (12 countries, UK North and UK South). All analyses were carried out for all centres combined and for each centre separately. Formal tests for heterogeneity of risk across centres were conducted by allowing for an interaction between centre and the exposure variables.

The analyses presented here focus on past mobile phone use as reported by or for the study subjects. The main analyses were based on conditional logistic regression for matched sets.[27] The date of diagnosis of the case was used as the reference date for cases and

controls in each matched set. For the main analyses, the reference category for odds ratios (ORs) was the set of subjects who reported that they had never been regular users. Exposure variables included ever having been a regular user (as defined above), time (years) since first regular use, cumulative number of calls and cumulative duration of calls. To allow for a latency period of 1 year, the year before the reference date was included in the reference category for time since first regular use and all other exposure variables were censored at 1 year before the reference date. Cumulative number and duration of calls were analysed as categorical variables, based on deciles of the distribution of these variables among all controls who were regular users, including those matched to patients with an acoustic neuroma or a parotid gland tumour, so that the same cut-off points are used in all analyses.[26] Cumulative use excluded use of mobile phones with hands-free devices: for all time periods for which the subject reported the use of hands-free devices the amount of use was reduced by 100, 75, 50 or 25% depending on whether hands-free devices were used always or almost always, more than half, about half or less than half of the time, respectively. For ease of presentation, some results are shown for the following grouping of deciles: 1, 2–5, 6–7, 8–9 and 10, chosen *post hoc* to reflect the spread of the highly skewed distribution of these variables. For convenience, we will systematically use the term 'regular user' in text and tables to refer to ever having been a regular user.

The reference group for these analyses, never regular users, included people who had some mobile phone use but never as much as one call a week on average for $\geqslant$6 months ($\sim$32% of meningioma and 26% of glioma cases, and 30% of meningioma and 26% of glioma controls) and people who had never used a mobile phone ($\sim$11% of meningioma and 9% of glioma cases, and 8% of meningioma and 6% of glioma controls). These percentages are approximate because never use and never regular use were defined at different dates; the reference date and the date of interview, respectively. We are not able to determine whether inclusion of subjects with some occasional mobile phone use in the reference group had a material effect on our results because this difference in definition dates prevented us from distinguishing participants with only occasional use from those with no use at all at their reference dates. Moreover, because numbers of never users at the date of interview were small, particularly in certain age- and gender-specific sub-groups (such as young men), never users were not a suitable reference group for this analysis.

All analyses were adjusted for educational level; an a priori decision had been made to adjust for it as a surrogate for socio-economic status (SES). Creation of consistent educational levels across the 13 countries is described elsewhere.[26] In practice, this adjustment had little impact on OR estimates, changing their values by $\leqslant$2% in most instances and in all cases by <5%. Using a 10% change-in-estimate criterion for confounding,[28] no other covariate among those collected (see list above) was included in the main analyses. The interval between the start date of interviews in the study centre and the date of each subject's interview was modelled by fitting the interaction of this interval with study centre.

A common protocol was applied to impute missing data for cases and controls.[26] The study questionnaire allowed ranges to be given instead of exact answers to a number of questions, including number and duration of calls and dates of start and end of mobile phone use; in such instances, the main analyses in this article were based on the mid-point of the reported range.

Because absorption of RF energy from mobile phones is highly localized,[29] three different types of analyses were conducted to account for tumour location. First, analyses were conducted by the anatomical lobe of the brain in which the tumour occurred. Secondly, separate analyses were conducted for the subjects who reported using the mobile phone mainly on one or the other side of the head, and the preferred side was compared with the side on which the tumour occurred. For this, each control was assigned the location of the tumour of his or her matched case. Exposure was considered to be ipsilateral if the phone was used predominantly on the same side as the tumour or on both sides of the head, and contralateral if used mainly on the side of the head opposite to the tumour. Laterality was not assigned if the tumour was reported to be centrally located (i.e. it crossed the midline of the brain); these cases were excluded from laterality analyses. Thirdly, case–case analyses were carried out on the concordance between tumour side and laterality of phone use using the method proposed by Inskip and collaborators.[18]

Sensitivity analyses

To complement these primary analyses, we undertook sensitivity analyses to try to determine whether any of the following might have biased the results: (i) any study centre; (ii) required mention of mobile phones in the introductory letter to subjects in some centres; (iii) centres with a hospital-based design or particularly low participation rates; (iv) respondents whose interviews were considered by the interviewer to be of poor quality; (v) subjects for whom proxies provided the responses or a telephone interview was given; (vi) interviewers who had little experience or who had unbalanced case to control workloads; (vii) difference between the interview dates of cases and their matched controls (on average, each control was interviewed 3 months later than its matched case[26] and mobile phone use was increasing rapidly during the study period); (viii) subject's choice between two ways of responding to call time questions (time per

day, week or month, or time per call); (ix) subjects who reported implausibly high amounts of mobile phone use (by excluding them or by retaining them and truncating their use at a specific lower value when they reported a higher one); (x) method of calculating accumulated call time; (xi) use of matching and conditional analysis; (xii) the choice of a particular imputation algorithm; and (xiii) adjustment for possible confounders.

Results

During the study period, 3115 meningioma and 4301 glioma cases, and 14 354 potential controls were identified. Interviews were completed with 2425 meningioma cases (78%; range 56–92%), 2765 glioma cases (64% participation; range by centre 36–92%) and 7658 controls (53%; range 42–74%; Appendix 1, Table 1, Supplementary data are available at *IJE* online). The most common reasons for non-participation were subject refusal (11% of meningiomas, 11% of glioma cases and 30% of controls); illness, death or physician refusal (4% of meningiomas, 20% of gliomas and 1% of controls); and inability to contact the subject (7% of meningiomas, 5% of gliomas and 15% of controls).

The main analyses, based on matched sets only, included 2409 meningioma cases with 2662 matched controls and 2708 glioma cases with 2972 matched controls. Among meningioma cases, 24% were men and 76% women; among glioma cases, 60% were men and 40% women (Table 1). Although the median age of meningioma cases was only slightly older than that of glioma cases (51 and 49 years, respectively), 23% of glioma cases were diagnosed before the age of 40, compared with 13% of meningioma cases.

The proportion of proxy interviews was higher in glioma cases (13%) than in controls (1%) or meningioma cases (2%). Whereas 17% of glioma cases who were regular users had imputations because of missing information in at least one of their mobile phone-related variables, the corresponding fractions were 9% among regular user meningioma cases and 8% among regular user controls. The proportion of subjects who answered questions about mobile phone use by giving a range of values rather than a particular amount of use (for any of the use dimensions) was very similar (~42%) for meningioma cases, glioma cases and controls.

The prevalence of regular mobile phone use 1 year before the reference date was 52% for meningioma cases (ranging from 34 to 73% across study centres) and 56% in matched controls (35–78%). It was higher for glioma cases (62% overall, range: 42–80%) and controls (64% overall, range: 45–84%), reflecting the different sex distributions of these tumours.

The majority of subjects in the study were not heavy mobile phone users; the median lifetime cumulative call time among meningioma controls using mobile phones was ~75 h, with a median call time of ~2 h/month and a median lifetime number of calls about 1500. Corresponding values for glioma controls were ~100 h lifetime, 2.5 h/month and about 2000 calls. The distributions of time since start of mobile phone use and cumulative call time were highly skewed, with few long-term and heavy users, and varied across study centres and by age and sex (not shown).

Relation between mobile phone use and risk of brain tumours

Meningioma

A reduced OR of meningioma was found for regular mobile phone use in the past $\geqslant 1$ year, OR 0.79 [95% confidence interval (CI) 0.68–0.91; Table 2]. There was some suggestion of heterogeneity of risk across centres ($P = 0.08$) with ORs <1.0 except in Canada, Denmark, Germany and Italy (data not shown). ORs were <1.0 for regular users in all categories of time since start of use and cumulative number of calls. Analyses by cumulative call time showed ORs <1.0 in the first nine deciles and an OR of 1.15 (95% CI 0.81–1.62) in the highest decile. Analyses of cumulative call time among recent-, medium- and long-term users (Table 3) showed no indication of excess risk except in the highest call time category in those who started phone use 1–4 years before the reference date: OR 4.80 (95% CI 1.49–15.4).

There was no appreciable effect modification by age or sex on any of these results (data not shown).

In analyses by anatomical location of the meningioma, the OR for temporal lobe tumours with regular use was 0.55 (95% CI 0.36–0.82) and the ORs were <1.0 in all categories of time since start of use, cumulative call time and cumulative number of calls. ORs for other lobes were also mostly <1.0 (Table 4).

The OR for mainly ipsilateral use among regular users was 0.86 (95% CI 0.69–1.08), and that for contralateral use was 0.59 (95% CI 0.46–0.76; Table 5). The ORs by time since start of use were <1.0 in all categories of ipsilateral and contralateral use. When analysing by any of the exposure metrics in Table 5, the ratios of the ORs for ipsilateral use to contralateral use were always one or above one regardless of level of exposure and they were highest (~2 or 3) for the two highest categories of cumulative call time and the second highest category of cumulative number of calls. A case–case analysis, based on Inskip's method, showed an OR of 1.07 (95% CI 1.00–1.16; Appendix 1, Table 2, Supplementary data are available at *IJE* online) for ipsilateral use.

The OR for those who reported regular use of only an analogue phone was 0.81 (95% CI 0.65–1.03) and for only a digital phone it was 0.79 (95% CI 0.68–0.92). Focussing on the highest decile of cumulative call time, the OR among those who used only an analogue phone was 0.50 (95% CI 0.25–0.99); among

Table 1 Selected characteristics of meningioma and glioma cases included in the main analyses[a]

Characteristics of the study population	Meningioma *n* (%)	Glioma *n* (%)
All interviewed cases	2425 (100)	2765 (100)
Cases included in main analysis[b]	2409 (99)	2708 (98)
Cases with histological confirmation	2249 (93)	2659 (98)
Demographic characteristics		
Men	572 (24)	1624 (60)
Women	1837 (76)	1084 (40)
Aged 30–39 years at diagnosis	316 (13)	635 (23)
Aged 40–49 years at diagnosis	806 (33)	841 (31)
Aged 50–59 years at diagnosis	1287 (53)	1232 (45)
Distribution by country		
Australia	253 (11)	296 (11)
Canada	94 (4)	170 (6)
Denmark	124 (5)	179 (7)
Finland	231 (10)	177 (7)
France	144 (6)	94 (3)
Germany	250 (10)	256 (9)
Israel	350 (15)	180 (7)
Italy	110 (5)	118 (4)
Japan	82 (3)	60 (2)
New Zealand	52 (2)	83 (3)
Norway	143 (6)	154 (6)
Sweden	183 (8)	222 (8)
UK North	173 (7)	421 (16)
UK South	220 (9)	298 (11)

[a]The controls for each case series have the same distributions of characteristics as the cases to which they are matched.
[b]Excluded are cases for whom no controls could be found (55 for glioma and 15 for meningioma) and cases in matched sets (two for glioma and one for meningioma), where the regular use status of the case or the control was unknown.

those who used only a digital phone it was 1.84 (95% CI 1.17–2.88); and among those using both 4.43 (95% CI 1.42–13.9; Appendix 1, Table 3, Supplementary data are available at *IJE* online).

Glioma

A reduced risk of glioma was seen for regular mobile phone use in the past $\geqslant 1$ year (OR 0.81, 95% CI 0.70–0.94; Table 2) relative to never regular users. There was little evidence of heterogeneity in results across centres ($P = 0.68$). ORs were <1.0 in all study centres except Australia, France and New Zealand.

Analyses by time since start of use showed a reduced OR in all categories of use; the OR for $\geqslant 10$ years since start of use was 0.98 (95% CI 0.76–1.26; Table 2). The pattern of results by duration of mobile phone use was similar (data not shown).

Analyses by categories of cumulative call time showed decreased ORs in eight of the first nine deciles (five of which had upper confidence bounds <1.0) and an increased OR of 1.40 (95% CI 1.03–1.89) in the highest exposure category, $\geqslant 1640$ h. Analyses by cumulative number of calls showed ORs <1.0 in all categories, with the OR in the highest decile approaching unity.

Analyses of cumulative call time stratified by short-, medium- and long-term use (Table 3) showed reduced risks in the lower call time categories in all strata of time since start of use and ORs >1.0 in the highest category ($\geqslant 1640$ h cumulative call time) in each of the three strata. The highest OR was in the short-term users but its CI was very wide.

The lobe of the brain in which the tumour was located was known for 96% of cases. The OR for temporal lobe tumours with regular use was 0.86 (95% CI 0.66–1.13; Table 4). The point estimates for the highest categories of cumulative call time, cumulative number of calls and time since start of use were higher for tumours in the temporal lobe than in other locations, but their 95% CIs were wide. Only

Table 2 ORs between mobile phone use and brain tumours (meningioma and glioma separately) by regular use, time since start of use, cumulative call time and cumulative number of calls—excludes use with hands-free devices

	Meningioma			Glioma		
	Cases	Controls	OR[a] (95% CI)	Cases	Controls	OR[a] (95% CI)
Regular use in the past ⩾1 year						
No	1147	1174	1.00	1042	1078	1.00
Yes	1262	1488	0.79 (0.68–0.91)	1666	1894	0.81 (0.70–0.94)
Time since start of use (years)						
Never regular user	1147	1174	1.00	1042	1078	1.00
1–1.9	178	214	0.90 (0.68–1.18)	156	247	0.62 (0.46–0.81)
2–4	557	675	0.77 (0.65–0.92)	644	725	0.84 (0.70–1.00)
5–9	417	487	0.76 (0.63–0.93)	614	690	0.81 (0.60–0.97)
⩾10	110	112	0.83 (0.61–1.14)	252	232	0.98 (0.76–1.26)
Cumulative call time with no hands-free devices (h)[b]						
Never regular user	1147	1174	1.00	1042	1078	1.00
<5 h	160	197	0.90 (0.69–1.18)	141	197	0.70 (0.52–0.94)
5–12.9	142	159	0.82 (0.61–1.10)	145	198	0.71 (0.53–0.94)
13–30.9	144	194	0.69 (0.52–0.91)	189	179	1.05 (0.79–1.38)
31–60.9	122	145	0.69 (0.51–0.94)	144	196	0.74 (0.55–0.98)
61–114.9	129	162	0.75 (0.55–1.00)	171	193	0.81 (0.61–1.08)
115–199.9	96	155	0.69 (0.50–0.96)	160	194	0.73 (0.54–0.98)
200–359.9	108	133	0.71 (0.51–0.98)	158	194	0.76 (0.57–1.01)
360–734.9	123	133	0.90 (0.66–1.23)	189	205	0.82 (0.62–1.08)
735–1639.9	108	103	0.76 (0.54–1.08)	159	184	0.71 (0.53–0.96)
⩾1640	130	107	1.15 (0.81–1.62)	210	154	1.40 (1.03–1.89)
Cumulative number of calls with no hands-free devices (in hundreds)[b]						
Never regular user	1147	1174	1.00	1042	1078	1.00
<1.5 × 100 calls	159	180	0.95 (0.72–1.27)	147	182	0.74 (0.55–0.99)
1.5–3.4	136	182	0.62 (0.46–0.83)	141	200	0.71 (0.54–0.95)
3.5–7.4	148	176	0.90 (0.68–1.19)	161	201	0.76 (0.58–1.00)
7.5–13.9	143	173	0.80 (0.61–1.07)	174	179	0.90 (0.68–1.20)
14–25.4	122	181	0.60 (0.45–0.81)	180	206	0.78 (0.59–1.02)
25.5–41.4	111	126	0.81 (0.58–1.13)	156	190	0.83 (0.62–1.10)
41.5–67.9	129	146	0.79 (0.58–1.09)	163	194	0.71 (0.53–0.94)
68–127.9	134	126	0.92 (0.67–1.26)	186	200	0.93 (0.70–1.23)
128–269.9	100	100	0.81 (0.57–1.16)	193	180	0.96 (0.72–1.28)
⩾270	80	98	0.80 (0.55–1.17)	165	162	0.96 (0.71–1.31)

[a]ORs adjusted for sex, age, study centre, ethnicity in Israel and education.
[b]Categories are based on the deciles of the distribution among all eligible regular user controls (see text).

for the highest decile of cumulative call time was the OR for temporal lobe tumours appreciably elevated (1.87, 95% CI 1.09–3.22).

For regular use in the past ⩾1 year, the OR for ipsilateral mobile phone use was 0.84 (95% CI 0.69–1.04) and that for contralateral use was 0.67 (95% CI 0.52–0.87; Table 5). The ORs by time since start of use were <1.0 in all categories, except for ipsilateral use beginning ⩾10 in the past (OR 1.21, 95% CI 0.82–1.80). The ORs by cumulative number of calls were <1.0 irrespective of laterality and exposure level, except for ipsilateral use in the two highest categories. The results by cumulative call time showed a similar pattern, but the OR for ipsilateral use in the highest category was appreciably elevated (OR 1.96, 95% CI 1.22–3.16) and that for contralateral use was slightly elevated (OR 1.25, 95% CI 0.64–2.42). The ratios of the ipsilateral ORs to the contralateral

Table 3 ORs between mobile phone use and brain tumours (meningioma and glioma separately) by cumulative call time, stratified by recency of starting regular use—excludes use with hands-free devices

	Meningioma			Glioma		
	Cases	Controls	OR[a] (95% CI)	Cases	Controls	OR[a] (95% CI)
Cumulative Call time (h)						
	Non-regular users					
	1147	1174	1.00	1042	1078	1.00
	Short-term users: start of phone use 1–4 years before reference date					
<5 h	150	186	0.92 (0.69–1.22)	127	182	0.68 (0.50–0.93)
5–114.9	401	500	0.74 (0.61–0.90)	449	533	0.82 (0.67–0.99)
115–359.9	95	126	0.79 (0.55–1.12)	121	154	0.74 (0.52–1.03)
360–1639.9	67	72	0.77 (0.49–1.20)	80	95	0.75 (0.50–1.13)
⩾1640	22	5	4.80 (1.49–15.4)	23	8	3.77 (1.25–11.4)
	Medium-term users: start of phone use 5–9 years before reference date					
<5 h	7	9	0.67 (0.23–1.96)	10	13	0.86 (0.32–2.28)
5–114.9	122	145	0.73 (0.54–0.98)	180	208	0.86 (0.66–1.12)
115–359.9	95	140	0.67 (0.48–0.93)	156	192	0.71 (0.53–0.95)
360–1639.9	129	131	0.83 (0.60–1.14)	174	204	0.72 (0.54–0.95)
⩾1640	64	62	1.03 (0.65–1.65)	94	73	1.28 (0.84–1.95)
	Long-term users: start of phone use ⩾10 years before reference date					
<5 h	3	2	1.31 (0.21–8.07)	4	2	1.13 (0.16–7.79)
5–114.9	14	15	0.79 (0.36–1.73)	20	25	0.63 (0.32–1.25)
115–359.9	14	22	0.49 (0.24–1.01)	41	42	0.89 (0.53–1.50)
360–1639.9	35	33	1.00 (0.58–1.72)	94	90	0.91 (0.63–1.31)
⩾1640	44	40	0.95 (0.56–1.63)	93	73	1.34 (0.90–2.01)

[a]ORs adjusted for sex, age, study centre, ethnicity in Israel and education.

ORs were all above one with one exception (0.99 for 2–4 years since start of use) and the highest (~2) were in 1–1.9 and ⩾10 years since start of use, the lowest category of cumulative call time, and the highest category of cumulative number of calls. For cumulative number of calls, there was a consistent trend towards increasing ratios with increasing exposure.

Case–case analyses of the concordance between tumour side and preferred side of phone use using the Inskip method showed an elevated risk for ipsilateral use among regular users (OR 1.27, 95% CI 1.19–1.37) and among those in the highest decile of cumulative call time (OR 1.55, 95% CI 1.24–1.99; Appendix 1, Table 2, Supplementary data are available at *IJE* online). When stratified on time since first use, the point estimate of the OR using Inskip's method in the highest decile was higher among short-term heavy users (OR 2.37, 95% CI 0.93–8.59) than among medium (OR 1.40, 95% CI 1.04–2.01) and long-term (OR 1.57, 95% CI 1.13–2.30) heavy users, resembling an analogous pattern in Table 3.

The OR for ever use of an analogue phone was 1.00 (95% CI 0.83–1.21) and for ever use of a digital phone 0.76 (95% CI 0.66–0.88). Increased ORs were seen in the highest decile of cumulative call time with analogue phones (OR 1.95, 95% CI 1.08–3.54) and with digital phones (OR 1.46, 95% CI 0.98–2.17; Appendix 1, Table 3, Supplementary data are available at *IJE* online).

There was no evidence of heterogeneity of effects across centres for cumulative call time, cumulative number of calls, time since start of use or ipsilateral or contralateral use. Nor was there any appreciable effect modification by age or sex in any of the results mentioned above (data not shown).

Sensitivity analyses

Selected findings of sensitivity analyses are shown in Table 6 and Appendix 1, Table 4 (Supplementary data are available at *IJE* online). Because of a hint of a possible excess risk in subjects in the highest decile of mobile phone cumulative call time, for glioma (OR 1.40) and to a lesser extent for meningioma (OR 1.15), we focus presentation of sensitivity analyses on the findings in this highest decile, corresponding to 1640 or more cumulative hours of use.

For meningioma, some point estimates differed from the OR of 1.15 from the main analysis, but the estimates were imprecise and, with one exception based

Table 4 ORs between mobile phone use and brain tumours (meningioma and glioma separately) by anatomical location of tumour[a] and by regular use, time since start of use, cumulative call time and cumulative number of calls – excludes use with hands-free devices

	Meningioma									Glioma								
	Tumour in temporal lobe			Tumour in parietal or frontal lobes			Tumour in other locations			Tumour in temporal lobe			Tumour in parietal or frontal lobes			Tumour in other locations		
	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)
Regular use in the past ⩾1 year																		
No	207	218	1.00	520	513	1.00	282	297	1.00	311	339	1.00	551	551	1.00	141	155	1.00
Yes	190	262	0.55 (0.36–0.82)	590	701	0.79 (0.63–0.99)	300	348	0.76 (0.56–1.04)	509	568	0.86 (0.66–1.13)	871	998	0.77 (0.62–0.95)	212	248	0.79 (0.51–1.23)
Time since start of use (years)																		
Never regular user	207	218	1.00	520	513	1.00	282	297	1.00	311	339	1.00	551	551	1.00	141	155	1.00
1–1.9	27	40	0.60 (0.29–1.27)	82	103	0.70 (0.46–1.06)	44	50	1.12 (0.63–1.99)	51	69	0.87 (0.54–1.41)	74	138	0.45 (0.30–0.70)	23	32	0.67 (0.30–1.47)
2–4	95	145	0.55 (0.34–0.89)	256	283	0.85 (0.65–1.12)	137	163	0.72 (0.50–1.06)	175	211	0.77 (0.55–1.08)	347	386	0.83 (0.64–1.08)	95	95	0.94 (0.57–1.52)
5–9	56	65	0.49 (0.27–0.88)	199	252	0.74 (0.56–1.00)	94	116	0.62 (0.40–0.94)	189	219	0.80 (0.56–1.13)	321	358	0.78 (0.60–1.02)	74	89	0.70 (0.40–1.22)
⩾10	12	12	0.60 (0.22–1.62)	53	63	0.76 (0.48–1.20)	25	19	1.02 (0.48–2.16)	94	69	1.36 (0.88–2.11)	129	116	0.92 (0.65–1.30)	20	32	0.41 (0.16–1.08)
Cumulative call time (h)[c]																		
Never regular user	207	218	1.00	520	513	1.00	282	297	1.00	311	339	1.00	551	551	1.00	141	155	1.00
<5 h	23	41	0.49 (0.24–1.01)	72	87	0.88 (0.58–1.33)	43	45	1.13 (0.64–1.99)	45	59	0.67 (0.40–1.13)	70	105	0.65 (0.42–1.01)	20	25	0.87 (0.37–2.04)
5–114.9	89	123	0.59 (0.36–0.97)	260	297	0.76 (0.58–0.98)	120	158	0.64 (0.44–0.93)	191	234	0.88 (0.63–1.21)	326	406	0.72 (0.56–0.93)	99	96	0.85 (0.52–1.38)
115–359.9	24	52	0.28 (0.13–0.59)	90	140	0.71 (0.49–1.03)	48	60	0.75 (0.43–1.31)	95	104	0.84 (0.55–1.28)	178	213	0.70 (0.51–0.96)	34	51	0.70 (0.35–1.40)
360–1639.9	33	32	0.75 (0.36–1.56)	111	118	0.82 (0.57–1.18)	56	59	0.71 (0.42–1.21)	100	124	0.71 (0.47–1.07)	192	189	0.87 (0.64–1.19)	41	58	0.63 (0.30–1.30)
⩾1640	21	14	0.94 (0.31–2.86)	57	59	1.08 (0.65–1.80)	33	26	1.05 (0.52–2.14)	78	47	1.87 (1.09–3.22)	105	85	1.25 (0.81–1.91)	18	18	0.91 (0.33–2.51)
Cumulative number of calls (in hundreds)[c]																		
Never regular user	207	218	1.00	520	513	1.00	282	297	1.00	311	339	1.00	551	551	1.00	141	155	1.00
<1.5 × 100 calls	26	35	0.66 (0.32–1.37)	73	87	0.83 (0.54–1.26)	41	39	1.30 (0.72–2.34)	44	54	0.72 (0.42–1.23)	74	95	0.65 (0.42–1.02)	19	25	0.82 (0.34–1.95)
1.5–25.4	85	128	0.57 (0.35–0.94)	262	311	0.77 (0.59–0.99)	127	175	0.64 (0.44–0.92)	191	235	0.83 (0.60–1.15)	334	423	0.69 (0.54–0.89)	106	98	0.91 (0.57–1.47)
25.5–67.9	24	58	0.28 (0.13–0.58)	114	121	0.94 (0.65–1.35)	57	57	0.73 (0.44–1.23)	96	113	0.81 (0.55–1.21)	176	207	0.76 (0.55–1.03)	34	44	0.63 (0.31–1.26)
68–269.9	43	25	0.88 (0.42–1.85)	106	129	0.71 (0.49–1.03)	56	55	0.80 (0.47–1.37)	117	110	1.04 (0.69–1.55)	201	191	0.95 (0.70–1.30)	41	62	0.63 (0.30–1.32)
⩾270	12	16	0.51 (0.19–1.38)	35	53	0.74 (0.42–1.31)	19	22	0.87 (0.37–2.04)	61	56	1.10 (0.65–1.85)	86	82	1.02 (0.67–1.57)	12	19	0.42 (0.13–1.33)

[a]A total of 115 gliomas and 357 meningiomas with unknown anatomical location are not included.
[b]ORs adjusted for sex, age, study centre, ethnicity in Israel and education.
[c]Deciles of exposure used in Table 2 have been collapsed into six categories for these analyses: deciles 1, 2–5, 6–7, 8–9 and 10.

Table 5 ORs between mobile phone use and brain tumours (meningioma and glioma separately) by side of use of mobile phones and by regular use, time since start of use, cumulative call time and cumulative number of calls[a]

	Meningioma							Glioma						
	Ipsilateral phone use			Contralateral phone use			Ratio[c] ipsi/contra	Ipsilateral phone use			Contralateral phone use			Ratio[c] ipsi/contra
	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)		Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)	
Regular use in the past ⩾1 year														
No	821	898	1.00	832	841	1.00		773	838	1.00	721	718	1.00	
Yes	424	479	0.86 (0.69–1.08)	281	406	0.59 (0.46–0.76)	1.46	677	753	0.84 (0.69–1.04)	328	437	0.67 (0.52–0.87)	1.25
Time since start of use (years)														
Not regular user	821	898	1.00	832	841	1.00		773	838	1.00	721	718	1.00	
1–1.9	54	79	0.71 (0.44–1.15)	41	59	0.67 (0.38–1.20)	1.06	69	91	0.77 (0.49–1.20)	24	58	0.38 (0.20–0.71)	2.03
2–4	198	203	0.89 (0.67–1.19)	118	196	0.54 (0.39–0.76)	1.65	261	300	0.80 (0.62–1.04)	145	178	0.81 (0.57–1.14)	0.99
5–9	132	155	0.87 (0.63–1.21)	100	126	0.64 (0.44–0.94)	1.36	239	280	0.81 (0.62–1.05)	110	145	0.65 (0.44–0.95)	1.25
⩾10	40	42	0.88 (0.52–1.47)	20	25	0.58 (0.29–1.16)	1.52	108	82	1.21 (0.82–1.80)	49	56	0.70 (0.42–1.15)	1.73
Cumulative call time with no hands-free devices (h)[d]														
Not regular user	821	898	1.00	832	841	1.00		773	838	1.00	721	718	1.00	
<5 h	48	71	0.76 (0.48–1.210	36	54	0.75 (0.42–1.31)	1.01	64	76	0.83 (0.53–1.31)	23	50	0.43 (0.22–0.84)	1.93
5–114.9	185	209	0.86 (0.65–1.15)	125	190	0.55 (0.40–0.75)	1.56	253	321	0.75 (0.58–0.97)	135	170	0.74 (0.53–1.03)	1.01
115–359.9	65	96	0.64 (0.42–0.97)	42	69	0.64 (0.39–1.06)	1.00	121	147	0.75 (0.53–1.07)	67	93	0.62 (0.39–0.97)	1.21
360–1639.9	80	68	1.09 (0.72–1.64)	50	65	0.55 (0.32–0.94)	1.98	139	147	0.88 (0.62–1.24)	64	93	0.60 (0.38–0.94)	1.47
⩾1640	46	35	1.45 (0.80–2.61)	28	28	0.62 (0.31–1.25)	2.34	100	62	1.96 (1.22–3.16)	39	31	1.25 (0.64–2.42)	1.57
Cumulative number of calls with no hands-free devices (in hundreds)[d]														
Not regular user	821	898	1.00	832	841	1.00		773	838	1.00	721	718	1.00	
<1.5 × 100 calls	51	72	0.77 (0.49–1.22)	32	49	0.76 (0.41–1.40)	1.01	61	71	0.66 (0.41–1.07)	26	44	0.61 (0.32–1.17)	1.08
1.5–25.4	187	229	0.80 (0.60–1.05)	131	191	0.59 (0.44–0.81)	1.36	263	318	0.80 (0.62–1.04)	138	179	0.69 (0.49–0.96)	1.16
25.5–67.9	80	81	0.89 (0.59–1.35)	51	77	0.61 (0.37–1.00)	1.46	115	159	0.69 (0.49–0.97)	64	91	0.59 (0.38–0.92)	1.17
68–269.9	76	61	1.22 (0.77–1.95)	49	66	0.39 (0.23–0.68)	3.13	164	145	1.09 (0.78–1.52)	72	86	0.81 (0.51–1.28)	1.35
⩾270	30	36	1.01 (0.56–1.82)	18	23	0.66 (0.30–1.46)	1.53	74	60	1.51 (0.91–2.51)	28	37	0.61 (0.32–1.18)	2.48

[a]Seventy-two glioma-matched sets and 43 meningioma-matched sets including subjects with unknown laterality of use or with cases with unknown side of tumour are excluded from these analyses. The reference category consists of subjects who were not regular users 1 year before the reference date. Because the main analyses in this article use matched conditional logistic regression, all matched sets in which the case and/or the control was a regular contralateral user are excluded from the ipsilateral analyses; similarly, sets in which the case and/or the control was a regular ipsilateral user are excluded from the contralateral analyses. This explains the differences in the numbers of cases and controls in the reference category and the fact that the number of ipsilateral and contralateral regular user cases (and controls) does not add up to the total number of regular users in the previous table.
[b]ORs adjusted for sex, age, study centre, ethnicity in Israel and education.
[c]Ratio of OR for ipsilateral tumours to OR for contralateral tumours.
[d]Deciles of exposure used in Table 2 have been collapsed into six categories for these analyses: deciles 1, 2-5, 6-7, 8-9 and 10.

Table 6 Results of sensitivity analyses on ORs between mobile phone use and brain tumours (meningioma and glioma separately) for the highest decile of cumulative call time, covering possible indicators of sample representativeness and response quality

Factors included in sensitivity analyses	Meningioma			Glioma		
	Cases	Controls	OR[a] (95% CI)	Cases	Controls	OR[a] (95% CI)
Main analysis (baseline for comparison)	130	107	1.15 (0.81–1.62)	210	154	1.40 (1.03–1.89)
Presentation of the study						
Explicit mention of mobile phones	62	61	0.91 (0.56–1.47)	101	81	1.30 (0.87–1.93)
Mobile phones mentioned, but not stressed	58	35	1.50 (0.86–2.59)	90	63	1.47 (0.89–2.44)
No mention of mobile phones	10	11	1.07 (0.17–6.83)	19	10	1.72 (0.38–7.85)
Participation rates						
Study centres with control participation rates <60%	75	45	1.44 (0.89–2.34)	142	99	1.39 (0.94–2.04)
Study centres with control participation rates ⩾60%	55	62	0.93 (0.56–1.55)	68	55	1.46 (0.89–2.39)
Excluding study centres with hospital based case ascertainment[b]	123	100	1.13 (0.80–1.60)	200	149	1.39 (1.02–1.88)
Quality and timing of interview						
Excluding proxy interviews	127	107	1.13 (0.80–1.59)	188	138	1.46 (1.05–2.04)
Excluding telephone interviews	120	103	1.04 (0.72–1.49)	194	150	1.30 (0.95–1.78)
With experienced interviewers only[c]	116	97	1.09 (0.76–1.56)	201	139	1.50 (1.10–2.06)
Balanced interviewer workload[d]	95	73	1.13 (0.75–1.69)	164	119	1.38 (0.97–1.96)
Control interviews within 1 month of case interview	35	21	1.32 (0.70–2.48)	46	30	1.43 (0.79–2.57)
Interviewer judgement of quality of response[e]						
Excluding non-responsive study subjects or subjects with poor memory	91	75	1.28 (0.85–1.93)	130	92	1.38 (0.94–2.03)
Duration of call time						
When answered by day/week/month	9	4	5.78 (0.81–41.06)	9	3	6.08 (0.72–51.65)
When answered by call	112	94	1.00 (0.69–1.45)	177	136	1.23 (0.89–1.70)
Truncation of phone use to 5 h/day[f]	130	107	1.15 (0.81–1.62)	208	153	1.38 (1.02–1.87)
Truncation of phone use to 1 h/day[f]	80	75	1.06 (0.70–1.60)	144	104	1.41 (0.99–1.99)
Assuming call time per day only concerns work days[g]	136	117	1.08 (0.78–1.51)	225	167	1.31 (0.98–1.75)
Exclusion of subjects who reported >5 h/per day[f]	106	94	1.02 (0.70–1.48)	169	134	1.27 (0.92–1.75)
Use of imputation and ranges						
Excluding responses with imputed items	104	81	1.21 (0.82–1.78)	157	115	1.34 (0.96–1.88)
Using minimum rather than median when range given	97	88	1.08 (0.74–1.58)	140	105	1.35 (0.94–1.93)

[a]ORs adjusted for sex, age, study centre, ethnicity in Israel and education.
[b]Japan and France–Paris excluded.
[c]Included only interviewers who conducted at least 20 interviews.
[d]Included only interviewers whose case/control interview ratio was between 1/4 and 3/4 (between 1/6 and 5/6 in Germany where two controls were matched to each case).
[e]Restricted to study subjects who the interviewers judged to be fairly or very cooperative and responsive and who were judged to remember fairly well, well or very well both their current and past mobile phone use history.
[f]Truncation and exclusion were based on all use of a mobile phone; that is, including when using hands-free devices.
[g]Working days were assumed to be 5.5 days/week for 50 weeks of the year and new deciles were created to reflect the changed total hours.

on nine cases and four controls, fell well within the CI of this 'benchmark' value.

For glioma, results from the various sensitivity analyses were generally similar to those from the primary analysis. All the OR estimates, except one based on nine cases and three controls, are well within the 95% CI of the OR from the main analysis. When subjects with high reported use were included, but with use truncated at 5 h/day, the OR was hardly affected. When subjects who reported >5 h call time/day (38 cases and 22 controls) were excluded altogether, on the premise that such responses were unreliable, the OR decreased to 1.27 (95% CI 0.92–1.75).

Results of sensitivity analyses focusing on the OR for regular use in the past $\geqslant 1$ year are shown in Appendix 1, Table 5 (Supplementary data are available at *IJE* online). All the OR estimates, except two ORs for meningioma relating to the presentation of the study, are well within the 95% CI of the OR from the main analysis.

Discussion

The INTERPHONE study is the largest case–control study of mobile phones and brain tumours conducted to date, including the largest numbers of users with at least 10 years of exposure and the greatest cumulative hours of use of any study. An exhaustive analysis of this large data set involved estimation of hundreds of ORs; rather than focus on the most extreme values, the interpretation should rest on the overall balance of evidence. The null hypothesis of no association would be expected to produce an approximately symmetric pattern of negative and positive log ORs. A skewed distribution could be due to a bias or to a true effect. Our results include not only a disproportionately high number of ORs <1, but also a small number of elevated ORs. This could be taken to indicate an underlying lack of association with mobile phone use, systematic bias from one or more sources, a few random but essentially meaningless increased ORs, or a small effect detectable only in a subset of the data.

For meningioma, there is little evidence to counter a global null hypothesis, and we conclude that INTERPHONE finds no signs of an increased risk of meningioma among users of mobile telephones.

For glioma, an increased OR was seen in analyses in the highest decile of cumulative call time, including tumours in the temporal lobe and subjects who reported having used the mobile phone mainly on the same side as where the tumour occurred. Still, the evidence for an increased risk of glioma among the highest users was inconclusive, as the increase could be due to one or more of the possible sources of error discussed below.

In the following sections, we explore possible explanations for the apparently decreased risk of meningioma and glioma for regular users compared with never regular users, and the apparently increased risk of glioma in a subset of users.

Decreased risk with ever regular use of a mobile phone

An apparently decreased risk of brain tumours with ever regular use of a mobile phone (relative to never regular use) has been seen in other studies.[18,23] Putting aside a genuine protective effect as implausible, we have considered other reasons for these observations.

Sampling bias

In all but two centres, a population-based design was used. This requires that the cases in the study were representative of all cases in the respective population and that the controls represented all non-cases, within matching strata. In practice, it is difficult to demonstrate that these conditions have been fulfilled in any case–control study. Cases may be missed due to lack of detection, misdiagnosis or incomplete registration (such problems may be more likely for meningioma than for glioma). It is uncertain whether the sampling frames used to select controls represented the study base in some countries. To the extent possible, we conducted sensitivity analyses that examined the effects of different recruitment strategies between centres; they did not show substantial changes in the results (Table 6).

Levels of participation

Constrained by the requirements of ethical review committees and facing the population's increasing reluctance to participate in interview studies, we attained participation rates of 78% among meningioma cases, 64% among glioma cases and 53% among controls.[26] Although such proportions are not unusually low, they raise the possibility of selection bias with respect to mobile phone use.

Controls in 11 centres and cases in 9 centres who refused the full interview were asked to respond to a brief non-respondent questionnaire on mobile phone use. The cases and controls who complied with this short inquiry reported a lower lifetime prevalence of ever regular use of a mobile phone than did respondents to the full interview, implying that information from those who participated in the full interview may overestimate prevalence among all eligible subjects. Because participation and refusal differed between cases and controls, such non-representativeness may have distorted the OR estimates.[30] Although caution is required in extrapolating from the findings of the sub-study, we estimated, in the more plausible scenarios, that non-participation bias may have led to a reduction in the ORs for regular use of 5–15%,[30] which is less than the observed reductions below the null in the ORs in ever regular mobile phone users for meningioma (21%, 95% CI 32–9) and glioma (19%, 95% CI 30–6; Table 2).

Prodromal symptoms

Prodromal symptoms of a brain tumour could dissuade subjects from becoming phone users or reduce their use before diagnosis (reverse causation). Glioma is typically diagnosed quite soon after first symptoms. Although prodromal symptoms might result in lowered ORs among very recent users (e.g. <2 years since starting use), these are unlikely to explain the reduction in ORs observed among the vast majority of the users in our study population who started using mobile phones 2–10 years before disease onset.

Timing of interviews

As the use of mobile phones has become more common over time, the later interview dates of controls could have spuriously increased the prevalence of exposure in the control group. However, restricting analyses to matched sets in which the cases and controls were interviewed within 1 month of each other resulted in very little change in the OR for regular use $\geqslant$1 year in the past (Table 6) and hence seems unlikely to explain the low ORs overall. Further, the use of a common reference date for each case and its matched control should have minimized any bias induced by differential timing of interviews.

Confounding

Higher socio-economic status has been associated with a higher risk of brain cancer in some but not all relevant studies,[31,32] and with mobile phone use, particularly when the technology was new.[9] We adjusted for education level in all analyses, but acknowledge this is an imperfect indicator of SES. Otherwise, there are few well-established risk factors for brain tumours; analyses adjusting for measured potential confounders had little impact on the ORs (Appendix 1, Table 4, Supplementary data are available at *IJE* online).

Low overall risks among mobile phone users

The reduced OR for regular users compared with never regular users seems unlikely to reflect a genuine protective effect and makes our results difficult to interpret.[33] It could result from the sources of error discussed above, although based on the evidence we have regarding their magnitude and effects[30,34] they may not account fully for the observed reduction in risk.

It might be possible to correct, at least crudely, for assumed downwards bias in the ORs for mobile phone use by undertaking a series of analyses using the lowest category of users as the reference category for OR estimates in higher categories. Results of such an analysis of the mobile phone use variables in Table 2 are shown in the Table of Appendix 2 (see Supplementary data available at *IJE* online), accompanied by a discussion of the strengths and weaknesses of this approach. We have also done some work to characterize possible sources of bias[30,34] and are currently exploring the possibility of correcting the OR estimates mathematically for their effects.

Elevated risks of glioma among heavy users

There was some evidence of an elevated risk of glioma in the highest decile of cumulative call time, with the highest point estimates seen for tumours in the temporal lobe and for subjects who reported having used their mobile phone mainly on the same side as that on which the tumour occurred. We explore here possible interpretations of these findings.

Biases related to possible differential quality of exposure data

When compared with controls, glioma cases had a higher proportion of proxy respondents, a higher number of imputations for missing values, and a higher proportion of subjects judged by their interviewer to be non-responsive or having poor memory (data not shown). However, sensitivity analyses showed that these differences, on their own, did not explain the results seen in the highest decile of cumulative call time (Table 6).

Differential error between cases and controls in reporting of mobile phone use could substantially affect our results; such information bias could arise from several sources. First, a brain tumour, particularly in the frontal or temporal lobes, may adversely affect cognition and memory.[35] Secondly, cases may be more motivated to recall and report a publicized potential risk factor for their disease.

To investigate the accuracy of self-reported phone use, two validation sub-studies were conducted in some of the INTERPHONE centres. Amongst healthy volunteers using software-modified phones (recording number and times of calls), phone use in the past year was reported with substantial random error; with over- and under-estimation both frequent.[36] Errors were larger for duration of calls than for number of calls, and phone use was under-estimated by light users and over-estimated by heavy users. In another sub-study, records of mobile phone use up to 6 years previously were obtained for some participants in three INTERPHONE centres, allowing us to compare the interview responses with the records.[37] Overall, there was little evidence that recall quality differed between cases and controls, but there was some indication of greater over-reporting by cases than by controls for the period 3–5 years before interview. These sub-studies provide no information regarding differential reporting error for periods more distant than 5 years before interview.

Some subjects reported very high daily average call times and this was more common among cases than controls. Thirty-eight cases and 22 controls reported >5 h use/day and 10 cases and no controls reported $\geqslant$12 h/day. There is reasonable doubt about the credibility of such reports. Excluding all subjects who reported >5 h use/day reduced the ORs in the highest

decile of cumulative time from 1.40 to 1.27 (95% CI 0.92–1.74). In contrast, truncating the average call time to 5 h/day had little effect on the OR. It is not clear which of these two approaches (if either) is more appropriate. However, the key question is whether these cases with unreasonably high values reflect a general tendency for cases to overestimate more than controls, which could contribute to the apparent excess risk in the highest decile. As noted earlier, there is evidence that cases tended to overestimate their past exposure more than controls did.[37]

Non-differential error (random variability or uncertainty in the exposure estimates) may also affect the findings. With dichotomous exposure indicators such bias is towards the null, but for polytomous variables the effect is difficult to predict.[38–40]

Location of tumours and laterality of use of phones

Absorption of RF energy from mobile phones is highly localized.[29] Thus, an association of phone use with tumours occurring near the location of the phone would constitute stronger evidence for aetiology than an association with more distant tumours.

Ipsilateral ORs were almost always greater than contralateral ORs. There was no consistent pattern with regard to level of exposure, although a trend towards a stronger effect of ipsilateral use relative to contralateral use with increasing exposure was observed for cumulative number of calls. Results of case–case analyses (using Inskip's method[18]) also suggested higher risks of gliomas with ipsilateral phone use, but again no consistent trend with increasing exposure. The observation of an unlikely ipsilateral effect in low exposure categories suggests that cases might have over-reported use on the side of the tumour.

There is, though, evidence of lack of such reporting bias from a sub-study. In three centres (Australia, Canada and Japan), participants (172 glioma and 160 meningioma cases and 340 controls who were regular users) were asked at the end of their interview to put a mobile phone to their ear as if answering a call. The concordance between the reported side of use of the phone and the side where it was held was lower for cases (72% glioma cases, 66% meningioma) than controls (95%). The greater degree of concordance among controls suggests differential reporting quality. Among cases, however, there was as much discrepancy in the contralateral direction (52 instances) as in the ipsilateral direction (48 instances). Thus, it is possible that the ipsilateral effect is a true effect, is due to reporting bias or is a mixture of both.

Few studies have related field strength to anatomic structures, but a recent investigation of 110 phone models found that exposure is generally highest in the temporal lobe.[29] While laterality analyses may be biased by the respondent's knowledge of the side of the tumour, results for tumours in different lobes are probably less susceptible to reporting bias. ORs for glioma in the highest exposure categories were higher for tumours in the temporal lobe than in other lobes, but the CIs around the lobe-specific estimates for each measure were wide.

Coherence and consistency

The strongest evidence of an increased risk of glioma was found for cumulative call time, which is a function of the number and duration of calls. Conceptually, cumulative call time might be the most relevant measure of exposure. However, in validation studies, the number of calls was recalled more accurately than the duration of calls.[36,37] For the cumulative number of calls, the ORs, while highest in the highest deciles, were consistently below one. In the absence of a known biological mechanism, it is hard to know whether more weight should be put on results from the more accurate or the conceptually preferred exposure measure.

The apparently increased risk of glioma for cumulative call time was restricted to the top decile, $\geqslant$1640 h. There was no upward trend across the first nine deciles of cumulative call time. In contrast with the excess risk seen on the scale of cumulative call time, risk did not appear to be increased by length of time since first exposure or by duration of exposure. The pattern of point estimates of ORs in the high call time categories in three strata of time since exposure started—3.8 in the most recent and 1.3 in the more distant ones (Table 3)—is not what one would expect if there were a causal association; although the CI in the newest users was wide and encompassed the point estimates for heavy use in the two longer use groups. By analogy with known carcinogens, the lack of a consistently increasing risk with dose, duration of exposure and time since first exposure weigh against cause and effect. Nevertheless, given the uncertainty surrounding possible effects of RF on the brain, no strong case can be made for the plausibility or implausibility of any observed exposure response pattern.

Comparison of meningioma and glioma results

While the ORs for meningioma were lower than that for glioma in high exposure subgroups, there were some similar patterns. First, the OR for all regular users compared with never regular users was very similar. Secondly, there was no trend in relation to cumulative call time except for an elevated OR in the highest decile. Thirdly, the increase in the last decile was more pronounced for cumulative call time than number of calls. Fourthly, the highest OR for cumulative call time was seen among subjects who had recently started regular use. Fifthly, the ORs were greater for ipsilateral than contralateral use and the ratios of ipsilateral ORs divided by their corresponding contralateral ORs were of a similar

magnitude. However, while there was evidence of a higher risk of gliomas in the temporal lobe than elsewhere with several different exposure metrics, there was no such evidence for meningioma. Although ORs for meningioma were generally lower than that for glioma, the otherwise similar patterns of associations of mobile phone use with meningioma and glioma could indicate shared aetiology or shared bias.

Interpretation of these findings

We have no certain explanation for the overall reduced risk of brain cancer among mobile phone users in this study, although selection bias is almost certainly a contributor. There is some evidence that very high users experienced excess risk of glioma, but that evidence is inconclusive because of possible bias. Further light may be shed on dose–response relations by work now being undertaken with the INTERPHONE data using precise coordinate localization of tumours within the brain in relation to estimates of absorbed RF energy.

The possibility of raised risk in heavy users of mobile phones is an important issue because of their ever-increasing use. Moreover, few subjects in our study had used mobile phones for >12 years; therefore, our results are uninformative with respect to lag periods longer than this.

Consistency with previous research

Our results are consistent with most of the research published to date. A large Danish cohort study of mobile telephone subscribers,[8,9] with an average follow-up time of 8.5 years, found no increased risk of brain tumours in subscribers of $\geqslant$10 years. The first case–control studies conducted included cases diagnosed in the mid-to-late 1990s and therefore could only address possible risks among short-term mobile phone users.[10,12,18,23] In addition, the highest cumulative call times in these studies were much less than in ours. Generally, these studies reported 'negative' results. In contrast, increased risks of malignant brain tumours at higher levels of accumulated use of analogue and digital mobile phones and cordless desktop phones were reported from a sequence of three case–control studies from the same authors with cases in the last diagnosed as late as 2003.[13–15] However, the methods of these studies have been questioned.[41]

Some of the INTERPHONE centres have published their results for brain tumours[11,16,17,19,22,24,25] and two pooled analyses from Northern European centres have also been published.[20,21] Most cases in these reports are included in the present analyses and constitute 69% of gliomas and 57% of meningiomas. The centre-specific analyses are consistent with our all-centre results.

Much biological research has been done in recent years on possible biological effects of RF fields. This work covers *in vitro* and *in vivo* exposure, alone and in combination with other physical or chemical agents, and has found no evidence that RF fields are carcinogenic in laboratory rodents or cause DNA damage in cells in culture.[42] Possible effects of RF fields on other biological endpoints are still being explored.

The possible effects of long-term heavy use of mobile phones on risk of brain tumours require further investigation, given increasing mobile phone use, its extension to children and its penetration worldwide. The problems presented by selection and information bias in this and probably other studies suggest that new studies should, in general, only be done if they can substantially reduce or eliminate selection bias, obtain detailed and high-quality exposure information over the full period of use and offer sufficient statistical power to detect comparatively small effects in people with heavy or long continued exposure. Monitoring of age- and gender-specific incidence rates may also be valuable, particularly if informed by good longitudinal data on mobile phone use by age and sex, and having regard to features such as brain tumour location that may allow more specific inferences about possible mobile phone use effects.

Conclusion

This is the largest study of the risk of brain tumours in relation to mobile phone use conducted to date and it included substantial numbers of subjects who had used mobile phones for $\geqslant$10 years. Overall, no increase in risk of either glioma or meningioma was observed in association with use of mobile phones. There were suggestions of an increased risk of glioma, and much less so meningioma, at the highest exposure levels, for ipsilateral exposures and, for glioma, for tumours in the temporal lobe. However, biases and errors limit the strength of the conclusions we can draw from these analyses and prevent a causal interpretation.

Supplementary data

Supplementary data are available at *IJE* online.

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KEY MESSAGE

- INTERPHONE is the largest case–control study of mobile phone use and brain tumours yet and includes the largest numbers of users with at least 10 years of exposure. A reduced OR for glioma and meningioma related to ever having been a regular mobile phone user possibly reflects participation bias or other methodological limitations. No elevated OR for glioma or meningioma was observed $\geqslant$10 years after first phone use. There were suggestions of an increased risk of glioma, and much less so meningioma, in the highest decile of cumulative call time, in subjects who reported usual phone use on the same side of the head as their tumour and, for glioma, for tumours in the temporal lobe. Biases and errors limit the strength of the conclusions that can be drawn from these analyses and prevent a causal interpretation.

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Appendix

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Acoustic neuroma risk in relation to mobile telephone use: Results of the INTERPHONE international case–control study

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ABSTRACT

Background: The rapid increase in mobile telephone use has generated concern about possible health risks of radiofrequency electromagnetic fields from these devices. *Methods:* A case–control study of 1105 patients with newly diagnosed acoustic neuroma (vestibular schwannoma) and 2145 controls was conducted in 13 countries using a common protocol. Past mobile phone use was assessed by personal interview. In the primary analysis, exposure time was censored at one year before the reference date (date of diagnosis for cases and date of diagnosis of the matched case for controls); analyses censoring exposure at five years before the reference date were also done to allow for a possible longer latent period. *Results:* The odds ratio (OR) of acoustic neuroma with ever having been a regular mobile phone user was 0.85 (95% confidence interval 0.69–1.04). The OR for ≥10 years after first regular mobile phone use was 0.76 (0.52–1.11). There was no trend of increasing ORs with increasing cumulative call time or cumulative number of calls, with the lowest OR (0.48 (0.30–0.78)) observed in the 9th decile of cumulative call time. In the 10th decile (≥1640 h) of cumulative call time, the OR was 1.32 (0.88–1.97); there were, however, implausible values of reported use in those with ≥1640 h of accumulated mobile phone use. With censoring at 5 years before the reference date the OR for ≥10 years after first regular mobile phone use was 0.83 (0.58–1.19) and for ≥1640 h of cumulative call time it was 2.79 (1.51–5.16), but again with no trend in the lower nine deciles and with the lowest OR in the 9th decile. In general, ORs were not greater in subjects who reported usual phone use on the same side of the head as their tumour than in those who reported it on the opposite side, but it was greater in those in the 10th decile of cumulative hours of use. *Conclusions:* There was no increase in risk of acoustic neuroma with ever regular use of a mobile phone or for users who began regular use 10 years or more before the reference date. Elevated odds ratios observed at the highest level of cumulative call time could be due to chance, reporting bias or a causal effect. As acoustic neuroma is usually a slowly growing tumour, the interval between introduction of mobile phones and occurrence of the tumour might have been too short to observe an effect, if there is one.

1. Background

Mobile phone use has increased rapidly since its introduction in the early to mid-1980s, with an estimated 5.3 billion mobile phone subscriptions world-wide at the end of 2010, according to the International Telecommunication Union (ITU; http://www.itu.int/net/pressoffice/press_releases/2010/39.aspx). Concerns about possible health effects have accompanied the expanding use of this technology. The INTERPHONE study was initiated as an international consortium of case–control studies with a common protocol focusing on four tumour types in tissues that absorb most RF energy emitted by mobile phones: glioma, meningioma, vestibular schwannoma (more commonly known as acoustic neuroma), and parotid gland tumours [1,2]. We recently reported on the association of mobile phone use with cerebral glioma and meningioma [3], and this paper reports results for acoustic neuroma.

Acoustic neuroma (AN), a benign tumour, arises in the eighth cranial nerve that leads from the inner ear to the brainstem. ANs are estimated to comprise about 5% of primary brain and central nervous system tumours and 63% of tumours of cranial and spinal nerves, with an estimated incidence rate of 10.4 per million person-years in the US during 2004–2007 [4]. Other estimated incidence rates from the US [5] or UK [6] were around 10 or lower per million person-years, but those from Denmark were about 20

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per million person-years [7]. Thus there may be variation in completeness of reporting of these tumours, in part at least to infrequent routine registration of benign tumours; the high Danish rates were from a specialised AN registry with population-wide ascertainment. The gender ratio in all reports was close to one and the incidence rate peak appeared to be in the age group of 50–65 years [4–7]. The Danish registry reported that AN rates had risen steeply from the mid-1970s until the mid-2000s and remained stable or fell slightly thereafter [7].

In principle, most ANs occur in tissue absorbing relatively high levels of RF energy when a mobile phone handset is held to the ear [8,9]. As ANs usually grow slowly and first symptoms may appear years before clinical diagnosis [10,11], assessment of mobile phone use well before tumour detection will provide greater confidence that exposure preceded disease and could have contributed to its development, if a positive association is observed.

Several studies have reported on the possible association between mobile phone use and the risk of AN. They include case–control studies in six countries reporting mainly INTERPHONE data [12–17], a Danish retrospective cohort study of mobile phone subscribers [18,19], two US case–control studies [20,21], three Swedish case–control studies [22–24] and a recent case–case study from Japan [25]. Their results were inconclusive, particularly for users of 10 years or more, as summarized in a recent European Commission risk assessment report [26]. All studies were limited by having few long-term and heavy mobile phone users. The present combined international analysis of the INTERPHONE study is based on the largest number of AN cases and, in particular, the largest number of long-term mobile phone users reported to date.

2. Materials and methods

2.1. Study design

INTERPHONE is an international, mainly population-based, case–control study. The common core study protocol is described in detail elsewhere [1,2]. Sixteen study centres from 13 countries (Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, and the UK) were included. To maximize statistical power, INTERPHONE focused on tumours in patients 30–59 years of age as they were expected to have had the highest prevalence of mobile phone use in the previous five to ten years, and on countries and regions (mainly large urban areas) likely to have the longest and highest use of mobile phones.

Eligible cases were all patients with a schwannoma of the acoustic nerve (ICD-9 code 225.1 or ICD-10 code D33.3, and ICD-O topography code C72.4 and morphology code 9560/0) diagnosed in the study regions during study periods of two to four years between 2000 and 2004. In most centres, cases were ascertained from neurological and neurosurgical facilities in the study region, in several centres also from otorhinolaryngological units or local cancer registries, and from one radiotherapy unit (in France). All diagnoses were histologically confirmed or based on the unequivocal diagnostic imaging. To facilitate interviews as soon as possible after diagnosis, cases were ascertained actively within treatment facilities wherever possible. Completeness of ascertainment was checked through secondary sources, such as population- or hospital-based cancer registries, medical archives and hospital discharge or billing files [2].

Two controls were selected for each case from a locally appropriate, population-based sampling frame [2]. The sampling procedure involved individual matching in seven centres (Canada – Ottawa, Canada – Vancouver, France, Israel, Japan, New Zealand and UK North) and frequency matching elsewhere. The matching variables were age (within 5 years), sex, and region of residence within each study centre. In Israel, subjects were also matched on ethnic origin. Where frequency matching had been used, individual matching was done post hoc, with cases being assigned two controls, interviewed as close as possible in time to the case, from those who fitted the matching criteria. While in some centres controls were specifically sampled for the AN cases, in other centres they were taken from the pool of INTERPHONE controls drawn for all tumours together, or a mixture of both approaches. The proportions of AN controls already used in the combined analyses of glioma and meningioma were 94% (Australia), 65% (Canada – Montreal), 32% (Denmark), 72% (Finland), 59% (Israel), 88% (Norway), 79% (Sweden), and 81% (UK South); it was 0% in all other centres [3].

Detailed information on past mobile phone use was collected during face-to-face interviews with the study subject or a proxy [2], with the median time between interview date and reference date being 171 days for cases and 320 days for controls. A proxy was sought when the study subject had died or was too ill to be interviewed. Proxy interviews were conducted with 3 cases (0.3%) and 43 controls (0.6%). The interviews were conducted using a computer-assisted questionnaire, except in Finland where a paper version was used. The questionnaire also included sections on socio-demographic factors, occupational exposure to electromagnetic fields and ionizing radiation, exposure to loud noise, medical history (subject's and family), ionizing and non-ionizing medical radiation exposures and smoking. Central workshops were held to train and retrain interviewer instructors who were responsible for training the interviewers of each centre and monitored interview quality; furthermore, questionnaire versions in languages other than English were back-translated to minimise inaccuracies introduced during translation and periodic meetings of fieldwork coordinators were held to deal with issues arising from the interviews.

2.2. Statistical methods

Data from countries with multiple centres were combined for the analyses, except in the UK where the UK South and UK North, each with large numbers of subjects, were kept separate. The word "centre" in the remainder of this paper is used to refer to these 14 analytic entities (12 countries, UK North and UK South). All analyses were carried out for all centres combined and for each centre separately. Formal tests for heterogeneity of risk across centres were conducted by allowing for an interaction between the centre and the exposure variables (no heterogeneity was identified; data not shown).

The analyses presented here focus on past mobile phone use as reported by the study subjects or their proxies. The analyses were based on the conditional logistic regression for matched sets. The date of diagnosis of the case was used as the reference date for the case and the controls in each matched set. For the main analyses, the reference category for odds ratios was the set of subjects who reported that they had never been regular users. Ever having been a regular user was defined a priori as at least one call per week on average for a period of six months or more. For convenience, the term "regular user" will be used in the text and in the tables to refer to ever having been a regular user. Numbers of never users at the date of interview were small, particularly in certain age- and gender-specific subgroups such as young men; consequently, never users were not considered a suitable reference group.

The exposure variables considered were: regular user status and time (years), cumulative number of calls and cumulative duration of calls (cumulative call time) since first regular use. Cumulative number of calls and cumulative call time were analyzed as categorical variables, based on the deciles of the

distribution of these variables among all controls who had ever been regular users, including those matched to patients with a glioma, meningioma or a parotid gland tumour, so that the same cut-off points are used in all combined analyses of the INTERPHONE group [3]. Cumulative use excluded use of mobile phones with hands-free devices. For all time periods for which the subject reported the use of hands-free devices, the amount of use was reduced by 100%, 75%, 50% or 25% depending on whether hands-free devices were used always or almost always, more than half, about half, or less than half of the time. For ease of presentation, some results are shown for the following five groups of exposure deciles – 1, 2–5, 6–7, 8–9 and 10 – chosen post hoc to reflect the spread of the highly skewed distribution of these variables. All analyses were adjusted for educational attainment, which served as a measure of socio-economic status. The interval between the start date of interviews in the study centre and the date of each subject's interview was included in the models by fitting the interaction of this interval with study centre. A common protocol was applied to impute missing data for cases and controls [2]. The study questionnaire allowed ranges to be given instead of exact answers to some of the questions, including number and duration of calls and dates of start and end of mobile phone use; in such instances, the main analyses in this paper were based on the mid-point of the reported range, whereas sensitivity analyses were conducted using the lower and upper bounds.

It should be noted that deciles to categorize cumulative number of calls and cumulative call time were determined from the total amount of use (including use of mobile phones with hands-free devices); therefore, for example, 10% of controls had a total cumulative call time of 1640 h or more. For this analysis, each subject's cumulative exposure was calculated excluding use with hands-free devices. Thus defining the exposure categories as described above means that less than 10% of subjects are allocated to upper categories of the distribution, e.g., 5% of acoustic neuroma controls in the highest category of $\geq$1640 h of mobile phone use without hands-free devices.

Because absorption of RF energy from mobile phones is highly localized [8,9], separate analyses were conducted for the subjects who reported using the mobile phone mainly on one or the other side of the head relative to the side on which the tumour occurred. For these analyses, each control was assigned the side of the head of the AN of his or her matched case. Exposure was considered to be ipsilateral if the phone was used predominantly on the same side as the tumour or on both sides of the head, and contralateral if used mainly on the side of the head opposite to the tumour. The question asked "When you use a mobile phone, do you generally use it on the right or left side of your head?" with left, right and both sides as response options.

All exposure variables, except time since first use, were censored at 1 year before the reference date, as in the previous analyses of glioma and meningioma [3]. In addition, for AN, we report also all exposure variables censored at 5 years before the reference date, in an attempt to take into account the slow growth and possible long diagnostic delay for AN (as described earlier). Within this long pre-diagnostic time period, hearing loss or hearing problems (such as tinnitus) are common symptoms, which might influence mobile phone use, either by reducing the likelihood the subject will start using a mobile phone or by leading to a reduction in mobile phone use, or a change in the preferred ear of use.

3. Results

Altogether, 1361 AN cases were identified during the study period. Interviews were completed with 1121 cases (82% participation; range by centre 70–100%). For 16 cases, no matching control was found, leaving 1105 cases for analyses. Overall, 14354 controls were considered eligible for the AN analysis, of which 7658 completed the interviews (53% participation; range by centre 35–74%). A total of 2145 controls was included in the final analysis matched either 1:1 (65 cases) or 1:2 (1040 cases) to the AN cases. The most common reasons for non-participation were subject refusal (11% of eligible cases and 30% of eligible controls); physician refusal or subject illness or death (2% cases, 1% of controls); and inability to contact the subject (3% cases, 16% controls).

Of the 1105 cases, 49% were men and 51% women and 22% were aged 30–39 years at diagnosis, 33% 40–49 years and 45% 50–59 years (Table 1). Among cases, 79% reported severe hearing difficulties, i.e., hearing loss or buzzing sounds in the ear, before diagnosis. One or both of these symptoms were recalled as appearing during the year before diagnosis in 22% of cases, 1–4 years before diagnosis in 33%, 5–9 years in 12%, and 10 or more years in 13%. Among controls the respective figures were 2%, 7%, 5%, and 10%, with 75% not reporting any hearing problems.

Overall, the odds ratio was 0.85 (95% confidence interval (CI) 0.69–1.04) for regular use of mobile phones when censoring exposure at one year before the reference date and 0.95 (CI 0.77–1.17) when censoring exposure at five years before the reference date (Table 2). Analyses by time since first use showed odds ratios close to or below one, including for users beginning 10 or more years ago, irrespective of the censoring. For cumulative call time, the highest odds ratios were observed in the highest category of use: the odds ratios for $\geq$1640 h were 1.32 (CI 0.88–1.97) when censoring exposure at one year and 2.79 (CI 1.51–5.16) when censoring exposure at five years. There was, however, no preceding trend: odds ratios fluctuated between 0.48 and 1.04 in the first nine categories (0.48, CI 0.30–0.78, in the 9th category) for censoring at

Table 1
Selected characteristics of acoustic neuroma cases and controls included in the analyses.

Characteristics of the study population	Cases, *n* (%)	Controls, *n* (%)
All interviewed	1121	7658
Included in main analysis[a]	1105 (100)	2145 (100)
Cases with histological confirmation	883 (80)	
Year of diagnosis[b]		
2000	137 (12)	
2001	431 (39)	
2002	338 (31)	
2003	199 (18)	
Sex		
Men	538 (49)	1035 (48)
Women	567 (51)	1110 (52)
Age		
Aged 30–39 at diagnosis	240 (22)	446 (21)
Aged 40–49 at diagnosis	364 (33)	720 (34)
Aged 50–59 at diagnosis	501 (45)	979 (46)
Centre		
Australia	127 (11)	254 (12)
Canada (centres combined)	84 (8)	168 (8)
Denmark	70 (6)	139 (6)
Finland	75 (7)	145 (7)
France	107 (10)	209 (10)
Germany	67 (6)	134 (6)
Israel	72 (7)	141 (7)
Italy	30 (3)	60 (3)
Japan	69 (6)	137 (6)
New Zealand	18 (2)	21 (1)
Norway	38 (3)	75 (3)
Sweden	102 (9)	197 (9)
UK North	94 (9)	170 (8)
UK South	152 (14)	295 (14)

[a] Cases for whom no matching controls could be found were excluded.
[b] Few cases in the year 2000 group were diagnosed in 1999 (n = 9) and few in the year 2003 group in 2004 (n = 19).

Table 2
ORs for acoustic neuroma with mobile phone use in categories of regular use, time since start of use, cumulative call time and cumulative number of calls – excludes use with hands-free devices.

	Exposure up to 1 year before reference date[a]			Exposure up to 5 years before reference date[a]		
	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)
Regular use in the past						
No	462	837	1.00	801	1560	1.00
Yes	643	1308	0.85 (0.69–1.04)	304	585	0.95 (0.77–1.17)
Time since start of use (years)						
Never regular user	462	837	1.00	801	1560	1.00
1–1.9	63	169	0.73 (0.49–1.09)			
2–4	276	554	0.87 (0.69–1.10)			
5–9	236	444	0.90 (0.69–1.16)	236	444	0.99 (0.78–1.24)
≥10	68	141	0.76 (0.52–1.11)	68	141	0.83 (0.58–1.19)
Cumulative call time with no hands-free devices (h)[c]						
Never regular user	462	837	1.00	801	1560	1.00
<5	58	144	0.77 (0.52–1.15)	42	80	1.07 (0.69–1.68)
5.0–12.9	63	129	0.80 (0.54–1.18)	30	53	1.06 (0.60–1.87)
13–30.9	80	136	1.04 (0.71–1.52)	40	59	1.32 (0.80–2.19)
31–60.9	66	131	0.95 (0.63–1.42)	36	70	0.86 (0.52–1.41)
61–114.9	74	137	0.96 (0.66–1.41)	21	71	0.63 (0.35–1.13)
115–199.9	68	128	0.96 (0.65–1.42)	22	53	0.71 (0.39–1.29)
200–359.9	50	144	0.60 (0.39–0.91)	29	49	0.83 (0.48–1.46)
360–734.9	58	126	0.72 (0.48–1.09)	26	60	0.74 (0.42–1.28)
735–1639.9	49	126	0.48 (0.30–0.78)	22	59	0.60 (0.34–1.06)
≥1640	77	107	1.32 (0.88–1.97)	36	31	2.79 (1.51–5.16)
Cumulative number of calls with no hands-free devices (in hundreds)						
Never regular user	462	837	1.00	801	1560	1.00
$<1.5 \times 100$	59	135	0.76 (0.51–1.14)	40	92	0.85 (0.54–1.34)
1.5–3.4	60	137	0.68 (0.45–1.03)	48	38	2.32 (1.39–3.87)
3.5–7.4	73	135	1.11 (0.76–1.61)	24	65	0.64 (0.35–1.17)
7.5–13.9	87	138	1.22 (0.84–1.77)	30	51	0.91 (0.51–1.61)
14–25.4	79	132	1.11 (0.75–1.64)	26	67	0.92 (0.53–1.58)
25.5–41.4	55	137	0.64 (0.42–0.98)	29	55	0.89 (0.53–1.51)
41.5–67.9	50	133	0.74 (0.49–1.12)	18	62	0.54 (0.30–0.97)
68–127.9	62	133	0.65 (0.43–0.98)	42	62	1.02 (0.63–1.66)
128–269.9	56	115	0.67 (0.44–1.02)	21	54	0.62 (0.34–1.12)
≥270	62	113	0.93 (0.61–1.41)	26	39	1.55 (0.84–2.86)

[a] The reference category consists of subjects who were not regular users 1 year (or 5 years) before the reference date.
[b] ORs adjusted for sex, age, study centre, ethnicity in Israel, and education.
[c] Categories of regular use are based on the deciles of the distribution among all eligible regular user controls.

one year and between 0.60 and 1.32 (0.60, CI 0.34–1.06, in the 9th category) for censoring at five years. For cumulative number of calls there was no trend across categories and little indication of higher ORs in the 10th category of use (Table 2).

As mobile phone use varies by age, we examined age groups <50 years at the reference date and 50–59 years separately, but effect estimates were generally similar or, if different, not consistently higher for either one of the two age groups. Effect estimates were usually somewhat higher for men than women, but their confidence intervals overlapped widely (data not shown).

The odds ratio for mainly ipsilateral regular use was 0.77 (CI 0.59–1.02), and that for mainly contralateral use 0.92 (CI 0.70–1.22), when censoring at one year before reference date; the respective odds ratios were 0.98 (CI 0.73–1.30) and 0.93 (CI 0.68–1.27) when censoring at five years before reference date (Table 3). All odds ratios for ipsilateral and contralateral use by time since first use and by cumulative use were close to or below one with no trend, except odds ratios in the highest categories of cumulative call time and cumulative number of calls. In the highest category of cumulative call time (≥1640 h), the odds ratios, censored at one year, were 2.33 (CI 1.23–4.40) for ipsilateral use and 0.72 (CI 0.34–1.53) for contralateral use and, censored at five years, 3.53 (CI 1.59–7.82) for ipsilateral use and 1.69 (CI 0.43–6.69) for contralateral use. These patterns for cumulative number of calls were similar but the odds ratios for ipsilateral use were weaker (Table 3).

The increased OR with ≥1640 h of mobile phone use shown in Table 2, was present only for people who started mobile phone use ≥10 years before the reference date (Table 4) and was limited to ipsilateral users. For these long-term users, however, there were much reduced ORs for intermediate categories of cumulative use both overall (ORs of 0.28 (CI 0.09–0.86) and 0.39 (CI 0.20–0.74) in the two intermediate categories) and for ipsilateral users (Table 4).

There were 16 cases (1.4%) and 22 controls (1.0%) who reported 5 h or more of mobile phone use per day, an implausible amount, most of them contributing to the category of ≥1640 h of cumulative call time. While truncation of use hardly altered the effect estimate for ≥1640 h of use, the odds ratios decreased somewhat when those subjects were excluded (Table 5; the small differences in the ORs for the standard analyses compared to those in Table 2 are due to combining deciles of intermediate categories).

We also conducted several sensitivity analyses to investigate the influence of various study indicators on the relative risk estimation, which had been defined in advance of the analyses [2]. Table B.1 shows the changes in the odds ratios of sub-group analyses by manner of presentation of the study, by centres with different participation rates, by indicators of interview quality and by use of imputations for missing values for the highest category of cumulative call time; no consistent patterns were detected.

4. Discussion

The INTERPHONE study provides the largest numbers of mobile phone users with at least 10 years of exposure and the greatest self-reported cumulative hours of use of any case–control study on the subject to date. The odds ratios for any regular use were below one. Odds ratios for the highest category of reported cumulative call time were above one, but with no evidence of a preceding trend and with the lowest OR in the 9th decile. In the highest cumulative use

Table 3
ORs for acoustic neuroma with mobile phone use according to side of use of mobile phones and in categories of regular use, time since start of use, cumulative call time and cumulative number of calls[a] – excludes use with hands-free devices.

	Exposure up to 1 year before reference date						Exposure up to 5 years before reference date					
	Ipsilateral phone use			Contralateral phone use			Ipsilateral phone use			Contralateral phone use		
	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)
Regular use in the past												
No	416	615	1.00	405	625	1.00	788	1399	1.00	770	1358	1.00
Yes	271	471	0.77 (0.59–1.02)	261	390	0.92 (0.70–1.22)	159	266	0.98 (0.73–1.30)	117	182	0.93 (0.68–1.27)
Time since start of use (years)												
Never regular user	416	615	1.00	405	625	1.00	788	1399	1.00	770	1358	1.00
1–1.9	23	62	0.42 (0.22–0.81)	32	51	1.75 (0.90–3.42)						
2–4	103	204	0.70 (0.49–1.00)	123	189	0.80 (0.56–1.13)						
5–9	101	153	0.95 (0.64–1.41)	89	120	0.96 (0.64–1.43)	112	196	0.95 (0.69–1.30)	100	141	1.06 (0.75–1.49)
≥10	44	52	1.18 (0.69–2.04)	17	30	0.69 (0.33–1.42)	47	70	1.05 (0.65–1.68)	17	41	0.58 (0.30–1.11)
Cumulative call time with no hands-free devices (h)[c]												
Never regular user	416	615	1.00	405	625	1.00	788	1399	1.00	770	1358	1.00
<5	23	44	0.81 (0.43–1.52)	28	56	0.83 (0.44–1.56)	21	36	1.00 (0.52–1.92)	18	25	1.46 (0.71–3.02)
5.0–114.9	108	200	0.71 (0.50–1.00)	131	151	1.28 (0.90–1.83)	58	116	0.78 (0.51–1.18)	58	79	1.08 (0.69–1.71)
115–359.9	47	95	0.67 (0.40–1.12)	49	92	0.66 (0.41–1.07)	25	45	0.71 (0.39–1.29)	18	34	0.61 (0.30–1.24)
360–1639.9	46	86	0.51 (0.30–0.88)	37	65	0.67 (0.38–1.15)	28	47	1.01 (0.57–1.78)	17	39	0.58 (0.30–1.12)
≥1640	47	46	2.33 (1.23–4.40)	16	26	0.72 (0.34–1.53)	27	22	3.53(1.59–7.82)	6	5	1.69 (0.43–6.69)
Cumulative number of calls with no hands-free devices (in hundreds)[c]												
Never regular user	416	615	1.00	405	625	1.00	788	1399	1.00	770	1358	1.00
$<1.5 \times 100$	24	46	0.67 (0.35–1.28)	29	49	0.98 (0.52–1.84)	20	42	0.85 (0.44–1.65)	17	26	1.32 (0.62–2.81)
1.5–25.4	108	193	0.81 (0.57–1.14)	143	158	1.36 (0.96–1.93)	60	105	0.90 (0.59–1.35)	58	68	1.28 (0.81–2.02)
25.5–67.9	48	108	0.56 (0.34–0.90)	34	90	0.51 (0.31–0.86)	25	46	0.80 (0.45–1.44)	15	45	0.45 (0.22–0.89)
68–269.9	50	81	0.68 (0.40–1.13)	44	66	0.67 (0.39–1.14)	36	52	1.13 (0.67–1.92)	21	34	0.68 (0.35–1.33)
≥270	41	43	1.67 (0.90–3.09)	11	27	0.52 (0.21–1.26)	18	21	2.00 (0.89–4.51)	6	9	1.40 (0.43–4.53)

[a] The reference category consists of subjects who were not regular users 1 year (or 5 years) before the reference date. Because the main analyses in this paper use matched conditional logistic regression, all matched sets in which the case and/or both controls were regular contralateral user are excluded from the ipsilateral analyses; similarly, sets in which the case and/or both controls were regular ipsilateral users were excluded from the contralateral analyses. This explains the differences in the numbers of cases and controls in the reference category and the fact that the number of ipsilateral and contralateral regular user cases (and controls) does not add up to the total number of regular users in the previous table.

[b] ORs adjusted for sex, age, study centre, ethnicity in Israel, and education.

[c] Deciles of exposure used in Table 2 have been collapsed into six categories for these analyses: deciles 1, 2–5, 6–7, 8–9 and 10.

Table 4
ORs for acoustic neuroma with mobile phone use according to side of use of mobile phones and in categories of cumulative call time, stratified by recency of starting regular use – excludes use with hands-free devices.

Cumulative call time (h)	Overall			Ipsilateral use[a]			Contralateral use[a]		
	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)
Non-regular users	462	837	1.00	416	615	1.00	405	625	1.00
Short-term users: start of phone use 1–4 years before reference date									
<5	54	130	0.81 (0.53–1.24)	21	39	0.71 (0.36–1.38)	26	51	0.84 (0.43–1.64)
5–114.9	198	387	0.92 (0.71–1.20)	72	155	0.62 (0.41–0.93)	95	112	1.23 (0.81–1.85)
115–359.9	57	126	0.74 (0.49–1.13)	23	43	0.59 (0.29–1.23)	22	48	0.60 (0.31–1.18)
360–1639.9	26	69	0.55 (0.29–1.03)	9	24	0.41 (0.14–1.18)	10	25	0.38 (0.13–1.07)
≥1640	4	11	0.63 (0.14–2.80)	1	5	0.80 (0.05–13.03)	2	4	1.22 (0.18–8.45)
Medium-term users: start of phone use 5–9 years before reference date									
<5	4	10	0.84 (0.21–3.40)	2	5	1.43 (0.20–10.23)	2	3	0.89 (0.09–8.57)
5–114.9	77	130	0.97 (0.67–1.41)	30	39	0.88 (0.45–1.70)	34	34	1.53 (0.84–2.79)
115–359.9	55	122	0.95 (0.62–1.45)	24	44	0.97 (0.49–1.94)	21	36	0.71 (0.35–1.47)
360–1639.9	64	123	0.74 (0.49–1.12)	27	41	0.68 (0.34–1.37)	22	34	0.79 (0.38–1.63)
≥1640	36	59	1.05 (0.62–1.78)	18	24	1.64 (0.70–3.82)	10	13	0.78 (0.29–2.10)
Long-term users: start of phone use ≥10 years before reference date									
<5	0	4	–	0	0	–	0	2	–
5–114.9	8	16	0.81 (0.30–2.14)	6	6	1.34 (0.34–5.30)	2	5	0.80 (0.14–4.64)
115–359.9	6	24	0.28 (0.09–0.86)	0	8	–	6	8	0.86 (0.22–3.29)
360–1639.9	17	60	0.39 (0.20–0.74)	10	21	0.37 (0.14–0.99)	5	6	1.04 (0.24–4.52)
≥1640	37	37	1.93 (1.10–3.38)	28	17	3.74 (1.58–8.83)	4	9	0.48 (0.12–1.94)

[a] Exposure was considered to be ipsilateral if the phone was used predominantly on the same side as the tumour or on both sides of the head, and contralateral if used mainly on the side of the head opposite to the tumour.
[b] ORs adjusted for sex, age, study centre, ethnicity in Israel, and education.

Table 5
ORs for acoustic neuroma with cumulative call time in the highest category of mobile phone use (1640 h and more) – overall and by laterality of use, excludes use with hands-free devices.[a]

	Exposure up to 1 year before reference date								
	Overall			Ipsilateral phone use			Contralateral phone use		
	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)
Standard analysis	77	107	1.30 (0.87–1.94)	47	46	2.33 (1.23–4.40)	16	26	0.72 (0.34–1.53)
Truncation of excessive phone use to 5 h/day	76	106	1.31 (0.88–1.96)	47	46	2.33 (1.23–4.40)	15	26	0.68 (0.31–1.47)
Exclusion of subjects with use 5 h/day or more	61	87	1.16 (0.75–1.80)	38	38	2.11 (1.06–4.20)	12	22	0.53 (0.22–1.25)
	Exposure up to 5 years before reference date								
	Overall			Ipsilateral phone use			Contralateral phone use		
	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)
Standard analysis	36	31	2.86 (1.55–5.28)	27	22	3.53 (1.59–7.82)	6	5	1.69 (0.43–6.69)
Truncation of excessive phone use to 5 h/day	36	30	3.03 (1.62–5.67)	27	21	3.92 (1.72–8.96)	6	5	1.69 (0.43–6.69)
Exclusion of subjects with use 5 h/day or more	27	24	2.86 (1.39–5.92)	20	18	3.14 (1.25–7.84)	4	4	1.06 (0.19–6.11)

[a] Deciles of exposure used in Table 2 have been collapsed into six categories for these analyses: deciles 1, 2–5, 6–7, 8–9 and 10; the small difference in the OR of the standard analysis compared to Table 2 are due to the collapsing of deciles of intermediate categories
[b] ORs adjusted for sex, age, study centre, ethnicity in Israel, and education.

category, odds ratios were higher with reported ipsilateral use than with reported contralateral use, although the confidence intervals overlapped and ORs were below unity in some of the intermediate exposure categories. The results for AN were broadly similar to those of published INTERPHONE analyses of meningioma and glioma [3].

A number of previous publications on mobile phone use and AN included cases (70%) in the present multicentre analysis, namely those from Denmark [12], Sweden [13], Japan [14], Germany [15], France [16], and the Nordic countries and UK together [17]; none of these results were dissimilar to the present findings. In a Danish nationwide cohort study of mobile phone subscribers a risk estimate below unity (SIR 0.88 CI 0.52–1.48) was observed in subscribers of 11+ years compared to short-term or never subscribers, which is compatible with our overall estimate of 0.85 [27]. Two hospital-based case–control studies from the US conducted in the late 1990s had very small numbers of long-term users; their effect estimates were 1.9 (CI 0.6–5.9) for >5 years of use [20] and 1.7 (CI 0.5–5.1) for 3–6 years of use [21], higher than in the present study but with wide confidence intervals and hence not incompatible with our estimates. One early study from Sweden found no increased risk of acoustic neuroma related to self-reported mobile phone use, although based on the small numbers [22]. However, two subsequent case–control studies by the same investigators, not overlapping with INTERPHONE, found a relatively strong association between mobile phone use and AN, with pooled odds ratios of 2.3 (CI 1.2–4.1) for analogue phone use with 1-5 years latency, 3.4 (CI 2.1–5.5) with >5–10 years, and 3.1 (CI 1.7–5.7) with >10 years [23,24]. A raised risk for digital phone use was also observed, with an odds ratio of 1.5 (CI 1.1–2.1), with >1 year latency. These results are not compatible with our findings. Results by cumulative use were reported by both studies from the US, but use levels were quite low, >100 h [20] and >60 h [21], and no consistent increases in risk were found. The two Swedish studies found considerable risk increases also for quite

low levels of use; pooled risk estimates were 2.5 (CI 1.6–4.0) and 3.6 (CI 2.2–5.8) for 1–85 h and >85 h of cumulative use of analogue phones, and 1.5 (CI 1.01–2.2) and 1.5 (CI 0.99–2.3) for 1–64 h and >64 h of cumulative use of digital phones [24]. These apparently large increases in risk with even low mobile phone use are not compatible with the present INTERPHONE results. A recent case–case study in Japan, including 787 AN cases investigating laterality of mobile phone use, reported risk ratios of 1.08 (CI 0.93–1.28) for regular mobile phone use at one year prior to diagnosis and 1.14 (CI 0.96–1.40) at five years prior to diagnosis [25]. The authors reported a significantly increased risk for self-reported mobile phone use for >20 min/day on average, though biases may explain these findings.

Several issues of importance to interpretation of our analyses of glioma and meningioma also apply to our AN analyses [3]. Selection bias occurs if the cases or the controls in a case–control study are not representative with respect to exposure of all eligible cases or all eligible controls in the relevant population. AN cases were recruited mainly through neurosurgical or otorhinolaryngological clinics within the study area; under-ascertainment might occur due to diagnosis and treatment outside the study area, diagnosis and treatment in non-participating clinics in the study area, or failure to identify tumours that had been diagnosed but not treated because they were small. It seems unlikely that mobile phone use would be associated with place of diagnosis or treatment, especially since in most countries the study was restricted to metropolitan areas. Mobile phone use, however, might lead to earlier diagnosis (due to presentation with difficulty hearing mobile phone conversations) which could over-representation of mobile phone users among cases. This effect, however, would probably be reduced in analyses in which exposure was censored at five years before the reference date.

The lower response proportion among controls compared to cases is of concern, especially since INTERPHONE's analyses of non-responder questionnaires indicated that regular users of mobile phones were more likely to participate than non-regular users [28]. We estimated, in the most plausible scenarios, that non-participation bias might have led to a reduction in the odds ratios for regular use of 5–15% [28], which could explain the 15% reduction in the overall effect estimate shown in Table 2.

Information bias is another concern, as INTERPHONE validation studies have shown substantial error in recall of past mobile phone use [29–31]. The observed errors could lead to underestimation of a true association or generate a spurious, or a spuriously strong, association, and we cannot readily ascertain where the overall impact of these errors lies. A generally large non-differential random error, as observed for healthy volunteers using software-modified phones (recording number and times of calls), would tend to weaken an association, if there was one [29]. Light users tended to under-estimate mobile phone use and heavy users overestimated it [30], which could lead to over-estimation of the strength of an association, if there was one [32]. Finally, greater over-estimation of more distant past use by cases than controls could produce a spurious positive association, particularly with higher accumulated use [30]. The preferred side of the head during mobile phone use may be inaccurately recalled and it might have been affected by early symptoms of a then undiagnosed AN. We did not specify a particular time of use when asking about the preferred side of use and thus cannot address possible effects of changes in preference.

Bias might also arise because controls were on average interviewed 320 days after the reference date, compared with 171 days for cases. This difference could affect reporting. However an analysis confined to matched sets with less than one month between the case and control interviews estimated ORs that were similar to the overall ORs (Table B.1).

Prodromal symptoms of an AN might have an important effect on the exposure of cases. Specifically, they might discourage affected people from becoming mobile phone users, reduce their use in the period before diagnosis, or lead to change in the preferred ear of use; particularly as unilateral hearing loss is a common early symptom [33]. In addition to censoring exposure at one year before the reference date we also censored it at five years in secondary analyses, which could reduce the effect of prodromal symptoms on the associations we studied. Censoring at five years before the reference date did not greatly change any patterns that were evident with censoring at one year.

Confounding is always a concern in epidemiological studies, but little is known of the causes of AN [34]. Neurofibromatosis type II, a rare hereditary disorder, is associated with a very high risk of AN, but only 10 cases reported having this disorder and exclusion of those subjects did not alter the results. Loud noise is thought to be a risk factor, but studies are inconsistent [15,35–38], and adjustment for this exposure did not alter our results. Neither did exclusion of cases and controls exposed to therapeutic doses of ionizing radiation. High socioeconomic status has been shown to be related to a higher incidence of AN in two recent studies [39,40], but adjustment for this factor had little impact on our results (data not shown).

As in our brain tumour analyses [3], we carried out additional analyses to assess the possible impact of various sources of error on effect estimates. More odds ratios were below one than above one, a pattern that could be due to selection bias among controls [28]. We therefore conducted an analysis restricted to regular users of mobile phones, the advantages and disadvantages of which have been discussed in Appendix 2 of our report on brain tumours [3]. It produced uniformly higher exposure-category-specific odds ratios (Table B.2), some of which were above one, but it did not show more evidence of a trend towards increasing risk with increasing mobile phone use than the original analysis (Table 2). We also examined the sensitivity of the effect estimate for the highest use category to implausible values for the amount of reported mobile phone use (Table 5). Truncation of implausible values to an assumed upper limit of plausibility (5 h use per day) had little impact on the effect estimate but exclusion of subjects with implausible values reduced it. Thus, the apparently somewhat increased risk of AN in those with heavy mobile phone use is influenced by implausible values. However, if these values reflect truly heavy use, even if not as high as stated, their exclusion would reduce an increased odds ratio for heavy use, if there truly was one.

In conclusion, we did not observe an increase in risk of AN with ever regular use of a mobile phone or in mobile phone users who began use 10 years or more before the reference date. Further, we did not see any trend in AN risk with increasing cumulative use; the lowest OR was in the 9th decile of cumulative call time. There was an increased odds ratio for those with heavy (1640 h or more) cumulative call time, particularly in long-term users and in those who reported use of a mobile phone on the same side of their head as the tumour occurred. This increase could be due to chance, reporting bias or a causal effect. It is possible too that the interval between introduction of mobile phones and occurrence of the tumour we studied was too short to observe an effect, if there is one, as acoustic neuroma is usually a slowly growing tumour.

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Conflicts of interest

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Appendix B

Table B.1
Results of sensitivity analyses on odds ratios between mobile phone use and acoustic neuroma for the highest decile of cumulative call time, covering possible indicators of sample representativeness and response quality.

Factors included in sensitivity analyses	Exposure up to 1 year before reference date			Exposure up to 5 years before reference date		
	Cases	Controls	OR[a] (95% CI)	Cases	Controls	OR[a] (95% CI)
Main analysis (baseline for comparison)	77	107	1.32 (0.88–1.97)	36	31	2.79 (1.51–5.16)
Presentation of the study[b]						
Explicit mention of mobile phones	49	60	1.63 (1.00–2.67)	23	19	2.63 (1.25–5.55)
Mobile phones mentioned, but not stressed	22	33	0.95 (0.41–2.21)	12	11	3.95 (1.19–13.06)
No mention of mobile phones	6	14	0.60 (0.12–2.94)	1	1	0.14 (0.0–37.72)
Participation rates						
Study centres with control participation rates $<60\%$	48	64	1.34 (0.79–2.27)	25	20	3.16 (1.48–6.77)
Study centres with control participation rates $\geq 60\%$	29	43	1.39 (0.74–2.63)	11	11	2.38 (0.81–7.02)
Interview characteristics						
Excluding proxy interviews	77	107	1.33 (0.89–1.98)	36	31	2.78 (1.51–5.15)
Excluding telephone interviews	74	102	1.26 (0.83–1.90)	34	31	2.36 (1.27–4.38)
With interviewers conducting at least 20 interviews only	70	96	1.33 (0.87–2.03)	33	27	3.03 (1.59–5.80)
Interviewers' workloads had similar numbers of cases and controls [c]	65	84	1.34 (0.86–2.08)	31	28	2.53 (1.33–4.80)
Control interviews within 1 month of case interview	25	17	1.52 (0.69–3.36)	10	3	4.16 (1.01–17.08)
Interviewer judgement of responsiveness of study subjects[d]						
Excluding non-responsive study subjects or subjects with poor memory	69	86	1.39 (0.90–2.15)	33	25	3.16 (1.57–6.37)
Use of imputation and ranges[e]						
Excluding responses with imputed items	63	77	1.40 (0.90–2.18)	28	21	2.49 (1.20–5.18)
Using minimum rather than median when range given	64	73	1.68 (1.07–2.63)	26	19	3.62 (1.68–7.78)
Using maximum rather than median when range given	96	133	1.15 (0.79–1.68)	41	48	1.65 (0.99–2.77)

[a] ORs adjusted for sex, age, study centre, ethnicity in Israel, and education.
[b] Indicates whether mobile phones as purpose of the investigation were mentioned in the invitation letters to cases and controls.
[c] Included only interviewers' whose case/control interview ratio was between 1/6 and 5/6.
[d] Restricted to study subjects who the interviewers judged to be fairly or very cooperative and responsive and who were judged to remember fairly well, well or very well both their current and past mobile phone use history; after an interview had been completed the interviewer recorded his or her impression of the reliability of information on a 5-point scale, overall and for each specific section [2].
[e] Indicates how missing values of amount of mobile phone use were treated in the calculation of cumulative call time

Table B.2
ORs between mobile phone use and acoustic neuroma tumours by regular use, time since start of use, cumulative call time and cumulative number of calls – excludes use with hands-free devices – overall and only regular user; censored at one year before reference date.

	Overall			Only regular users		
	Cases	Controls	OR[a] (95% CI)	Cases	Controls	OR[a] (95% CI)
Time since start of use (years)						
Never regular user	462	837	1.00			
1–1.9	63	169	0.73 (0.49–1.09)	51	93	1.00
2–4	276	554	0.87 (0.69–1.10)	225	330	1.41 (0.82–2.40)
5–9	236	444	0.90 (0.69–1.16)	209	300	1.38 (0.80–2.39)
≥ 10	68	141	0.76 (0.52–1.11)	64	106	1.08 (0.58–2.04)
Cumulative call time with no hands-free devices (h)[b]						
Never regular user	462	837	1.00			
<5	58	144	0.77 (0.52–1.16)	43	81	1.00
5.0–114.9	283	533	0.93 (0.74–1.19)	232	317	1.12 (0.66–1.93)
115–359.9	118	272	0.77 (0.56–1.05)	103	184	0.92 (0.52–1.62)
360–1639.9	107	252	0.61 (0.44–0.85)	99	178	0.74 (0.41–1.34)
≥ 1640	77	107	1.30 (0.87–1.94)	72	69	1.74 (0.90–3.36)
Cumulative number of calls with no hands-free devices (in hundreds)[b]						
Never regular user	462	837	1.00			
$<1.5 \times 100$	59	135	0.76 (0.51–1.14)	46	71	1.00
1.5–25.4	299	542	1.02 (0.81–1.29)	243	337	1.20 (0.71–2.03)
25.5–67.9	105	270	0.68 (0.50–0.94)	90	165	0.86 (0.48–1.54)
68–269.9	118	248	0.65 (0.47–0.90)	111	172	0.87 (0.49–1.54)
≥ 270	62	113	0.92 (0.61–1.39)	59	84	1.01 (0.53–1.95)

[a] ORs adjusted for sex, age, study centre, ethnicity in Israel, and education.
[b] Deciles of exposure used in Table 2 have been collapsed into six categories for these analyses: deciles 1, 2–5, 6–7, 8–9 and 10.

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