Further aspects on cellular and cordless telephones and brain tumours

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Abstract. We included in a case-control study on brain tumours and mobile and cordless telephones 1,617 patients aged 20-80 years of both sexes diagnosed during January 1, 1997 to June 30, 2000. They were alive at the study time and had histopathology verified brain tumour. One matched control to each case was selected from the Swedish Population Register. The study area was the Uppsala-Örebro, Stockholm, Linköping and Göteborg medical regions of Sweden. Exposure was assessed by a questionnaire that was answered by 1,429 (88%) cases and 1,470 (91%) controls. In total use of analogue cellular telephones gave an increased risk with odds ratio (OR)=1.3, 95% confidence interval (CI)=1.04-1.6, whereas digital and cordless phones did not overall increase the risk significantly. Ipsilateral use of analogue phones gave OR=1.7, 95% CI=1.2-2.3, digital phones OR=1.3, 95% CI=1.02-1.8 and cordless phones OR=1.2, 95% CI=0.9-1.6. The risk for ipsilateral use was significantly increased for astrocytoma for all studied phone types, analogue phones OR=1.8,95% CI=1.1-3.2, digital phones OR=1.8, 95% CI=1.1-2.8, cordless phones OR=1.8, 95% CI=1.1-2.9. Use of a telephone on the opposite side of the brain was not associated with a significantly increased risk for brain tumours. Regarding anatomical area of the tumour and exposure to microwaves, the risk was increased for tumours located in the temporal area on the same side of the brain that was used during phone calls, significantly so for analogue cellular telephones OR=2.3, 95% CI=1.2-4.1. For acoustic neurinoma OR=4.4, 95% CI=2.1-9.2 was calculated among analogue cellular telephone users. When duration of use was analysed as a continuous variable in the total material, the risk increased per year for analogue phones with OR=1.04, 95% CI=1.01-1.08. For astrocytoma and ipsilateral use the trend was for analogue phones OR=1.10, 95% CI=1.02-1.19, digital phones OR=1.11, 95% CI=1.01-1.22, and cordless phones OR=1.09, 95% CI=1.01-1.19. There was a tendency of a shorter tumour induction period for ipsilateral exposure to microwaves than for contralateral, which may indicate a tumour promotor effect.

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Introduction

Recently we published results from a large new case-control study on the use of cellular and cordless telephones and the risk for brain tumours (1). We have now used the database for some further analyses.

During cellular phone calls radio frequency (RF) signals are transmitted and received in the range of 400-2,000 MHz. In Sweden the analogue (Nordic Mobile Telephone System; NMT) was introduced in 1981 operating at 450 MHz, often in a car with fixed external antenna, but from 1984 the first portable analogue phones were available. The analogue 900 MHz system operated in Sweden between 1986 and 2000. The digital system (Global System for Mobile Communication; GSM) started in 1991 and is the most common phone since the end of the 1990s in Sweden. Moreover desktop cordless telephones are used in Sweden since 1988. First the analogue system in the 800-900 MHz RF range was used, but now digital cordless telephones that operate at 1,900 MHz are available. In the following we report additional results from our case-control study.

Materials and methods

The geographical study area was the Uppsala-Örebro, Stockholm, Linköping and Göteborg medical regions of Sweden and encompassed patients diagnosed during January 1, 1997 to June 30, 2000. Only incident cases of both sexes with histopathology diagnosis of brain tumour were included aged 20-80 years at the time of diagnosis. They were reported in a consecutive way to us from the four regional cancer registries in these medical regions and were alive at the study start. The physicians were contacted for permission to include the patient in the study.

One control to each case was drawn from the population register, matched for sex and age and living in the same geographical area (region) of Sweden as the cases. Matching

on age was done in 5-year age groups and the control was selected at random from this age group. Controls were only selected for the finally included living cases. Each study subject received a unique ID-number that did not show if it was a case or control.

Assessment of exposure. The ethics committee at Örebro university hospital approved the investigation. Exposures were assessed by a questionnaire including also exposure to certain agents and lifetime work history. Thereby it was possible to assess socio-economic index (SEI) for each case and control. A trained nurse supplemented the answers over the phone using a written protocol. Telephone interviews of the whole questionnaire were performed for 12 cases and 13 controls that did not want to fill in the questionnaire but still agreed to participate.

For cellular telephones questions were asked on type of phone and years of use. Also the first part of the phone number (prefix) was asked for so as to check if it was an analogue (010) or digital (070) phone. Mean number of daily calls and minutes were asked for and after that cumulative use in hours for all years was calculated. Data were also collected on use in a car with fixed external antenna or a hands-free device with an earpiece outside a car, both taken as no exposure to microwaves. In one question the ear most frequently used during cellular phone calls was asked for, or if both sides were equally used. Regarding cordless phones the years of use, mean number of minutes per day and ear used were asked for in the same way.

Subjects that started their use of a mobile or cordless phone within one year prior to diagnosis were regarded as unexposed. Thereby the same year was used for the matched control as for the corresponding case. Cumulative exposure was calculated in hours from the first year of use up to the year before diagnosis. If the first year was apparently incorrect, i.e., before the respective phone use was on the market, this was corrected during the interviews and coding of exposure.

Histopathology was obtained from the cancer registry. Information on tumour localisation was also available for many cases in the Cancer Registry report. In order to get correct diagnosis and tumour localisation copies of reports of neuroradiology investigations were requested from the radiology units at different hospitals. This was done after informed consent from the cases. All coding of anatomical area for the tumour was done without knowing if the subject was exposed to cellular or cordless phones.

Statistical methods. Unconditional logistic regression analysis was used to calculate odds ratios (OR) and 95% confidence intervals (CI), (SAS Institute, Cary, NC). The material was divided into two groups, exposed and unexposed. The exposed cases and controls were further divided according to phone type, analogue, digital and cordless. Note that a person may have been using more than one type of telephone. The unexposed group consisted of cases and controls without exposure to cellular or cordless telephones. Adjustment was made for sex, age and SEI-code. In the calculations of laterality of exposure the corresponding control was assigned the same anatomical localisation as for the respective case.

Table I. Number of cases aged 20-80 years reported from regional oncology centers.

Total reported	2,561
Metastasis or other localization than brain based on oncology centre reports	133
Other localization or diagnosis than brain based on neuroradiology records	99
Other year than study period for diagnosis	58
Histopathology missing	4
Not resident in study area	14
Deceased	540
Refused by treating physician to be included	35
Unknown address	2
Not capable of participating for medical reasons as reported by case or relative	59
Total included in study	1,617

Results

In Table I inclusion of the cases is displayed. In total 2,561 cases were reported from the regional cancer registries. Finally 1,617 (63%) cases fulfilled the inclusion criteria. Of these 1,617 cases 1,429 (88%) and of the 1,617 controls 1,470 (91%) answered the questionnaire, in total 1,243 men and 1,656 women. The median age for both cases and controls was 54 years.

Table II gives the results for use of cellular phones. A significantly increased risk was found for analogue telephones with OR=1.3, 95% CI=1.04-1.6 increasing to OR=1.4, 95% CI=1.03-1.8 with >5 year latency (tumour induction) period and OR=1.6, 95% CI=1.1-2.5 with >10 year latency period. No significantly increased risk was found for digital telephones, although OR=1.4, 95% CI=0.9-2.1 was obtained for >5 year latency period in the highest exposed group. For cordless phones OR=1.4, 95% CI=1.1-1.8 was found in the group with >5 year latency period. The risk for cordless phones was highest in the >10 year latency period group with longest duration of use with OR=2.1, 95% CI=0.7-6.3.

Anatomical localisation of the tumour was available for 1,358 patients. For tumours in the temporal area analogue phones yielded OR=2.1, CI=1.3-3.3 (Table III) increasing to OR=3.1, 95% CI=1.2-7.7 in the group with >10 year latency period (19 exposed cases, 7 exposed controls). For digital telephones increased risk was found for >5 year latency period with OR=1.6, 95% CI=0.7-3.6 (17 exposed cases, 11 exposed controls). Since the study period ended June 30, 2000 and the digital system was introduced in 1991 no subjects were exposed with a latency period of >10 years (data not shown in Table III).

Also cordless telephones yielded an increased risk for tumours in the temporal area with latency >5 years with OR=1.8, 95% CI=1.1-3.1 (50 exposed cases, 28 exposed

Table II. Odds ratio (OR) and 95% confidence interval (CI) for use of cellular or cordless telephones.[a]

	>1 year latency			>5 year latency			>10 year latency		
	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI
Analogue									
450 MHz	102/98	1.2	0.9-1.6	84/64	1.5	1.04-2.1	41/27	1.8	1.1-3.0
900 MHz	178/146	1.4	1.1-1.9	103/86	1.4	1.01-1.9	28/20	1.6	0.9-2.9
All	247/218	1.3	1.04-1.6	160/135	1.4	1.03-1.8	61/44	1.6	1.1-2.5
≤85 h	134/115	1.3	0.995-1.7	69/51	1.5	1.02-2.2	12/13	1.03	0.5-2.3
>85 h	113/103	1.3	0.95-1.8	91/84	1.3	0.9-1.8	49/31	1.9	1.2-3.1
Digital	423/433	1.04	0.9-1.3	66/66	1.1	0.8-1.6	-	-	-
≤55 h	230/217	1.1	0.9-1.4	17/26	0.7	0.4-1.4	-	-	-
>55 h	193/216	0.9	0.7-1.2	49/40	1.4	0.9-2.1	-	-	-
Cordless	402/396	1.1	0.9-1.3	164/129	1.4	1.1-1.8	10/10	1.1	0.4-2.6
≤183 h	183/208	0.9	0.7-1.2	50/47	1.2	0.8-1.8	0/5	-	-
>183 h	219/188	1.2	0.99-1.6	114/82	1.5	1.1-2.1	10/5	2.1	0.7-6.3

[a]Number of exposed cases (Ca) and controls (Co) is given. Dose-effect calculations were made with median number of hours for controls as cut-off. Unconditional logistic regression adjusted for age, sex and SEI. Unexposed group consisted of cases and controls with no exposure to cellular or cordless phones, as in all calculations.

controls). Only 3 cases and 3 controls reported use of a cordless phone with >10 year latency time.

Results for different anatomical parts of the tumour and side of head (ear) used during a call are given in Table III. Regardless of type of phone increased risk was found for tumour in the brain hemisphere with ipsilateral exposure; analogue phones OR=1.7; 95% CI=1.2-2.3, digital phones OR=1.3, 95% CI=1.02-1.8, and cordless phones OR=1.2, 95% CI=0.9-1.6.

For the temporal area and analogue phones the risk increased for ipsilateral use of the phone to OR=2.3, CI=95% 1.2-4.1, Table III. The corresponding result for digital phones was OR=1.4, 95% CI=0.9-2.3 and for cordless phones OR=1.3, 95% CI=0.8-2.0. No significantly increased risks were found for other parts of the brain than the temporal.

In Table IV histopathology types of the different brain tumours is shown. Significantly increased risks were found for astrocytoma and ipsilateral use of all three phone types, analogue OR=1.8, 95% CI=1.1-3.2, digital OR=1.8, 95% CI=1.1-2.8 and cordless phones OR=1.8, 95% CI=1.1-2.9. The risk was highest for high-grade astrocytoma, a group including glioblastoma multiforme, whereas no significantly increased risks were found for low-grade astrocytoma. Regarding benign tumours a significantly increased risk was found for acoustic neurinoma for use of analogue phones, OR=4.4, 95% CI=2.1-9.2. The risk was significantly increased for both ipsilateral and contralateral use.

Multivariate analysis of the whole material, Table V, yielded similar results as in the corresponding univariate analysis although with somewhat lower effect estimates, c.f. Table II.

Table VI displays the trend in OR per year when duration of phone use is used as a continuous variable. This yielded for analogue phones OR=1.04, 95% CI=1.01-1.08. For tumours in the temporal area and ipsilateral use the risk increase was OR=1.19, 95% CI=1.07-1.33. For astrocytoma and ipsilateral use OR increased significantly for cellular and cordless phones. For acoustic neurinoma analogue phones yielded OR=1.29, 95% CI=1.11-1.50.

We also analysed tumour laterality and ear used during calls with an analogue phone for the 247 exposed cases. For 110 cases (44.5%) the tumour was right-sided, 101 (40.9%) left-sided, 31 (12.6%) not applicable or central tumour, and 5 (2.0%) no information. The ear used during calls was right for 117 cases (47.4%), left for 104 (42.1%) and varying equally left and right ear for 26 (10.5%). Thus there was good agreement between anatomical localisation of the tumour and ear used during calls.

When the analysis was done for groups of persons having used only one type of telephone (analogue, digital, or cordless) the number of cases and controls was low. For analogue phones OR=1.3, 95% CI=0.9-1.8 was obtained, whereas no increased risk was found for digital or cordless phones.

Discussion

Previously we performed a smaller case-control study on brain tumours where also a number of other exposures such as lifetime work history, ionising radiation and use of different agents were assessed. Increased risks were found for tumours in temporal and occipital brain area in patients

Table III. Numbers of exposed case (Ca) or control (Co), odds ratio (OR) and 95% confidence interval (CI) for exposure to cellular or cordless telephones for different tumour localisations in relation to ear used during a phone call (side of head: ipsilateral, same side; contralateral, opposite side; ipsi-/contralateral, used both sides equal amount of time).[a]

Localisation/type of telephone	All Ca/Co OR (CI)	Ipsilateral Ca/Co OR (CI)	Contralateral Ca/Co OR (CI)	Ipsi-/contralateral Ca/Co OR (CI)
Brain hemisphere (All)				
Analogue phone	247/218	121/73	68/72	22/21
	1.3	1.7	1.0	1.1
	1.04-1.6	1.2-2.3	0.7-1.4	0.6-2.0
Digital phone	423/433	182/132	138/142	44/43
	1.0	1.3	0.9	1.0
	0.9-1.3	1.02-1.8	0.7-1.2	0.6-1.6
Cordless phone	402/396	173/135	127/136	39/34
	1.1	1.2	0.9	1.1
	0.9-1.3	0.9-1.6	0.7-1.2	0.7-1.8
Temporal area				
Analogue phone	84/45	41/20	30/21	12/4
	2.1	2.3	1.6	3.1
	1.3-3.3	1.2-4.1	0.8-2.9	0.96-10
Digital phone	113/104	50/37	50/48	13/19
	1.1	1.4	1.1	0.7
	0.8-1.6	0.9-2.3	0.7-1.7	0.3-1.5
Cordless phone	111/100	58/44	38/43	14/12
	1.1	1.3	0.9	1.2
	0.8-1.5	0.8-2.0	0.5-1.5	0.5-2.6
Other areas than temporal				
Analogue phone	157/143	80/53	38/51	9/17
	1.1	1.4	0.7	0.5
	0.8-1.4	0.96-2.1	0.5-1.2	0.2-1.2
Digital phone	297/258	132/94	87/93	31/24
	1.1	1.3	0.9	1.3
	0.8-1.3	0.96-1.8	0.6-1.2	0.7-2.2
Cordless phone	276/244	114/90	89/93	25/22
	1.1	1.2	0.9	1.1
	0.9-1.4	0.9-1.7	0.6-1.3	0.6-2.0

[a]Latency period >1 year. Note, tumour site missing for a number of cases.

with ipsilateral use of a cellular phone, mainly analogue phones, i.e., in the highest exposed parts of the brain (2,3). In a multivariate analysis adjusting for other risk factors, i.e., medical diagnostic X-ray investigation of the head and neck and laboratory work, the risk was significantly increased with OR=2.62, 95% CI=1.02-6.71.

Some other studies have also investigated use of mobile phones and the risk for brain tumours. In a study from Finland (4) a significantly increased risk was found for glioma among analogue cellular phone users, OR=2.1, 95% CI=1.3-3.4. The risk increased significantly with duration of use as a continuous variable, OR=1.2 per year, 95% CI=1.1-1.5. In a study from USA increased risk was found for anaplastic astrocytoma OR=1.8, 95% CI=0.7-5.1 (5). The risk for neuroepithelioma was increased in another USA study and ipsilateral use was more common for tumours in the temporal

Table IV. Numbers of exposed case (Ca) or control (Co), odds ratio (OR) and 95% confidence interval (CI) for exposure to cellular or cordless telephones for different tumour types in relation to ear used during a phone call (side of head: ipsilateral, same side; contralateral, opposite side; ipsi-/contralateral, used both sides equal amount of time).[a]

Localisation/type of telephone	All Ca/Co OR (CI)	Ipsilateral Ca/Co OR (CI)	Contralateral Ca/Co OR (CI)	Ipsi-/contralateral Ca/Co OR (CI)
Malignant				
Analogue phone	110/96	64/40	30/37	11/13
	1.2	1.7	0.8	0.9
	0.8-1.7	1.1-2.7	0.5-1.4	0.4-2.1
Digital phone	204/167	98/66	60/58	26/21
	1.2	1.5	1.0	1.3
	0.9-1.6	1.1-2.3	0.7-1.6	0.7-2.4
Cordless phone	179/143	86/61	62/51	18/16
	1.2	1.4	1.2	1.1
	0.9-1.7	0.97-2.1	0.8-1.9	0.6-2.3
Astrocytoma				
Analogue phone	77/62	47/30	20/20	9/9
	1.4	1.8	1.1	1.2
	0.9-2.2	1.1-3.2	0.6-2.3	0.5-3.3
Digital phone	147/122	77/51	41/42	18/15
	1.4	1.8	1.1	1.5
	0.96-1.9	1.1-2.8	0.6-1.8	0.7-3.3
Cordless phone	128/95	69/43	40/33	12/9
	1.5	1.8	1.3	1.6
	1.02-2.1	1.1-2.9	0.8-2.3	0.6-3.9
Astrocytoma high grade				
Analogue phone	63/52	40/24	17/17	6/8
	1.4	2.0	1.1	1.0
	0.8-2.2	1.1-3.6	0.5-2.4	0.3-3.0
Digital phone	115/89	62/40	31/29	15/11
	1.4	1.9	1.1	1.8
	0.96-2.1	1.1-3.1	0.6-2.0	0.8-4.4
Cordless phone	99/76	53/35	32/26	9/8
	1.4	1.7	1.3	1.3
	0.9-2.1	1.01-2.9	0.7-2.5	0.5-3.7
Astrocytoma low grade				
Analogue phone	14/10	7/6	3/3	3/1
	1.4	1.1	1.2	2.4
	0.5-3.9	0.3-3.9	0.2-7.6	0.2-27
Digital phone	32/33	15/11	10/13	3/4
	1.2	1.7	1.2	0.5
	0.6-2.6	0.6-5.0	0.4-3.9	0.1-3.3
Cordless phone	29/19	16/8	8/7	3/1
	2.1	2.3	1.9	3.1
	0.9-5.2	0.7-7.1	0.5-7.3	0.2-52

Table IV. Continued.

Localisation/type of telephone	All Ca/Co OR (CI)	Ipsilateral Ca/Co OR (CI)	Contralateral Ca/Co OR (CI)	Ipsi-/contralateral Ca/Co OR (CI)
Benign				
Analogue phone	137/97	57/33	38/35	11/8
	1.4	1.6	1.1	1.4
	1.01-1.9	0.98-2.6	0.6-1.8	0.5-3.5
Digital phone	219/213	84/66	78/84	18/22
	0.9	1.2	0.9	0.8
	0.7-1.2	0.8-1.7	0.6-1.2	0.4-1.5
Cordless phone	223/218	87/74	65/85	21/18
	0.9	1.0	0.7	1.1
	0.7-1.2	0.7-1.5	0.5-1.1	0.6-2.1
Meningioma				
Analogue phone	78/70	32/26	19/27	6/7
	1.0	1.1	0.6	0.8
	0.7-1.5	0.6-1.9	0.3-1.2	0.3-2.6
Digital phone	144/151	60/48	50/61	11/12
	0.8	1.1	0.7	0.8
	0.6-1.1	0.7-1.7	0.5-1.1	0.3-1.9
Cordless phone	154/154	58/51	46/61	13/13
	0.8	1.0	0.7	0.9
	0.6-1.1	0.6-1.5	0.4-1.04	0.4-1.9
Acoustic neurinoma				
Analogue phone	47/15	23/7	18/7	5/1
	4.4	4.2	3.7	5.6
	2.1-9.2	1.6-11	1.4-9.8	0.6-52
Digital phone	51/44	21/16	23/19	7/9
	1.4	1.5	1.6	0.9
	0.8-2.4	0.7-3.2	0.8-3.4	0.3-2.7
Cordless phone	50/44	27/21	15/19	8/3
	1.4	1.3	1.1	3.2
	0.8-2.3	0.7-2.7	0.5-2.3	0.8-13

[a]Latency period >1 year. Note, tumour site missing for a number of cases.

Table V. Multivariate analysis of exposure.[a]

	>1 year latency			>5 year latency			>10 year latency		
	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI
Analogue	247/218	1.2	0.99-1.5	160/135	1.2	0.96-1.6	61/44	1.5	1.02-2.3
Digital	423/433	1.0	0.8-1.2	66/66	1.0	0.7-1.4	-	-	-
Cordless	402/396	1.0	0.9-1.2	164/129	1.3	1.01-1.7	10/10	0.9	0.4-2.3

[a]OR, odds ratio; CI, 95% confidence interval and number of exposed cases (Ca) and controls (Co) are given.

Table VI. Trend in odds ratio (OR) and 95% confidence interval (CI) per year when duration is used as a continuous variable.

	All OR (CI)	Temporal area, ipsilateral OR (CI)	Astrocytoma, ipsilateral OR (CI)	High-grade astrocytoma, ipsilateral OR (CI)	Acoustic neurinoma, All OR (CI)	Acoustic neurinoma, ipsilateral OR (CI)
Analogue	1.04	1.19	1.10	1.11	1.29	1.38
	1.01-1.08	1.07-1.33	1.02-1.19	1.02-1.21	1.11-1.50	1.10-1.74
Digital	1.01	1.10	1.11	1.11	1.05	1.13
	0.97-1.05	0.97-1.24	1.01-1.22	0.998-1.24	0.92-1.21	0.94-1.37
Cordless	1.03	1.08	1.09	1.10	1.10	1.10
	0.996-1.06	1.000-1.17[a]	1.01-1.19	0.999-1.20	1.003-1.21	0.98-1.23

[a]p=0.0488.

area (6). The risk for neuroepithelioma was significantly increased as reported in one of the two publications from this study, OR=2.6, 95% CI=1.2-5.4 (7). A Danish register study did not find an increased risk, but average duration of subscription was very short, only 3.5 years for analogue phones and 1.9 years for digital phones (8). As we have discussed elsewhere one major shortcoming of these studies is the short tumour induction period (9-11). A significantly increased risk was found for uveal melanoma in one study (12).

Both experimental and human data show that RF exposure may have biological effects in target cells or tissue. Experimental studies have shown the potential for neoplastic change of cells (13), accelerated development of spontaneous and benzopyrene-induced skin cancer (14), and promotion of brain tumours (15). Increased number of DNA breaks in rats has been reported after exposure to 2,450 MHz RF radiation (16,17), although not confirmed in other studies (18-20). Induction of micronuclei in human lymphocytes exposed *in vitro* to microwave radiation has been shown (21-23). Plasma protein extravasation in rat brain and dura mater was recently presented (24). The effect was seen at both 0.5 and 2 W/kg. Chronic activation of heat shock protein (hsp) has been suggested to provide a possibility of a direct association between mobile phone use and cancer (25). Weak microwave exposure with SAR-values in the range mW/kg has been shown to induce increase of hsp in cell cultures (26,27). An increase of hsp-27 in a human endothelial cell line exposed for 1 h to 900 MHz GSM signal at 2 W/kg was reported (28). The effect was not detectable in the cells 2 and 5 h after the exposure, which agrees with the known behaviour of hsp-27 to other stressors.

An increased incidence of lymphoma in transgenic mice exposed to pulsed 900 MHz RF radiation has been reported (29). This was not replicated in a later study (30). However, the incidence of neurological tumour in transgenic mice was doubled in the exposed group compared with controls. This was based on low numbers and no dose-response was seen. The total tumour incidence was somewhat higher in the exposed group, mostly in the highest exposure group. However, in the controls a very high incidence of tumours were reported, 74%, and in the report of Repacholi *et al* (29) the incidence was of the order of 20%.

Our population based case-control study included patients with a histopathology diagnosis of brain tumour. Of the initially reported cases from the cancer registries only 61% fulfilled the inclusion criteria. This shows that adequate inclusion of cases with brain tumour is not obtained using cancer registry data without checking diagnosis (9). In the analyses adjustment was made for age, sex and SEI-code. As unexposed all subjects without any exposure to RF microwaves were included. This differed from our previous analysis, since the unexposed group may have included subjects with other phone types than the analysed one (1).

The main result in this study was an increased risk for brain tumours associated with the use of analogue cellular phones. The risk increased further with tumour induction period. For cordless phones a significantly increased risk was found if tumour induction period of >5 years was allowed.

Considering ipsilateral use of a phone the risk was higher than overall for all studied phone types, c.f., Table IV, significantly so for analogue and digital phones. For astrocytoma significantly increased risk was found in the ipsilateral group of use for analogue, digital and cordless phones. The risk increased further if high-grade astrocytoma (including glioblastoma multiforme) was studied. This seems to be of biological relevance since contralateral use did not significantly increase the risk. Thus, there seems to be a biological dose-response effect in these results.

For benign tumours the increased risk was mainly found for acoustic neurinoma, although a somewhat increased risk was found for meningioma in the temporal area, OR=2.5, 95% CI=0.7-8.7, n=11 cases and 4 controls (data not shown). For acoustic neurinoma increased risk was also found for contralateral exposure. One explanation is that impaired hearing may be an early sign of the tumour causing shifting of the ear during phone calls. This is a tumour type occurring in a high exposure area.

Dose-effect calculations were made using the median number of hours for exposure among the controls. An effect was seen for analogue cellular phones and cordless phones if a latency period of >10 years was used. For digital and cordless phones a tendency of an effect was found in the group with >5 year latency period. However, microwave exposure from the different phones is not known as well as the absorbed dose in the brain.

The digital cellular phones and cordless phones have not been used for as long period as the analogue ones, which could be of importance for carcinogenesis. In our study the median time of use (tumour induction period) was 7 years for analogue phones, 3 years for digital phones and 5 years for cordless phones. Certainly it is of interest that in general the latency period was shorter for ipsilateral exposure than for contralateral. Thus, median latency period for analogue phones was for malignant brain tumours for ipsilateral exposure to microwaves 7 years, but for contralateral 9 years, digital phones 3 vs. 4 years and cordless phones 5 years in both groups. The corresponding latency periods for astrocytoma were for analogue phones 7 vs. 9.5 years, for digital phones 3 vs. 4 years and for cordless phones 5 vs. 5.5 years. For high-grade astrocytoma ipsilateral vs. contralateral latency period was for analogue phones 7 vs. 8 years, digital phones 3 vs. 4 years, and cordless phones 5 vs. 6 years. The shortened latency period may be consistent with a tumour promoting effect from microwaves (31). This pattern was not seen for the matched controls. For acoustic neurinoma no effect of laterality was seen, but as has been discussed before, an increased risk was also found for contralateral exposure and the cases tended to shift ear during the progress of the disease.

In a case-control study recall bias can always influence the results. Also observational bias can be introduced during the interviews. The questionnaires were blinded as to if it was a case or a control. All coding of data was done without knowing the subject identity. Furthermore, tumour localisation and type of tumour were assessed without knowledge of exposure data. Recall and observational bias were elucidated and our conclusion is that such bias could not explain the results (1). The consistently highest risk in the anatomical area with highest exposure strengthens that conclusion.

In summary our present study showed an increased risk for brain tumours among users of analogue cellular telephones. For digital cellular phones no significantly increased risk was found overall, but ipsilateral exposure increased the risk significantly. Cordless phones yielded significantly increased risk overall with a >5-year latency period.

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References

1. Hardell L, Hallquist A, Hansson Mild K, Carlberg M, Påhlson A and Lilja A: Cellular and cordless telephones and the risk for brain tumours. Eur J Cancer Prev 11: 377-386, 2002.
2. Hardell L, Näsman Å, Påhlson A, Hallquist A and Hansson Mild K: Use of cellular telephones and the risk for brain tumors: a case-control study. Int J Oncol 15: 113-116, 1999.
3. Hardell L, Hansson Mild K, Påhlson A and Hallquist A: Ionzing radiation, cellular telephones and the risk for brain tumours. Eur J Cancer Prev 10: 523-529, 2001.
4. Auvinen A, Hietanen M, Luukkonen R and Koskela RS: Brain tumours and salivary gland cancers among cellular telephone users. Epidemiology 13: 356-359, 2002.
5. Inskip PD, Tarone RE, Hatch EE, *et al*: Cellular-telephone use and brain tumors. N Engl J Med 344: 79-86, 2001.
6. Muscat JE, Malkin MG, Thompson S, *et al*: Handheld cellular telephone use and risk of brain cancer. JAMA 284: 3001-3007, 2000.
7. Muscat JE: Wireless phone use and the risk of primary brain cancer. In: Wireless Phone and Health II, State of the Science. Carlo GL and Thibodeau PM (eds). Kluwer Academic Publishers Boston, Dordrecht, London, pp207-213, 2001.
8. Johansen C, Boice J, McLaughlin JK and Olsen JH: Cellular telephones and cancer - a nationwide cohort study in Denmark. J Natl Cancer Inst 93: 203-207, 2001.
9. Hardell L, Näsman Å, Påhlson A, Hallquist A and Hansson Mild K: Use of cellular phones and the risk for brain tumors: a case-control study (correspondence). Int J Oncol 15: 1045-1047, 1999.
10. Hardell L and Hansson Mild K: Handheld cellular telephones and brain cancer risk. JAMA 285: 1838, 2001.
11. Hardell L and Hansson Mild K: Re: Cellular telephones and cancer - a nationwide cohort study in Denmark. J Natl Cancer Inst 93: 952, 2001.
12. Stang A, Anastassiou G, Ahrens W, Bromen K, Bornfeld N and Jöckel KH: The possible role of radiofrequency radiation in the development of uveal melanoma. Epidemiology 12: 7-12, 2001.
13. Balcer-Kubiczek E and Harrison GH: Neoplastic transformation of C3H/10T½ cells following exposure to 120-Hz modulated 2.45-GHz microwaves and phorbol ester tumour promotion. Radiat Res 126: 65-72, 1991.
14. Szmigielski S, Szudzinski A, Pietraszek A, Bielec M, Janiak M and Wrembel JK: Accelerated development of spontaneous and benzopyrene-induced skin cancer in mice exposed to 2450 MHz microwave exposure. Biolectromagnetics 3: 179-191, 1982.
15. Zook BC and Simmens SJ: The effects of 860 MHz radiofrequency radiation on the induction of promotion of brain tumours and other neoplasms in rats. Radiat Res 155: 572-583, 2001.
16. Lai H and Singh NP: Acute low-intensity microwave exposure increases DNA single-strand breaks in rat brain cells. Bioelectromagnetics 16: 207-210, 1995.
17. Lai H and Singh NP: Single- and double-strand DNA breaks in rat brain after acute exposure to radiofrequency electromagnetic radiation. Int J Radiat Biol 69: 513-526, 1996.
18. Malyapa RS, Ahren EW, Straube WL, Moros EG, Pickard WF and Roti Roti JL: Measurement of DNA damage after exposure to 2450 MHz electromagnetic radiation. Radiat Res 148: 608-617, 1997.
19. Malyapa RS, Ahren EW, Straube WL, Moros EG, Pickard WF and Roti Roti JL: Measurement of DNA damage after exposure to electromagnetic radiation in the cellular phone communication frequency band (835.62 and 847.74 MHz). Radiat Res 148: 618-627, 1997.
20. Malyapa RS, Ahren EW, Bi C, *et al*: DNA damage in rat brain cells after *in vivo* exposure to 2450 MHz electromagnetic radiation and various methods of euthanasia. Radiat Res 149: 637-645, 1998.
21. Garaj-Vrhovac A, Fucic D and Horvat D: The correlation between the frequency of micronuclei and specific chromosome aberrations in human lymphocytes exposed to microwave radiation *in vitro*. Mutat Res 281: 181-186, 1992.
22. Zotti-Martelli L, Peccatori M, Scarpato R and Migliore L: Induction of micronuclei in human lymphocytes exposed *in vitro* to microwave radiation. Mutat Res 472: 51-58, 2000.

23. Tice RR, Hook GG, Donner M, McRee D and Guy AW: Genotoxicity of radiofrequency signals. I. Investigation of DNA damage and micronuclei induction in cultured human blood cells. Bioelectromagnetics 23: 113-126, 2002.
24. Töre F, Duloc PE, Haro E, Veyret B and Aubineau P: Two-hour exposure to 2-W/kg, 900 MHz GSM microwaves induces plasma protein extravasation in rat brain and dura mater. EBEA Proceedings, 6-8 September, Helsinki, Finland, pp43-45, 2001.
25. French PW, Penny R, Laurence JA and McKenzie DR: Mobile phones, heat shock proteins and cancer. Differentiation 67: 93-97, 2000.
26. De Pomerai D, Daniells C, David H, *et al:* Non-thermal heat-shock response to microwaves. Nature 405: 417-418, 2000.
27. Kwee S, Raskmark P and Velizarov S: Changes in cellular proteins due to environmental non-ionizing radiation. I. Heat shock proteins. Electro- and Magnetobiology 20: 141-152, 2001.
28. Leszczynski D, Joenväärä S, Reivinen J and Kuokka R: Non-thermal activation of the hsp27/p38MAPK stress pathway by mobile phone radiation in human endothelial cells: molecular mechanism for cancer-and blood-brain barrier-related effects. Differentiation 70: 120-129, 2002.
29. Repacholi MH, Basten A, Gebski V, Noonan D, Finnie J and Harris AW: Lymphomas in E mu-Pim1 transgenic mice exposed to pulsed 900 MHz electromagnetic fields. Radiat Res 147: 631-640, 1997.
30. Utteridge TD, Gebski V, Finnie JW, Vernon-Roberts B and Kuchel TR: Long-term exposure of Eμ-*Pim 1* transgenic mice to 898.4 MHz microwaves does not increase lymphoma incidence. Radiat Res 158: 357-364, 2002.
31. Pitot HC and Loeb DD: The natural history of neoplastic development: progression. In: Fundamentals of Oncology. Pitot HC and Loeb DD (eds). Marcel Dekker, Inc. New York, Basel, pp335-371, 2002.