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RESEARCH ARTICLE

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Case-control study on occupational exposure to extremely low-frequency electromagnetic fields and glioma risk

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Background: Exposure to extremely low-frequency electromagnetic fields (ELF-EMF) was in 2002 classified as a possible human carcinogen, Group 2B, by the International Agency for Research on Cancer at WHO.

Methods: Life time occupations were assessed in case-control studies during 1997-2003 and 2007-2009. An ELF-EMF Job-Exposure Matrix was used for associating occupations with ELF exposure (μT). Cumulative exposure (μT-years), average exposure (μT), and maximum exposed job (μT) were calculated.

Results: Cumulative exposure gave for astrocytoma grade IV (glioblastoma multiforme) in the time window 1-14 years odds ratio (OR) = 1.9, 95% confidence interval (CI) = 1.4-2.6, p linear trend <0.001, and in the time window 15+ years OR = 0.9, 95%CI = 0.6-1.3, p linear trend = 0.44 in the highest exposure categories 2.75+ and 6.59+ μT years, respectively.

Conclusion: An increased risk in late stage (promotion/progression) of astrocytoma grade IV for occupational ELF-EMF exposure was found.

KEYWORDS

astrocytoma, electromagnetic fields, ELF-EMF, glioma, occupational exposure, RF-EMF, risk factors, wireless phones

1 | INTRODUCTION

Few risk factors are established for brain tumors except ionizing radiation.[1] In 2002 International Agency for Research on Cancer (IARC) classified extremely low-frequency electromagnetic fields (ELF-EMF) as "possibly carcinogenic to humans," Group 2B based on an increased risk for childhood leukemia.[2] More recently a pooled analysis showed about twofold increased risk for childhood leukemia at exposure level above 0.3-0.4 μT,[3] further supporting the association. Some other malignant diseases have been associated with ELF-EMF exposure such as breast cancer,[4,5] and malignant lymphoma and leukemia in adults.[6] In a review of published literature up to July 1, 1994 an increased risk for childhood leukemia was found for the existence of, or distance to power lines in the vicinity of residence.[7] An increased risk of chronic lymphocytic leukemia (CLL) was found for occupational ELF-EMF exposure. Furthermore the review showed an increased risk for brain tumor in the electronic/electric industry.[7]

During more recent years additional studies have been performed. In a small study from Sweden on 84 glioma cases, 20 meningioma cases, and 155 controls an elevated risk for glioma was seen in exposed occupations with an average mean value of >0.4 μT.[8] In a Canadian case-control study on brain tumors highest occupational average ELF-EMF exposure >0.6 μT compared to exposure < 0.3 μT gave for astrocytoma grade IV (glioblastoma multiforme) odds ratio (OR) = 5.36, 95% confidence interval (CI) = 1.16-24.78, adjusted for exposure to ionizing radiation and vinyl chloride.[9] Higher OR was obtained for the last held job. The authors concluded that exposure to ELF-EMF may increase the risk of brain tumors and influence the risk as promoters. The risk for brain tumors was assessed for occupational exposure to ELF-EMF in a case-control study from USA.[10] Exposure was assessed for 489 glioma cases, 197 meningioma cases, and 799 controls. No statistically significant increased risk was obtained for these tumor types including glioblastoma multiforme. Results for different time windows (time before tumor diagnosis) were not given.

In a French case-control study on occupational ELF-EMF exposure a somewhat increased risk was seen for glioma, OR = 1.20, 95% CI = 0.66-2.17, and for meningioma OR = 3.02, 95%CI = 1.10-8.25.[11] This was a small study including only 105 glioma cases, 67 meningioma cases, and 442 controls. No statistically significant association between occupational ELF-EMF exposure and brain tumors was found in a cohort

study from the Netherlands.[12] The results were based on 233 cases. In a study on U.K. electricity supply workers no evidence was found for increased glioma risk for distant or recent estimated ELF-EMF exposure based on job title.[13] No results were given for subtypes of glioma.

A meta-analysis on the association between EMF-ELF and the susceptibility to cancer was based on 42 studies.[14] A weak association between ELF-EMF exposure and all cancer was seen when all the eligible studies were pooled; OR = 1.08, 95%CI = 1.01-1.15, regardless of the exposure models. The results for brain tumors was based on 12 studies yielding OR = 1.10, 95%CI = 0.96-1.26.

Thus the results on ELF-EMF exposure and glioma risk are mostly inconsistent and hampered by small studies, different methods, and lack of results on subtypes of glioma including exposure in specific time windows.

In laboratory studies ELF-EMF was mutagenic, but also potentiated the mutagenicity of ionizing radiation using microsatellite analysis for DNA damage in human glioma cells.[15] A possible involvement of O6-methylguanine DNA adducts in the development of glioma was discussed by Ohgaki.[16]

Animal studies on ELF-EMF exposure alone have been inconclusive. Long-term ELF-EMF exposure was a risk factor for chronic myeloid leukemia in female mice.[17] Rat studies showed that exposure to ELF-EMF enhanced the carcinogenic effect of γ radiation[18] and that life-span exposure to ELF-EMF and formaldehyde induced statistically significant carcinogenic effect.[19]

During the last couple of decades an increasing number of studies have associated brain tumors with use of wireless phones.[20–23] During use they emit radiofrequency electromagnetic fields (RF-EMF). In May 2011 IARC evaluated the carcinogenic potential from RF-EMF. The expert group classified RF-EMF in the frequency range 30 kHz-300 GHz as "possibly carcinogenic to humans," Group 2B.[24,25]

In the international Interphone study glioma was associated with occupational ELF-EMF exposure in recent time windows whereas no increased risk was found for meningioma.[26] The authors concluded that such exposure may play a role in late stage carcinogenesis of glioma.

Similarly, as in Interphone, our results on use of wireless phones and brain tumor risk were based on case-control studies. We used a structured questionnaire but here with certain differences regarding the Interphone study, such as that we used postal questionnaires sent to cases and controls supplemented over the phone instead of personal interviews, even bedside interviews of cases as performed in Interphone. Furthermore we assessed in addition to mobile phones also use of cordless phones (DECT); the latter use not assessed by Interphone. Detailed comparison of the studies may be found elsewhere.[27]

ELF-EMFs are generated by alternating electric current. Most common exposure to ELF-EMFs is from appliances operating on the mains power. The frequency of the mains power is 50 Hz in the most of the world, but also at 60 Hz used in Americas and in some parts of Asia. The exposure to the ELF magnetic fields depends on the current—the more electrical power is used the higher the magnetic field. Therefore, next to the electrical appliances, high exposure to the ELF-EMFs may also occur where electrical power is generated and distributed, example power lines, transformers etc. Another typical high ELF magnetic field exposure source is the electrical motors and other devices incorporating coils. By increasing turns of electrically conductive element that is wire by which the electrical current flows, also the magnetic field is multiplied. Therefore, occupations involving powerful electrical motors in the working area, for example electrical transport, are usually accompanied by strong ELF-EMFs. As powerful electrical motors and other strong magnetic fields generating devices could also be found in many industrial settings, the workers' exposure level in such cases depend on the distance to the magnetic field source. For example, people working with hand-held electrical power tools are having a strong magnetic fields exposure, whereas others further away from even stronger sources, may be exposed at insignificant levels. The design of the instrumentation and the working areas in regard to where the people are located in respect to the appliances, plays a crucial role in determining the resultant exposure level.

Our case-control studies had detailed occupational history including job titles, branch of different occupations, and years for the specific jobs. Thus it was possible to calculate ELF-EMF job exposure for cases and controls using a job-exposure matrix (JEM).

2 | MATERIALS AND METHODS

Similar methods were used in all of our studies. Detailed information on materials and methods has been published previously.[28,29] In short, six administrative regions with oncology centres covering Sweden registered new cancer cases. For 1997-2003, cases and controls covered central Sweden,[29] whereas the 2007-2009 study included the whole country.[28] The oncology centers reported new cases with histopathologically verified brain tumor, either benign or malignant, to us during these periods, although the actual reporting interval varied for center to center. Both men and women were included aged 20-80 years (1997-2003) and 18-75 years (2007-2009) at the time of diagnosis. Only living cases were included after asking the responsible physician for permission before inclusion in the study. Tumor localisation in the brain was based on reports to the cancer registries and medical records, which were obtained after informed consent from the patients.

Controls were ascertained from the Swedish Population Registry. The registry is continuously updated, so that each person could be traced by a unique ID number. It also records the address to each person. For each case, one control subject of the same gender and in the same 5-year group was drawn at random from the Population Registry. They were assigned the same year for cut-off of all exposure as the year of diagnosis of the respective case. All these controls were used in the analysis of risk of glioma.

Exposure was assessed using a mailed questionnaire sent to each person.

The questionnaire contained a number of questions relating to the overall working history, exposure to different chemicals, and other agents, smoking habits, X-ray investigations of the head and neck, and heredity traits for cancer. Regarding use of a mobile phone and cordless phone, time period, average daily use (min per day), use of

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hands free device, and external antenna in a car were asked for. The ear mostly used during phone calls, or equally both, was also noted. Use of the wireless phone was referred to as ipsilateral (≥50% of the time) or contralateral (<50% of the time) in relation to tumor side. The same method was also applied for the control group; the subjects were assigned the same "tumor" side as the respective case to the matched control.

When questionnaire answers were unclear, they were resolved by phone using trained interviewers. Thereby, a written protocol was used for clarification of each question. The interviewer supplemented the whole questionnaire during the phone call. Each questionnaire had received a unique ID-number that did not disclose whether it was a case or a control; that is the interviewer was unaware of the status during further data processing. All information was coded and entered into a database. Case or control status was not disclosed until statistical analyses were undertaken.

In this study we included only glioma cases. As comparison group all controls were used. This was possible since we adjusted for potential confounding factors such as year of diagnosis (each control had the same year of "diagnosis" as the respective case), age at diagnosis, gender, and socioeconomic index (SEI).

The questions regarding occupations included job title, branch, and first and last year for each job in the work history of each participant. The INTEROCC ELF Magnetic Field Job-Exposure Matrix (ELFJEM) was used for associating occupations with ELF exposure (μT).[26] The JEM used International Standard Classification of Occupations 1988 (ISCO88) four digit codes for most jobs included; ISCO68 five digit codes were used for more specific electrical jobs. The online version of the JEM is available at: http://www.crealradiation.com/index.php/en/databases?id=55. Job codes were coded using the Nordisk Yrkesklassificering (NYK 85; five digit codes) system and their validity was checked before they were translated to the International Standard Classification of Occupations 1988 (ISCO88; four digit codes) using a coding key provided by Dr Erik Bihagen at Stockholm University.[30] For translation to the 1968 ISCO version for specific jobs (ISCO68; five digit codes) we compared with the NYK 85 system manually and selected the most proper codes to be translated. Job exposure the year before diagnosis was excluded. No job was reported for 34 cases and 45 controls, so they were excluded from the analyses.

2.1 | Statistical methods

StataSE 12.1 (Stata/SE 12.1 for Windows; StataCorp., College Station TX) was used for the analyses. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression including the whole control sample (ie, matched to both malignant and benign cases) to increase the power.

Cumulative exposure (μT-years), average exposure (μT), and maximum exposed job (μT) were calculated for the included cases and controls for lifetime work history and in time windows. Two sets of time windows were analyzed, 1-4, 5-9, 10-14, 15-19, and 20+ years before diagnosis and 1-14 and 15+ years before diagnosis. Cut points at the 25th, 50th, 75th, and 90th percentile for controls were used to categorize the exposure variables with the lowest category (<25th percentile) as reference group (OR = 1.0). Tests for linear trends were performed using the Wald test with the median of each category included as an ordinal variable in the analyses. Interaction with use of wireless phones (mobile and/or cordless phone) was investigated on the multiplicative scale counting exposure ≥25th percentile as exposed.

Restricted cubic splines were used to display the relationship between cumulative exposure to ELF-EMF (μT-years) in time windows and glioma. Four knots were used at the 5th, 35th, 65th, and 95th percentiles, as suggested by Harrell.[31]

In all analyses adjustment was made for the matching variables gender, age (as a continuous variable) and year of diagnosis and also for socioeconomic index (SEI) divided into three categories (blue-collar worker, white-collar worker, self-employed).

3 | RESULTS

The results were based on analyses of 1346 glioma cases (86% of included; 11.4% did not answer the questionnaire and 2.4% were excluded since they had no job codes registered) and 3485 controls (86% of included; 12.6% did not answer the questionnaire and 1.1% were excluded since they had no job codes registered). The mean age

TABLE 1 Odds ratio (OR) and 95% confidence interval (CI) for all glioma (*n* = 1346) for occupational exposure to ELF-EMF

	Glioma (*n* = 1346)		
Exposure metric	**Ca/Co**	**OR**	**95%CI**
Cumulative exposure (μT-years)			
<2.33	368/870	1.0	-
2.33 to <3.79	306/872	0.9	0.7-1.1
3.79 to < 5.55	287/869	0.9	0.7-1.1
5.55 to <8.52	219/525	0.9	0.7-1.2
8.52+	166/349	1.0	0.8-1.4
p, linear trend			0.45
Average exposure (μT)			
<0.11	285/830	1.0	-
0.11 to <0.13	330/912	1.1	0.9-1.3
0.13 to < 0.18	316/871	1.0	0.8-1.2
0.18 to <0.27	234/523	1.1	0.9-1.4
0.27+	181/349	1.3	1.003-1.6
p, linear trend			0.04
Maximum exposed job (μT)			
<0.13	284/823	1.0	-
0.13 to <0.16	291/812	1.1	0.9-1.3
0.16 to <0.24	379/968	1.0	0.8-1.2
0.24 to <0.60	234/532	1.1	0.9-1.3
0.60+	158/350	1.1	0.9-1.5
p, linear trend			0.29

Cut points at 25th, 50th, 75th, and 90th percentile for controls.
Unconditional logistic regression, adjusted for age at diagnosis, gender, socio-economic index (SEI), and year of diagnosis. Exposure the year before diagnosis was excluded ("1-year lag").

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of the cases was 53 years (median 55, range 19-80) and of the controls 54 years (median 56, range 20-80). Of the glioma cases 803 were men, versus 1472 male controls. The gender difference was explained by the fact that also controls to meningioma cases were used; meningioma is about twice as common in females than in males.

The mean number of jobs for cases were 2.6 (median = 2, min = 1, max = 10) and for controls 2.7 (median = 2, min = 1, max = 12). More than 80% of both cases and controls worked all years in each of the four time windows up to 19 years. Since the last time window, 20+ years, did not have a closed interval such a calculation was not possible. Cumulative lifetime exposure to ELF-EMF varied between 0.05 and 556 μT-years for glioma cases and 0.04 to 468 μT-years for the controls. The main occupations among those with high ELF exposure (≥8.52 μT-years) were machine-tool operators (28 cases, 56 controls) and welders and flame cutters (26 cases, 57 controls). These occupations were also the main ones in all time windows. In Table 1 results for cumulative exposure in μT-years, average exposure in μT, and maximum exposed job (μT) are shown. In the highest average exposure category >0.27 μT an increased risk for glioma of borderline significance was found; OR = 1.3, 95%CI = 1.003-1.6, p linear trend = 0.04.

Table 2 displays the same results as in Table 1 for different types of glioma. For astrocytoma grade I-II no statistically significant risks were found. For astrocytoma grade III an increased risk with linear trend was found in the highest average exposure category ≥ 0.27 μT; OR = 1.5, 95%CI = 0.9-2.7, p linear trend = 0.048. Also in the highest category for maximum exposed job, ≥0.60 μT, an increased risk was seen, OR = 1.6, 95%CI = 0.9-2.8, p linear trend = 0.04. Regarding astrocytoma grade IV (glioblastoma multiforme) an increased risk was found in all cumulative exposure categories, however without a statistically significant trend, p linear trend = 0.12. Average exposure in the two highest exposure categories yielded increased risk of borderline statistical significance, however without a statistically significant trend, p linear trend = 0.07.

Results for cumulative exposure in μT-years for all glioma in different time windows (years before diagnosis) are shown in Table 3. No statistically significant increased risks or linear trends were found.

Cumulative exposure in μT-years in different time windows for different types of glioma is shown in Table 4. Regarding astrocytoma grade I-II and astrocytoma grade III no statistically significant results were obtained. For astrocytoma grade IV increased risks were obtained in the highest exposure categories in the time windows 1-4, 5-9, and 10-14 years whereas no pattern of an association was found in the time windows 15-19 and 20+ years. Thus in the time window 1-4 years and cumulative exposure ≥0.69 μT-years OR = 1.6,

TABLE 2 Odds ratio (OR) and 95% confidence interval (CI) for astrocytoma grade I-II (*n* = 206), astrocytoma grade III (*n* = 157), and astrocytoma grade IV (*n* = 687) for occupational exposure to ELF-EMF

	Astrocytoma, grade I-II (*n* = 206)			Astrocytoma, grade III (*n* = 157)			Astrocytoma, grade IV (*n* = 687)		
Exposure metric	**Ca/Co**	**OR**	**95%CI**	**Ca/Co**	**OR**	**95%CI**	**Ca/Co**	**OR**	**95%CI**
Cumulative exposure (μT-years)									
<2.33	106/870	1.0	-	53/870	1.0	-	92/870	1.0	-
2.33 to <3.79	38/872	0.8	0.5-1.2	39/872	1.1	0.6-1.7	161/872	1.4	1.01-1.8
3.79 to <5.55	31/869	0.8	0.5-1.3	24/869	0.7	0.4-1.2	186/869	1.4	1.01-1.8
5.55 to <8.52	15/525	0.6	0.3-1.2	28/525	1.2	0.6-2.1	142/525	1.4	0.97-1.9
8.52+	16/349	0.9	0.5-1.7	13/349	0.8	0.4-1.7	106/349	1.5	1.05-2.1
p, linear trend			0.74			0.65			0.12
Average exposure (μT)									
<0.11	43/830	1.0	-	35/830	1.0	-	128/830	1.0	-
0.11 to <0.13	56/912	1.2	0.8-1.9	27/912	0.7	0.4-1.2	177/912	1.2	0.97-1.6
0.13 to <0.18	44/871	0.9	0.6-1.4	42/871	1.1	0.7-1.7	167/871	1.2	0.9-1.5
0.18 to <0.27	42/523	1.3	0.8-2.0	27/523	1.1	0.6-1.8	125/523	1.4	1.02-1.8
0.27+	21/349	1.0	0.5-1.8	26/349	1.5	0.9-2.7	90/349	1.4	1.03-2.0
p, linear trend			0.89			0.048			0.07
Maximum exposed job (μT)									
<0.13	46/823	1.0	-	33/823	1.0	-	141/823	1.0	-
0.13 to <0.16	47/812	1.2	0.8-1.9	30/812	0.9	0.6-1.6	142/812	1.0	0.8-1.4
0.16 to <0.24	59/968	1.0	0.7-1.6	43/968	0.9	0.6-1.5	205/968	1.1	0.9-1.4
0.24 to <0.60	33/532	1.1	0.7-1.9	26/532	1.0	0.6-1.7	120/532	1.0	0.8-1.4
0.60+	21/350	1.2	0.7-2.2	25/350	1.6	0.9-2.8	79/350	1.1	0.8-1.5
p, linear trend			0.61			0.04			0.75

Cut points at 25th, 50th, 75th, and 90th percentile for controls.
Unconditional logistic regression, adjusted for age at diagnosis, gender, socio-economic index (SEI), and year of diagnosis. Exposure the year before diagnosis was excluded ("1-year lag").

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95%CI = 1.2-2.3, p linear trend = 0.02, time window 5-9 years and cumulative exposure ≥0.92 μT-years OR = 1.9, 95%CI = 1.4-2.6, p linear trend <0.001, and time window 10-14 years and cumulative exposure ≥0.92 μT-years OR = 1.7, 95%CI = 1.3-2.4, p linear trend = 0.003, were obtained. Using the time windows 1-14 and 15 + years strengthened the association of increased risks further for astrocytoma grade IV in the 1-14 year period while no risks were found for 15+ years, Table 5.

Restricted cubic spline plots for astrocytoma grade IV and cumulative exposure to ELF-EMF in μT-years in two time windows (1-14 and 15+ years) are shown in Figures 1 and 2. As indicated in Table 5, the risk increased with increasing cumulative exposure in the 1-14 year time window whereas no statistically significant increased risk was found in the 15+ year group.

We analyzed interaction between exposure to ELF-EMF and use of mobile and/or cordless phones and the risk for all glioma as well as different types without any statistically significant interaction. Results for all glioma and astrocytoma grade IV and use of wireless phones and occupational exposure to ELF-EMF are shown in Table 6. Regarding astrocytoma grade IV somewhat higher ORs were obtained in the categories of use of wireless phones and cumulative exposure ≥2.33 μT-years and also average exposure ≥0.11 μT, respectively, but without a statistically significant interaction.

Since we have consistently found an increased risk for glioma associated with ipsilateral use of mobile or cordless phone[23] we also analyzed such use and occupational ELF-EMF exposure. No statistically significant interaction was found. In fact ORs were of the same magnitude for ipsilateral mobile phone use for those with low (<25th percentile) and high (≥25th percentile) ELF-EMF exposure. The results were similar for glioma in total and astrocytoma grade IV (data not in Table).

4 | DISCUSSION

This was a large case-control study on brain tumors and occupational exposure to ELF-EMF. All types of brain tumors were included but here results are shown only for glioma. One reason to focus on glioma was that the INTEROCC study showed an association between exposure to ELF-EMF and glioma, but not for meningioma.[26] The INTEROCC results were based on 1939 glioma cases and 5404 controls to be compared with 1346 participating glioma cases and 3485 participating controls in our study. Thus, the results in both studies were based on large numbers of cases and controls. However, in contrast to INTEROCC, we had high participation rate among both cases and controls thus minimizing selection bias. The INTEROCC data were based on results from seven countries of the 13 included in Interphone; Sweden was not included. It is an advantage with a study in only one country, as our investigation, for methodological, and logistic reasons, for example better with one study group instead of multiple as in Interphone (13 countries), differences in response rates in different populations, access to registers, trained interviewers, etc. Furthermore we had a wider age span for included cases and controls, 18-80 years in total, compared to 30-59 years for the majority of included countries in INTEROCC. Thus, we covered the whole lifetime period of occupations in contrast to INTEROCC that did not include occupations in older persons for most countries.

One advantage in our study was that we could make a histopathological classification of the glioma cases. Cumulative

TABLE 3 Odds ratio (OR) and 95% confidence interval (CI) for all glioma (*n* = 1346) for occupational exposure to ELF-EMF in time windows; 1-4, 5-9, 10-14, 15-19, and 20+ years before diagnosis

	Glioma (*n* = 1346)		
Cumulative exposure (μT-years)	Ca/Co	OR	95%CI
1-4 years			
<0.27	243/647	1.0	-
0.27 to <0.36	234/646	1.1	0.9-1.3
0.36 to <0.45	257/633	1.1	0.9-1.3
0.45 to <0.69	213/496	1.0	0.8-1.3
0.69+	155/298	1.2	0.9-1.5
p, linear trend			0.31
5-9 years			
<0.36	257/703	1.0	-
0.36 to <0.48	250/754	1.0	0.8-1.2
0.48 to <0.60	262/680	1.0	0.8-1.3
0.60 to <0.92	245/543	1.1	0.9-1.4
0.92+	165/306	1.2	0.97-1.6
p, linear trend			0.06
10-14 years			
<0.36	254/724	1.0	-
0.36 to <0.48	250/675	1.1	0.9-1.4
0.48 to <0.61	327/897	1.0	0.9-1.3
0.61 to <0.92	186/420	1.1	0.9-1.4
0.92+	165/350	1.1	0.9-1.5
p, linear trend			0.35
15-19 years			
<0.40	285/724	1.0	-
0.40 to <0.48	180/598	0.9	0.7-1.1
0.48 to <0.64	315/895	0.9	0.8-1.1
0.64 to <0.96	208/459	1.0	0.8-1.3
0.96+	132/299	1.0	0.8-1.3
p, linear trend			0.77
20+ years			
<1.08	272/733	1.0	-
1.08 to <2.06	243/747	0.8	0.7-1.1
2.06 to <3.51	241/744	0.8	0.6-1.02
3.51 to <5.64	184/445	0.9	0.7-1.2
5.64+	125/297	0.9	0.6-1.2
p, linear trend			0.80

Cut points at 25th, 50th, 75th, and 90th percentile for controls in each time window.
Unconditional logistic regression, adjusted for age at diagnosis, gender, socio-economic index (SEI), and year of diagnosis. Exposure the year before diagnosis was excluded ("1-year lag").

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TABLE 4 Odds ratio (OR) and 95% confidence interval (CI) for astrocytoma grade I-II (n = 206), astrocytoma grade III (*n* = 157) and astrocytoma grade IV (n = 687) for occupational exposure to ELF-EMF in time windows; 1-4, 5-9, 10-14, 15-19, and 20+ years before diagnosis

	Astrocytoma, grade I-II (*n* = 206)			Astrocytoma, grade III (*n* = 157)			Astrocytoma, grade IV (*n* = 687)		
Cumulative exposure (μT-years)	**Ca/Co**	**OR**	**95%CI**	**Ca/Co**	**OR**	**95%CI**	**Ca/Co**	**OR**	**95%CI**
1-4 years									
<0.27	41/647	1.0	-	38/647	1.0	-	112/647	1.0	-
0.27 to <0.36	43/646	1.2	0.8-1.9	24/646	0.8	0.5-1.3	114/646	1.4	1.02-1.9
0.36 to <0.45	35/633	1.0	0.6-1.6	34/633	1.0	0.6-1.6	118/633	1.2	0.9-1.6
0.45 to <0.69	45/496	1.3	0.8-2.0	23/496	0.7	0.4-1.3	101/496	1.2	0.9-1.7
0.69+	24/298	1.0	0.6-1.8	19/298	0.9	0.5-1.6	79/298	1.6	1.2-2.3
p, linear trend			0.89			0.74			0.02
5-9 years									
<0.36	44/703	1.0	-	37/703	1.0	-	110/703	1.0	-
0.36 to <0.48	34/754	0.9	0.5-1.4	24/754	0.7	0.4-1.3	132/754	1.4	1.1-1.9
0.48 to <0.60	34/680	1.0	0.6-1.6	31/680	0.9	0.5-1.5	141/680	1.4	1.03-1.8
0.60 to <0.92	47/543	1.3	0.8-2.1	26/543	0.9	0.5-1.5	126/543	1.5	1.1-2.0
0.92+	17/306	0.8	0.4-1.4	20/306	1.1	0.6-1.9	92/306	1.9	1.4-2.6
p, linear trend			0.81			0.68			< 0.001
10-14 years									
<0.36	49/724	1.0	-	30/724	1.0	-	102/724	1.0	-
0.36 to <0.48	27/675	0.8	0.5-1.4	36/675	1.6	0.95-2.6	125/675	1.4	1.1-1.9
0.48 to <0.61	39/897	0.9	0.6-1.4	28/897	0.8	0.5-1.4	201/897	1.5	1.2-2.0
0.61 to <0.92	33/420	1.3	0.8-2.2	20/420	1.1	0.6-2.0	105/420	1.5	1.1-2.1
0.92+	15/350	0.6	0.3-1.1	18/350	1.1	0.6-2.1	99/350	1.7	1.3-2.4
p, linear trend			0.33			0.93			0.003
15-19 years									
<0.40	48/724	1.0	-	30/724	1.0	-	126/724	1.0	-
0.40 to <0.48	21/598	0.7	0.4-1.3	18/598	0.9	0.5-1.7	105/598	1.2	0.9-1.6
0.48 to <0.64	34/895	0.8	0.5-1.2	28/895	0.8	0.5-1.5	199/895	1.2	0.96-1.6
0.64 to <0.96	20/459	0.7	0.4-1.3	25/459	1.3	0.8-2.3	125/459	1.3	1.002-1.8
0.96+	15/299	0.6	0.3-1.2	14/299	1.1	0.5-2.1	77/299	1.3	0.9-1.8
p, linear trend			0.22			0.56			0.19
20+ years									
<1.08	43/733	1.0	-	39/733	1.0	-	117/733	1.0	-
1.08 to <2.06	28/747	0.8	0.5-1.4	18/747	0.5	0.3-0.95	158/747	1.1	0.8-1.5
2.06 to <3.51	19/744	0.7	0.3-1.3	20/744	0.6	0.3-1.2	161/744	1.0	0.7-1.3
3.51 to <5.64	8/445	0.5	0.2-1.2	23/445	1.1	0.5-2.2	120/445	0.9	0.7-1.3
5.64+	13/297	1.0	0.4-2.4	11/297	0.8	0.4-2.0	85/297	0.9	0.6-1.3
p, linear trend			0.85			0.63			0.36

Cut points at 25th, 50th, 75th, and 90th percentile for controls in each time window.
Unconditional logistic regression, adjusted for age at diagnosis, gender, socio-economic index (SEI) and year of diagnosis. Exposure the year before diagnosis was excluded ("1-year lag").

exposure in μT-years or maximum exposed job yielded no statistically significant risk for all glioma, whereas the result for average exposure in μT was of borderline significance, see Table 1.

We analyzed separately low-grade glioma (astrocytoma grade I-II) and high-grade glioma divided into astrocytoma grade III and the most malignant type astrocytoma grade IV (glioblastoma multiforme). For astrocytoma grade I-II and grade III no statistically significant risks were found, see Table 2.

Cumulative exposure in μT-years in different time windows did not give statistically significant risks for glioma overall. Of interest is that dividing glioma in different types yielded only for astrocytoma grade IV statistically significant increased risks in the shortest latency

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TABLE 5 Odds ratio (OR) and 95% confidence interval (CI) for all glioma (*n* = 1,346) and astrocytoma grade IV (*n* = 687) for occupational exposure to ELF-EMF in time windows; 1–14 and 15+ years before diagnosis

	Glioma (*n* = 1346)			Astrocytoma, grade IV (*n* = 687)		
Cumulative exposure (μT-years)	Ca/Co	OR	95%CI	Ca/Co	OR	95%CI
1-14 years						
<0.91	260/770	1.0	-	106/770	1.0	-
0.91 to <1.42	311/872	1.1	0.9-1.3	138/872	1.3	0.96-1.7
1.42 to <1.82	317/778	1.2	0.95-1.4	187/778	1.8	1.4-2.3
1.82 to <2.75	240/537	1.2	0.95-1.5	129/537	1.8	1.3-2.4
2.75+	162/329	1.2	0.9-1.5	89/329	1.9	1.4-2.6
p, linear trend			0.12			<0.001
15+ years						
<1.44	319/782	1.0	-	119/782	1.0	-
1.44 to <2.55	257/777	0.8	0.7-0.999	154/777	1.1	0.8-1.4
2.55 to <4.17	264/787	0.8	0.6-1.01	173/787	1.0	0.7-1.3
4.17 to <6.59	190/471	0.9	0.7-1.1	126/471	0.9	0.7-1.3
6.59+	132/313	0.8	0.6-1.1	88/313	0.9	0.6-1.3
p, linear trend			0.71			0.44

Cut points at 25th, 50th, 75th, and 90th percentile for controls in each time window.
Unconditional logistic regression, adjusted for age at diagnosis, gender, socio-economic index (SEI) and year of diagnosis. Exposure the year before diagnosis was excluded ("1-year lag").

periods 1-4, 5-9, and 10-14 years whereas no risk for occupational ELF-EMF was seen for longer latency. This indicates a late carcinogenic effect with tumor promotion/progression. INTEROCC showed an increased risk for all glioma in the 1-4 years latency period but not for longer lag times. The results were similar for low-grade and high-grade glioma. One difference to our results is that some diagnoses in Interphone were histologically confirmed, but some were based on diagnostic imaging.[21] Thus the diagnostic procedure was less stringent than in our study. In fact a number of cases might have been misclassified in Interphone since tumor pathology was not available for all cases. Furthermore no results were given for astrocytoma grade IV separately. Anyhow, the results in both INTEROCC and in our studies are similar with a late carcinogenic effect from occupational ELF-EMF exposure for glioma. These results are supported by laboratory studies showing increasing proliferative activity of neuroderived malignant cells.[32]

Of interest is that we did not find any interaction between occupational ELF-EMF exposure and wireless phone use. Thus exposure to ELF-EMF and RF radiation seem to be independent risk factors for glioma. However, the digital GSM (Global System for Mobile Communication) mobile phone and to a lesser extend the DECT (Digital Enhanced Cordless Communications) phones emit in addition to RF radiation also

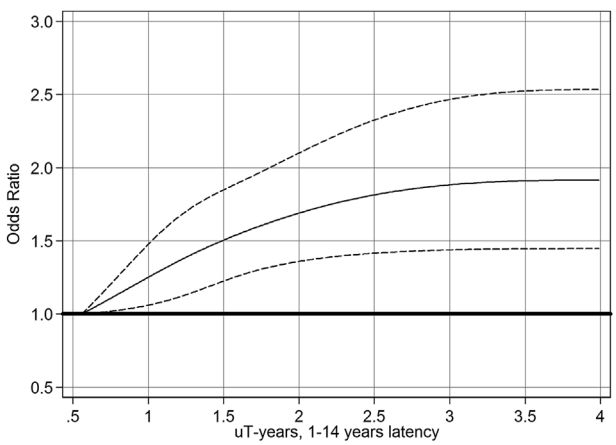


FIGURE 1 Restricted cubic spline plot of the relationship between cumulative exposure to ELF-EMF in μT-years and astrocytoma grade IV in the 1-14 years latency group. The solid line shows the OR estimate and the broken lines represent the 95%CI. Adjustment for age at diagnosis, gender, SEI-code, and year of diagnosis was made. Population based controls were used

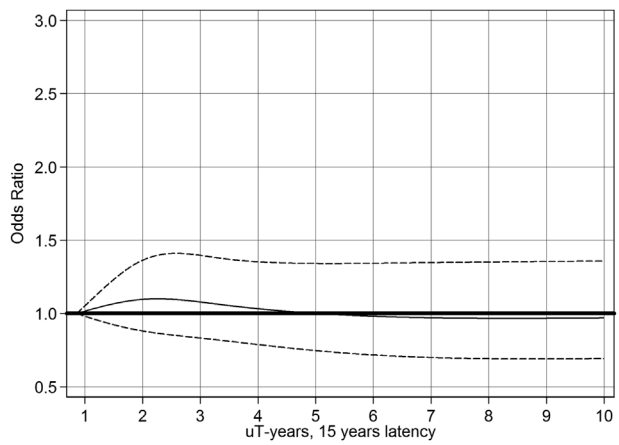


FIGURE 2 Restricted cubic spline plot of the relationship between cumulative exposure to ELF-EMF in μT-years and astrocytoma grade IV in the 15+ years latency group. The solid line shows the OR estimate and the broken lines represent the 95%CI. Adjustment for age at diagnosis, gender, SEI-code, and year of diagnosis was made. Population based controls were used

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TABLE 6 Odds ratio (OR) and 95% confidence interval (CI) for all glioma (n = 1,346) and astrocytoma grade IV (n = 687) for occupational exposure to ELF-EMF and interaction with use of wireless phones (mobile and/or cordless phone)

Exposure metric	Glioma (n = 1346)			Astrocytoma, grade IV (n = 687)		
Wireless phone	**Ca/Co**	**OR**	**95%CI**	**Ca/Co**	**OR**	**95%CI**
Cumulative exposure (μT-years)						
No use of wireless phone,<2.33	79/261	1.0	-	26/261	1.0	-
Use of wireless phone,<2.33	289/609	1.3	0.99-1.8	66/609	1.2	0.7-2.0
No use of wireless phone, ≥2.33	221/775	0.9	0.7-1.2	145/775	1.2	0.8-2.0
Use of wireless phone, ≥2.33	757/1840	1.2	0.9-1.6	450/1840	1.6	1.04-2.5
p, interaction	0.77			0.75		
Average exposure (μT)						
No use of wireless phone, <0.11	57/232	1.0	-	28/232	1.0	-
Use of wireless phone, <0.11	228/598	1.4	0.99-2.0	100/598	1.5	0.95-2.4
No use of wireless phone, ≥0.11	243/804	1.2	0.8-1.6	143/804	1.4	0.9-2.2
Use of wireless phone, ≥0.11	818/1851	1.5	1.1-2.0	416/1851	1.8	1.2-2.8
p, interaction	0.54			0.50		
Maximum exposed job (μT)						
No use of wireless phone, <0.13	55/222	1.0	-	27/222	1.0	-
Use of wireless phone, <0.13	229/601	1.4	0.96-1.9	114/601	1.7	1.05-2.7
No use of wireless phone, ≥0.13	245/814	1.1	0.8-1.6	144/814	1.3	0.9-2.1
Use of wireless phone, ≥0.13	817/1848	1.4	1.02-1.9	402/1848	1.7	1.1-2.6
p, interaction	0.69			0.26		

Unconditional logistic regression, adjusted for age at diagnosis, gender, socio-economic index (SEI), and year of diagnosis. Exposure the year before diagnosis was excluded ("1-year lag").

ELF-EMF from the battery.[33,34] Analog mobile phones do not create pulsed RF-EMF. Our data suggest that RF radiation is the major risk factor for glioma during mobile phone use since the OR was similar regardless of level of occupational exposure to ELF-EMF and no statistically significant interaction was found. Linde and Hansson Mild reported the highest magnetic flux density for a GSM phone to be 1.8 μT.[33] A single phone transmits one-eighth of the time yielding mean exposure 0.225 μT. In this study 884 cases had used a GSM mobile phone. According to the Linde and Hansson Mild results this yielded cumulative mean battery ELF-EMF exposure = 0.16 μT-years (median = 0.04, range = 0.00013-3.92). The results for the 2014 exposed control subjects were mean = 0.09 μT-years (median = 0.02, range = 0.00013-2.52). Only 4 cases and 2 controls were exposed ≥2.33 μT-years, thus higher level than for the reference category in this study, see Table 1. These results support that RF-EMF from wireless phones is an independent risk factor for glioma.

Occupation may give an indication of the exposure to the ELF magnetic fields, but is nevertheless subject to confounding effects, as people at the same occupation may have different exposure levels due to the type and model of work instrumentation used and the neighbouring electromagnetic sources. By phasing out the cathode-ray tube type visual display units and with the introduction of power saving information technologies, the office workers have commonly quite low exposure to ELF magnetic fields. On the another hand, offices located next to a transformer are likely to have significantly high magnetic field levels, comparable to those found in industrial settings around high power equipment.

Patients in our study with histopathological verification of a malignant brain tumor were reported to us from the cancer registries in Sweden. Controls were selected from the same geographical area as the cases, with matching made on year of diagnosis, gender and age, making the controls comparable with the cases. All the controls could be included in the unconditional logistic regression analysis because adjustment was made for potential confounding factors. In the laterality analysis, the matched control was assigned the same side of localisation as the tumor for the respective case.

One strength of our study was the high percentage of participating cases and controls making it unlikely that selection bias influenced the results. Recall bias might have been an issue, but that seems to be unlikely in relation to reporting different occupations. As JEM is calculated based on samples of same type of occupations, it may not always characterize exposure correctly on an individual level, as workstations and work assignments vary within each job category. However, such differences are likely nondifferential. Furthermore, the level of occupational exposure to ELF-EMF, if any, would in general not have been known for the study subjects, and thus not influence the type of reported occupation. Observational bias might have been introduced by the supplementary phone interviews, but is unlikely as to occupation. The identity of the subjects either as a case or a control was not disclosed during supplementary phone calls and further data processing. A structured protocol was used and the interviewer had to follow that procedure strictly during the interviews. Histopathological classification of the tumor was made without knowledge of exposure. Tumor pathology was coded in a separate data file that was not disclosed before statistical analysis.

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Excluding deceased glioma cases from the study might have biased the results towards unity. In total, 1055 cases with malignant brain tumor were omitted from the studies (1997-2003, 2007-2009). Histopathology data were not available for all of these individuals; however the majority would be glioma. Most of these cases would have been diagnosed with astrocytoma grade IV (glioblastoma multiforme) that have a shorter survival than other types of glioma. The results might have been biased if ELF-EMF exposure is associated with decreased survival of patients with glioblastoma multiforme, cf, our findings on RF-EMF exposure and survival of patients with glioblastoma multiforme.[35]

Glioma is the most common malignant brain tumor and represents about 60% of all central nervous system tumors. The most common glioma subtype is astrocytoma. Astrocytic tumors are divided in two groups depending on the malignant potential; low-grade (WHO grades I-II) and high-grade (WHO grades III-IV). Low-grade astrocytoma has a relatively favourable prognosis, whereas survival is shorter for patients with high-grade glioma. Glioblastoma multiforme (WHO grade IV) accounts for 60-75% of all astrocytoma. The peak incidence is between 45 and 75 years of age with median survival less than one year.[36] Thus, one disadvantage of the Interphone study was that only cases aged 30-59 years at the time of diagnosis were included for the majority of included countries[26] in contrast to our range 18-80 years.

We know little about the earliest events in the genesis of glioma in humans for obvious reasons. However, progression of glioma has been studied in a large series of tumors of different malignancy grades. Patients with low-grade glioma have been followed with later progression to high-grade glioma.[37] The natural history of most glioma cases, from earliest events to clinical manifestation, is unknown.

5 | CONCLUSION

In conclusion this study showed an increased risk in late stage (promotion/progression) of astrocytoma grade IV for occupational ELF-EMF exposure.

AUTHORS' CONTRIBUTIONS

Lennart Hardell was the principal investigator and made the draft of the article. Tarmo Koppel and Mikko Ahonen evaluated occupational ELF-EMF exposure and Michael Carlberg made all statistical analyses. All authors participated in writing of the final version of the article, and agree that this version is ready for submission to the American Journal of Industrial Medicine.

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ETHICS APPROVAL AND INFORMED CONSENT

All studies were approved by the Ethical Committee (Örebro County Hospital DNR 351/96, Uppsala University DNR 2005:367) and all study subjects participated after informed consent.

DISCLOSURE (AUTHORS)

The authors report no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

Steven Markowitz declares that he has no competing or conflicts of interest in the review and publication decision regarding this article.

DISCLAIMER

None.

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