Research Article

Occupational Exposure to Extremely Low-Frequency Magnetic Fields and Brain Tumor Risks in the INTEROCC Study

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Abstract

Background: Occupational exposure to extremely low-frequency magnetic fields (ELF) is a suspected risk factor for brain tumors, however the literature is inconsistent. Few studies have assessed whether ELF in different time windows of exposure may be associated with specific histologic types of brain tumors. This study examines the association between ELF and brain tumors in the large-scale INTEROCC study.

Methods: Cases of adult primary glioma and meningioma were recruited in seven countries (Australia, Canada, France, Germany, Israel, New Zealand, and the United Kingdom) between 2000 and 2004. Estimates of mean workday ELF exposure based on a job exposure matrix were assigned. Estimates of cumulative exposure, average exposure, maximum exposure, and exposure duration were calculated for the lifetime, and 1 to 4, 5 to 9, and 10+ years before the diagnosis/reference date.

Results: There were 3,761 included brain tumor cases (1,939 glioma and 1,822 meningioma) and 5,404 population controls. There was no association between lifetime cumulative ELF exposure and glioma or meningioma risk. However, there were positive associations between cumulative ELF 1 to 4 years before the diagnosis/reference date and glioma [odds ratio (OR) $\geq$ 90th percentile vs. < 25th percentile, 1.67; 95% confidence interval (CI), 1.36–2.07; $P_{Linear\ trend}$ < 0.0001], and, somewhat weaker associations with meningioma (OR $\geq$ 90th percentile vs. < 25th percentile, 1.23; 95% CI, 0.97–1.57; $P_{Linear\ trend}$ = 0.02).

Conclusions: Results showed positive associations between ELF in the recent past and glioma.

Impact: Occupational ELF exposure may play a role in the later stages (promotion and progression) of brain tumorigenesis. *Cancer Epidemiol Biomarkers Prev; 23(9); 1863–72. ©2014 AACR.*

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Introduction

There are few established risk factors for brain tumors (1). In countries with cancer registries, it is estimated that the annual age-standardized incidence rate of primary malignant tumors of the brain and nervous system is between 3 and 4 per 100,000. It is slightly higher among males than females and in developed than developing countries (1, 2). Small increases in the incidence of some types of brain tumors have been observed over recent decades, because of changes in diagnosis, classification, and coding (1, 3).

Although ionizing radiation is an established risk factor for the disease, it accounts for a small fraction of the total number of cases (4, 5). Possible associations between occupational exposure to nonionizing radiation sources, in particular extremely low-frequency magnetic fields (ELF), which occur during the generation, distribution, and use of alternating current electricity, and brain tumors have been examined; however, results are inconsistent and limited by small study sizes and a lack of occupational history data (6). Previous studies have also varied widely in terms of

methodology. There have been studies of highly exposed occupational groups, including for example electrical workers, railway professionals, and resistance welders, with study designs ranging from job title–based studies, comparing rates of brain tumors to those expected in the general population (7–9), to studies based on detailed measurements and modeling (10), or job exposure matrices (JEM; refs. 11 and 12). There are also general population studies with ELF exposure assessments ranging from self-report or expert judgment through to JEMs (13–17).

A meta-analysis of 48 studies published during 1993 to 2007 reported a small positive association between occupational ELF and brain tumors overall [relative risk (RR) = 1.14; 95% confidence interval (CI), 1.07–1.22]; however, there was no exposure–response relationship using approximations of ELF exposure categories in the original papers (18). Study characteristics that tended to be associated with stronger positive findings included a poor-quality exposure assessment, a poorly defined comparison group, as well as an adequate study design.

Most recently, a U.S. study of 489 glioma cases, 197 meningioma cases, and 799 controls reported no association between ELF and glioma [odds ratios (OR) cumulative exposure >45 milligauss (mG)-years (1 μT = 10 mG) vs. 0 exposure > 1.5 mG = 0.8; 95% CI, 0.5–1.2] or meningioma risk (OR, 1.0; 95% CI, 0.6–1.8; ref. 19). A French study of 221 cases of central nervous system (CNS) tumors and 442 controls reported a positive association between ELF and meningioma (OR, 3.02; 95% CI, 1.10–8.25; ref. 17). No association between ELF and incident brain tumors ($n = 233$) was observed in the Netherlands Cohort Study (20) nor in a study of U.K. electricity supply workers ($n = 266$; ref. 21).

The International Agency for Research on Cancer (IARC) classified ELF as possibly carcinogenic to humans (Group 2B), based on studies of childhood leukemia, but with *inadequate evidence* for all other cancers (22). Similar conclusions have been reached more recently (6, 23, 24). Mechanistically, any role of ELF would likely manifest on the later stages of tumor development, specifically in cancer promotion/progression as suggested by some co-carcinogenicity studies (22, 24, 25). Few epidemiological studies have had sufficient power to address this hypothesis. Results from some, but not all, studies have observed stronger associations between ELF and brain tumors in the more recent compared with the more distant past, or with more aggressive forms of glioma (11, 13, 16, 26–29).

This study assesses the role of occupational ELF exposure for specific histologic types of brain tumors, namely glioma and meningioma, using data from the large-scale INTEROCC study. Detailed lifetime occupational histories were collected, providing a unique opportunity to examine the potential impact of ELF exposure overall and in specific exposure time windows.

Materials and Methods

Study population

The INTEROCC study is based on a subset of countries from INTERPHONE, a large, 13-country, population-based case–control study conducted according to a common protocol (30). Cases of primary brain (glioma, meningioma), CNS (acoustic neuroma), and salivary gland tumors, aged between 30 and 59 years were recruited between 2000 and 2004. Although INTERPHONE's primary objective was to examine whether radiofrequency (RF) field exposure from cellular telephones was associated with cancer risk, 7 of INTERPHONE 13 countries collected detailed occupational data and participated in the subsequent INTEROCC study to address outstanding questions about occupational agents in glioma and meningioma.

Incident cases were rapidly recruited (median delay from diagnosis to interview ~3 months) from major treatment centers in areas of Australia, Canada, France, Germany, New Zealand, the United Kingdom, and nationwide in Israel, with completeness verified through secondary sources. An expanded age range was used for INTEROCC with Germany including cases ages up to 69 years, the United Kingdom 18 to 69 years, and in Israel cases ages 18+ years were recruited to allow for greater case ascertainment. Cases were confirmed histologically or through unequivocal diagnostic imaging.

Controls were randomly selected from electoral lists (Australia, Canada-Montreal, France, New Zealand), population-based registries (Canada-Vancouver, Germany, Israel), patient lists (United Kingdom), or random digit dialing (Canada-Ottawa) according to study center. Controls were either frequency or individually matched to cases by sex, age (5-year groups), and study center within country.

Although the original INTERPHONE protocol called for the selection of only one control for each case of glioma or meningioma, all eligible controls were used here to maximize statistical power. The reference date of controls was calculated as the date of interview minus the median difference between the date of case diagnosis and interview by country. Participants provided written informed consent before interview. There were 5,399 eligible brain tumor cases (3,017 gliomas and 2,382 meningiomas) and 11,112 controls (identified from the sampling frame) among whom 3,978 cases (2,054 gliomas and 1,924 meningiomas) and 5,601 controls were interviewed. Major reasons for nonparticipation among controls in the overall INTERPHONE study include refusal (64%) and inability to contact (27%; ref. 30). Overall participation rates for high- and low-grade glioma cases were also similar (67% vs. 71%, respectively; 30). Ethics approval was obtained from appropriate national and regional research ethics boards, including the Ethical Review Board of IARC (Lyon) for INTERPHONE and the Municipal Institute for Medical Investigation (IMIM) Barcelona for INTEROCC.

Data collection

Eligible participants were interviewed by trained interviewers using a computer-assisted personal interview questionnaire. If the participant had died or was unable to participate, a proxy respondent was allowed. The questionnaire captured detailed data on a range of personal and family characteristics. Participants also completed a lifetime occupational calendar for all jobs held for a minimum of 6 months, including job title, company name, company description, and start and stop year.

Exposure assessment

A total of 35,862 jobs were reported. A total of 599 jobs (1.7%) were excluded (assigned no ELF exposure) because of invalid start/stop dates; and an additional 23 jobs (0.06%) excluded that ceased before age 14 years. Job titles were coded to the International Standard Classification of Occupations 1988 (ISCO88) 4-digit codes as well as 1968 (ISCO68) 5-digit codes, because it contains codes for occupations in the utility industry. Coding guidelines were provided to study centers and an intercoding trial conducted to ensure consistency (31). The mean (SD) number of jobs per subject was 3.9 (±2.6) for glioma cases, 3.6 (±2.6) for meningioma cases, and 3.8 (±2.5) for controls. A small number of participants (103 glioma cases, 95 meningioma cases, and 122 controls) who reported having never been employed were excluded here.

Estimates of mean workday-average ELF exposures came from an enhancement of a measurement-based JEM (32). The JEM was linked to the ISCO88 code for each job unless a JEM estimate was available for a more specific electrical job in ISCO68. The JEM was substantially enhanced by including measurement data on jobs included in the INTEROCC study based on summary statistics or primary data from published occupational studies in Canada, England, Finland, Italy, the Netherlands, New Zealand, Sweden, and the United States. These studies used personal monitors to measure ELF exposure reporting the full-shift time-weighted average (TWA) "resultant" of the magnetic flux density in µT. All measurements were made using monitors with bandwidths within a range of 3 to 1,000 Hz.

Pooling studies in the JEM, estimates of geometric mean (GM) were calculated for 278 primary ISCO codes. Where there were no measurement data for a specific ISCO code, exposures were inferred based on similar jobs within the ISCO hierarchy (72 ISCO codes, 4.2% of the jobs of INTEROCC subjects) or estimated using expert judgement (60 ISCO codes, 1.8% of INTEROCC jobs). Jobs classified as an unknown occupation ($n = 105$, 0.3% of jobs) were assigned the geometric mean of control values by centre. Supplementary Table S1 presents a description of ELF levels in selected participant jobs. An online version of the JEM is available at: http://www.crealradiation.com/index.php/en/databases?id = 55.

Statistical analysis

Conditional logistic regression models were used to obtain adjusted ORs and 95% CIs for the association between occupational ELF and brain tumors in 7 countries combined stratified by region, country, sex, and 5-year age group, and adjusted for education. Categorical indicators of cumulative and average ELF exposure with cut points based on the 25th, 50th, 75th, and, because of the skewed nature of the distribution, the 90th percentile of the control exposure distribution were examined for the lifetime (1-year lag) and in separate exposure-time windows defined *a priori*, 1 to 4, 5 to 9, and 10+ years before the date of diagnosis/reference date. Because ELF exposure is ubiquitous, the reference group consisted of participants in the lowest exposure category. Because the most relevant ELF metric, if any, is unknown (19), indicators of maximum exposed job and duration of employment in a job in the highest quartile of participant jobs (≥ 0.18 µT) were also examined.

Potential confounding by marital status, cigarette smoking, socioeconomic position [standard international occupational prestige scale (SIOPS); ref. 33], allergy history, occupational ionizing radiation (reported wearing a radiation badge), occupational cosmic radiation (prior flight-related occupation), and cumulative cellular telephone use (deciles of minutes of call time for Australia, Canada, France, Israel, New Zealand) were examined but produced virtually no change (<10%) in ORs (not presented; refs. 34–36). Potential confounding by ever exposure to 29 occupational chemicals selected *a priori* was also examined, based on chemical exposure estimates assigned based on a modified version of the Finnish JEM (FINJEM) to study participants as part of INTEROCC (37).

Sensitivity analyses were conducted excluding proxy interviews (30), participants who were judged by the interviewer to be reticent and uninterested in the interview and, participants >69 years of age, participants with a history of self-reported physician-diagnosed neurofibromatosis or tuberous sclerosis, and for low- and high-grade glioma separately. Potential effect modification by country, age, sex, and education was assessed by entering product terms into conditional logistic regression models and assessing their significance according to the likelihood ratio test. Analyses were conducted using SAS version 9.3 (38).

Results

A total of 1,939 (94.4%) glioma cases, 1,822 (94.7%) meningioma cases, and 5,404 (96.5%) controls were retained for analysis. The majority of glioma cases were male (62.0%), with meningioma cases being predominantly female (72.5%; Table 1). The mean (SD) age of study participants was 51.0 (±12.3) years for glioma cases, 54.7 (±11.6) years for meningioma cases, and 51.8 (±11.3) years for controls. The majority of participants had at least a high school education. Levels of lifetime cumulative ELF exposure ranged from 0.02 to 0.05 µT-years to

Table 1. Characteristics of case and control participants at enrollment in INTEROCC study, 2000–2004, Australia, Canada, France, Germany, Israel, New Zealand, and the United Kingdom

	Glioma cases ($n = 1,939$)	Meningioma cases ($n = 1,822$)	Controls[a] ($n = 5,404$)
	%	%	%
Sex			
Male	62.0	27.5	45.2
Female	38.0	72.5	54.8
Age at reference date, y			
<35	11.0	4.4	7.3
35–39	9.3	5.4	8.7
40–44	11.1	9.2	11.6
45–49	12.3	14.8	13.8
50–54	18.0	20.4	18.3
55–59	16.1	17.1	18.7
60–64	9.9	10.3	9.2
65–69	6.8	8.7	7.9
70+	5.6	9.8	4.4
Education			
High school or less	52.4	59.1	53.6
Medium-level technical school	19.7	19.5	19.0
University	28.0	21.4	27.4
Country			
Australia	14.2	13.9	12.3
Canada	8.6	5.1	11.6
France	4.8	7.6	8.5
Germany	18.6	20.3	27.5
Israel	20.5	36.8	17.3
New Zealand	3.4	2.7	2.7
United Kingdom	30.0	13.5	20.1

[a]Glioma and meningioma controls combined.

467.83 to 715.93 µT-years in cases (glioma/meningioma) and 0.03 µT-years to 609.38 µT-years in controls (Supplementary Table S2).

For glioma, there was no association with lifetime cumulative exposure, average exposure, maximum exposed job, or duration of exposure, and there was no exposure–response relationship (Table 2). However, for cumulative ELF there were positive associations in the 1 to 4 year time window before tumor diagnosis/reference date, with ORs ranging from 1.19 (95% CI, 1.00–1.43) to 1.67 (95% CI, 1.36–2.07) in the highest exposure category ($\geq$90th percentile; $P_{\text{Linear trend}}$ < 0.0001; Table 3), comprising ~76% of participants in that time window, relative to those <25th percentile. There were weaker positive associations in the 5- to 9-year time window. In the 10+-year time window, there was a weak, nonmonotonic inverse association with increasing ELF exposure (OR $\geq$ 90th percentile vs. <25th percentile, 0.77; 95% CI, 0.60–0.99; $P_{\text{Linear trend}}$ = 0.04). ORs (95% CIs) from a simultaneous exposure time windows model, including cumulative ELF from all 3 exposure time windows together in the same model, are

presented in Fig. 1A. Strong correlations between levels of cumulative ELF were observed for glioma cases and controls in the 1- to 4- and 5- to 9-year time windows (Supplementary Table S3), but were weaker for other time windows. Results were similar for both high- and low-grade glioma (Supplementary Table S4). Results for average exposure were generally similar in the 5- to 9- and 10+-year time windows, but in the 1- to 4-year time window, the positive association was attenuated (Supplementary Table S5). For maximum exposed job, there was a significant inverse trend (P = 0.003) in the 10+-year time window (Supplementary Table S6).

For meningioma, there was no association with lifetime cumulative exposure, average exposure, or maximum exposed job (Table 2). However, there was an elevated OR in the highest exposure duration group (25+ years vs. < 5 years; OR, 1.30; 95% CI, 1.03–1.64). There was also a significant positive linear trend (P = 0.02) with cumulative ELF exposure 1 to 4 years before tumor diagnosis/reference date (Table 3). No associations were seen in the 5- to 9- or 10+-year time windows. Figure 1B presents ORs (95% CIs) from

Table 2. Adjusted ORs (95% CIs)[a] for glioma and meningioma in relation to categorical indicators of occupational ELF exposure overall (1-year lag), INTEROCC study, 2000 to 2004, Australia, Canada, France, Germany, Israel, New Zealand, and the United Kingdom

Exposure metric	Glioma			Meningioma		
	Cases	Controls	OR (95% CI)[a]	Cases	Controls	OR (95% CI)[a]
Cumulative exposure (μT-years)						
<2.11	475	1,334	1.00 (ref.)	473	1,265	1.00 (ref.)
2.11–<3.40	454	1,327	1.00 (0.85–1.18)	465	1,278	0.96 (0.82–1.13)
3.40–<5.00	441	1,344	0.93 (0.78–1.11)	414	1,295	0.84 (0.70–0.99)
5.00–<7.50	370	808	1.07 (0.88–1.31)	290	783	1.05 (0.86–1.29)
7.50+	199	540	0.80 (0.63–1.00)	180	524	0.89 (0.70–1.12)
P_{Trend}-value			0.08			0.51
Average exposure (μT)						
<0.11	423	1,268	1.00 (ref.)	426	1,224	1.00 (ref.)
0.11–<0.13	398	1,273	0.96 (0.82–1.13)	419	1,244	0.94 (0.79–1.10)
0.13–<0.17	551	1,411	1.04 (0.89–1.22)	510	1,345	1.18 (1.00–1.38)
0.17–<0.24	330	856	0.95 (0.80–1.14)	262	809	1.03 (0.85–1.25)
0.24+	237	545	1.00 (0.82–1.23)	205	523	1.08 (0.87–1.33)
P_{Trend}-value			0.99			0·41
Maximum exposed job (μT)						
<0.13	453	1,370	1.00 (ref.)	505	1,341	1.00 (ref.)
0.13–<0.17	458	1,290	0.92 (0.79–1.08)	439	1,247	1.03 (0.88–1.20)
0.17–<0.23	430	1,202	0.85 (0.73–1.00)	362	1,146	0.98 (0.83–1.16)
0.23–<0.62	382	947	0.92 (0.78–1.09)	286	891	1.01 (0.84–1.21)
0.62+	216	544	0.80 (0.65–0.98)	230	520	1.15 (0.94–1.42)
P_{Trend}-value			0.08			0·16
Exposure duration (y)						
<5	1,333	3,849	1.00 (ref.)	1,324	3,716	1.00 (ref.)
5–<15	295	805	0.90 (0.77–1.05)	255	754	0.99 (0.84–1.17)
15–<25	142	371	0.94 (0.76–1.16)	104	353	0.85 (0.67–1.08)
25+	169	328	1.22 (0.99–1.51)	139	322	1.30 (1.03–1.64)
P_{Trend}-value			0.26			0.20

[a]OR estimated using conditional logistic regression models stratified by country, region, sex, and 5-year age group at the reference date and adjusted for level of educational attainment. Cut points based on the 25th, 50th, 75th, and 90th percentile of the control exposure distribution. Tests for linear trend used Wald χ^2 tests, with categorical medians modeled as ordinal variables.

a simultaneous exposure time windows model. For maximum exposed job, there was a significant positive trend ($P = 0.03$) in the 1- to 4-year time window (Supplementary Table S6).

Results for glioma with cumulative ELF in the 1- to 4-year time window were virtually unchanged with adjustment for occupational chemical exposures, with the exception of adjustment for benzo(*a*)pyrene (BAP) or polycyclic aromatic hydrocarbon (PAH) exposures, where ORs increased in the highest ELF exposure categories (Supplementary Table S7). ORs in some categories increased for both glioma and meningioma when excluding participants who were judged by the interviewer to be reticent and uninterested in the interview for cumulative ELF in the 1- to 4-year time window, however in the 10+-year time window, the weak inverse trend attenuated (Table 4). There was no significant effect modification observed.

Discussion

Results from this large-scale study revealed no association between lifetime occupational exposure to ELF, but positive associations with cumulative ELF 1 to 4 years before the diagnosis/reference date and glioma. Weaker positive associations were observed for meningioma. There was also a weak inverse association for glioma with ELF exposure in the distant past (10+-year time window), which attenuated when subjects judged to be reticent and unresponsive were excluded from analyses.

Some studies reported stronger associations with occupational ELF in more recent exposure time windows. Among general population studies, Villeneuve and colleagues (16), in a study of 543 incident brain tumor cases and controls, observed positive associations in the highest category of average ELF exposure ($\geq$0.6 μT vs. <0.3 μT) for all brain tumors (OR, 1.33; 95% CI, 0.75–2.36) and

Table 3. Adjusted ORs (95% CIs)[a] for glioma and meningioma in relation to categorical indicators of cumulative occupational ELF exposure in 3 separate exposure time windows, 1- to 4-, 5- to 9-, and 10+-years before the date of diagnosis/reference date, INTEROCC study, 2000 to 2004, Australia, Canada, France, Germany, Israel, New Zealand, and the United Kingdom

Exposure metric	Glioma			Meningioma		
Cumulative exposure (μT-years)	Cases	Controls	OR (95% CI)[a]	Cases	Controls	OR (95% CI)[a]
1–4 years						
<0.34	332	1,115	1.00 (ref.)	315	1,054	1.00 (ref.)
0.34–<0.46	338	1,012	1.19 (1.00–1.43)	301	970	1.00 (0.83–1.21)
0.46–<0.58	432	1,140	1.42 (1.19–1.69)	350	1,093	1.12 (0.93–1.34)
0.58–<0.80	297	632	1.54 (1.27–1.88)	210	593	1.30 (1.05–1.62)
0.80+	237	439	1.67 (1.36–2.07)	142	420	1.23 (0.97–1.57)
P_{Trend}-value			<0.0001			0.02
5–9 years						
<0.45	358	1,112	1.00 (ref.)	367	1,057	1.00 (ref.)
0.45–<0.59	391	1,126	1.12 (0.95–1.33)	391	1,075	1.00 (0.84–1.20)
0.59–<0.77	491	1,268	1.22 (1.03–1.43)	398	1,228	1.03 (0.86–1.22)
0.77–<1.07	263	671	1.09 (0.89–1.32)	185	636	0.97 (0.78–1.20)
1.07+	204	447	1.19 (0.96–1.47)	117	423	0.88 (0.68–1.13)
P_{Trend}-value			0.20			0.31
10+ years						
<1.38	442	1,277	1.00 (ref.)	435	1,198	1.00 (ref.)
1.38–<2.48	432	1,300	0.96 (0.81–1.15)	436	1,251	0.91 (0.77–1.08)
2.48–<3.98	435	1,290	0.90 (0.75–1.09)	433	1,247	0.90 (0.75–1.08)
3.98–<6.23	326	787	0.91 (0.73–1.13)	279	762	0.99 (0.80–1.23)
6.23+	197	522	0.77 (0.60–0.99)	189	510	0.92 (0.72–1.17)
P_{Trend}-value			0.04			0.76

[a]OR estimated for each exposure time window separately using conditional logistic regression models stratified by country, region, sex, and 5-year age group at the reference date and adjusted for level of educational attainment. Cut points based on the 25th, 50th, 75th, and 90th percentile of the control population's exposure distribution for each time window. Different cutoff points used for each time window because of differences in exposure distribution. Different numbers of cases/controls in different time windows due to the exclusion of participants from particular time windows where they reported not being employed. Tests for linear trend used Wald χ^2 tests, with categorical medians modeled as ordinal variables.

glioblastoma multiforme (OR, 5.36; 95% CI, 1.16–24.78), which strengthened for ELF in the last held job [OR, 12.59; 95% CI, 1.50–105.6, number of cases (controls) = 18; ref. 6)]. Floderus and colleagues (13), in a study of 261 brain tumor cases and 1,112 controls, noted positive associations between ELF in the longest job 10 years before diagnosis.

Among more highly exposed occupational groups, previous results were mixed, however there were small numbers of cases and few examined associations in different time windows (10). Savitz and colleagues (27), in a case–cohort study including 145 brain tumor deaths from 5 U.S. electric utility companies, reported positive associations with cumulative ELF (OR, 1.79; 95% CI, 0.69–4.65 highest exposed group; 4.33–12.20 vs. 0–0.65 μT-years) that strengthened 2 to 10 years in the past (OR highest exposed group, 1.14–2.23 vs. 0 μT-years = 2.62; 95% CI 1.15–5.97). Hakansson and colleagues (11) in a cohort of more than 700,000 resistance welders, observed positive

associations between average ELF and astrocytoma in women ($n = 66$, $P_{Trend} = 0.004$) in 10 years of follow-up. However, this was not observed in other studies (21, 28, 29).

Although ELF exposure in the 1- to 4-year time window represents a small proportion of total lifetime occupational ELF exposure, these results are compatible with a role in tumor promotion. ELF cannot impart enough energy to DNA molecules to create mutations, however it may act on signal transduction, cell proliferation, reactive oxygen species generation, the neuroendocrine or immune system, or interact with other chemical exposures (24, 25). Villeneuve and colleagues (16) suggested that stronger associations observed with more aggressive forms of glioma may also provide support for a promotional role of ELF, however similar findings were observed for both high- and low-grade glioma here. There was also a weak positive association between ELF in the longest exposure duration category and meningioma (and possibly

Figure 1. A, adjusted ORs (95% CIs) for glioma in relation to categories of cumulative occupational ELF exposure in the 1- to 4-, 5- to 9-, and 10+-year time windows before the date of diagnosis/reference date from a simultaneous exposure time windows model with cut points based on the 25th, 50th, 75th, and 90th percentiles, INTEROCC study, 2000 to 2004, Australia, Canada, France, Germany, Israel, New Zealand, and the United Kingdom. B, adjusted ORs (95% CIs) for meningioma in relation to categories of cumulative occupational ELF exposure in the 1- to 4-, 5- to 9-, and 10+-year time windows before the date of diagnosis/reference date from a simultaneous exposure time windows model with cut points based on the 25th, 50th, 75th, and 90th percentiles, INTEROCC study, 2000 to 2004, Australia, Canada, France, Germany, Israel, New Zealand, and the United Kingdom.
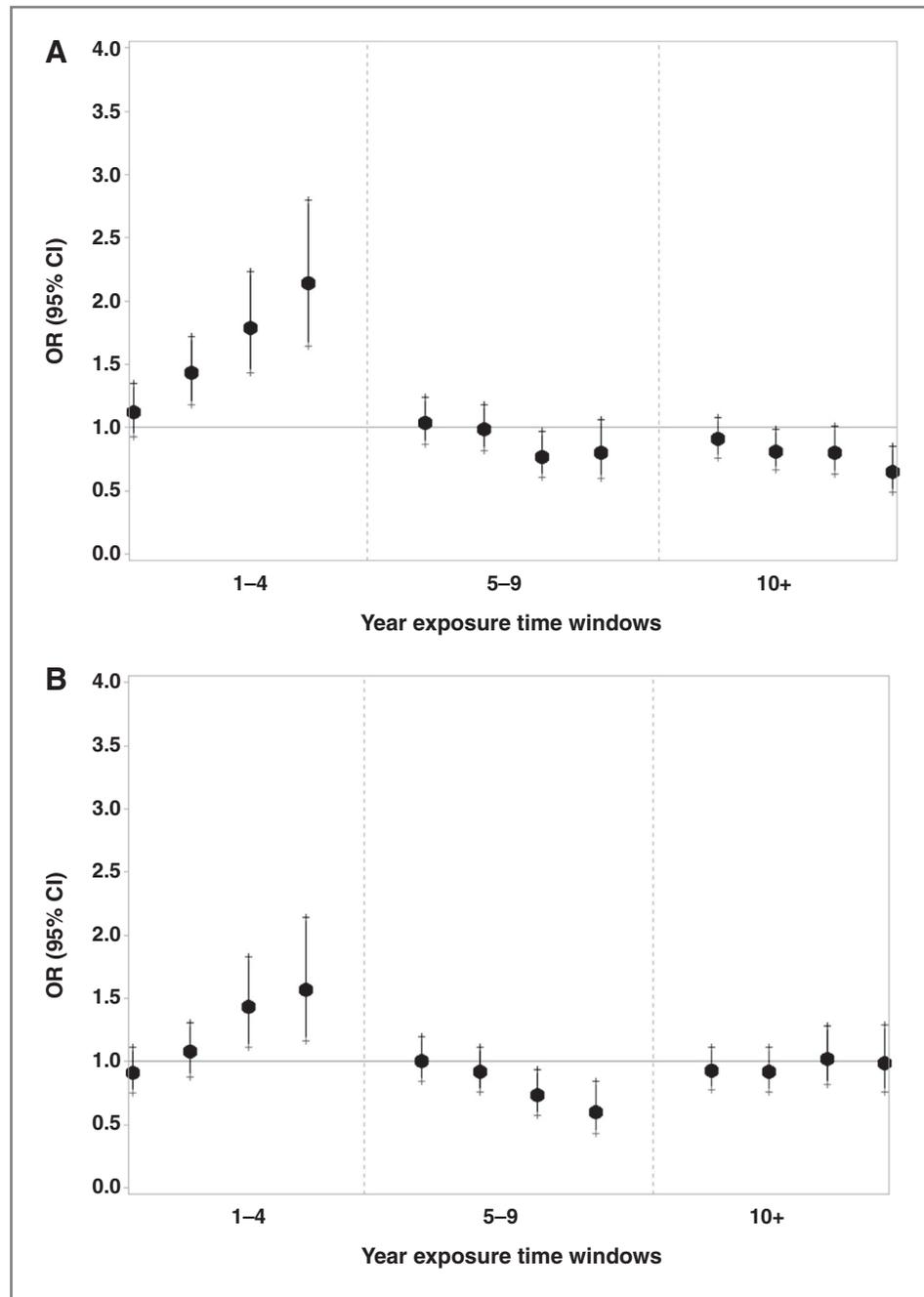
glioma), possibly suggesting a role for prolonged ELF exposure for that slower growing tumor. Alternatively, findings in different time windows of exposures may be due to chance.

Potential limitations include low participation rates, particularly among controls (ranging from 35% to 74%; ref. 30). The Swedish INTERPHONE study noted participation was positively associated with working status, income, and education (39). However, education was similar for participating cases and controls here. Cases and controls reported a similar number of lifetime jobs.

Mean (SD) weighted indicators of occupational prestige (SIOPS) were similar [glioma = 43.0 ($\pm$11.7), meningioma = 42.2 ($\pm$12.4), controls = 43.8 ($\pm$12.0)].

The positive association between ELF and glioma in the 1- to 4-year time window was seen for all exposure categories, including a large majority ($\sim$76%) of participants, across a wide spectrum of occupations, not solely "electrical occupations." Although preclinical symptoms of a brain tumor might lead to earlier diagnosis in certain jobs, they might also influence changes in occupation in different time windows, particularly for

Table 4. Adjusted ORs (95% CIs)[a] for glioma and meningioma in relation to categorical and continuous indicators of cumulative occupational ELF exposure in the 1- to 4- and 10+-year time window before the date of diagnosis/reference date, including only participants who were very cooperative, responsive, and interested as determined by the interviewer, INTEROCC study, 2000 to 2004, Australia, Canada, France, Germany, Israel, New Zealand, and the United Kingdom

Cumulative exposure (μT-years)	Glioma			Meningioma		
	Cases	Controls	OR (95% CI)[a]	Cases	Controls	OR (95% CI)[a]
1–4 years						
<0.34	218	826	1.00 (ref.)	201	758	1.00 (ref.)
0.34–<0.46	218	729	1.21 (0.97–1.51)	201	677	1.07 (0.85–1.35)
0.46–<0.58	301	825	1.54 (1.24–1.90)	248	778	1.24 (0.98–1.55)
0.58–<0.80	186	450	1.52 (1.20–1.94)	133	400	1.39 (1.06–1.82)
0.80+	149	304	1.76 (1.35–2.28)	90	282	1.30 (0.96–1.77)
P_{Trend}-value			<0.0001			0.03
10+ years						
<1.38	291	930	1.00 (ref.)			
1.38–<2.48	287	910	1.06 (0.85–1.32)			
2.48–<3.98	271	916	0.99 (0.78–1.25)			
3.98–<6.23	214	539	1.14 (0.87–1.50)			
6.23+	109	335	0.88 (0.64–1.21)			
P_{Trend}-value			0.44			

[a]OR estimated for each exposure time window separately using conditional logistic regression models stratified by country, region, sex, and 5-year age group at the reference date and adjusted for level of educational attainment. Cutoff points from Table 3 used here. Tests for linear trend used Wald χ^2 tests, with categorical medians modeled as ordinal variables.

low-grade glioma. The mean (SD) difference between average ELF levels in the 10+ and 1- to 4-year time windows was 0.001 (±0.58) for glioma cases and 0.02 (±0.31) for controls, indicating slight increases in ELF in more recent years. The preclinical phase of brain tumors is poorly understood. Fewer participants reported working in a job in the 1- to 4-year time window, however this seems to be unrelated to case/control status with 84% and 82% of included glioma cases and controls, respectively, reporting a job in this time window. The association with glioma remained, although attenuated slightly, upon restriction to participants who worked for a full 4 years in the 1- to 4-year time window (OR ≥ 90th percentile vs. <25th percentile, 1.44; 95% CI, 1.02–2.05; $P_{Linear\ trend}$ = 0.05).

We also excluded a small number ($n = 320$) of participants who reported having never been employed from analysis in an attempt to avoid potential selection bias by socioeconomic and/or employment status in analysis (5% of glioma cases, 5% of meningioma cases, and 2% of controls). Results including never employed participants in the reference category attenuated somewhat for glioma for ELF in the 1- to 4-year time window (OR ≥ 90% vs. < 25%, 1.45; 95% CI, 1.20–1.76) but the positive linear trend remained ($P < 0.0001$). For meningioma, the weak positive trend for ELF in the 1- to 4-year time window disappeared (OR ≥ 90% vs. OR < 25%, 1.07; 95% CI, 0.86–1.34) and was no longer significant ($P = 0.28$).

The weak inverse association between ELF in the 10+-year time window and glioma attenuating when subjects judged to be reticent and unresponsive were excluded from analyses may reflect some form of reporting bias among these subjects. Reticence and unresponsiveness was based solely on the personal opinion of the 130 interviewers in INTEROCC study countries.

Limitations of using a JEM include exposure misclassification, although it is likely nondifferential. A U.S. study modified JEM values based on time and distance information for ELF sources for 24% of jobs (19). This increased the ELF exposure category for 27% of jobs and decreased it for 15% of jobs. The modification also did not include the magnitude of a source's ELF emissions, which may introduce further misclassification.

The representativeness of the JEM across different countries and time periods is also unclear. Although here we relied on the overall JEM estimates, in sensitivity analyses using country-specific estimates where they were available in the JEM, as well as sex and time period–specific estimates, results were virtually identical to those obtained here. This study's focus on the TWA of the ELF magnetic field resultant also neglects other potentially important aspects of electromagnetic environment such as the magnetic field frequency spectrum, its polarization, intermittency, electric fields, shocks, contact currents, and neighboring bands of the EM spectrum. There is little

evidence for a role of ELF electric fields in carcinogenesis (40).

In conclusion, in this large-scale study we observed no association with lifetime occupational ELF exposure. However, results from this, and several smaller previous studies showed positive associations between ELF in the more recent past and glioma, and probably with meningioma. Future work to better understand possible biological mechanism of action, interactions with other occupational exposures, associations with other occupational EMF exposures, including intermediate and RFs, and to consider interindividual variation in ELF exposure is needed.

Disclosure of Potential Conflicts of Interest

D. Krewski is a CEO and Chief Risk Scientist at Risk Sciences International and he also reports receiving a commercial research grant from Natural Sciences and Engineering Research Council of Canada. No potential conflicts of interest were disclosed by the other authors.

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