Interactive Effect of Chemical Substances and Occupational Electromagnetic Field Exposure on the Risk of Gliomas and Meningiomas in Swedish Men

Ana Navas-Acién, Marina Pollán,[1] Per Gustavsson, Birgitta Floderus, Nils Plato, and Mustafa Dosemeci

Environmental and Cancer Epidemiology Area, National Center for Epidemiology, Carlos III Institute of Health, 28029 Madrid, Spain [A. N-A., M. P.]; Department of Occupational Health, Stockholm County Council, Stockholm, Sweden [P. G., N. P.]; Division of Occupational Health, Department of Public Health Sciences [P. G., N. P.], and Institute of Environmental Medicine [B. F.], Karolinska Institutet, Stockholm, Sweden; National Institute for Working Life, Stockholm, Sweden [B. F.]; and Rockville, Maryland [M. D.]

Abstract

The objective of our study was to investigate the possible interactive effect of occupational exposure to extremely low-frequency magnetic field (ELFMF) and to known or suspected carcinogenic chemicals on the incidence of the two main histological types of brain cancer, gliomas and meningiomas, in a cohort of male Swedish workers.

The historical cohort of all Swedish men gainfully employed in 1970 were followed 19 years (1971–1989). Exposure to ELFMF and to nine chemicals were assessed using two Swedish job exposure matrices based on occupational codes and industrial activity. Relative risks adjusted for age, period, geographical area, and town size were computed using log-linear Poisson models.

The main finding was the absence of ELFMF effect on glioma risk in the absence of a simultaneous exposure to chemical products. The effect of petroleum products was independent of the intensity of ELFMF exposure whereas solvents, lead, and pesticides/herbicides were only associated with glioma in workers also exposed to moderate or high levels of ELFMF. On the other hand, whereas ELFMF seemed to enhance the effect of specific chemicals in the causation of gliomas, we did not find a relationship between ELFMF exposure and meningiomas.

The potential for ELFMF to act as an effect modifier of the association of chemical agents and glioma is an interesting new finding. It would be worthwhile to evaluate this hypothesis for other tumors. Also, it is necessary to confirm these results in epidemiological studies with individual exposure assessments, and in experimental studies that may elucidate whether there is a true causal mechanism for the results we observed.

Introduction

The effect of occupational exposure to ELFMFs[2] on brain cancer risk has been extensively investigated in the past 20 years by using exposure information based on job titles or tasks with presumed or measured exposure levels (1). Twenty-nine independent studies performed in 12 different countries, with sufficient information about exposure, and published before 1995 were summarized in a meta-analysis (2) showing a small elevation in risk for the group of electrical occupations, but with considerable heterogeneity among the results and no dose-response pattern. Many more studies were published after 1995, and in 1999 the data of the four studies based on measurements among electric utility workers were combined, suggesting a small increase in risk of brain cancer in those exposed to ELFMF (3). An occupational group where the ELFMF effect has been investigated because of the extremely high exposure levels and limited job changes is railway workers, showing a possible elevation in risk for some occupations but no dose-response relation (4, 5).

After all these efforts, the results are still contradictory and the relationship between ELFMF and brain cancer remains unclear. Recently, Savitz (6) concluded that, given the large size and high quality of a number of previous studies, additional studies similar to past ones are unlikely to yield important new insights. Consequently, new approaches and hypotheses are needed to bring a better understanding of this relevant question.

If there is a risk associated with ELFMF exposure, either it is very small, or it may be dependent on contributing causes that are comparatively rare in the population at large. The inability of nonionizing radiation to break DNA indicates that ELFMFs could not be mutagenic *per se* and would require the presence of an initiator to start the process of cancer development. Supporting this hypothesis, in a previous study on breast cancer in men and ELFMF exposure, an exposure-response trend was detected only in transport and communication, production, and service workers whereas no effect was observed among those in professional, managerial, and administrative sectors (7). This difference might suggest the influence of additional exposures, more prevalent in the first mentioned group. Another likely possibility is that the ELFMF exposures themselves are fundamentally different. Regarding occupational exposure to chemicals, there is inconclusive evidence of an increased risk of brain cancer among those exposed to solvents (8), chlorinated aliphatic hydrocarbons (9, 10), pesticides (11, 12), petroleum products (13, 14), and lead (15).

The objective of the present study was to investigate the possible interaction between occupational exposure to ELFMF and chemical substances with known or suspected carcinogenic

effect and their influence on brain tumor risk by histological type using the population cohort of male Swedish workers. To our knowledge, this hypothesis has not been tested before.

Materials and Methods

The base population for this historical cohort comprised all Swedish men who: were gainfully employed at the time of the 1970 census; had also been recorded in the 1960 census; were still alive and over age 24 as of January 1, 1971; and with a job title included in the JEM used for ELFMF exposure assessment (16). This encompassed 1,516,552 men 25–64 years of age at the beginning of the study in 1971 and subsequently followed for 19 years until year-end 1989, rendering a total of 26,654,664 person-years, comprising the 84% of the overall cohort of Swedish male workers.

Information was drawn from four data sets; the first source of data was the Swedish cancer environment register, comprising all cancer cases including information on occupation, industrial branch, residence, and different demographic variables from the 1960 and 1970 censuses (17, 18). This register was used to compute specific rate numerators. Brain tumors were coded under the rubric 193.0 of the *International Classification of Diseases* (7th revision). Based on the histological classification (WHO 1957), gliomas and meningiomas were analyzed separately. Among gliomas, only astrocytomas were selected, excluding oligodendrogliomas and ependymomas. A histopathological code was available for more than 90% of the cases. The second data source comprised all individuals in the 1970 census, with information on occupation, industrial branch, and residence in 1970, and, if applicable, date of death. This register was used to calculate specific rate denominators. It was not possible to censor the follow-up of workers who emigrated during the study period. Nevertheless, the annual emigration rate among Swedish citizens during this period was very low, approximately 1/1000 (19, 20). The third source was a JEM comprising estimates of magnetic field exposures for the 100 most common jobs for men in Sweden according to the census of 1990 (16). For these occupations, exposure levels have been estimated based on at least four full-shift measurements from a total of more than 1000 measurements. In addition, 10 comparatively rare occupations with estimates based on less than four measurements, but with definitely high exposures, were added [occupations according to Table 10 of Floderus *et al.* (16)]. Different metrics of exposure have been computed. In the present study, we used the geometric mean of the work day arithmetic mean values for all individuals in an occupation (hereafter called average mean value). Finally, another Swedish JEM was used to ascertain the exposition to chemical substances, as it is explained below.

Exposure to eight chemical factors was assessed by linking any combination of occupation and industrial branch to a JEM that classifies each combination as "no exposure," possible," or "probable" in the gainfully employed Swedish population for 1970. The JEM was originally developed for a study of bladder cancer and occupational exposures (21), which was extended and updated for an evaluation of exposure to potential carcinogens in the Swedish workforce (22). Industrial branch was coded according to the Nordic Registry of Industries on a four-digit level (23). The exposure to arsenic, chromium/nickel, lead, mercury, metallic compounds (explained in detail below), pesticides or herbicides, pesticides or herbicides on peak exposure (mainly applicators), petroleum products, and solvents was evaluated for 11,227 combinations of occupation (291 occupations) and industry branch (239 industries). Combina-

tions of occupation and industry with less than 10 persons were not evaluated. Possible exposure means than between 10% and 66% of the subjects in the occupation and industry combination were exposed to levels >10% of the Threshold Limit Value (TLV) for each chemical, and probable exposure means that more than 66% of the subjects were exposed to these levels. Metallic compounds include both paint pigments exposure among painters, lacquerers, as well as chromium in cement for masons, or chemical process workers in certain industries, chemists or laboratory technicians, and battery workers. Lead exposure occurred among battery workers, in soldering operations in the electronic industry, in pigments for painters, and in soldering in automobile cooling systems. Mercury exposure occurred mainly within dental activities.

The overall person-time that each worker contributed to the study was allocated to the corresponding cells of the variables of stratification. These variables were (a) occupation; (b) 5-year age group, from 25–29 to 75–79; (c) calendar time period (1971–1975, 1976–1980, 1981–1985, and 1986–1989); (d) county of residence; and (e) town size. In the 1970 census, job titles were coded according to the Nordic Classification of Occupations (18). Every occupation was represented by a three-digit number. The first digit referred to 1 of 10 major occupational sectors (0–9), where higher numbers indicate manual occupations, and lower numbers nonmanual occupations often requiring longer education associated with a higher socioeconomic status. Exposure to ELFMFs was assessed by linking occupations to the above-mentioned matrix. Four exposure groups were formed with cut off points at the 33rd, 66th, and 90th percentiles of the exposure distribution in the cohort, with the lowest group as reference.

The expected number of cases in any given occupation was computed taking age- and period-specific rates of the overall cohort of gainfully employed men in 1970 as reference. On the assumption that the observed number of cases in each stratum was distributed as a Poisson variable, log-linear Poisson models were fitted replacing occupation by the ELFMF exposure group for each tumor type, adjusting for geographical risk area and town size, because brain cancer risk proved to be associated with these two variables. The geographical risk area was defined as: the 24 Swedish counties were grouped into three categories depending on the age-standardized incidence ratio (number of observed cases *versus* number of expected cases × 100) of glioma and meningioma, respectively. The three categories corresponded to counties with standardized incidence ratios: <87; 87–115; and >115. Town size was categorized in three groups: less than 20,000 inhabitants; between 20,000 and 100,000; and more than 100,000. The categories of geographical area and town size were represented by dummy variables in the regression. In these models, the number of expected cases was introduced as an offset (24). Given that the expected number was computed on the basis of the age- and period-specific reference rates, the RR for each ELFMF exposure group was likewise age and period adjusted. Furthermore, the statistical significance of a gradient of risk with increasing exposure was tested, including the ELFMF categories of exposure as a continuous variable.

The investigation of the interaction considering simultaneously ELFMF and chemical substances was done in the subcohort of subjects with information available for both exposures. This subcohort included 21,476,363 person-years (80.6%) and rendered 2,156 (75.4%) gliomas and 753 (75.8%)

Table 1 Glioma risk associated with exposure to occupational magnetic fields and occupational factors among men adjusted for age, period, geographical category, and town size

| Occupational exposure factors[b,c] | Occupational magnetic fields exposure[a] | | | | | | | | |
| | <0.13 μT | | | 0.13–0.20 μT | | | >0.20 μT | | |
	OC[d]	RR	95% CI	OC	RR	95% CI	OC	RR	95% CI
Chromium/nickel									
No exposure	724	1.00		813	1.09	0.98–1.20	539	1.05	0.94–1.17
Possible/probable	19	0.99	0.63–1.56	16	1.30	0.79–2.14	45	1.19	0.88–1.61
Lead									
No exposure	743	1.00		822	1.09	0.98–1.21	581	1.05	0.94–1.18
Possible/probable				7	1.22	0.58–2.57	3	3.91	1.26–12.15
Mercury									
No exposure	743	1.00		829	1.09	0.99–1.20	572	1.05	0.94–1.17
Possible/probable							12	1.76	0.99–3.11
Metallic compounds									
No exposure	743	1.00		813	1.09	0.98–1.20	528	1.05	0.94–1.17
Possible/probable				16	1.27	0.77–2.08	56	1.18	0.90–1.55
Pesticides/herbicides									
No exposure	743	1.00		829	1.09	0.98–1.20	574	1.06	0.95–1.18
Possible/probable				0			10	1.22	0.66–2.29
Pesticides/herbicides peak exposure									
No exposure	528	1.00		795	1.09	0.97–1.21	579	1.07	0.95–1.20
Possible/probable	215	1.04	0.89–1.23	34	1.57	1.11–2.22	5	2.08	0.86–5.02
Petroleum products									
No exposure	735	1.00		781	1.09	0.98–1.21	565	1.05	0.94–1.18
Possible/probable	8	2.30	1.14–4.62	48	1.21	0.90–1.63	19	1.51	0.96–2.38
Solvents									
No exposure	617	1.00		615	0.97	0.88–1.08	541	0.97	0.88–1.08
Possible/probable	126	0.93	0.82–1.05	214	0.98	0.84–1.14	43	1.55	1.14–2.12
Arsenic									
No exposure	743	1.00		796	1.07	0.97–1.19	556	1.06	0.95–1.19
Possible/probable				33	1.73	1.22–2.45			

[a] JEM for the 100 most common jobs in Sweden based on measurements involving more than 1000 workers, all men, who carried a dosemeter for 6,8 hours on average.
[b] JEM for combinations of occupation and industry in the Swedish workforce for 1970. Some combinations were not assessed because of the small numbers of persons.
[c] Classified as no exposure, possible (prevalence > 1 of 10 and <2 of 3 of the subjects), and probable (>2 of 3 of the subjects follow the criteria to the exposure levels >10% of the TLV for each factor).
[d] OC, observed cases.

meningiomas. The effect of ELFMFs in the presence and absence of each chemical was studied by log-linear Poisson models for each tumor type adjusted for age, period, geographical risk area, and town size. The two upper categories for ELFMFs were grouped in one, and possible and probable exposure for the chemicals were combined in the analysis because of the small number of subjects. The RRs for each ELFMF exposure group in workers exposed or not to a specific chemical were obtained using as reference those in the lowest group of ELFMFs and not exposed to the specific chemical substance. The relative excess risk due to interaction (25) was calculated for those chemicals with subjects exposed in all the categories of ELFMF exposure and that showed a possibility of interaction in the previous joint effect analysis. The CIs were computed using bootstrapping methods, with 2,000 iterations (26).

Results

During follow-up a total of 2859 gliomas and 993 meningiomas were reported in the study cohort. Occupational ELFMF exposure using as reference those with an average mean below 0.13 μT (33rd percentile) was related to a weak increased risk of gliomas in the second exposure group [0.13–0.20 μT; RR, 1.12 (95% CI, 1.02–1.22)] and in the third group [0.20–0.30 μT; RR 1.12 (95% CI, 1.01–1.25)], but it was not maintained above 0.30 μT (90th percentile; RR, 1.07; 95% CI, 0.94–1.21). In-

creasing ELFMF exposure was not associated with glioma in occupational sectors 0 to 3 (professional, managerial, administrative, and clerical workers) whereas among sectors 6 to 9 (transport and communication, production, and service workers) the risk was higher in all groups above 0.13 μT. We failed to detect any association between ELFMF exposure and meningioma risk, neither in the overall analysis nor in that stratified by occupational sectors (data not shown).

Table 1 presents the risk of glioma across the ELFMF exposure groups stratified by chemical exposure. Among subjects not exposed to the chemicals, RRs for increasing electromagnetic exposure were close to unity, with no evidence of a dose-response pattern. Regarding the effect of chemical substances in the group of workers with low exposure to ELFMF, a 2-fold increased risk was observed for petroleum products, and no association was detected for pesticides/herbicides on peak-exposure and solvents. For the rest of the substances, the risk estimation was unrealizable because no persons were included in these categories. In the medium ELFMF exposure category, statistically significant increased risks were detected for those also exposed to arsenic or pesticides/herbicides on peak exposure, and slightly elevated risks for those also exposed to chromium/nickel or petroleum products. Last, in the highest ELFMF exposure group, we found statistically significant RRs with exposure to lead or solvents and elevated risks for chromium/nickel, metallic compounds, or petroleum prod-

Table 2 Occupational codes included in the JEMs under the categories of possible/probable exposure to the following chemical factors by electromagnetic exposure groups

Chemicals[b]	ELFMF[a]		
	<0.13 μT	0.13–0.20 μT	>0.20 μT
Chromium/nickel	781 Painter	11 Chemist	755 Welder & flame cutter
	791 Bricklayer	750 Toolmaker, setter and operator	
Lead		11 Chemist	751 Machinery fitter, assembler
		764 Radio/TV assemble and repairmen	
Mercury			32 Dentist
Metallic compounds		11 Chemist	4 Chemical engineer
		55 Vocational studies teacher	735 Blacksmith, forger
		750 Toolmaker, setter and operator	741 Precision toolmaker
			751 Machinery fitter, assembler
			755 Welder and flame cutter
Pesticides/herbicides		11 Chemist	4 Chemical engineer
Pesticides/herbicides peak exposure	401 Farmer, wood and horticulture enterprises	404 Horticultural supervisor	678 Railway linesmen
	402 Farm managers and supervisor	412 Horticultural worker	
	403 Forestry managers and supervisor		
Petroleum products	401 Farmer, wood and horticulture enterprises	3 Mechanical engineer	4 Chemical engineer
	876 Greaser	11 Chemist	302 Working proprietor, retail trade
		331 Commer. traveler, buyer, dealer	332 Shop manager
		333 Shop assistant	338 Filling stat attend, demonst
		750 Toolmaker, setter, and operator	741 Precision toolmaker
		801 Typographer, litographer	
Solvents	781 Painter	6 Engineer and technician other	4 Chemical engineer
	793 Industrial spray painter	11 Chemist	32 Dentist
	876 Greaser	331 Commer. Traveler, buyer, dealer	81 Sculptor, painter, photograph artist
	883 Store and warehouse worker	333 Shop assistant	302 Working proprietor, retail trade
		750 Toolmaker, setter and operator	332 Shop manager
		771 Construction carpenter and joiner	741 Precision toolmaker
		772 Bench carpenter and cabinet maker	751 Machinery fitter, assembler
		852 Plastic products worker	753 Sheet metal worker
Arsenic		412 Horticultural worker	

[a] JEM for the 100 most common jobs in Sweden based on measurements involving more than 1000 workers, all men, who carried a dosemeter for 6 and 8 hours, on average.
[b] JEM for combinations of occupation and industry in the Swedish workforce for 1970. Some combinations were not assessed because of the small numbers of persons.

ucts. For lead the result was based only on three cases, but for solvents the number of cases allowed a more detailed scaling, splitting the highest group in two with the 90th percentile as cutoff. Between 0.20 and 0.30 μT, the risk for probable/possible exposure to solvents was 1.58 (95% CI, 1.01–2.46) and above 0.30 μT (RR, 1.54; 95% CI, 1.01–2.33). Finally, the only statistically significant relative excess risk due to interaction was observed for those with ELFMF exposure above 0.20 μT who were also exposed to solvents, 0.50 (95% CI, 0.04–1.00).

The analysis of the joint effect of ELFMF and chemicals for meningiomas was limited by a small number of cases in some of the categories but, in general, no pattern was observed across the exposure group for neither ELFMF exposure nor for chemicals (data not shown). The only substance with an increased risk of meningiomas in combination of ELFMF exposure was lead (RR, 2.73; 95% CI, 1.12–6.61), although it was based just on five cases, all of them in the medium ELFMF exposure group.

For interpretation purposes, the occupational codes included under the categories of possible or probable exposure to the different chemicals of the study and classified by ELFMF exposure groups are listed in Table 2.

Discussion

The present cohort study among Swedish men displayed a discrepancy across occupational sectors in the risk of gliomas with increasing exposures to ELFMF. There were some indications of an increased risk in association with ELFMF exposure in the sectors of transport and communication, production, and service workers, whereas no effect was noted in the other sectors. When exposure to chemical substances was taken into account, the results indicated that ELFMF had no effect on glioma risk in the absence of a simultaneous exposure to other potential carcinogens such as solvents, lead, mercury, petroleum products, arsenic, and pesticides/herbicides. Furthermore, occupational exposure to solvents, lead, and pesticides/herbicides on peak exposure was associated with a high risk of gliomas only among those workers also exposed to moderated or high levels of ELFMF. Although ELFMF seemed to have a

role as enhancer of the effect of specific chemical substances in the causation of gliomas, we did not find any relationship between ELFMF exposure and meningiomas, reinforcing the broader evidence that gliomas and meningiomas seem to have distinctive risk factors (2, 27).

Exposure classification based on JEMs is a rough proxy measure for the individual's current as well as previous exposure, with large variability within occupational groups and changes for several occupations across periods of time. However, compared with occupational titles, JEMs offer the advantage of greater statistical power resulting from joining subjects with common exposures from various occupations. The two JEMs used in our study were developed with different methodologies and for working populations in different periods of time. The JEM for ELFMF was based on direct measurements for the 100 most common jobs in Sweden according to the 1990 census, whereas chemical exposures were estimated through a qualitative matrix that aimed to be representative of the 1970 Swedish labor force and that took into account industrial branch as well as occupation. Another source of misclassification could be the allocation of occupation based on the subjects' occupational category at the beginning of the study. The possibility of misclassification might bias RRs toward the null hypothesis, and, thus, greater real risks should be expected if there was no uncontrolled confounding. This study was able to adjust only for age, period, geographical area, and town size. Because very little is known about brain tumor etiology, adjustment for other confounding factors would be limited anyway. Taking these limitations into account, our results must be considered as hypothesis generating and need confirmation in studies with a more detailed assessment of exposure both to ELFMF and chemicals.

The effect of occupational exposure to chemicals without taking ELFMF into account has been previously studied in the same cohort (27). The main findings were the increased risk of gliomas with exposure to arsenic, mercury, and petroleum products and of meningioma with lead. The potential modification from chemical agents adds a new aspect to the simple and extensively evaluated analytical models of the ELFMF-cancer link. Some strengths of the present study are the large number of persons involved, the long period of follow-up, the stratification of the analysis by histological type, and the completeness of histological confirmation.

The effect of ELFMF and glioma risk observed in the overall cohort does not support the hypothesis of a causal link with glioma, with no effect in the group of exposure above the 90th percentile and a weak association in groups of medium exposure. This absence of a clear association is consistent with the contradictory results obtained by the investigations carried out during the last 20 years. However, the effect of ELFMF seemed to be different by occupational sectors, with a concentration of the increased risk in those sectors where additional exposures were more prevalent. Minder and Pfluger (4) analyzed the effect of increasing ELFMF exposures in four different occupations in Swiss railway employees and observed an association with glioma only in two of them, concluding that these two occupations may have had a common exposure that caused brain tumors and that it was unlikely that electromagnetic fields were solely responsible for this finding. In a meta-analysis of occupational exposure to ELFMF, greater pooled RRs were obtained for specific occupations than when a broad definition of ELFMF was used, reflecting perhaps the importance of specific coexposures present only in those particular jobs (2).

There is consensus that, if ELFMF contributes to cancer development, it would act as a promoter, requiring the presence of initiators to develop cancer. Experimental evidence has not provided a definite mechanism linking ELFMF to cancer, although some biological effects have been identified (1), and regarding brain tumors, some of them could be important, such as the increase of the blood-brain barrier permeability (28–30). For hormonal-dependent tumors, the influence of electromagnetic fields on the pineal gland with a decreased secretion of melatonin and the interaction with the endocrine/immune system has been suggested as a possible mechanism (31, 32), and this endocrinological mechanism is also supported by epidemiological evidence (33). Brain tumors and specifically gliomas may be hormonal dependent (33–36). Immunological status may also play a role in glioma development, and chronic stimulation of the immunological system seems to reduce the risk of glioma because a lower incidence was reported in persons with a previous diagnosis of allergy or with antecedents of infectious diseases (36).

The results for gliomas in the present study showed that although the effect for petroleum products was independent of ELFMF, occupational exposure to lead, solvents, and pesticides/herbicides on peak exposure seemed to interact with ELFMF. The risk of glioma among subjects exposed to these substances was enhanced with increasing electromagnetic fields exposure, with lower RRs in low and moderate exposure groups than in the category with the highest daily average mean. However, it was not possible to assess the effect of lead in the lowest group of ELFMF exposure because there were no workers exposed to lead in that group. For chromium/nickel and for metallic compounds, RRs were weaker and far from the statistical significance level, although the risk was below unity in the lowest group of ELFMF exposure and above for moderate and high exposures. Finally, it was impossible to assess whether the effect detected for arsenic and mercury was independent of ELFMF, given that all the subjects exposed to these chemicals were from one occupation (see Table 2), and, thus, all these cases were classified in only one category of ELFMF exposure. In general, for the substances that allowed the study of effect modification in the three ELFMF groups, the results of low, medium, and high exposure strengthened the evidence of interaction. Whereas the combination of the second and third tertiles of ELFMF would have served to increase the statistical power, we have kept these two categories to show that the increase in risk indicated for combined exposures was not attributable to "one single" occupation.

Concerning meningiomas, no increased risk was observed by ELFMF exposure groups, and the study of effect modification showed no clear pattern of interaction with any of the chemical substances with ELFMF although the number of cases in general was insufficient. The two main histological groups of brain tumors, gliomas and meningiomas, differ in terms of their localization, embryology, and probably also etiology. When they were analyzed separately, very limited support was provided for an association of ELFMF with meningiomas, whereas its possible effect on brain cancer appeared mainly related to gliomas (2).

The main finding of this study was the absence of ELFMF effect on glioma risk in the absence of the known/suspected carcinogens studied. Furthermore, the effect of petroleum products was independent of electromagnetic fields whereas solvents, lead, and pesticides/herbicides on peak exposure were only associated with glioma in workers also exposed to moderate or high levels of ELFMF. Potential modification from chemical agents is an interesting new angle for the assessment of the ELFMF-cancer link. It would be interesting to test this

hypothesis in other tumors where ELFMFs have been involved. Also, it is necessary to confirm these results in epidemiological studies that include individual exposure assessments and in experimental studies that explore the biological plausibility of the proposed mechanism of interaction.

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