

Occupational and environmental risk factors for brain cancer: a pilot case-control study in France

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Résumé

Facteurs de risque professionnels et environnementaux des tumeurs cérébrales malignes : une étude pilote cas-contrôle en France

Introduction > L'augmentation de l'incidence des tumeurs malignes cérébrales primitives (TCMP) rapportée dans plusieurs études pourrait être due à des facteurs environnementaux. Afin d'estimer les facteurs de risques chimiques et physiques des tumeurs cérébrales malignes primitives (TCMP) dans le sud-est de la France, une étude pilote, cas-contrôle, a inclus tous les nouveaux cas de TCMP diagnostiqués en 2005 dans les principaux centres du secteur ouest de la région Provence-Alpes-Côte d'Azur (PACA).

Méthodes > Les cas et les contrôles appariés selon le sexe et l'âge ont été recensés dans le département de neurochirurgie du même centre hospitalier. Un spécialiste en médecine du travail a collecté les informations sur les facteurs de risques suspectés de TCMP à travers un interrogatoire individuel et en utilisant un

Summary

Introduction > The increased incidence of malignant primary brain tumors (MPBT) reported in several studies could be due to environmental factors. To estimate the chemical and physical risk factors of these tumors in southeastern France, a pilot case-control study that included all new MPBT cases diagnosed in 2005 in the main brain cancer treatment centers in the western section of the Provence-Alpes-Côte d'Azur (PACA) region.

Material and Methods > Age-, sex-, and hospital-matched controls were selected from the neurosurgery department of the same hospital. An occupational physician, using a standardized questionnaire, collected information on suspected risk factors of MPBT in a face-to-face interview at the hospital of all case and control subjects. Data collected included jobs held, various exposures throughout working life, and leisure time activities.

Results > The study included 122 cases and 122 controls. No particular job was identified as a major risk factor for brain cancer. Risk was significantly higher among those who used glue (OR = 17.58, 95% CI

questionnaire identique pour tous les cas et les témoins. Les données sur la profession et sur les différentes expositions ont été recueillies en tenant compte de l'ensemble du cursus professionnel et des loisirs.

Résultats > Sur les 122 cas inclus, aucune profession n'a été trouvée comme étant un facteur de risque majeur de tumeur cérébrale maligne. Une augmentation significative du risque a été décelée pour l'utilisation de colles (OR = 17.58, 95 % CI 1.75 – 176.62) au cours des loisirs et une diminution significative du risque a été mise en évidence concernant le lieu de résidence près d'une antenne d'émission de téléphones cellulaires (OR = 0.49, 95 % CI 0.26 – 0.92).

Discussion > De nouvelles recherches sur les effets des antennes de téléphones cellulaires et des expositions chimiques mériteraient d'être effectuées par des études analytiques.

The past three decades have seen an increase in the incidence of malignant primary brain tumors (MPBT) in industrialized countries, especially gliomas in adults and still more

1.75 – 176.62) during leisure activities and significantly lower among those residing near cellular telephone towers (OR = 0.49, 95% CI 0.26 – 0.92).

Discussion > Several new hypotheses about the effects of cellular telephone towers and chemical exposure merit further analytic studies.

particularly, in the elderly [1–6]. Improvements in diagnostic methods, especially imaging, help to explain this phenomenon [2–7]. Between 1983 and 1990, the incidence of malignant astrocytomas in the population older than 65 years increased at a rate of 5% a year in France [2]. The US National Institute of Environmental Health Sciences reports that 70% of cancers are due to environmental factors, including lifestyle, occupation, diet, and rural or urban residence. It is suspected that risk factors for glioma might include numerous chemical and physical agents, among them, pesticides [8–9], metals [10], polycyclic aromatic hydrocarbons (PAHs) [11–12], solvents [13], ionizing radiation, and electromagnetic fields [14–15]. An increased risk has been reported for metal industries [13], agriculture [16–17], the electrical/electronics industry [18], and textile manufacturing [19]. The cause of this increase in gliomas remains unknown [2,20]. An international case-control study coordinated by the International Agency for Research on Cancer (IARC) from 1980 through 1991 studied occupational risk factors for gliomas; its results did not support the hypothesis that occupational exposure is a major risk factor [10]. Over the past decade, no study in France has examined potential exposure during leisure activity in assessing the associations between MPBT, occupational sectors, and environmental factors. We conducted a pilot study in southeastern France of incident cases of adult MPBT to measure the distribution of these tumors according to occupational sector and leisure-time exposures. We evaluated the correlations between MPBT and carcinogenic chemical exposures.

What was known

- The cause of the increased incidence of brain cancer over the past 3 decades in industrialized countries is unknown. Data from the International Agency for Research on Cancer (IARC) failed to support the hypothesis that occupational exposure is a major risk factor for gliomas.
- Suspected risk factors include pesticides, metals, polycyclic aromatic hydrocarbons, solvents, ionizing radiation, and electromagnetic fields.
- No French study has investigated the associations between brain cancer, occupational sectors, and environmental factors, including potential leisure-time exposure.

What this study adds

- No association was found between any of the occupational sectors suspected of association with brain cancer and an elevated risk of brain cancer.
- Glue use in leisure activities was associated with an increased risk of brain cancer, and living near cellular telephone towers was found to be protective.
- Further epidemiologic studies should analyze exposure during leisure activity as well as occupational and environmental exposure.

Patients and methods

Study population

This pilot case-control study included all new cases of adult MPBT diagnosed between January 2005 and December 2005 in

the public reference hospitals of Marseilles (district of Bouches-du-Rhône) and Sainte Anne's Hospital in Toulon (district of Var). These hospitals are the principal reference centers for brain cancer in the western part of the Provence-Alpes-Côte d'Azur (PACA) and provide the therapeutic management for almost 85% of the incidental cases of MPBT in this geographic area. To be eligible for the study, patients had to be 18 years old at the time of diagnosis. Inclusion criteria for potential case subjects included diagnosis of previously untreated glioma, grade II to IV according to WHO criteria [21]. Because they affect mainly children, pilocytic astrocytomas (WHO grade I) were excluded, as were recurrences of previous MPBT. For each case, one control, matched for age (within 5 years) and gender and hospitalized for reasons unrelated to cancer, was randomly selected from the neurosurgery department of the same hospitals. An additional inclusion criterion for cases and controls was that they reside in the western half of PACA.

Data collection

The neuro-oncologists contributing to this study recruited participants. Patients were included only after they furnished fully informed consent. The diagnosis of MPBT was provided by pathology findings at the time of stereotactic biopsy or tumor removal and based on the WHO classification. Because the elderly (>70 years) may represent up to 20% of the population with high-grade glioma, incidence is higher in this age bracket, and a significant proportion of these patients may not be considered for surgery because of their significant morbidity-mortality risk, we included these patients, especially because the increase in MPBT incidence concerns precisely this age bracket. Most case subjects were interviewed after surgery and before tumor progression. An occupational physician collected information on suspected risk factors for MPBT through a face-to-face interview at the hospital, as soon as the patient's health permitted (and no later than 3 months after surgery). All cases and controls were interviewed with the same method and according to the same standardized questionnaire. At the same time, the occupational physician checked all items completed by the patient in a preliminary self-assessment questionnaire. Data on jobs and various exposures covered lifelong occupational history and leisure time habits. The interview took an average of 30 minutes. Information was collected on any history of cancer treatment, exposure to medical ionizing irradiation, computer use, cell-phone use, occupational history of exposure to chemical and physical agents (ionizing and non-ionizing irradiation), and chemical exposure during leisure activities (for example, painting, do-it-yourself home repair, and gardening). Job titles were subsequently classified according to the International Standard Classification of Occupations (ISCO-88).

Exposure definition

Chemical exposures

Occupational history data included the start/end dates of each job and a detailed description of the tasks, including the intensity and period of chemical exposure. We established a list of substances known to cause glioma (nitroso compound) or highly suspected of causing brain cancer (for example, pesticides, metals, PAHs, and solvents) and of all substances known to cause occupational cancer or environmental cancers, such as asbestos. During the interview, we inquired as precisely as possible into the circumstances of exposure to these substances. Furthermore, chemical exposure during leisure activities such as do-it-yourself home repair, painting, and gardening was evaluated according to the same methods. Patients were asked to explain in detail the nature of exposure, how the material was used, what protective clothing was worn, and whether ventilation was provided (protective devices). They estimated the exposure for each hazard as number of days per week, per month, or per year. Then an exposure score based both on duration and on the intensity of exposure was defined by the same expert in occupational disease for both sources of chemical exposure (occupational and leisure activities). For each risk factor studied, the duration of exposure was expressed as a full-time year equivalent, allowing correction for part-time workers by making the assumption of a cumulative risk function (2 years of part-time exposure being equivalent to one year full-time). The duration was then classified into three groups (< 2 years, 2-10 years, > 10 years). Finally, the expert, masked to case-control status, classified all cases and controls in three broad classes according to their global occupational history and global leisure exposure. These classes were: no or slight exposure, moderate exposure, and high exposure. For the high exposure class, details of chemical exposure were obtained by questions based on a list previously collected of primary substances suspected of causing brain cancer or classified as carcinogenic by IARC. Similarly, subjects detailed exposure from a non-exhaustive list of the principal chemical agents related to three leisure activities: do-it-yourself home repair, gardening, and painting.

Radiation exposure

Cell phone use was categorized according to the duration of the monthly subscription (< 2 hours, 2 to 6 hours and > 6 hours per month) and years of use (< 2 years, 2 to 6 years and more than 6 years). Cumulative cell-phone use was evaluated in hour-years (number of hours of subscription per month X number of years of use). The categories were no or little use (≤ 4 hour-years), moderate (4 to 36 hour-years), and high (≥ 36 hour-years).

The subjects evaluated the amount of time they spent using a computer during leisure time and at work over the past five years. Computer time was assessed in hours per day (none, less

than, or 4 or more hours/day) for occupational use and in hours per week for leisure time (none, less than, or 5 or more hours/week).

Exposure to medical ionizing radiation was evaluated mainly for the head and neck region during the past five years. Patients were asked if they had had radiography, computed tomography (CT) or scintigraphy, besides examinations related to the disease for which they were currently hospitalized. Radiotherapy was considered for all the parts of the body, but radiotherapy on the head and neck region was always explicitly specified.

A list drawn up beforehand, detailing the main occupational sectors and the types of radiation associated with them, was used to inquire about occupational exposure to radiation. For ionizing radiation it highlighted medical and paramedical occupations, research and nuclear technology, and some industries (for example, gammagraphy and sterilization). For non-ionizing radiation it distinguished extremely low frequency electromagnetic fields (electric wiring, magnets), radiofrequency electromagnetic fields (telecommunications, electrothermics), and ultraviolet and infrared radiations.

Residential setting

To assess chemical exposure related to residential environment, subjects were asked whether they lived near (< 500m) any chemical plants, vineyards, agricultural fields, or dump

sites. Exposure to radiation was assessed by question about high-tension cables, cell phone towers, airports, and highways.

Statistical analysis

We used exposure odds ratios (OR), and 95% confidence intervals (CI), to determine whether the risk factors considered were associated with an increased risk of developing MPBT. The unconditional logistic regression included the matching covariates of age and gender. Other adjustments were used to take potential confounders into account. All analyses used SPSS software version 13.0 (SPSS Inc, Chicago, IL, USA).

Results

General characteristics of the population

We identified 162 eligible cases that met the study criteria: 5 (3%) refused to participate, 20 (12.3%) died before the interview, and 21 (12.9%) dropped out. Complete questionnaires were obtained for 116 patients (71.6%) and incomplete questionnaires (only the preliminary self-administered questionnaire) for 6 patients (3.7%), who died or dropped out before the interview. Data for 122 cases (complete and incomplete questionnaires) were analyzed (72 men and 50 women). Overall, 51.9% of case subjects and 90.2% of control subjects completed the preliminary questionnaire themselves; the others were helped by family members. During the risk factors

TABLE I

Selected characteristics of case and control subjects and of malignant brain tumors among case subjects (frequency and percentage), western PACA, 2005

Characteristics	Details	Cases		Controls		p-value
		N = 122	%	n = 122	%	
Gender	Men	72	64,7	72	64,7	1
Age	Mean (range)	57.0 (20.4; 86.3)			57.0 (20.7; 86.6)	0.98
History of Cancer treatment ^a	Radiotherapy	2	1.7	1	0.9	0.62
	Chemotherapy	2	1.7	0	0	0.50
Smoking habits	Smokers or Past smokers	62	53.4	68	56.9	0.86
Pathology findings	Astrocytoma	1	0.9			
	Oligodendroglioma	19	16.4			
	Oligoastrocytoma	23	19.8			
	Glioblastoma	72	62.1			
Medical imaging ^b	Gliomatosis cerebri	1	0.9			
	suspected MPBT	6	4.5			
Glioma grade N = 119	Grade II	21	16.5			
	Grade III	27	21.2			
	Grade IV	71	56			

^aBefore MPBT diagnosis.

^bSensitivity analysis for results by excluding cases that did not have histological confirmation showed that odd ratios were materially unchanged.

^cAccording to WHO classification.

TABLE II

Risk of malignant brain cancer according to job (longest job held: (Odds ratio and 95% confidence intervals), western PACA, 2005

Job titles ISCO-88	Cases		Controls		OR ^a	95% IC
	n = 111	%	N = 110	%		
Armed forces	0	0	3	2.7	Cannot be estimated	Cannot be estimated
Legislators, senior officials and managers	8	7.2	12	10.9	0.88	0.28 – 2.82
Professionals	14	12.6	9	8.2	2.08	0.69 – 6.29
Technicians and associated professionals	10	9	12	10.9	1.14	0.38 – 3.41
Clerks	21	18.9	14	12.7	2.28	0.85 – 6.09
Service workers and shop and market sales workers	15	13.5	12	10.9	1.78	0.64 – 4.96
Skilled agricultural and fishery workers	4	3.6	4	3.6	1.36	0.28 – 6.49
Craft and related trade workers	18	16.2	18	16.4	1.32	0.49 – 3.54
Plant and machine operators and assemblers	7	6.3	6	5.5	1.55	0.42 – 5.75
Elementary occupations ^b (unskilled workers)	14	12.6	20	18.2	1.111	-

^aAdjusted for sex and age.^bReference category.

interview, 98% of case patients responded themselves, and all control patients. *Table I* summarizes the characteristics of the study population, including gender, age, cancer treatment, smoking habits, histology of MPBT, and glioma grade. The causes of hospitalization for the 122 controls were herniated intervertebral disk, intracranial aneurysm, neurological traumatism requiring surgery, and epidural hematoma. No control patients had active cancer. The median age for all patients was 57 years (range: 20.4-86.3).

Occupational activities

Table II shows the ORs for the risk of MPBT among cases and controls according to the job they held longest among the different occupational categories. When they had worked in several jobs for the same length of time, the latest job was taken into account. Because some subjects had never worked,

occupational information was available from only 111 cases and 110 controls. None of the pooled ORs for the occupational categories reached statistical significance, although a trend towards significance was observed for clerks (OR: 2.28; 95% CI: 0.85 – 6.09). The same analyses, based on the last job held and on the principal job held during the past 10 years, did not show any increased risk (data not shown).

Chemical exposure

Exposure levels include all chemical exposures that occurred during occupational history and leisure time activities. ORs for the risks of MPBT according to global chemical exposure during occupational and leisure-related activities are reported in *Table III*. An inverse association was observed between moderate global chemical exposure and the risk of MPBT (OR = 0.25, 95% CI 0.10 – 0.58). For high-level exposure, no

TABLE III

Risk of malignant brain cancer according to chemical exposure during occupational and leisure-time activities; odds ratio and 95% confidence intervals, western PACA, 2005

CHEMICAL EXPOSURE LEVELS ^a	OCCUPATIONAL EXPOSURE				EXPOSURE DURING LEISURE TIME							
	CASES		CONTROLS		OR ^b	95% IC	CONTROLS		OR ^a	95% IC		
	n = 116	%	n = 116	%			n = 116	%				
No or slight ^c	100	86.2	84	72.4	1	-	89	76.7	91	78.4	1	-
Moderate	8	6.9	26	22.4	0.25 ^d	0.10-0.58	22	19	19	16.4	1.20	0.59-2.41
High	8	6.9	6	5.2	1.03	0.33-3.21	5	4.3	6	5.2	0.86	0.25-2.94

^aExposure score based both on the duration and in the intensity of exposure to compounds suspected of causing occupational or environmental cancers.^bAdjusted for sex and age^cReference category^dIndicates significant OR.

TABLE IV

Risk of malignant brain cancer according to chemical exposure during leisure time activities (Odds ratio and 95% confidence intervals), western PACA, 2005

EXPOSURE	Cases		Controls		OR ^a	95 % CI
	n = 122	%	n = 122	%		
DO-IT-YOURSELF HOME REPAIRS	52	42.6	43	35.2	1.88 ^b	0.49 – 7.27
Glue	42	34.4	23	18.9	17.58 [*]	1.75 – 176.62
Coat of plaster	35	28.7	21	17.2	3.51	0.70 – 17.58
Wood	50	41	43	35.2	0.47	0.17–1.29
Varnish	38	31.1	26	21.3	0.55	0.05 – 6.29
Plaster	32	26.2	25	20.5	0.47	0.07 – 3.02
Glass wool	25	20.5	19	15.6	0.20	0.03 – 1.46
Silicone gaskets	25	20.5	14	11.5	1.68	0.31 – 9.27
Cement	30	24.6	19	15.6	0.99	0.21 – 4.78
PAINTING	18	14.8	26	21.3	0.50 ^b	0.15 – 1.73
Oil paint	13	10.7	9	7.4	0.72	0.14 – 3.63
Acrylic paint	13	10.7	13	10.7	0.55	0.14 – 2.27
Water-based paint	9	7.4	7	5.7	0.66	0.12 – 3.51
White spirit	13	10.7	10	8.2	1.08	0.20 – 5.94
Turpentine	12	9.8	4	3.3	4.02	0.48– 33.54
Resin, lacquer	6	4.9	2	1.6	2.77	0.18– 42.13
GARDENING	50	41	44	37.1	1.36 ^b	0.34 – 5.44
Fertilizer	24	19.7	14	11.5	0.97	0.24 – 3.94
Natural fertilizer	20	16.4	21	17.2	0.21 [*]	0.06 – 0.72
Pest control sprays	28	23	14	11.5	2.57	0.54 – 12.35
Weed killer	25	20.5	11	9	3.41	0.85 – 13.59
Mole poison	9	7.4	3	2.5	2.98	0.57– 15.58
Insecticide	27	22.1	17	13.9	0.66	0.12 – 3.68

^a Adjusted for sex, age, leisure time exposure levels and residence during the past five years.

^b Adjusted for duration of fixing thing, duration of painting, duration of gardening, **N = 231**.

^{*} Indicates significant OR.

significant association was observed, nor could odds ratios be calculated for individual agents, because of the small numbers involved. Details nonetheless suggested that more cases than controls used fertilizer, insecticide, solvents, paint, wood, and glue.

Details of chemical exposure during leisure time are set forth in *Table IV*. We evaluated specific exposures from the list of chemical agents used in leisure-time activities and found a significantly increased risk associated with glue use (OR: 17.58; CI: 1.75 – 176.62) and a significantly decreased risk associated with natural fertilizer (OR = 0.21, 95% IC 0.06 – 0.72).

Radiation exposure

Table V summarizes the intensity of cell-phone and computer use. This estimate covers the past five years for each. Overall computer exposure was not significantly associated with brain cancer. Occupational computer exposure less than four hours

per day (OR = 1.93, 95% CI 1.03 3.65) was significantly associated with MPBT. No significant risk was observed with the use of cell phone.

Exposure to occupational and medical radiation is presented in *Table VI*. Few patients reported exposure to either electromagnetic fields or ionizing radiation. None of the occupational sectors where radiation exposure was probable were significantly associated with an increased odds ratio for developing intracranial brain tumors. An inverse association with CT (OR = 0.18, 95% CI 0.08 – 0.40) was observed.

Environment and habitat

Table VII reports the chemical and physical exposures near subjects' homes (<500 meters). No significant risk factor was observed, although a trend was noted for chemical plants. An inverse association with cell phone towers (OR = 0.49, 95% CI 0.26 – 0.92) was observed.

TABLE V

Risk of malignant brain cancer according to cell-phone and computer use: Odds ratios and 95% confidence intervals, western PACA, 2005

		CASES		CONTROLS		OR ^a	95% IC	
		n = 122	%	n = 122	%			
Work with a computer during the past 5 years	Occupational or leisure-time exposure	68	55.7	64	52.5	1.18	0.68 – 2.06	
	NO ^b	61	50	67	54.9	1	-	
	Leisure	< 5 h/week	21	17.2	29	23.8	0.84	0.42 – 1.68
		≥ 5 h/week	40	32.8	26	21.3	1.80	0.94 – 3.45
Global cell phone use (in hour-years)		n = 116	%	n = 116	%			
	NO ^b	65	56	78	67.2	1	-	
	Occupational	< 4h/day	36	31	23	19.8	1.93 [*]	1.03 – 3.65
		≥ 4h/day	15	12.9	15	12.9	1.23	0.55 – 2.77
	No phone ^b	≤ 4	8	6.9	11	9.5	0.86	0.30 – 2.44
		4 to 36	58	50	48	41.4	1.45	0.75 – 2.80
≥ 36		13	11.2	15	12.9	1.07	0.41 – 2.82	

^aAdjusted for sex and age^bReference category^{*}Indicates significant OR.

TABLE VI

Risk of malignant brain cancer according to levels of occupational and medical radiation: Odds ratios and 95% confidence intervals, western PACA, 2005

RADIATION EXPOSURE	Details	CASES		CONTROLS		OR	95% IC
		n = 116	%	n = 116	%		
Occupational exposure^a	Ionizing radiation	2	1.7	1	0.9	1.44	0.12 – 17.70
	Electromagnetic field	16	13.8	13	11.2	1.90	0.61 – 5.91
	Microwave frequency	7	6	4	3.4	1.20	0.30 – 4.77
	Visible, infrared and ultraviolet radiation	6	5.2	6	5.52	0.80	0.16 – 3.96
Medical exposure^b	Radiography	30	26.3	40	34.5	0.66	0.37 – 1.18
	Computerized tomography	9	7.9	37	31.9	0.18 [*]	0.08 – 0.40
	Scintigraphy	3	2.7	6	5.2	0.49	0.11 – 2.09
	Radiotherapy	2	1.7	1	0.9	2.03	0.18 – 23.09

^aAdjusted for sex, age, educational level and occupational exposure levels. N = 192 (excluding subjects who have never held a job).^bCentered around head and neck during the past 5 years and adjusted for sex and age.^{*}Indicates significant OR.

Discussion

Numerous occupations and industries have been inconsistently associated with the risk of brain cancer in epidemiologic studies. The low incidence rates of MPBT make the debates about these results and the causes of tumors in adults still more difficult to resolve. In our work, the relatively small study sample and recall bias related to having brain cancer could both have affected the assessment of occupational and

environmental risk factors. Similarly, the controls were not a representative cross-section of the population, since they were principally hospitalized in the neurosurgery department. It might have been useful to conduct sensitivity analyses by excluding specific diagnostic subgroups of controls, as in the study by Brenner et al. [22], but unfortunately, diagnoses were not always recorded for controls, and we had fewer participants than did Brenner et al. The lack of blinding might also have led

TABLE VII

Place of residence of cases and controls and exposure due to environment (Odds ratios and 95% confidence intervals), western PACA, 2005

	CASES		CONTROLS		OR ^a	95% IC
	n = 121	%	n = 121	%		
Main place of residence in town	65	53.3	52	43	1.51	0.91 – 2.52
High-tension cable	18	14.8	25	20.7	0.66	0.33 – 1.29
Chemical plant	18	14.8	14	11.6	1.34	0.62– 2.88
Vineyard	29	23.8	35	28.9	0.77	0.43 – 1.36
Agricultural field	31	25.4	37	31.6	0.77	0.44 – 1.36
Cell phone tower	19	15.6	33	27.3	0.49*	0.26 – 0.92
Dump site	8	6.6	14	11.6	0.54	0.22 – 1.33
Highway	21	17.2	23	19	0.88	0.46 – 1.70
Airport	2	1.6	5	4.1	0.38	0.07 – 2.03

^a Adjusted for sex and age.

* Indicates significant OR.

to differences in interviewing styles between cases and controls.

Low- and high-grade gliomas have different natural histories, reflected, in part, by their different ages at onset. They may therefore involve different carcinogenesis patterns, possibly influenced by different risk factors. The well-known difficulties in glioma grading and the relatively small number of patients in our study justified the global analysis of our population.

Unlike the recent IARC report [10], our results did not indicate that any job or occupational exposure was a major risk factor for MPBT development. Skilled agricultural and fishery workers did not have a significantly elevated brain tumor risk (OR: 1.36; CI: 0.28 – 6.49), but the frequency of this occupation was low (< = 5) in both groups, and the association was not accurately measured. This result is inconsistent with the meta-analyses of brain cancer and farming by Khuder et al [16], but agrees with other recent American [23–24] and European [25] studies. The IARC report [10] even indicated an inverse association with the “agriculture” category for women.

An upward trend was highlighted for clerks (OR: 2.28; 95% CI: 0.85 – 6.09), consistently with the findings of several other studies [26–28]. The ORs for MPBT associated with chemical occupational exposure was significantly different from zero. The inverse association observed between moderate global chemical exposure and the risk of MPBT does not permit the conclusion that chemical exposure is a risk factor for brain cancer. On the contrary, it indicates that it is protective against it. The distribution of occupations showed the same result since the leading occupation among cases was “clerks”, who are thought generally to have minimal occupational toxic exposure. Nevertheless, details about high levels of

occupational exposure showed that cases used slightly more fertilizer, insecticide, wood, and glue.

The retrospective nature of our study certainly increased the difficulty of evaluating chemical exposure. Although self-reports can identify exposure circumstances, e.g. to carcinogens, they are limited by the lack of relative or objective benchmarks against which working or leisure conditions can be judged. Bias might have resulted from the greater likelihood for cases to remember their exposure, compared with controls, as well as from their potential memory loss due to neurological damage. To our knowledge, few studies have assessed the risk factors for brain cancer development in leisure activities. We found no significant difference in ORs for risk of MPBT according to global estimated chemical exposure during leisure activities. Data adjusted for occupational exposure levels showed a significantly increased risk of MPBT associated with leisure time glue exposure, although the estimation of the true effect of this factor is imprecise. This result suggests a potentially carcinogenic exposure. In 2005, Lee et al. reported significant associations between some specific agricultural pesticides and glioma incidence [9]. Exposure to other chemicals, such as solvents [13] or PAHs [11–12], has been associated with an increased risk of MPBT. The composition of the glue was not defined in our study, however, and it can contain, in particular, solvents. Solvent use during leisure activities should be considered an important cause of chemical exposure. Moreover, subjects might be more exposed then, because they might be less likely to use protective devices than during occupational exposure. In our study we did not find a significantly increased MPBT risk associated with pesticide usage; this result is consistent with recent findings in an American study [29]. The

protective effect of natural fertilizer might be due to information bias or to the adjustment for chemical fertilizer.

A number of studies have looked at the relation between cell-phone use and brain tumors. Our results did not show a significant difference in cell-phone use between cases and controls (Table V), a finding that is in line with those from the recent studies by Lahkola et al [30] (OR = 0.78; CI: 0.68 – 0.91) and by the Interphone Study Group (Germany) [31]. Our assessment is limited by its measurement of the length of telephone subscriptions rather than actual time of use and by our failure to distinguish between analog and digital phones. The accumulated dose of radiofrequency in electromagnetic fields was not measured precisely.

The use of computers at home and at work has become an integral part of life over the past few decades. This technology is an additional source of exposure to (extremely low frequency) electromagnetic fields and has been evaluated only rarely in brain cancer studies. Mezei et al in 2001 showed computer use to be the main source of exposure to electromagnetic fields (9% of the global exposure in a day) [32]. In 2003, De Roos et al found that several occupational groups had an elevated incidence of glioma, including computer programmers and analysts, unrelated to years in the job or cumulative hours of use (OR = 2.0; CI: 1.0 – 3.8) [33]. Our results did not show a significant difference between the groups for overall computer exposure. We did, however, find an association for occupational use, and further analytic studies should explore the significantly increased risk we observed associated with computer use for less than 4 h/day (OR = 1.93; CI: 1.03 – 3.65) (Table V).

Ionizing radiation is a well-established risk factor for brain tumors, especially at high exposure levels (e.g., radiotherapy). The linear-no-threshold hypothesis for cancer risk supposes that low-level radiation is also carcinogenic. The low doses of radiation used to treat tinea capitis and skin hemangioma in children or infants have been associated with an elevated relative risk of malignant and benign brain tumors [34–35]. In our study, exposure to ionizing radiation for medical imaging in the head and neck region during the past five years had a significant inverse association with MBPT (OR: 0.18, CI: 0.08 – 0.40). Possible bias due to the cause of hospitalization in neurosurgical departments for controls (such as head injury or cerebral hemorrhage) is improbable, since examinations related to the index hospitalization were not taken into account. On the other hand, a high proportion of control patients had undergone CT (29%), much higher than expected in clinical practice. Our findings differ from those reported by Hardell et al [15], who showed a significantly increased risk of brain tumors associated with diagnostic radiography of the head and neck region (OR; 1.64, 95% CI: 1.04– 2.58). We also note that Feinendegen defends the hypothesis of a threshold for exposure to ionizing radiation, based on adaptive protection at low doses that outweighs the radiogenic damage [36].

Residential environment must also be considered as a possible cause of chemical or physical exposure. Our study did not find any effect from domestic electromagnetic fields, although studies have shown that such exposure is not negligible in comparison to occupational exposure [37–38]. We considered chemical exposure in the home environment, but found no risk factors related to it, although a trend towards significance was observed for chemical plants. Several studies have examined the association between brain cancer and chemical plants, especially petrochemical plants [11,39], but to our knowledge, no reports discuss possible chemical exposure due to proximity between homes and chemical plants. We found that more cases subjects lived in urban areas, but this difference was not significant. Chemical or physical exposures near their homes (<500 meters) were imprecisely evaluated. Sometime patients were unable to respond, and many characteristics were not taken into account, including precise distance, type of industry, and duration of exposure. These items considered only the longest place of residence and ignored other possible exposures after moving. Nevertheless, we observed an inverse association between MPBT frequency and residence near cell phone towers. This result may be explained by the fact that there is no electromagnetic field on the lower part of the base stations, or by the fact that because cell phone connections are better near towers, the cell phones emit less radiation [40]. However, our study did not take into account the precise location of the residence in relation to the emission area. Despite many epidemiologic studies and meta-analyses about brain cancer, the results remain inconsistent, and the causes of its increased incidence is still unknown. In our case-control study, no occupational sector suspected of involvement in brain cancer development was significantly associated with it. We might thus suppose that occupational exposure is not a major risk factor, as the study by Schlehofer et al concluded [10]. At the same time, for leisure activities, specific substances, such as glue, were linked to this risk. Living near cell phone towers had a protective effect. No definitive conclusions can be reached on the basis of these results, but several new leads merit further analytic studies. In particular, further epidemiologic studies of brain tumors, taking tumor type and grade and age at onset into account, should include analysis of exposure during leisure activities as well as during occupational and environmental exposure. Other factors (food habits, psychological factors, life events, stress, etc.) not related to chemical or physical exposure and so not considered in this article, but likely to influence the emergence of the disease, should be studied.

Conflicts of interests : none.

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