Occupational exposure to pesticides and central nervous system tumors: results from the CERENAT case–control study

Isabelle Baldi1,2 · Lucie De Graaf1 · Ghislaine Bouvier1 · Anne Gruber1 · Hugues Loiseau3,4 · Matthieu Meryet-Figuier5,6 · Sarah Rousseau1,2 · Pascale Fabbro-Peray7,8 · Pierre Lebailly5,6

Received: 17 October 2020 / Accepted: 30 March 2021 / Published online: 19 April 2021 © The Author(s), under exclusive licence to Springer Nature Switzerland AG 2021

Abstract

Background The etiology of the central nervous system (CNS) tumors remains largely unknown. The role of pesticide exposure has been suggested by several epidemiological studies, but with no definitive conclusion.

Objective To analyze associations between occupational pesticide exposure and primary CNS tumors in adults in the CERENAT study.

Methods CERENAT is a multicenter case–control study conducted in France in 2004–2006. Data about occupational pesticide uses—in and outside agriculture—were collected during detailed face-to-face interviews and reviewed by experts for consistency and exposure assignment. Odds ratios (ORs) and 95% confidence intervals (95% CI) were estimated with conditional logistic regression.

Results A total of 596 cases (273 gliomas, 218 meningiomas, 105 others) and 1,192 age- and sex-matched controls selected in the general population were analyzed. Direct and indirect exposures to pesticides in agriculture were respectively assigned to 125 (7.0%) and 629 (35.2%) individuals and exposure outside agriculture to 146 (8.2%) individuals. For overall agricultural exposure, we observed no increase in risk for all brain tumors (OR 1.04, 0.69–1.57) and a slight increase for gliomas (OR 1.37, 0.79–2.39). Risks for gliomas were higher when considering agricultural exposure for more than 10 years (OR 2.22, 0.94–5.24) and significantly trebled in open field agriculture (OR 3.58, 1.20–10.70). Increases in risk were also observed in non-agricultural exposures, especially in green space workers who were directly exposed (OR 1.89, 0.82–4.39), and these were statistically significant for those exposed for over 10 years (OR 2.84, 1.15–6.99).

Discussion These data support some previous findings regarding the potential role of occupational exposures to pesticides in CNS tumors, both inside and outside agriculture.

Keywords Central nervous system tumor · Glioma · Meningioma · Etiology · Pesticides · Agriculture · Green spaces · Occupational exposures

Introduction

Epidemiological knowledge regarding central nervous system (CNS) tumors, including incidence data and etiological research, remains limited. Data from several population-based cancer registries demonstrate that their annual incidence reaches as much as 20/100,000 [1–3], when considering all histological subtypes, both malignant and non-malignant. While diagnosis and prognosis of CNS tumors has gradually improved over time, their incidence

1 Univ. Bordeaux, INSERM U1219, EPICENE Team, 146 rue Léo Saignat, 33076 Bordeaux, France
2 Department of Occupational and Environmental Medicine, CHU Bordeaux, 33000 Bordeaux, France
3 Department of Neurosurgery, CHU Bordeaux, 33000 Bordeaux, France
4 Univ. Bordeaux, EA 7435, IMOTION Team, 33076 Bordeaux, France
5 Univ. Caen Basse-Normandie, INSERM U1086, ANTICIPE Team, 14000 Caen, France
6 François Baclesse Center, 14000 Caen, France
7 University of Montpellier, 34000 Montpellier, France
8 Nimes University Hospital, 30000 Nîmes, France
has been observed to increase in several countries, most notably among the elderly [2, 4, 5]. This trend is probably not fully explained by population ageing, changes in case registration or improvement in health access and in diagnosis. In this context, the role of risk factors must be explored [2]. Beside intrinsic factors (gender, ethnic groups, allergic conditions, family and personal history, genetic polymorphisms), some exogenous agents are demonstrated (ionizing radiations) or suspected (pesticides, electromagnetic fields, diet, solvents, hormonal factors) as being risk factors for CNS tumors [6, 7]. The pesticide hypothesis dates back to the 1980s when excess CNS brain tumor mortality was repeatedly observed in farmers’ historical cohorts. Case–control studies and historical cohorts before the 2000s relied on crude exposure parameters such as job titles and their results were non-consistent [8–14], although a study in Northern Italy found a four times higher risk of glioma with exposure to nitrosofungicides or insecticides [15]. More recent studies have used refined pesticide exposure assessment based on detailed questionnaires and/or expertise and analyzed CNS tumor by subtypes. In the Upper Midwest Study, a large case–control study in the USA including 341 brain tumors in women and 457 in men, no increase in risk was observed for glioma with pesticide exposure globally [16, 17], in men [18], and only a trend restricted to carbamate insecticide use in women [19]. Another case–control study in Nebraska observed an increase in risk only for workers involved in farming for 55 years and over [20]. Using a job-exposure matrix for pesticide use definition, a third case–control study in the USA evidenced a doubling in the risk of meningioma in women exposed to herbicides, while no association was found between gliomas and pesticide exposure [21]. In a case–control study conducted in southwestern France, an increase in risk was shown among the individuals who were the most exposed to pesticides, especially in vineyards and it was more pronounced for gliomas [22]. More recently, additional results were obtained from two large prospective agricultural cohorts. The Agricultural Health Study in the USA found a significant fourfold increase in farmers most exposed to chlorpyrifos [23] and a threefold increase in their spouses using domestic or occupational organochlorines [24]. In the French Agrican cohort, elevated risks were observed in farmers exposed to specific crops (peas, beets, potatoes) and risk doubled in those who applied pesticides [25]. Analysis focused on carbamate insecticides, fungicides and herbicides pointed to some specific active ingredients being associated with a high increase in the risk [26, 27].

We present here new results from a multicenter case–control study in France, exploring the relationship between the major CNS tumors and pesticide occupational exposures, taking into account the CNS subtypes and areas of use of pesticides.

Methods

Population

Briefly, the CERENAT case–control study, has been described in detail elsewhere [28]: it was conducted in four French administrative areas (Gironde, Calvados, Manche and Hérault) and included (i) patients aged 16 and over with a diagnosis of incident benign or malignant CNS (brain and spinal cord) tumor between June 2004 and May 2006, established either by a neuro-pathological assessment or by clinical and radiological assessment for cases with no histological diagnosis and living in one of the four areas when diagnosed, (ii) for each case, two controls with no history of CNS tumor, randomly selected from the local electoral rolls during the period 2005–2008, individually matched on age (± 2 years), sex and area of residence.

Primary brain tumors with the following ICD-O-3 topography codes were included: C70.0–C70.9, C71.0–C71.9 and C72.2–C72.9. Patients with recurrent tumors, metastases, pituitary tumors, genetic syndrome or AIDS were excluded. Cases were grouped by morphology codes as gliomas, meningiomas, and other tumors (acoustic neuromas, lymphomas and other unspecified primary brain tumors).

Data collection

Data were collected in standardized questionnaires by trained interviewers during face-to-face structured interviews. When patients were in a severe clinical condition or deceased, a proxy was invited to complete a simplified questionnaire. For all participants, socio-demographic characteristics, medical history, lifestyle, environmental data and complete occupational histories with beginning and end dates (including kind of industry, activity and main tasks) were collected.

Pesticide exposure assessment

Besides job calendars, in-depth life-long questionnaires on pesticide exposures were completed by all subjects who gave a positive answer to one or more of the following 4 screening questions “Have you ever worked on a farm?”, “Have you ever applied pesticides on crops?”, “Have you ever worked in contact with crops?”, “Have you ever used pesticides in non-agricultural jobs?”. The specific questionnaires included
detailed information on various tasks (beginning and end dates, number of days per year, equipment used) including treatment (mixing, spraying, equipment cleaning) and other tasks (pruning, thinning, bending/tying up, harvesting, etc.). Three experts in pesticide exposure (PFP, PL, IB) reviewed all the job calendars and specific questionnaires independently for consistency and to determine exposure parameters for each individual: direct or indirect exposure in vineyard, open field, fruit and vegetable growing, gardening, wood industry and pest-control. Generally speaking, direct exposure referred to exposure during the use of pesticides by the person himself during the treatment days: this included operations for preparing and mixing the mixtures, applying the mixtures, cleaning and repair of treatment equipment. Indirect exposures occurred during contact with surfaces or plants after treatment operations: during work in the fields for farmers, tasks on plants for gardeners, contact with treated wood for workers in the wood industry…

The questionnaire included specific items on each of these tasks. In analysis, we considered a hierarchy between direct and indirect exposures: people who had been exposed in both ways were classified in directly exposed while people who had never been exposed directly but indirectly fell into the category of indirect exposures. Duration of exposure (in years and in cumulated life-long days) was determined for each type of exposure and the median of the distribution was considered as the threshold for exploring risks in those most exposed.

Analysis

The index date for each case and his two matched controls was the date of case diagnosis. Pesticide exposure was considered as a binary variable (yes/no) for each exposure parameter, and also according to the median of cumulative exposure defined in controls. Cumulative exposure was defined as the sum of lifetime days of treatment for agricultural exposures and as the duration of jobs (in years) for non-agricultural exposures. Conditional logistic regression for matched sets was used to estimate odds ratios and 95% confidence intervals. All statistical tests were two-sided and a global test for each categorical indicator was performed. The following variables were considered as potential confounders: level of education (primary school or less, secondary school, high school and university), smoking (in pack-years), alcohol consumption (classified as excessive in men over 21 glasses of wine, cider, beer or spirits per week and over 14 glasses per week in women). None of these variables was retained in the final analysis as alcohol and smoking were not associated with health outcome and level of education was closely correlated to the jobs and exposures under study. However we tested the influence of adjustment on educational level on final results. To address the question of temporality of exposure, we analysed the role of living on a farm in early childhood, and also the changes in risk when considering the delay between first exposure and diagnosis (under or above the median of the delay). On main results, we also run analysis excluding proxy respondents. Separate analyses were run for each histological type. We used two-sided statistical tests and a 5% significance level. Analyses were performed with the SAS® software, version 9.2 (SAS Institute Inc, Cary, NC, United States).

Results

Population characteristics

Among the eligible subjects, 95% of cases and 61% of controls were reached. A total of 596 (73%) cases and 1,192 (45%) controls were finally included in the CERENAT study. The participation rate was 66% for glioma cases and 75% for meningioma cases. The main reasons for non-participation were refusals, severe condition or death without proxy. Non-included cases were older than included cases (mean age: 63 years vs. 58 years).

The cases were 273 patients with gliomas, 218 with meningiomas, and 105 with other brain tumors (68 neurinomas, 12 lymphomas, and 25 undefined or others). The proportion of proxy interviews was 25% for gliomas, 6% for meningiomas and 18.5% for other brain tumors. The average age was 55.4 years for patients with gliomas, 60.2 years for meningiomas and 57.6 for other tumors (Table 1). Women represented 42.1%, 75.7% and 53.3% of the population for each type of tumor, respectively. The level of education was higher in controls than in cases whatever the type of tumor. The proportion of alcohol excessive consumers was slightly higher in controls (8.5%) than in cases (6.2%). Life-long tobacco smoking concerned half of the population, in a comparable proportion in cases and controls, although the proportion of smokers who exceeding 20 pack-years life-long was slightly higher in cases (41.2%) than in controls (34.8%).

Description of pesticide exposure

Information on occupational pesticide exposure was available for all subjects, and about 2% of data on exposure duration were missing. Figure 1 presents the proportion of individuals exposed to pesticides according to the status (all controls, all cases, gliomas, meningiomas) and the type of exposure (direct and indirect in agriculture and outside agriculture).
Table 1 Demographic and lifestyle characteristics of cases and controls overall and by histological subtype, CERENAT (N=1,788)

|                      | All tumors | Gliomas | Meningiomas | Other brain tumors |
|----------------------|------------|---------|-------------|--------------------|
|                      | Cases (N=596) | Controls (N=1,192) | Cases (N=273) | Controls (N=546) | Cases (N=218) | Controls (N=436) | Cases (N=105) | Controls (N=210) |
| Age (mean ± std) (N=1,788) | 596 57.6±14.7 | 1,192 57.5±14.5 | 273 55.4±16.0 | 546 55.4±15.7 | 218 60.2±11.5 | 436 60.1±11.5 | 105 57.6±16.3 | 210 57.6±16.0 |
| Sex (N=1,788) | | | | | | | | |
| Men | 260 43.62 | 520 43.62 | 158 57.88 | 316 57.88 | 53 24.31 | 106 24.31 | 49 46.67 | 98 46.67 |
| Women | 336 56.38 | 672 56.38 | 115 42.12 | 230 42.12 | 165 75.69 | 330 75.69 | 56 53.33 | 112 53.33 |
| Level of education (N=1,785) | | | | | | | | |
| Primary | 153 25.76 | 243 18.82 | 63 23.16 | 88 16.12 | 60 27.52 | 115 26.38 | 30 28.85 | 40 19.14 |
| Secondary | 221 37.21 | 376 29.12 | 97 35.66 | 173 31.68 | 86 39.45 | 129 29.59 | 38 36.54 | 74 35.41 |
| High School | 100 16.84 | 326 25.25 | 53 19.49 | 112 20.51 | 37 16.97 | 81 18.58 | 10 9.62 | 33 15.79 |
| University | 120 20.20 | 346 26.80 | 59 21.69 | 173 31.68 | 35 16.06 | 111 25.46 | 26 25.00 | 62 29.67 |
| Tobacco smoking in pack. year (N=1,774) | | | | | | | | |
| 0 | 285 48.22 | 586 49.54 | 111 41.26 | 250 46.13 | 118 54.13 | 238 54.84 | 56 53.85 | 98 47.34 |
| [0–7.65] | 88 14.89 | 213 18.01 | 43 15.99 | 105 19.37 | 28 12.84 | 66 15.21 | 17 16.35 | 42 20.29 |
| [7.65–22.40] | 100 16.92 | 199 16.82 | 54 20.07 | 93 17.16 | 34 15.60 | 71 16.36 | 12 11.54 | 35 16.91 |
| [22.40–157.00] | 118 19.97 | 185 15.64 | 61 22.68 | 94 17.34 | 38 17.43 | 59 13.59 | 19 18.27 | 32 15.46 |
| Alcohol consumption in Glasses/week (N=1,504) | | | | | | | | |
| No | 255 50.90 | 328 32.73 | 102 48.57 | 121 28.81 | 107 51.94 | 148 35.92 | 46 54.12 | 59 34.71 |
| Moderate | 205 40.92 | 550 54.89 | 89 42.38 | 238 56.67 | 84 40.78 | 219 53.16 | 32 37.65 | 93 54.71 |
| Excessive | 41 8.18 | 124 12.38 | 19 9.05 | 61 14.52 | 15 7.28 | 45 10.92 | 7 8.24 | 18 10.59 |
A total of 754 subjects (42.2%) were classified as exposed to pesticides in agriculture. One hundred and twenty five individuals (7.0%) had sprayed pesticides on crops during their occupational life. These direct exposures concerned 65 subjects in vine-growing (3.6%), 46 in open field (2.6%) and 39 in fruit or vegetable-growing (2.2%). The median duration of direct exposure was 15, 21 and 12 years respectively for the three types of crops, corresponding to a median of 114, 54 and 55 cumulated days of treatment life-long.

More than a third of the population (N = 629, 35.2%) had never sprayed pesticides but had been working in contact with crops for one year or more. The proportions of subjects reporting these indirect exposures were respectively 23.6% (N = 423) in vine-growing including harvesting (N = 351) and other re-entry tasks (N = 72), 12.6% in open field (N = 226) including hay making (N = 77), cereal harvesting or sowing (N = 149) and 11.7% in fruit and vegetable growing (N = 209) for picking and pruning. The median duration of indirect exposure was 5 years in vine-growing (5 for harvesting and 12 for other re-entry tasks), 7 years in open field and 8 years for fruit & vegetable growing.

Non-agricultural pesticide exposures
One hundred and forty-six subjects (8.2%) were classified as exposed to pesticides in non-agricultural occupations: 36 (2.0%) in gardening & landscape (24 of them exposed in treatment tasks and 12 through indirect exposures), 90 (5.0%) in the wood industry (20 directly and 70 indirectly exposed), and 21 (1.2%) in insect control for public health (15 directly and 6 indirectly exposed). The medians of the duration of exposure were 10 years in gardening, 14 years in wood industry and 15 years in pest control.

Risks associated with agricultural exposures
Associations between agricultural exposures and CNS tumors are presented in Table 2. Direct agricultural exposure was not significantly associated with an increase in risk for all brain tumors together and all types of exposures (OR 1.04, 0.69–1.57) but a slightly positive trend was observed when restricting the analysis to gliomas (OR 1.37, 0.79–2.39), while a decrease in risk was observed in meningiomas (OR 0.79, 0.36–1.76) and other tumors (OR 0.65, 0.23–1.87) (Table 3). In the most exposed farmers (life-long number of days of treatment over the median), the risk of brain tumors overall was increased (OR 1.58, 0.83–3.01) and the risk of glioma was doubled (OR 2.22, 0.94–5.24).
Table 2  Association between agricultural pesticide exposures and brain tumors, overall and by subtypes, CERENAT (N=1,788)

|                      | All tumors | Gliomas | Meningiomas | Other brain tumors |
|----------------------|------------|---------|-------------|-------------------|
|                      | Cases      | Controls| Cases       | Controls          | Cases       | Controls| Cases         | Controls         |
|                      | (N=596)    | (N=1,192) | (N=273)     | (N=546)           | (N=218)     | (N=436) | (N=105)       | (N=210)          |
| Agriculture overall  |            |          |             |                   |            |         |               |                  |
| No                   | 374        | 660     | 167         | 295               | 147        | 247     | 60            | 118              |
| Indirect             | 176        | 29.5    | 453         | 38.0              | 61         | 28.0    | 38.5          | 36.2             |
| Direct               | 46         | 7.7     | 79          | 6.6               | 29         | 10.6    | 7.1           | 6.7              |
| Direct >86 days*2    | 20         | 4.0     | 27          | 2.7               | 13         | 6.2     | 3.5           | 7.0              |
| Vinegrowing (N=1,788)|            |          |             |                   |            |         |               |                  |
| No                   | 457        | 843     | 209         | 377               | 168        | 309     | 80            | 157              |
| Indirect /Reentry    | 23         | 3.9     | 49          | 4.1               | 10         | 3.7     | 3.3           | 2.8              |
| Indirect /Harvesting | 93         | 15.6    | 258         | 21.6              | 40         | 14.6    | 24.0          | 18.0             |
| Direct               | 23         | 3.9     | 42          | 3.5               | 14         | 5.1     | 3.7           | 1.6              |
| Direct >14 days*2    | 10         | 2.0     | 17          | 1.7               | 7          | 3.3     | 2.1           | 1.6              |
| Open field farming (N=1,788)| 517 | 999 | 234 | 461 | 198 | 367 | 85 | 171 |                  |
| Indirect (Harvest)   | 19         | 3.2     | 58          | 4.9               | 6          | 2.2     | 4.8           | 2.5              |
| Indirect (Reentry)   | 39         | 6.5     | 110         | 9.2               | 20         | 7.3     | 47            | 8.6              |
| Direct               | 21         | 3.5     | 25          | 2.1               | 13         | 4.8     | 12            | 2.2              |
| Direct >54 days*2    | 10         | 2.0     | 7           | 0.7               | 6          | 2.9     | 4.0           | 1.0              |
| Fruit/vegetable growing (N=1,788)| 513 | 1,027 | 233 | 466 | 192 | 385 | 88 | 176 |                  |
| Indirect             | 70         | 11.7    | 139         | 11.7              | 30         | 11.0    | 66            | 12.1             |
| Direct               | 13         | 2.2     | 26          | 2.2               | 10         | 3.7     | 14            | 2.6              |
| Direct >55 days*2    | 4          | 0.8     | 6           | 0.6               | 3          | 1.4     | 2.0           | 0.5              |

Bold was used for significant results (p < 0.05)

*1 p < 0.05
*2 median of the distribution of duration values (in number of days life-long)
Table 3  Association between non-agricultural pesticide exposures and CNS tumors, overall and by subtypes, CERENAT (N = 1,788)

| Subtype                | All tumors | Gliomas | Meningiomas | Other brain tumors |
|------------------------|------------|---------|-------------|-------------------|
|                        | Cases      | Controls | Cases       | Controls | Cases     | Controls | Cases     | Controls |
|                        | (N=596)    | (N=1,192) | (N=273)    | (N=546)  | (N=218)  | (N=436)  | (N=105)  | (N=210)  |
| Outside Agriculture    |            |          |            |          |          |          |          |          |
| No                     | 541        | 1,107    | 247        | 506      | 202      | 410      | 92       | 191      |
| Indirect               | 31         | 5.2      | 15         | 5.5      | 10       | 4.6      | 6         | 5.7      |
| Direct                 | 24         | 4.0      | 11         | 4.0      | 6        | 2.8      | 7         | 6.7      |
| Green Spaces           |            |          |            |          |          |          |          |          |
| No                     | 580        | 1,173    | 266        | 536      | 213      | 435      | 101      | 202      |
| Indirect               | 5          | 0.8      | 2          | 0.8      | 3        | 1.4      | 0.0      | 1.0      |
| Direct                 | 11         | 1.8      | 5          | 1.9      | 2        | 0.9      | 4         | 3.3      |
| Duration > 10 years    | 12         | 2.0      | 5          | 1.8      | 5        | 2.3      | 3         | 2.9      |
| Wood industry          |            |          |            |          |          |          |          |          |
| No                     | 562        | 1,136    | 256        | 521      | 208      | 414      | 98       | 201      |
| Indirect               | 27         | 4.5      | 13         | 4.8      | 8        | 3.7      | 6         | 3.7      |
| Direct                 | 7          | 1.2      | 4          | 1.5      | 2        | 0.9      | 1         | 0.5      |
| Duration > 14 years    | 19         | 3.2      | 8          | 2.9      | 4        | 1.8      | 5         | 4.8      |
| Pest control           |            |          |            |          |          |          |          |          |
| No                     | 587        | 1,180    | 270        | 541      | 216      | 432      | 101      | 207      |
| Indirect               | 2          | 0.3      | 1          | 0.4      | 0        | 0.0      | 1         | 0.0      |
| Direct                 | 7          | 1.2      | 2          | 0.7      | 2        | 0.7      | 3         | 0.0      |
| Duration > 15 years    | 0          | 0.0      | 0          | 0.0      | 0        | 0.0      | 2         | 1.9      |

Bold was used for significant results (p < 0.05)

*p < 0.05

**Median of the distribution of duration values (in years)
Considering the crops separately, only slight increases were observed for direct exposure when considering all tumors together and regardless of exposure level in vine-growing (OR 1.05, 0.54–1.64) and in open field (OR 1.63, 0.88–3.04), and no increase was seen in fruit/vegetable growing. Risks increased in the most exposed (life-long cumulative days over the median) and became significant in open field (OR 3.58, 1.20–10.70). This increase was explained by an increase in the risk of gliomas in the most exposed (OR 1.68, 0.54–5.23 in vine-growing, OR 3.02, 0.84–10.79 in open field, OR 2.99, 0.50–17.89 in vegetable and fruit-growing).

For indirect exposures, a decrease in risk was observed for all tumors (OR 0.68, 0.54–0.84) and for gliomas and meningiomas separately. This decrease remained when considering re-entry tasks that can happen during the treatment season and harvesting separately.

No increase in risk was observed in people living on a farm in early childhood. Risks did not vary in open field when considering a delay between first exposure and diagnosis below or above 46 years (median). Excluding proxy respondents generally increased the strength of the associations, that became statistically significant in open field (OR 2.05 [1.02–4.14]) and for gliomas (OR 2.64 [1.03–6.73]). Adjustment on educational level did not change these results.

Risks associated with non-agricultural pesticide exposures

Associations between non-agricultural exposures and CNS tumors are presented in Table 3. In green spaces, where 16 cases and 19 controls were exposed, overall risk of brain tumors tended to increase in subjects directly exposed to pesticides (OR 1.89, 0.82–4.39), and to a lesser extent in indirectly exposed subjects (OR 1.43, 0.45–4.50). The risk was more than doubled and significant for subjects with the longest exposures (over 10 years) (OR 2.84, 1.15–6.99). Increases in risk were found in analysis restricted to gliomas (direct exposure: OR 2.19, 0.58–8.36) while numbers were too limited for conclusions in meningioma (5 cases and 1 control). Risks were increased when considering a delay between first exposure and diagnosis over the median (18 years for all tumors and 16 years for glioma) for tumors overall (OR 2.68 [1.01–7.09]) and for gliomas (OR 2.26 [0.49–10.41]). Excluding proxy respondents did not change the results, neither did adjustment on educational level.

In the wood industry, where 34 cases and 56 controls were exposed, a slight increase was observed for all CNS tumors, in indirectly (1.27, 0.78–2.08) and directly exposed subjects (OR 1.09, 0.44–2.74), essentially explained by increases in gliomas (indirect exposure OR 1.45, 0.71–2.96, direct exposure OR 1.16, 0.34–3.98). When restricting the analysis to specific industries, the highest risks were observed in railroad workers in charge of treating wood crossbars (OR 2.38, 0.72–7.78) and in sawmill workers (OR 1.90, 0.90–4.01).

In pest control workers, only 9 cases and 12 controls were exposed and the risk of brain tumor was increased only in directly exposed (OR 1.75, 0.64–4.83) with too limited numbers for conclusions by subtypes.

Discussion

In this case–control study in France, increases in the risk of central nervous system tumors were observed in relation to various occupational pesticide exposures in agriculture but also outside agriculture. In the most exposed individuals, the risk of glioma was non-significantly trebled in open field and in fruit-growing and multiplied by 1.68 in vine-growing. Elevated risks of glioma were also observed for non-agricultural use of pesticides, especially in workers in green spaces and in the wood industry, and to a lesser extent in pest control workers. Inconsistent results were observed for meningioma. Although the total number of cases included was quite large, most of the elevated risks we found did not reach the statistical significance because of limited numbers when considering tumor subtypes together with specific uses of pesticides. Thus, these results can only be interpreted as trends, but they are important to consider because of the strength of some associations that we observed. Moreover, these results were globally consistent, showing higher risks in gliomas and in most exposed individuals for almost all the types of pesticide use.

The main strengths of this study include the enrolment of incident cases supported by population-based cancer registries, face-to-face interviews, the analysis of sub-types of tumors (gliomas, meningiomas), accurate pesticide exposure assessment (exploring agricultural and non-agricultural jobs, direct and indirect exposures). Considering the 73% participation rate in cases and 45% in controls, we cannot rule out selection bias. However, the lower participation of subjects with gliomas and elderly people, more frequently exposed to pesticides as shown by observations of participants, is likely to have decreased our risk estimates and biased our results toward the null. Apart from this, we do not see any clear reasons why the participation would be related to pesticide exposures especially as the study was presented to participants as dealing with environmental and occupational factors and CNS health in general, without mentioning the hypothesis on pesticides. Recall bias is a concern in our study as in any retrospective study. However, we believe that this bias was limited by the review of exposure data by experts, who considered job titles as well as responses to specific questionnaires to ensure exposure assessment consistency.
One of the lessons from our study, as already raised by results from a previous study, is the difficulty of highlighting associations when histological types of CNS tumors and kind of exposures are not analyzed separately. This could explain why studies using imprecise metrics for pesticide exposure, such as job titles, have failed to demonstrate an association [10, 11]. In our study, the highest risks were observed for gliomas in open field farmers. Wheat and corn were the main crops they had treated in their occupational lives, sometimes in combination with other crops, such as potato, sunflower, rape or beet. Some of them have also raised livestock and may have used insecticides on them. This open field context implies the use of a wide variety and combination of pesticides during a given season and even more life-long, leading to complex toxicological issues. Our result is not in line with those of studies developed in the US in open field farming: associations between pesticide use and risk of brain tumors were unclear in the Upper Midwest Study [18, 19] and so far limited to chlorpyrifos in applicators [23] and organochlorines (lindane and chlordane) in spouses in the Agricultural Health Study [24], while these two studies covered areas (Iowa, South Carolina, Michigan, Minnesota, Wisconsin) devoted to open field farming (wheat, corn, beet, etc.). However, American farming differs from French, by larger and more frequently monocultural farms, that may be associated with different practices, work organization and equipment, all factors that can influence pesticide exposures. But our result in open field farming is consistent with those from the French Agrican cohort that found elevated risks for CNS tumors in farmers using pesticides, more pronounced in those growing peas, beets and potatoes [25]. Even if not significant, we also found elevated risk of gliomas in relation with the longest pesticide exposures in vine-growing, consistent with the historical case–control study by Mussico in Italy [15], with an ecological analysis performed on vine-growing at the national scale in France [29], and with a previous case–control study we conducted in the Bordeaux area [22]. Results on fruit and vegetable growing are less conclusive, but indicated a trend towards an increased risk of glioma in the most exposed, for which no other evidence in the literature has been found. Few studies have explored the association of CNS tumors with pesticide exposures outside agriculture. We observed a significant doubling in risk in green space workers, consistent with a study in golf course workers that found an elevated mortality for CNS tumors compared to the USA general population [12]. The non-significant doubling of risk that we found in some workers exposed in the wood industry (railroad workers in charge of treating wood crossbars and sawmill workers) is in line with a case–control study on gliomas that showed a raised risk among wood workers, attributed to exposure to organochlorine wood preservative and solvents [8]. Our conclusions on pest control workers are limited because of small numbers, but the slight increase in risk we found in the most exposed is in line with a study in Roma that found an excess in CNS tumor mortality in a retrospective cohort of pest control workers [9].

In this study, we have not explored the role of specific active ingredients, as people generally cannot remember them life-long and the numbers of individuals were limited. However, the increases in risk we observed across several crops and also outside agriculture, suggest either of the role of a large range of pesticides or of the role of pesticides that have been indicated for multiple uses. Carbamates, that have been pointed out by several studies [19, 26, 26, 30], fulfill the second hypothesis as they have been used as insecticides on crops (including seed treatment) and animals, as well as herbicides and fungicides (mainly dithiocarbamates), but we cannot rule out the possibility that several other molecules, among the more than 1,000 that have been marketed since 1950, could play a role. To date, the carcinogenicity of less than 60 active ingredients out of the more than 1,000 could be evaluated by IARC. Three of them (arsenicals, lindane and pentachlorophenol) were classified in the Group 1 as definitely carcinogenic and eight of them (aldrin, captafol, DDT, diazinon, diehdrin, ethylene dibromide, glyphosate and malathion) as probable carcinogens (Group 2A).

**Conclusion**

In conclusion, our study brings new evidence on the association of pesticides and CNS tumors in agriculture: the associations were statistically significant in open field workers, but trends were also observed in vine-growing and fruit growing, especially for gliomas and for the most exposed workers. Even newer evidence are the associations we found outside agriculture, with almost a trebling in risk among green spaces workers exposed for more than 10 years. These results have implications for enhancing preventive measures in agriculture but also for paying particular attention to pesticide exposures outside agriculture.

**Acknowledgments** The authors thank JM. Constans, O. Coskun, S. Eimer and A. Vital for their radiological or pathological expertise, C. Auguin, G. Blaizot, AS. Lacauve, L. Molinari, E. Niez, X. Schwall and S. Schwall for interviewing the subjects, A. Jaffré, V. Loyant, N. Bousquet, E. Berteaud and C. Dantas for their helpful collaboration in the study, and all the clinicians who helped us to contact the patients.

**Funding** The study was supported by grants from the Fondation de France, the Agence Française de Sécurité Sanitaire de l’Environnement et du Travail, the Association pour la Recherche contre le Cancer, the Ligue contre le Cancer, the Institut National de la Santé Et de la Recherche Médicale—ATC Environnement et Santé.
participate. Consent to participate Participants signed an informed consent to participate.

Declarations

Conflict of interest The authors declare they have no actual or potential competing financial interests.

Ethical approval The study protocol was approved by an ethic committee.

Consent to participate Participants signed an informed consent to participate.

References

1. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS (2018b) CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011–2015. Neuro Oncol 20:v1–v86
2. Pouget C, Gruber A, Berteaud E, Ménégot P, Monteil P, Huchet A et al. (2018) Increasing incidence of central nervous system (CNS) tumors (2000–2012); findings from a population based registry in Gironde (France). BMC Cancer 18:653
3. Wöhner A, Waldhör T, Heinzl H, Hackl M, Feichtinger J, Gruber-Mösenbacher U et al. (2009) The Austrian Brain Tumour Registry: a cooperative way to establish a population-based brain tumour registry. J Neurooncol 95:401–411
4. Miranda-Filho A, Piñeros M, Soerjomataram I, Deltour I, Bray F (2017) Cancers of the brain and CNS: global patterns and trends in incidence. Neuro Oncol 19:270–280
5. Philips A, Henshaw DL, Lamborn G, O’Carroll MJ (2018) Brain tumours: rise in glioblastoma multiforme incidence in England 1995–2015 suggests an adverse environmental or lifestyle factor. J Environ Public Health 2018:7910754
6. Ostrom QT, Gittleman H, Stetson L, Virk S, Barnholtz-Sloan JS (2018a) Epidemiology of intracranial gliomas. Prog Neurol Surg 30:1–11
7. Wrensch M, Mian Y, Chew T, Bondy M, Berger MS (2002) Epidemiology of primary brain tumors: current concepts and review of the literature. Neuro Oncol 4:278–299
8. Cordier S, Poisson M, Gerin M, Varin J, Conso F, Hemon D (1988) Gliomas and exposure to wood preservatives. Br J Ind Med 45:705–709
9. Figà-Talamanca I, Mearelli I, Valente P, Bascherini S (1993) Cancer incidence. Neuro Oncol 4:278–299
10. Figà-Talamanca I, Mearelli I, Valente P, Bascherini S (1993) Cancer incidence. Neuro Oncol 4:278–299
11. Forastiere F, Quercia A, Miceli M, Settimi L, Terenzoni B, Rapiti E et al. (1993) Cancer among farmers in central Italy. Scand J Work Environ Health 19:382–389
12. Kross BC, Burmeister LF, Ogilvie LK, Fuertes LJ, Fu CM (1996) Proportionate mortality study of golf course superintendents. Am J Ind Med 29:501–506
13. Morrison HI, Wilkins K, Semenciw R, Mao Y, Wigle D (1992) Herbicides and cancer. J Natl Cancer Inst 84:1866–1874
14. Smith-Rooker JL, Garrett A, Hodges LC, Shue V (1992) Prevalence of glioblastoma multiforme subjects with prior herbicide exposure. J Neurosci Nurs 24:260–264
15. Muscico M, Sant M, Molinari S, Filippini G, Gatta G, Berrino F (1988) A case-control study of brain gliomas and occupational exposure to chemical carcinogens: the risk to farmers. Am J Epidemiol 128:778–785
16. Ruder AM, Waters MA, Carreón T, Butler MA, Davis-King KE, Calvert GM et al. (2006) The Upper Midwest Health Study: a case-control study of primary intracranial gliomas in farm and rural residents. J Agric Saf Health 12:255–274
17. Yin JH, Ruder AM, Stewart PA, Waters MA, Carreón T, Butler MA et al. (2012) The Upper Midwest Health Study: a case-control study of pesticide applicators and risk of glioma. Environ Health 11:39
18. Ruder AM, Waters MA, Butler MA, Carreón T, Calvert GM, Davis-King KE et al. (2004) Gliomas and farm pesticide exposure in men: the upper midwest health study. Arch Environ Health 59:650–657
19. Carreón T, Butler MA, Ruder AM, Waters MA, Davis-King KE, Calvert GM et al. (2005) Gliomas and farm pesticide exposure in women: the upper midwest health study. Environ Health Perspect 113:546–551
20. Lee WJ, Colt JS, Heineeman EF, McComb R, Weisenburger DD, Ljinsky W et al. (2005) Agricultural pesticide use and risk of glioma in Nebraska, United States. Occup Environ Med 62:786–792
21. Samanic CM, De Roos AJ, Stewart PA, Rajaraman P, Waters MA, Inskip PD (2008) Occupational exposure to pesticides and risk of adult brain tumors. Am J Epidemiol 167:976–985
22. Provost D, Cantagrel A, Lebailly P, Jaffre F, Loyant V, Loiseau H et al. (2007) Brain tumours and exposure to pesticides: a case-control study in southwestern France. Occup Environ Med 64:509–514
23. Lee WJ, Blair A, Hoppin JA, Lubin JH, Rusiecki JA, Sandler DP et al. (2004) Cancer incidence among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study. J Natl Cancer Inst 96:1781–1789
24. Louis LM, Lerro CC, Friesen MC, Andreotti G, Koutros S, Sandler DP et al. (2017) A prospective study of cancer risk among Agricultural Health Study farm spouses associated with personal use of organochlorine insecticides. Environ Health 16:95
25. Piel C, Pouchieu C, Tual S, Migault L, Lermarchand C, Carles C et al. (2017) Central nervous system tumours and agricultural exposures in the prospective cohort AGRICAN. Int J Cancer 141:1771–1782
26. Piel C, Pouchieu C, Carles C, Béziat B, Boulanger M, Bureau M et al. (2019) Agricultural exposures to carbamate herbicides and fungicides and central nervous system tumour incidence in the cohort AGRICAN. Environ Int 130:104876
27. Piel C, Pouchieu C, Migault L, Béziat B, Boulanger M, Bureau M et al. (2019) Increased risk of central nervous system tumours with carbamate insecticide use in the prospective cohort AGRICAN. Int J Epidemiol 48:512–526
28. Courgeau G, Bouvier G, Lebailly P, Fabbro-Peraux P, Gruber A, Lefondre K et al. (2014) Mobile phone use and brain tumours in the CERENAT case-control study. Occup Environ Med 71:514–522
29. Vieil JF, Challier B, Pitard A, Pobel D (1998) Brain cancer mortality among French farmers: the vineyard pesticide hypothesis. Arch Environ Health 53(1):65–70. https://doi.org/10.1007/BF02181516
30. Navas-Acien A, Pollán M, Gustavsson P, Floderus B, Plato N, Dosemeci M (2002) Interactive effect of chemical substances and occupational electromagnetic field exposure on the risk of gliomas and meningiomas in Swedish men. Cancer Epidemiol Biomark Prev 11:1678–1683

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.