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Environmental risk factors of primary brain tumors: a review

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Abstract

Adult primary tumors of the central nervous system are rare, but the incidence is increased in some European countries. Several environmental exposures have been investigated as potential risk factors, but for most, scientific evidence is still lacking. Here we review studies of environmental factors potentially involved in the carcinogenesis of brain tumors: the potential association between primary central nervous system tumors and ionizing radiation, some toxic agents (N-nitroso compounds, pesticides), air pollution, and radiofrequency electromagnetic waves. Brain-ionizing irradiation, especially during childhood, constitutes a well-established risk factor for brain tumors. Exposure to environmental toxins has been poorly explored and data give inconsistent clues about N-nitroso compounds or pesticides as risk factors of brain tumors even for prenatal exposure. For out-door pollution and risk of brain tumour, results of large prospective studies are contradictory. The effect of mobile phones on the risk of developing brain tumors has not been established for glioma and meningioma in adults, but the link with acoustic neurinoma is becoming robust. The effect of mobile phones has still not been explored in children.

INTRODUCTION

Adult primary tumors of the central nervous system (CNS) are rare, with an incidence of 7.0 per 100,000 person-years in Europe [1]. However, they are associated with poor overall prognosis, with a rate of mortality of 5.4 per 100,000 person-years [1]. In children, these tumors are the most frequent solid tumor, inducing significant mortality in this population [2]. In some European countries, there is a trend toward an increase in incidence [3]. Hypotheses for this increase include exposure to exogenous risk factors [3–5]. Several environmental exposures have been investigated as potential risk factors, but for most, scientific evidence is still lacking. To date, the International Agency for Research on Cancer (IARC) has classified only ionizing radiation as an established carcinogen (group 1). Other environmental factors are debated.

The present review focused on environmental factors potentially involved in brain tumor carcinogenesis: studies dealing with the potential association between primary CNS tumors and ionizing radiation, some toxic agents (N-nitroso compounds, pesticides), air pollution, and radiofrequency (RF) electromagnetic waves.

1. Ionizing radiation

The role of ionizing radiation as a risk factor for brain tumors, and especially glioma, meningioma and nerve sheath tumors, is well established, especially in patients who underwent brain high-dose radiotherapy for cancer treatment in childhood [6,7]. Moreover, among 10,834 patients receiving low-dose cranial and cervical irradiation for tinea capitis (mean dose to neural tissue: 1.5 Gy), the relative risk (RR) of developing a tumor was 6.9; the risk for glioma was 2.6 [8]. CT scans of the head in childhood expose the brain to radiation doses of up to 40 to 50 mGy. Also, recent follow-up studies of large cohorts of children and adolescents exposed to diagnostic CT scans of the head have reported an excess RR (ERR) for brain cancer as large as 23 per Gy [9,10]. To date, the CT-scan effect has not been demonstrated in adults. Nevertheless, epidemiological studies are less numerous and less powerful in adults. Thus, brain irradiation even at low doses and especially in childhood constitutes a well-established risk of (second) brain tumor.

Fortunately, ionizing radiation is not an usual environmental factor, even though environmental non-ionizing radiation occurred during atomic bomb detonations

(Hiroshima and Nagasaki), after which a high incidence of certain brain tumors was observed. Shintani et al. reported increased incidence of meningioma in adults as soon as 5 years after the bombing (5 per 100,000), which increased to 15 per 100,000 at 20 years later [11]. The incidence was correlated with the dose of radiation received (evaluated by distance from the hypocenter). For all types of brain tumors, the dose–response relation, measured by ERR per Gy, was greater with exposure at younger ages, as was previously reported for the Life Span Study cohort [12,13].

2. Toxic

2.1. N-nitroso compounds (NOCs)

Among potential risk factors, NOC exposure has long been suspected as a risk factor of brain tumor [14]. NOCs are potent carcinogens in animal models. They are classified in group 2A (probable carcinogen) by the IARC. NOCs include nitrosamines, which require metabolic activation to a carcinogenic form, and nitrosamides, which do not require activation. Nitrosamines can form endogenously from foods treated with sodium nitrite, and certain foods such as bacon and beer contain pre-formed nitrosamines [15]. Although pre-formed nitrosamine levels in beer and nitrite levels have declined substantially since the 1980s, the small amounts of nitrosamines in food are nonetheless significant because humans may be more sensitive to these carcinogens than laboratory rodents [15].

A long-standing hypothesis in the epidemiology of gliomas is that NOC exposure may increase the risk. The hypothesis that NOCs may be involved in the etiology of brain tumors comes both from observations of animal studies that these compounds may be able to pass through the blood–brain barrier and that such compounds may be highly carcinogenic in animals. The most recent and pertinent studies are presented in Table 1.

Transplacental exposure to ethylnitrosourea, a nitrosamide, results in formation of brain tumors including gliomas in rodents and primates [16]. The addition of vitamin C to the diet prevents tumor formation in this model. Human NOC exposure is divided equally between exogenous and endogenous sources. Nitrosamines in tobacco (mainly sidestream smoke), cosmetics, automobile interiors, and cured meats are the best-established exogenous (environmental) sources of NOC exposure. Other sources include rubber products (baby

pacifiers, bottle nipples) and certain drugs including antihistamines, diuretics, oral hypoglycemic agents, antibiotics, tranquilizers, and narcotics. N-Nitrodiethanolamine, a carcinogen in animal models, occurs mainly as a contaminant in cosmetic products, soaps, shampoos, and hand lotions. Some environmental sources may contain both nitrosamines and nitrosamides. The endogenous formation of NOCs is a complex process that occurs in the stomach. It depends on the presence of NOC precursors (i.e., nitrates and nitrites), gastric pH, the presence of bacteria, and other physiological parameters [17].

Measurement of NOC exposure is difficult, given the many exogenous and endogenous sources. Thus, misclassification of exposure is a major limitation for any study on this topic. However, because processed and cured meats are sources of NOC precursors and some pre-formed nitrosamines, dietary assessment may be a useful surrogate marker for NOC exposure [18].

Epidemiological support for NOC exposure as a risk factor for brain tumors comes mostly from studies of pediatric brain tumors and maternal diet. Several studies have assessed the association between maternal diet and childhood brain tumor risk [19]. A meta-analysis determined that frequent intake of processed meats during pregnancy was associated with an elevated risk of childhood brain tumors (RR 1.68; 95% confidence interval [CI], 1.30–2.17) [20]. However, the authors of this meta-analysis caution against drawing definitive conclusions because of several study design limitations such as recall and selection bias. A recent international, collaborative, pooled case–control study assessed maternal diet during pregnancy (including cured meat intake) and risk of childhood brain tumors in children of the mothers [21]. It included 9 studies, involving centres from 7 countries. Most of the 1218 cases were diagnosed between 1982 and 1992, and 2223 controls were included. The age of children ranged from 0 to 19 years. Mothers were asked about their food consumption during the past year and during the index pregnancy (i.e., pregnancy with the study participant). The dietary questionnaire focused on foods high in nitrates and/or nitrites and foods containing nitrosation inhibitors (i.e., vitamins C and E). Dietary consumption was estimated in average grams per day. Cured meat consumption by the mother during pregnancy was associated with increased risk of all brain tumors combined, but particularly astroglial tumors. The multivariable odds ratio (OR) for the top versus bottom quartile of consumption was 1.5 (95% CI, 1.1–2.1; $P_{\text{trend}} = 0.03$) for all brain tumors combined and 1.8 (95% CI, 1.2–2.6; $P_{\text{trend}} = 0.01$) for astroglial tumors. The Working Group concluded that this was an informative study

because of the large study size, the geographical variation of the pooled studies, and the large number of food items investigated, including cured meats. However, recall bias by mothers could not be excluded.

Case-control studies provide inconsistent results about dietary intake of foods containing pre-formed nitrosamines or compounds that can be converted to nitrosamines and risk of brain tumour in adults, although a few case-control studies reported strong positive associations [22,23]. The potential for bias in these studies is high. A collaborative, pooled case-control study of cured meat consumption and risk of adult brain tumors [24] did not show an association between cured meat consumption and adult brain tumors. Two large prospective cohort studies examined consumption of meat and foods high in nitrites or nitrates and risk of brain tumour. Michaud et al. (2009) [25] analysed combined data from 3 US prospective cohort studies with 335 adult glioma cases diagnosed during 24 years of follow-up. No associations were observed between consumption of red meat, processed meat, bacon, or hot dogs and risk of glioma. Another large US cohort study of 585 adult glioma cases found no significant trends for glioma risk with consumption of red or processed meat [26]. Data from these 2 large studies, which are less prone to bias than case-control studies, provide little evidence for the NOC hypothesis, at least as it pertains to adult gliomas.

Vitamins C and E inhibit nitrosation reactions in vivo, and intake of these vitamins can reduce the endogenous formation of NOCs in the stomach. Epidemiological studies have demonstrated that consumption of vitamin C reduces the risk of gastric cancer [27], a tumor for which NOCs may be a risk factor [28]. Statistically significant inverse associations with dietary vitamin C or supplemental intake have been observed in a few case-control studies [29]. Furthermore, no associations were observed in a large prospective cohort study examining intake of vitamins C and E and a total antioxidant score and risk of glioma [25]. Currently, evidence does not support a causation for vitamin intake and risk of glioma.

2.2. Pesticides

The role of pesticides in CNS tumor risk was first suggested by studies of mortality rates in farmers in the United States and Scandinavia. In fact, farmers globally present a lower risk of cancer than the general population but a higher risk for certain cancer sites, including the CNS. This result was consistent across studies, and confirmed by a review and a meta-

analysis [30,31]. One study found a statistically significant 30% increase in risk of brain tumors in farmers. Several risk factors may explain this finding, including exposure to not only pesticides but also viruses, solvents and fertilizers. Arsenicals, which are widely used in vineyards, for potatoes and tree crops, have been classified by the IARC as carcinogenic in humans, whereas non-arsenical insecticides as well as glyphosate, diazinon and malathion used in agriculture have been classified as probably carcinogenic to humans (2A).

Yet, there is no evidence of an association between these agents and brain tumors. Some pesticides are proven carcinogens in animals, so pesticide exposure could play a role in brain tumors. However, data for specific pesticides are lacking owing to the marketing of more than 1000 such molecules in recent decades.

In the literature, several case-control studies and a few cohort studies evaluated the possible association between pesticide exposure and CNS tumors, especially gliomas and meningiomas (Table 2). The results do not all converge. Indeed, some authors report no association, whereas others report increased risk [32] with duration of use [33] or a dose effect [34]. The potential role of agricultural pesticides was evaluated in cohorts of nearly 200000 French farmers [35]. Analyses showed several increased risks of CNS tumors in farmers, especially in pesticide users (hazard ratio = 1.96; 95% confidence interval: 1.11-3.47). Associations varied with tumor subtypes and kinds of crop and animal farming. The main increases in risk were observed for meningiomas in pig farmers and in farmers growing sunflowers, beets and potatoes and for gliomas in farmers growing grasslands. In most cases, more pronounced risk excesses were observed among pesticide applicators. Even if we cannot completely rule out the contribution of other factors, pesticide exposures could be of primary concern to explain these findings.

Few epidemiological studies have provided a detailed estimation of exposures. For instance, lists of pesticides were suggested in the US Upper Midwest Health Study, with pesticides grouped according to their chemical properties [36]. A recent study showed increased risk of CNS tumors with overall exposure to carbamate insecticides [33]. A French study observed an association between brain tumors and exposure to pesticides in vineyards, but the agents potentially involved could not be identified [37].

This is not only a concern for farmers *per se*. Indeed, in the general population, Carles et al. found a significant association between meningioma and residential proximity to open field crops, but no significant association was found between glioma and residential proximity to agricultural land [38].

Regarding the risk of childhood brain tumors and parental exposure of pesticides, results are inconsistent. A meta-analysis of 16 case-control and five cohort studies found a significantly increased risk (30–50%) related to occupational exposure to pesticides among mothers during the prenatal period [39]. Another meta-analysis identified residential/domestic exposure to pesticides as a risk factor for childhood brain tumor, particularly for indoor exposure, involving insecticides [40]. Data from 2 French national population-based, case-control studies found childhood brain tumors significantly associated with maternal home use of pesticides during pregnancy (OR 1.4, 95% CI 1.2-1.8) and more specifically with insecticides (OR 1.4, 1.2-1.8) [41]. In a recent international prospective study, paternal exposure to pesticides and animals was not associated with increased risk of childhood CNS tumors [42]. To date, the small samples and the weakness in exposure quantification in these studies do not allow for accepting the ERR due to parental pesticide exposure.

In general, data on pesticide exposure and brain tumors are inconsistent. Study validity is often questionable, and exposure assessment using biological measures of exposure is mostly lacking. Despite the large number of studies in several occupational settings, an increased risk of brain tumor development based on occupational status is not established. While waiting for more reliable studies, one should proceed with caution with pesticide exposure.

3. Outdoor air pollution

Outdoor air pollution is a global public health problem, particularly prevalent in megalopolis and southern countries but also important in developed European countries [43]. It results from multiple sources including transport, industrial activity and power generation, biomass burning, and domestic heating, lighting, and cooking based on solid fuel [44]. Outdoor air varies substantially both in space and time because of the mix of sources and the external effects, including oxidation and weather.

In 2013, members from the IARC unanimously classified outdoor air pollution as carcinogenic, with a strong causal association with lung cancer in particular [45]. Several diseases of the CNS, including ischemic stroke [46–48] and Parkinson disease, were linked to pollution exposure [49]. Outdoor air pollution comprises several potentially carcinogenic factors: particulate matter (PM), black carbon, heavy metals (e.g., vanadium, nickel, and manganese), environmental tobacco smoke, organic compounds (e.g., polycyclic aromatic hydrocarbons and endotoxins) and gaseous pollutants (e.g., O₃, NO₂, SO₂, CO). PM and O₃ are thought to be the 2 most important dangers to public health [50,51].

However, data regarding brain tumors are scarce. In addition to biological and animal models, only a few epidemiological studies exist: 2 ecological studies [52,53], 4 cohort studies [54–57] and 1 case–control study [58] (Table 3).

Studies of animals argue for the penetrance of particles and mineral magnetite into the CNS, which causes neuroinflammation [59,60]. Brain inflammation within a tumor microenvironment is thought to increase oxidative stress and DNA damage, thus stimulating both genetic and epigenetic changes that occur during glioma evolution [61].

Conflicting results arise from epidemiological studies. The European Study of Cohorts for Air Pollution Effects [57] reported evidence of an association between traffic-related air pollution, using PM_{2.5} (PM with a diameter of less than 2.5 micrometers) absorbance as a proxy, and brain tumors. However, McKean-Cowdin et al. and Valberg et al. found a negative association between sulfur dioxide, nitrogen dioxide, and carbon monoxide exposure and nervous system cancer mortality or incidence [52,62]. The authors proposed that the protective effect is induced by chronic immune stimulation. Indeed, immune hyperactivity is characteristic of allergies and asthma, both conditions inversely correlated with brain cancer risk in most studies [63–67] if not all [68]. Another incoherence was found in the Danish population: in a first nationwide cohort study [55], Poulsen et al. identified an exposure-response linear association between nitrogen oxides at the residence – as a proxy of outdoor pollution – and risk for brain cancer. They found contradicting evidence in another nationwide case–control study [58], where they could not replicate this association. Still, this second study highlighted an increased risk of non-glioma tumours with high exposures (nitrogen oxides concentration $\geq 100\mu\text{g}/\text{m}^3$) with an OR of 2.3 (95% CI 1.2-4.6).

As a whole, data for the effect of outdoor air pollution on brain cancerogenesis mostly rely on a small number of studies that are exploratory in nature. Thus, to date, we lack evidence to incriminate air pollution in the development of brain tumors.

4. Radiofrequency electromagnetic waves

Radiofrequency (RF) radiation is a form of non-ionizing radiation that can be emitted by diverse instruments such as mobile phones and their base stations but also radio and television broadcasting, wireless networks such as Wi-Fi, satellite communications, microwave ovens or radar. The exposure to RF is ubiquitous, but recent research focused principally on mobile phones because they are placed near the head and brain. According to the Global System for Mobile Communications, 5.1 billion people around the world, accounting for 67% of the global population, subscribed to mobile services by the end of 2018. With this overwhelming increase in cell-phone use, widespread concerns have been raised about the effects of exposure to radiofrequency electromagnetic waves. In fact, there is abundant literature consisting of biological and animal studies, several case-control and cohort studies and a few reviews and meta-analyses on the possible association between mobile phone use and CNS tumors, especially gliomas, meningiomas or nerve sheath tumors (acoustic neuroma in particular).

First, the possible biological carcinogenic effects of exposure of the CNS tissue to RF was studied with cell or animal models. Even though these results could not be applied to humans directly, they provide basic information on the possible underlying phenomenon [69]. According to these studies, long-term exposure to RF triggers molecular changes, inducing cell proliferation or cell death [69–71]. Indeed, modification of signaling occurs because of altered ionic distribution and permeability or membrane fluidity [72]. Modification of neuronal activity was observed [73–75], which may be related to increased temperature [69,76,77]. Still, discrepancies between studies exist, depending mainly on protocols (duration, frequency, amplitude of exposures), which warrant further analysis [72].

Nine meta-analyses have been published to study the association between mobile-phone use and brain cancer incidence. Their characteristics are in Table 4. Included brain cancers are of 3 main types: glioma (with a distinction between low-grade and high-grade glioma in some studies only), acoustic neurinoma and meningioma. Their results are partly ambiguous, which

may be explained by heterogeneity in the selection criteria and the statistical analysis. These meta-analyses are mostly based on studies performed by the Hardell or Interphone group. The Interphone interview-based multicenter case–control study is the largest study to date. It was conducted in 13 countries and included 2708 glioma and 2409 meningioma cases and matched controls [78]. The risk of glioma or meningioma was not increased in the whole population of mobile-phone users. Suggestive evidence was found for increased incidence of glioma but not meningioma, when exposure levels overpassed a certain level. Adjustment for possible bias, performed by another team, did not significantly change the results [79]. The 2 most recent meta-analyses of epidemiological studies were published in 2017. One meta-analysis found a significant association for prolonged exposure (≥ 10 years) and ipsilateral location for all CNS tumors (no difference between glioma, meningioma and acoustic neuroma) and all phone types [80]. The second meta-analysis focused on the risk of mobile-phone use on gliomas but found no association when pooling all durations of use but did find an association among long-term users, ≥ 10 years. Risk of phone use was correlated with low-grade glioma, particularly for long-term users [81].

The ORs for both these meta-analyses and the other 7 published earlier are shown in Table 5. As a whole, they converge toward an increased risk for glioma and acoustic neuroma but not meningioma with long-time mobile-phone use (≥ 10 years, with this threshold set arbitrarily) on the side of the tumor. When pooling all durations of use and both sides of the head to compute, results were much more discordant across studies. Indeed, both restrictions to ipsilateral location and long duration of use should be arguments favoring a carcinogenic effect of RF on CNS tissue. Indeed, because RF exposure is localized, tumors should predominate in regions with the highest energy absorption. As discussed by Dimbylow and Mann and later by Cardis et al., more than 90% of the energy is absorbed in the side of the head the phone is placed close to, with 50% to 60% localized in the temporal lobe [82,83]. Indeed, some studies report increased risk in the temporal and overlapping lobes [78,84]. The association of mobile-phone use and brain tumors restricted to long duration of use (≥ 10 years in most studies) [78,84,85] argues for a dose-effect with a dependence on cumulative use.

The difference seen between low- and high-grade gliomas was hypothesized to be due to the natural history difference between low- (WHO grade I and II) and high- (WHO grade III and IV) grade gliomas. Indeed, relative to high-grade glioma, especially primary glioblastoma, low-grade gliomas occur at lower ages and have a long latency period [81]. Therefore, these

two types may involve different carcinogenesis pathways, with different risk factors. A high proportion of grade III gliomas are degenerated low-grade gliomas. However, because they are generally analyzed together with primary glioblastoma, which progresses fast with both a short latency period and disease course, the analysis might overlook the association between mobile-phone use and grade III gliomas [81].

Hardell and Carlberg (2013) evaluated the Bradford Hill criteria for causality between long-term mobile-phone use (≥ 10 years) and brain cancer. The authors concluded that all 9 issues in causation were now fulfilled [86]. On the basis of epidemiological studies, they concluded that the criteria for strength, consistency, specificity, temporality, and biologic gradient were fulfilled for evidence of increased risk for glioma and acoustic neuroma. Biological and animal laboratory studies brought additional evidence for plausibility and analogy. Support for coherence came from data on the incidence of brain tumors, which showed increased incidence of brain tumors, especially in heavily exposed areas. The experiment criterion was supported by 2 observations: first, several studies found antioxidants protective of the generation of reactive oxygen species involved in biologic effects, although a direct mechanism for brain tumor carcinogenesis has not been described. Second, studies involving phones used within cars with fixed antennas showed no increased risk of brain tumors.

Still, limitations of the meta-analyses and the underlying studies are numerous. First, included studies are mostly of limited quality (case–controls, with small group numbers) [44]. Prospective cohorts would address the question more specifically [87], but the low incidence of brain tumors would require a high number of participants, and the long latency would require a long follow-up period. Still, one prospective cohort study found an association between mobile-phone use and acoustic neuroma, although the time from exposure to tumor onset was limited to 10 years [88]. Another concern regards the quantification of exposure level. Indeed, mobile-phone use is difficult to assess precisely because the level of exposure depends on the phone type and generation. For instance, the average output power of calls with the Global System for Mobile Communications and Universal Mobile Telecommunications Service differs by a factor of 100 to 500 [89,90]. Besides, patterns of phone use change over time [91]. In terms of these difficulties, the exposure assessment seems highly insufficient. In cohort studies, the assessment relied on information from operators — a person classified as a user if he/she subscribed to a mobile-phone service — or

to a vague statement “telephone use likely or certain” [4,13]. In case–control studies, interviews allowed for recovering more specific information.

Still, most of the time, evaluations seem largely unsatisfactory in some studies. First, response rates were low, averaging 50% (45% in the CERENAT study [92] and 53% in the Interphone study [78]). Second, in some studies, as in the CERENAT study, regular mobile phone use was defined as use at least once a week for at least 6 months without further difference between an occasional user (once a week) and heavy user (several times a day). Another problem was with the use of Digital Enhanced Cordless Telecommunications cordless phones. Hardell et al. [93,94], Hansson Mild et al. [95] and Morgan et al. [96] pointed out that cordless phone users were wrongly classified as mobile-phone non-users in some studies. Indeed, Hardell et al. mentioned that calls are usually longer with cordless phones than mobile phones [51,52]. Also, latency periods were limited to 2 to 10 years in the first studies, which is too short to be sensitive enough for determining long-term risk [81, 97, 98]. Newer studies tend to include patients with long-term use (≥ 10 years). Another problem is that childhood exposures have been largely unexplored [99–101]. Also, meta-analyses all report substantial between-study heterogeneity and low number of studies for subgroup analysis. Only low adjustment for confounding factors was sometimes possible [81].

On the whole, we have no strong and consistent evidence for a causal relation between RF exposure and CNS tumors, but we have evidence for an association with acoustic neurinoma in long-term users. Nevertheless, studies have many limitations that preclude definitively ruling out the association. Further studies, especially prospective studies, should be performed to further assess whether mobile-phone exposure is associated with brain tumor risk [80,100,102,103]. In 2011, based on the available conflicting scientific evidence, the IARC classified RF in the carcinogenic group 2B, that is, among possible carcinogens [104]. However, for some authors, the evidence is strong enough to support a change in the IARC classification and classify RF as a probable carcinogen (group 2A) [96] or even carcinogen (group 1) [86,105].

CONCLUSION

To date, the causal factors of brain tumors remain unknown. This unanswered question constitutes an additional disappointing fact for patients and their relatives when they are

diagnosed with a brain tumor. Moreover, brain tumor incidence is continuously increasing, although slightly, in developed countries. Therefore, identifying the potential causes or risk factors is pressing. Yet, environmental exposure has been poorly explored. The low incidence rates of brain tumors, their appearance probably a long time after exposure, and reliable quantification of the exposure to environmental factors are the main difficulties to overcome to correctly explore potential risk factors. In that regard, prospective studies on long-term effects of a given exposure remain the only way to definitively link a risk factor to brain tumors.

Here we reviewed the literature to evaluate the association between a range of environmental exposures and primary brain tumors. To date, only few environmental exposures have been explored in terms of brain tumor risk. Brain ionizing irradiation, even at low doses, and especially during childhood, constitutes a well-established risk factor of brain tumors and has been an environmental concern in areas subjected to atomic bomb radiation exposure. Few studies exist of environmental toxins, and they give inconsistent conclusions on the role of NOCs or pesticides as brain tumor risk factors, even for prenatal exposure. Out-door pollution with several compounds was incriminated in brain-tumor carcinogenesis. However, results of large prospective studies lasting more than 10 years are contradictory. Still, fine microparticles from pollution, PM_{2.5}, have been incriminated as brain-tumor risk factors in several robust studies. In contrast to toxin studies, many studies have addressed the effect of mobile phones on brain-tumor risk. Despite several ambitious and well-designed international studies, this effect has not been established in adults for glioma and meningioma, but the link with acoustic neurinoma is becoming robust. Besides, the effect of mobile phone use has still not been explored in children.

Based on the available literature and following on a precautionary principle, we can thus make a few recommendations regarding environmental exposures and risk of brain tumours:

- Ionizing radiation : the radiation burden of radiological interventions should be weighted at all ages, and especially in children.
- N-nitroso compounds : pregnant women should limit the consumption of cured meat.
- Pesticides: people, and farmers in particular, should protect themselves during pesticide use.
- Outdoor pollution : national and local strategies to reduce outdoor air pollution should be supported. Individuals can participate in improving air quality levels in their communities by lowering their personal emission of fossil-fuel (eating local food,

using more sustainable modes of transportation like car-pooling, mass transport, cycling, or walking, using clean and renewable energy, and installing effective insulation in their homes).

- Mobile phones : when not used, mobile phones should be switched off or set to an airplane mode. Hands-free telephones may also be useful. Children, and especially toddlers, should be kept away from their use.

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Tables

Table 1 – Characteristics of recent studies evaluating the association between N-nitroso compounds and brain tumor

<i>Authors</i>	<i>Type of study</i>	<i>Country</i>	<i>Evaluation</i>	<i>Participants (cases)</i>	<i>Type of tumor</i>	<i>Type of food</i>	<i>Results</i>
Michaud et al. 2009	Prospective cohort	United States	Consumption of red/processed meats and risk of glioma	289915 (335)	Glioma	Red meat, processed meat, bacon, hot dog	Negative RR 0.92, 95% CI 0.48-1.77)
Dubrow et al. 2010	Prospective cohort	United States	Red/processed meat consumption and risk of glioma	545770 (585)	Glioma	Red meat, processed meat	Negative RR 1.05 (0.80–1.37) for processed meat 0.85 (0.65–1.11) for red meat
Pogoda, 2009	Case–control	International 7 countries	Maternal diet during pregnancy and risk of childhood brain tumors	34 441 (1 218)	All brain tumors	Foods high in nitrates and/or nitrites	Positive particularly for astrocytomas OR (1.8-2.5), p ≤ 0.03
Terry et al. 2009	Case–control	International 6 countries	Cured meat consumption and risk of glioma	3 671 (1185)	All brain tumors	Food groups including cured meats	Negative RR 0.9 (0.7–1.2)

RR, relative risk; OR, odds ratio. Significant ORs are in bold type.

Table 2 – Characteristics of recent studies evaluating the association between pesticides and brain tumor.

<i>Authors</i>	<i>Type of study</i>	<i>Country</i>	<i>Evaluation</i>	<i>Participants (cases)</i>	<i>Type of tumor</i>	<i>Results</i>
<i>Risk of adult brain tumors exposure of pesticides</i>						
<i>Piel, 2017</i>	Prospective	French	Exposure of farmers and pesticide users and the incidence of CNS tumors	181 842 (273)	Gliomas and meningiomas	Positive (HR 1.96; 95% 1.11-3.47)
<i>Piel 2018</i>	Prospective	French	Potential exposure to carbamate insecticides and the incidence of CNS tumors	181 842 (381 incident cases)	All brain tumors	Positive
<i>Fallahi, 2017</i>	Case–control	Italy	Risk for brain tumors and rural activity	696 (174)	Gliomas and meningiomas	Positive
<i>Carles 2017</i>	Case–control	French	Residential proximity to agricultural land and risk of brain tumor in the general population	1470 (490)	Gliomas and meningiomas	Positive (OR 2.30 95% CI 1.04-5.10) for meningioma and proximity to open field crops, negative for glioma and proximity to agricultural land
<i>Samanic, 2008</i>	Case–control	United States	Occupational exposure to insecticides and herbicides and risk of glioma and meningioma	1422 (657)	Gliomas and meningiomas	Negative for glioma and exposure to insecticides or herbicides Positive (OR 2.4, 95% 1.4-4.3) for meningioma and women who used herbicides
<i>Provost 2007</i>	Case–control	France	Exposure to pesticides and risk of brain tumor in adults	663 (221)	All brain tumors	Negative except in the highest quartile of the cumulative index, a significant association was found for brain tumors (OR 2.16, 95% CI 1.10-4.23) and for gliomas (OR 3.21, 95% CI 1.13-9.11) but not meningiomas.
<i>Ruder, 2006</i>	Case–control	United States	Intracranial glioma in the non-metropolitan population	1 973 (798)	All brain tumors	Farm or rural residence and summary farm exposure associated with decreased glioma risk

Lee, 2005	Case-control	US	Adult glioma and risk of agricultural pesticide use	749 (251)	All brain tumours	Positive for men ever living or working on a farm and duration of farming and glioma (≥ 55 years on a farm; OR 3.9, 95% CI 1.8-8.6)
<i>Risk of childhood brain tumors and parental exposure of pesticides</i>						
Patel, 2019	Prospective	International	Parental occupational exposure and risk of childhood CNS tumors	329 658 (158)	All brain tumors	Negative
Vidart, 2018	A pooled analysis of 2 case-control studies	French	Maternal residential pesticide use during pregnancy and risk of malignant childhood brain tumors	3 539 (437)	All brain tumors	Positive (OR 1.4, 95% CI 1.2-1.8) and, more specifically, with insecticides (OR 1.4, 1.2-1.8)
Febvey 2016	Case-control	European	CNS tumors in children and related to parental occupational pesticide exposures	6859 (1361)	All brain tumors	Negative (OR 0.76, 95% CI 0.41-1.41)
Greenop 2013	Case-control	australian	Exposure to pesticides before pregnancy, during pregnancy and during childhood and risk of brain tumor.	1698 (335)	All brain tumors	Positive association between home pesticide use in the year before pregnancy and the risk of childhood brain tumor (OR 1.90, 95% CI 1.08-3.36)

CNS, central nervous system; OR, odds ratio; HR, hazard ratio; 95% CI, 95% confidence interval. Significant ORs are in bold type.

Table 3 – Characteristics of meta-analysis evaluating the association between air-pollution and brain tumor incidence or mortality

<i>Authors</i>	<i>Journal</i>	<i>Study type</i>	<i>Tumor type</i>	<i>Country</i>	<i>Population</i>	<i>Pollutants</i>	<i>Analysis method</i>	<i>Results</i>
Andersen 2018	Neuro-Oncology	Prospective cohort (12 years of follow-up)	malignant brain tumor, non malignant brain tumor	12 cohorts from 6 European countries	- malignant brain tumors: 282 194 participants, from which 466 developed malignant brain tumors - malignant and non malignant brain tumors: 106 786 participants, from which 176 developed non malignant and 190 developed malignant brain tumors	annual average concentrations of: - nitrogen dioxide, nitrogen oxides, PM _{2.5} , PM ₁₀ at baseline residence for each participant (standardized area-specific land-use regression models) - 8 elements in PM _{2.5} and PM ₁₀ (copper, iron, zinc, sulfur, nickel, vanadium, silicon and potassium) - traffic intensity	- cohort specific analysis: association between each pollutant absorbance and brain tumor (malignant, non malignant, total) in each cohort - meta-analysis: combination of the estimates from each cohort, for each pollutant and each brain tumor subtype	- association between traffic-related PM _{2.5} absorbance and malignant brain tumors - no association with overall or nonmalignant brain tumors
Boeglin 2006	Environmental Research	retrospective epidemiological	nervous system cancer	Indiana (United States)	92 counties	release of volatile organic compounds 8 years prior to cancer incidence (1988)	relationship between the amount of volatile organic compounds released in each county (Toxic Release Inventory), and the county-by-county incidence of nervous system cancer	association with non chlorinated stack, total stack and non chlorinated total of volatile organic compounds
McKean-Cowdin 2009	Cancer Causes Control	Prospective cohort (18 years of follow-up)	nervous system cancer	United States	630 487 participants, 1 284 deaths due to brain cancer	follow-up duration average concentrations of: PM _{2.5} and PM ₁₀ , total suspended particles, sulfur dioxide, nitrogen dioxide, carbon monoxide, ozone	hazard ratios for mortality due to nervous system cancer	- no positive association between any listed pollutant and nervous system cancer mortality - small protective effect of sulfur dioxide, nitrogen dioxide, carbon monoxide on nervous system cancer mortality
Valberg 2012	Air Qual Atmos Health	retrospective epidemiological	nervous system cancer	United States	brain cancer incidence: 875 counties brain cancer mortality: 821 counties.	2008 average concentrations of: - PM, nitrogen dioxide, sulfur dioxide, ozone, carbon monoxide - 30 ambient air pollutants that were either IARC Group 1 carcinogens (e.g., arsenic, beryllium, benzene, and vinyl chloride), or compounds that have been suggested as hypothetical brain cancer risk factors	Pearson product-moment correlation coefficients with brain cancer mortality or brain cancer incidence	- small positive association between ozone and nervous system cancer incidence - small protective effect of some pollutants on nervous system cancer incidence
Raaschou-Nielsen 2011	Environmental Health	Prospective cohort (13 years of follow-up)	brain cancer	Danemark	54 304 participants	- concentration of nitrogen oxides - presence of a street with a traffic density > 10,000 vehicles per day within 50 m of the residence - total number of kilometers driven	Pearson product-moment correlation coefficients with brain cancer incidence	- association between nitrogen oxide concentration and brain cancer: unadjusted: HR 2.28; 95% CI 1.24-4.17 adjusted: HR 2.28; 95% CI 1.25-4.19 - association between proximity to major

						by vehicles within 200 m of the residence each day.		street (<50 m) and brain cancer: unadjusted: HR 1.89; 95% CI: 1.07–3.34 adjusted: HR 1.89; 95% CI 1.07–3.36
Poulsen 2016	Cancer Causes Control	Case–control	glioma, non glioma brain cancer	Danemark	4 183 cases, 8 018 controls	concentration of nitrogen oxides	odd ratios for brain cancer incidence	- no association between nitrogen oxides concentration and brain tumors. Tendency for elevated risk among subjects with average lifetime nitrogen oxides concentration ≥ 80 ug/m3. - small association between nitrogen oxides concentration and non-glioma tumors.
Jørgensen 2016	Neurotoxicology	Prospective cohort (15.7 years of follow-up)	brain or meninges tumor, malignant or non malignant nervous system tumor	Danemark	25 143 participants, from which 121 developed a nervous system tumor	annual average concentrations of nitrogen oxides, nitrogen dioxide, PM _{2.5} , PM ₁₀	hazard ratios for tumor incidence	- weak positive associations of PM _{2.5} and nitrogen dioxide with brain tumors incidence - associations were strongest for tumors located in the meninges and for benign tumors - association of PM _{2.5} with brain tumors was significantly enhanced in obese women

HR, hazard ratio; 95% CI, 95% confidence interval. Significant HRs are in bold type.

PM: particulate matter; PM_{2.5}: PM with a diameter of less than 2.5 micrometers; PM₁₀: PM with a diameter of 2.5 to 10 micrometers.

Table 4 – Characteristic of meta-analysis evaluating the relationship between mobile-phone use and brain tumor incidences

<i>Authors</i>	<i>Journal</i>	<i>Number of studies</i>	<i>Tumor type</i>	<i>Inclusion criteria</i>
Bortkiewicz 2017	Int J Occup Med Environ Health	24 case–control	26 846 cases, 50 013 controls	- papers in English - original, case–control peer-reviewed studies published till the end of March 2014 - measures of association (odds ratio and confidence interval of the effect measured) - data on individual exposure
Gong 2014	Zhonghua Yi Xue Za Zhi	[article in chinese]	[article in Chinese]	[article in chinese]
Hardell 2008	Int J Oncol	16 case–control	not given (one study without numbers)	- case–control studies other criteria not defined precisely
Kan 2008	J. Neurooncol.	9 case–control	5 259 cases, 12 074 controls	- papers in English - case–control studies - sufficient data so that the crude odds ratios (ORs) could be derived - data on individual exposure clearly defined and evaluated to minimize misclassification exclusion: exposure other than cellular phones (e.g., cordless phones)
Khurana 2009	Surg Neurol	11 case–control	Not specified	- publication in a peer-reviewed journal - inclusion of participants using cell phones for ≥ 10 years - incorporation of a laterality analysis of long-term (≥ 10 -year) users.
Lagorio 2014	Bioelectromagnetics	29 case–control	Not specified	- individuals as units of information (cohort, case- control) - mobile phone use or as the exposure of interest - providing incidence-based (as opposed to mortality-based) estimates of the relative risk (RR) of disease among the exposed in the whole target population - focusing on morphology-specific groups of neoplasms in homogenous age classes - analyses based on comparable exposure metrics and categories - single risk estimate per neoplasm and exposure category per independent study (or distinct pooled analysis)
Lahkola 2006	Scand J Work Environ Health	11 case–control 1 cohort	2780 cases gliomas: 1352 cases, 339 classified as exposed meningiomas: 527 cases, 149 classified as exposed acoustic neuromas: 605 cases, 167 classified as exposed	- original publications - case–control or cohort publications - using individual exposure data - reporting information needed for the estimation of confidence intervals (standard error or confidence interval of the effect measure or the number of persons by exposure and outcome status)
Myung 2009	JCO	23 case–control	12 344 cases, 25 572 controls	- case–control studies - reported outcome measures with adjusted odds ratios and 95% CIs, crude odds ratios and 95% CIs, or values in cells of a 2 x 2 table (from which odds ratios could be calculated)
Yang 2017	Plos One	11 case–control	6 028 cases, 11 488 controls	- average weekly mobile phone use frequency and ≥ 6 months of continuous use - recorded side of head predominantly used - reported glioma pathology - reported sample size and odds ratios for case–control studies - digital and/or mobile phone types - the control group comprised healthy subjects; who are not regularly exposed to radiation from mobile phones or other related sources of electromagnetic radiation Exclusion criteria: - tumor not classified and/or data related to glioma not extracted - Insufficient follow-up time

Table 5 – Pooled odd-ratios in meta-analysis evaluating the association between mobile-phone use and brain tumor incidence.

				Bortkiewicz 2017	Gong 2014	Hardell 2008	Kan 2008	Khurana 2009	Lagorio 2014	Lahkola 2006	Myung 2009	Yang 2017
all mobile phone types	all intracranial tumors	all use duration	both sides	0.94 [0.86–1.03]	-	-	0.90 [0.81–0.99]	-	several analysis: include 1	-	0.98 [0.89–1.07]	-
			ipsilateral	1.29 [1.06–1.57]	-	-	-	-	-	-	-	-
		use ≥ 10 years*	both sides	1.46 [1.07–1.98]	-	-	1.25 [1.01–1.54]	1.1 [0.8–1.4]	-	0.98 [0.83–1.16]	1.18 [1.04–1.34]	-
			ipsilateral	-	-	-	-	1.3 [0.9–1.8]	-	1.36 [0.99–1.87]	-	-
	glioma	all use duration	both sides	0.92 [0.83–1.03]	-	-	-	-	several analysis: include 1	-	-	0.98 [0.88–1.1]
			ipsilateral	-	-	-	-	-	-	-	-	0.97 [0.88–1.06]
		use ≥ 10 years*	both sides	1.46 [1.07–1.98]	-	1.2 [0.8–1.9]	-	-	-	0.96 [0.78–1.18]	-	1.44 [1.08–1.91]
			ipsilateral	-	1.46 [1.12, 1.92]	2.0 [1.2–3.4]	-	1.9 [1.4–2.4]	-	1.33 [0.78–2.28]	-	1.46 [1.12–1.92]
	low-grade glioma	all use duration	both sides	-	-	-	1.14 [0.91–1.43]	-	-	-	-	-
			ipsilateral	-	-	-	-	-	-	-	-	-
		use ≥ 10 years*	both sides	-	-	-	-	-	-	-	-	-
			ipsilateral	-	2.27 [1.81, 2.85]	-	-	-	-	-	-	-
	high-grade glioma	all use duration	both sides	-	-	-	0.86 [0.70–1.05]	-	-	-	-	-
			ipsilateral	-	-	-	-	-	-	-	-	-
		use ≥ 10 years*	both sides	-	-	-	-	-	-	-	-	-
			ipsilateral	-	-	-	-	-	-	-	-	-
	acoustic neuroma	all use duration	both sides	0.96 [0.87–1.06]	-	0.9 [0.7–1.1]	0.96 [0.83–1.10]	-	several analysis: include 1	-	-	-
			ipsilateral	-	-	-	-	-	-	-	-	-
		use ≥ 10 years*	both sides	-	-	1.3 [0.6–2.8]	-	-	-	1.07 [0.89–1.30]	-	-
			ipsilateral	-	-	2.4 [1.1–5.3]	-	1.6 [1.1–2.4]	-	1.05 [0.41–2.67]	-	-
	meningioma	all use duration	both sides	0.72 [0.6–0.86]	-	0.8 [0.7–0.99]	0.64 [0.56–0.74]	-	several analysis: include 1	-	-	-
			ipsilateral	-	-	-	-	-	-	-	-	-
		use ≥ 10 years*	both sides	-	-	1.3 [0.9–1.8]	-	-	-	0.87 [0.72–1.05]	-	-
			ipsilateral	-	-	1.7 [0.99–3.1]	-	1.3 [0.9–1.8]	-	1.16 [0.82–1.63]	-	-
analog phone	all intracranial tumors	all use duration	both sides	1.09 [0.91–1.3]	-	-	1.13 [0.83–1.54]	-	-	1.17 [0.91–1.49]	-	-
			ipsilateral	-	-	-	-	-	-	-	-	-
		use ≥ 10 years*	both sides	-	-	-	-	-	-	-	-	-
			ipsilateral	-	-	-	-	-	-	-	-	-
digital phone	all intracranial tumors	all use duration	both sides	-	-	-	0.86 [0.68–1.09]	-	-	1.04 [0.80–1.35]	-	-
			ipsilateral	-	-	-	-	-	-	-	-	-
		use ≥ 10 years*	both sides	-	-	-	-	-	-	-	-	-
			ipsilateral	-	-	-	-	-	-	-	-	-

Data are ORs (95% CIs). Significant ORs are in bold type.

* 5 years for Lahkola 2006