WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 13, 867-892. Review Article ISSN 2277– 7105

A REVIEW ON BRAIN TUMOR

Patel Meet*[1], Vaghela Kuldeepsinh[2], Prajapati Rushil[3], Patel Dixita[4], Pooja Patel[5] and Dr. Umesh Upadhyay[6]

Author[1], Co-author[2], Co-author[3], Co-author[4], Asst. Professor[5], Principal[6]

Department of Pharmacology, Sigma Institute of Pharmacy, Bakrol, Vadodara-390019(Gujarat, India)

Article Received on
08 Sept. 2021,

Revised on 28 Sept. 2021,
Accepted on 18 October 2021

DOI: 10.20959/wjpr202113-22152

***Corresponding Author**
Patel Meet
Author, Department of Pharmacology, Sigma Institute of Pharmacy, Bakrol, Vadodara-390019(Gujarat, India)

ABSTRACT

Adult primary tumors of the central system area unit rare, however the incidence is magnified in some European countries. many environmental exposures are investigated as potential risk factors, except for most, scientific proof remains lacking. Here we have a tendency to review studies of environmental factors probably concerned within the carcinogenesis of brain tumors: the potential association between primary central system tumors and radiation, some ototoxic agents (N-nitroso compounds, pesticides), pollution, and radiofrequency electromagnetic waves. Brain-ionizing irradiation, particularly throughout childhood, constitutes a well-established risk issue for brain tumors. Exposure to environmental toxins has been poorly explored and information provide inconsistent clues regarding N-nitroso compounds or pesticides as risk factors of brain tumors even for antenatal exposure. For out-door pollution and risk of brain growth, results of enormous prospective studies area unit contradictory. The result of mobile phones on the chance of developing brain tumors has not been established for brain tumor and meningioma in adults, however the link with acoustic nonmalignant tumor is changing into strong. The result of mobile phones has still not been explored in youngsters.

KEYWORDS:

INTRODUCTION

Adult primary tumors of the central systema nervosum (CNS) area unit rare, with Associate in Nursing incidence of seven. 0 per 100,000 person-years in Europe.[1] However, they're

related to poor overall prognosis, with a rate of mortality of five.4 per 100,000 person-years.[1] In youngsters, these tumors area unit the foremost frequent solid growth, causation vital mortality during this population.[2]

In some European countries, there's a trend toward a rise in incidence.[3] Hypotheses for this increase embody exposure to exogenous risk factors.[3–5] many environmental exposures are investigated as potential risk factors, except for most, scientific proof is still lacking. To date, the International Agency for analysis on Cancer (IARC) has classified only radiation as a longtime matter (group 1). different environmental factors are debated.

The present review centered on environmental factors probably concerned in brain tumour carcinogenesis: studies managing the potential association between primary central nervous system tumors and radiation, some cyanogenetic agents (N-nitroso compounds, pesticides), pollution, and radiofrequency (RF) magnetic attraction waves.

1. Radiation

The role of radiation as a risk issue for brain tumors, and particularly brain tumour, meningioma and nerve sheath tumors, is well established, particularly in patients United Nations agency underwent brain high-dose therapy for cancer treatment in childhood.[6,7] Moreover, among 10,834 patients receiving low-dose bone and cervical irradiation for roundworm (mean dose to neural tissue: one.5 Gy), the relative risk (RR) of developing a growth was six.9; the risk for brain tumour was two. 6.[8] CT scans of the top in childhood expose the brain to radiation doses of up to forty to fifty mGy. Also, recent follow-up studies of huge cohorts of youngsters and adolescents exposed to diagnostic CT scans of the top have according Associate in Nursing excess RR (ERR) for brain cancer as massive as twenty three per Gy.[9,10] To date, the CT-scan result has not been demonstrated in adults. however, medical specialty studies area unit less varied and fewer powerful in adults. Thus, brain irradiation even at low doses and particularly in childhood constitutes a well-established risk of (second) brain tumour.

Fortunately, radiation isn't Associate in Nursing usual environmental issue, even supposing environmental non-iatrogenic radiation occurred throughout plutonium bomb detonations(Hiroshima and Nagasaki), when that a high incidence of sure brain tumors was discovered.

Shintani et al. according accrued incidence of neoplasm in adults as shortly as five years when the bombing (5 per a hundred,000), that accrued to fifteen per a hundred,000 at twenty years later.[11] The incidence was related with the dose of radiation received (evaluated by distance from the hypocenter). For all kinds of brain tumors, the dose–response relation, measured by ERR per Gy, was bigger with exposure at younger ages, as was antecedently according for the generation Study cohort.[12,13]

2. Toxic

2.1. N-nitroso compounds (NOCs)

Among potential risk factors, operative exposure has long been suspected as a risk issue of brain tumor.[14] NOCs square measure potent carcinogens in animal models. they're classified in cluster 2A (probable carcinogen) by the IARC. NOCs embody nitrosamines, that need metabolic activation to a cancer type, and nitrosamides, that don't need activation.

Nitrosamines will type endogenously from foods treated with nitrite, and bound foods like bacon and brewage contain pre-formed nitrosamines.[15] though pre-formed nitrosamine levels in brewage and group levels have declined well since the Nineteen Eighties, the small amounts of nitrosamines in food square measure yet important as a result of humans could also be more sensitive to those carcinogens than laboratory rodents.[15]

A long-standing hypothesis within the medicine of gliomas is that operative exposure could increase the chance. The hypothesis that NOCs could also be concerned within the etiology of brain tumors comes each from observations of animal studies that these compounds could also be ready to pass through the blood–brain barrier which such compounds could also be extremely cancer in animals. the foremost recent and pertinent studies square measure conferred in Table one.

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

Authors	*Type of study*	*Country*	*Evaluation*	*Participants (cases)*	*Type of tumor*	*Type of food*	*Results*
Michaud et al. 2009	Prospectve 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	Prospectve 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)

Transplacental exposure to ethylnitrosourea, a nitrosamide, ends up in formation of brain tumors together with gliomas in rodents and primates.[16] The addition of antioxidant to the

diet prevents growth formation during this model. Human operative exposure is split equally between exogenous and endogenous sources. Nitrosamines in tobacco (mainly sidestream smoke), cosmetics, automobile interiors, and cured meats square measure the best-established exogenous (environmental) sources of operative exposure. different sources embody rubber product (baby pacifiers, bottle nipples) and bound medicine together with antihistamines, diuretics, oral hypoglycemic agents, antibiotics, tranquilizers, and narcotics. N-Nitrodiethanolamine, a carcinogen in animal models, happens principally as a material in cosmetic product, soaps, shampoos, and hand lotions. Some environmental sources could contain each nitrosamines and nitrosamides. The endogenous formation of NOCs could be a advanced method that happens within the stomach. It depends on the presence of operative precursors (i.e., nitrates and nitrites), gastric pH, the presence of microorganism, and different physiological parameters.[17]

Measurement of operative exposure is tough, given the numerous exogenous and endogenous sources. Thus, misclassification of exposure could be a major limitation for any study on this subject.

However, as a result of processed and cured meats square measure sources of operative precursors and a few pre-formed nitrosamines, dietary assessment could also be a helpful surrogate marker for operative exposure.[18]

Epidemiological support for operative exposure as a risk issue for brain tumors comes principally from studies of paediatric brain tumors and maternal diet. many studies have assessed the association between maternal diet and childhood tumour risk.[19] A meta-analysis determined that frequent intake of processed meats throughout physiological state was related to associate elevated risk of childhood brain tumors (RR one.68; ninety fifth confidence interval [CI], 1.30–2.17).[20] However, the authors of this meta-analysis caution against drawing definitiveconclusions thanks to many study style limitations like recall and choice bias. A recent international, cooperative, pooled case–control study assessed maternal diet throughout pregnancy (including cured meat intake) and risk of childhood brain tumors in youngsters of the mothers.[21] It enclosed nine studies, involving centres from seven countries. Most of the 1218 cases were diagnosed between 1982 and 1992, and 2223 controls were enclosed. The age of children ranged from zero to nineteen years. Mothers were asked regarding their food consumption throughout the past year and through the index physiological state (i.e., physiological state with the study participant). The dietary form

targeted on foods high in nitrates and/or nitrites and foods containing nitrosation inhibitors (i.e., vitamins C and E). Dietary consumption was calculable in average grams per day. Cured meat consumption by the mother throughout physiological state was related to increased risk of all brain tumors combined, however significantly astroglial tumors. The multivariable odds magnitude relation (OR) for the highest versus bottom mark of consumption was one.5 (95% CI, 1.1–2.1; Ptrend = zero.03) for all brain tumors combined and one.8 (95% CI, 1.2–2.6; Ptrend = 0.01) for astroglial tumors. The unit ended that this was associate informative study thanks to the big study size, the geographical variation of the pooled studies, and therefore the giant number of food things investigated, together with cured meats. However, recall bias by mothers could not be excluded.

Case–control studies give inconsistent results regarding dietary intake of foods containing pre-formed nitrosamines or compounds that may be regenerate to nitrosamines and risk of brain tumour in adults, though a couple of case–control studies reportable robust positive associations.[22,23] The potential for bias in these studies is high. A cooperative, pooled case–control study of cured meat consumption and risk of adult brain tumors[24] didn't show associate 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 tumour. Michaud et al. (2009)[25] analysed combined knowledge from three US prospective cohort studies with 335 adult brain tumour cases diagnosed throughout twenty four years of follow-up. No associations were determined between consumption of white meat, processed meat, bacon, or hot dogs and risk of brain tumour. Another giant United States of America cohort study of 585 adult brain tumour cases found no important trends for brain tumour risk with consumption of red or processed meat.[26] knowledge from these a pair of giant studies, that square measure less liable to bias than case–control studies, provide very little proof for the operative hypothesis, a minimum of because it pertains to adult gliomas.

Vitamins C and E inhibit nitrosation reactions in vivo, and intake of those vitamins will scale back the endogenous formation of NOCs within the abdomen. medical specialty studies have demonstrated that consumption of antioxidant reduces the chance of stomachic cancer[27], a tumor for which NOCs could also be a risk issue.[28] Statistically important inverse associations with dietary water-soluble vitamin or supplemental intake are determined in an exceedingly few case–control studies[29] moreover, no associations were determined in an

exceedingly massive prospective cohort study examining intake of vitamins C and E and a complete inhibitor score and risk of brain tumour.[25]

Currently, proof doesn't support a deed for nutriment intake and risk of brain tumour.

2.2. Pesticides

The role of pesticides in central nervous system growth risk was initial instructed by studies of mortality rates in farmers within the us and Scandinavia. In fact, farmers globally gift a lower risk of cancer than the final population however a better risk sure enough cancer sites, as well as the CNS. This result was consistent across studies, and confirmed by a review and a meta analysis.[30,31] One study found a statistically important half-hour increase in risk of brain tumors in farmers. many risk factors could make a case for this finding, as well as exposure to not only pesticides however additionally viruses, solvents and fertilizers. Arsenicals, that square measure wide employed in vineyards, for potatoes and tree crops, are classified by the IARC as malignant neoplastic disease in humans, whereas non-arsenical pesticides additionally as glyphosate, diazinon and insect powder used in agriculture are classified as in all probability malignant neoplastic disease to humans (2A).

Yet, there's no proof of associate degree association between these agents and brain tumors. Some pesticides square measure verified carcinogens in animals, therefore chemical exposure might play a task in brain tumors. However, knowledge for specific pesticides square measure lacking attributable to the promoting of quite 1000 such molecules in recent decades.

In the literature, many case–control studies and a couple of cohort studies evaluated the potential association between chemical exposure and central nervous system tumors, particularly gliomas and meningiomas (Table 2).

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

Authors	Type of study	Country	Evaluation	Participants (cases)	Type of tumor	Results
Risk of adult brain tumors exposure of pesticides						
Piel, 2017	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**)
Piel 2018	Prospective	French	Potential exposure to carbamate insecticides and the incidence of CNS tumors	181 842 (381 incident cases)	All brain tumors	Positive
Fallahi, 2017	Case–control	Italy	Risk for brain tumors and rural activity	696 (174)	Gliomas and meningiomas	Positive
Carles 2017	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
Samanic, 2008	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
Provost 2007	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.
Ruder, 2006	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 tumous	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**)
Risk of childhood brain tumors and parental exposure of pesticides						
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**)

The results don't all converge. Indeed, some authors report no association, whereas others report exaggerated risk[32] with length 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 many exaggerated risks of central nervous system tumors in farmers, particularly in chemical users (hazard magnitude relation = one.96; ninety fifth confidence interval: one.11-3.47). Associations varied with growth subtypes and forms of crop and animal farming. The main will increase in risk were determined 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 determined among chemical applicators. though we tend to cannot completely rule out the contribution of alternative factors, chemical exposures can be of primary concern to clarify these findings.

Few medical specialty studies have provided a close estimation of exposures. for example, lists of pesticides were instructed within the North American nation higher geographical

region Health Study, with pesticides grouped per their chemical properties.[36] A recent study showed exaggerated risk of CNS tumors with overall exposure to salt pesticides.[33] A French study determined an association between brain tumors associate degreed exposure to pesticides in vineyards, however the agents potentially concerned couldn't be known.[37]

This is not solely a priority for farmers in and of itself. Indeed, within the general population, Carles et al. found a big association between neoplasm and residential proximity to open field crops, however no important association was found between brain tumour and residential proximity to agricultural land.[38]

Regarding the danger of childhood brain tumors and parental exposure of pesticides, results square measure inconsistent. A meta-analysis of sixteen case–control and 5 cohort studies found a considerably increased risk (30–50%) associated with activity exposure to pesticides among mothers throughout the antepartum amount.[39] Another meta-analysis known residential/domestic exposure to pesticides as a risk issue for childhood brain tumour, significantly for indoor exposure, involving pesticides.[40] knowledge from two French national population-based, case–control studies found childhood brain tumors considerably related to maternal home use of pesticides throughout maternity (OR one.4, 95% CI 1.2-1.8) and additional specifically with pesticides (OR 1.4, 1.2-1.8).[41] in an exceedingly recent international prospective study, paternal exposure to pesticides and animals wasn't related to exaggerated risk of childhood central nervous system tumors.[42]

To date, the little samples and therefore the weakness in exposure quantification in these studies don't allow for acceptive the ERR because of parental chemical exposure.

In general, knowledge on chemical exposure and brain tumors square measure inconsistent. Study validity is often questionable, and exposure assessment victimization biological measures of exposure is generally lacking. Despite the massive range of studies in many activity settings, associate degree exaggerated risk of brain tumour development supported activity standing isn't established. whereas anticipating more reliable studies, one ought to proceed with caution with chemical exposure

3. Out of Doors Pollution

Outdoor pollution may be a international public unhealthiness, significantly current in megalopoles and southern countries however additionally vital in developed European

countries.[43] It results from multiple sources as well as transport, industrial activity and power generation, biomass burning, and domestic heating, lighting, and preparation supported solid fuel.[44] out of doors air varies well each in area and time thanks to the combo of sources and therefore the external effects, as well as reaction and weather.

In 2013, members from the IARC nemine contradicente classified out of doors pollution as carcinogenic, with a robust causative association with carcinoma above all.[45] Several diseases of the central nervous system, as well as ischaemia[46–48] and Parkinson sickness, were connected to pollution exposure.[49] out of doors pollution contains many doubtless malignant neoplastic disease factors: stuff (PM), black carbon, serious 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 O3are thought to be the two most significant dangers to public health.[50,51]

However, knowledge concerning brain tumors square measure scarce. additionally to biological and animal models, only a couple of medical specialty studies exist: two ecological studies[52,53], four cohort studies.[54–57] and one case–control study[58] (Table 3).

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

Authors	*Journal*	*Study type*	*Tumor type*	*Country*	*Population*	*Pollutants*	*Analysis method*	*Results*
Andersen 2018	Neuro-Oncology	Prospectve 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	Prospectve 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	Prospectve 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	Prospectve 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 developped 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

Studies of animals argue for the penetrance of particles and mineral iron ore into the central nervous system, which causes neuroinflammation.[59,60] Brain inflammation inside a growth microenvironment is believed to extend aerophilic stress and desoxyribonucleic acid injury, so stimulating both genetic and epigenetic changes that occur throughout brain tumor evolution.[61] Conflicting results arise from medical specialty studies. the ecu Study of Cohorts for Air Pollution Effects[57] rumored proof of AN association between traffic-related pollution, using PM2.5 (PM with a diameter of but two.5 micrometers) absorbance as a proxy, and brain tumors. However, McKean-Cowdin et al. and Valberg et al. found a negative association between gas, gas, and CO exposure and nervous system cancer mortality or incidence.[52,62] The authors planned that the protective impact is elicited by chronic immune stimulation. Indeed, immune upset is characteristic of allergies and asthma attack, each conditions reciprocally related to with brain cancer risk in most studies[63–67] if not all.[68] Another incoherence was found within the Danish population: in a very initial nationwide cohort study[55], Poulsen et al. known AN exposure-response linear association between element oxides at the residence – as a proxy of outside pollution – and risk for brain cancer. They found contradicting proof in another nationwide case–control study[58], wherever they might not replicate this association. Still, this second study highlighted AN redoubled risk of non-glioma tumours with high exposures (nitrogen oxides concentration ≥100µg/m3) with AN OR of two.3 (95% CI one.2-4.6).

As a whole, knowledge for the impact of outside pollution on brain cancerogenesis principally have confidence a small variety of studies that square measure wildcat in nature. Thus, to date, we have a tendency to lack proof to incriminate pollution within the development of brain tumors.

4. Radiofrequency magnetism waves

Radiofrequency (RF) radiation may be a sort of non-ionizing radiation that may be emitted by diverse instruments like mobile phones and their base stations however conjointly radio and tv broadcasting, wireless networks like Wi-Fi, satellite communications, microwave ovens or

radar. The exposure to RF is present, however recent analysis centered primarily on mobile phones as a result of they're placed close to the pinnacle and brain. in step with the worldwide System for Mobile Communications, 5.1 billion folks round the world, accounting for sixty seven of the global population, signed to mobile services by the top of 2018. With this overwhelming increase in cell-phone use, widespread issues are raised concerning the results of exposure to radiofrequency magnetism waves. In fact, there's torrential literature consisting of biological and animal studies, many case–control and cohort studies and some reviews and meta-analyses on the doable association between movable use and central nervous system tumors, particularly gliomas, meningiomas or nerve sheath tumors (acoustic neoplasm in particular).

First, the doable biological cancer effects of exposure of the central nervous system tissue to RF was studied with cell or animal models. albeit these results couldn't be applied to humans directly, they supply basic info on the doable underlying development.[69]

According to these studies, long exposure to RF triggers molecular changes, inducing cell proliferation or death.[69–71] Indeed, modification of communication happens attributable to altered ionic distribution and porousness or membrane liquidity.[72] Modification of neuronal activity was discovered[73–75], which can be associated with increased temperature.[69,76,77] Still, discrepancies between studies exist, relying in the main on protocols (duration, frequency, amplitude of exposures), that warrant any analysis.[72]

Nine meta-analyses are printed to check the association between mobile-phone use and brain cancer incidence. Their characteristics square measure in Table four. enclosed brain cancers square measure of 3 main types: brain tumour (with a distinction between inferior and finest brain tumour in some studies only), acoustic benign tumour and tumour. Their results square measure partially ambiguous, which can be explained by nonuniformity within the choice criteria and therefore the applied mathematics analysis. These meta-analyses square measure largely supported studies performed by the Hardell or intercommunication system cluster. The Interphone interview-based multicenter case–control study is that the largest study to this point. It was conducted in thirteen countries and enclosed 2708 brain tumour and 2409 tumour cases and matched controls.[78] the danger of brain tumour or tumour wasn't increased within the whole population of mobile-phone users. Suggestive proof was found for increased incidence of glioma however not tumour, once exposure levels overpassed a particular level. Adjustment for possible bias, performed by another team, failed to considerably modification

the results.[79] The 2 most recent meta-analyses of medicine studies were printed in 2017. One meta-analysis found a big association for prolonged exposure (≥10 years) and ipsilateral location for all central nervous system tumors (no distinction between brain tumour, tumour and acoustic neuroma) and every one phone sorts.[80] The second meta-analysis centered on the danger of mobile-phone use on gliomas however found no association once pooling all durations of use however did notice an association among long users, ≥10 years. Risk of phone use was correlative with low-grade brain tumour, notably for long users.[81]

The ORs for each these meta-analyses and therefore the different seven printed earlier square measure shown in Table five.

As a whole, they converge toward AN increased risk for brain tumour and acoustic neoplasm however not meningioma with long-time mobile-phone use (≥ ten years, with this threshold set arbitrarily) on the aspect of the neoplasm. once pooling all durations of use and either side of the pinnacle to compute, results were rather more discordant across studies. Indeed, each restrictions to ipsilateral location and long period of use ought to be arguments affirmative a cancer effect of RF on central nervous system tissue. Indeed, as a result of RF exposure is localized, tumors ought to predominate in regions with the best energy absorption. As mentioned by Dimbylow and Mann and later by Cardis et al., quite ninetieth of the energy is absorbed within the aspect of the head the phone is placed getting ready to, with five hundredth to hr localized within the lobe.[82,83] (Table 4)

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

Authors	*Journal*	*Number of studies*	*Tumor type*	*Inclusion criteria*
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

Indeed, some studies report increased risk within the temporal and overlapping lobes.[78,84] The association of mobile-phone use and brain tumors restricted to long length of use (≥10 years in most studies)[78,84,85] argues for a dose-effect with a dependence on additive use.

The distinction seen between low- and finest gliomas was hypothesized to flow from to the natural history distinction between low- (WHO grade I and II) and high- (WHO grade III and IV) grade gliomas. Indeed, relative to finest brain tumor, particularly primary spongioblastoma, low-grade gliomas occur at lower ages and have a protracted latency stage.[81] Therefore, these 2 sorts might involve completely different carcinogenesis pathways, with completely different risk factors. A high proportion of grade III gliomas area unit degenerated inferior gliomas. However, as a result of they are usually analyzed along side primary spongioblastoma, that progresses quick with each a short latency stage and malady course, the analysis may overlook the association between mobile-phone use and grade III gliomas.[81]

Hardell and Carlberg (2013) evaluated the pressman Hill criteria for relation between long-term mobile-phone use (≥10 years) and brain cancer. The authors all over that every one nine problems in exploit were currently consummated.[86] On the premise of epidemiologic studies, they all over that the standards for strength, consistency, specificity, temporalty, and

biological gradient were fulfilled for proof of accumulated risk for brain tumor and acoustic tumour. Biological and animal laboratory studies brought extra proof for believability and analogy. Support for coherence came from knowledge on the incidence of brain tumors, that showed accumulated incidence of brain tumors, particularly in heavily exposed areas. The experiment criterion was supported by a pair of observations: 1st, many studies found antioxidants protecting of the generation of reactive O species concerned in biological effects, though an immediate mechanism for tumor carcinogenesis has not been delineated. Second, studies involving phones used at intervals cars with fastened antennas showed no accumulated risk of brain tumors.

Still, limitations of the meta-analyses and therefore the underlying studies area unit various. First, included studies area unit largely of restricted quality (case–controls, with little cluster numbers).[44]

Prospective cohorts would address the question a lot of specifically[87], however the low incidence of brain tumors would need a high variety of participants, and therefore the long latency would require a protracted follow-up amount. Still, one prospective cohort study found Associate in Nursing association between mobile-phone use and acoustic tumour, though the time from exposure to tumour onset was restricted to ten years.[88] Another concern regards the quantification of exposure level. Indeed, mobile-phone use is troublesome to assess exactly as a result of the amount of exposure depends on the phone sort and generation. as an example, the common output power of calls with the worldwide System for Mobile Communications and Universal Mobile Telecommunications Service differs by an element of one hundred to five hundred.[89,90] Besides, patterns of phone use amendment over time.[91] In terms of those difficulties, the exposure assessment seems extremely shy. In cohort studies, the assessment relied on data from operators — an individual classified as a user if he/she signed to a mobile-phone service — or to a imprecise statement "telephone use seemingly or certain".[4,13] In case–control studies, interviews allowed for convalescent a lot of specific data.

Still, most of the time, evaluations appear mostly inadequate in some studies. First, response rates were low, averaging five hundredth (45% within the CERENAT study[92] and fifty three within the intercom study.[78]). Second, in some studies, as within the CERENAT study, regular movable use was outlined as use a minimum of once every week for a minimum of vi months while not any distinction between Associate in Nursing occasional user (once a week)

and serious user (several times a day). Another problem was with the utilization of Digital increased conductor Telecommunications conductor phones. Hardell et al.[93,94], Hansson gentle et al.[95] and Morgan et al.[96] found out that cordless phone users were wrong classified as mobile-phone non-users in some studies.

Indeed, Hardell et al. mentioned that calls area unit sometimes longer with conductor phones than mobile phones.[51,52] Also, latency periods were restricted to a pair of to ten years within the 1st studies, which is too short to be sensitive enough for determinant long risk.[81,97,98] Newer studies tend to incorporate patients with long use (≥10 years). Another drawback is that childhood exposures are mostly undiscovered.[99–101] Also, meta-analyses all report substantial between-study heterogeneousness and low variety of studies for subgroup analysis. Only low adjustment for unsupportive factors was typically attainable.[81]

On the complete, we've got no sturdy and consistent proof for a causative relation between RF exposure and systema nervosum centrale tumors, however we've got proof for Associate in Nursing association with acoustic benign tumour in long users. however, studies have several limitations that preclude definitively ruling out the association. any studies, particularly prospective studies, ought to be performed to any assess whether or not mobile-phone exposure is related to tumor risk.[80,100,102,103] In 2011, supported the out there conflicting scientific proof, the IARC classified RF within the cancer cluster 2B, that is, among attainable carcinogens.[104] (table 5)

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 Lakhola 2006

However, for a few authors, the proof is robust enough to support a amendment within the IARC classification and classify RF as a probable matter (group 2A)[96] or perhaps matter (group 1).[86,105]

CONCLUSION

To date, the causative factors of brain tumors stay unknown. This unrequited question constitutes an extra unsatisfying truth for patients and their relatives after they ar diagnosed with a tumor. Moreover, tumor incidence is incessantly increasing, although slightly, in developed countries. Therefore, characteristic the potential causes or risk factors is pressing. Yet, environmental exposure has been poorly explored. The low incidence rates of brain tumors, their look most likely an extended time once exposure, and reliable quantification of the exposure to environmental factors ar the most difficulties to beat to correctly explore potential risk factors. in this regard, prospective studies on long effects of a given exposure stay the sole thanks to definitively link a risk issue to brain tumors.

Here we tend to reviewed the literature to guage the association between a variety of environmental exposures and first brain tumors. To date, solely few environmental exposures are explored in terms of tumor risk. Brain ionised irradiation, even at low doses, and especially throughout childhood, constitutes a well-established risk issue of brain tumors and has been Associate in Nursing environmental concern in areas subjected to atom bomb radiation exposure. Few studies exist of environmental toxins, and that they offer inconsistent conclusions on the role of NOCs or pesticides as tumor risk factors, even for prenatal exposure. Out-door pollution with many compounds was incriminated in brain-tumor carcinogenesis. However, results of large prospective studies lasting quite ten years ar contradictory. Still, fine microparticles from pollution, PM2.5, are incriminated as brain-tumor risk factors inseveral strong studies. In distinction to poisonous substance studies, several studies have self-addressed the impact ofmobile phones on brain-tumor risk. Despite many formidable and well-designed international studies, this impact has not been established in adults for brain tumor and tumour, however the link with acoustic benign tumor is turning into strong. Besides, the impact of movable use has still not been explored in kids.

Based on the offered literature and following on a preventive principle, we are able to so make a number of recommendations relating to environmental exposures and risk of brain tumours:

• radiation : the radiation burden of tomography interventions ought to be weighted in the least ages, and particularly in kids.

• N-nitroso compounds : pregnant girls ought to limit the consumption of cured meat.

• Pesticides: individuals, and farmers specifically, ought to shield themselves throughout pesticide use.

• out of doors pollution : national and native methods to cut back out of doors pollution ought to be supported. people will participate in up air quality levels in their communities by lowering their personal emission of fossil-fuel (eating native food, exploitation a lot of property modes of transportation like car-pooling, mass transport, cycling, or walking, exploitation clean and renewable energy, and putting in effective insulation in their homes).

• Mobile phones : once not used, mobile phones ought to be shifted or set to Associate in Nursing airplane mode. Hands-free telephones might also be helpful. Children, and particularly toddlers, ought to be unbroken faraway from their use.

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer Oxf Engl 1990, 2018; 103: 356–87. doi:10.1016/j.ejca.2018.07.005.
2. McNeill KA. Epidemiology of Brain Tumors. Neurol Clin, 2016; 34: 981–98. doi:10.1016/j.ncl.2016.06.014.
3. Philips A, Henshaw DL, Lamburn G, O'Carroll MJ. Brain Tumours: Rise in Glioblastoma Multiforme Incidence in England 1995–2015 Suggests an Adverse Environmental or Lifestyle Factor. J Environ Public Health, 2018; 2018. doi:10.1155/2018/7910754.
4. Binder-Foucard F, Bossard N, Delafosse P, Belot A, Woronoff A-S, Remontet L, et al. Cancer incidence and mortality in France over the 1980-2012 period: solid tumors. Rev Epidemiol Sante Publique, 2014; 62: 95–108. doi:10.1016/j.respe.2013.11.073.
5. Baldi I, Gruber A, Alioum A, Berteaud E, Lebailly P, Huchet A, et al. Descriptive epidemiology of CNS tumors in France: results from the Gironde Registry for the period 2000-2007. Neuro-Oncol, 2011; 13: 1370–8. doi:10.1093/neuonc/nor120.
6. Ron E, Modan B, Boice JD, Alfandary E, Stovall M, Chetrit A, et al. Tumors of the brain and nervous system after radiotherapy in childhood. N Engl J Med, 1988; 319: 1033–9. doi:10.1056/NEJM198810203191601.

7. Karlsson P, Holmberg E, Lundell M, Mattsson A, Holm LE, Wallgren A. Intracranial tumors after exposure to ionizing radiation during infancy: a pooled analysis of two Swedish cohorts of 28,008 infants with skin hemangioma. Radiat Res., 1998; 150: 357–64.
8. Shore RE, Albert RE, Pasternack BS. Follow-up study of patients treated by X-ray epilation for Tinea capitis; resurvey of post-treatment illness and mortality experience. Arch Environ Health, 1976; 31: 21–8.
9. Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ, 2013; 346: f2360. doi:10.1136/bmj.f2360.
10. [10] Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet Lond Engl, 2012; 380: 499–505. doi:10.1016/S0140-6736(12)60815-0.
11. Shintani T, Hayakawa N, Hoshi M, Sumida M, Kurisu K, Oki S, et al. High incidence of meningioma among Hiroshima atomic bomb survivors. J Radiat Res (Tokyo), 1999; 40: 49–57. doi:10.1269/jrr.40.49.
12. Smoll NR, Brady Z, Scurrah K, Mathews JD. Exposure to ionizing radiation and brain cancer incidence: The Life Span Study cohort. Cancer Epidemiol, 2016; 42: 60–5. doi:10.1016/j.canep.2016.03.006.
13. Preston DL, Ron E, Yonehara S, Kobuke T, Fujii H, Kishikawa M, et al. Tumors of the Nervous System and Pituitary Gland Associated With Atomic Bomb Radiation Exposure. JNCI J Natl Cancer Inst, 2002; 94: 1555–63. doi:10.1093/jnci/94.20.1555.
14. Bartsch H. N-nitroso compounds and human cancer: where do we stand? IARC Sci Publ, 1991: 1–10.
15. Lijinsky W. N-Nitroso compounds in the diet. Mutat Res., 1999; 443: 129–38.
16. Rice JM, Rehm S, Donovan PJ, Perantoni AO. Comparative transplacental carcinogenesis by directly acting and metabolism-dependent alkylating agents in rodents and nonhuman primates. IARC Sci Publ, 1989: 17–34.
17. Kyrtopoulos SA. N-nitroso compound formation in human gastric juice. Cancer Surv, 1989; 8: 423–42.
18. IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. Red Meat and Processed Meat. Lyon (FR): International Agency for Research on Cancer, 2018.

19. Dietrich M, Block G, Pogoda JM, Buffler P, Hecht S, Preston-Martin S. A review: dietary and endogenously formed N-nitroso compounds and risk of childhood brain tumors. Cancer Causes Control CCC, 2005; 16: 619–35. doi:10.1007/s10552-005-0168-y.
20. Huncharek M, Kupelnick B. A meta-analysis of maternal cured meat consumption during pregnancy and the risk of childhood brain tumors. Neuroepidemiology, 2004; 23: 78–84. doi:10.1159/000073979.
21. Pogoda JM, Preston-Martin S, Howe G, Lubin F, Mueller BA, Holly EA, et al. An international case-control study of maternal diet during pregnancy and childhood brain tumor risk: a histology-specific analysis by food group. Ann Epidemiol, 2009; 19: 148–60. doi:10.1016/j.annepidem.2008.12.011.
22. Blowers L, Preston-Martin S, Mack WJ. Dietary and other lifestyle factors of women with brain gliomas in Los Angeles County (California, USA). Cancer Causes Control CCC, 1997; 8: 5–12.
23. Lee M, Wrensch M, Miike R. Dietary and tobacco risk factors for adult onset glioma in the San Francisco Bay Area (California, USA). Cancer Causes Control CCC, 1997; 8: 13–24.
24. Terry MB, Howe G, Pogoda JM, Zhang FF, Ahlbom A, Choi W, et al. An international case-control study of adult diet and brain tumor risk: a histology-specific analysis by food group. Ann Epidemiol 2009;19:161–71. doi:10.1016/j.annepidem.2008.12.010.
25. Michaud DS, Holick CN, Batchelor TT, Giovannucci E, Hunter DJ. Prospective study of meat intake and dietary nitrates, nitrites, and nitrosamines and risk of adult glioma. Am J Clin Nutr, 2009; 90: 570–7. doi:10.3945/ajcn.2008.27199.
26. Dubrow R, Darefsky AS, Park Y, Mayne ST, Moore SC, Kilfoy B, et al. Dietary components related to N-nitroso compound formation: a prospective study of adult glioma. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol, 2010; 19: 1709–22. doi:10.1158/1055-9965.EPI-10-0225.
27. La Vecchia C, Franceschi S. Nutrition and gastric cancer. Can J Gastroenterol J Can Gastroenterol, 2000; 14 Suppl D: 51D-54D. doi:10.1155/2000/869862.
28. Neugut AI, Hayek M, Howe G. Epidemiology of gastric cancer. Semin Oncol, 1996; 23: 281–91.
29. Preston-Martin S, Mack W. Gliomas and meningiomas in men in Los Angeles County: investigation of exposures to N-nitroso compounds. IARC Sci Publ, 1991: 197–203.
30. Acquavella J, Olsen G, Cole P, Ireland B, Kaneene J, Schuman S, et al. Cancer among farmers: a meta-analysis. Ann Epidemiol, 1998; 8: 64–74.

31. Khuder SA, Mutgi AB, Schaub EA. Meta-analyses of brain cancer and farming. Am J Ind Med, 1998; 34: 252–60.
32. Fallahi P, Foddis R, Cristaudo A, Antonelli A. High risk of brain tumors in farmers: a mini-review of the literature, and report of the results of a case control study. Clin Ter, 2017; 168: e290–2. doi:10.7417/T.2017.2022.
33. Piel C, Pouchieu C, Migault L, Béziat B, Boulanger M, Bureau M, et al. Increased risk of central nervous system tumours with carbamate insecticide use in the prospective cohort AGRICAN. Int J Epidemiol, 2018. doi:10.1093/ije/dyy246.
34. Samanic CM, De Roos AJ, Stewart PA, Rajaraman P, Waters MA, Inskip PD. Occupational exposure to pesticides and risk of adult brain tumors. Am J Epidemiol, 2008; 167: 976–85. doi:10.1093/aje/kwm401.
35. Piel C, Pouchieu C, Tual S, Migault L, Lemarchand C, Carles C, et al. Central nervous system tumors and agricultural exposures in the prospective cohort AGRICAN. Int J Cancer, 2017; 141: 1771–82. doi:10.1002/ijc.30879.
36. Ruder AM, Waters MA, Carreón T, Butler MA, Davis-King KE, Calvert GM, et al. The Upper Midwest Health Study: a case-control study of primary intracranial gliomas in farm and rural residents. J Agric Saf Health, 2006; 12: 255–74.
37. Provost D, Cantagrel A, Lebailly P, Jaffré A, Loyant V, Loiseau H, et al. Brain tumours and exposure to pesticides: a case-control study in southwestern France. Occup Environ Med, 2007; 64: 509–14. doi:10.1136/oem.2006.028100.
38. Carles C, Bouvier G, Esquirol Y, Piel C, Migault L, Pouchieu C, et al. Residential proximity to agricultural land and risk of brain tumor in the general population. Environ Res., 2017; 159: 321–30. doi:10.1016/j.envres.2017.08.025.
39. Van Maele-Fabry G, Hoet P, Lison D. Parental occupational exposure to pesticides as risk factor for brain tumors in children and young adults: a systematic review and meta-analysis. Environ Int., 2013; 56: 19–31. doi:10.1016/j.envint.2013.02.011.
40. Van Maele-Fabry G, Gamet-Payrastre L, Lison D. Residential exposure to pesticides as risk factor for childhood and young adult brain tumors: A systematic review and meta-analysis. Environ Int., 2017; 106: 69–90. doi:10.1016/j.envint.2017.05.018.
41. Vidart d'Egurbide Bagazgoïtia N, Bailey HD, Orsi L, Lacour B, Guerrini-Rousseau L, Bertozzi A-I, et al. Maternal residential pesticide use during pregnancy and risk of malignant childhood brain tumors: A pooled analysis of the ESCALE and ESTELLE studies (SFCE). Int J Cancer, 2018; 142: 489–97. doi:10.1002/ijc.31073.

42. Patel DM, Jones RR, Booth BJ, Olsson AC, Kromhout H, Straif K, et al. Parental occupational exposure to pesticides, animals and organic dust and risk of childhood leukemia and central nervous system tumors: Findings from the International Childhood Cancer Cohort Consortium (I4C). Int J Cancer, 2019. doi:10.1002/ijc.32388.
43. Molina MJ, Molina LT. Megacities and Atmospheric Pollution. J Air Waste Manag Assoc., 2004; 54: 644–80. doi:10.1080/10473289.2004.10470936.
44. Bruce N, Perez-Padilla R, Albalak R. Indoor air pollution in developing countries: a major environmental and public health challenge. Bull World Health Organ, 2000; 78: 1078–92.
45. Loomis D, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, et al. The carcinogenicity of outdoor air pollution. Lancet Oncol, 2013; 14: 1262–3.
46. Hong Y-C, Lee J-T, Kim H, Kwon H-J. Air pollution: a new risk factor in ischemic stroke mortality. Stroke, 2002; 33: 2165–9.
47. Lisabeth L, Escobar J, Dvonch J, Sanchez B, Majersik J, Brown D, et al. Ambient air pollution and risk of ischemic stroke and TIA. Ann Neurol, 2008; 64: 53–9. doi:10.1002/ana.21403.
48. Lokken RP, Wellenius GA, Coull BA, Burger MR, Schlaug G, Suh HH, et al. Air Pollution and Risk of Stroke: Underestimation of Effect Due to Misclassification of Time of Event Onset. Epidemiol Camb Mass, 2009; 20: 137–42.
49. Finkelstein MM, Jerrett M. A study of the relationships between Parkinson's disease and markers of traffic-derived and environmental manganese air pollution in two Canadian cities. Environ Res., 2007; 104: 420–32. doi:10.1016/j.envres.2007.03.002.
50. Brook RD, Rajagopalan S, Pope CA, Brook JR, Bhatnagar A, Diez-Roux AV, et al. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation, 2010; 121: 2331–78. doi:10.1161/CIR.0b013e3181dbece1.
51. Block ML, Calderón-Garcidueñas L. Air pollution: mechanisms of neuroinflammation and CNS disease. Trends Neurosci, 2009; 32: 506–16. doi:10.1016/j.tins.2009.05.009.
52. Valberg PA, Long CM. Do brain cancer rates correlate with ambient exposure levels of criteria air pollutants or hazardous air pollutants (HAPs)? Air Qual Atmosphere Health, 2012; 5: 115–23. doi:10.1007/s11869-010-0122-3.
53. Boeglin ML, Wessels D, Henshel D. An investigation of the relationship between air emissions of volatile organic compounds and the incidence of cancer in Indiana counties. Environ Res., 2006; 100: 242–54. doi:10.1016/j.envres.2005.04.004.

54. Jørgensen JT, Johansen MS, Ravnskjær L, Andersen KK, Bräuner EV, Loft S, et al. Long-term exposure to ambient air pollution and incidence of brain tumours: The Danish Nurse Cohort. Neurotoxicology, 2016; 55: 122–30. doi:10.1016/j.neuro.2016.06.003.
55. Raaschou-Nielsen O, Andersen ZJ, Hvidberg M, Jensen SS, Ketzel M, Sørensen M, et al. Air pollution from traffic and cancer incidence: a Danish cohort study. Environ Health Glob Access Sci Source, 2011; 10: 67. doi:10.1186/1476-069X-10-67.
56. Calle EE, Peters JM, Henley J, Hannan L, Thurston GD, Thun MJ, et al. Ambient air pollution and brain cancer mortality. Cancer Causes Control CCC, 2009; 20: 1645–51. doi:10.1007/s10552-009-9412-1.
57. Andersen ZJ, Pedersen M, Weinmayr G, Stafoggia M, Galassi C, Jørgensen JT, et al. Long-term exposure to ambient air pollution and incidence of brain tumor: the European Study of Cohorts for Air Pollution Effects (ESCAPE). Neuro-Oncol, 2018; 20: 420–32. doi:10.1093/neuonc/nox163.
58. Poulsen AH, Sørensen M, Andersen ZJ, Ketzel M, Raaschou-Nielsen O. Air pollution from traffic and risk for brain tumors: a nationwide study in Denmark. Cancer Causes Control CCC, 2016; 27: 473–80. doi:10.1007/s10552-016-0721-x.
59. Heusinkveld HJ, Wahle T, Campbell A, Westerink RHS, Tran L, Johnston H, et al. Neurodegenerative and neurological disorders by small inhaled particles. Neurotoxicology, 2016; 56: 94–106. doi:10.1016/j.neuro.2016.07.007.
60. Maher BA, Ahmed IAM, Karloukovski V, MacLaren DA, Foulds PG, Allsop D, et al. Magnetite pollution nanoparticles in the human brain. Proc Natl Acad Sci., 2016; 113: 10797–801. doi:10.1073/pnas.1605941113.
61. Sowers JL, Johnson KM, Conrad C, Patterson JT, Sowers LC. The role of inflammation in brain cancer. Adv Exp Med Biol., 2014; 816: 75–105. doi:10.1007/978-3-0348-0837-8_4.
62. McKean-Cowdin R, Calle EE, Peters JM, Henley J, Hannan L, Thurston GD, et al. Ambient air pollution and brain cancer mortality. Cancer Causes Control CCC, 2009; 20: 1645–51. doi:10.1007/s10552-009-9412-1.
63. Brenner AV, Linet MS, Fine HA, Shapiro WR, Selker RG, Black PM, et al. History of allergies and autoimmune diseases and risk of brain tumors in adults. Int J Cancer, 2002; 99: 252–9. doi:10.1002/ijc.10320.
64. Wiemels JL, Wiencke JK, Sison JD, Miike R, McMillan A, Wrensch M. History of allergies among adults with glioma and controls. Int J Cancer, 2002; 98: 609–15.

65. Schwartzbaum J, Jonsson F, Ahlbom A, Preston-Martin S, Lönn S, Söderberg KC, et al. Cohort studies of association between self-reported allergic conditions, immune-related diagnoses and glioma and meningioma risk. Int J Cancer, 2003; 106: 423–8. doi:10.1002/ijc.11230.
66. Cahoon EK, Inskip PD, Gridley G, Brenner AV. Immune-related conditions and subsequent risk of brain cancer in a cohort of 4.5 million male US veterans. Br J Cancer, 2014; 110: 1825–33. doi:10.1038/bjc.2014.97.
67. Hwang C-Y, Chen Y-J, Lin M-W, Chen T-J, Chu S-Y, Chen C-C, et al. Cancer risk in patients with allergic rhinitis, asthma and atopic dermatitis: a nationwide cohort study in Taiwan. Int J Cancer, 2012; 130: 1160–7. doi:10.1002/ijc.26105.
68. Turner MC, Chen Y, Krewski D, Ghadirian P, Thun MJ, Calle EE. Cancer mortality among US men and women with asthma and hay fever. Am J Epidemiol, 2005; 162: 212–21. doi:10.1093/aje/kwi193.
69. Kim JH, Lee J-K, Kim H-G, Kim K-B, Kim HR. Possible Effects of Radiofrequency Electromagnetic Field Exposure on Central Nerve System. Biomol Ther, 2019; 27: 265–75. doi:10.4062/biomolther.2018.152.
70. Moulder JE, Erdreich LS, Malyapa RS, Merritt J, Pickard WF, Vijayalaxmi null. Cell phones and cancer: what is the evidence for a connection? Radiat Res., 1999; 151: 513–31.
71. Ertilav K, Uslusoy F, Ataizi S, Nazıroğlu M. Long term exposure to cell phone frequencies (900 and 1800 MHz) induces apoptosis, mitochondrial oxidative stress and TRPV1 channel activation in the hippocampus and dorsal root ganglion of rats. Metab Brain Dis., 2018; 33: 753–63. doi:10.1007/s11011-017-0180-4.
72. Hossmann K-A, Hermann DM. Effects of electromagnetic radiation of mobile phones on the central nervous system. Bioelectromagnetics, 2003; 24: 49–62. doi:10.1002/bem.10068.
73. Jiang D-P, Li J-H, Zhang J, Xu S-L, Kuang F, Lang H-Y, et al. Long-term electromagnetic pulse exposure induces Abeta deposition and cognitive dysfunction through oxidative stress and overexpression of APP and BACE1. Brain Res., 2016; 1642: 10–9. doi:10.1016/j.brainres.2016.02.053.
74. Kleinlogel H, Dierks T, Koenig T, Lehmann H, Minder A, Berz R. Effects of weak mobile phone - electromagnetic fields (GSM, UMTS) on event related potentials and cognitive functions. Bioelectromagnetics, 2008; 29: 488–97. doi:10.1002/bem.20418.

75. Jeong YJ, Kang G-Y, Kwon JH, Choi H-D, Pack J-K, Kim N, et al. 1950 MHz Electromagnetic Fields Ameliorate Aβ Pathology in Alzheimer's Disease Mice. Curr Alzheimer Res., 2015; 12: 481–92.
76. Wyde ME, Horn TL, Capstick MH, Ladbury JM, Koepke G, Wilson PF, et al. Effect of cell phone radiofrequency radiation on body temperature in rodents: Pilot studies of the National Toxicology Program's reverberation chamber exposure system. Bioelectromagnetics, 2018; 39: 190–9. doi:10.1002/bem.22116.
77. Wainwright P. Thermal effects of radiation from cellular telephones. Phys Med Biol, 2000; 45: 2363–72.
78. INTERPHONE Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. Int J Epidemiol, 2010; 39: 675–94. doi:10.1093/ije/dyq079.
79. Momoli F, Siemiatycki J, McBride ML, Parent M-É, Richardson L, Bedard D, et al. Probabilistic Multiple-Bias Modeling Applied to the Canadian Data From the Interphone Study of Mobile Phone Use and Risk of Glioma, Meningioma, Acoustic Neuroma, and Parotid Gland Tumors. Am J Epidemiol, 2017; 186: 885–93. doi:10.1093/aje/kwx157.
80. Bortkiewicz A, Gadzicka E, Szymczak W. Mobile phone use and risk for intracranial tumors and salivary gland tumors - A meta-analysis. Int J Occup Med Environ Health, 2017; 30: 27–43. doi:10.13075/ijomeh.1896.00802.
81. Yang M, Guo W, Yang C, Tang J, Huang Q, Feng S, et al. Mobile phone use and glioma risk: A systematic review and meta-analysis. PloS One, 2017; 12: e0175136. doi:10.1371/journal.pone.0175136.
82. Cardis E, Deltour I, Mann S, Moissonnier M, Taki M, Varsier N, et al. Distribution of RF energy emitted by mobile phones in anatomical structures of the brain. Phys Med Biol, 2008; 53: 2771–83. doi:10.1088/0031-9155/53/11/001.
83. Dimbylow PJ, Mann SM. SAR calculations in an anatomically realistic model of the head for mobile communication transceivers at 900 MHz and 1.8 GHz. Phys Med Biol, 1994; 39: 1537–53.
84. Hardell L, Carlberg M, Söderqvist F, Mild KH. Case-control study of the association between malignant brain tumours diagnosed between 2007 and 2009 and mobile and cordless phone use. Int J Oncol, 2013; 43: 1833–45. doi:10.3892/ijo.2013.2111.
85. Lahkola A, Auvinen A, Raitanen J, Schoemaker MJ, Christensen HC, Feychting M, et al. Mobile phone use and risk of glioma in 5 North European countries. Int J Cancer, 2007; 120: 1769–75. doi:10.1002/ijc.22503.

86. Hardell L, Carlberg M. Using the Hill viewpoints from 1965 for evaluating strengths of evidence of the risk for brain tumors associated with use of mobile and cordless phones. Rev Environ Health, 2013; 28: 97–106. doi:10.1515/reveh-2013-0006.
87. Gale BD, Juran D. Cellular telephones and risk for brain tumors: a population-based, incident case-control study. Neurology, 2006; 66: 781. doi:10.1212/01.wnl.0000205131.20290.46.
88. Benson VS, Pirie K, Schüz J, Reeves GK, Beral V, Green J, et al. Mobile phone use and risk of brain neoplasms and other cancers: prospective study. Int J Epidemiol, 2013; 42: 792–802. doi:10.1093/ije/dyt072.
89. Persson T, Törnevik C, Larsson L-E, Lovén J. Output power distributions of terminals in a 3G mobile communication network. Bioelectromagnetics, 2012; 33: 320–5. doi:10.1002/bem.20710.
90. Gati A, Hadjem A, Wong M, Wiart J. Exposure induced by WCDMA mobiles phones in operating networks. IEEE Trans Wirel Commun, 2009; 8: 5723–7. doi:10.1109/TWC.2009.12.080758.
91. Langer CE, de Llobet P, Dalmau A, Wiart J, Goedhart G, Hours M, et al. Patterns of cellular phone use among young people in 12 countries: Implications for RF exposure. Environ Int., 2017; 107: 65–74. doi:10.1016/j.envint.2017.06.002.
92. Coureau G, Bouvier G, Lebailly P, Fabbro-Peray P, Gruber A, Leffondre K, et al. Mobile phone use and brain tumours in the CERENAT case-control study. Occup Environ Med, 2014; 71: 514–22. doi:10.1136/oemed-2013-101754.
93. Hardell L, Mild KH, Carlberg M, Hallquist A. Cellular and cordless telephone use and the association with brain tumors in different age groups. Arch Environ Health, 2004; 59: 132–7. doi:10.3200/AEOH.59.3.132-137.
94. Hardell L, Mild KH, Carlberg M, Söderqvist F. Tumour risk associated with use of cellular telephones or cordless desktop telephones. World J Surg Oncol, 2006; 4: 74. doi:10.1186/1477-7819-4-74.
95. Hansson Mild K, Carlberg M, Wilén J, Hardell L. How to combine the use of different mobile and cordless telephones in epidemiological studies on brain tumours? Eur J Cancer Prev Off J Eur Cancer Prev Organ ECP, 2005; 14: 285–8.
96. Morgan LL, Miller AB, Sasco A, Davis DL. Mobile phone radiation causes brain tumors and should be classified as a probable human carcinogen (2A) (review). Int J Oncol, 2015; 46: 1865–71. doi:10.3892/ijo.2015.2908.

97. Hardell L, Carlberg M, Söderqvist F, Hansson Mild K. Meta-analysis of long-term mobile phone use and the association with brain tumours. Int J Oncol, 2008; 32: 1097–103.
98. Hardell L, Carlberg M, Söderqvist F, Mild KH, Morgan LL. Long-term use of cellular phones and brain tumours: increased risk associated with use for ⩾10 years. Occup Environ Med, 2007; 64: 626–32. doi:10.1136/oem.2006.029751.
99. Ahlbom A, Green A, Kheifets L, Savitz D, Swerdlow A, ICNIRP (International Commission for Non-Ionizing Radiation Protection) Standing Committee on Epidemiology. Epidemiology of health effects of radiofrequency exposure. Environ Health Perspect, 2004; 112: 1741–54. doi:10.1289/ehp.7306.
100. Lagorio S, Röösli M. Mobile phone use and risk of intracranial tumors: a consistency analysis. Bioelectromagnetics, 2014; 35: 79–90. doi:10.1002/bem.21829.
101. Swerdlow AJ, Feychting M, Green AC, Leeka Kheifets LK, Savitz DA, International Commission for Non-Ionizing Radiation Protection Standing Committee on Epidemiology. Mobile phones, brain tumors, and the interphone study: where are we now? Environ Health Perspect, 2011; 119: 1534–8. doi:10.1289/ehp.1103693.
102. IARC. IARC classifies Radiofrequency Electromagnetic Fields as possibly carcinogenic to humans 2011: 6.
103. Mornet E, Kania R, Sauvaget E, Herman P, Tran Ba Huy P. Vestibular schwannoma and cell-phones. Results, limits and perspectives of clinical studies. Eur Ann Otorhinolaryngol Head Neck Dis., 2013; 130: 275–82. doi:10.1016/j.anorl.2012.05.005.
104. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans – IARC n.d. https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-14/ (accessed May 27, 2019).
105. Miller AB, Morgan LL, Udasin I, Davis DL. Cancer epidemiology update, following the 2011 IARC evaluation of radiofrequency electromagnetic fields (Monograph 102). Environ Res., 2018; 167: 673–83. doi:10.1016/j.envres.2018.06.043.
106. Environmental factor of Brain tumors, 2019, Version of Record: https://www.sciencedirect.com/science/article/pii/S0035378719307258 Manuscript_f4d75ffcc1b0621be2567b3a94a27a7ehttps://www.elsevier.com/open-access/userlicense/1.0.