Malignant tumors of the central nervous system

Anssi Auvinen, Diana Withrow, Preetha Rajaraman, Hannu Haapasalo and Peter D. Inskip

University of Tampere, Faculty of Social Sciences (AA), Faculty of Medicine (HH) Tampere, Finland
STUK – Radiation and Nuclear Safety Authority, Environmental Surveillance, Helsinki, Finland (AA)
U.S. National Cancer Institute, Division of Cancer Epidemiology and Genetics, Maryland and Department of Health and Human Services, Office of Global Affairs (DW, PR)
Fimlab Laboratories, Department of Pathology, Tampere, Finland (HH),
National Cancer Institute, Division of Cancer Epidemiology and Genetics, Rockville, Maryland (PDI)

1. Classification

Brain cancer is an extremely heterogeneous group of tumors with 37 entries under gliomas alone in ICD-O-3 and 54 codes for neuroepithelial tumors in the WHO classification (1). The grouping of brain cancer is based on histopathology, i.e., morphological appearance in microscopic examination, with a relation to the presumed cell type of origin [Figure 1], but also increasingly in genetic alterations of the tumor (1). Malignant tumors of the brain arise primarily from the neuroepithelial tissue, mainly glial cells and their precursors. Glial cells include astrocytes and oligodendrocytes, which constitute 85% of the cells of the brain. The diversity of diagnostic entries involves, however, a large number of relatively rare tumor types and astrocytic tumors make up at least two thirds of all primary brain cancers, more when only adults are concerned. Other main types of gliomas include oligodendroglioma and ependymoma, At present, all infiltrating gliomas – whether astrocytic or oligodendroglial – can be grouped as diffuse gliomas. As this publication focuses on occupational factors, childhood brain tumors are not covered here in any detail. Central nervous system (CNS) malignancies can also arise

e.g. from the lymphatic system (lymphoma, with a frequency 2-5% of the tumors) and connective tissue (sarcoma, rare) in the CNS.

Astrocytomas account for three quarters of all gliomas. They include diffuse astrocytoma (WHO grade II, approximately 5% of all astrocytic tumors), anaplastic astrocytoma (WHO grade III, 10% of all astrocytomas) and glioblastoma (WHO grade IV, also called glioblastoma multiforme, 60% of astrocytomas). Diffuse and anaplastic tumors have a tendency to progress toward a more malignant phenotype. The number of genetic aberrations (mutations and chromosomal changes) within a tumor increases with grade with a broad spectrum of changes in complex combinations. Diffusely infiltrating grade II-IV astrocytomas are subdivided into isocitrate dehydrogenase (IDH) –mutant and IDH-wildtype tumors (2). Other common mutations include tumor suppressor TP53, alpha-thalassemia/mental retardation syndrome X-linked gene (ATRX) and telomerase reverse transcriptase (TERT) promoter region. Also, methylation of MGMT promoter region is frequently encountered.

The key features defining the grade are anaplasia (assessed as nuclear atypia), proliferative capacity (indicated by mitotic activity), as well as neovascularisation and necrosis (the latter two features defining glioblastoma). Morphologically, grade II tumors show atypia, grade III also increased mitotic activity and grade IV vascular proliferation and/or necrosis (3). Perhaps the sharpest distinction is between grade I and grade II astrocytoma, which are regarded as distinct entities. The other neuroepithelial tumors, i.e. oligodendrogliomas and ependymomas are also divided into grades II and III (anaplastic tumors), with also some grade I tumor types for ependymoma (subependymoma and

myxopapillary ependymoma). Grades I-II are sometimes referred to as low-grade tumors, while III-IV are termed high-grade cancers.

2 Pathogenesis

The presumed cell type of origin for astrocytic tumors is the glial cell, though it remains uncertain if the main route of gliomagenesis is dedifferentiation of mature cells or transformation of stem or progenitor cells (4). Within a single tumor, heterogeneity in various cellular features can be found, including a mixed pattern of differentiation. Diverse genetic alterations are encountered in gliomas, and genetic characterization of brain cancers is becoming increasingly important in the diagnosis of glioma, complementing classic morphologic criteria. For astrocytoma, the diversity of genetic and molecular alterations increases with grade [Table 1].

Changes involving the BRAF gene involved in the mitogen-activated protein kinase (maPK) pathway occur mainly in low-grade glioma. Other early events in glioma tumorigenesis include isocitrate dehydrogenase (IDH1) and p53 mutations, as well as platelet-derived growth factor (PDGF) overexpression (5,6). In addition to IDH mutation, chromosome 1p loss or 1p/19q co-deletion is typical for oligodendrogliomas (1). IDH1 and IDH2 mutations in diffuse (grade II) and anaplastic (grade III) astrocytomas are associated with improved survival.

The spectrum of genetic changes in anaplastic astrocytoma resembles those in GBM, but with lower frequency, e.g. anaplastic tumors commonly harbor phosphatase and tensin homologue (PTEN) mutations, epidermal growth factor (EGFR) abnormalities and p16/CDKN2A (cyclin-dependent kinase inhibitor) loss or downregulation (5).

Multiple molecular and chromosomal abnormalities are typical for glioblastoma. Features that can distinguish glioblastoma from anaplastic astrocytoma, which mostly harbor IDH mutation, include p16 and PTEN deletions or mutations, as well as EGFR amplification (1,3).

Primary glioblastoma arises *de novo*, while the less common secondary glioblastoma is preceded by a lower grade astrocytoma and evolves through gradual dedifferentiation (5). These two tumor types are thought to involve partly different genetic mechanisms. Epidermal growth factor receptor (EGFR) mutation, overexpression or amplification is common in primary glioblastoma, and also PDGFR amplification appears important for GBM (1,4,6). Both are surface receptors for growth factors involved in controlling cell proliferation with ras- and Akt-mediated signaling pathways linked to the cyclin-dependent kinase CDKN2 (4). Another related event is MDM2/MDM4 (murine double minute) amplification (6). The normal function of EGFR is transducing both EGF and TGF signals from the membrane to the cell, resulting in tyrosine kinase activation and other mechanisms increasing proliferation and decreasing apoptosis. Amplification or overexpression of MDM2, which codes for a transcription factor that interacts with p53, occurs in about one tenth of glioblastomas (5). PTEN mutations (or 10q loss) are found in a third of GBM cases, but rarely encountered in low-grade glioma (6). Methyl-guanine methyl transferase (MGMT) promoter methylation is found in both glioblastoma and other gliomas, and it can be used to assess sensitivity to alkylating agent-based chemotherapy. In terms of chromosomal alterations, loss of heterozygosity on chromosome 10 is common in glioblastoma (3).

In oligodendroglioma, the IDH mutations and combined LOH of 1p and 19q are diagnostic (1). The 1p/19q co-deletion is also important in the sense that it predicts a favorable therapeutic response and survival (5). p53 mutations, on the other hand, are clearly less frequent than in other gliomas.

IDH mutations do not occur in ependymomas. These tumors display several cytogenetic aberrations, and genetic characteristics include NF2 mutation, YAP1 fusion gene and RELA fusion gene. The latter genetic change defines a new ependymoma subtype in the novel WHO classification, RELA-positive ependymoma (7).

More detailed and distinctive molecular characterization has also led to suggestions of abandoning the term oligoastrocytic tumors, as these appear to be mixed oligodendroglial and astrocytic components, and not a cell type of its own (1).

3 Occurrence

Brain and other CNS cancers make up 1.8% of all primary cancers (excluding skin cancer) and, with a global total of 256,000 cases in 2012, rank as the 17th most common type of cancer (8). Age-standardized incidence among men was estimated as 3.9 per 100,000 and 3.0 per 100,000 among women. The age-standardized incidence rates for more developed countries were reported as 5.9 per 100,000 in men and 4.4 per 100,000 in women, while the corresponding rates in less developed populations were 3.3 and 2.7 (9). In the global burden of cancer project, it was estimated that brain and CNS cancer cause 84 disability-adjusted life-years (DALYs) per 100,000 in men and 69 in women (10).

Occurrence estimates from different source are strongly affected by the reference population used in age-standardization. For instance, the weighting factor for the age

group 0-19 years ranges from < 20% to >30% in widely used standard populations, and weights for the age group 75+ years range from 2% to 8%, with the world population representing the youngest age structure. The incidence of brain cancer reported by SEER with the US 2000 standard population as reference is nearly a quarter higher than that shown using the world standard population.

The quality of the incidence estimates depends on completeness of coverage and ascertainment, availability of histological diagnosis, exclusion of metastases and extent of double counting (failure to eliminate duplicate records). Classification of nervous system tumors is very heterogeneous in different registers, which makes compilation of information in a consistent fashion challenging. Revisions in diagnostic classification also make it demanding to provide incidence data with consistent definitions and comparable classifications over time.

First, brain tumors are not always reported separately from other central nervous system or nervous system tumors, though brain tumors make up approximately 90% of CNS tumors. Brain is the site of gliomas in >95% of cases, though spinal and optic nerve gliomas also occur.

Second, benign tumors sometimes also are included. GloboCan (8) and Cancer Incidence in Five Continents (11) databases cover only malignant brain and nervous system tumors, while SEER and NordCan include both malignant and benign brain tumors. In the U.S., the Central Brain Tumor Registry of the United States (CBTRUS) nowadays compiles detailed information on malignant and benign brain tumors from cancer registries within the SEER and NPCR programs covering all U.S. states (12).

Yet another factor to be considered is the proportion of microscopically verified diagnoses, as brain metastases from other cancer sites (particularly breast and lung) are more common than primary brain cancer. Finally, the proportion of cases with specific histological type versus unspecified glioma or astrocytoma affects the rates by tumor subtype (13). Similarly, more comprehensive reporting of tumor location can interfere with trends by specific site (14).

There is a slight male predominance in astrocytic tumors, with a male:female ratio of 1.2-1.5, with a slightly lower sex ratio for oligodendroglioma and little gender difference for ependymoma (12,15-16). In the U.S. SEER data, whites have higher incidence rates than other, with 30-50% lower rates for black and Asian people (17). Hispanic whites also show lower rates than non-Hispanic.

Glioblastoma is by far the most common malignant brain tumor type in adults. The age-standardized incidence of glioblastoma has ranged from 3 to 5 per 100,000 among men and 2-3 per 100,000 in women (12,13,16,18-20) [Figure 2]. Anaplastic astrocytomas constitute less than 10% of all gliomas and diffuse astrocytoma somewhat less. Incidence rates of around 0.3-0.4 per 100,000 have been reported for oligodendroglioma, while rates for ependymoma are slightly lower (12,13,16,18-19).

Gliomas in adults occur mainly in supratentorial parts of the brain, most commonly in anterior and cortical areas (12). Frontal lobe is the most frequent location, also when adjusted for the difference in volume between the lobes (14,22)

The age-specific incidence of all brain tumors combined in adults increases monotonically with age up to approximately 75 years, but then flattens or turns downward, possibly reflecting under-ascertainment at older ages rather than a true

reduction in incidence (15). The spectrum of astrocytic tumors changes with age, with the proportion of poorly differentiated tumors increasing (20). For instance, diffuse astrocytomas tend to occur approximately five years earlier than anaplastic astrocytoma (median age at diagnosis 48 vs 53 years), and age at diagnosis for glioblastoma is again 10 years older (median age 64) (12). The age gradient for astrocytic tumors is steeper than for ependymoma and oligodendroglioma and, consequently, the proportion of astrocytic tumors increases with age.

An increase in brain cancer incidence from the mid-20th century to the 1970s has been reported, particularly in the older age groups. However, relatively stable rates since the 1990s have been reported in several studies in Europe and the United States (13,15-16,18, 21,23-25). It is unclear to what extent the earlier increase reflects improved coverage of registers and more accurate diagnostics, with developments in diagnostic technologies, primarily computer-assisted tomography (mainly in the late 1970s and early 1980s) and magnetic resonance imaging (in the 1980s and 1990s).

Differences in availability of detection methods also may explain some of the geographic variation in brain cancer incidence, though the differentials between populations among high-resource countries are not as striking as for some other types of cancer, particularly when comparing Caucasian populations in Europe, North America and Australasia. Age-specific incidence rates are largely comparable in Europe and the U.S. The incidence rate of astrocytic tumors in the age group around 50 years for both sexes combined was roughly 6-7 per 100,000 and increase for ages 60 years and older, though the morphological classification are not entirely consistent in various reports (12,15-16,18). In Asia, lower brain tumor rates are reported compared with the Caucasian

populations, for instance in India, Japan and Korea often around 3 per 100,000 in men and 2 per 100,000 in women (though somewhat higher in China) (11). Within the US, incidence rates of malignant brain tumors vary between the states by a factor of 1.3 at most compared to the average national rate (12).

Globally, mortality from brain and nervous system cancer in 2012 has been estimated as 2.5 per 100,000 (3.0 for men and 2.1 for women), with 174,000 deaths occurring annually (8). These figures place brain cancer as the 13th most common cause of cancer death. No substantial increase in brain cancer mortality is obvious from the international compilation of cancer statistics (11). Mortality-incidence ratio of 0.7-0.8 indicates a high case-fatality.

Survival in adult brain tumors varies by histological type, molecular-genetic features and patient's age. Generally, the outcome of astrocytic tumors is poorer than other gliomas of similar grade. The median survival for glioblastoma is only one year or less, 2-3 years have been reported for anaplastic (grade III) astrocytoma and 4-8 years for diffuse (grade II) astrocytoma (21,26-29). Five-year relative survival (survival among patients compared with population same age and sex) for glioblastoma is close to 5%, 30% for anaplastic astrocytoma and 50% for diffuse astrocytoma (12,30). In low-grade glioma and anaplastic astrocytoma, cases with IDH mutation have twice as long median survival as wild-type tumors (31). In oligodendroglioma, substantially lower five-year relative survival has been reported from Europe compared with the U.S. (40% vs 50-80%)(12,30). The median survival has been 2-5 years for cases without 1p/19q co-deletion, and as high as 10+ years for those with this favorable prognostic indicator (32-33). Ependymoma has the most favorable prognosis of the main glioma types in adults,

with median survival of approximately 10 years, and 5-year relative survival of 84% in the US and 40-70% in Europe depending on age (12,30,34-35). The decrease in survival with age is more striking for astrocytic than oligondendroglial or ependymal tumors.

4 Non-occupational risk factors for brain cancer in adults

Few etiologic factors have been firmly established for adult brain cancer. The known determinants are hereditary factors and high doses of ionizing radiation, but they account only for a minor fraction of all cases.

A two-fold risk of glioma has been found in first-degree relatives of glioma patients (36-40). A number of rare hereditary syndromes including tuberous sclerosis, hereditary non-polyposis colorectal cancer syndrome (Lynch or Turcot syndrome involving mutations in DNA mismatch repair genes) and Li-Fraumeni syndromes (inherited mutation of the p53 gene), as well as neurofibromatosis 1/2, carry an increased risk of astrocytic tumors (as well as other cancers). However, known hereditary syndromes account for only 1-5% of all adult brain cancers, as they are very rare (the most common being neurofibromatosis which affects 1/3000). Genome-wide association studies have indicated more than 20 polymorphisms associated with an increased glioma risk, though most showing only small to moderate effect sizes with odds ratios of 1.2-1.4 (41-43). They involve genes such as EGFR, TERT, RTEL and others. These explain only a minority of the estimated heritability of gliomas (44).

Several studies on the relation between allergic conditions and glioma have consistently shown a reduced risk associated with asthma and eczema by 20-50% (40,45-53). Meta-analyses have confirmed the protective effect for asthma, allergy and eczema

(54-55). Also, other markers of atopic constitution such as serum IgE levels and use of antihistamines have been associated with a reduced risk (46,48,56-62). This has been postulated to result from immunological factors, possibly involving increased immunosurveillance with improved antitumor defense mechanisms. A study focusing on oligodendroglioma showed results that were comparable to glioma: a reduced risk related to allergy and elevated risk for family history of brain tumors (40).

History of chickenpox and antibodies against varicella zoster virus has also been associated with a reduced risk of malignant brain tumors in several studies (63-67).

N-nitroso compounds have been associated with brain tumors in animal models. For humans, the exposure patterns are complex, with intake from both diet and tobacco and alcohol with formation, metabolism and elimination regulated by several hereditary and physiological factors. A meta-analysis did not find consistent evidence for consumption of cured meat, an important dietary source of N-nitroso compounds (68). Several studies have been conducted on smoking and alcohol use but with inconsistent results (69-71). A meta-analysis of 17 studies showed a pooled RR of 1.1 for ever smokers (72). As for nutritional factors, studies on consumption of coffee and tea or cured meat and fish have not shown consistent results, but some studies have suggested a protective effect of vitamin supplement use (73-74), which could potentially be related to the N-nitroso compound hypothesis, as some antioxidant vitamins (C and E) reduce formation of such compounds.

5 Occupational risk factors

Exposure assessment

Several large studies have used job titles as exposure indicators, in some cases only a single occupation was obtained e.g. from the death certificate. Very crude classification such as ‘electric occupations’ or farm-related occupations as proxies for pesticide exposure may lack both sensitivity and specificity. Even detailed classifications of occupational titles may fail to adequately classify people in terms of exposure to a specific agent. More detailed and comprehensive occupational histories are obtained from census data, but sufficient information for assessing presence, intensity, frequency and duration of exposure for a particular agent can be elicited primarily from personal interview, with information on specific tasks, locations and processes involved at work. Nevertheless, self-reported exposure data should be assessed in separate validation studies to evaluate the extent of misclassification and bias. In malignant brain tumors, the rapid disease progression and potential deterioration of recall and cognitive abilities pose additional challenges for retrospective collection of exposure data in case-control studies (75).

The use of job-exposure matrices offers some refinement over occupational title, though level of information attainable depends heavily on the input to the matrix, i.e. level of detail in linking tasks, equipment and facilities to categories used. A key characteristic is homogeneity of exposure within occupational groups, as a small but highly exposed sub-group is difficult to place meaningfully within a broader stratum. For instance, a job-exposure matrix may accurately reflect exposure within a manufacturing plant, but could add little to a job title if applied to a nationwide study. Direct measurement of exposure at the relevant time-period can be regarded as the gold standard for exposure classification, but is achievable only in prospective cohort studies.

Few studies have been able to address the etiology of specific subtypes of brain cancers, particularly other than glioma, due to their rarity. In practice, the results of all studies pertain to astrocytic tumors, above all glioblastoma. In studies prior to the 1990s, brain cancer was rarely distinguished from other central nervous system tumors.

Occupations and branches of industry

Putative clusters of brain cancers have been reported from several workplaces including farming, physicians and several chemical industries, but generally investigations have failed to identify an agent that could account for the apparent excess.

Exploratory analyses have given some indications for several job titles and branches of industry. The consistency of the findings across studies has, however, been low raising the possibility of false positive results owing to multiple comparisons (some studies have compared up to >100 occupations).

Brain cancer risk among farmers and agricultural workers received attention after several studies had shown increased risks, in particular an early cohort study of pesticide applicators (76). Prior to the mid-1990s, at least a dozen studies were reported, but with equivocal overall results. Meta-analyses of some 30 studies conducted up to the mid-1990s showed pooled rate ratios of 1.0-1.3, depending on inclusion criteria (77-78). Findings from the Agricultural Health Study do not show excess brain and nervous system cancer incidence or mortality (79-81).

A related occupational group consists of workers involved in pesticide manufacture or spraying (applicators). The epidemiological studies on this population

have, however, been based on relatively small numbers of exposed cases and the results are not consistent (82-85). Contacts with farm animals have not been associated with an increased risk (86-89).

Other studies addressing specific hypotheses have suggested increased risks in petroleum and pulp industries (90-92), but the results have not been consistent. Brain cancer risk among workers in the petrochemical industry was evaluated in more than 10 studies in the 1980's, but they failed to provide consistent evidence. A meta-analysis of cohort studies with 350,000 workers in various branches of the petroleum industry showed an overall SMR of 1.01 (95% CI 0.93-1.09) (93). An international collaborative cohort study with 60,000 workers in pulp and paper industries did not indicate increased mortality from brain cancer (94).

Increased risks have also been reported for health care workers, mainly physicians, in several studies (90,95-101). Improved diagnostic ascertainment is unlikely to explain the finding for malignant tumors, though no specific agent has been identified. See also below for formaldehyde.

Several studies have evaluated brain cancer risk related to employment in the rubber industry with exposure to dusts, fumes and solvents, as well as some other carcinogens including aromatic amines (95,102-104). In 1982, IARC concluded that the evidence for rubber industry was inadequate for brain tumors and in the latest evaluation brain cancer was not among the tumors linked to rubber industry (105). A review covering a total of 90 studies also concluded that the results concerning brain tumors were inconsistent (106).

Some studies have reported elevated risks in the metal industry, but these have been obtained mainly in large exploratory studies (90,98,107-108).

Specific agents

Ionizing radiation

Ionizing radiation refers to particles or waves with sufficient energy to remove electrons from atoms or molecules, consequently inducing a charge (examples include gamma rays and X-rays). Unlike chemical and viral agents, ionizing radiation is unaffected by the blood-brain barrier and other cellular and tissue boundaries and independent of the presence or absence of specific cellular receptors. Exposure to ionizing radiation in humans occurs in variety of settings, including fractionated high-dose exposures (e.g. patients undergoing cancer radiotherapy), moderate to high dose exposures (e.g. Japanese atomic bomb survivors); chronic low-dose exposures (e.g. radiation workers) and fractionated low dose exposures (e.g. x-rays in diagnostic medical examinations). Currently, the primary sources of ionizing radiation to the population at large are through natural background radiation (e.g., residential radon) and from medical procedures and diagnostic tests (e.g., computed tomography (CT) scans). Occupations that involve exposure to higher than average levels of ionizing radiation include airline crew, physicians and medical technicians, uranium miners, nuclear workers and laboratory researchers. Occupational exposure tends to be very low dose and highly fractionated. The magnitude of risk associated with these types of exposures, particularly for rare outcomes such as brain cancer, is difficult to estimate in epidemiological studies.

Biological damage by ionizing radiation occurs when energy absorbed by biological tissue interacts directly or indirectly with atoms of critical targets. As radiation moves through the tissue, energy is deposited along the track, causing ionization along the track as well as some clustering at the ends. Direct action occurs when the radiation itself causes ionization of the critical target(s). The majority of damage, however, is caused by indirect action that occurs when radiation interacts with other atoms or molecules in the cell, such as water, to produce reactive free radicals that can break chemical bonds and damage critical target(s). This initiates a series of biological events that eventually leads to cancer or other disease outcomes (109).

In 2000, the International Agency for Research on Cancer (IARC) classified ionizing radiation as a Class 1 Carcinogen (110). It is noteworthy that this conclusion was based primarily on studies of medical and environmental exposures in childhood, rather than occupational or adult exposures.

At the time of publication of the 2000 IARC monograph, the authors reported an absence of convincing evidence of a significant excess of brain or CNS cancer associated with radiation in any occupational study (110-113). Since then, several more occupational cohorts have been analyzed and published. Although there was some indication of increased brain cancer mortality in radiologic technologists that reported performing or conducting fluoroscopically--guided interventional procedures (Rajaraman 2016), a cohort-wide analysis of occupational dose to the brain in the same cohort showed no association with malignant tumor mortality (Kitahara, 2017). Other independent studies and reviews have also indicated null findings for the association between occupational radiation exposure and brain cancer risk. across a wide range of

professions including nuclear workers, airline crew, physicians/medical technicians (114-118)[Table 2]. These have also indicated null findings for the association between occupational radiation exposure and brain cancer risk.

The concept of variability in individual sensitivity to radiation has long been supported by data from patients with some rare hereditary conditions such as Ataxia Telangiectasia. Consequently, there has been increasing interest in extending the characterization of radiation risk beyond traditional assessment by epidemiologic methods to incorporate the biological evaluation of differences in susceptibility between individuals. Empirical studies of gene-radiation interactions, however, have yielded no convincing signals to date (119). As tools for characterizing biological effects improve, it will be important to continue monitoring the possibility of increased risks in susceptible subgroups.

Non-ionizing radiation

Non-ionizing radiation is lower energy than ionizing radiation and includes the radiofrequency fields produced by mobile phones and extremely low frequency range electromagnetic fields (EMF).

While not explicitly an occupational risk, the association between cellular phone use and brain cancer has been studied extensively. In 2011, based mainly on epidemiologic evidence of increased risk of gliomas and vestibular schwannomas in heavy cell phone users, the IARC monograph program deemed radiofrequency electromagnetic fields a Class 2B, i.e. “Possible” carcinogen largely based on studies of cellular phone use and brain tumors (120). Studies published since the monograph have

had mixed findings. Two case-control studies reported an association between self-reported cell phone use and risk of glioma (121-122), but large cohort studies in Denmark and the UK did not replicate the findings (123-124). No association or dose-response association was reported between mobile phone use and malignant brain cancer risk in either cohort study. Possible risks associated with occupational exposures to RF-EMF have been evaluated in both cohort studies [Table 5] and case-control studies [Table 6]. Results of cohort studies have been consistently negative and case-control studies have shown some hints of increased brain tumor risks, but no consistent or convincing evidence overall.

Occupational groups believed to have the potential for high exposure to magnetic fields include electronics, electrical and electric utility workers. Early studies of electrical workers reported increased risk of brain cancer compared to the general population (125-128). These studies were criticized for a lack of information about individual-level exposures to EMF and incomplete accounting for other possible risk factors such as soldering fumes and solvents. More recently conducted cohort studies that included transportation workers and welders and used job exposure matrices and cumulative exposure measures have not found a significant association (129-133). However, one Swedish cohort study reported a potential association between occupational EMF exposure among women, but not among men, and two case-control studies, one focusing on occupational exposure (134), reported increased risk of brain cancer within a specific exposure category (≥3.0 mG average dose and glioblastoma risk)(135) and latency (1-4 years prior to diagnosis)(136). These specific findings amidst otherwise null results suggest potential Type I error as a result of multiple testing, but may nevertheless merit

further exploration. It has been hypothesized that occupational EMF exposure may influence brain cancer risk as an effect modifier of chemical exposure risk (e.g. to inorganic lead), but this has not been heavily explored or conclusively established (137). [Tables 3-4]

Chemical agents

Pesticides. Perhaps the most extensively studied class of occupational chemical exposures thus far is pesticides. Evaluation of the carcinogenicity of most pesticides by IARC has classified evidence as inadequate, due to lack or insufficient human data. An international study of nearly 70,000 workers exposed to phenoxy herbicides found no excess of brain cancer mortality (138). Also, some indirect exposure indicators (not washing or changing clothes after handling/spraying) have been associated with glioma risk, but this could be due to recall bias (89). However, with a substantial number of studies, with refined research hypotheses pertaining to specific classes or agents, the balance of evidence seems to weigh against an increased risk [Table 7].

Other chemical exposures. Some studies have suggested an increased risk of brain cancer related to occupational exposure to various organic solvents, mainly organochlorides or chlorinated hydrocarbons (chemically related to several pesticides), but overall the results do not indicate clearly increased risks (139-144).

Vinyl chloride is used in the plastics industry and classified as a human carcinogen based on increased risk of liver angiosarcoma. A large US cohort showed an increased brain cancer mortality of borderline significance, but this was not seen in a European study (145-146). A meta-analysis of five studies gave a pooled SMR of 1.26

(0.98-1.62) for brain cancer deaths, which excludes a large excess risk but leaves open the possibility of a slight increase (147).

The epidemiological evidence regarding occupational exposure to lead has failed to lend consistent material support for the hypothesis of increased risk of brain cancer (145,151-155). The potential excess risk was originally proposed in a study with measured blood lead concentrations but only 16 cases (152). Possible gene-environment interaction has been proposed that might modify the susceptibility to glioblastoma in relation to lead exposure (156).

Acrylonitrile is widely used (e.g., in the plastics and rubber industries) and has been shown to cause nervous system tumors in experimental animals. Several epidemiological studies have evaluated brain tumor incidence or mortality among workers exposed to acrylonitrile. The largest was a US cohort with more than 25,000 subjects with an average of 21 years of follow-up (153). It did not find an association between exposure to acrylonitrile and brain cancer mortality. A meta-analysis with 12 studies and a more recent summary of the later research also confirmed the lack of excess risk (154,155).

Formaldehyde is widely used in several industries, but exposure also occurs in farming as well as certain occupations in health care and biomedical research. A nested case-control study of funeral workers showed some indication of increased risk of brain cancer with any exposure to formaldehyde in embalming, but no dose-response in terms of duration or cumulative formaldehyde exposure (156). A meta-analysis reported no excess among industrial workers exposed to formaldehyde, but an increased mortality from brain cancer was found for professionals, mainly pathologists (157).

A large cohort study (92) suggested possible risks related to occupational exposure to mercury, but the result was confined to men, with no excess risk among women. Smaller earlier studies have not revealed an association with inorganic mercury.

Concluding remarks

In summary, occupational etiology of adult brain cancers has not been well established. Increased brain cancer risks have been reported in agricultural occupations and among physicians. However, the specific agents that could explain the excesses have not been identified. High doses of ionizing radiation increase the risk, but the role of the doses within the current workplace regulations is unclear, with the effect size predicted by linear extrapolation from higher doses being very low. Despite considerable efforts, no consistent evidence linking occupational exposure to electromagnetic fields or pesticides with brain cancer risk has been obtained. Large epidemiological studies with detailed assessment of exposure to specific agents and refined diagnostic classification appear to provide the best approach to advance knowledge in the area.

REFERENCES

1 Louis DN, Ohgaki H, Wiestler OD, et al. The WHO classification of tumors of the central nervous system. *IARC, Lyon 2016*

2 Eckel-Passow JE, Lachance DH, Molinaro AM, et al. Glioma groups based on 1p/19q, IDH and TERT promoter muations in tumors. *N Engl J Med* 2015;372:2499-2508

3 Burger PC, Scheithauer BW. Tumors of the nervous system. American Registry of Pathology 2007

4 Van Meir EG, Hadjipanayis CG, Norden AD, et al. Exciting new advances in neuro-oncology. *CA Cancer J Clin* 2010;60:166-93

5 Gladson CL, Prayson RA, Liu WM. The pathobiology of glioma tumors. *Annu Rev Pathol* 2010;5:33-50

6 Huse JT, Holland EC. Targeting brain cancer: advances in molecular pathology of malignant glioma and medulloblastoma. *Nat Rev Cancer* 2010;10:319-31

7 Parker M, Mohankumar KM, Punchihewa C, et al. C11orf95-RELA fusions drive oncogenic NF-kappaB signalling in ependymoma. *Nature* 2014;506:451-455

8 Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 Cancer incidence and mortality worldwide. International Agency for Research on Cancer, Lyon, France 2013. Available from http://globocan.iarc.fr, accessed 16 Aug 2017

9 Torre LA, Bray F, Siegel RL, et al. Global cancer statistics 2012. *CA Cancer J Clin* 2015;65:87-108

10 Soerjomataram I, Lortet-Tieulent J, Parkin DM, et al. Global burden of disease in 2008. *Lancet* 2012;380:1840-50

11 CI5. Cancer Incidence in Five Continents Vol XI. Bray F, Colombet M, Mery L, et al. (Eds). International Agency for Research on Cancer, Lyon 2017. Available from ci5.iarc.fr

12 Ostrom QT, Gittleman H, Farah P, et al. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2008-2012. *Neuro-Oncology* 2015;17 (Suppl 4):1-56

13 Ho VKY, Reijneveld JC, Enting RH, et al. Changing incidence and improved survival of gliomas. *Eur J Cancer* 2014;50:2309-18

14 Zada G, Bond AE, Wang YP, et al. Incidence trends in the anatomic location of primary malignant brain tumors in the United States. *World Neurosurg* 2012;77:518-24

15 Kohler BA, Ward E, McCarthy BJ, et al. Annual report to the nation on the status of cancer, 1975-2007, featuring tumors of the brain and other nervous system. *J Natl Cancer Inst* 2011;103:714-736

16 Crocetti E, Trama A, Stiller C, et al. Epidemiology of glial and non-glial brain tumours in Europe. *Eur J Cancer* 2012;48:1532-42

17 SEER Cancer Stat Facts: Brain and Other Nervous System Cancer. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/brain.html

18 Lönn S, Klaeboe L, Hall P, et al. Incidence trends of adult primary intracerebral tumors in four Nordic countries. *Int J Cancer* 2004;108:450-5

19 Arora RS, Alston RD, Eden TO, et al. Are reported increases in incidence of primary CNS tumours real? *Eur J Cancer* 2010;46:1607-16

20 Dubrow R, Darefsky AS. Demographic variation in incidence of adult glioma by subtype, United States 1992-2007. *BMC Cancer* 2011;11:325

21 Brodbelt A, Greenberg D, Winters T, et al. Glioblastoma in England: 2007-2011. *Eur J Cancer* 2015;51:533-542

22 Larjavaara S, Mäntylä R, Salminen T, et al. Incidence of gliomas by anatomic location. *Neuro-Oncology* 2007;9:319-25

23 Deltour I, Johansen C, Auvinen A, et al. Time trends in brain tumor incidence rates in Denmark, Finland, Norway, and Sweden, 1974-2003. *J Natl Cancer Inst* 2009;101:1721-4

24 Inskip PD, Hoover RN, Devesa SS. Brain cancer incidence trends in relation to cellular telephone use in the United States. *Neuro-Oncology* 2010;12:1147-51

25 De Vocht F, Burstyn I, Cherrie JW. Time trends in brain cancer incidence rates in relation to mobile phone use in England. *Bioelectromagnetics* 2011;32:334-9

26 Scoccianti S, Magrini SM, Ricardi U, et al. Patterns of care and survival in a retrospective analysis of 105 patients with glioblastoma multiforme. *Neurosurgery* 2010;67:446-58

27 Schomas DA, Laack NN, Rao RD, et al. Intracranial low-grade gliomas in adults. *Neuro-Oncology* 2009;11:437-45

28 Ohgaki H, Kleihues P. Population-based studies on incidence survival rates and genetic alterations in astrocytic and oligodendroglial gliomas. *J Neuropathol Exp Neurol* 2005;64:479-89

29 Buckner JC. Factors influencing survival in high-grade gliomas. *Semin Oncol* 2003;30 (Suppl 19):10-14

30 Visser O, Ardanaz E, Botta L, et al. Survival of adults with primary malignant brain tumors in Europe. *Eur J Cancer* 2015;51:2231-41

31 van den Bent MJ, Smits M, Kros JM, et al. Diffuse infiltrating oligodendroglioma and astrocytoma. *J Clin Oncol* 2017;35:2394-401

32 Kouwenhoven MC, Gorlia T, Kros JM, et al. Molecular analysis of anaplastic oligodendroglial tumors in a prospective randomized study. *Neuro-Oncology* 2009;11:737-46

33 Parkinson JF, Afabhi V, Payne CA, et al. The impact of molecular and clinical factors on patient outcome in oligodendroglioma. *J Clin Neurosci* 2011;18 :320-33

34 Reni M, Brandes AA, Vavassori V, et al. A multicenter study of prognosis and treatment of adult brain ependymal tumors. *Cancer* 2004;10:1221-9

35 Armstrong TS, Vera-Bolanos E, Bekele BN, et al. Adult ependymal tumors. *Neuro-Oncology* 2010;12 :862-70

36 Hill DA, Inskip PD, Shapiro WR, et al. Cancer in first-degree relatives and risk of glioma in adults. *Cancer Epidemiol Biomarkers Prev* 2003;12:1443-8

37 Malmer B, Henriksson R, Grönberg H. Familial brain tumours - genetics or environment? A nationwide cohort study of cancer risk in spouses and first-degree relatives of brain tumour patients. *Int J Cancer* 2003;106:260-3

38 Hemminki K, Tretli S, Sundqvist et al. Familial risks in nervous-system tumours: a histology-specific analysis from Sweden and Norway. *Lancet Oncol* 2009;10:481-8.

39 Scheurer ME, Etzel CJ, Liu M, et al. Familial aggregation of glioma: a pooled analysis. *Am J Epidemiol* 2010;172:1099-107

40 McCarthy BJ, Rankin KM, Aldape K, et al. Risk factors for oligodendroglial tumors. *Neuro-Oncology* 2011;13:242-50

41 Rajaraman P, Melin BS, Wang Z, et al. Genome-wide association study of glioma and meta-analysis. *Hum Genet* 2012;131:1877-88

42 Kinnersley B, Laboussiere M, Holroyd A, et al. Genome-wide association study identifies multiple susceptibility loci for glioma. *Nat Commun* 2015a;6:8559

43 Melin BS, Barnholtz-Sloan JS, Wrensch MR, et al. Genome-wide association study of glioma subtypes identifies specific differences in genetic susceptibility to glioblastoma and non-glioblastoma tumors. *Nat Genet* 2017;49:789-94

44 Kinnersley B, Mitchell JS, Gousias K, et al. Quantifying the heritability of glioma using genome-wide complex trait analysis. *Sci Rep* 2015b;5:17267

45 Brenner AV, Linet MS, Fine HA, et al. History of allergies and autoimmune diseases and risk of brain tumors in adults. *Int J Cancer* 2002;99:252-9

46 Wiemels JL, Wiecke JK, Patoka J, et al. Reduced immunoglobulin E and allergy among adults with glioma compared with controls. *Cancer Res* 2004;64:8468-73

47 Wigertz A, Lönn S, Schwartzbaum J, et al. Allergic conditions and brain tumor risk. *Am J Epidemiol* 2007;166:141-50

48 Scheurer ME, El-Zein R, Thompson PA, et al. Long-term anti-inflammatory and antihistamine medication use and risk of adult glioma. *Cancer Epidemiol Biomarkers Prev* 2008 ;17 :1277-81

49 Lachance DH, Yang P, Johnson DR, et al. Associations of high-grade glioma with glioma risk alleles and histories of allergy and smoking. *Am J Epidemiol* 2011;174:574-581

50 Turner M, Krewski D, Armstrong BK, et al. Allergy and brain tumors in the INTERPHONE study. *Cancer Causes Control* 2013;24:949-60

51 Safaeian M Rajaraman P, Hartge P, et al. Joint effects between five identified risk variants, allergy and autoimmune conditions on glioma risk. Cancer Causes Control 2013;24:1885-91

52 Cahoon EK, Inskip PD, Gridley G, Brenner AV. Immune-related conditions and subsequent brain cancer in a cohort 4.5 million U.S. male veterals. *Br J Cancer* 2014;110:1825-33

53 Krishnamachari B, Il'yasova D, Scheurer ME, et al. A pooled multisite analysis of the effects of atopic medical condition in glioma risk in different ethnic groups. *Ann Epidemiol* 2015;25:270-274

54 Linos E, Raine T, Alonso A, et al. Atopy and risk of gliomas. *J Natl Cancer Inst* 2007;99:1544-50

55 Chen C, Xu T, Chen J, et al. Allergy and risk of glioma. *Eur J Neurol* 2011;18:387-95

56 Schlehofer B, Blettner M, Preston-Martin S, et al. Role of medical history in brain tumour development. *Int J Cancer* 1999;82:155-60

57 Scheurer ME Amirian ES, Davlin SL, et al. Effects of antihistamine use and anti-inflammatory medication use on risks of specific glioma histologies. Int J Cancer 2011 ;129 :2290-6

58 Wiemels JL, Wilson D, Patil C, et al. IgE, allergy, and risk of glioma. *Int J Cancer* 2009;125:680-7

59 Calboli FC, Cox DG, Buring JE, et al. Prediagnostic plasma IgE leves and risk of adult glioma in four prospective cohort studies. *J Natl Cancer Inst* 2011;103:1588-95

60 Schlehofer B, Sigmund B, Linseisen J, et al. Primary brain tumors and specific immunoglobulin E: A case-control study nested in the EPIC cohort. *Allergy* 2011;16:1434-41

61 Schwartzbaum J, Seweryn M, Holloman C, et al. Association between prediagnostic allergy-related serum cytokines and glioma. PLoS One 2015; 10:e0137503

62 Amirian ES, Marquez-Do D, Bondy ML, et al. Antihistamine use and immunoglobulin E levels in glioma risk and prognosis. *Cancer Epidemiol* 2013;37:908-12

63 Wrensch M, Lee M, Miike R, et al. Familial and personal medical history of cancer and nervous system conditions among adults with glioma and controls. *Am J Epidemiol* 1997;145:581-93

64 Wrensch M, Weinberg A, Wiencke J, et al. Prevalence of antibodies to four herpes viruses among adults with glioma and controls. *Am J Epidemiol* 2001;154:161-5

65 Wrensch M, Weinberg A, Wiencke J, et al. History of chickenpox and shingles and prevalence of antibodies to varicella zoster virus and three other herpes viruses among adults with glioma and controls. *Am J Epidemiol* 2005;161:929-38

66 Sjöström S, Hjalmars U, Juto P, et al. Human immunoglobulin G levels and associated glioma risk. *Cancer Causes Control* 2011;22:1259-66

67 Amirian ES, Scheurer ME, Zhou R, et al. History of chickenpox in glioma risk. *Cancer Med* 2016;5:1352-8

68 Huncharek M, Kupelnick B, Wheeler L. Dietary cured meat and the risk of adult glioma: a meta-analysis of nine observational studies. *J Environ Pathol Toxicol Oncol* 2003;22:129-37

69 Efird J, Friedman GD, Sidney S, et al. The risk for malignant primary adult-onset glioma in a large, multiethnic, managed-care cohort: cigarette smoking and other lifestyle behaviors. *J Neuro-Oncol* 2004;68:57-69

70 Holick CN, Giovannucci E, Rosner B, et al. Prospective study of cigarette smoking and adult glioma. *Neuro-Oncology* 2007;9:326-34

71 Benson VS, Pirie K, Green J, et al. Lifestyle factors and primary glioma and meningioma tumours in the Million Women Study cohort. *Br J Cancer* 2008;99:185-90

72 Mandelzweig L, Novikov I, Sadetzki S. Smoking and risk of glioma. *Cancer Causes Control* 2009;20:1927-38

73 Holick CN, Smith SG, Giovannucci E, Michaud DS. Coffee, tea, caffeine intake, and risk of adult glioma in three prospective cohort studies. *Cancer Epidemiol Biomarkers Prev* 2010;19:39-47

74 Michaud DS, Gallo V, Schlehofer B, et al. Coffee and tea intake and risk of brain tumors in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. *Am J Clin Nutr* 2010b;92:1145-50

75 Johansen C, Schüz J, Andreasen AS et al. Study design may influence results. *Br J Cancer* 2017;116:841-8

76 Blair A, Grauman DJ, Lubin JH, Fraumeni JF Jr. Lung cancer and other causes of death among licensed pesticide applicators. *J Natl Cancer Inst* 1983;71:31-7

77 Acquavella J, lsen G, Cole P, et al. Cancer among farmers: a meta-analysis. *Ann Epidemiol* 1998;8:64-74

78 Khuder SA, Mutgi AB, Schaub EA. Meta-analyses of brain cancer and farming. *Am J Ind Med* 1998;34:252-260

79 Alavanja MCR, Sandler DP, Lynch CF, et al. Cancer incidence in the Agricultural Health Study. *Scand J Work Environ Health* 2005;21 (Suppl 1): 39-45

80 Waggoner JK, Kullman GJ, Henneberger PK, et al. Mortality in the Agricultural Health Study, 1993-2007. *Am J Epidemiol* 2010;173:71-83

81 Ruder AM, Waters MA, Carreón T, et al. The Upper Midwest Health Study: Indusry and occupation of glioma cases and controls. *Am J Ind Med* 2012;55:747-755

82 Ruder AM, Waters MA, Butler MA et al. Gliomas and farm pesticide exposure in men. *Arch Environ Health* 2004;59:650-7

83 Lee WJ, Colt JS, Heineman EF et al. Agricultural pesticide use and risk of glioma in Nebraska, United States. *Occup Environ Med* 2005 ;62 :786-792

84 Samanic CM, de Roos AJ, Stewart PA, et al. Occupational exposure to pesticides and risk of adult brain tumors. *Am J Epidemiol* 2008;167:676-85

85 Yiin JH, Ruder AM Stewart PA, et al. The Upper Midwest health study: A case-control study of pesticide applicators and risk of glioma. *Environ Health* 2012;11:39

86 Reif J, Pierce N, Fraser J. Cancer risks in New Zealand farmers. *Int J Epidemiol* 1989;18:768-74

87 Morrison HI, Semenciw RM, Morison D, et al. Brain cancer and farming in western Canada. *Neuroepidemiology* 1992;11:267-76

88 Ménégoz F, Little L, Colonna M, et al. Contacts with animals and humans as risk factors for adult brain tumors. *Eur J Cancer* 2002:38:696-704

89 Ruder AM, Carreon T, Butler MA, et al. Exposure to farm crops, livestock, and farm tasks and risk of glioma: the Upper Midwest Health Study. *Am J Epid* 2009;169:1479-91

90 McLaughlin JK, Malmer H, Blot WJ, et al. Occupational risks for intracranial gliomas in Sweden. *J Natl Cancer Inst* 1987;78:253-7

91 Andersson E, Nilsson R, Toren K. Gliomas among men employed in the Swedish pulp and paper industry. *Scand J Work Environ Health* 2002;28:333-40

92 Navas-Acién A, Pollán M, Gustavsson P, Plato N. Occupation, exposure to chemicals and risk of gliomas and meningiomas in Sweden. *Am J Ind Med* 2002;42:214-27

93 Wong O, Raabe GK. A critical review of cancer epidemiology in the petroleum industry. *Regul Toxicol Pharmacol* 2000;32:78-98.

94 McLean D, Pierce N, Langseth H, et al. Cancer mortality in workers exposed to organochlorine compounds in the pulp and paper industry. *Environ Health Persp* 2006;114:1007-12

95 Heineman EF, Gao YT, Dosemeci M , et al. Occupational risk factors for brain tumors among women in Shanghai, China. *J Occup Environ Med* 1995;37:288-93

96 Rix BA, Lynge E. Cancer incidence in Danish health care workers. *Scand J Soc Med* 1996;24:114-20

97 Carpenter LM, Swerdlow AJ, Fear NT. Mortality of doctors in different specialties. *Occup Environ Med* 1997;54;388-95

98 Aronson KJ, Howe GR, Carpenter M, et al. Surveillance of potential associations between occupations and causes of death in Canada, 1965-91. *Occup Environ Med* 1999;56:265-9

99 Carozza SE, Wrensch M, Miike R, et al. Occupation and adult gliomas. *Am J Epid* 2000;152:838-46

100 de Roos AJ, Stewart PA, Linet MS, et al. Occupation and the risk of adult glioma in the United States. *Cancer Causes Control* 2003;14:139-150

101 Krishnan G, Felini M, Carozza SE, et al. Occupation and adult gliomas in San Francisco bay area. *J Occup Environ Med* 2003;45:639-47

102 Negri E, Piolatto G, Pira E, et al. Cancer mortality in a Northern Italian cohort of rubber workers. *Br J Ind Med* 1989;46:624-628

103 Preston-Martin S, Mack W, Henderson BE. Risk factors for gliomas and meningiomas in males in Los Angeles County. *Cancer Res* 1989;49:6137-43

104 Zheng T, Cantor KP, Zhang Y, et al. Occupational risk factors for glioma. *J Occup Environ Health* 2001;43:317-324

105 IARC Monographs on the evaluation of carcinogenic risks to humans, Vol 100F. Chemical agents and related occupations (Occupational exposures in the rubber-manufacturing industry). International Agency for Research on Cancer, Lyon, France 2012.

106 Kogevinas M, Sala M, Boffetta P, et al. Cancer risk in the rubber industry. *Occup Environ Med* 1998;55:1-12

107 Pan SY, Ugant AM, Mao Y. Occupational risk factors for brain cancer in Canada. *J Occup Environ Med* 2005;47:704-17

108 Parent ME, Turner MC, Lavoué J, et al. Lifetime occupational exposure to metals and welding fumes, and risk of glioma. *Environ Health* 2017:16:90

109 Hall, Giaccia 2006 [from Preetha]

110 IARC Monographs on the evaluation of carcinogenic risks to humans, Vol 75. Ionizing Radiation, Part 1: X- and Gamma (γ)-Radiation, and Neutrons. International Agency for Research on Cancer, Lyon, France 2000

111 Cardis E, Vrijheid M, Blettner M, et al. The 15-Country collaborative study of cancer risk among radiation workers in the nuclear industry: estimates of radiation-related cancer risks. *Radiat Res* 2007;167:396-416

112 Muirhead CR, O'Hagan JA, Haylock RGE, et al. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. *Br J Cancer* 2009;100:206-12

113 Richardson DB, Cardis E, Daniels RD et al. Site-specific cancer mortality after exposure to ionising radiation: a cohort of workers (INWORKS). *Epidemiology* 2018 (E-publication)

114 Hammer G, Auvinen A, de Stavola BL, et al. Mortality from cancer and other causes in commercial airline crews. *Occup Environ Med* 2014;71:312-322

115 Sokolnikov M, Preston D, Gilbert E, et al. Radiation effects on mortality from slid cancer other than lung, liver and bone in the Mayak worker cohort 1948-2008. *PLoS One* 2015;10:e01177842015

116 Berrington de Gonzalez A, Ntowe E, Kitahara E, et al. Long-term mortality in 43,763 US radiologists compared with 64,990 psychiatrists. *Radiology* 2016;281:847-857

117 Kitahara CM, Linet MS, Balter S, et al. Occupational radiation exposure and deaths from malignant intracranial neoplasms of the brain and CNS in US radiologic technologsts 1983-2012. *Am J Roentgenol* 2017;208:1278-84

118 Linet MS, Kitahara CM,Ntowe E, et al. Mortality in US physicians likely to perform fluoroscopy-guided interventional procedures compared with psychiatrists 1979-2008. *Radiology* 2017;284:482-494

119 Rajaraman P, Hauptmann M, Boufller S, Wojcik A. Human individual radiation sensitivity and prospects for prediction. *Ann ICRP* 2018;146645318764091

120 IARC Monographs on the evaluation of carcinogenic risks to humans, Vol 102. Non-Ionizing Radiation, Part 2. Radiofrequency electromagnetic fields. International Agency for Research on Cancer, Lyon, France 2012.

121 Hardell L, Carlberg M, Söderqvist F, Mild KH. Case-control study of the association between malignant brain tumors diagnosed between 2007 and 2009 and mobile and cordless phone use. *Int J Oncol* 2013;43:1833-45

122 Coureau G, Bouvier G, Lebailly P, et al. Mobile phone use and brain tumors in the CERENAT case-control study. *Occup Environ Med* 2014;71:514-522

123 Frei P, Poulsen AH, Johansen C, et al. Use of mobile phone sand risk of brain tumours: Update of Danish cohort study. *BMJ* 2011;343:d63872011

124 Benson VS, Pirie K, Schüz J, et al. Mobile phone use and risk of brain neoplasms and other cancers. *Int J Epidemiol* 2013;42:792-802

125 Lin RS, Dischinger PC, Conde J, Farrell KP. Occupational exposure to electromagnetic fields and the occurrence on brain tumors. *J Occup Med* 1985;27:413-419

126 Thomas TL, Stolley P, Stemhagen A, et al. Brain tumor mortality risk among men with electrical and electronics jobs: a case-control study. *J Natl Cancer Inst* 1987;79:233-8

127 Speers MA, Dobbins JG, Miller VS. Occupational exposures and brain cancer mortality. *Am J Ind Med* 1988;13:629-638

128 Loomis DP, Savitz DA. Mortality from brain cancer and leukaemia among electrical workers. *Br J Ind Med* 1990;47:633-638

129 Röösli M, Lörtscher M, Egger M, et al. Leukaemia, brain tumours and exposure to extremely low frequency magnetic fields: a cohort study of Swiss railway employees. *Occup Environ Med* 2007;64:553-9

130 Karipidis KK, Benke G, Sim MR, et al. Occupational exposure to ionising and non-ionising radiation and risk of glioma. *Occup Med* 2007;57:518-524

131 Karipidis KK, Benke G, Sim MR, et al. Occupational exposure to low frequency magnetic fields and the risk of low grade and high grade glioma. *Cancer Causes Control* 2007;18:305-313

132 Kheifets L, Monroe, Vergara, et al. Occupational electromagnetic fields and leukemia and brain cancer: An update to two meta-analyses. J Occup Environ Med 2008;50:677-688

133 Koeman T, van den Brandt PA, Slottje P, et al. Occupational extremely low frequency magnetic field exposure and selected cancer outcomes in a prospective Dutch cohort. *Cancer Causes Control* 2014;25:203-214

134 Håkansson N, Floderus B, Gustavsson P, et al. Cancer incidence and magnetic field exposure in industries using resistance welding in Sweden. *Occup Environ Med* 2002;59:481-486

135 Coble JB, Dosemeci M, Stewart PA, et al. Occupational exposure to magnetic fields and the risk of brain tumors. *Neuro-Oncology* 2009;11:242-9

136 Turner MC, Benke G, Bowman JD, et al. Occupational exposure to extremely low frequency magnetic field and brain tumor risks in the INTEROCC study. *Cancer Epidemiol Biomarkers Prev* 2014;23:1863-72

137 Navas-Acién, Pollán M, Gustavsson P, et al. Interactive effect of chemical substances and occupational electromagnetic field exposure on the risk of gliomas and meningiomas in Swedish men. *Cancer Epidemiol Biomarkers Prev* 2002;11:1678-83

138 Kogevinas M, Becher H, Benn T, et al. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols and dioxins. *Am J Epidemiol* 1997;145:1061-75

139 Heineman EF, Cocco P, Gómez MR, et al. Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer. *Am J Ind Med* 1994;26:155-169

140 Cocco P, Heineman EF, Dosemeci M. Occupational risk factors for cancer of the central nervous system among US women. *Am J Ind Med* 1999;36:70-74

141 Wesseling C, Pukkala E, Neuvonen K et al. Cancer of the brain and nervous system and occupational exposures in Finnish women. *J Occup Environ Med* 2002;44:663-8

142 Neta G, Stewart PA, Rajaraman P, et al. Occupational exposure to chlorinated solvents and risks of glioma and meningioma in adults. *Occup Environ Med* 2012;69:793-801

143 Ruder AM, Yiin JH, Waters MA, et al. The Upper Midwest Health Study: gliomas and occupational exposure to chlorinated solvents. *Occup Environ Med* 2013;70:73-80

144 Benke G, Turner MC, Fleming S, et al. Occupational solvent exposure and risk of glioma in the INTEROCC study. *Br J Cancer* 2017;117:1246-54

145 Boffetta P, Matisane L, Mundt KA, Dell LD. Meta-analysis of studies of occupational exposure to vinyl chloride in relation to cancer mortality. *Scand J Work Environ Health* 2003;29:220-229

146 Mundt KA, Dell LD, Austin RP, et al. A historical cohort study of 10,109 men in the American vinyl chloride industry. *Occup Environ Med* 2000;57:774-81

147 Ward E, Boffetta P, Andersen A, et al. Update of the follow-up for mortality and incidence of cancer among European workers employed in the vinyl chloride industry. *Epidemiology* 2001;12:710-718

148 Cocco P, Dosemeci M, Heineman EF. Brain cancer and occupational exposure to lead. *J Occup Environ Med* 1998;40:937-942

149 Rajaraman P, Stewart PA, Samet JM , et al. Lead, genetic susceptibility and risk of adult brain tumors. *Cancer Epidemiol Biomarkers Prev* 2006;15:2514-20

150 Van Wijngaarden E, Dosemeci M. Brain cancer mortality and potential occupational exposure to lead. *Int J Cancer* 2006;119:1136-44

151 Bhatti P, Stewart PA, Hutchinson A, et al. Lead exposure, polymorphisms in genes related to oxidative stress, and risk of adult brain tumors. *Cancer Epidemiol Biomarkers Prev* 2009;18:1841-8

152 Anttila A, Hiekkilä P, Nykyri E, et al. Risk of nervous system cancer among workers exposed to lead. *J Occup Environ Med* 1996;38:131-6

153 Blair A, Stewart PA, Zaebst DD, et al. Mortality in industrial workers exposed to acrylonitrile. *Scand J Work Environ Health* 1998;24 (Suppl 2):25-41

154 Collins JJ, Strather DE. CNS tumors and exposure to acrylonitrile. *Neuro-Oncology* 1999;1:221-30

155 Cole P, Mandel JS, Collins JJ. Acrylonitrile and cancer. *Regul Toxicol Pharmacol* 2008;52:342-51

156 Hauptmann M, Stewart PA, Lubin JH, et al. Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. *J Natl Cancer Inst* 2009;101:1696-708

157 Bosetti C, McLaughlin JK, Tarone RE, et al. Formaldehyde and cancer risk. *Ann Oncol* 2008;19:29-43