Occupational and Environmental Risk Factors of Adult Primary Brain Cancers: A Systematic Review

J Gomes[1,2,3], A Al Zayadi[1], A Guzman[1]

[1]Interdisciplinary School of Health Sciences, Faculty of Medicine, University of Ottawa, Ottawa, Canada
[2]Environmental Health Research Unit, University of Ottawa, Ottawa, Canada
[3]McLaughlin Center for Population Health Risk Assessment, University of Ottawa, Ottawa, Canada

Correspondence to
James Gomes MSc, PhD, Faculty of Health Sciences, University of Ottawa, 43 Templeton Street, Room 211 Ottawa, ON, K1N 6N5, Canada
Email: jgomes@uottawa.ca
Tel: +1-613-562-5800 Ext 8426

Abstract

The incidence of brain neoplasm has been progressively increasing in recent years in the industrialized countries. One of the reasons for this increased incidence could be better access to health care and improved diagnosis in the industrialized countries. It also appears that Caucasians have a higher incidence than blacks or Hispanics or Asians. A number of risk factors have been identified and described including the genetic, ethnic and age-based factors. Certain occupational and environmental factors are also believed to influence the risk of primary adult brain tumors. Potential occupational and environmental factors include exposure to diagnostic and therapeutic radiations, electromagnetic radiation from cellular phones and other wireless devices, infectious agents, air pollution and residence near landfills and high-voltage power lines and jobs as firefighters, farmers, physician, chemists and jobs in industries such as petrochemical, power generation, synthetic rubber manufacturing, agricultural chemicals manufacturing. The purpose of this systematic review is to examine occupational and environmental risk factors of brain neoplasm. A range of occupational and environmental exposures are evaluated for significance of their relationship with adult primary brain tumors. On the basis of this review we suggest a concurrent evaluation of multiple risk factors both within and beyond occupational and environmental domains. The concurrent approach needs to consider better exposure assessment techniques, lifetime occupational exposures, genotypic and phenotypic characteristics and lifestyle and dietary habits. This approach needs to be interdisciplinary with contributions from neurologists, oncologists, epidemiologists and molecular biologists. Conclusive evidence that has eluded multitude of studies with single focus and single exposure needs to multifaceted and multidisciplinary.

Keywords: Brain neoplasm; occupational risk factors; environmental risk factors; glioma; meningioma; astrocytoma

Introduction

The reported average incidence of brain tumors (benign or malignant) in the US is 14 per 100 000 people (14.2/100 000 for men and 13.9/100 000 for women); approximately half of these tumors are malignant.[1] Males have a slightly higher incidence compared to the females for all brain neoplasm types except for meningiomas which affects women (80%) more than men (20%).[1] The rates in Western Europe, North America, and Australia have been observed at 6–11 new cases per 100 000 for men, and 4–11 new cases per 100 000 for women in recent years.[2]

The incidence rate of brain neoplasm has been progressively increasing in recent years in the industrialized countries. Primary malignant brain tumors tend to be more prevalent in industrialized countries where there is access to advanced medical care. The real reason for the increased
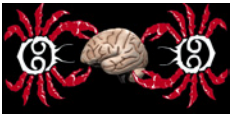
incidence and prevalence in the industrialized countries is not known, however, it is believed that it may be attributed to greater improvements in clinical diagnostic tests and high-resolution neuroimaging[2]. But occupational and environmental exposures and certain lifestyle factors may also play a role.

Many of the agricultural chemicals including pesticides are believed to be neurotoxic and carcinogenic. A meta-analyses conducted in 1998 by Kuder *et al* showed a moderately increased risk that was statistically significant for primary brain tumors among farmworkers.[3] However, a review by Bohnen and Kurland showed mixed results.[4] They have reported a median three-fold increased relative risk for pesticide applicators.[4] Some of the agricultural chemicals and pesticides are believed to induce neoplasm in experimental animals.[5]

Most of the early studies on cell phone use and brain neoplasm did not show any association, however, in recent years some evidence of association has been reported.[6] Nonetheless, the International Commission on Non-Ionizing Radiation Protection, the International Committee on Electromagnetic Safety and the World Health Organization appear to suggest that there is no proven health risk from cell phone use.[7]

In spite of significant amount of research that has been conducted to understand the etiology of primary brain tumors very little progress has been made. The evidence for most of the associations that have been explored still remains to be conclusive. The relationship between exposure to ionizing radiations and primary brain tumor risk is suggestive; but the evidence is inconclusive.[6] The risk of brain tumors from hereditary genetic mutations is believed to be strong, but the evidence for this is limited and elusive.[8] Occupational and environmental exposures are believed to be etiologically associated with primary brain neoplasm but the evidence is still inconclusive. Potential environmental risk factors include exposure to infectious agents (zoonoses), traffic-related air pollution, residence near low frequency electromagnetic fields and volatile organic and non-organic compounds from landfills, and exposure to ionizing radiation from diagnostic tests and hospital equipment. Some of the occupations with higher levels of exposure to chemicals are reported to contribute to higher incidences of brain neoplasm.[2] Workers in these occupations where the potential for exposure to chemicals is high, include firefighters, farmers, physicians, chemists, and factory workers.[2] The workers in these occupations are potentially exposed to petrochemicals, nitriles, nitrites, amides, lead, pesticides, herbicides and insecticides.[2,8] Some of these organic and inorganic chemicals and metals are reported neuro-carcinogens and are possible etiologic agents for brain neoplasm.

A number of studies have examined the relationship between cell phone use and the risk of glioma. Studies with and without consideration of the latency period and studies with increased sample size and long-term use of cell phones have been inconsistent and inconclusive.[6] A comprehensive review conducted in 2002 by Wrensch, *et al*, suggested that established causes of brain tumors accounted for only a small proportion of cases.[8] We conducted this systematic review to examine updates in the role of occupational and environmental risk factors of primary brain cancers in recent years.

Materials and Methods

Relevant scientific literature was systematically reviewed from different databases in the public domain for all years until the end of 2010. The search strategy was de-

signed to identify previous observational epidemiologic studies (*i.e.*, case-control, cohort and case-case studies) that examined the relationship between brain neoplasms and occupational and environmental exposures as potential risk factors for disease etiology. Initial searches were conducted in Scopus Medline to inform the design of the actual search strategy. The optimized search strategy developed from Scopus Medline was later employed to search other relevant databases as described below. Literature search specialist at the University of Ottawa library was consulted in designing the search strategy.

Having designed and tested a search strategy it was used in conducting the literature search. The different relevant scientific databases, PubMed, Cancer Letters, EMBASE and Scholars Portal were searched using a specifically designed search strategy described above. The search terms were divided into disease terms, exposure terms and hedge terms. Disease terms that were used were brain neoplasm, cancer and tumor; exposure terms were environmental and occupational exposures and environmental and occupational risk factors; and the hedge terms were risk factor and attributable risk; these terms were used to bridge the disease and exposure terms. The searches were combined using logical operators such as "OR" and "AND." "MeSH" and "textword" search strategies were used to retrieve original research articles relating to adult brain cancer. The search was limited to original research articles on human over 19 years of age; only articles written in the English were included.

The inclusion criteria were original research articles on adult brain cancer etiology in males and females and research articles that identified and reported risk of brain neoplasm from exposure to occupational and/or environmental factors. All relevant original research articles pub-

lished in English until the end of 2010 were included for review. The exclusion criteria were if the original research article was a randomized or non-randomized clinical trial or a clinical study that reported on diagnostic, therapeutic or outcome, editorials or commentaries on disease states. Research articles on animal experiments or not in English language were also excluded. Studies on children (younger than 19 years of age) were excluded too. The numbers of original research articles searched and abstracted are shown in Table 1.

Critical appraisal of the retrieved articles

The original research articles were selected according to the said inclusion and exclusion criteria and were reviewed for relevance by reading different sections of the complete article. The first test of relevance was conducted by reading the title and the abstract after which a total of 783 articles were retained. The second test was applied which included reading the whole research article; at this stage, 384 articles were retained. The third level of scrutiny produced a total of 184 research articles as relevant, which were selected for inclusion in this review. The required data was abstracted as described by the PRISMA guidelines from all the original research articles that were retained for this review.[9] None of the articles identified for disability adjusted life years (DALY) and potential years of life lost were included in this review because of their lack of relevance to the disease etiology and risk factors.

All the relevant data was abstracted from the short-listed articles independently by the authors of this study (AAZ, AG and JG). A standard data abstraction form was specifically designed (according to PRISMA guidelines) to collect the necessary information which included the citation, population studied, research subject selection, methods used, exposure assessment, results reported and the

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Table 1: Search terms, number of articles retrieved and used in this paper

Step	Search terms used	Number of articles retrieved	Number of articles used
1	Brain neoplasm / cancer / tumor	73 534	
2	Environment / environmental exposure / risk factors	3 832 085	
3	Occupation / occupational exposure / risk factors	3 791 294	
4	Results from step #1 AND Results from step #2	25 819	
5	Results from step #1 AND Results from step #3	25 820	
6	Limits* applied to step #4	218	
7	Limits* applied to step #5	3121	
8	Combine results from step #6 AND step #7	3121	
9	Application of hedge terms	1121	
10	Level one review of title and abstract	783	
11	Level two review of the whole article for relevance	384	
12	Level three review for relevance to etiology	184	184
13	Brain neoplasm AND disability adjusted life years	2	0
14	Brain neoplasm AND years of potential life lost	17	0

*Limits applied include publication years from 1985 to 2010; age groups include all adults over 19 years of age; original research articles (case-control, cohort and cross-sectional studies) on human; research articles dealing with cancer etiology; focus on research cancer; only English language articles.

inferred conclusions. All reported risk estimates (odds ratio, relative risk, standardized incidence rates, standardized mortality rates) were recorded along with 95% confidence interval (95% CI) and/or statistical significance.

Results

This review mainly focuses on adult primary malignant brain tumors. Childhood brain tumors and tumors that develop from neurons, choroid plexus tumors, pineal tumors, embryonal tumors, ependymal tumors, tumors of the cranial and paraspinal nerves, lymphomas and hematopoietic neoplasams and other tumors such as the germ cell tumors or tumors of the sellar regions will not be discussed. About 90% of primary malignant central nervous system tumors are malignant gliomas[10] and about 94% of the primary malignant central nervous system tumors occur in the brain[11]. The literature described in this review focuses on intracranial malignant gliomas, astrocytomas and meningiomas. Occupational risk factors of primary brain tumors include a wide spectrum of jobs that may have the potential to expose workers to carcinogenic and other toxic substances. The jobs with a higher potential to development of brain neoplasm are in industries such as petrochemicals, health care, firefighting, rubber manufacturing, and chemical manufacturing among others.[12] Mortality studies among workers in oil refineries who are exposed to petrochemicals have been reported to have been higher from brain neoplasm, however, other studies have not confirmed this relationship.[13] Firefighters, on the other hand, have been reported to have a moderately higher risk for brain neoplasm compared to other occupations.[14] Elevated mortality from brain tumors has been reported for white-collar workers including financial managers, accountants, sales agents, engineers, teachers, lawyers, judges and scientists.[15]

Environmental risk factors are those exposures which occur at locations other than workplace and include farm related

TAKE-HOME MESSAGE

- Workers in petrochemical refineries, synthetic rubber manufacturing, nuclear and power generation industries, workers with occupational exposure to metals and firefighters had moderately higher risk for brain neoplasm compared to workers in other occupations.

- Exposure to agricultural chemicals such as, pesticides, insecticides, and herbicides, diagnostic and therapeutic radiations and exposure of residents to landfill pollution is among the most important risk factors for brain tumor.

- The evidence for the association between brain tumors and cell phone usage appears to be inconclusive when the statistical significance is considered.

- In assessing different risk factors, it is necessary to quantify exposures appropriately and acknowledge confounders such as ethnicity, age and gender.

exposures, landfill exposures and exposures at place of residence and cell phone usage. The environmental factors which have been investigated for association with adult primary brain tumors include exposure to farming chemicals such as pesticides, insecticides, and herbicides, exposure to landfill pollution, cell phone use and exposure to electromagnetic and ionizing radiations. Environmental exposure to pesticides and other toxic chemicals are also reported to increase the risk of neoplasm in the exposed population.[16] Recent studies suggest increased rates for brain neoplasm and acoustic neuroma on the same side of the head as the preferred side of cell phone use by individuals. The risk was higher among younger individu-

als as compared to the older individuals.[17] Analyses of neoplasm incidence in five continents using the cancer registry data indicated that the rates of adult brain neoplasm among Eastern and Southeast Asians and Pacific Islanders were one-third or two-fifths the rates among the North American non-Hispanic whites suggesting environment in general may be a risk factor.[18] It is also believed that interplay between genetic susceptibility and lifestyle and environmental and occupational exposures may play a role in initiating and promoting brain neoplasm.

Occupational exposures as risk factors

Although the identification of specific occupations or occupational exposures associated with brain neoplasm has remained elusive it is believed that a number of occupational exposures may increase the risk of brain tumors on the basis of a number of epidemiological studies. However, a causal relationship between these agents and primary brain cancers still remains to be established except for a few cases.[2] Having analyzed the New Zealand cancer registry data, Reif *et al*, reported an increased risk of brain neoplasm among workers in some occupations including agriculture (OR=1.1; 95% CI: 0.8–1.55), forestry (OR=1.2; 95% CI: 0.4–3.25), fishing (OR=0.48; 95% CI: 0.07–3.04) and livestock farming (OR=2.59; 95% CI: 1.41–4.75).[19] The reported risk was substantial and significant only for livestock farming but not for the others. A causal relationship has been proposed between some parental occupations and central nervous tumors in the offspring.

The International Agency for Research on Cancer (IARC) monographs on evaluation of carcinogenic risks in humans have assessed more than 900 occupational exposures including chemicals, complex mixtures, dusts and infectious agents.[20] Only nine of these exposures (*i.e.*, beryl-

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lium, epichlorohydrin, chlordane/heptachlor, methylthiouracil, thioracil, propylthiouracil, lead and di-isopropylsulfate) have been suggested to have possible or weak association with nervous system tumors in humans.[2] Exposures to these substances could occur among farmers and a number of other occupations.[3,21] Other occupations believed to be associated with elevated risks of gliomas include physicians and firefighters.[22,23] Servicemen in health related occupations are also believed to have an increased risk of deaths from brain tumors (Proportionate mortality ratio [PMR]=2.7; 95% CI: 1.1–6.5) compared to general population.[2,8,24] Veterinarians are also reported to have an increased risk (RR=2.51; 95% CI: 1.04–6.03) for brain neoplasm among other neoplasm.[8,25]

Certain white-collar and blue-collar occupations are reported to have an increased risk for primary brain tumors. Those in white-collar occupations who are at a higher risk of developing brain neoplasm include social science professionals, financial managers and accountants, sales agents, engineers, teachers, lawyers and judges, postal clerks, and armed forces employees. Social sciences professionals are reported to have a significantly higher risk of brain tumors (OR=6.1; 95% CI: 1.5–26).[26] The other white-collar occupations are reported to have a non-significantly elevated rates, these include occupations in engineering (OR=2.1; 95% CI: 0.4–10.3), agriculture (OR=1.5; 95% CI: 1.0–2.4), printing and publishing (OR=2.8; 95% CI: 1.0–8.3) and brickmasons and tilesetters (OR=2.5; 95% CI: 0.5–11.5).[27] Non-significantly to significantly increased risk of brain neoplasm among blue-collar workers, especially in the textile industry (OR=2.2; 95% CI: 1.0–4.8), construction industry (OR=9.8; 95% CI: 1.0–92.9) and motor vehicle operators (OR=2.8; 95% CI: 1.3–6.2) has been described earlier.[28]

Kang, *et al*, studied white male firefight-

ers and concluded that firefighters were at a moderately elevated risk of death from brain neoplasm (Standardized mortality ratio [SMR]=1.9; 95% CI: 1.1–3.4) compared to those in other jobs.[29] Bates also studied firefighters in California and observed that firefighters are at a marginally increased risk (OR=1.35; 95% CI: 1.1–1.7) of developing a number of neoplasms, including the brain neoplasm.[14] It is believed that firefighters may have a higher risk of developing brain neoplasm because they are exposed to a number of harmful chemicals, including vinyl chloride, benzene, n-hexane, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, N-nitroso compounds, lead, arsenic and mercury among others and many of these chemicals are neurotoxic and carcinogenic.[14,30]

The results of an exploratory case-control study conducted in 1987 by Burch, *et al*, indicated that a job in the rubber industry increased the risk of brain neoplasm nine-fold.[31,32] Occupation in a synthetic rubber industry and exposure to synthetic rubber products is reported to increase the risk of glioma.[31] Exposures to plastics are reported to increase glioma risk.[31] It is believed that the increased risk among woodworkers is due to increased exposure to organochlorinated wood preservatives and other organic chemicals used in wood processing. Also workers at pulp and paper mill are reported to be at statistically non-significant increased risk of dying from brain neoplasm (SMR=1.39; 95% CI: 0.96–1.96).[33]

Preston-Martin, *et al*, have reported of a dose-response relationship between the frequency of serious head injuries and meningioma risk.[31] These researchers have also reported that meningioma—but not glioma—is associated with serious head injury with a latency period of 20 years or more (OR=2.3; 95% CI: 1.1–5.4).[31] Three or more injuries are reported to significantly elevate the risk of brain neoplasm

(OR=6.2; 95% CI: 1.2–31.7).[31] Although most of the studies indicated an increased risk of brain neoplasm, Burch, *et al*, reported that injury or trauma to the head did not increase the risk.[32]

Cordier, *et al*, examined the risk of brain neoplasm among workers at a biomedical research institute and observed that the risk was more than double in the exposed group.[34] A case-control study conducted among the inpatients of a neurological hospital in Paris indicated a significantly increased risk to brain neoplasm among teachers (OR=4.1) and woodworkers (OR=1.6).[35] Although the nature of the neurological problem is not known, it appears that neurological problems increase the risk of brain neoplasm. Although the etiological relation for the increased risk of neurological conditions among teachers is not known, there appears to be a biological plausibility for woodworkers because of exposure to a range of substances in woodworking.

Industrial exposures

Exposure to specific neurotoxic chemicals in animal models has been shown to induce glioma under experimental conditions. After direct implantation of polyaromatic hydrocarbons and intravenous administration of nitroso compounds (N-methyl-N-nitrosourea and N-ethyl-N-nitrosourea) rats are reported to have developed brain neoplasm.[36,37] Maekawa and Mitsumori have reported that exposure to ethylurea and nitrite causes brain tumors in all offspring of pregnant rats.[37] Chemicals such as hydrazo, azo, and azoxy compounds; aryl-dialkyl-triazenes; alkylsulfates and sulfonates; propane-sulfone; propylene imine; acrylonitrile; vinyl chloride; and ethylene oxide are all reported to induce brain tumours in laboratory rats.[38] However, the extent of neuro-oncogenesis by these chemicals in the human body remains to be substantiated despite of bio-

logical plausibility of brain tumors in experimental animals.

In studies with human subjects exposure to chemicals such as polycyclic aromatic hydrocarbons, organic solvents, plastic monomers and polymers, metallic compounds, organometallic catalysts and their complexes, and aromatic acids commonly occurs among laboratory technicians, chemists, and those working in petrochemical industry or oil refineries.[39] Workers in catalyst development and testing are exposed to polyethylene and polypropylene. Also, workers working with flame retardants and measurement of physical properties of plastic and petroleum products are exposed to harmful petrochemicals. While the risk of developing brain neoplasm from exposure to these substances remains to be elucidated, the risk of developing brain neoplasm from exposure to some of these substances has been described. The risk or brain neoplasm is reported to be significantly elevated for workers exposed to n-hexane for at least four years (OR=16.2; 95% CI: 1.1–227.6).[39] Employment at sulphite and sulphate mills is reported to increase the risk of gliomas although specific exposures are not identified (sulphite: OR=3.3; 95% CI: 2.12–8.9; sulphate: OR=2.6; 95% CI: 1.2–5.3).[40] Significantly increased mortality from brain tumors has been observed among workers exposed to low levels of vinyl chloride monomer (SMR=229; 95% CI: 84–498) at polyvinyl chloride processing plant.[41]

However, a number of other observational studies have reported statistically non-significant risk of brain neoplasm from industrial exposures. Austin, *et al*, conducted a case-control study among petrochemical workers and observed that exposure to potentially carcinogenic chemicals did not increase the risk to brain neoplasm.[42] Similar observations were made by Bertazzi, *et al*.[15] Statistically non-

significant increases in brain tumors have been reported for men exposed to metals at workplace.[43] In another population based case-control study, a significantly elevated risk of meningioma has been reported among those who worked for 1–4 years in the metal sector (OR=2.6; 95% CI: 1.05–6.53).[44] Brain tumor risk among workers at a Japanese chromium electroplating industry was studied in 2010 by Hara, *et al*, for 26 years.[45] These authors reported increased mortality rates among those exposed (SMR=9.14; 95% CI: 1.81–22.09). Increased but non-significant risk has been reported by Rodvall, *et al*, for workers in forestry and logging and basic metal industries.[46] A case-control study among Canadian workers found a small and non-significant increase in brain neoplasm risk from exposure to asbestos (OR=1.23; 95% CI: 0.95–1.59), benzene (OR=1.34; 95% CI: 0.96–1.97), mineral or lubricating oil (OR=1.18; 95% CI: 0.93–1.43), isopropyl oil (OR=1.40; 95% CI: 0.89–2.37), and wood dust (OR=1.21; 95% CI: 0.97–1.39).[47] In a population based cohort study conducted in 1996 in Sweden by Rodvall, *et al*, increased risk has been reported for men exposed to solvents (RR=2.6; 95% CI: 1.3–5.2); pesticides (RR=1.8; 95% CI: 0.6–5.1) and for exposure from manufacturing plastic materials (RR=3.6; 95% CI: 1.0–12.4).[46]Exposure to a number of different substances either concurrently or subsequently or to mixtures of substances is believed to increase the risk of brain neoplasm. Increased exposure to ionizing radiations and metals and industrial solvents is reported to increase the risk of developing brain neoplasm.[48]

Deaths from brain neoplasm have been examined for association with industrial exposures by a number of authors. Brain cancer death rates were reported to be elevated among workers at a nuclear weapons manufacturing plant where the workers were exposed to low dose alpha radiations as well as to other substances such as beryllium, mercury, solvents, and other industrial agents.[45] Examination of brain biopsies during autopsy in a case-control study for the presence of metals indicated that silicon, magnesium, calcium and zinc were significantly higher in brains diagnosed with brain neoplasm compared to brains without malignant neoplasm.[49] However, non-significantly increased mortality (OR=3.9; 95% CI: 0.3–43.6) from brain cancers has been reported for exposures to high concentration of nitrosamines among workers at rubber industry.[50] Mortality rates from brain tumors have been reported to be not associated with exposure to polychlorinated biphenyls among electrical capacitors manufacturing workers.[51] In a similar manner, Ruder *et al*, studying the capacitor manufacturing workers who were exposed to polychlorinated biphenyls reported that brain tumor related mortality did not demonstrate a clear dose-response relationship with estimated cumulative exposures.[52] The evidence of mortality from brain neoplasm with association to industrial exposures have so far produced mixed results and conclusive results still remain to be reported.

Petrochemical production

A review on occupational exposures and brain tumors conducted on the basis of four cohort studies in the US, Canada and the UK reported of an association between exposures to petrochemicals and brain cancers with the relative risk ranging from 1.5 to 3.9.[53] An increased risk of gliomas for workers in petrochemical industry is believed to be the result of exposures to a number of occupational factors.[50] These observations were in agreement with the findings by Delzell, *et al*, a few years later when they reported that for petrochemical research facility employees the incidence of brain cancers was higher in

those working with organic solvents, plastic monomers and polymers, metals, aromatic acids, and organometallic catalysts (Standardized incidence ratio [SIR]=2.3; 95% CI:1.2–4.2).[54] Sathiakumar, *et al*, also found that there was an increased incidence of brain cancers (SIR=222; 95% CI: 81–484) among white employees who worked as scientists or technicians at a petrochemical facility in the US.[55] Beall, *et al*, studied employees at a petrochemical research facilities in US and found that the risk for gliomas was elevated for self-reported exposure to ionizing radiation (OR=15.7; 95% CI: 1.4–179.4), organometallics (OR=9.4; 95% CI: 1.5–59.7), and amines (OR=6.0; 95% CI: 1.0–35.7).[56]

However, a statistically non-significantly increased SMR has been reported for petrochemical industry workers in administration (SMR=2.3; 95% CI: 0.7–5.3), non-research technical division (SMR=2.3; 95% CI: 0.8–5.5) and technical division (SMR=2.1; 95% CI: 0.3–7.6) sectors.[57] These findings are in agreement with the observations made by Buffler, *et al*, who reported a weak and non-significant association between occupational petrochemical exposure and brain cancer incidence (OR=1.04; 95% CI: 0.26–3.73).[58] Tsai, *et al*, studied mortality from brain tumors among petrochemical and refinery plant workers and failed to observe any increased mortality (SMR=0.34; 95% CI: 0.04–1.23).[59] A study conducted among Shell Oil Company workers reported a non-significant increase in brain tumor mortality (SMR=1.82; 95% CI: 0.67–3.97).[60] Austin, *et al*, studied the risk of brain neoplasm from exposure to carcinogenic chemicals at a petrochemical plant and failed to find any increase in risk among the exposed workers after a latency of 15 years.[42]

It has been observed that workers at oil refineries are two times more likely to die from brain tumors than the expected.[16]

But these authors also observed exposure misclassification resulting in lowering of risk estimates. A moderate and significant increase in mortality rates was reported for employees of petrochemical research facilities compared to the general population (OR=1.3; 95% CI: 1.06–1.72) by Rodu *et al*.[61] A meta-analysis study conducted by Wong and Raabe indicated that workers of the petroleum industry had non-significantly increased mortality rate from brain tumours.[62] The critics of this meta-analysis, however, suggest that the study did not include many of the large studies that did show increased worker mortality due to brain tumour.[8] Other studies that observed increased mortality from brain neoplasms among industrial workers could not associate it with any specific exposures on the job.[63] To appreciate the appropriate relationship between the development of brain tumors or mortality, it may be necessary to examine specific exposures and the duration of exposure with consideration of latency period and characteristics of the exposed individual including genotypic and phenotypic data.

Petroleum refining and petrochemical production industry workers had been under much attention and a number of studies have been conducted on petrochemical industry workers, yet the association between petrochemicals and brain tumors remains elusive. Some studies suggest that workers in this industry who are exposed to carcinogenic chemicals are at an increased risk for the development of brain tumors. Specifically, workers at the refineries who worked in research, quality control analysis, and lube oil refining sectors had an estimated four times the risk of brain tumors as other workers.[62] The evidence of increased risk of brain neoplasm among petrochemical refinery workers although appears to be high for some petrochemical workers, is low or non-significant for the others; the rela-

tionship, therefore, remains inconclusive.

Synthetic rubber industry

Occupational exposure to polymer forming compounds, polyvinyl chloride and nitrile amines in a rubber production plant in Louisville, Kentucky, is reported to increase the risk of glioma in men who were exposed to these agents for at least 21 years (OR=1.9; 95% CI: 1.10–3.26).[64] The workers in synthetic rubber production industry are believed to be at a higher risk of developing brain tumors because they are exposed to chemicals used in rubber production processes (coal tars, carbon tetrachloride, nitroso compounds, and carbon disulfide). Some of these chemicals used in rubber production are known carcinogens. A hospital based case-control study and a registry-based case-neighbourhood control study both reported that cases were six to nine times more likely than controls to have worked in rubber industry.[32,65] Burch, *et al*, through an exploratory case-control study in Southern Ontario concluded that an occupation in rubber industry increased the risk nine-fold.[32] In a similar manner, Solinova, *et al*, evaluated cancer incidence and mortality among workers at a rubber manufacturing facility and observed significantly increased incidence (SIR=500; 95% CI: 233–767).[66] However, a few of the other studies have reported a non-significant increases in the risk of developing brain tumors including an incidence study conducted in Los Angeles County which reported that glioma cases among rubber and other plastic workers were only 1.4 times more compared to that in controls.[67] The preponderance of studies on workers in synthetic rubber production has shown an increased risk of brain tumors either statistically significantly or non-significantly. Although causal relationship remains to be established the evidence seems to indicate increased risk of brain neoplasm.

Other occupations with multiple exposures

A number of occupations with multiple exposures have been identified by several authors as high risk occupations for brain neoplasm. Increased odds of developing brain neoplasm has been reported for physicians from exposure to radiations and infectious agents (OR=2.73; 95% CI: 0.86–8.64), for janitors from exposure to different chemical cleaning agents (OR=8.84; 95% CI: 1.11–70.44), for electronic equipment operators due to exposure to electromagnetic radiations (OR=2.39; 95% CI: 0.73–7.83), for painters from to exposure to methylene chloride, oil-based paints, and solvents in the solutions used for cleaning of surfaces and for paint applicators from similar exposures (OR=2.16; 95% CI: 0.19–24.0).[22] These findings are in agreement with previously reported associations between gliomas and multiple occupational exposures.[21,23] Workers at a uranium processing plant in the US were observed to have a non-significant increased risk of brain neoplasm (OR=1.27; 95% CI: 0.66–2.22) from cumulative exposure to trichloroethylene, cutting fluid and kerosene in a cohort study.[68] The risk increased with the duration of exposure and the level of concentration of contaminant. Bond, *et al*, have reported a significantly elevated odds ratio for employment at a chemical manufacturing plant from one to five years, and significantly decreased odds ratio for employment greater than ten years.[69] It has also been observed that glassblowers have an increased risk, however, the nature of exposures have not been specifically identified.[70]

The workers in the pulp and paper mill industry were reported to have a moderately increased risk of glioma (OR=1.5; 95% CI: 1.1–2.1) and (OR=1.5; 95% CI: 1.0–2.2), respectively.[40] These workers are

believed to be exposed to organic solvents, wood dust, terpenes, mold and endotoxins. Moderately elevated rates (OR=1.3; 95% CI: 1.1–1.6) have been reported for workers at paper mills by Carozza, *et al*.[23] An association between primary brain tumors and occupational exposure to chemicals at nuclear facilities was examined by Carpenter, *et al*, and an increased risk was reported (OR=7.0; 95% CI: 1.2–41.1).[71] An examination of brain tumors among chemical plant employees conducted by Reeve, *et al*, indicated that those employed prior to 1945 had an increased risk (SMR=184) while those employed after 1945 had a lower risk (SMR=59).[72] Hauptmann, *et al*, have recently reported of an increased risk among embalmers from exposure to formaldehyde exposure.[73] However, no increased risk from brain neoplasm related mortality was observed among workers in formaldehyde industries (SMR=0.92; 95% CI: 0.68–1.23).[74] Overall, it appears that most of the studies report of an increased risk of brain tumors or increased mortality from brain tumors in industries with multiple exposures to industrial chemicals. Although causal relationship has not been established the existence of a relationship appears to have been confirmed and is biologically plausible.

Ionizing radiations and nuclear power plants

Occupational exposures to ionizing radiations both therapeutic and diagnostic are believed to increase the risk of brain neoplasm. In his paper on epidemiology of brain tumors, Ohgaki wrote that therapeutic irradiation is unequivocally associated with increased risk of brain neoplasm.[26] A number of other studies have explored the risk of brain neoplasm from therapeutic and diagnostic exposures to ionizing radiations either as a professional or as a patient.[75] A high prevalence of exposure to radiations from previous radiation thera-

pies for other cancers has been reported in glioblastoma and glioma patients.[76-78] Combined exposure from radiotherapy of the head and neck region non-significantly increased the risk (OR=3.61; 95% CI, 0.65–19.9); use of cell phone increased the risk of ipsilateral tumors in temporal, temporoparietal, and occipital areas (OR=2.42; 95% CI: 0.97–6.05)[79]. In a study of dentists and dental nurses in Sweden, it has been reported that they had an increased glioblastoma risk, whereas physicians and their nurses had a non-significant moderate increase in risk.[38] A higher risk of meningioma due to radiotherapy of head and neck (OR=3.7; 95% CI: 1.5–9.5) has been reported by Phillips, *et al*.[80] Although Blettner, *et al*, made similar observations (OR=2.32; 95% CI: 0.90–5.96) their findings were not statistically significant.[81] A statistically significant positive association of brain tumor with exposure to dental x-rays bas been reported by Neuberger, *et al*.[82] Increased frequency of full mouth dental x-ray examination after age 25 years were positively related to both glioma (p=0.04 for trend) and meningioma (p=0.06 for trend).[83] However, x-ray imaging effect on the development of brain tumors was unclear.[2]

A moderate increase in brain neoplasm incidence (SIR=2.14; 95% CI: 1.07–3.83), but no evidence of dose-response relationship, has been reported in two cohorts of Chernobyl cleanup workers from Estonia and Latvia, thereby supporting the association between exposure to ionizing radiations and brain tumors.[84] Relative risk for brain tumors have been reported to exceed 1.0 at eight of the ten nuclear facilities in the US.[85] However, Carpenter, *et al*, studied central nervous system cancers including brain neoplasm among workers at nuclear facilities and reported that no association exists between deaths from brain neoplasm and exposure to external ionizing radiations.[86] Mixed re-

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sults for brain neoplasm mortality have been reported for airline pilots who are believed to be exposed to higher levels of cosmic radiations.[87,88] There appears to be preponderance of studies with a positive relationship either statistically significant or non-significant; therefore, suggesting that diagnostic or therapeutic exposure to ionizing radiations may increase the risk of brain neoplasm.

High voltage power lines and electromagnetic radiations

Exposure to non-ionizing radiations appears to increase the risk of brain neoplasm as reported by several studies. Electricians who are exposed to non-ionizing radiation (*i.e.*, electromagnetic, thermal, neutron, black-body radiation, and light) were observed to be at an increased risk. Electrical workers employed in the US construction industry are reported to have a slightly elevated PMR of 136 (95% CI: 112–163, p<0.01).[89] Robinson, *et al*, have reported of moderately elevated PMR for indoor electrical workers (PMR=163; 95% CI: 117–221, p<0.01) and outdoor electrical workers (PMR=127; 95% CI: 92–72, p <0.01).[89] It is believed that the higher death rates in the electricity industry are associated with occupational exposure to electric and magnetic fields. Exposure to electromagnetic radiations among naval soldiers increased the risk of developing brain neoplasm (OR=4.63; 95% CI: 2.54–8.45).[90] Lin, *et al*, has reported that men employed in electricity-related occupations such as electricians, engineers and utility company servicemen had a significantly elevated proportion of primary brain tumors.[91] The increase in the odds ratio for brain tumors were found to be positively related to electromagnetic field exposures (OR=2.15; 95% CI: 1.10–4.06).[91]

Electricity generation workers including shunt-yard engineers who are exposed to electromagnetic fields at work are reported to have a statistically significant increased risk (SMR=5.06; 95% CI: 1.21–21.2) for brain tumors.[92] It has been reported that exposures to electromagnetic fields >0.2 μT increased the latency period for brain tumors by six years for males and four years for females.[93] Occupational risk factors of brain tumors from a population based case-control study in Germany were reported to significantly increase in risk of brain tumor development for women in electrical occupations (OR=5.2; 95% CI: 1.4–20.1) but not for men (RR=0.9; 95% CI: 0.3–2.3).[94] Tornqvist, *et al*, studied incidence of brain tumors in electrical occupations and reported of a statistically significantly increased risk for all brain tumors (OR=2.9; 95% CI: 1.2–5.9) and glioblastomas (OR=3.4; 95% CI: 1.1–8.0).[95] In a population based mortality study, it was reported that male workers employed in occupations associated with electricity or electromagnetic fields had an elevated risk for brain neoplasm (OR=3.9; 95% CI: 1.52–10.20).[96] These authors also reported of a linear relationship between the probability of exposure to electromagnetic fields and brain neoplasm. A nominally significant increase in mortality from brain tumors was reported for power generation plant workers (Observed: 55, Expected: 36, SMR=1.53).[97]

Combined effect of exposure to chemicals and occupational electromagnetic field were examined in Swedish men for the risk of gliomas and meningiomas.[98] The risk from exposure to low electromagnetic fields alone was marginally high but not statistically significant, whereas a moderately increased risk was observed for exposures to solvents and low electromagnetic fields in the range of 0.20 and 0.30 T.[98] Statistically significantly increased risk was also observed for exposure to lead and low electromagnetic fields (RR=2.73; 95% CI: 1.12–6.61).[98]

Glioma, but not meningioma risk was associated with the duration of job involving exposure to electric and magnetic fields. The risk increased with the duration of the exposure (p=0.05 for trend). The risk was greatest for astrocytoma (OR=4.3; 95% CI: 1.2–15.6).[65]

A non-significantly increased risk (OR=1.33; 95% CI: 0.75–2.36) of brain tumor has been reported for those men who had ever held a job with an average magnetic field exposure of more than 0.6 µT compared to men with an exposures less than 0.3 µT.[99] Similar findings have been reported among Swedish workers.[100] Karipidis, et al, have reported that exposure to low frequency magnetic fields non-significantly elevated risk of glioma (OR=1.4; 95% CI: 0.85–2.27).[101] Observations among workers exposed to electromagnetic radiations were also statistically non-significant for brain neoplasm.[102] Karipidis, et al, conducted a case-control study among Australian workers exposed to ultraviolet radiofrequency radiations and reported a non-significantly increased risk (OR=1.60; 95% CI: 0.95–2.69) for the highest exposed group of men and a non-significantly decreased risk for the highest exposed group of women (OR=0.54; 95% CI: 0.27–1.07).[103] Occupational exposure to electromagnetic fields among railway workers in Norway did not support an association between exposure to electric or magnetic fields and increased risk for brain tumors.[104] In a cohort study on occupational exposure to magnetic field among electrical workers in Canada, it was reported that cumulative exposure to magnetic fields above 15.7 µT-years produced a non-significantly elevated risk for brain neoplasm (RR=1.95; 95% CI: 0.76–5.0).[105] Occupational exposure to electromagnetic fields was examined by Floderus, et al, but they failed to find elevated risk of brain neoplasm from cumulative exposure.[106]

Physician were reported to have a non-significant increased risk of glioma from exposure to radiation from diagnostic instruments (OR=6.00; 95% CI: 0.62–57.7).[75,107] Electrical workers and power plant operators also were reported to have a non-significantly increased risk (RR=1.64; 95% CI: 0.89–3.03, and RR=1.28; 95% CI: 0.48–3.47, respectively).[108] Wrensch, et al, studied residential exposure to electromagnetic field exposure from power lines in the San Francisco Bay area and failed to observe statistically significant increased risk both for longest held residence and level of exposure.[109] A nested case-control study concluded that residents near high voltage power lines in Norway had non-significantly elevated risk of developing brain neoplasm from exposure to high tension power lines at 0.05–0.19 µT (OR=1.6; 95% CI: 0.9–2.7).[110] Roosli, et al, and Sahl, et al, studied the association between brain neoplasm and exposures to extremely low frequency magnetic fields and reported that there was no association.[111,112] Juutilainen, et al, studied male industrial workers in Finland and reported that workers who were probably exposed to extremely low frequencies had a non-significant increased risk (RR=1.31; 95% CI: 0.7–2.3).[113]

A non-significant increase in mortality from brain neoplasm has been reported by Baris, et al (SMR=1.13; 95% CI: 0.69–1.75).[114] Mortality rates in workers who were exposed to extremely low frequency electromagnetic fields (16⅔ Hz) were observed to be not associated with exposure to electromagnetic fields (SMR=1.0; 95% CI: 0.2–4.6).[92] Mortality rates in a cohort study among former power generation employees failed to show any significant positive trends for risks of brain tumors from cumulative exposure to magnetic fields.[115] When the deaths of the navy veterans of Korean War were investigated, no association was observed between deaths due to brain neoplasm and exposure

to non-ionizing electromagnetic radiation ranging from 300 MHz to 300 GHz (SMR=0.9; 95% CI: 0.7–1.1).[116] Savitz and Loomis reported that brain neoplasm risk increased non-significantly by a factor of 1.94 per µT-year of magnetic field exposure in the previous 2–10 years and mortality rate ratio of 2.6 in the highest exposure category.[108]

Studies on electromagnetic field exposures and the risk of brain neoplasm are inconsistent. Although exposures to electromagnetic and magnetic fields are likely to occur at workplace and at home, the risk of developing brain tumors is inconclusive. The biological plausibility is not strong because the energy in the electromagnetic and magnetic fields is not sufficient to damage the DNA. However, improvements are certainly needed in both ascertaining and quantifying the exposure, uniform consideration of latency period and contribution by associated risk factors and confounders. As noted for other risk factors of brain neoplasm larger studies with sufficient sample size and accurate exposures are needed.

Cellular phones and cordless phones usage

In recent years electromagnetic energy (radio frequencies) from cellular phones tends to indicate a positive relationship.[117] A study in Sweden reported that cases of malignant brain tumors diagnosed between 1997 and 2000 from ipsilateral radio frequency exposure because of the use of cellular phones lead to an increased risk of brain neoplasm (OR=1.85; 95% CI: 1.16–2.96) to the same side of the head as the predominant side of cellular phone usage.[118] The risk for astrocytoma was also reported to be increased (OR=1.95; 95% CI: 1.12–3.39) from cell phone use.[117] The use of analogue cellular phone was observed to significantly increase the risk (OR=1.3; 95% CI: 1.02–1.6) of brain neoplasm, and;

with the tumor induction period of more than ten years the risk increased further (OR=1.8; 95% CI: 1.1–2.9).[119] No clear association was found for digital or cordless phones. For analogue cellular telephones the risk for tumors increased in the temporal area of the brain on the same side of the brain as that was used during the phone call (OR=2.5; 95% CI: 1.3–4.9). The risk had not increased for the opposite side of the brain.[119]

However, Johansen, *et al*, found no association between cell phone use and the risk of developing cancer of the brain or nervous system in a retrospective nationwide cohort study from 1982-1995 in Denmark.[120] Another study in five North European countries in 2007 showed no increased risk of glioma in relation to cell phone use although the study did find possible link between cell phone use and the risk of brain neoplasm on the same side of the head (OR=1.39; 95% CI: 1.01–1.92).[26] Lonn, *et al*, reported that for regular cell phone use odds ratio was not elevated (OR=0.8; 95% CI: 0.6–1.0) for brain neoplasm and also for meningioma (OR=0.7; 95% CI: 0.5–0.9).[121] The risk of brain tumors among the users of cellular phones and cordless phones was examined by the INTERPHONE Study Group in Germany.[122] The authors did not observe an increased risk for glioma (OR=0.98; 95% CI: 0.74–1.29) and for meningioma (OR=0.84; 95% CI: 0.62–1.13) among the German users of cellular phones between 30 and 69 years of age.[122] However, among those who used cellular phones for over ten years, a non-significantly increased risk was observed for glioma (OR=2.20; 95% CI: 0.94–5.11) and for meningioma (OR=1.09; 95% CI: 0.35–3.31).[122] In the same study, Schuz, *et al*, have also reported that there is no increased risk for ipsilateral phone use for tumors located in the temporal and parietal lobes.[122] In a related study by Schuz, *et al*, examined

exposure to electromagnetic radiations from cordless phones by measuring the distance of the base station of cordless phone from the bed and observed that the cordless phone usage was not associated with glioma (OR=0.82; 95% CI: 0.29–2.33) or with meningioma (OR=0.83; 95% CI: 0.29–2.36).[123] In a nation-wide cohort study with just under half a million people Schuz, *et al*, observed that cellular telephones were not associated with increased risk for brain tumors (SIR=0.66; 95% CI: 0.44–0.95).[124] In a similar study in Denmark, Christensen, *et al*, reported the risk estimates were closer to unity for low-grade gliomas (OR=1.08; 95% CI: 0.58–2.00) and meningioma (OR=1.0; 95% CI: 0.54–1.28).[125]

The evidence for the association between brain tumors and cell phone usage appears to be inconclusive when the statistical significance is considered. However, most of the studies reported increased risk of brain tumors and a few studies reported no relationship between cell phone use and brain neoplasm. The suggested improvements needed in future research include proper quantification of exposure from cell phone usage, energy of the wavelength and consideration of demographic profile, and other associated factors related to the user including their genotype and phenotype. Studies with better study power are also needed in which the study population is stratified by age.

Metals

Occupations in firefighting, lead-smelting, lead-battery manufacturing, the printing industry, and in industries where workers are exposed to lead appeared to increase the risk for brain neoplasm. Cocco, *et al*, demonstrated a two-fold increased risk (OR=2.1; 95% CI: 1.1–4.0) for brain neoplasm in white men who had been exposed to higher levels of lead in comparison to the control group.[126] Similar findings have been reported among Swedish workers by Navas-Acien, *et al,* who reported an increased risk (OR=2.36; 95% CI: 1.12–4.96) from occupational exposure to lead.[127] Occupational exposure to lead also increased the risk to meningioma in individuals with ALAD2 variant of delta-aminolevulinic acid dehydratase allele. The risk increased with the level of exposure to lead from the lowest exposure level at 1–49 μg/m³/year (OR=1.1; 95% CI: 0.3–4.5) to the highest exposure level at >100 μg/m³/year (OR=12.8; 95% CI: 1.4–120.8).[12] Other metals such as arsenic, mercury, chromium, silicon, magnesium and calcium have been associated with increased risk of cancer. Workers exposed to metals like arsenic and mercury on their job were observed to be at an increased risk of glioma.[2] Mortality rates among Japanese chromium platers were reported to be significantly higher from brain neoplasm (SMR=9.14; 95% CI: 1.81–22.09).[45] Occupational exposures to silicon (p=0.01), magnesium (p=0.01) and calcium (p=0.03) were reported to significantly increase the risk of brain neoplasm.[49] Zinc was associated with borderline significance (p=0.05) but not nickel (p=0.74).[49]

Other studies have not reported of an increased risk from exposure to metals including lead. A non-significantly increased glioma risk (OR=11.0; 95% CI: 1.0–630) has been reported for lifetime occupational exposure to lead.[128] Workers in the US who are occupationally exposed to lead were shown to have a non-significantly higher brain cancer mortality rates compared to those not exposed to lead at work (Hazard ratio [HR]=1.5; 95% CI: 0.9–2.3).[129] An evaluation of lifetime occupational history to examine the association between occupational exposure to metals and brain neoplasm indicated that occupational exposure to iron (SIR=2.15; 95% CI: 0.96–4.8); chromium compounds (SIR=1.51; 95% CI: 0.85–2.67);

lead (SIR=1.27; 95% CI: 0.81–2.01); and cadmium (SIR=1.26; 95% CI: 0.72–2.22) non-significantly increased the risk of brain neoplasm.[13]Exposure to metals in most of the studies appears to significantly or non-significantly increase the risk of brain tumors including glioma and meningioma. Mortality from brain neoplasm also appears to be increased in those who were exposed to metals. The limited numbers of studies that focus on exposure to metals impose limitations on the overall inferences that can be drawn from these studies. Further studies with sufficient sample size and proper quantification of exposure to metals and consideration of latency period are needed to make the evidence conclusive. In spite of these limitations the overall trend appears to indicate that occupational exposure to metals may increase the risk of brain neoplasm.

Environmental risk factors

Farming is considered an environmental risk factor because farmers are exposed to agricultural chemicals, pesticides, herbicides, and insecticides in both occupational and environmental settings; and because farmers live and work on their farms. Farmers are believed to have a higher risk of brain neoplasm because of exposure to agricultural chemicals including insecticides and herbicides and microorganism infections. Significantly elevated risk of brain neoplasm has been reported for farmers (RR=1.6, p<0.0025) from exposure to insecticides, fungicides, herbicides and fertilizers.[131] Lee, *et al*, have reported that men who have ever lived or worked on a farm have a significantly increased risk of glioma (OR=3.9; 95% CI: 1.8–8.6).[132] These authors have also reported that men living or working on a farm had an increased risk of developing glioma, and the risk increased with the length of the period of farming.[132] The risk of brain neoplasm for those who

worked for 55 years or more was reported to be approximately four times higher (OR=3.9; 95% CI: 1.8–8.9).[132] Lee, *et al*, have also reported of a significant increase in glioma from exposure to herbicide metribuzin (OR=3.4; 95% CI: 1.2–9.7), and insecticide chlorpyrifos (OR=22.6; 95% CI: 2.7–191) among farmers in the US.[132] A significant increase in risk of meningioma from exposure to herbicide in women (OR=2.7; 95% CI: 1.2–5.5) with increasing number of years of herbicide exposure has been reported.[131] Among the investigated agrochemicals, the use of insecticides or fungicides was associated with a significant increase in relative risk (RR=2.0, p<0.001).[133] A cohort study among the workers of agricultural research institute workers reported an excess risk of brain neoplasm (RR=4.69; 95% CI: 1.2–11.4) but the increased risk was not associated with any specific exposures on the farm.[134] Investigations of brain tumor clusters in Western Missouri have indicated a significantly elevated SMR from occupational or residential exposure to several chicken hatcheries.[135]

Many of the pesticides, insecticides, and herbicides have been suspected to be carcinogenic, farmers who are mostly exposed to these agents are often but not always reported to develop brain tumors. Musico, *et al*, in a hospital based study in Northern Italy observed that farmers were five times more likely than non-farming controls to develop brain neoplasm.[136] The increased risk was attributed to increased exposure to organochlorine pesticides. Farmers were also observed to have an increased risk for brain neoplasm from increased exposure to insecticides and herbicides.[133] Farmers were also observed to have an increased risk of brain tumors because of exposure to alkyl urea, and elaiomycin (structurally similar to nitrosourea).[137] Smith-Rooker, *et al*, has reported that glioblastoma cases were more

likely to reside in counties in which rice, cotton or wood products were produced in the state of Arkansas of the US.[138]

However, a number of studies have shown that the use of insecticides, herbicides or fungicides is not associated with an increased risk of gliomas. A non-statistically significant association between glioma and exposure to herbicide or insecticide in men or women (OR=1.0; 95% CI: 0.7–1.5) has been reported by Samanic, *et al*.[131] In another study, Provost, *et al*, has reported of a non-significant increased risk (OR=1.47; 95% CI: 0.81–2.66) of brain neoplasm from pesticide exposure.[139] Carreon, *et al*, examined the risk of gliomas and farm pesticide use in the non-metropolitan areas of Iowa, Michigan, Minnesota and Wisconsin and reported that there is no association between the use of pesticides and the risk of glioma for men or women.[140] These researchers and others have also found statistically non-significant association between pesticide exposure and brain neoplasm (OR=1.4; 95% CI: 0.9–2.2) and have suggested that other factors in farming may be the cause for adult glioma.[140,141] Living in quarters adjacent to storage sites of pesticides on the farm has been reported to be associated with a higher (but non-significant) risk of glioma.[141] Ruder, *et al*, have reported a significant decreased risk of brain tumors from exposure to insecticides (OR=0.75; 95% CI: 0.59–0.95) and farm animals (OR=0.48; 95% CI: 0.25–0.90).[142] Examination of brain cancer risk among the residents in the proximity of cranberry cultivation in the Upper Cape Cod area of Massachusetts revealed a two-fold non-significant increased risk (95% CI: 0.8–4.9) and a 6.7-fold increase of astrocytoma (95% CI: 1.6–27.8) from pesticide drift.[13]

In addition to exposure to insecticides, herbicides, and pesticides that may increase risk of developing glioma among farmers, contact with animals was another environmental risk factor that is believed to increase the risk of brain neoplasm. However, general farm workers have been reported to have a reduced risk compared with workers who had no contact with animals (OR=0.66; 95% CI: 0.5–0.9).[143] Farmers at all ages were reported to have a non-significant excess death risk from brain neoplasm (PMR=1.10; 95% CI: 0.92–1.32).[144] Similar observations were made by Lee, *et al*.[145] It appears that no particular occupational or environmental exposure other than farming has been identified as a major risk factor for brain cancer, although a number of exposures appear to increase the risk. Risk was significantly higher among those who used glue (OR=17.58; 95% CI: 1.75–176.62) during leisure activities and significantly lower among those residing near cellular telephone towers (OR=0.49; 95% CI: 0.26–0.92).[146]

Overall, occupational or environmental exposure to agricultural chemicals appears to increase the risk of brain tumors among farmers and farmworkers. Environmental exposure to pesticides form pesticide drift among residents also appears to increase the risk to brain tumors. Glioma and glioblastoma cases appear to be higher in regions were rice, cotton and wood products are produced. A meta-analyses of studies on brain neoplasm and farming indicated an estimated elevated risk (OR=1.3; 95% CI: 1.09–1.56) for all farmers and a non-significant risk for female farmers (OR=1.04; 95% CI: 0.84–1.29).[88]

Emissions from landfill sites

It is believed that landfill sites contain many potentially harmful chemicals including methane, carbon dioxide, hydrogen sulphide, benzene, formaldehyde, styrene, volatile organic compounds and metal vapors of cadmium and lead. Williams and Jalaludin studied Australians who resided beside hazardous waste de-

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pot and observed that male brain neoplasm cases were more likely to live near a waste depot (SIR=380; 95% CI:139.4–826.6) compared to controls who were cancer free.[147] However, another study in a community in Britain living 2 km away from a landfill reported a relative risk of RR=0.98 (95% CI: 0.96–0.99) which indicated absence of any meaningful relationship between landfill emissions and brain neoplasm.[148] Insufficient information is available for evidence to be conclusive; more studies are needed to confirm the association between exposure to emissions from landfill and the risk of brain tumors.

Air pollution

Environmental exposure to petrochemical air pollution having lived in the vicinity of petrochemical refineries appeared to increase the risk (OR=1.65; 95% CI: 1.0–2.73) of brain tumors.[149] A case-control study conducted in Taiwan concluded that individuals who lived in a group of municipalities with the highest levels of petrochemical air pollution had a non-significant increased risk of developing brain cancer than the group who lived in municipalities with the lowest petrochemical air pollution levels (OR=1.65; 95% CI: 1.00–2.73).[150] Other studies, however, did not find increased risk (OR=0.96; 95% CI: 0.79–1.17) of brain neoplasm among those residing in the vicinity of petrochemical facilities.[151] Communities living beside oil refinery in Kansas, US, were observed to have no significant increase in the incidence of brain neoplasm, (Observed: 12, Expected: 9.46, SMR=1.27).[152] In a similar manner, McKean-Cowdin, *et al*, have reported that there is a decrease in risk of brain neoplasm with increasing levels of exposure to sulphur dioxide, nitrogen dioxide and carbon monoxie.[153] Most of the original research studies among the few that have explored air pollution in the vicinity of a petrochemical plant seem to in-

dicate that the pollution is not associated with the risk of brain neoplasm. Further research in this area is needed to answer the question convincingly.

Discussion

It is believed that brain tumors are etiologically associated with workplace and residential (environmental) exposures but conclusive evidence has been elusive.[8] A number of occupations are reportedly associated with elevated risk for primary brain neoplasm including physicians, firefighters, farmers, servicemen, sales agents, janitors and cleaners, petrochemicals and oil production workers, synthetic rubber manufacturers and social sciences professionals. The risk for primary brain tumors is mostly elevated for these occupations although in many cases non-significantly and in many of these cases it appears to be chance finding. Systematic reviews and meta-analyses by several authors have reported mixed results with no definitive causal association between any single occupational group and primary brain tumors because of relatively low odds ratios for some studies and confidence intervals that straddle unity for the others.[2,3,8,62,154-158]

It is believed that hereditary syndromes (adenomatous polyposis, Li-Fraumeni and family syndrome), head trauma, allergies, diet and vitamins play a role in adult brain cancers and need to be considered. Furthermore, other factors associated with the development of the disease which include genetic factors such as alterations in cell cycle genes and DNA damage repair genes, deletions or mutations of TP53, RB or PTEN, amplifications or mutations in EGFR, deletions in chromosomes constitutive polymorphisms in glutathione transferase cytochrome (P450 2D6), 1A1 N-acetyltransferase, XRCC1 and XRCC2 need to be examined.[8] The evidence of etiological relationship between occupa-

tional and environmental exposures could be stronger if multiple factors and interactions between these factors are considered. The Brain Tumor Epidemiology Consortium (BTEC) suggests that small sample sizes of individual studies, lack of data on tumor types and methods of classification and inability to examine interactions are some of the reasons for lack of clarity on etiological relationship between occupational and environmental risk factors and primary brain cancers.[159]

Workers in occupational and industrial setting are exposed to a range of substances from neurotoxic to neurocarcinogenic to neurogenotoxic and include chemical compounds such as organic solvents, lubricating oils, varnishes and paints, formaldehyde, acrylonitrile, phenols and phenolic compounds, polycyclic aromatic hydrocarbons and metals. Some of these chemicals (pesticides, other agricultural chemicals, alkylureas, copper sulphates and vinyl chlorides) are known to induce brain tumors in experimental animals.[8] Examination of individual exposures as etiological agents of brain neoplasm may fail to reach significance for causality because of small sample size, deficiencies in exposure measurements and lack of details on tumor subtypes. It may be worthwhile to evaluate the exposures along with other factors such as genetic susceptibility, lifestyle and behavior factors and concomitant exposures. To date, etiological studies on brain tumors have examined exposures unilaterally and without the recognition of other putative risk factors. Interactions between genes and gene products and occupational and environmental factors have been suggested, therefore, it may be necessary to examine single nucleotide polymorphisms in genes associated with DNA repair, cell cycle, metabolism and inflammation in context with occupational and environmental exposures and molecular subtypes of brain neoplasm.[160,161] It

has been reported that the T1 null genotype for glutathione S-transferase was significantly associated with the risk of meningioma (OR=1.95; 95% CI: 1.02–3.76) but not with the M1 variant.[162]

A number of agricultural chemicals including pesticides have been examined for association with brain neoplasm. Although the overall findings indicate mixed results, most of the original research presented in this review reported an increased risk either statistically significant or nonsignificant from exposure to agricultural chemicals; while very few articles reported no risk or decreased risk. The proposition that exposure to agricultural chemicals increases the risk to brain neoplasm could be biologically plausible because many of these chemicals are genotoxic and mutagenic. A number of studies have reported of a strong association for male and female pesticide applicators,[4] for women exposed to insecticides and herbicides,[163] and for male and female workers on wheat producing acreage that used chlorphenoxy herbicides[164]. An ecological study by Schreinemachers has reported of a positive association between wheat producing acreages in the wheat producing States in the US and brain tumor related mortality.[164] A meta-analysis of the risk of brain neoplasm among farmers has reported a moderately increased risk (RR=1.3; 95% CI: 1.1–1.6) of brain neoplasm from exposure to agricultural chemicals.[3] However, a number of other reviewers reporting on pesticide applicators and workers at pesticide manufacturing facilities have reported of mixed results.[8,159] A preponderance of scientific literature suggests a positive association between farming and brain neoplasm, but causal relationship is still elusive. Additional research to examine neurotoxicity of agricultural chemicals supplemented by investigation of molecular sub-types of brain tumors and appropriate quantification of exposures to ag-

ricultural chemicals and consideration of latency period in a uniform manner may provide better evidence.

Exposures among workers at petrochemical, petroleum and oil production industries seem to suggest a cautious admission of an increased risk of brain neoplasm. Increased risk of brain neoplasm and increased mortality from brain neoplasm has been reported for the US oil production workers by several authors.[165] Other researchers have observed of an excess of benign brain tumors, but a deficit of brain cancer deaths.[57,61] Buffler, *et al*, have reported risk of brain neoplasm at around unity.[58] A review and meta-analyses of a combined database of over 350 000 workers by Wong and Raabe, suggested no increased risk of brain neoplasm among petrochemical workers.[166] Overall, there appears to be an increased risk of brain neoplasm among the workers at petrochemical and oil production workers, but it is really mixed results. Although a causal association has been proposed, lack of identification of a causal agent or specific exposure confounds the causal connection. Additional research on brain neoplasm sub-types and specific exposures in the petrochemical industry with sufficient sample size and study power may provide some conclusive evidence.

In this review, exposures to ionizing radiations and other chemicals at nuclear power plants were observed to be associated with elevated rates of brain neoplasm either statistically significant or non-significant. Elevated risks were also observed for exposure to non-ionizing radiations. Some of these studies were statistically significant while others were not. Similar mixed results have been observed for exposure to electromagnetic fields. Although a number of occupational studies have reported of a positive relationship between occupational exposures to electromagnetic fields,[87,92] a number of other researchers

have not observed any relationship.[167,168] Inaccuracies in measurements of exposure to electromagnetic field and latency period make it difficult to prove the existence of a causal relationship. The evidence is, therefore, inconclusive as has been reported earlier.[8,107] There is also a lack of biologic plausibility of disease causation although it is reported that electromagnetic field exposures to the mammalian brain depresses nocturnal melatonin levels which are believed to have oncostatic effects.[169]

Ionizing radiations and therapeutic ionizing radiations are reported to increase the risk of brain neoplasm[170,171] whereas diagnostic radiations have not been associated with increased risk of gliomas.[8] The review by Wrensch, *et al*, identified an increased risk either statistically significantly or non-significantly.[8] Increased risk of meningiomas has been reported from exposure to dental x-rays.[171] Studies with the survivors of the atomic bombing indicate a higher incidence of meningioma with a dose-response relationship.[172] Elevated risk (RR=1.2, 95% CI: 0.8–2.0) for brain neoplasm among workers of nuclear facility and nuclear material production workers may be confounded by other chemical exposures in the industry.[48,173] A review by Wrensch, *et al*, has indicated that neither dental nor non-dental x-rays to the head and the neck have been associated with increased risk of gliomas.[107] Exposures to ionizing radiations appear to be more consistently associated with increased risk of brain tumors than other exposures and the relationship appears to be biologically plausible. Exposures to diagnostic radiations appear to increase the risk of meningiomas but not gliomas.

The exposures at synthetic rubber facility include coal tars, carbon tetrachloride, N-nitroso compounds and carbon disulfide. Some of these compounds in experimental animals are shown to be

carcinogenic but the evidence of causality for brain neoplasm still remains to be conclusive. However, overall, it appears that the risk of brain neoplasm among workers at synthetic rubber facility is increased. It is also believed that exposure to vinyl chloride appears to increase the risk of brain neoplasm as observed in this review. However, recent studies did not support the causal relationship between exposure to vinyl chloride and brain neoplasm incidence or mortality.[174,175] Additional research is needed to determine the neurotoxicity of vinyl chloride and job at a synthetic rubber facility.

A number of reviews and original research articles have articulated an increased risk of brain neoplasm from head injuries.[31,32] Evidence has also been presented of a positive relationship between head injuries and meningiomas and acoustic trauma.[171] Increased risk for meningiomas in men with a latency of 15 to 20 plus years has been reported.[176] Head injuries, therefore, appears to be causally associated with brain neoplasm.

Scientists and biomedical professionals are believed to be at an increased risk of brain neoplasm; however, neither specific occupational exposures nor specific medical specialties have been identified. Embalmers, pathologists, anatomists and other professional exposed to formaldehyde are believed to be at an increased risk, but these findings are not consistent with other industrial workers.[177] Wrensch, *et al*, reviewed the risk among firefighters and reported an increased risk with increased number of years as a firefighter.[8] However, these conclusions have been drawn from studies with a limited number of cases and a weak association with the number of years as a firefighter. Firefighters are exposed on the job to a number of substances and overall it appears that firefighters are at an increased risk. However, additional research is needed to determine the causal relationship between exposures and brain neoplasm risk. Non-significantly increased risk has been reported for biologic laboratory workers,[178] non-elevated risk to brain cancer has been reported for clinical laboratory technicians, radiologic technicians and science technicians.[179] Non-significantly increased risks have been reported for glioma among artists in the San Francisco Bay area and also for social service workers, shipper, janitors, motor vehicle operators and aircraft operators.[17]

On the basis of a population based study, Zheng, *et al*, reported of a significantly increased risk for men in roofing, siding, sheet metal works, newspapers, rubber and plastic products, manufacturing industries, electrical service, wholesale trade of durable goods, farm products and grain and field beans and gasoline service stations and in women for those working in industries such as agriculture, apparel and textile products.[180] For men occupations with significantly increased risk was observed for guards, janitors and cleaners, mechanics and repairmen, supervisors in construction and for women retail sales and commodities sales occupations and general farmworkers. The findings of this study may not be conclusive because of the small number of study subjects, and some of the observed associations may be by chance alone. These findings are in agreement with a population based study in northeastern China.[181] These authors have also reported that occupational exposure to metals like lead, tin and cadmium was positively associated with increased risk of meningioma.[181] Occupational exposure to metals among the blue-collar workers is reported to be significantly associated with increased risk of brain neoplasm.[63] Metals like nickel, cadmium, arsenic, beryllium and chromium, therefore, appear to be associated with increased risk of brain neoplasm, but the relationship remains

confounded because of lack of evidence of causality. Industrial and or occupational exposures may not be the sole cause but a contributing cause and therefore needs to be examined in the context of biological, genetic, lifestyle, dietary and other factors.

Concerns over cellular telephones and electromagnetic fields have increased in recent years, however, conclusive evidence has remained elusive. A recent study has reported of doubling of the risk of brain tumors on the same side of the head as that preferred for cell phone use with period of use over ten years.[182] However, Lahkola, *et al*, examined the risk of glioma among analogue and digital cell phone users and reported that there is no increased risk.[183] Mixed results have been reported by Krewski, *et al*, having exhaustively reviewed adverse health effects including cancer from exposure to radiofrequency fields.[184] They have also examined and characterized possible biological mechanisms. However, a recent study by Hardell, *et al*, has observed an elevated but statistically non-significant risk of brain tumors from cellular phone use on the same side of the head as the phone use.[79] The evidence remains inconclusive in human studies although biological plausibility has been shown to exist in animal models.[185,186] However, no association between the use of cellular phones and the duration of use and brain cancer incidence has been reported by a number of other studies.[187,188] Inskip, *et al*, have reported of no relationship between cellular phone use and incidence of gliomas, meningiomas and acustic neuromas.[154] The risk did not change with the duration of use or cumulative time used. Evidence may not improve with further studies unless better methods for quantification of exposure from cellular phone use are available. The overall evidence suggests an increased risk of brain neoplasm but insufficient information on exposure and duration of exposure.[189]

Conclusion

Occupational and environmental risk factors of brain neoplasm were examined by conducting a systematic review of literature. Evaluation of the occupational risk factors have indicated that workers in petrochemical refineries, synthetic rubber manufacturing, nuclear and power generation industries, workers with occupational exposure to metals and firefighters had moderately higher risk for brain neoplasm compared to workers in other occupations. Among the most reported environmental risk factors were exposure to agricultural chemicals such as, pesticides, insecticides, and herbicides, diagnostic and therapeutic radiations and exposure of residents to landfill pollution. Occupational and environmental exposures rarely occur in isolation and at a workplace there may be one dominant exposure but there are a number of secondary exposures which may be equally harmful. A number of these factors may be acting concurrently or subsequently and may have residual carryover effects.

The incidence of brain neoplasm appears to be dependent on a number of collaborating factors including level of industrial development, air quality, air pollution and lifestyle and not just the presence or absence of etiological agents. Additionally, these exposures could occur under certain predisposing conditions, and these include lifestyle, physiological and genetic factors. It is also important to consider individual characteristics including genetic physiological profile and efficient determination of exposure and latency. It is also necessary to quantify exposures appropriately and acknowledge confounders such as ethnicity, age and gender. The question of uncertain quantification of exposure is not unique to brain neoplasm for

it is a central issue in all examinations of all disease-exposure relationships. However, it appears that these are the issues that plague the association studies and cause problems with internal and external validity and render the findings inconclusive. Although it is known for many years that primary brain tumors in adults are gender based with gliomas being more prevalent among men and meningiomas among women, till the present time little information is available to elucidate a hypothesis for the gender preponderance of cancer sub-types. It may be necessary for different specialties such as epidemiology, neurology, oncology and molecular biology to collaborate to jointly develop preventive, diagnostic and therapeutic options to overcome brain cancers.

Finally, as we look towards the future with the hope that we may find some conclusive evidence on the etiology of brain neoplasm further research is needed to confirm those risk factors in the context of primary and secondary exposures believed to be associated with brain neoplasm. It is also necessary to determine the exposures correctly and confirm the same using appropriate biomarkers of exposure or effect. Data from multicenter studies needs to be pooled to produce sufficient number of cases for each of the sub-types of brain cancers so as to answer the research question with sufficient study power. The recent developments in systematically determining the role of electromagnetic radiations from cellular phones and other wireless hardware by conducting global studies seem to indicate a new trend. The conclusive evidence that has eluded us for a long time may only be captured through holistic experiments by considering total exposures, individual characteristics, latency considerations and with sufficient study power; and a truly global approach.

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