

Risk factors for gliomas. An extensive review

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Abstract

Primary brain tumors consist are a heterogenic group of malignancies. Gliomas represent subtypes which include all tumors arising from glial cells. The risk factors for gliomas are until today unclear. The aim of this study was to summarize all possible connections between suspected risk factors and glial brain tumors.

Introduction

Primary brain tumors consist of a heterogenic group of malignancies. They have a relative small incidence when compared to other neoplasms. Their incidence varies according to different classification techniques used. According to Central Brain Tumor Registry of the United States (CBTRUS), in 2004-2008, their incidence in the US was 19.89 per 100,000 person-years (1). In the GLOBOCAN 2008 series published by the International Agency for Research on Cancer (IARC), brain tumors represented 1,9% of all cancers excluding non-melanoma skin cancer (2)*. In the CBTRUS statistics, gliomas represent 30% of all primary CNS tumors and 80% of malignant ones (1).

Epidemiologic studies offer the possibility of understanding how a disease acts and who, when, where and why is exposed. They constitute the basis of

understanding a disease and offer a chance on preventing and treating it. Epidemiologic studies concerning risk factors for gliomas have studied a multitude of possible elements, but their results until now have been mostly inconclusive. This is due to the small number of cases, to the heterogeneity of study designs, inconsistent approach to suspected risk factors. The goal of this review is to provide up to date knowledge concerning risk factors for gliomas and offer an overview of epidemiologic literature data available for glial tumors.

Material and methods

This article includes data from studies indexed by MEDLINE. We used the terms “brain tumors” or “gliomas” in combination with “epidemiology” or “risk factors”. All articles, including reviews were covered. Articles published in the last five years were the first used when discussing a certain topic. When not available, older articles were included. All related abstracts to those initially used, were included. Three large epidemiological reviews were extensively used in order to create specific categories of risk factors (3-5). We have to mention that our search did not exclude articles cited by these reviews. We also have to state that we used data from experimental research in order to highlight certain facts. For every

category of risk factors the terms (e.g. ionizing radiation) combined with “brain tumors” and “gliomas” were again searched for on Medline.

Age and race

Brain tumors affect more Caucasians than African or Asian descendants, this being true for all ages (4). The CBTRUS report indicates that whites are affected twice more frequent than blacks. Also, for all brain tumors, whites are affected more frequent than Hispanics. The incidence in Japan is half of that seen in Northern Europe (3).

Age-adjusted incidence tends to be higher in developed countries (4). For gliomas the peak incidence is situated in the 75-84 years interval (1). Age-adjusted incidence rates follow an ascending route, except the decrease in incidence in the 85+ years (1).

Gender, hormonal status, exogenous hormones and risk for developing gliomas.

The fact that glioma incidence varies according to gender is now admitted by most studies. Given the fact that gliomas are less frequent in women, their age at diagnosis is higher, researchers have tried to study a possible link between female gender and gliomas (3). Data available from the CBTRUS shows a higher incidence in males than females (7.17/100 000 person-years vs. 5.07/100 000 person-years) (1). According to the same registry, gender is also important in survival, with females having longer survival rates for most types of tumors, except brain stem and pineal glands. While age alone should not disqualify patients from receiving complete treatment (6), a study found that women were older when diagnosed than men, and this was contraindication for treatment after surgery (7). Data from GLOBOCAN

shows a higher incidence of new cases of brain tumors in men vs. women (127000 vs. 110000) (2). The number of deaths due to brain cancer is smaller in women vs. men (77000 vs. 97000) (2).

Experimental research, in which rats were transplanted with glial tumors, showed a slower rate growth in female rats, a longer survival for females and for the group estrogen treated group (both males and females) (8).

A review of current knowledge between hormonal status and gliomas, published in 2010, included 15 articles concerning gliomas. The final conclusion of the study is that female sex hormones are protective against gliomas and constitute risk factors for meningiomas (9). In contradiction, in the EPIC study no connection between feminine hormones and gliomas was found (10).

An older age at menarche was associated with a higher risk of gliomas in the NIH-AARP Diet and Health Study (11). This conclusion was also drawn by researchers in other studies to (9). The NIH-AARP Diet and Health Study found no other link between female hormones and risk of gliomas (11). Ever being pregnant had a protective effect in one study (12). Some studies also found pregnancy to be a protective factor, while others found no relation between the two (9).

Research concerning the effect of exposure to exogenous hormones either by oral contraceptives or hormone replacement therapy and glioma risk had mixed results. Studies found a slightly higher risk (13), no influence (10, 14) or a protective role of this therapy (9). The later study combines conclusions from 15 studies, and majority of these studies

sustain a protective role of exogenous hormone therapy against gliomas (9).

Genetic risk factors – family aggregation, genetic syndromes and gene polymorphism

The existence of a family member with a glioma, could represent a risk factor for the other members. Wrensch and all conducted a study where they showed that OR of a primary brain tumor (PBT) in family members of patients with PBT was 2.3 (95% CI=1.0-5.8 (15)). In a study of Malmer, the authors obtained similar results (16). The same author investigated if genetic factors or genetic ones were the cause of a higher incidence of brain tumors in families having one member already affected by the disease (17). The study revealed that standardized incidence ratio (SIR) among spouses of HGG patients was the same as in the general population, while SIR was 2.30 (95% CI=1.66-3.11) for first degree relatives of patients diagnosed with HGG (17). Segregation analysis showed that family aggregation could explain only 5% of glioma cases, and that a recessive gene model fits in about 2% of all cases (18, 19). On the other hand, family aggregation wasn't confirmed by a study in Iceland (20).

There is strong evidence that some inherited genes influence the risk of developing a glioma. Some familial cancer syndromes are associated with brain tumors (4). The most important of these syndromes and the associated genes are Li-Fraumeni syndrome (TP53 mutations), type 1 and 2 neurofibromatosis (NF1 and NF2), tuberous sclerosis (TSC 1 and 2), retinoblastoma (RB1), and Turcot syndrome (APC and hMLH1/hPSM2 mutations) (4, 5).

Li-Fraumeni syndrome is characterized by a familial aggregation of tumors, with about 70% of cases carrying TP53 mutations (4). In the IARC database of Li-Fraumeni syndromes, 14% of cases had a brain tumor, thus suggesting that familial gliomas could be related to p53 mutations (21). A study of 18 families with 2 or more cases of glioma, didn't show any connection to p53 mutations, infirming this hypothesis (22). It must be said that these families did not meet classic Li-Fraumeni criteria.

Neurofibromatosis type 1 is an autosomal dominant disorder characterized by cafe-au-lait spots and multiple neurofibromas and an increased incidence of diffuse astrocytomas, glioblastomas, optic nerve gliomas (4). Neurofibromatosis type 2 is characterized by dysplastic and neoplastic lesions of the Schwann cells, meningeal and glial ones (4). About 80% of gliomas that occur in NF2 patients are tumors of the spinal cord and cauda equine (4).

Turcot syndrome is also an autosomal dominant disease, characterized by colonic adenomatous polyps and nervous system tumors, usually medulloblastomas (23).

Gene polymorphism has been intensively studied by researchers. Genes involved in DNA repair are probably the most studied category, because their role in preventing carcinogenesis (5). The methylation status of MGMT is not only involved in gliomagenesis but also it can predict tumor response to temozolamide treatment (24, 25). MGMT methylation together with microRNAs miR-21, miR-181c, miR-195 are correlated to progression-free survival of GBM (26). MGMT F84L has been proven to be an important risk factor for gliomas (27). Individuals carrying wild-type genotypes of

MGMT F84L and PARP1 A762VA, exposed to ionizing radiation have a much higher risk (27). A genotype, rs1760944 GG of APE1/Ref-1 promoter, involved both in DNA repair and redox activity, has been shown to exert protective roles in glioblastomas (28).

A genetic variant of the CHAF1A gene is linked to an increased risk of disease (29). An AA or AC variant of the 8092 nucleotide of ERCC1 was 4.6 times more frequent in individuals with oligoastrocytoma (30). Another study showed that individuals homozygous for ERCC1 c8092a and ERCC2 k751q have an increased risk for gliomas (31). Other subtypes of ERCC2 were also incriminated (g3). Chen identified that carriers of the two "CGT" haplotypes of Vascular Endothelial Growth Factor Receptor 2 (VEGFR 2) in a Chinese population had a 42% reduced risk of developing gliomas compared to noncarriers (32). Other genetic variants of four genes - rs4295627, a variant of CCDC26, rs4977756, a variant of CDKN2A and CDKN2B and rs6010620, a variant of RTEL1- were associated with glioma risk in a female population (33).

Tayrac and all identified a 4-gene signature (CHAF1B, PDLIM4, EDNRB, and HJURP), that strongly correlated with survival of HGG patients (34). But this thesis needs to be verified, since it has been proven that susceptibility variants published in glioma Genome-wide association studies (GWAS) are different between GBM, low grade astrocytomas or oligodendrogliomas (35).

Exposure to ionizing radiation

Ionizing radiation is the only carcinogenic agent that has been classified by IARC as being a certain risk factor for brain tumors. Studies have shown increased

incidence of gliomas or PNETs in children that received prophylactic CNS irradiation for acute lymphoblastic leukemia (4). Various studies conducted to observe the effects of ionizing radiation on children treated for tinea capitis found that risk for gliomas increased immediately post-radiation, being higher even after ≥ 30 years, dose related, with no relation to gender or origin (4).

Different studies have analyzed effects of ionizing radiation after the exposure of the Japanese population to atomic bomb irradiation in Nagasaki and Hiroshima (3-5). They all found an increased incidence of all brain tumor types, including gliomas. One study from Hiroshima found a direct relation between risk and the distance from explosion epicenter (36).

TABLE I

Gene mutations, gene polymorphism, gene variants possibly implicated in glioma risk

Gene mutations/gene variants/genotypes	Relation to glioma risk	No. of Ref.
Tp53	Increased or no connection	21,22-mixed results
MGMT methylation	Increased risk. Predicts tumor response to temozolomide	24,25
PARP1 A762VA genotype	Increased risk	27
MGMT F84L	Increased risk	27
rs1760944 GG genotype of APE1/Ref-1	Decreased risk	28
CHAF1A - rs243356	Increased risk	29
ATR (<i>MIM 601215</i>) RPA3 (<i>MIM 179837</i>)	Could determine genetic glioma risk	29
ERCC1c8092a and ERCC2 k751q	Increased risk	31

homozygous individual		
CGT haplotypes of VEGFR 2	Increased risk	32

The effect of medical exposure to ionizing radiation is yet to be clarified. Various studies assessed effect of either occupational exposure to ionizing radiation by technicians, radiologists or low-dose irradiation for diagnostic procedures- dental X-rays, head and neck X-rays, or CT of those areas (37). An INTERPHONE study found an insignificant increased risk for meningiomas or acoustic neuromas, but an inexplicable statistically significant lower risk for gliomas after any kind of medical exposure (37). Another study found an increased risk in a population that underwent ≥ 3 CTs, but only in those with a family history of cancer (38).

Electromagnetic fields and use of mobile phones

Probably the most important debate our days, concerning risk factors for malignant brain tumors, lies in the use of mobile phones. Several authors and institutions have conducted multiple studies that frequently show mixed results, and, moreover, results from one study are often contested by others conducting research in the same domain.

One of the most active organizations that published studies regarding the use of mobile phones is the Interphone Group that functions under the Auspices of IARC. Their international study comprised 2708 glioma and 2409 meningioma cases, from 13 countries (39). The authors found no link between either glioma or meningioma risk and the use of mobile phones, even after 10 years of usage. The Interphone study found only a higher risk for gliomas in the temporal lobe, and for those subjects

that reported repeated use on the same side, but the CI varied in very large limits. The OR was 0.81 (95% CI 0.70-0.94) in the regular mobile phone users group-defined by the authors as at least one call per week for more than six months. The OR was 1.40 (95% CI 1.03-1.89) in the group that stated they used mobile phones more than 1640 h. But the authors of the study argued that values for mobile phone use in this group, was very unlikely.

The results of the Interphone study were extensively contradicted. In an article from 2008, by Hardell and all (40) suggest that the results of the Interphone study are largely affected by bias, so that results could not be considered valid. Conclusions from the Swedish team of the Interphone Group that concluded that no relation exists between mobile phone use and risk of developing gliomas (41) were challenged by several researchers (42-44). Hardell conducted several studies where the researchers found a link between mobile phones and risk for developing several types of tumors, including gliomas(45-48). In one study they found an increased risk for developing gliomas in people that used mobile phones for more than 10 years (OR=2.7, 95% CI 1.9-3.7), this risk being even higher in those who started to use mobile phones before the age of 20 (OR=4.9, CI = 2.2-11)(45). Another study of the same author found a higher risk (OR=3.4, 95% CI 1.6-7.1) for those who used mobile phones for more than 2000 hours (46). A latency period of more than 10 years was a risk factor for developing gliomas (OR=2.0, 95% CI 1.2-3.4), even in a meta-analysis where results were compared with 16 other studies (49).

Results from five countries in the Interphone group, showed a higher

incidence of gliomas in people that had a higher exposure to radio frequency fields (RF) from mobile phones (OR=1.91, 95% CI 1.05-3.47)(50).

The conclusions of a long-term Danish cohort study published in 2011, was that no link exists between mobile phones and malignant brain tumors (51). This research updates information from a 2006 study (52), which in turn is an update of a study started in 2001 (53). The results of these particular analysis were contested, partially for its design and extensive bias possibilities, and partially because the financing was done in part by companies that were involved in mobile telecommunications (54-56).

In 2011, 30 scientists met at IARC, with the goal of establishing the impact that RF electromagnetic fields had on carcinogenesis. During that meeting, they established that RF magnetic fields are a potential risk factor for developing gliomas in humans (57). Their conclusions were based mainly on two studies, cited in this paper, one being the Interphone study and the other the study of Hardell and all.

The conclusions of the IARC group were compared by Little and all with the effect of RF magnetic fields on glioma risk in the US population, based on 12 registries of the SEER database (58). The conclusion was that the US data, could be compatible with the information obtained in the Interphone study (moderate risk when mobile phones are excessively used) but in contradiction with the results of Hardell's study.

Finally we can say that the debate surrounding the influence of mobile phones on the risk of developing glial tumors is far from being over. In 2009, in a review of available data (59), Kundi stated

that four epidemiological aspects should be taken into account when analyzing this subject: temporal relation (the exact time when a brain tumor appeared), association (assessed as possible counterarguments for a possible relation), environmental factors (risk factors that could coexist with mobile phone usage) and finally population equivalence (both cases and controls should come from the same type of population). It is almost impossible for a case-control study, and most studies so far have been done using this approach, to follow these guidelines. A final conclusion on mobile phones-glioma risk relation will come probably, only when researchers will create a new model for a possible study.

Lifestyle factors

There is still little evidence of an association between any lifestyle factors and an elevated risk for malignant gliomas. Although certain factors like alcohol, diet, smoking have proven to be in relation to certain types of tumors (colonic, rectal, breast, lung) studies up to day were unable to identify any relevant link between a certain lifestyle and brain tumors. The main cause is the fact that gliomas are not a common disease in the general population. This means that cohort studies cannot gather sufficient information, which in turn determines that data can only be collected from case-control studies (60).

Diet and eating habits have not yet been proven to exert any certain influence on the development of gliomas. A study by Hu and all, in a hospital based case-control showed a relation between certain foods and gliomas (61). Consumption of fresh vegetables and fruits was inversely associated with gliomas (OR=0.29). The same effect was found for fresh fish. The consumption of salted vegetables

determines a high risk for brain tumors (OR=2.54). This is explained by the high content of N-nitroso compounds (NOC) and NOC precursors. The study value is limited, as it is a hospital-based case-control study of diet and by the low number of cases (73 glioma patients). A study conducted in California in 1997 among women with gliomas, also demonstrated a correlation between cured meat and an increased risk of gliomas, risk that was reduced by consumption of vegetables (62). Vegetable intake also decreased risk in another large cohort study (63).

Two recent studies have shown that high coffee and tea intake are inversely correlated with glioma risk (64, 65). The first one reflects data from three independent cohort studies. Tea (more than five cups a day) and coffee reduced the risk for glioma (RR=0.60, 95% CI 0.41-0.87). No association was found between decaffeinated coffee and risk of glioma, suggesting that caffeine has protective effects. In the second study, high coffee and tea intake (>100ml/day) were both associated with a significant lower risk for glial tumors.

Vitamin intake, especially vitamins A, D and E was correlated with a lower risk for gliomas, both in population and experimental studies. Both food and supplement vitamins had this effect (61, 62, 66). Retinoids, compounds related to vitamin A, have a significant anti oncogenic effect (66). Alfacalcidol, a vitamin D analog also has anti proliferative effects on glioma cell cultures (67). Tocopherols (vitamin E) also exert anti oncogenic effects on glioma cells (66). Dietary minerals, especially calcium and zinc, have protective effects against tumors, including gliomas (68, 69). No correlation between acrylamide, present

in several heat-prepared foods and glioma risk was found by a study (70).

Obesity and an increased body mass index (BMI) have been proven to be risk factors for gliomas in at least four studies (60). Obesity and its direct consequences, hyperglycemia and type 2 diabetes mellitus, were also found to be independent risk factors for a poor outcome in patients with HGG (71,72) while an increased BMI didn't influence survival in another study (73).

Caloric restriction may have an important role in improving outcome for gliomas (74). This is based on the fact that while normal glial cells can adapt their metabolism, tumor cells cannot do the same. Dietary restriction reduced angiogenesis in a orthotopic mouse brain tumor model and also in human glioma cultures (75, 76). Also normal nervous cells can use ketone bodies for energy, while tumor cells are highly dependent on glycolysis (77). This is the rationale for using a high-fat, low-carbohydrate diet (ketogenic diet) as adjuvant therapy for gliomas (77). The ketogenic diet also enhanced the anti-tumor effect of radiation in a study (78). Caloric restriction with glucose withdrawal could cause phosphorylation of AMP-activated protein kinase (AMPK), and this may cause apoptosis in astrocytoma cells but not in normal cells under similar energy stress (79).

There is no certain evidence linking alcohol or smoking to an increased risk for gliomas. This is due to the small number of cases in different studies, the incomplete research hypothesis and deficitary patient selection (80). In the Melbourne Collaborative Cohort study, alcohol was associated with the risk for developing

gliomas in a dose-response relation (81). But an older study from some of the members of the same team did not reveal any link between alcohol usage and gliomas (82). A study by DeVito and all, showed that ethanol inhibited the stimulation of ICAM-1 (an adhesion molecule) by TNF- α (83). ICAM-1 is an important molecule in the neuroimmune response, and its inhibition by ethanol, could explain a lower response of the CNS to injury, including gliomas (83).

In a cohort study, Efirid and his team found an increased risk for gliomas in smokers, marijuana consumers, and coffee drinkers (>7 cups/day) (84). A study on a population of 22.946 icelanders, also found smoking as a risk factor of cancer for all sites, except endometrium (85). Multiple studies did not find any relation between smoking and glioma risk (82, 86-88), while others have mixed conclusions (89). Alcohol and cigarette smoking are not currently considered to be risk factors for malignant brain tumors (90). A review of studies concerning marijuana smoking and risk for cancer did not find any increase in the risk for gliomas (91), but some studies support the hypothesis of cannabinoids as an effective adjuvant therapy (92, 93).

Allergies, atopic conditions, infections, other disease, medication

Allergies have clearly been indicated by most studies regarding this subject, as protective conditions against gliomas (94-101). In a meta-analysis published in 2011, by Chen and coworkers, that included 12 studies, authors conclude that allergies could significantly decrease the risk of gliomas (102). Moreover, some studies have shown that, the number of allergies for a patient is directly proportional with a smaller risk (98, 101). In a study risk

decreased with 31-45% for every new atopic condition (98). Antihistamine usage was not correlated with this risk (101). In most studies the levels of IgE, an objective assessment tool for allergic conditions, correlated with the risk for glioma. The risk increased inversely with the levels of IgE (100, 103-105). It seems that function of immune cells is altered in patients with GBM, in the sense that instead of preventing tumor appearance, immunity mechanisms support it (106). sCD23, a soluble marker, part of the humoral immune system, that enhances inflammatory response, is lower in GBM patients than controls (107). sDC14 that inhibits inflammatory response, is higher in GBM group vs. controls (107). Two subtypes of Interleukin (IL)-4 and IL-3 were also associated with GBM, and OR for GBM were opposite of the ones for asthma (108). In a study, GBM patients having high levels of IgE survived 9 month longer, than those with normal levels (109). Autoimmune disease were also inversely correlated with GBM, in one study (OR=0.49, 95% CI= 0.35-0.69), the most significant being diabetes (96). Another study showed that patients reporting a previous infectious disease had a RR of 0.72, 95% CI 0.61-0.85 of developing GBM (95).

Until now some viruses of the Polyoma family, like BK virus, simian vacuolating virus 40 (SV40) and especially JC virus (JCV), have been proven to have oncogenic effect for GBM in experimental conditions (110). JCV proved oncogenic effect for malignant brain tumors in test animals. IgG antibodies to the capsid of JCV, proved to increase OR for developing GBM to 1.46, CI=0.61-3.5 in a group of patients (111). IgG for varicella zoster was inversely

correlated with glioma and some studies reported multiple HCMV gene products in glial tumors when compared to normal tissue (5). VZV IgG levels were more common in glioma cases vs. controls in another study (OR=0.68, 95% CI= 0.41-1.13)(112).

Another condition investigated for a possible connection with HGG was epilepsy. A study found a 6-fold increase of risk for glioma in patients suffering from epilepsy in the last 2 years prior to diagnostic (95). The risk was highest for epilepsy for 20 years or less prior to diagnostic, although epilepsy > 20 years still had a higher risk. The Interphone Group also found a high risk of gliomas in patients with epileptic seizures (99). The authors conclude that seizures suggest a long preclinical evolution of gliomas, since they did not create two separate groups for low or high grade tumors.

A family history of cancer could be a risk factor for developing brain tumors. A study found that risk of gliomas increases 1.4-3.4 fold familial history is positive for stomach, colon, prostate or Hodgkin disease cancers (113). The authors found no connection between glioma risk and a family history of brain tumors. However a study from Sweden found an increased risk for gliomas for people who had a parent suffering from this disease (114). A family history of brain tumors also increased risk for oligodendrogliomas in a mixt Scandinavian-US pooled analysis of 7 case-control studies (115).

Non-steroidal anti-inflammatory drugs (NSAID) were correlated with a lower risk for developing GBM. In a study by Sivak-Sears and all, GBM cases reported a smaller use of NSAIDS than controls (116). The findings were strongest for aspirin and ibuprofen. Another case-control study

found a 33% lower risk for GBM in those reporting a regular use of NSAID (117). The authors failed in showing which NSAID had this effect. The influence of NSAID on gliomas, could be explained by the fact that they inhibit prostaglandins, inflammation mediators, that have a potential oncogenic effect (116). Angiogenesis, a vital tumor growth process, is linked to cyclooxygenase-2 driven inflammation, and this enzyme is irreversibly blocked by aspirin for example (116).

TABLE II

Medical conditions and relation to glioma risk

Condition	Relation to glioma risk	No. of ref.
Allergies	Decreased risk	94-101
Increased IgE levels	Decreased risk	100,103-105
Autoimmune disease	Decreased risk	96
Polyoma virus infections	Increased risk (experimental)	110
Epilepsy	Increased risk	95,99
NSAID consumption	Decreased risk	116, 117

Occupation and environment factors

Determining a relation between a certain occupation and the risk for brain tumors is difficult. In most professional areas, workers are exposed to more than one possible risk factor (3). It is hard to determine what is the total risk determined by all these factors together. For example, even if a certain chemical is proven to be an oncogenic agent, it's interaction with other elements, could increase or decrease risk (3). Moreover, chemicals that have been proven to favor tumor genesis, had that effect on lab animals, where they were directly implanted. Their effect through another type of contact (touching,

inhalation) could be different (3). All these things make it difficult to link certain professional factors with the risk of brain tumors.

A case-control study from Germany, did not find any association between a certain occupational field and the risk for developing gliomas. Authors studied six occupational sectors -chemical, agricultural, transport, electric/electronic, construction, metal- but found no significant risk in any profession (118). In the San Francisco Bay Area, physicians, surgeons, artists, foundry and smelter workers and petroleum and gas workers were at a higher risk for gliomas (119). A possible explanation is that health practitioners have raised access to diagnostic procedures that could explain some of the higher incidence (119). This is no longer a plausible factor because the access and quality of diagnostic procedures have increased dramatically. Also, medical staff has contact with a large number of agents, i.e. disinfectants, biological agents, radiation, that could lead to an increased risk (119). Parental work in agriculture, motor-vehicle related, electric domain determined an increased incidence in children in another study (120). This association was valid for both parents, while work in the textile industry was true only for mothers. A retrospective research found a positive association between children gliomas and father exposure to lead, cleaning solvents, pesticides from lawn care, during pregnancy period or immediately after birth (121). It must be noted that this study only took into consideration exposure resulting from hobbies, not occupational.

Exposure to pesticides was largely investigated as a risk factor for cancers. Phenoxy herbicides were proven as a cause for malignant lymphoma and soft-tissue

sarcoma (122). A hospital-based, case-control study did not prove any association between insecticides or herbicides and gliomas, although women exposed to herbicides were at a much larger risk of developing meningiomas than those that were not exposed to these substances (123). Opposite results were obtained in a retrospective study from India, which showed that gliomas were much more frequent in orchard workers, residents or children playing in orchards that were exposed to numerous chemicals (chlorpyrifos, dimethoate, mancozeb and captan) for more than 10 years (124). A study of residents of rural zones from several US regions also proved that not washing or changing clothes immediately after applying pesticides constitutes a risk factor for developing gliomas (125). Occupational exposure did not increase risk of gliomas instead it determined a higher risk of meningiomas (126). A study noted a higher incidence of gliomas in professionals of the following domains: IT, farm workers, financial, medicine, management, while it found a decreased incidence in childcare workers (127). A possible link between gliomas and physiological stress was also investigated, and found that major life events in a 5 years period prior to diagnostic, constituted a risk factor (128). Studies trying to find a connection between sociodemographic variables and gliomas found mixed or inconclusive results (129).

Head trauma

An association between trauma and brain tumors has not yet been clearly demonstrated. Although that there are some reports of a positive association, the relation is either non-significant or inconsistent (4). Associations have been made between perinatal or adult head trauma or combined

perinatal and adult head trauma (4). In a study OR for gliomas following any head injury was only 1.2 (95% CI 0.9-1.5) in men, and lower for females (130). In a Danish cohort study, that included patients hospitalized for concussion, fractured skull or any other head trauma, the incidence of gliomas was the same as for the general population (131). Several authors reported cases that indicated head trauma as the cause of gliomas and its influence needs to be further investigated (132).

Other suspected risk factors

There have been several sporadic studies investigating potential risk factors for gliomas. Use of hair dye could increase the risk of bladder and hematopoietic cancers, but no association was found with glioma (133). High birth weight (>4000g) was associated with an increased risk for astrocytoma, and this risk was 19% higher for every 1000g (134). Birth anomalies or season of birth were not associated with an increased risk for glial tumors (135).

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