# Risk Factors of Glioblastoma Multiforme

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Glioblastoma multiforme (GBM) is one of the most aggressive malignancies and also the most common malignant primary tumor of the brain and central nervous system, accounting for 14.5% of all central nervous system tumors and 48.6% of malignant central nervous system tumors. The median overall survival (OS) of GBM patients is low, at only 15 months.

glioblastoma multiforme | risk factor | Smoking | head injury | alcohol use | electromagnetic radiation

## 1. Tobacco Smoking and Nitrosamines

Cigarette smoking has not been clearly linked to an increased risk of developing Glioblastoma multiforme (GBM)[1][2] and glioma [1][2][3]. Because of the mixed findings, further attempts to establish a correlation or lack thereof are desirable, especially because cigarette smoke is a proven risk factor for the development of malignancies in certain organs. Cigarette smoke mutagens, such as tobacco-specific nitrosamines (TSNAs) and polycyclic aromatic hydrocarbons (PAHs), penetrate the blood–brain barrier [4], which may potentially affect the development of central nervous system tumors [5]. Considerable scientific evidence also points to the carcinogenic effect of TSNA in causing malignancies of the lung, pancreas, esophagus, and oral cavity. The most recent International Agency for Research on Cancer (IARC) monograph did not classify the nervous system as an organ in which carcinogenesis is caused by tobacco products [5].

Nitrosamines can originate from cigarette smoke, but also from the reaction of nitrates and nitrites used in meat products—hams, bacon, and sausages. N-nitrosodimethylamine (NDMA) is one of the most common nitrosamines in food [6][7][8]. NDMA is a potent carcinogen capable of inducing cancer in animal models [9]. Nitrates present in food entering the digestive system are absorbed into the blood and then secreted into the saliva. Following ingestion, they are passed into the stomach, where they are converted to nitrosamines in an acidic environment [10]. A study of patients diagnosed between 1987 and 1991 in Israel found that N-nitroso compounds were not directly linked to brain tumors [11].

In a study by Michaud et al. [12], neither the group consuming the most processed meat products nor the nitrate-exposed group had an increased risk of glioma (RR: 0.92; 95% CI: 0.48, 1.77 and RR: 1.02; 95% CI: 0.66, 1.58, respectively).

A meta-analysis by Saneei et al. [13] included data from 18 observational studies and found no association between the consumption of processed red meat and increased incidence of glioma.

## 2. Race/Ethnicity

There is a limited association between specific ethnic groups and the risk of developing GBM. Ostrom et al. [14] reported a 2.97 times higher incidence of GBM in Caucasians compared to Asians, and a 1.99 times higher incidence in Caucasians compared to African Americans.

A 2006 study by Fukushima et al. [15] compared mutations found in primary GBM in a Japanese group with mutations found in the Swiss group described by Ohgaki et al. [16]. The results of the study by Fukushima et al. [15] suggest high molecular similarity of GBM, despite the different genetic backgrounds of Asians and Caucasians.

## 3. Ionizing Radiation

Ionizing radiation is a recognized risk factor for many cancers. Direct damage to genetic material or the generation of free radicals in the vicinity of DNA strands results in an increased incidence of mutations within the genetic material of cells. Since controlled clinical trials on the effects of radiation on carcinogenesis are not feasible for ethical reasons, case–control studies play a major role in describing this phenomenon. Ron et al. [17] already in 1988 linked doses of 1–2 Gy to an increased risk of neuronal tumors. A review by Bowers et al. [18] in 2013 documented an 8.1–52.3 times increased risk of central nervous system cancer after radiotherapy to the head for a CNS tumor in childhood compared to the general population, proportional to dose.

Most studies on the relationship between computed tomography (CT) and the risk of glioma development in children have not shown an increased risk, apart from a study describing one excess brain tumor per 10,000 patients over a 10-year period after exposure to one CT scan [19].

## 4. Head Injury

Because of the described anecdotal cases of CNS tumors (not just GBM) being diagnosed after head trauma, further studies on head trauma as an etiologic factor of brain tumors have been conducted, with mixed results. Unfortunately, the available research is quite limited. Proving a causal relationship is very difficult in this case [20]. In a study on the Danish population, gliomas were not diagnosed more frequently in patients after head injury—the standardized incidence ratio (SIR) after the first year was 1.0 for glioma (CI = 0.8–1.2) compared to the general Danish population. Tumors detected during the first-year period were not considered due to the detection of incidental lesions already existing during the trauma [21]. A study conducted in 1980 showed an increased odds ratio (odds ratio = 2.0, $p$ = 0.01) in women compared with the control group in the incidence of meningiomas following head trauma [22]. In contrast, a case–control study evaluating the incidence of meningiomas and gliomas after head injury documented a higher risk of meningiomas, but a lower risk of gliomas (OR = 1.2, 95% CI: 0.9–1.5

for any injury; OR = 1.1, 95% CI: 0.7–1.6) [23]. Potential problems with the study may include the use of diagnostic methods using ionizing radiation, which is a proven risk factor for cancer, and potential problems with recalling past injuries and the non-standardized assessment of their extent.

## 5. Obesity

Adipose tissue has many functions in the human body. In addition to storing nutrients in the form of fats, it has a secretory role, for example, secreting estrogens [24] and pro-inflammatory substances [25][26]. For these reasons, it may have a potential impact on the development of cancer, including GBM.

Low body weight (BMI < 18.5 kg/m$^2$) at age 21 is associated with a lower risk of developing gliomas later in life, although the results were only statistically significant in the group of women [27]. Moore et al. [28] found that patients who were obese at age 18 (BMI 30.0–34.9 kg/m$^2$) had nearly four times the risk of developing gliomas compared to those who had a BMI of 18.5–24.9 kg/m$^2$ at age 18 (RR = 3.74; 95% CI = 2.03–6.90; *p* trend = 0.003).

In the study by Kaplan et al. [11], increased fat and cholesterol consumption was inversely related to the incidence of glioma (high fat intake OR = 0.45, 95% CI 0.20–1.07; high cholesterol intake: OR = 0.38, 95% CI 0.14–1.01). Cote et al. [24] observed an inverse relationship between hyperlipidemia and glioma.

A study on a group of patients diagnosed between 1987 and 1991 in Israel found a relationship between the occurrence of gliomas and meningiomas and a protein-rich diet (OR = 1.94, 95% CI 1.03–3.63) [11]. Wiedmann et al. [29] did not observe an increased risk of glioma in overweight or obese individuals.

Seliger et al. [30] described a decrease in the risk of GBM in people with diabetes (OR = 0.69; 95% CI = 0.51–0.94). The decrease in risk was most pronounced in men with more than 5 years of disease or with poor glycemic control (HbA1c ≥ 8). In contrast, the effect of lower GBM risk was absent in women (OR = 0.85; 95% CI = 0.53–1.36).

## 6. Growth

Although a tall stature is associated with a higher incidence of certain cancers [31][32], the exact mechanism of this phenomenon has not been explained. It is likely that the insulin-like growth factor (IGF) and growth hormone (GH) pathways, which determine growth and final height in humans, are involved. The IGF concentrations peak at puberty and then decline in the third decade of life [33]. More than 80% of GBM tumors overexpress insulin-like growth factor binding protein-2 (IGFBP-2), one of the biomarkers of GBM malignancy [34][35]. In less aggressive tumors, IGFBP-2 is usually undetectable and appears with tumor progression [36].

In the paper published by Moore et al. [28], the risk of developing glioma among tall people (over 190 cm) was twice as high as that among people less than 160 cm tall (multivariate relative risk [RR] = 2.12; 95% confidence interval [CI] = 1.18–3.81; *p* trend = 0.006). In contrast, a study by Little et al. [26] did not link adult height to the risk of developing glioma.

## 7. Metals

The International Agency for Research on Cancer (IARC) lists cadmium, cadmium compounds, chromium compounds, and nickel compounds as human carcinogens, with lead as a potential carcinogen. None of these have been found to be associated with brain tumors. The ability of some heavy metals to penetrate the blood–brain barrier and to enter through the olfactory nerve pathway [37] prompts a closer examination of their effects on the risk of GBM.

A study conducted in 1970 examining job-exposure matrix (JEM)-based exposures to individual metals did not observe an increased risk of glioma in relation to occupational exposure to chromium, nickel, or lead among 2.8 million male workers (*n* = 3363 cases of glioma).

Parent et al. [38] reported an increased incidence of glioma associated with occupational exposure to arsenic, mercury, and petroleum products. However, they did not report an increased OR for glioma for welders exposed to lead, cadmium, or welding fumes [38]. Lead may also induce oxidative stress and disturbances in energy metabolism, induce apoptosis, and affect certain signaling pathways [38][39][40][41][42]. A meta-analysis by Ahn et al. [43] reported an increased risk of malignant brain tumors associated with lead exposure (pooled OR = 1.13, 95% CI: 1.04–1.24). Rajaraman et al. [44] observed no relationship between lead exposure and glioma risk.

Bhatti et al. [42] examined the potential carcinogenicity of lead by analyzing the modification of single-nucleotide polymorphisms (SNPs) within genes functionally related to oxidative stress. The study included 494 controls, 176 GBM patients, and 134 meningioma patients who were evaluated for occupational lead exposure. *Rac family small GTPase 2* (*RAC2)* and *glutathione peroxidase 1* (*GPX1)* gene polymorphisms significantly modified the relationship between cumulative lead exposure and GBM risk.

## 8. Nutritional Factors, Chemicals, and Pesticides

Brain tissue necrosis associated with GBM invasion leads to the release of triglycerides and may be accompanied by the release of toxins co-stored in phospholipid-rich neural tissue [45].

In a 1992 study using data from the Canadian National Cancer Incidence Database and Provincial Cancer Registries, Morrison et al. [46] found a statistically significant relationship between the risk of death from GBM and increased exposure to fuel/oil emissions (test for trend $p = 0.03$, RR for highest-exposure quartile was 2.11, 95% confidence interval = 0.89–5.01). They further suggested inverse associations of cholesterol and fat consumption with brain tumor risk, which they described as inconsistent with other studies [11].

In a study on T98G and U138-MG GBM cells, researchers attempted to determine the cytotoxic or proliferative effects of chemical compounds. The proliferative effect occurred only for the T98G line with perfluorodecanoic acid (PFDA), perfluoroacetate sulfonate (PFOS), and testosterone. However, perfluorinated salt (ammonium

perfluoroacetate) and dehydroepiandrosterone (DHEA) showed no proliferation-stimulating effect, suggesting that the proliferative effect is not mediated by androgen receptor activation.

An in vitro study subjected the U87 GBM cell line to long-term exposure to low doses of a mixture of pesticides (chlorpyrifos-ethyl, deltamethrin, metiram, and glyphosate). Exposure resulted in the development of resistance to chemotherapeutics (cisplatin, telosomide, 5-fluorouracil, among others) and increased expression of ATP-binding cassette (ABC) proteins [47].

Kuan et al. [48] reported weak or null associations between food groups, nutrients, or dietary patterns and glioma risk. They found no trends of decreasing glioma risk with increasing intake of total fruit, citrus fruit, and fiber, and a healthy diet.

## 9. Coffee and Tea

Coffee and tea may have potential cancer-protective effects. The presence of antioxidants, such as polyphenols, caffeic acid, diterpenes (including kahweol and cafestol), and heterocyclic compounds [49][50][51][52], could explain the molecular basis for this finding. A study by Kang et al. [52] reported the inhibition of GBM cell growth in vitro after exposure to caffeine by the inhibition of inositol trisphosphate receptor subtype 3. Polyphenol (2)-epigallocatechin-3-gallate restores the expression of methylated (silenced) genes in cancer cells, including MGMT, a protein with a DNA repair function [53]. Huber et al. [54] described elevated MGMT protein levels in rat livers after exposure to Kahweol and Cafestol (diterpenes).

Studies on the effects of coffee and tea on glioma risk are inconclusive. Holick et al. [55] reported an inverse relationship between caffeine consumption and glioma risk among men, but not among women. In contrast, in a cohort of 545,771 participants, Dubrow et al. [56] found no reduction in glioma risk with increased coffee and tea consumption. However, in a full multivariate model, there was an almost statistically significant inverse relationship between the highest level of tea consumption (three cups per day) and glioma risk (HR = 0.75; 95% CI, 0.57–1.00).

In a more recent study on a British population cohort (2,201,249 person-years and 364 GBM cases), Creed et al. [57] observed an inverse relationship between tea consumption and glioma risk that was statistically significant for all gliomas, and for GBM in men. In the same year, Cote et al. [58] published a paper using data from the Nurses' Health Study (NHS), Nurses' Health Study II (NHSII), and Health Professionals Follow-Up Study (HPFS) (6,022,741 person-years; 362 cases of GBM).

Michaud et al. [59] observed a statistically significant inverse relationship between coffee intake and glioma risk in a group consuming 100 mL or more of coffee or tea per day compared to a group consuming less than 100 mL of coffee or tea per day. Based on the six studies included in the meta-analysis, Malerba et al. [60] suggested no association between coffee or tea consumption and the risk of glioma, but their work had limitations due to the small number of papers analyzed.

## 10. Alcohol Use

Alcohol can cross the blood–brain barrier and, therefore, can affect glial cells; in addition, it is a recognized risk factor in multiple cancers [61]. The metabolism of alcohol (at higher concentrations in the body) produces acetaldehyde and reactive oxygen species that have toxic effects on cells; acetaldehyde has been shown to be neurocarcinogenic in animals [62]. Additionally, alcoholic beverages contain N-nitroso compounds that cause brain tumors in animals [62][63][64]. Despite this, the study by Qi et al. [65] based on 19 meta-analyses reported no association between glioma incidence and alcohol consumption. These observations were confirmed by a recent study by Cote et al. [66], who even indicated that low to moderate alcohol consumption may reduce the risk of glioma.

## 11. Sleep and Melatonin

Samatic et al. [67] noticed that sleep duration is not linked with the risk of glioma. Oreskovic et al. [68] reported that there are mechanisms of pro-tumor effects of sleep disorders, including phase shifts, decreased antioxidant levels, immunosuppression, metabolic changes, melatonin deficiency, cognitive impairment, or epigenetic changes. All of these changes significantly affect the poorer prognosis of patients with malignant brain tumors and are potential exacerbating factors for tumor progression. In addition, the occurrence of a brain tumor contributes to sleep disorders.

Lissoni et al. [69] evaluated the effects of melatonin co-treatment in patients with GBM undergoing radical or adjuvant radiotherapy. They observed that the patient survival percentage of the RT and melatonin group was significantly higher than that of the RT alone group (6/14 vs. 1/16 patients).

Cutando et al. [70] reported that melatonin administration reduces the incidence of malignant tumors in vivo and increases the survival time of patients with GBM treated by radiotherapy. A study by Martin et al. [71] showed that melatonin sensitizes human malignant glioma cells against TRAIL-induced cell death. Furthermore, the melatonin/TRAIL combination significantly increases apoptotic cell death compared to TRAIL alone. A study by Zheng et al. [72] confirmed the anti-glioma function of melatonin to be mediated partly by suppressing glioma stem cell (GSC) properties through EZH2-NOTCH-1 signaling.

## 12. Inflammation

Even in a healthy body, gene mutations can lead to tumorigenesis and GBM. Numerous mechanisms are in place to offset these processes so that altered cells are effectively destroyed by the immune system before tumor formation [73][74]. Even when a tumor forms, the immune system can destroy it at an early stage. A molecular mechanism that facilitates this process is inflammation [75]. Chronic inflammation, on the other hand, can facilitate tumor formation [76] by damaging DNA, resulting in mutations and tumorigenesis [76][77]. Additionally, chronic inflammation triggers mechanisms that can inhibit an otherwise robust immune system response [78] and thus inhibit the immune system from fighting newly formed cancer cells. For this reason, the factors that trigger this

physiological state will increase susceptibility to cancer. Some of the best-studied inflammation-related factors involved in GMB are tumor necrosis factor α (TNFα) and interleukins 1 and 6 (IL-1 and IL-6).

Tumor necrosis factor α (TNFα) is a soluble cytokine involved in directing the systemic inflammatory response [79]. It can exert antitumor effects on glioma cells, but can also enhance tumor progression. TNFα can facilitate angiogenesis by increasing epidermal growth factor receptor (EGFR) activity [80]; it induces immune cell suppression through the activation of the NF-κB and STAT3 pathways [81], and decreases the expression of the tumor-suppressor gene PTEN in glioma [82]. TNFα is involved in reduced macrophage infiltration, suggesting that TNFα plays a suppressive role by demonstrating the ability to promote tumorigenesis [83]. Since abnormal epidermal growth factor receptor EGFR signaling is widespread in GBM, EGFR inhibition seemed to be a promising therapeutic strategy. However, EGFR inhibition in GBM causes a rapid upregulation of TNFα, which in turn leads to the activation of the JNK-Axl-ERK signaling pathway involved in resistance to EGFR inhibition [84]. A study showed that TNFα induces the upregulation of angiogenic factors in malignant glioma cells, which plays a role in RNA stabilization [85]. This confirms that TNFα in GBM cells may play an important role in tumor progression.

Interleukin 1 (IL-1) is a potent inducer of proangiogenesis and proinvasion factors, such as VEGF, in human astrocytes and glioma cells. IGF2 induction [86][87] is strongly stimulated by IL-1 in astrocytes [88]. IL-1 is also a major inducer of astrocyte/glioma miR-155, a microRNA involved in inflammation-induced cancer formation [89]. The specific microRNA (miR-155) targets cytokine signaling suppressors, potentially leading to the overactivation of STAT3, a transcription factor important in glioma progression.

IL-1α has been implicated in cancer pathogenesis, but there is little evidence of its role in GBM. To date, its function has been shown to be both pro- and anti-tumor in various cancer types [90]. IL-1α secretion by tumor cells causes the constitutive activation of NF-κB, which results in the expression of genes involved in the cascade of metastatic processes and angiogenesis [91].

GBMs have been shown to produce large amounts of IL-1β, which plays a key role in glioma aggressiveness and survival. IL-1β is a major pro-inflammatory cytokine that triggers a number of tumorigenic processes by activating various cells to upregulate key molecules involved in oncogenic events. Elevated levels of IL-1β have been observed in cultures of GBM cell lines [92] and in samples from human GBM tumors [93]. IL-1β receptor (IL-1R) is found in GBM cells and tissues [94]. The binding of IL-1β to IL-1R activates a cascade of NF-κB and mitogen-activated protein kinase (MAPK) signaling pathways [95]. IL-1β-induced ERK activation can also have mitogenic effects on human glioma U373MG cells and significantly increase GBM cell proliferation [96]. IL-1β-dependent activation of the NF-κB, p38 MAPK, and JNK pathways in GBM cells also leads to increased expression of VEGF, which promotes angiogenesis, migration, and invasion [97]. In addition, IL-1β-mediated up-regulation of factor HIF-1 [98] is involved in molecular responses to hypoxia, which is a key component of GBM progression.

The glioma environment is subject to chronic inflammation, and IL-6 is one of the cytokines strongly associated with the chronic inflammatory phenotype often associated with GBM. Tumor-associated macrophages make up a large majority of noncancerous cells in tumors and are major producers of IL-6 [99]. Interleukin 6 (IL-6) has been

shown to be a factor involved in the malignant progression of glioma [100]—it promotes regeneration, invasion, and angiogenesis. In glioma, the elevated expression of IL-6 and its receptor is associated with poor patient survival [101]. IL-6 promotes tumor survival by suppressing immune surveillance through the recruitment and stimulation of tumor-associated myeloid-derived suppressor cells and neutrophils. This paralyzes the response of surrounding type-1 helper T cells and cytolytic T cells, ultimately leading to T cell dysfunction and the inhibition of tumor cell clearance. IL-6 is specifically involved in GBM as the stimulation of brain tumor cells by IL-6 promotes three major signal transduction pathways involved in gliogenesis—(1) p42/p44-MAPK, dysregulated in approximately one-third of all cancers and strongly involved in the detection and processing of stress signals [102]; (2) PI3K/AKT, a signaling pathway associated with enhancing angiogenesis, activating the EMT transition to increase invasion, and promoting metastasis [103]; and (3) JAK-STAT3, a pathway that blocks tumor recognition by immune cells and promotes cell cycle progression and the inhibition of apoptosis [104].

## 13. Electromagnetic Radiation

With the popularization of electronic devices, such as microwave ovens and cell phones, the impact of exposure to electromagnetic waves and the risk of developing CNS tumors became a controversial topic. The impact of phones on tumor development remains inconclusive due to the mixed results from studies, the relatively short time since the prevalence of smartphones, and the numerous confounding factors in the research.

Today, people are commonly exposed to radio-frequency electromagnetic fields (RF-EMF) (30 kHz–30 GHz) through electronic devices, such as cell phones, cordless phones, radios, and Bluetooth. These devices are located in close proximity to users so that even low-power transmitters are not precluded from potential effects on health. The specific RF energy absorption rate (SAR) of the most common source, mobile telephones, is influenced by many factors, such as the design of the device, the position of the antenna in relation to the user's head, the anatomy of the user's head, how the phone is held, and the quality of the connection between the cell phone and the network station. A working group [105] in 2011 concluded that, despite the high risk of error in the available studies, the potential carcinogenic effects of RF-EMF cannot be ruled out.

A pooled analysis of Swedish case–control studies of people who had used cell phones for more than 25 years was conducted by Hardell and Carlberg [106], showing that the OR of developing glioma was 3.0 (95% CI: 1.7–5.2). In contrast, Villeneuve et al. [107] suggested that the lack of increase in glioma incidence rates with the increasing popularization of cell phones supports the lack of a causal relationship.

In a study published in 2010 [108], a group who used a cell phone at least once a week over a six-month period had a lower risk of developing glioma than the group who never used a cell phone (OR = 0.81 (95% CI: 0.70–0.94)), but the most exposed (10th decile (≥1640 h)) in terms of cumulative exposure had a 40% higher risk of developing glioma (OR = 1.40, 95% CI = 1.03–1.89). This indicates the possible presence of confounding factors, study biases, and suboptimal selection of study participants.

In studies on the effect of cellphone use on the survival of GBM patients, Olsson et al. [109] did not report any reduced OS compared to those who did not use cell phones regularly.

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