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Modulation of glioma risk and progression by dietary nutrients and anti-inflammatory agents

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Abstract

Gliomas are tumors of glial origin formed in the central nervous system and exhibit profound morphological and genetic heterogeneity. The etiology of this heterogeneity involves an interaction between genetic alterations and environmental risk factors. Scientific evidence suggests that certain natural dietary components, such as phytoestrogens, flavonoids, polyunsaturated fatty acids and vitamins may exert a protective effect against gliomas by changing the nature of the interaction between genetics and environment. Similarly, certain anti-inflammatory drugs and dietary modifications, such as methionine restriction and the adoption of low-calorie or ketogenic diets, may take advantage of glioma and normal glial cells' differential requirements for glucose, methionine, and ketone bodies and may therefore be effective as part of preventive or treatment strategies for gliomas. Treatment trials of glioma patients and chemoprevention trials of individuals with a known genetic predisposition to glioma using the most promising of these agents, such as the anti-inflammatory drugs curcumin and gamma-linolenic acid, are needed to validate or refute these agents' putative role in gliomas.

Keywords

glioma; glioblastoma; prevention; diet; vitamins

INTRODUCTION

The etiology of human gliomas implicates a complex combination of known and unknown environmental risk factors and cancer-predisposing constitutive genetic alterations that ultimately result in abnormal proliferation and malignant transformation of glial cells (1). Previous exposure to high-dose ionizing radiation is the only proven environmental risk factor for brain tumors (2). There is also experimental evidence that genetically determined increased sensitivity to radiation is an independent risk factor for gliomas (3). The incidence of malignant gliomas could be potentially reduced by either preventing gliomas from forming or preventing low-grade gliomas from developing into high-grade gliomas (4). The hypothesis that genetically determined sensitivity to other environmental carcinogens may

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contribute to the pathogenesis of these tumors, while logical in its construct, is not yet strongly supported by scientific evidence.

What are the plausible environmental factors that might, under appropriate circumstances, modify the risk of acquiring a glioma or of having a glioma progress from low grade to high grade? Previous studies have indicated that vitamin supplements provide a protective effect against gliomas, with increased protection resulting from increasing frequency of use (5). Dietary factors (6,7), especially those that add to the total body burden of oxidants (8), may be implicated in the development of cancers such as gliomas. It has been suggested that a glioma's degree of aggressiveness can be modulated by dietary interventions and that some phytochemicals with antioxidant properties participate in that process (9). In addition, as with other cancers, inflammatory or infective processes may contribute to the development and possible aggressiveness of gliomas (10–12). Thus, it is possible that medications and natural compounds found in spices and herbs that have anti-inflammatory properties may likewise mitigate glioma malignancy. In this review, we profile the most important natural dietary constituents and anti-inflammatorydrugs that have been proposed to either reduce or increase the risk of glioma development and progression and discuss how modification of their intake may affect the prevention or treatment of gliomas (Table 1).

VITAMINS

Vitamins A, C, D, and E and their derivatives may have anti-cancer properties and may modulate gliomagenesis. In this section, we specifically discuss the in vitro and in vivo evidence pointing to these effects.

Retinoids

Retinoids are chemical compounds related to vitamin A. They strongly inhibit the proliferation and migration of cells in primary cultures of human glioblastoma multiforme but not in established cell lines, probably because the two types of cells have different retinoid receptor expression patterns (13). Retinoic acid (RA) up-regulated RA receptor (RAR)-alpha and RAR-beta mRNAs, but only RAR-beta proteins, in glioma cell lines, suggesting that RA conferred its effects at a post-transcriptional level (14). The RA-induced growth inhibition in glioma cells may arise, at least in part, through alterations in the epidermal growth factor (EGF) receptor and its structure (15). Clinical phase 2 trials of isotretinoin (13-cis-retinoic acid) have shown that RA has activity against glioblastoma (16,17). However, results with all-trans retinoic acid (ATRA) were not as successful in clinical phase 2 trials (18). Nonetheless, a combination of ATRA and interferon-gamma could control the growth of both PTEN-proficient and PTEN-deficient glioblastoma cells by arresting cell division and inducing differentiation and apoptosis (19).

In addition, glioblastoma cell lines and fresh glioblastoma tissue samples, but not normal human glial tissue, expressed high levels of peroxisome proliferator-activated receptor-gamma (PPARγ). In addition, the PPARγ ligand pioglitazone, induced apoptosis and inhibited proliferation of glioblastoma cells; these effects were associated with downregulation of bcl-2 and upregulation of bax proteins (20). An enhanced effect was observed when pioglitazone and ATRA were combined, suggesting that these ligands may possess an additive therapeutic effect for patients with glioblastoma (20).

The synthetic retinoid N-(4-hydroxyphenyl) retinamide (4-HPR or fenretinide) is in clinical trials for the treatment of several malignancies. It was shown that fenretinide induces apoptotic cell death in human glioma and medulloblastoma cells *in vitro*, in part by activating caspase-3-dependent cell death (21); this effect could be partially blocked by the antioxidant l-ascorbic acid, suggesting that free-radical intermediates might be involved in

fenretinide's effects (22). Similar results were reported for ATRA (23). Unfortunately, fenretinide was not active in a phase 2 study of patients with recurrent high-grade gliomas (24).

Vitamin C

In one study, ascorbyl stearate, a lipophilic derivative of ascorbic acid (or vitamin C), had antiproliferative and apoptotic effects on T98G glioma cells, probably through modulation of IGF-IR expression and consequent facilitation of programmed cell death (25). Further studies, both *in vitro* and *in vivo* are needed to further examine if vitamin C has any role in glioma prevention or treatment.

Vitamin D

Vitamin D receptor has important effects not only on physiological processes related to Ca^{2+} metabolism but also on cell growth and differentiation. Vitamin D receptor mRNA levels have been reported to be significantly higher in glioblastomas than in both low-grade and anaplastic astrocytomas (26), and there is *in vitro* evidence that vitamin D metabolites alone or in combination with retinoids may be potentially useful agents in the differentiation therapy of human malignant gliomas (27). The effects of vitamin D metabolites on brain tumor cells may be at least partially independent from the activation of the classic nuclear receptor pathway and are possibly mediated through the sphingomyelin pathway (28).

The secosteroid 1,25-dihydroxyvitamin D3 $1,25(OH)_2D_3$ is the major biologically active metabolite of vitamin D. Evidence suggests that $1,25(OH)_2D_3$ has a cytotoxic effect on rat and human glioma cells (29). *In vitro* studies of the effect of several vitamin D3 analogues on glioma cell growth have suggested that $1,25(OH)_2D_3$ analogues such as KH 1060, EB 1089, or CB 1093, alone or in combination with other therapeutic approaches, could have the potential to treat brain glial tumors. The vitamin D3 effect seems to be mediated by apoptosis (30). *In vitro* evaluation of the apoptotic potential of a representative set of vitamin D analogues, each of them in the 3alpha and 3beta conformations, and of natural vitamin D metabolites in the rat C6 glioma cell line, demonstrated that the 3alpha epimers showed equivalent or even higher activity than their respective 3beta forms, suggesting that these 3alpha epimers would have advantages over the 3beta epimers (31). However, further studies in the rat glioma cell line C6.9 showed that noradrenaline and the beta-adrenoceptor agonist isoproterenol inhibited $1,25(OH)_2D_3$-induced apoptosis and that the beta-adrenoceptor antagonist propanolol reversed this inhibition. These findings suggest that the efficiency of antiproliferative vitamin D-related therapies could be influenced by endogenous levels of noradrenaline (32). Furthermore, changes in the DNA methylation pattern could suppress $1,25(OH)_2D_3$-mediated apoptosis via expression of hypermethylated genes, such as proto- oncogenes, with death-repressor activity (33).

Alfacalcidol, a vitamin D analogue able to bind to nuclear receptors regulating mitotic activity, was tested in 11 patients in a phase 2 trial involving surgery or biopsy, radiotherapy, chemotherapy with teniposide-lomustine or fotemustine, and alfacalcidol at a daily dose of 0.04 mcg/kg for the treatment of malignant gliomas. Three of the 11 patients (27%), 2 with glioblastomas and 1 with a grade III astrocytoma, exhibited a response, consisting of progressive regression of the lesion on radiographic imaging, with a decrease of the gadolinium-enhanced area, and complete clinical remission, observed for 7, 5 and 4 years, respectively. These results suggest that alfacalcidol may be able to induce in some patients with malignant gliomas durable remissions when combined with classical surgery-radiotherapy-chemotherapy regimens (34).

Vitamin E

Studies on the effects of several tocopherols (the most abundant/common of which is vitamin E) on the proliferation and death of murine glioma C6 cells demonstrated that gamma-tocopherol was an effective inhibitor of cell cycle progression, leading to lowered expression of cyclin E and cyclin-dependent kinases 2 and 4 and overexpression of p27. This cytostatic effect suggests a possible chemopreventive role for vitamin E in gliomas (35). No in vivo studies or clinical trials have expanded on this premise, however.

FATTY ACIDS

Both n-6 and n-3 polyunsaturated fatty acids are dietary fats important for cell function and possibly supportive of tumorigenesis. One study found that levels of the polyunsaturated fatty acid docosahexaenoic acid were significantly reduced and of the n-6 polyunsaturated fatty acid linoleic acid were significantly increased in glioma tissue compared to control samples, indicating that the fatty acid composition of human gliomas differs from that of nonmalignant brain tissue (36). In addition, conjugated linoleic acid, found in ruminant meat (beef and lamb) and dairy products, was shown to exert antineoplastic activity *in vitro* (37). Further *in vitro* studies showed that gamma-linolenic acid (GLA), a major ingredient in borage oil, induced apoptosis of tumor cells without harming normal cells by increasing levels of free radicals and lipid peroxides, decreasing the expression of the oncogenes *Ras* and *Bcl-2*, and enhancing the activity of *p53* (38). Unexpectedly, the anti-oxidant vitamin E blocked the tumoricidal action of GLA. In three open-label clinical studies, intra-tumoral injection of GLA significantly reduced the size and number of glioma lesions without causing any significant side effects (39). Furthermore, GLA enhanced the radiosensitivity of astrocytoma tumor cells but not normal astrocytes *in vivo* (40), suggesting that it may be suitable to consider using GLA for adjunctive therapy of gliomas and/or to prevent glioma recurrence in high-risk patients whose cancer is in remission. To date, however, neither use of GLA has been tested.

CALCIUM, COPPER, AND ZINC

Calcium may exert a protective effect against gliomas through induction of apoptosis, DNA repair, or other mechanisms. A comparison of the consumption of calcium and other dairy components and dairy foods (cholesterol, fat, protein, calories, milk, and cheese) between 337 astrocytic glioma case patients and 450 healthy controls in the San Francisco Bay Area Adult Glioma Study, 1991–1995, showed a statistically significant inverse association between dietary calcium intake and glioma incidence for women but not men. Since increased levels of circulating estradiol in women stimulate intestinal absorption of calcium, this may account for the lower incidence of gliomas in women consuming greater amounts of calcium in foods and supplements (41).

Penicillamine is an oral agent used to treat intracerebral copper overload in Wilson's disease. The copper ion, a co-factor of angiogenesis, is sequestered in human brain tumors and the adjacent normal brain tissue and may be involved in glioma invasion. Animal experiments indicated that copper depletion inhibited the infiltrative spread of the normally invasive 9L gliosarcoma (42–44). However, a clinical study in 40 patients with newly diagnosed glioblastoma multiforme who received a low-copper diet and escalating doses of penicillamine along with radiation therapy failed to demonstrate that a reduction of serum copper levels improved survival rates (45).

Zinc is a trace metal important to the function of many enzymes in the body, some of which have a role in DNA and RNA synthesis (46–48). As a result, body levels of zinc might be expected to have a role on glioma and other cancer cells. In one population-based case-

control study of 637 patients diagnosed with a glioma or meningioma and 876 controls in the UK, zinc intake was found to have no significant effect on the risk of glioma or meningioma (49).

ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-inflammatory drugs (NSAIDs) can suppress the growth of various malignancies by inhibiting cyclooxygenase-2 (*COX-2*) enzyme activity. *In vitro* studies have revealed that aspirin strongly inhibits the growth of rat glioma (RG 2) cells in concentrations used in medicine for rheumatic diseases (50). NSAIDs may also inhibit the growth of glioblastoma multiforme cells through *COX-2*-independent mechanisms, such as up-regulation of the key prostaglandin catabolic enzyme 15-hydroxyprostaglandin dehydrogenase (15-PGDH) and the cell cycle inhibitor *p21* (51). NSAIDs such as indomethacin, acetaminophen, and sulindac sulfide inhibited C6 rat glioma cell proliferation (52). Moreover, the effect was more potent when indomethacin-loaded nanocapsules and indomethacin ethyl ester-loaded nanocapsules were used (53). In addition, indomethacin inhibited the invasion of gliomas by downregulating the expression of matrix metalloproteinase (MMP)-2, MMP-9 (54), and laminin (55). Furthermore, indomethacin enhanced the cytotoxic effects of doxorubicin and vincristine in T98G human malignant glioma cells; this effect was associated with inhibition of the multidrug resistance-associated protein (MRP) (56). Epidemiologic studies have reported that the regular use of NSAIDs is associated with a 33% reduction in the risk of glioma, suggesting possible antitumor activity (11).

While one cannot always draw inferences about one cancer from observations in another, in light of NSAIDs' effects on glioma cells, it is worth considering the impressive reported effects of sulindac and alpha-difluoromethylorinithine (DFMO) in the treatment of malignant colon polyps (57). In this randomized trial, the combination of sulindac and DFMO reduced the number of malignant colon polyps formed by 92%? Or please explain nature of the improvement] in a high-risk population. Since DFMO has shown activity against gliomas as a single agent and in combination with cytotoxic drugs (58,59), it is not unreasonable to expect that DFMO and sulindac might help to maintain remissions in glioma patients. On the other hand, since DFMO does not cross the intact blood-brain barrier well, its use will require that gliomas treated have permeability greater than normal brain (60–62).

DIET AND LIFE STYLE FACTORS INCREASING RISK

In addition to the dietary factors discussed earlier, some effort has been made to understand other dietary factors and the total body burden of oxidants (6,7) on the development of brain tumors. A population-based study of 94 women with intracranial gliomas and 94 individually matched controls in Los Angeles County found that dietary sources of nitroso compounds, such as cured meats like bacon, may be important in the development of gliomas (63). Similarly, another population-based case-control study in southwest Germany in 1987–88 involving 115 glioma patients and 418 randomly selected controls found that a higher than average intake of processed meat, especially cooked ham, processed pork, and fried bacon, was significantly associated with an increased risk of glioma (64). Although tobacco products are major contributors of exogenous N-nitroso compounds, there is consistent evidence that cigarette smoking is not associated with an appreciably elevated risk of adult glioma (65).

In a small prospective study to determine the relationship between processed meat consumption and risk of primary malignant brain tumors there was a suggestion of a dose-response trend, with increasing consumption of processed meat leading to increased risk in

men. Specifically, consuming three or four servings per week of processed meat was associated with increased glioma risk compared to no or low consumption for men but not for women (66). Another population-based case-control study of 416 adults with gliomas and 409 age- and sex-matched controls conducted in Melbourne, Australia, between 1987 and 1991 reported an increased odds ratio (OR) for glioma in males who consumed high levels of bacon, corned meats, apples, melons, and oil and decreased ORs in men consuming cabbage and cola drinks and women consuming whole-grain bread, pasta, corned meat, bananas, cauliflower, broccoli, cola drinks and nuts. Elevated ORs for glioma in men, but not women, were associated with the intake of N-nitroso dimethylamine, retinol, and vitamin E (67). A hospital-based case-control study in northeast China showed that consumption of fresh vegetables such as cabbage and onions, fruits, fresh fish, and poultry was inversely related to the risk of developing brain cancer (68). While vitamin E and calcium exerted a protective effect, the study reported, the consumption of salted vegetables and salted fish increased risk (68).

A population-based case-control study of adults with glioma in Nebraska evaluated the effects of exposure to nitrates in utility-supplied drinking water over a 20-year period and found that the nitrate levels present did not significantly increase glioma risk (69). A meta-analysis of nine epidemiological studies also showed that the available data do not provide clear support for the suspected causal association between ingestion of N-nitroso compounds from cured meat in adults and subsequent brain tumor risk, suggesting that uncontrolled confounding may have accounted for the previously noted positive association seen in some epidemiological studies (70). Thus, there is no conclusive evidence that consumption of N-nitroso compounds from cured meats increases the risk of glioma development.

DIET AND LIFESTYLE FACTORS MITIGATING RISK

Epidemiological studies have suggested that dietary flavonoids found in oranges, tangerines, lemons, and grapefruit--in particular, quercetin--may play a beneficial role by preventing or inhibiting tumorigenesis. *In vitro* studies showed that quercetin decreased the proliferation and viability of U138MG human glioma cells while exerting a cytoprotective effect in normal cell cultures (71). In addition, grapefruit is very high in levels of exogenous polyamines that are important polycations required for DNA and RNA function (72–74).

Studies examining fruit and vegetable consumption and risk of glioma have reported inconsistent results. The incidence of glioma was inversely related to the intake of dark yellow vegetables and beans, but no association was seen between glioma risk and dietary sources of nitrosamines or high-nitrate vegetables (75). Overall, there was a significant inverse association between the risk of adult glioma and dietary intake of pro-vitamin A carotenoids, alpha-carotene, beta-carotene, and fiber from beans. However, there was no significant association between risk of adult glioma and intake of nitrate, nitrite, vitamin C, vitamin E, saturated fat, cholesterol, dietary fiber from grain products, or fiber from fruit and vegetables (75). A prospective study that examined the relationship between consumption of fruit and carotenoids and the risk of glioma among men and women in 3 large US cohort studies--the Health Professionals Follow-Up Study and the Nurses' Health Studies I and II--found that fruit, vegetable, and carotenoid consumption is not likely associated strongly with the risk of adult glioma (76).

In rodent models of glioma, methionine restriction in combination with chloroethylnitrosoureas resulted in lengthened survival. Chronic depletion of plasma methionine in experimental animals could result in regression of high-grade gliomas, probablybecause these tumors require high amounts of methionine to maintain a state of active proliferation (77). Similar results were obtained by other investigators: methionine

deprivation and methionine analogues inhibited cell proliferation and growth of human xenografted gliomas (78). A phase 1 clinical trial of dietary methionine restriction in association with chloroethylnitrosourea (cystemustine) treatment for patients with recurrent glioma or metastatic melanoma demonstrated the feasibility and tolerability of the association of a methionine-free diet and cystemustine treatment, and a phase 2 clinical trial has been initiated to test the activity of this regimen (79). Methionine depletion resulted in a decrease of O6- methylguanine-DNA methyltransferase (MGMT) in the peripheral blood mononuclear cells of patients treated with cystemustine, suggesting that methionine-induced regulation of MGMT activity may serve as a mechanism for an anti-glioma effect (80). A later report indicated that methionine depletion had the potential to enhance the antitumor effects of chemotherapeutic agents in chemotherapy-resistant tumors such as gliomas (81).

The diet-derived isothiocyanate iberin, a bioactive agent in Brassicaceae species, inhibited growth of glioma cells in proliferation assays, enhanced cytotoxicity, and induced apoptosis by activation of caspase-3 and caspase-9, indicating potential usefulness in the prevention of brain tumors (82).

Curcumin (diferuloylmethane), is found in the spice turmeric and has been known for its anti-inflammatory activity for hundreds of years. Extensive research has indicated that curcumin can regulate numerous transcription factors, cytokines, protein kinases, adhesion molecules, reactive oxygen species, and enzymes that have been linked to inflammation (83). Since the process of inflammation may play a role in neoplastic disease, curcumin it may have a role in the prevention of proinflammatory states that precede cancer. Curcumin has been shown to have direct effects on glioma cells by affecting apoptosis (84–86), the MMPs and invasion (87,88), and cell cycle arrest (84,89). While curcumin has limited use in gliomas, it has generated much interest in prevention trials for several other cancers (90–97).

OXIDATIVE STRESS

In contrast to brain tumor cells, which lack metabolic flexibility and are largely dependent on glucose for growth and survival, normal brain cells can metabolize both glucose and ketone bodies for energyModerate dietary restriction of total food and caloric intake without causing nutritional deficiencies may shift the tumor microenvironment from proangiogenic to antiangiogenic (98). In addition, the effect of restricting dietary caloric intake by 40% in experimental animals resulted in decreased vascularity(as determined by testing for factor VIII) and increased apoptosis (as determined by terminal deoxynucleotidyl transferase-mediated nick end labeling) in all tumors (99). Further studies by the same group of investigators indicated that caloric restriction may activate AMP-activated protein kinase (AMPK), a known physiological cellular energy sensor, which becomes phosphorylated in response to changes in cellular ATP levels. Thus, energy stress induced by glucose withdrawal caused more ATP depletion, AMPK phosphorylation, and apoptosis in glioma cells than in normal astrocytes. These results suggest that use of an AMPK activator in combination with a glycolysis inhibitor may be an effective therapy for treating malignant astrocytoma (100).

Studies of two children with gliomas who were placed on a ketogenic diet showed that blood glucose levels declined to low-normal levels, blood ketones were elevated 20- to 30-fold, and there was a mean 22% decrease in glucose uptake at the tumor site, as shown on PET. One patient exhibited significant clinical improvements in mood and new skill development and stabilization of her disease for 12 months (101). A study demonstrated that KetoCal, a nutritionally balanced high-fat/low-carbohydrate ketogenic diet, has antitumor and antiangiogenic effects in experimental mouse tumors (99). The therapeutic effect of KetoCal for brain cancer management was due largely to the reduction of total caloric content, which

reduced the circulating glucose required for rapid tumor growth. This preclinical study thus indicates that restricted KetoCal is a safe and effective diet therapy, but a large randomized study showing benefit in malignant brain cancer is needed before it can be considered an alternative therapeutic option (102).

Studies to date suggest that a starvation-based differential stress resistance strategy has the potential to maximize chemotherapy's differential toxicity to normal and cancer cells and enhance its efficacy against gliomas (103). The antioxidant and weak estrogenic properties of dietary phytoestrogens may attenuate oxidative stress, which mayplay a role in adult glioma formation. A study that evaluated the long-term consumption of dietary antioxidants and phytoestrogens, such as genistein, daidzein, biochanin A, formononetin, matairesinol, secoisolariciresinol and coumestrol, yielded data supporting an inverse association between glioma occurrence and a higher dietary antioxidant index and a higher intake of certain phytoestrogens, especially daidzein (7).

CLOSING REMARKS

In this paper we highlight potential research areas of various dietary and nutraceutical approaches that might prevent gliomas or reduce their rate of transformation to a higher grade (figure 1). Certain natural dietary components - such as phytoestrogens found in soy and flavonoids found in oranges, lemons, grapefruits, and dark yellow vegetables--may exert a protective effect against gliomas. Similar effects may result from pro-vitamin A carotenoids and beans. Methionine restriction may modulate MGMT activity and polyamine activity and may be useful for the therapy of gliomas when combined with chemotherapy. Since glioma cells depend mainly on glucose for survival, in contrast to normal glial cells, which can also utilize ketone bodies, ketogenic diets and overall calorie restriction may be an adjunct to other treatment modalities for gliomas. Anti-inflammatory drugs, curcumin, retinoids, and certain polyunsaturated fatty acids such as GLA (found in borage oil) may exert antineoplastic activity against gliomas without harming normal cells. Certain vitamin D3 analogues and calcium may be proven either therapeutic or preventive agents for gliomas. These agents could be tested in individuals or families with a genetic predisposition to glioma and patients with gliomas as adjuncts to standard therapies (figure 1).

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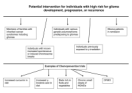

Figure 1.
Potential chemoprevention for gliomas. Inherited cancer syndromes with gliomas include the Li-Fraumeni syndrome (119), melanoma-astrocytoma syndrome (120,121), neurofibromatosis 1 (122) and 2 (123), Turcot's syndrome (124,125) and BRCA syndrome (126). The various studies describing the individuals with increased chromosome breaks and genetic polymorphisms predisposing to gliomas have been recently reviewed (1). NSAIDs: non steroidal anti-inflammatory drugs; DFMO: alpha-difluoromethylorinithine.

Table 1

Natural dietary components or derivatives and anti-inflammatory drugs with potential benefit in prevention and treatment of gliomas

Dietary component or derivative	Foods in which it is found	Mode of action	Potential prevention	Potential treatment	Human studies
Pro-vitamin A (α-carotene, β-carotene)	Carrots, spinach	Differentiation	Yes	Unknown	Case-control study (75)
Retinoic acid and fenretinide	Oxidized form of vitamin A	Differentiation (19), Modification of EGF-receptor (15), apoptosis (19,22,23)	Unknown	Yes	Phase 2 trial (104) Case report (105)
Vitamin D analogues and metabolites	Fish, mushrooms, milk, cereal	Differentiation (27), apoptosis (30), DNA methylation (33)	Unknown	Yes	Phase 2 trial (34)
Vitamin E derivatives	Sunflower seeds, almonds, olives, papaya	Cytostatic effect (35)	Yes	Unknown	No
Ascorbyl stearate (lipophilic derivative of vitamin C)	Additive in various foods	Apoptosis (25)	Unknown	Unknown	No
Conjugated linoleic acid	Meat, dairy products	Apoptosis (36,37,40)	Yes	Yes	Review of 3 open-label clinical studies (39,106,107)
gamma-linolenic acid	Borage oil				
Calcium	Dairy products, cabbage, broccoli	Apoptosis, DNA repair	Yes	Unknown	Case-control study (41)
Nitrosamine	Cured meats (bacon, ham, pork)	Known carcinogen	Yes, with lower intake	No	Case-control studies (63,64,66,67)
Flavonoids: quercetin	Oranges, lemons, grapefruits, onions	Decrease proliferation and viability of glioma cells; protect normal cells (71)	Yes	Unknown	No
epicatechin	Dark chocolate				
Methionine restriction	Sesame seeds, Brazil nuts, meat, fish	Higher requirement for methionine by glioma (78,108) Decrease in MGMT activity (80)	Unknown	Yes, in combinati on with chemother apy (57,59)	Phase 1 trial (79)
Isothiocyanate iberin	Cabbage, broccoli, cauliflower	Apoptosis	Yes	Unknown	No
NSAIDs: indomethacin, aspirin, acetaminophen, sulindac		Upregulation of 15-PGDH and p21 Downregulation of MMP-2, MMP-9 (51) (54) and laminin (55) Inhibition of the MRP (56)	Yes	Suggested	Only epidemiologic studies (11)

Dietary component or derivative	Foods in which it is found	Mode of action	Potential prevention	Potential treatment	Human studies
Curcumin (diferuloylmethane)	Spice turmeric	Anti- inflammatory action (61) (regulation of transcription factors (109–111), cytokines, redox status (112), enzymes (88,113)) Apoptosis (84–86,114–117) Autophagy (84,118) Anti-invasion (87,88) Cell cycle arrest (84,89)	Yes	Unknown	Yes in other cancers (90–97), but not in gliomas
Ketone bodies	Ketogenic diets	Differential requirement for energy of glioma and normal glial cells	Unknown	Yes (98–100,102)	Case report (101)
Phytoestrogens (genistein, daidzein, biochanin A, formnonetin, matairesinol, secoisolariciresinol, coumestrol)	Soy, cereal, legumes	Antioxidant	Yes	Suggested (103)	Case-control study (7)

15-PGDH: 15-hydroxyprostaglandin dehydrogenase; MRP: multidrug resistance-associated protein; EGF: epidermal growth factor; MMP: matrix metalloproteinase