

Review

Season of Birth and Risk for Adult Onset Glioma

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Received: 6 January 2010; in revised form: 4 February 2010 / Accepted: 11 February 2010 /

Published: 28 April 2010

Abstract: Adult onset glioma is a rare cancer which occurs more frequently in Caucasians than African Americans, and in men than women. The etiology of this disease is largely unknown. Exposure to ionizing radiation is the only well established environmental risk factor, and this factor explains only a small percentage of cases. Several recent studies have reported an association between season of birth and glioma risk. This paper reviews the plausibility of evidence focusing on the seasonal interrelation of farming, allergies, viruses, vitamin D, diet, birth weight, and handedness. To date, a convincing explanation for the occurrence of adult gliomas decades after a seasonal exposure at birth remains elusive.

Keywords: gliomas; farming; allergies; handedness

1. Introduction

Gliomas are a heterogeneous group of neoplasms in terms of cellular origin and location. They represent the most common malignant brain tumors [1]. Despite considerable efforts to unravel the etiologic basis for this cancer and attempts to find a cure, gliomas largely remain refractory to treatment. Except for a small percentage of cases, the tumors continue to show high morbidity and mortality. Established risk factors include ionizing radiation and a few genetic syndromes [2]. However, the attributable risk for these factors is small and can only explain a fraction of cases.

Evidence of an association between adult-onset glioma and date of birth suggests an etiologic role for a seasonally variable environmental exposure occurring prenatally around the time of birth. The period between an environmental exposure and the appearance of cancer may be lengthy, as illustrated

by the development of vaginal cancer in daughters years after their mothers used diethylstilbestrol (DES) during pregnancy [3]. Similarly, exposure to asbestos 70 years prior to the development of mesothelioma [4], suggests a “one insult, co-carcinogenic model” of cancer development [5]. Risk factors that may exhibit seasonal epidemicity include exposure to infectious agents, allergens, pesticides, indoor environmental tobacco smoke, and other sources of polycyclic aromatic hydrocarbons (e.g., soot from fires for home heating), and use of antihistamines. Other putative candidates include harmonic variation in population mixing, diet, temperature, humidity, sunlight/photoperiod, levels of vitamin D3, and endogenous hormones [6,7].

The origins of many childhood and adult malignancies are believed to be determined during a finite perinatal window. During this period the brain and immune systems are less developed, undergoing greater cell growth and differentiation, and possibly more susceptible to DNA and epigenetic changes underlying cancer development in the near or distant future [5,8-13]. In this model, environmental exposures and lifestyle changes that occur afterwards play a mainly secondary role to the programming or imprinting that occurs during pregnancy and/or early infancy [14,15].

2. Methods

2.1. Search Strategy

Articles were identified by systematically searching the Medline/PubMed database from inception to January 2010 using the key words: brain tumors and season of birth. Furthermore, we manually examined the bibliography of the papers that were identified electronically. We also searched for unpublished studies, PhD dissertations, internal reports, and conference proceedings/abstracts. Finally, to make our search inclusive of those studies in which season of birth was a secondary factor we checked the tables of every article known to us that examined risk factors for brain tumors. A similar process was used to identify papers on risk factors related to season of birth.

2.2. Inclusion Criteria

Studies were included only if the target population, outcome and exposures of interest were clearly defined and results were based on valid statistical methodology with evaluation of errors and discussion of study bias. Studies in which participants were chosen at convenience were not considered in this review. In the case of a cohort appearing in the literature multiple times only the most recent version was included since it provided the largest number of cases and the longest follow-up. Priority was given to papers that presented original data rather than reviews or meta-analyses.

3. Review of Literature

Several recent studies have explored season of birth as a risk factor for adult glioma, but results have been mixed (Table 1). Three independent reports have observed a peak risk for winter births [16-18], while no seasonal variation for risk was noted in two other epidemiologic studies [19,20]. A multi-centered study of four Midwest states examining rural and farm exposures observed a statistically significant increased risk of adult gliomas for springtime births, but only among those born “off” a farm [21]. Similarly, the study of childhood brain tumors and season of birth have yielded equivocal results [22-26].

Table 1. Summary of studies on season of birth and adult glioma risk.

Reference, Year, Country	Study design	Cases (M = Male, F = Female)	Referents	Risk estimates and/or p-values	Comments
Brenner, <i>et al.</i> 2004 U.S.A [16]	Case-referent	Low-grade glioma, n = 135. High-grade glioma, n = 354. 63% of the low-grade gliomas were oligo-dendroglioma, astrocytoma, or mixed gliomas. 86% of high-grade gliomas were glioblastoma or anaplastic astrocytoma. M/F ratio = 1.3. Mean age = 52yrs.	Frequency matched (by hospital, age, sex, race, ethnicity, and distance of residence from hospital), n = 799.	Sinusoidal test of periodicity, $\chi^2 = 6.1$ (2df), p = 0.04. Risk peaked in February and troughed in August (OR = 1.5, CI not provided).	Incident cases. Hospital-based referents. Adjustment by education, marital status, place of birth, handedness, birth order, and history of allergy or auto immune disease did not change results. Excluding different diagnostic subgroups of referents from the analysis did not materially change the estimated parameters of the periodic function.
Efird 2009 U.S.A. [21]	Case-referent	Primary intracranial gliomas, n = 797.	Frequency matched within state of current residence to cases (2:1 to projected number of cases) by age and sex, n = 1,174.	Sinusoidal logistic regression model. All participants, peak day = 169, p = 0.0469. Born “on” farm, peak day = 283, p = 0.1579. Born “off” farm, peak day = 150, p = 0.0049. GBM, peak day = 146, p = 0.1456. Non-GBM, peak day = 187, p = 0.0603.	Adjusted for age, sex, and state of residence. Population-based controls. Participants were not asked about handedness.
Houben, <i>et al.</i> 2005 The Netherlands [20]	Tumor registry cases to all cancer patients comparison.	Pilocytic astrocytoma, n = 37. Other astrocytoma, n = 1,064. Oligodendroglioma, n = 131. Other glioma, n = 234. 59.5% males. Median age = 52yrs. Age range = 0–92yrs.	Monthly births adjusted to all cancer patients registered by the cancer registry.	Edward’s test for sinusoidal variation, p < 0.05.	Hospital-based referent population. Adults analyzed together with children.

Table 1. Cont.

Koch, <i>et al.</i> 2006 Germany [17]	Tumor registry to population cases comparison.	Glioblastoma, n=299M, 202F. Mean age (\pm SD) = 57.1 \pm 14.2 yrs.	Population normalized monthly births	Circannual cosinor model, $r^2 = 0.34$, $p < 0.05$. Maximum frequency of births was found in Jan. Monthly mean birth freq = 127.9 (SEM = 7.1).	Analysis not adjusted for age, sex. Did not specify the reference years of the birth rates used for normalization of the observed incidence data.
Mainio, <i>et al.</i> 2006 Finland [18]	Surgical record cases to population census comparison.	Grade I-II glioma, n = 9M, 10F. Grade III-IV glioma, n = 14M, 8F. Meningioma, n = 7M, 26F. Pituitary adenoma, n = 5M, 3F. Acoustic neurinoma, n = 4M, 3F. Other, n = 0M, 6F. Mean age (\pm SD), F = 49.4 \pm 11.5 yrs., M = 49.4 \pm 11.5 yrs.	Monthly births in the general population over the years corresponding to the entire range of year of births of the brain tumor patients (born in the years 1915–1971).	Observed to expected ratio = 1.3 (95%CI = 1.01–1.77). Comparison: December–February to March–November. Winter trough of births reported for low-grade glioma (adj. ratio = 0.4, CI not provided).	Risk only separately reported for low-grade gliomas. Excluded cases not surgically treated.
Staykov, <i>et al.</i> 2009 Germany [19]	Tumor registry cases to population census comparison.	Mixed glioma, n = 46M, 32F. Ependymoma, n = 48M, 51F. Other glioma, n = 34M, 17F. Anaplastic astrocytoma, n = 122M, 99F. Pilocytic astrocytoma, 15M, 8F. Other astrocytoma, n = 138M, 97F. Glioblastoma, 805M, 560F. Oligodendroglioma, 52M, 50F. Mean age (\pm SD), M = 54 \pm 14, F = 54 \pm 14.	Monthly births for the years 1931 to 1986 (except 1944) in the general Bavarian population.	Roger-test of seasonality, $p=0.54$ F, $p=0.11$ M. The estimated peak-trough ratio of glioma in persons born in the month with the greatest number of cases compared to month with lowest number was 1.07 in M (95%CI=1.00-1.25) and 1.16 in F (95%CI=1.00-1.39).	Incident cases. Data not analyzed separately by low- and high-grade glioma. The analysis of time trends in the distribution of monthly births adjusted for length of month revealed a pronounced absolute maximum of monthly births in February and March prior to 1965, which has gradually decreased in prominence during the subsequent decades. Analysis not adjusted for handedness, education level, or history of allergy/autoimmune disease.

4. Risk Factors Related To Season of Birth

The underlying rationale for the occurrence of a glioma decades after a seasonal exposure remains elusive. No specific etiologic agent to date has been identified to support such a long induction period for this cancer. Several hypothetical arguments have been offered in explanation of a season of birth effect for adult gliomas, if such an association exists. Thus far, the major evidence in support of a seasonal effect involves farming, allergies/immunity, viruses, and vitamin D. Other possible factors related to seasonal birth are diet, birth weight, and handedness.

4.1. Farming

Farming, by virtue of its seasonal nature, conveys increased risk at certain times of the year of exposure to pesticides and other agricultural chemicals. Insecticides and herbicides constitute the bulk of farm chemical exposures: two key routes of exposure are dermal and respiratory [27], bypassing detoxification in the liver. Many farm chemicals are classified as probable or likely human carcinogens by the US Environmental Protection Agency (EPA), most notably acephate, dichlorvos, dimethoate, lindane, parathion, phosmet, and tetrachlorvinphos [28].

Indoor exposures to these agents frequently occur [29,30]. Parents and other individuals track dust and dirt into the home, on shoes and clothes, after working on the farm. Household dust concentrations of azinphosmethyl, chlorpyrifos, parathion, and phosmet have been found to be significantly higher in farmer or farmworker homes than in referent homes [29]. Similarly, indoor-outdoor pets are efficient carriers of agents into the home, and also pose an exposure source for pesticides from anti flea/tick collars, sprays, and shampoos. Homes with high pet activities have been shown to have greater levels of pesticide residues in sampled carpet dust than homes with low pet activities [31,32]. Airborne farm pollutants also may enter the home environment by way of the wind, after spraying, gassing, or open-air application. Newborn and infant children have greater contact with these contaminants since they lie, crawl and play near the ground and frequently place their hands, objects or food in their mouths [29,33,34].

In tandem with living on a farm, infants have unique vulnerabilities that may lead to higher levels of exposures in the same environment than adults [9]. For example, their skin surface area is comparatively larger and more permeable to lipophilic compounds, which serves to maximize the absorption of compounds such as pesticides into the bloodstream [35-37]. Dryness, rashes, and related skin conditions, to which infants may be particularly susceptible, serve to disrupt the protective barrier of the skin [36,38]. Once in the circulatory system, compounds enter the brain of the infant relatively quickly as the blood-brain barrier is not fully operational until at least 6 months of age [10].

At birth, children are less able to detoxify chemicals and other inorganic substances commonly used on farms [33,34], and they tend to have higher concentrations in their blood due to a decreased capacity to bind plasma protein [35]. They drink more water and eat more foods per unit of body weight than adults and will therefore ingest more toxins from well water and agriculturally treated foods [33,34]. Furthermore, they are more sensitive to airborne chemicals since their resting air intake is about twice that of an adult [34]. The commonly used organophosphate pesticide chlorpyrifos

(CPF) is known to specifically target the immature brain, from the early embryonic stage to the postweaning period, and it causes a host of irreversible changes to developing brain cells [39]. (Pesticides also are used outside the farm in urban schools, homes, and day-care centers for control of roaches, rats, and other vermin, and conceivably their peak period of application may differ seasonally from that on farms [33,40].)

While farmers live longer than the population-at-large [41], and die less frequently from cancer in general [42], several epidemiologic studies have found an increased risk for brain cancer in this group [43-50]. Farmers represent a diverse group (e.g., with dairy, field crop, hog, beef cattle, poultry, fish, marijuana, cotton, and organic), and the heterogeneity of brain cancer risk for farmers could reflect differences in activities, as well as in the type, magnitude, and seasonality of exposures.

4.2. Allergies and Immunity

The perinatal period represents a time of heightened sensitivity to environmental allergens [51,52]. Within this window the peak for immune system priming or susceptibility is believed to vary differentially in response to presenting antigens [53,54]. Contact with allergens during early childhood may enhance the risk of developing allergies later in life, especially in individuals with a predisposition for atopic and allergic conditions [51,55].

Efforts to reduce allergen exposure immediately after birth often only delay the onset of allergic conditions, rather than preventing it, suggesting that immunologic memory may predate birth [15]. While genetics constitute a key determinant of immunologic memory and immune system maturation [56-58], environmental factors also are believed to play an important role in the development of allergies, as illustrated by the discordance of allergies in twin studies [59], the increasing prevalence of atopic diseases over time [15,60], and the different incidence of allergies in immigrant and country of origin populations [61].

In a number of studies, season of birth has been associated with the development of allergic conditions later in life, such as asthma [61-65], atopic dermatitis [66], house dust mite allergy [60,61,65,67-69], cockroach allergy [70,71], grass/birch/hay and other pollen allergy [51,60,63,67, 68,72-76], animal dander allergy [51,67], mold allergy [74], food allergy [51,55,67], allergic rhinitis [62,77], and otherwise unspecified atopy (NOS) [55,78]. In the case of cockroach sensitivity, over 60% of inner-city residents with asthma test positive for cockroach allergen [79], with black children and those receiving public assistance most likely to be sensitized [70]. The rate of cockroach sensitization at the age of 5 years was higher for winter births (72%), than for spring (48%), summer (42%) and fall (43%) births [70].

Factors known to influence the development of asthma include race [80,81], low yearly family income [81], less than a high school education [81], residence in high poverty areas [81], exposure to urban air pollution [64] and childhood viral infections [64,82]. A significant percent of infants with a history of respiratory syncytial virus (RSV) bronchiolitis infection, which peaks during the winter season, develop asthma [64].

Asthma, allergies, and other atopic diseases have been inversely associated with adult glioma risk in several epidemiologic studies and meta-analyses [83-93], although some reports do not support

this conclusion [94-98]. The exact biologic mechanisms underlying a protective effect are not clearly understood. It has been suggested that the inverse association may reflect increased immune surveillance on the part of the atopic individual [91,93]. Glioma patients are known to suffer from an impaired immune system [99], and the reduced association with allergies alternatively could be due to immunosuppression induced by the tumor (*i.e.*, reverse causality) [84]. Inflammatory responses also may favor tumor development [93]. In animal studies, therapeutic immunity to intracranial tumors has been induced by peripheral immunization with interleukin-4 (IL-4) transduced glioma cells [100,101].

Being raised on a farm [102-114] or in a rural area [115] has been shown in some studies to protect against asthma, hay fever, and atopic sensitization. Although farm children are exposed to higher concentrations of airborne allergens, paradoxically they become sensitized less often and manifest a weaker sensitization response than non-farm controls [113]. Some researchers have hypothesized that the protective effect may be attributed to a form of “tolerance”. Such tolerance could conceivably develop early in life, following repeated exposure to high levels of allergens such as organic dusts, fungi, and endotoxins; this is perhaps the result of component lipopolysaccharides that excite Th1 responses and suppress the development of immunoglobulin-E (IgE)-antibodies [109,116].

Little is known about specific determinants of asthma and atopy in the farm setting. Any relationship with glioma risk is probably complex and must be interpreted in light of differences in farming practices and the protective ability of farming environments, especially with respect to microbial exposures [102,103,114]. While farmers and their families have greater contact with seasonal elements, they may be less prone to “sick building syndrome” than residents of urban areas [117]. The latter tend to live and work in a more closed indoor environment and thus suffer greater exposure to indoor pollutants (e.g., polychlorinated biphenyls, phthalates, phenols, flame retardants) [29]. Other mitigating factors may include a greater intake of saturated fat in the form of milk and butter, as well as a greater number of older siblings living at home in rural/farm communities [116]. Furthermore, farmers usually are non-smokers and healthier than the population-at-large [43,116,118-120]. By self-selection, those who manifest seasonal allergies may choose a career path other than farming (*i.e.*, healthy worker effect) [116].

Differences in the definition of atopy, a lack of objective measures of atopy, residual confounding, and bias (e.g., detection, selection, interview, recall) are important to consider when interpreting the above studies [92,121]. Furthermore, regarding the role of allergies and immunity, there is no clear trend toward a decreasing risk for glioma with younger ages at onset of the allergic condition [121].

Interestingly, increased risk for glioma has been observed in patients with AIDS-related immunosuppression [122-124], but not in those with iatrogenic immunosuppression [125].

4.3. Viruses

Environmental exposures to viruses, microbes and other pathogens generally tend to occur more often in particular seasons [25,126,127]. Polyomaviruses have been shown to induce brain tumors in animals [128-131] and have been detected in human gliomas [132]. Other neuro-oncogenic viruses

implicated in gliomas under laboratory conditions include human adenovirus type 12 and Rous sarcoma virus [133]. Some tumor viruses must be injected in animals on the first day of life to be effective, although they may not cause cancer until years later [7].

Epidemiologic evidence in support of a viral or pathogenic etiology for adult brain tumors remains controversial and the windows of interest of these studies have been outside the perinatal period. In adults, *Toxoplasma gondii* infection has been associated with a greater prevalence of astrocytomas [134], while decreased glioma risk has been associated with a history of infections/colds [88], and chicken pox [135,136]. On the other hand, increased risk for childhood brain tumors has been associated in some studies with a history of chicken pox [137], influenza [138,139], measles [138], general viral infections [140,141], and neonatal urinary tract infections [141]. In particular, a 7.5-fold OR (95% CI = 1.3–44.9) for low grade astrocytoma has been observed for neonatal urinary tract infections [141]. Bacterial urinary tract infections have been shown to follow a well defined seasonal pattern with a peak in August [127]. Similarly, seasonal occurrence has been observed for chicken pox, measles, influenza and many other common childhood infectious diseases [7,142].

A seasonal infectious etiology for disease is complicated by many factors [126]. The same infectious agent may present a different pattern of incidence depending on the host location. A seasonal peak evident in the general population may not behave uniformly within certain subpopulations. Temperature, humidity, precipitation, and indoor air quality are among the mitigating factors that may affect the survival and transmissibility of a pathogen and explain different seasonal peaks for a disease in different studies. Other factors include poor nutrition, crowding, seasonal travel, hygiene practices, cultural practices in food consumption/preparation, changes in herd immunity, or evolution of the infectious agent over time. Furthermore, seasonal variation in immune function may increase host susceptibility to infections at certain times of the year [143,144]. Given the rarity of some infections and brain tumors, the interpretability of seasonal patterns, or the lack thereof, may be confounded by time- and/or space-dependent factors [126].

4.4. Vitamin D

Vitamin D is a fat-soluble prohormone which operates via a nuclear receptor [145]. Maternal serum vitamin D levels tend to be closely correlated with infant cord serum levels [146,147]. This light synthesized steroid, resulting from the absorption of ultraviolet B photons by 7-dehydrocholesterol in the skin [148], has been suggested as a possible factor underlying the season of birth risk for adult gliomas observed in some studies [145]. Levels of vitamin D are known to fluctuate depending on sunlight exposure, which is highest in the summer for the northern hemisphere and tends to increase for latitudes nearer the equator [145,148-150].

Antiproliferative and proapoptotic activity of vitamin D₃ has been noted in model glioma cell lines and a primary culture, as well as tumor tissue experiments [145]. Further, prenatal vitamin D₃ depletion has been associated with altered brain development in rodent studies [151]. Vitamin D receptors are present in most cells and tissues in the body [152], including the brain [148], so this

hormone is believed to play an important role in disease management and cancer prevention as a modulator of immune system activity [148,153-155].

Children who live in polluted, inner city environments and who are deprived of regular sunlight exposure have been shown to suffer a higher prevalence of rickets (due to vitamin D deficiency) than children in rural areas [148]. Seasonal variation in vitamin D levels also has been suggested as a factor differentially affecting newborn growth plate width, and this may explain why babies born in Australia around October (spring) are relatively heavier than those born at other times [156].

4.5. Diet

The “developmental plasticity hypothesis” refers to the critical developmental period *in utero* when the fetus is plastic and adaptively imprints to its environment. *In utero* adaptation may lead to lifelong changes in the body’s metabolism, hormone regulation, and the number of cells present in key organs [14,157,158]. If this is the case, adult health outcomes may reflect season of birth if food intake is seasonal, and if exposure occurs at a critical stage of fetal development. Certain foods and the chemicals contained in these foods may be more or less available at particular times of the year due to crop cycles, storage capability, transportation access, and cost; and the use of preservatives in foods also may vary accordingly. N-nitroso compounds are a potent inducer of cancer and brain tumors in various animal species [159,160], and fetal exposure produces more tumors than postnatal exposure [161]. Foods high in N-nitroso compounds have been associated with an increased risk for brain tumors in some studies [162-165]. These compounds may be present in foods through their use as preservatives or in fertilizers [166].

Vitamin C, which is mostly found in seasonal fruits and vegetables, can react with and then inhibit nitrite formation of nitrosamines [163]. An 18-fold greater risk of primary adult brain tumors has been found among individuals who consumed large amounts of processed meats (high in N-nitroso content) and drank orange/grapefruit juice once per week or less, than among those who consumed less processed meat and drank orange/grapefruit juice more often [164]. However, a recent multi-centered international case-control study of adult diet and brain tumor risk found no evidence of confounding or effect modification by vitamin supplementation, especially in the association between consumption of cured meats (containing high levels of nitrates) and gliomas [167].

4.6. Birth Weight

Birth weight has been reported to vary by season of birth [168-170]. High birth weight is an important predictor of adult obesity [171], and a higher body mass index (BMI) has been linked to greater risk for adult-onset glioma [172]. In children, high birth weight has been associated with increased risk for astrocytoma and medulloblastoma/primitive neuroectodermal tumors (PNET) [173]. Temporal patterns in birth weight may result from seasonal variations in food availability. For example, birth weights in agricultural societies are highest at the peak of the dry season, corresponding to the time of harvesting and greatest food availability [174]. Interestingly,

very low birth weight has been associated with left- or mix-handedness [175,176], a factor associated in some studies with season of birth [177] and reduced glioma risk [178].

4.7. Handedness

Handedness is believed to be determined *in utero* [179], possibly through hormonal influences [180-183], and has been linked with immune disease [184,185], various developmental learning disorders [184], epilepsy [186], and breast cancer risk in both pre- and post-menopausal women [187-190]. Exposure to a high level of testosterone during the earlier part of pregnancy is thought to promote right brain development and influence hand preference, although the evidence in support of a relationship is not conclusive [191]. Testosterone, progesterone, oestradiol, and lutenising hormone levels in women have been reported to be higher in spring than in autumn [192-194].

Results from several studies hint that non-genetic factors may play an important role in the determination of handedness. Women exposed *in utero* to the estrogen-like compound DES show a higher prevalence for left handedness [195,196]. Similarly, left-handedness has been linked to congenital adrenal hyperplasia, a condition characterized by high *in utero* levels of androgenizing hormones [197]. Of note, brain tumors are known to contain sex steroid receptors (e.g., estrogen, androgen, progestin) [198], and sex hormones have been shown to promote brain tumors in animal studies [199,200]. Mice reared under conditions favoring the right limb develop a right-limb preference, and vice versa [201], further suggesting that environmental factors influence handedness. Additionally, the discordance of handedness in twin studies illustrates that genetics alone cannot explain the development of handedness [202-207].

Handedness has been shown to follow a gender-invariant seasonal pattern, with more left-handers than right-handers born between March and July [177,178]. Being right-handed has been associated with a greater risk for glioma than being left-handed or ambidextrous [178]. However, for left-handed and ambidextrous participants born from late fall through early spring, glioma risk also has been shown to be higher than for those born at other times of the year [16]. A study of 15,390 Brazilian students was unable to detect a difference in the season of birth between right- and left-handers. However, little seasonal variation exists in the light/dark cycle in the area where the majority of study participants were born [208].

The putative connection between handedness, season of birth, and glioma risk remains difficult to interpret. For example, glioma risk is greater for males than females [2], yet the pattern of seasonal influence upon handedness does not vary significantly between females and males [177]. A higher incidence of sinistrality has been observed for individuals born in winter and autumn than for those born summer and spring [191]. The incidence of left-handedness is disproportionately higher among males [202], a finding which is consistently observed across species [201,209-212]. Risk for glioma also is nearly equal for left-handed and ambidextrous individuals but higher for right-handers. Overall, handedness appears to be a surrogate marker for an underlying but unidentified risk factor that interacts with seasonality and other factors to possibly explain glioma risk.

5. Discussion

Season of birth in its own right cannot be deemed a cause for glioma. Rather, it is a surrogate marker for underlying risk factors that may offer subtle clues about the possible perinatal etiology of adult gliomas.

There is probably no specific etiologic agent acting in isolation that completely explains a season of birth association with adult glioma risk. If an association exists the effect probably represents the interplay between various environmental, genetic, lifestyle, and socioeconomic factors, operating on mother and child within a precise window of vulnerability. The mechanism of action may involve epigenetic processes or DNA changes with the capacity to modulate or influence oncogenic outcomes in the distant future. A patient's innate and adaptive immune response and a host of hormonal and metabolic factors, likely play important and closely interrelated roles in understanding the complex biologic and etiologic mechanisms in the season of birth effect for adult gliomas.

In the studies conducted to date, risk estimates and p-values for the association between season of birth and glioma risk have been nominal to borderline in strength. However, a weak association does not necessarily imply the absence of causality, nor is a strong association necessary or sufficient for causality [213,214]. The ability to find associations between specific seasonal risk factors occurring around the time of birth and adult glioma incidence is limited by the rarity of this cancer in the population and the vast time period from exposure to disease. While the risk factors outlined in this review do not conflict with our current understanding of the natural history of cancer or glioma specifically, the evidence in support of a causal relationship has not been consistent. To some degree, effect modification or publication bias may explain the inconsistencies. At minimum, if a causal relationship exists, season of birth meets the criteria of temporality as the period surrounding birth clearly predates disease occurrence. However, the exact window of exposure when the underlying risk factor(s) most occur to cause disease is unknown.

On the present evidence, it is not possible to definitively answer the question of how season of birth influences glioma risk, or to favor any specific hypothesis. Many questions remain and future research will benefit from focused studies aimed at specific exposures and subpopulations, allowing for more detailed analyses by histologic subtypes.

Acknowledgements

This manuscript was made possible by a grant from NCMHD/NIH (P20MD002289) entitled "Teamwork in Research and Intervention to Alleviate Disparities Project (TRIAD)". Elizabeth Tornquist (UNC-CH) and Debra C. Wallace (UNCG) offered valuable comments during the writing of this manuscript and their knowledge and insight are greatly appreciated. The author also thanks Helen Sedwick, Caitlin Fehrenbacher and Carol Zurcher for administrative and proofreading assistance, and Ruirui Jiang for carefully checking references. The contents of this publication are solely the responsibility of the author and do not necessarily represent the views of any funding agency.

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