Pediatric Brain Tumors: Descriptive Epidemiology, Risk Factors, and Future Directions

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ABSTRACT

Brain tumors are the most common solid tumors in children and remain a significant contributor to death by disease in this population. Pediatric brain tumors (PBT) are broadly classified into two major categories: glial and neuronal tumors. Various factors, including tumor histology, tumor location, and demographics, influence the incidence and prognosis of this heterogeneous group of neoplasms. Numerous epidemiologic studies have been conducted to identify genetic and environmental risk factors for these malignancies. Thus far, the only established risk factors for PBTs are exposure to ionizing radiation and some rare genetic syndromes. However, relatively consistent evidence of positive associations for birth defects, markers of fetal growth, advanced parental age, maternal dietary *N*-nitroso compounds, and exposure to pesticides have been reported. The genetic variants associated with susceptibility to PBTs were predominantly identified by a candidate-gene approach. The identified genetic variants belong to four main pathways, including xenobiotic detoxification, inflammation, DNA repair, and cell-cycle regulation. Conducting large and multi-institutional studies is warranted to systematically detect genetic and environmental risk factors for different histologic subtypes of PBTs. This, in turn, might lead to a better understanding of etiology of PBTs and eventually developing risk prediction models to prevent these clinically significate malignancies.

Introduction

Primary brain tumors are the most common solid tumors in children and the leading cause of cancer mortality in this population, in high-income countries. Pediatric brain tumors (PBT) are heterogeneous in histopathology, molecular features, and prognosis, and they are classified into two major categories including glial and neuronal tumors (1). The most common forms of glioma in children are astrocytomas, oligodendrogliomas, ependymomas, brain stem gliomas, and optic nerve gliomas. Another rare, but often fatal glial tumor that occurs in children is diffuse intrinsic pontine glioma, or DIPG. The majority of neuronal tumors are embryonal tumors of which the most common types are: medulloblastoma, atypical teratoid/rhabdoid tumors, and central nervous system primitive neuroectodermal tumors (CNS PNET; refs. 2, 3). The term PNET was removed with the 2016 World Health Organization Classification of CNS tumors (3). The new classification is based on amplification of the C19MC region on chromosome 19 (19q13.42). Embryonal tumors with abundant neuropil and true rosettes, ependymoblastomas, and some medulloepithelioma were reclassified as embryonal tumor with multilayered rosettes C19MC-altere. Without C19MC amplification, they should be classified as embryonal tumor with multilayered rosettes, NOS (not otherwise specified) or medulloepithelioma, depending on their histologic features. The term CNS embryonal tumor, NOS is used for CNS PNETs without classifiable genetic mutations (3). **Table 1** summarizes the most commonly occurring brain tumor histologies in children (3, 4).

The frequency of different histologic subtypes of PBTs varies by age. According to the Central Brain Tumor Registry of the United States (CBTRUS), in children 0–14 years old, glioma accounted for 53% of all primary brain and other CNS tumors. Among gliomas, the majority were pilocytic astrocytoma (33%) followed by other low-grade gliomas (27%). In addition, 15% of all primary CNS tumors were embryonal tumors of which medulloblastoma (62%) and atypical teratoid/rhabdoid tumors (15%) were the most common histologic subtypes (5).

Incidence and prognosis of PBTs varies greatly and depends on various factors including tumor histology, tumor location, age at diagnosis, race, ethnicity, and sex. Despite their prevalence and clinical importance, knowledge on the etiology and molecular characterizations of pediatric brain tumors is limited. In this review article, serving as an update to the review article by Johnson and colleagues (6), we summarize the descriptive epidemiology and the current knowledge on etiology of primary pediatric brain tumors.

Descriptive Epidemiology

Incidence

The incidence of PBTs differs by age, sex, geography, race, and ethnicity. In the United States, from 2012 to 2016, the incidence of all primary brain and other CNS tumors in children and adolescents <20 years of age was 6.06 per 100,000 children. Approximately, 58% of cases were malignant and 42% were nonmalignant (4). The incidence was reported to be higher in non-Hispanics compared with Hispanics (6.35 vs. 5.14 per 100,000) as well as in Whites compared with Blacks (6.29 vs. 4.71 per 100,000). The largest differences were observed in incidence of neuroepithelial tissue tumors and cranial and spinal nerves tumors between non-Hispanics and Hispanics, while between Blacks and Whites, the largest differences were found in incidence of neuroepithelial tissue tumors, cranial, spinal nerves tumors, germ cell tumors, and tumors of sellar region (4). In addition, the incidence of all primary brain and other CNS tumors was higher in girls compared with boys (6.13 vs. 5.98 per 100,000; ref. 4); however, this is not

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Table 1. Most common brain tumor histologies in children 0–19 years old in the United States.

Histology	Subtype	Incidence per 100 000 Population in the United States[a]	WHO grade[b]
Glioma	Pilocytic astrocytoma	0.91	I
	Diffuse astrocytoma	0.24	II
	Ependymoma	0.29	I–III
Embryonal tumors	Medulloblastoma	0.40	IV
	Atypical teratoid/rhabdoid tumors	0.09	IV
	Primitive neuroectodermal tumors	0.07	IV
Nerve sheath tumors	Vestibular schwannoma (acoustic neuroma)	0.32	I
Germ cell tumors	Germ cell tumors	0.23	Not graded
Tumors of the pituitary	Pituitary adenoma	0.78	Not graded

[a]Data from Ostrom QT, Cioffi G, et al. (4).
[b]Information from Louis DN, Perry A, et al. (3).

consistent with previous reports indicating higher incidence for most histologies in boys compared with girls (5.44 vs. 5.07 per 100,000; for all brain and CNS tumors), during 2007–2011 in the United States (5). The observed elevated incidence for all primary brain and other CNS tumors in girls might be driven by meningioma in 15–19 years old females that were not included in the previous studies, reported on the basis of 0–14 years old children. Among other histologies, medulloblastoma was more common in males compared with girls (0.60 vs. 0.38 per 100,000; ref. 5). According to the CBTRUS report, among children 0–4 years of age diagnosed with brain and other CNS tumors, the highest incidence was attributable to pilocytic astrocytomas (1.15 per 100,000); however, the incidence of this histologic subtype decreased with advancing age. Among children ages 5–9, pilocytic astrocytoma (1.04 per 100,000) followed by malignant glioma (0.88 per 100,000) showed the highest incidence. In addition, the highest incidence of medulloblastoma was observed among children 5–9 years of age (0.59 per 100,000). Among children ages 10–14 and 15–19, the highest incidence was attributable to tumors of the sellar region (0.86 per 100,000) and tumors of the pituitary (2.30 per 100,000), respectively (4).

Survival after Diagnosis

Survival for patients with PBTs also varies by histology, tumor location, age at diagnosis, race, and ethnicity. The 10-year survival for children ages 0–19 diagnosed with malignant brain and other CNS tumors was estimated at 72% with lowest (17%) and highest (96%) survival rates being attributable to glioblastoma and pilocytic astrocytoma, respectively. In addition, in the United States, 96% of children 0–19 years old with nonmalignant tumors survived 10 years after diagnosis (4). Overall, tumors located in the brain stem showed the poorest survival compared with tumors located at any other site, while tumors of the cranial nerves showed the highest survival (5). Also, survival is better for children diagnosed at an older age, because younger children cannot be treated as intensively as older children (1, 5). Therefore, the difference in survival by age is more pronounced for medulloblastoma and PNETs because their treatment depends more on radiotherapy (5). Survival was reported to be poorer among non-Hispanic Blacks and Hispanic patients compared with non-Hispanic Whites (7–10); in the United States for the period of 2001–2008, 5-year relative survival was reported as 77.6% for non-Hispanic White patients, 69.8% for non-Hispanic Black patients, and 72.9% for Hispanic patients (7). In contrast, among adults ages 18 years or older, in the United States, during 2000–2014, the survival for many tumor types was reported to be poorer in non-Hispanic Whites, while it was relatively comparable in Hispanics and Blacks (11).

Risk Factors

Known and suspected genetic risk factors

Cancer predisposition syndromes

There is an established increased risk of PBTs associated with rare single-gene disorders or genetic syndromes, which may occur *de novo* or may be inherited. However, only a small proportion (∼4%) of PBTs are attributable to these rare autosomal dominant or autosomal recessive disorders. The most common genetic syndromes (and their related genes) predisposing to nervous system tumors include: neurofibromatosis type 1 (*NF1*), neurofibromatosis type 2 (*NF2*), tuberous sclerosis complex (*TSC1* or *TSC2*), Li-Fraumeni (*TP53*), Gorlin syndrome (*PTCH1*), familial adenomatous polyposis (*APC, MMR*), glioma susceptibility 3 (*BRCA2*), and biallelic mismatch repair deficiency (*MSH2, MLH1, MSH6, PMS2*; refs. 12–14).

Family history

A modest risk of developing CNS tumors among the siblings of PBT cases has been reported. In particular, a higher risk was observed if both children have been diagnosed with medulloblastoma and PNET. Children with a parent diagnosed with a CNS tumor showed an elevated risk of developing brain tumors; however, these observed associations were based on small numbers of affected families. In general, there is limited evidence for an association between family history of cancer and nonsyndromic PBTs (6, 15).

Rare variants

Because of rarity of PBTs and further rarity of familial PBTs, little knowledge is available on genetic variants contributing to the genetic architecture of familial PBTs. Backes and colleagues (16) performed a study in a family with two unaffected parents and two siblings diagnosed with glioblastoma. By using whole-exome sequencing, they identified three significant pathways containing at least three affected genes, including: focal adhesion, extracellular matrix–receptor interaction, and complement and coagulation cascades. Of all the identified genes, 32 genes were located on chromosomes 1, 11, and 22. More specifically, the affected genes were accumulated on 22q12.2 and 1p36.33 (16).

Germline mutations associated with sporadic PBTs vary by histologic subtype, and about 10% of sporadic PBT cases harbor a predisposition mutation. To date, the conducted studies have been mainly focused on high-penetrant germline mutations in known cancer predisposition genes; therefore, the contribution of rare high-penetrant mutations in the risk of PBTs is largely unknown (17). Recently, a large study, performed on childhood high-grade glioma by using whole-exome sequencing, identified that the rare germline variants associated with risk of PBTs are mainly located in 24 genes largely involved in DNA repair and cell-cycle pathways, predominantly in the *TP53* and *NF1* genes (18). In addition, Waszak and colleagues, by employing rare variant burden analysis, estimated that 6% of medulloblastoma diagnoses are attributable to germline mutations and identified *APC, BRCA2, PALB2, PTCH1, SUFU*, and *TP53* as consensus medulloblastoma predisposition genes. They reported that the prevalence of genetic predispositions differs among molecular subgroups of medulloblastoma, with the highest prevalence being attributable to patients in the Sonic HedgeHog (SHH) subgroup. Also, correlations between specific germline mutations and development of specific molecular subgroups of medulloblastoma were detected (19). Furthermore, they identified *ELP1* as the most common medulloblastoma predisposition gene and found that *ELP1* rare variants occurred in 14% of medulloblastoma SHH subgroup and elevated the prevalence of genetic predisposition to 40% among patients in this molecular subgroup (20). Begemann and colleagues, by investigating 1,044 medulloblastoma cases, identified that heterozygous germline mutations in the G protein–coupled receptor 161 (*GPR161*) gene was exclusively associated with SHH subgroup and accounted for 5% of infants with SHH subgroup in their medulloblastoma cohort (21).

Common genetic variants and sporadic brain tumors

Very few and generally small genetic association studies have been conducted on brain tumors in children and adolescents. To date, there is one published genome-wide association study (GWAS) of medulloblastoma. This study identified 13 genetic variants associated with medulloblastoma risk located in *CD83* (6p23), *MAGI2* (7q21.11), *CSMD1* (8p23.2), *DOCK1* (10q26.2), *PTPRM* (18p11.23), and 8q24.12 (22). The genetic variants associated with risk of PBTs have been mainly identified by candidate-gene association studies conducted on pooled histologic subtypes of PBTs (12). The identified genetic variants mainly belong to genes involved in xenobiotic detoxification (*CYP1A1, GSTT1, GSTM1*; refs. 23, 24), inflammation (*NOS1*; ref. 24), DNA repair (*ERCC1, ERCC2, CHAF1A, XRCC1, EME1, ATM, GLTSCR1, XRCC4, PALB2*; refs. 22, 24–26), and cell-cycle regulation (*AICDA, CASP1, IRS2, EGFR, PTCH1*; refs. 22, 25–27). It has been shown that the validated genetic variants identified by GWAS on adult glioma are also associated with risk of PBTs. These variants are predominantly located in *TERT* (5p15.33), *RTEL1* (20q13.33), *CCDC26* (8q24.21), and *CDKN2BAS* (9p21.3; refs. 28–30). A recent study was performed in a U.S. population to assess whether genome-wide ancestry differences are associated with risk of ependymoma. In addition, admixture mapping was conducted to detect associations with local ancestry. The results revealed significant associations between eastern European ancestral substructure and ependymoma risk among Hispanics and non-Hispanic Whites. Furthermore, a significant peak located at 20p13 was detected to be associated with increased local European ancestry (31). Given the limited knowledge available on the germline variants associated with PBTs and the rarity of these malignancies, utilizing various approaches, including Mendelian randomization, are needed for a better understanding of the etiology of PBTs and assessing their risk factors (32). **Table 2** summarizes the identified genetic variants associated with PBT risk.

Maternal genetic effect

Despite the potentially important role of maternal genetics on the risk of PBTs by affecting the *in utero* environment of the developing embryo, limited knowledge is available on role of maternal genetic variations in the etiology of these tumors. Lupo and colleagues (33), in the only available study of its kind, investigated the role of maternal variation in xenobiotic detoxification genes and the risk of pediatric medulloblastoma using a case-parent triad study design. The results indicated that maternal variation in *EPHX1* (rs1051740) was associated with elevated risk of pediatric medulloblastoma (relative risk = 3.26; 95% confidence interval, 1.12–9.53; ref. 33).

Known and suspected nongenetic risk factors

Ionizing radiation

Exposure to moderate-to-high doses of ionizing radiation is the only established environmental risk factor for PBTs (34). Compared with adults, children are more radiosensitive and have a longer life expectancy to experience the carcinogenic effects of ionizing radiation (35). There is evidence that radiotherapy for early-onset childhood cancers, particularly children who received radiotherapy for acute lymphoblastic leukemia that included exposure to the brain, is correlated with an increased risk of brain tumor development later in life (12, 34, 36). In addition, some studies have reported that maternal diagnostic radiation during pregnancy is associated with an increased risk of brain tumors in offspring (34, 37). The effect of diagnostic radiation during early childhood on subsequent brain tumor risk was evaluated, and a 29% excess risk was reported for children exposed to one or more head CT scans (35, 37–39). This finding should be interpreted with caution because pre-existing cancer in children with high susceptibility may lead to undergoing more head CT scans (39).

Non-ionizing radiation

The effects of non-ionizing radiation, including radiofrequency, microwaves, and extremely low-frequency (ELF) magnetic fields, on the risk of PBTs have been investigated by some studies. Despite the classification of radiofrequency fields as a possible carcinogen by the International Agency for Research on Cancer (IARC) in 2011, no significant associations were observed for cellular phone use or other radiofrequency radiation exposure by recent high-quality studies. In addition, in 2002, based on the available findings, IARC concluded that there are not sufficient data to classify ELFs as a risk factor for brain tumors (6, 12).

Allergic conditions

Although there is consistent evidence for an association between personal medical history of allergies and decreased risk of adult glioma, inconsistent evidence of reduced risk of PBTs associated with allergic and atopic conditions (such as asthma, wheezing, and eczema), as well as early life exposure to infections, has been reported previously (6, 40–42). It is unclear whether history of allergies and atopic diseases decrease the risk of PBTs or PBTs prevents allergic and atopic conditions, further investigations are warranted to clarify the action of these effects (42).

Parental factors

Advanced parental age, as a marker for accumulated genetic aberrations in the parents' DNA, has been reported to be associated

Table 2. Summary of common genetic variants associated with risk of pediatric brain tumors.

Reference	Population	Subject number	Genetic variant	Locus	Gene	Minor allele	OR (95% CI)	P^a
(25)	Asian	70 children with brain tumors and 140 controls	rs12306110	12p13.31	*AICDA*	C	2.8 (1.25–6.46)	0.016
			rs3794318	12p13.31	*AICDA*	C	2.6 (1.14–5.76)	0.019
			rs2518144	12p13.31	*AICDA*	A	2.5 (1.04–6.11)	0.044
			rs8110862	19p13.12	*CASP14*	C	0.4 (0.19–0.95)	0.038
(27)	Asian	48 patients with pediatric medulloblastoma and 190 controls	rs7987237	13q34	*IRS2*	T	2.95 (1.43–6.11)	0.002
			rs913949	13q34	*IRS2*	G	2.25 (1.20–4.22)	0.009
			rs4590656	1q43	*AKT3*	T	1.96 (1.18–3.24)	0.007
			rs897959	1q43	*AKT3*	T	1.85 (1.11–3.08)	0.016
(22)	Caucasian	Discovery: 244 medulloblastoma cases and 247 controls	rs853362	6p23	*CD83*	G	2.06 (1.51–2.83)	8.2×10^{-6}
			rs853372	6p23	*CD83*	A	2.05 (1.49–2.82)	1.0×10^{-5}
			rs10266582	7q21.11	*MAGI2*	T	0.32 (0.21–0.50)	5.6×10^{-7}
		Validation: 249 medulloblastoma cases and 629 controls	rs17404544	8p23.2	*CSMD1*	C	2.58 (1.70–3.93)	1.0×10^{-5}
			rs80012312	8q24.12	–	G	7.35 (3.31–16.30)	9.2×10^{-7}
			rs7077776	10q26.2	*DOCK1*	C	1.85 (1.41–2.43)	9.8×10^{-6}
			rs11661715	18p11.23	*PTPRM*	G	3.83 (2.28–6.43)	3.8×10^{-7}
			rs11873445	18p11.23	*PTPRM*	T	3.91 (2.37–6.45)	9.3×10^{-8}
			rs12185387	18p11.23	*PTPRM*	G	3.63 (2.23–5.90)	1.9×10^{-7}
			rs12956144	18p11.23	*PTPRM*	C	3.81 (2.30–6.30)	1.9×10^{-7}
			rs78021424	18p11.23	*PTPRM*	T	3.77 (2.27–6.25)	2.7×10^{-7}
			rs1468707	18p11.23	*PTPRM*	A	3.69 (2.23–6.09)	3.3×10^{-7}
			rs1942957	18p11.23	*PTPRM*	G	3.69 (2.23–6.09)	3.3×10^{-7}
(23)	Caucasian	284 patients with various types of brain tumors (glial and embryonal tumors) and 464 controls	rs2606345	15q24.1	*CYP1A1*	G	1.59 (1.07–2.35)	0.022
			rs4646903	15q24.1	*CYP1A1*	C	1.46 (1.02–2.10)	0.04
			rs1048943	15q24.1	*CYP1A1*	G	1.71 (1.01–2.90)	0.048
			Del(D/D)-Ins (I/D+I/I)	1p13.3	*GSTM1*	D/D	2.0 (1.47–2.70)	8.3×10^{-6}
(24)	Caucasian	172 children with malignant CNS tumors and 183 controls	rs260634	15q24.1	*CYP1A1*	G	1.50 (1.11–2.03)	0.009
			Del(D/D)-Ins (I/D+I/I)	22q11.2	*GSTT1*	D/D	1.96 (1.16–3.32)	0.013
(26)	Caucasian	245 cases of pediatric brain tumors (glioma and PNETs) and 489 controls	rs730437	7p11.2	*EGFR*	A	0.59 (0.42–0.83)	0.002
			rs11506105	7p11.2	*EGFR*	A	0.71 (0.51–0.98)	0.036
			rs9642393	7p11.2	*EGFR*	C	2.21 (1.13–4.35)	0.021
			rs3212986	19q13.32	*ERCC1*	A	1.53 (1.11–2.09)	0.009
			rs2992	19p13.3	*CHAF1A*	C	0.67 (0.45–0.99)	0.049
			rs25487	19q13.31	*XRCC1*	T	0.66 (0.44–0.97)	0.033
			rs12450550	17q21.33	*EME1*	C	2.48 (1.42–4.33)	0.001
			rs170548	11q22.3	*ATM*	C	1.57 (1.02–2.42)	0.041
			rs1035938	19q13.3	*GLTSCR1*	T	2.14 (1.09–4.19)	0.027
			rs7721416	5q14.2	*XRCC4*	A	0.51 (0.27–0.94)	0.032
			rs2662242	5q14.2	*XRCC4*	C	0.49 (0.26–0.91)	0.024

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Table 2. Summary of common genetic variants associated with risk of pediatric brain tumors. (Cont'd)

Reference	Population	Subject number	Genetic variant	Locus	Gene	Minor allele	OR (95% CI)	P^a
(28)	Caucasian	245 cases of pediatric brain tumors (glioma and PNETs) and 489 controls	rs2736100	5p15.33	*TERT*	A	0.66 (0.46–0.93)	0.018
			rs1063192	9p21.3	*CDKN2BAS*	G	1.53 (1.07–2.19)	0.021
			rs2157719	9p21.3	*CDKN2BA*	C	1.53 (1.08–2.19)	0.018
			rs1412829	9p21.3	*CDKN2BA*	G	1.45 (1.02–2.05)	0.037
			rs4977756	9p21.3	*CDKN2BA*	G	1.45 (1.03–2.06)	0.036
			rs6089953	20q13.33	*RTEL1*	A	0.64 (0.43–0.96)	0.032
			rs6010620	20q13.33	*RTEL1*	A	0.66 (0.44–0.99)	0.048
			rs2297440	20q13.33	*RTEL1*	T	0.64 (0.41–0.98)	0.038
			rs4809324	20q13.33	*RTEL1*	C	1.54 (1.04–2.28)	0.033
			rs10464870	8q24.21	*CCDC26*	C	1.70 (1.11–2.60)	0.014
			rs891835	8q24.21	*CCDC26*	G	1.59 (1.04–2.44)	0.032
(30)	Caucasian	854 patients with glioma and 3,689 controls	rs634537	9p21.3	*CDKN2BA*	G	1.21 (1.09–1.35)	0.0006
			rs2157719	9p21.3	*CDKN2BA*	C	1.21 (1.09–1.35)	0.0006
			rs145929329	9p21.3	*CDKN2BAS*	ATT	1.19 (1.07–1.33)	0.0017
			rs4252707	1q32.1	*MDM4*	A	1.27 (1.08–1.50)	0.0045
			rs7572263	2q34	*C2orf80*	A	1.54 (1.05–2.25)	0.0270
			rs2736100	5p15.33	*TERT*	C	1.20 (1.00–1.44)	0.0460
			rs11598018	10q24.33	*STN1*	C	1.12 (1.00–1.25)	0.0413
			rs7107785	11q21	*MAML2*	T	1.24 (1.03–1.48)	0.0242
(31)	Non-Hispanic White, Hispanic White, African American, American Indian/ Alaska Native, Asian or Pacific Islander	327 cases of ependymoma and 1,970 controls	rs6039499	20p13	*RSPO4*	G	1.99 (1.45–2.73)	2.2×10^{-5}

[a]Unadjusted for multiple testing.

with an elevated risk of brain tumors in offspring (43). There is more consistent evidence of increased risk of PBTs associated with advanced paternal age at birth than advanced maternal age at birth (6, 44). Despite the extensive research on the association between parental occupational exposures and risk of brain tumors in offspring, inconsistent findings have been reported. However, the results from the studies of parental occupational/residential exposure to pesticides are more consistent and the meta-analysis studies indicate a positive association between risk of PBTs and exposure to pesticides (6, 12, 45, 46). In addition, positive associations between parental high socioeconomic status (47, 48) as well as maternal intake of dietary *N*-nitroso compounds (NOC) and risk of PBTs in offspring have been reported by meta-analysis (6, 12, 49).

Birth characteristics and structural birth defects

Of the investigated birth characteristics, large studies and meta-analyses provide evidence that high birth weight (>4,000 g) is associated with an increased risk of pediatric CNS tumors, particularly astrocytoma and embryonal tumors (50, 51).

Approximately 7% of PBTs can be attributable to nonchromosomal structural birth defects, which is one of the most consistent risk factors for childhood cancer overall (12, 52). Large, population-based studies

Table 3. Summary of suspected nongenetic risk factors associated with risk of pediatric brain tumors (recent studies 2014–2020).

Risk factors	Population	Subject number	Exposure type	OR (95% CI)	Reference
Allergic conditions	Caucasian	469 cases and 2,719 controls	Asthma/wheezing	0.8 (0.56–1.1)	(40)
	Caucasian	352 cases and 646 controls	Atopic disorder	1.03 (0.70–1.34)	(42)
Early life exposure to infections	Caucasian	469 cases and 2,719 controls	Day-care attending	0.9 (0.7–1.2)	(40)
			Common infections	0.9 (0.7–1.2)	
			Farm visits	0.6 (0.5–0.8)	
			Contact with pets	0.8 (0.6–1.0)	
Parental age	Caucasian, Asian, African American, Hispanic	456 ependymomas and choroid plexus tumors and 1,677 controls	Maternal age	3.71 (1.77–7.76)	(43)
			Paternal age	0.97 (0.56–1.69)	
		1,950 astrocytomas and 7,335 controls	Maternal age	1.38 (0.95–2.01)	
			Paternal age	0.82 (0.62–1.07)	
		1,002 embryonal tumors and 3,767 controls	Maternal age	1.17 (0.69–2.01)	
			Paternal age	1.29 (0.88–1.89)	
		573 other gliomas and 2,136 controls	Maternal age	1.57 (0.83–2.95)	
			Paternal age	1.14 (0.71–1.85)	
		558 other specified intracranial and intraspinal neoplasms and 2,075 controls	Maternal age	1.65 (0.82–3.33)	
			Paternal age	1.48 (0.92–2.39)	
	Hispanic	62 cases and 124 controls	Maternal age	0.88 (0.26–2.97)	(44)
			Paternal age	0.99 (0.34–2.85)	
Parental exposure to pesticides	Caucasian and Asian	Meta-analysis of 18 studies	Residential exposure to pesticides	1.26 (1.13–1.40)	(45)
	Caucasian	437 cases and 3,102 controls	Maternal residential pesticide use during pregnancy	1.4 (1.2–1.8)	(46)
Parental high socioeconomic status	Caucasian	1,273 cases and 5,086 controls	Maternal income during pregnancy	1.24 (0.97–1.57)	(47)
			Paternal income during pregnancy	0.90 (0.73–1.12)	
			Maternal education during pregnancy	1.12 (0.93–1.36)	
			Paternal education during pregnancy	1.10 (0.91-1.34)	
	Caucasian, Asian, African American, Hispanic	3,022 cases and 10,791 controls	Maternal education at birth	1.05 (0.93–1.20)	(48)
			Paternal education at birth	1.07 (0.90–1.28)	
High birth weight	Caucasian, Asian, African American, Hispanic	Meta-analysis of 22,330 cases	Birth weight >4,000 g	1.14 (1.08–1.20)	(50)
	Caucasian, Asian, African American, Hispanic	Meta-analysis of 11 studies on astrocytoma	Birth weight >4,000 g	1.60 (1.23–2.09)	(51)
		Meta-analysis of 8 studies on ependymoma		1.18 (0.97–1.43)	
		Meta-analysis of 11 studies on embryonal tumors		1.20 (1.07–1.35)	

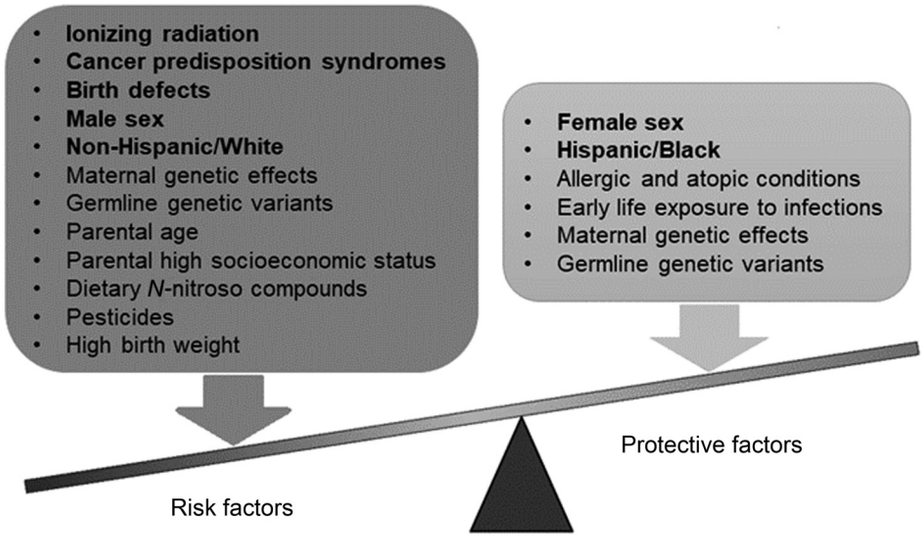

Figure 1.
Summary of risk and protective factors related to pediatric brain tumors.

reported that birth defects are associated with approximately 2-fold elevated risk of brain tumors in children. (12, 53, 54). Children with CNS birth defects or with a neurologic anomalies showed an even higher susceptibility to developing PBTs (12, 55). **Table 3** summarizes the suspected nongenetic risk factors associated with PBT risk.

Conclusions and Future Directions

PBTs represent a complex heterogeneous group of neoplasms with different histopathology, molecular features, and etiology. Various factors including tumor histology, tumor location, age at diagnosis, sex, race, and ethnicity are correlated with the incidence and prognosis of PBTs. Exposure to ionizing radiation and some rare genetic syndromes are the only established risk factors for PBTs; although relatively consistent evidence of positive associations for birth defects, markers of fetal growth, advanced parental age, maternal dietary NOCs, and exposure to pesticide has been reported (summarized in **Fig. 1**); however, the findings of these studies should be interpreted with caution as some of the studies are based on small sample sizes and exhibit some methodologic challenges.

Performing large, collaborative, and multi-institutional genetic studies based on SNP-array and next-generation sequencing data to identify common and rare germline variants associated with risk of PBTs, in different ethnic groups, is an important research priority. Considering the heterogeneity of PBTs, the studies that aim to evaluate histology-specific risk variants are also needed. Utilizing high-quality publicly available genetic and environmental data as well as data from cancer and birth defect registries are beneficial for studies of these rare tumors. Gene–environment interaction studies will play an important role to increase our understanding of the etiology of PBTs. Incorporating genetic and environmental data may lead to the development of comprehensive risk prediction models that could be leveraged for the prevention of these tumors. To conclude, the literature on the risk factors for PBTs is currently an amalgam of small, underpowered studies, many of which also suffer design flaws that limit their generalizability. As such, the PBT etiologic literature suffers from extensive publication bias. Thus, large-scale, well-powered systematic collaborative studies conducted by researchers from multiple institutions are warranted in the pediatric brain tumor research field to improve our knowledge of PBT risk factors; which would lead to the development of prevention measures and better management of pediatric brain tumors.

Authors' Disclosures

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