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Risk factors for childhood and adult primary brain tumors

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Abstract

Primary brain tumors account for ~1% of new cancer cases and ~2% of cancer deaths in the United States; however, they are the most commonly occurring solid tumors in children. These tumors are very heterogeneous and can be broadly classified into malignant and benign (or non-malignant), and specific histologies vary in frequency by age, sex, and race/ethnicity. Epidemiological studies have explored numerous potential risk factors, and thus far the only validated associations for brain tumors are ionizing radiation (which increases risk in both adults and children) and history of allergies (which decreases risk in adults). Studies of genetic risk factors have identified 32 germline variants associated with increased risk for these tumors in adults (25 in glioma, 2 in meningioma, 3 in pituitary adenoma, and 2 in primary CNS lymphoma), and further studies are currently under way for other histologic subtypes, as well as for various childhood brain tumors. While identifying risk factors for these tumors is difficult due to their rarity, many existing datasets can be leveraged for future discoveries in multi-institutional collaborations. Many institutions are continuing to develop large clinical databases including pre-diagnostic risk factor data, and developments in molecular characterization of tumor subtypes continue to allow for investigation of more refined phenotypes.

Key Points

1. Brain tumors are a heterogeneous group of tumors that vary significantly in incidence by age, sex, and race/ethnicity.
2. The only well-validated risk factors for brain tumors are ionizing radiation (which increases risk in adults and children) and history of allergies (which decreases risk).
3. Genome-wide association studies have identified 32 histology-specific inherited genetic variants associated with increased risk of these tumors.

Primary brain tumors (BTs) account for approximately 1% of all newly diagnosed cancers in the United States, and about 2% of cancer deaths.[1,2] BTs are the most common pediatric solid tumors and represent a substantial burden in terms of morbidity and mortality in children.[3] Central nervous system (CNS) tumors are heterogeneous, including tumors of the

brain, cranial nerves, spinal nerves, and meninges, and comprise over 100 histologic types based on cell of origin and other histopathological features.[4] BTs can be broadly classified as malignant or non-malignant (benign) tumors, and graded from I to IV using a classification scheme specified by the World Health Organization (WHO) (see Table 1 for an overview of the most common BT histologies discussed in this review). The majority of BTs diagnosed in the US are non-malignant (WHO grades I and II), of which the majority are meningiomas.[1] The most common malignant BTs (WHO grades III and IV) are gliomas, of which glioblastoma (GBM) is the most common histologic subtype.[1] The goal of this review is to serve as an update to Ostrom et al[5] and Johnson et al.[3]

Genetic Risk Factors

Mendelian Cancer Syndromes and Rare Variants

The majority of glioma cases occur in individuals without a family history of glioma, but approximately 5% of gliomas are familial.[6] An even smaller proportion of gliomas are due to known Mendelian disorders or inherited syndromes, approximately 1–2% of adult and 4% of pediatric cases.[3,5] Most of these syndromes are characterized by loss-of-function mutations in tumor suppressor genes, which may arise de novo or may be inherited, most commonly in either autosomal dominant or autosomal recessive fashion[7,8]; a summary of these is included in Table 2.

Sporadic Brain Tumors and Common Variants

Common genetic variants in adult brain tumors.

—Since the development of rapid whole genome genotyping, 8 genome-wide association studies (GWAS) of glioma,[9–16] 2 GWAS in meningioma,[17,18] 1 GWAS in pituitary adenoma[19], and 1 in primary CNS lymphoma[20] have been conducted. Together, these studies identified 30 genomic variants associated with increased BT risk (25 variants for

Table 1 Overview of most commonly occurring brain tumor histologies

Major Histology	Histologic Subtypes	Percent of All CNS Tumors in the US[a]	Incidence per 100 000 Population in the US[a]	Behavior (WHO grade)	Most Commonly Affected Population
Glioma	GBM	14.7	3.21	Malignant (grade IV)	Older adults, more common in males than females
	Pilocytic astrocytoma	1.3	0.35	Non-malignant (grade I)	Children
	Diffuse astrocytoma	1.9	0.46	Malignant (grade II)	Children and older adults
	Anaplastic astrocytoma	1.7	0.41	Malignant (grade III)	Adults
	Oligodendroglioma	1.3	0.34	Malignant (grades II–III)	Adults
	Ependymoma	1.7	0.43	Non-malignant and malignant (grades I–III)	All ages
Meningioma	Benign meningioma	34.9	7.82	Non-malignant (grade I)	Adults, more common in females than males
	Atypical meningioma	1.8	0.40	Malignant (grade II)	Adults
	Malignant meningioma	0.5	0.10	Malignant (grade III)	Adults
Embryonal tumors	Medulloblastoma	0.6	0.15	Malignant (grade IV)	Children
	Primary neuroectodermal tumors	0.1	0.04	Malignant (grade IV)	Children
	Atypical teratoid/rhabdoid tumors	0.1	0.03	Malignant (grade IV)	Children
Nerve sheath tumors	Vestibular schwannoma (also known as acoustic neuroma)	8.2	1.90	Mostly non-malignant (grade I)	Adults
Pituitary tumors	Pituitary adenoma	16.5	3.94	Non-malignant (not graded)	Adults
Germ cell tumors	Germ cell tumors	0.4	0.10	Not graded	Children
Lymphomas and hematopoietic neoplasms	Primary central nervous system lymphoma	1.9	0.43	Malignant	Older adults

For more information on CNS tumor classification, see Louis, Perry, Reifenberger, et al.[4]
[a] Incidence data from Ostrom, Gittleman, Truitt, et al.[1]

Table 2 Inherited syndromes associated with brain and other CNS tumors

Gene (chromosome location)	Disorder/Syndrome (OMIM ID)	Mode of Inheritance	Phenotypic Features	Associated Brain Tumors
AIP (11q13.2)	Pituitary adenoma predisposition (102200)	Dominant	Familial aggregation of pituitary adenoma; acromegaly or Cushing disease secondary to hormone-secreting tumors	Pituitary adenomas
APC, MMR (5q21)	Familial adenomatous polyposis (FAP, 175100), Turcot's syndrome type 2	Dominant	Development of multiple adenomatous colon polyps (>100), predisposition to colorectal cancer, and brain tumors	Medulloblastoma, glioma
ATM (11q22.3)	Ataxia-telangiectasia (208900)	Autosomal recessive trait	Progressive cerebellar ataxia, susceptibility to infections, predisposition to lymphoma and lymphocytic leukemia	Astrocytoma and medulloblastoma
BAP1 (3p21.1)	BAP1 tumor predisposition syndrome (614327)	Dominant	Predisposition to melanoma, mesothelioma, and other cancers.	Meningioma
CDKN2A (9p21.3)	Melanoma-neural system tumor syndrome (155755)	Dominant	Predisposition to malignant melanoma and malignant brain tumors	Glioma
CREBBP, *EP300* (16p13.3, 22q13.2)	Rubinstein–Taybi syndrome (180849)	Dominant	Dysmorphic facial features, intellectual disability, and predisposition to cancers including CBTs, neuroblastoma, rhabdomyosarcoma, leukemia, lymphoma, and others	Medulloblastoma, oligodendroglioma, and meningioma
DICER1, DROSHA (14q32.13, 5p13.3)	*DICER1* syndrome	Dominant	Impaired DNA damage response; embryonal tumors; kidney, ovary, and thyroid tumors; goiter	Pineoblastoma, pituitary blastoma
FANCA (16q24.3)	Fanconi anemia (227650)	Autosomal recessive trait	Heterogeneous congenital malformations, bone marrow failure, and acute myeloid leukemia	Medulloblastoma
IDH1/IDH2 (2q33.3/15q26.1)	Ollier disease	Acquired post-zygotic mosaicism, dominant with reduced penetrance	Development of intraosseous benign cartilaginous tumors, cancer predisposition	Glioma
MEN1 (11q13.1)	Multiple endocrine neoplasia, type 1 (131100)	Dominant	Hyperparathyroidism; predisposition to tumors at multiple sites including thyroid, adrenal gland, pancreas, duodenum	Pituitary prolactinoma, meningioma
MLH1, PMS2	Turcot's syndrome type 1	Autosomal recessive trait	Development of multiple adenomatous colon polyps (<100), predisposition to colorectal cancer, and brain tumors	Medulloblastoma, glioma,
MSH2,MLH1,MSH6,PMS2	Lynch syndrome (120435), biallelic mismatch repair deficiency, constitutional MMR *deficiency*	Dominant	Predisposition to gastrointestinal, endometrial, and other cancers	Glioblastoma, other gliomas
MSH2,MLH1,MSH6,PMS2	Mismatch repair deficiency syndrome (276300)	Recessive	Pediatric cancer predisposition; café-au-lait spots; colon polyps	Glioma
NF1 (17q11.2)	Neurofibromatosis 1 (NF1) (162200)	Dominant	Neurofibromas, schwannomas, café-au-lait macules	Astrocytoma, schwannomas, optic nerve glioma

Table 2 Continued

Gene (chromosome location)	Disorder/Syndrome (OMIM ID)	Mode of Inheritance	Phenotypic Features	Associated Brain Tumors
NF2 (22q12.2)	Neurofibromatosis 2 (NF2) (101000)	Dominant	Acoustic neuromas, meningiomas, neurofibromas, eye lesions	Acoustic neuromas, meningiomas, Ependymoma
PRKAR1A (17q24.2)	Carney complex (160980)	Dominant	Pigmented nevi; myxomas of the skin, breast, and other sites	Pituitary adenomas
PTCH1 (9q22.3)	Gorlin's syndrome (nevoid basal cell carcinoma)	Dominant	Development of basal cell carcinomas, benign jaw tumors, fibromas of the heart or ovaries, and medulloblastoma	Medulloblastoma, meningioma
PTEN (10q23.31)	Cowden syndrome 1 (158350)	Dominant	Macrocephaly; breast, endometrial and thyroid cancer predisposition	Cerebellar gangliocytoma, meningioma
RB1 (13q14)	Retinoblastoma	Dominant	Development of multiple tumors of the eye, increased risk of some brain tumors	Retinoblastoma, Pineoblastoma, Malignant glioma
RECQL2 (8p12)	Werner syndrome (277700)	Recessive	Diabetes mellitus; early-onset cataract; premature graying of the hair and an aged appearance	Meningioma
SMARCB1 (22q11.23), SMARCE1 (17q21.2), SUFU (10q24.32), MN1 (22q12.1), PDGFB (22q13.1)	Familial meningiomatoses (607174)	Dominant	Familial meningioma aggregation	Meningioma
TP53 (17p13.1)	Li–Fraumeni syndrome (151623)	Dominant	Predisposition to numerous cancers, especially breast, brain, and soft-tissue sarcoma	Glioblastoma, other gliomas
TSC1, TSC2 (9q34.14, 16p13.3)	Tuberous sclerosis (TSC) (191100, 613254)	Dominant	Development of multisystem non-malignant tumors	Giant cell astrocytoma
VHL (3p25)	Von Hippel–Lindau syndrome (193300)	Dominant	Predisposition to kidney cysts, renal cell carcinoma, pancreatic neuroendocrine tumors; pheochromocytomas, endolymphatic sac tumors, and brain tumors	Hemangioblastoma

For more information, see Supplementary Note 1:

Abbreviations: AIP: aryl hydrocarbon receptor interacting protein; APC: adenomatous polyposis coli;BAP1: BRCA1 associated protein 1; CBT: childhood brain tumor; CDKN2A: cyclin-dependent kinase inhibitor 2A;DICER1: dicer 1, ribonuclease III;DROSHA: drosha ribonuclease III; IDH1: isocitrate dehydrogenase 1; IDH2: isocitrate dehydrogenase 2; MEN1: menin 1; MLH1: mutL homolog 1, colon cancer, nonpolyposis type 2;MN1: MN1 proto-oncogene, transcriptional regulator; MSH2: mutS protein homolog 2; MSH6: mutS protein homolog 6; NF1: neurofibromin 1; NF2: neurofibromin 2;PDGFB: platelet derived growth factor subunit B; PMS2: PMS1 homolog 2, mismatch repair system component; PTCH1: Patched 1;PTEN: phosphatase and tensin homolog;PRKAR1A: protein kinase cAMP-dependent type I regulatory subunit alpha; RB1: RB transcriptional corepressor 1;RECQL2 (WRN): Werner syndrome RecQ like helicase;SMARCB1: SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1;SMARCE1: SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily e, member 1; TP53: tumor protein p53; TSC1: TSC complex subunit 1; TSC2: TSC complex subunit 1;SUFU: SUFU negative regulator of hedgehog signaling; VHL: von Hippel–Lindau tumor suppressor

Table 3 Previously reported brain tumor risk loci identified by GWAS, by histology including allele frequencies, *P*-values, OR, and 95% CI

Histology	SNP rs ID[a] (locus)	Associated Gene	Population	RAF in Studied Population[b]	*P*-value	Odds Ratio (95% CI)	Associated Brain Tumor Type
All glioma	rs1920116 (3q26.2)	*TERC*	European/East Asian	Eur: 0.720 EA: 0.389	Eur: 7.36×10^{-5} EA: 0.0060	Eur: 1.08 (1.04–1.13) EA: 1.20 (1.05–1.36)	All glioma subtypes
	rs10069690 (5p15.33)	*TERT*	European	0.276	2.71×10^{-66}	1.45 (1.39–1.51)	All glioma subtypes
	rs2853676 (5p15.33)	*TERT*	European/East Asian	Eur: 0.290 EA: 0.611	Eur: 4.0×10^{-14} EA: 0.0001	Eur: 1.26 (1.20–1.32) EA: 1.53 (1.21–1.94)	Astrocytoma
	rs2252586 (7p11.2)	*EGFR*	European	0.281	1.38×10^{-13}	1.16 (1.11–1.20)	All glioma subtypes
	rs648044 (11q23.2)	*PHLDB1*	European	0.390	4.66×10^{-12}	1.19 (1.13–1.25)	All glioma subtypes
	rs17748 (11q23.2)	*PHLDB1*	East Asian	0.227	2.36×10^{-5}	1.36(1.17–1.59)	All glioma subtypes
	rs2236661 (11q23.2)	*PHLDB1*	East Asian	0.231	1.0×10^{-5}	1.46 (1.23–1.72)	All glioma subtypes
	rs494560 (11q23.2)	*PHLDB1*	East Asian	0.326	4.23×10^{-5}	0.71 (0.60–0.85)	All glioma subtypes
	rs10842893 (12p11.23)	*STK38L*	East Asian	0.035	2.33×10^{-12}	2.07 (1.71–2.50)	All glioma subtypes
	rs4774756 (15q21.3)	*RAB27A*	East Asian	0.297	6.12×10^{-8}	1.24 (1.15–1.33)	All glioma subtypes
	rs78378222 (17p13.1)	*TP53*	European	0.013	8.64×10^{-38}	2.53 (2.19–2.91)	All glioma subtypes
	rs6010620 (20q13.33)	*RTEL1*	European/ East Asian	Eur: 0.794 EA: 0.293	Eur: 2.81×10^{-40} EA: 0.021	Eur: 1.34 (1.29–1.40) EA: 1.28 (1.04–1.57)	All glioma subtypes
Glioblastoma	rs12752552 (1p31.3)	*RAVER2*	European	0.870	2.04×10^{-9}	1.22 (1.15–1.31)	Glioblastoma
	rs11979158 (7p11.2)	*EGFR*	European	0.831	1.94×10^{-19}	1.31 (1.24–1.39)	Glioblastoma
	rs730437 (7p11.2)	*EGFR*	East Asian		0.0160	1.32 (1.05–1.66)	Glioblastoma
	rs1468727 (7p11.2)	*EGFR*	East Asian		0.0080	1.31 (1.04–1.65)	Glioblastoma
	rs11233250 (11q14.1)	Intergenic	European	0.868	9.95×10^{-10}	1.24 (1.16–1.33)	Glioblastoma
	rs2562152 (16p13.3)	*RHBDF1*	European	0.850	1.93×10^{-8}	1.21 (1.13–1.29)	Glioblastoma
	rs10852606 (16q12.1)	*HEATR3*	European	0.713	1.29×10^{-11}	1.18 (1.13–1.24)	Glioblastoma
	rs2235573 (22q13.1)	*SLC16A8*	European	0.507	1.76×10^{-10}	1.15 (1.10–1.20)	Glioblastoma
Lower grade glioma	rs4252707 (1q32.1)	*MDM4*	European	0.220	3.34×10^{-9}	1.19 (1.12–1.26)	Lower grade glioma
	rs12076373 (1q44)	*AKT3*	European	0.837	2.63×10^{-10}	1.23 (1.16–1.32)	Lower grade glioma
	rs7572263 (2q33.3)	*C2orf80*	European	0.756	2.18×10^{-10}	1.20 (1.13–1.26)	Lower grade glioma
	rs11706832 (3p14.1)	*LRIG1*	European	0.456	7.66×10^{-9}	1.15 (1.09–1.20)	Lower grade glioma
	rs55705857 (8q24.21)	*CCDC26*	European	0.057	7.28×10^{-149}	3.39 (3.09–3.71)	Lower grade glioma, in particular IDH-mutant tumors

Table 3 Continued

Histology	SNP rs ID[a] (locus)	Associated Gene	Population	RAF in Studied Population[b]	*P*-value	Odds Ratio (95% CI)	Associated Brain Tumor Type
	rs4977756 (9p21.3)	*CDKN2B-AS1*	European	0.400	2.28×10^{-14}	1.20 (1.15–1.26)	Lower grade glioma, in particular WHO grade II-IV astrocytic tumors
	rs11598018 (10q24.33)	*OBFC1*	European	0.462	3.39×10^{-8}	1.14 (1.09–1.20)	Lower grade glioma
	rs11599775 (10q25.2)	*VTI1A*	European	0.620	3.44×10^{-9}	1.16 (1.10–1.22)	Lower grade glioma
	rs7107785 (11q21)	*MAML2*	European	0.479	3.87×10^{-10}	1.16 (1.11–1.21)	Lower grade glioma
	rs498872 (11q23.3)	*PHLDB1*	European	0.307	8.46×10^{-33}	1.35 (1.28–1.41)	Lower grade glioma, in particular IDH-mutant gliomas
	rs1275600 (12q21.2)	Intergenic	European	0.595	3.72×10^{-9}	1.16 (1.10–1.21)	Lower grade glioma
	rs10131032 (14q12)	*AKAP6*	European	0.916	5.07×10^{-11}	1.33 (1.22–1.44)	Lower grade glioma
	rs1801591 (15q24.2)	*ETFA*	European	0.088	6.36×10^{-13}	1.33 (1.23–1.44)	Lower grade glioma
	rs3751667 (16p13.3)	*RHBDF1*	European	0.208	2.61×10^{-9}	1.18 (1.12–1.25)	Lower grade glioma
Meningioma	rs11012732 (10p12.31)	*MLLT10*	European	0.320	1.88×10^{-14}	1.46 (1.32–1.61)	Meningioma
	rs2686876 (11p15.5)	Possibly *RIC8A*	European	0.906	9.86×10^{-9}	1.44 (1.27–1.63)	Meningioma
Pituitary adenoma	rs2359536 (10p12.31)	*MIR4675, NEBL*	East Asian	0.082	2.25×10^{-10}	1.44 (1.29–1.62)	Pituitary adenoma
	rs10763170 (10q21.1)	*PCDH15*	East Asian	0.201	6.27×10^{-10}	1.28 (1.18–1.39)	Pituitary adenoma
	rs17083838 (13q12.13)	*CDK8*	East Asian	0.104	1.89×10^{-8}	1.37 (1.23–1.53)	Pituitary adenoma
Primary central nervous system lymphoma	rs41289586 (3p22.1)	*ANO10*	European	0.021	1.87×10^{-8}	3.82 (2.39–6.09)	Primary central nervous system lymphoma
	rs116446171 (6q25.3)	*EXOC2, IRF4*	European	0.021	1.53×10^{-13}	4.99 (3.26–7.65)	Primary central nervous system lymphoma

For more information, see Supplementary Note 2:

Abbreviations: AKAP6: A-kinase anchoring protein 6; AKT3: AKT serine/threonine kinase 3; ANO10: anoctamin 10; C2orf80: chromosome 2 open reading frame 80; CCDC26: CCDC26 long non-coding RNA; CDKN2B-AS1: cyclin dependent kinase inhibitor 2B antisense RNA 1; CDK8: cyclin-dependent kinase 8; EGFR: epidermal growth factor receptor; ETFA: electron transfer flavoprotein subunit alpha; EXOC2: exocyst complex component 2; HEATR: HEAT repeat containing 3; IRF4: interferon regulatory factor 4; LRIG1: leucine rich repeats and immunoglobulin like domains 1; MAML2: mastermind like transcriptional coactivator 2; MDM4: MDM4 regulator of p53; MIR4672: microRNA 4672; MLLT10: MLLT10 histone lysine methyltransferase DOT1L cofactor; NEB: Nebulin; OBFC1: STN1 subunit of CST complex; PCDH15: protocadherin related 15; PHLDB1: pleckstrin homology like domain family B member 1; RAF: risk allele frequency; RAVER2: ribonucleoprotein, PTB binding 2; RHBDF1: rhomboid 5 homolog 1; RIC8A: RIC8 guanine nucleotide exchange factor A; RTEL: regulator of telomere elongation helicase 1; SLC16A8: solute carrier family 16 member 8; SNP: single nucleotide polymorphism; TERT: telomerase reverse transcriptase; TP53: tumor protein p53; VTI1A: vesicle transport through interaction with t-SNAREs 1A

a.Included SNPs are those identified within cited publications, and generally represent the strongest independent association within a linkage block.

b.Allele frequencies from: 1000 genomes project phase 3 (The 1000 Genomes Project Consortium, Auton A, Brooks LD, et al. A global reference for human genetic variation. Nature. 2015;526(7571):68–74.), and gnomAD (Lek M, Karczewski KJ, Minikel EV, et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature. 2016;536(7616):285–291.)

Neuro-Oncology

adult glioma, 2 for meningioma, 3 for pituitary adenoma and 2 for primary CNS lymphoma Table 3). The proportion in incidence variance of glioma estimated as being attributable to genetic factors is 25%, and ~30% of this is explained by currently identified variants, with 70% of the genetic risk unexplained.[13,21] Many of these factors have stronger associations with specific grades and histologies of glioma, though some confer increased risk for all types. Eleven of 25 single nucleotide polymorphisms (SNPs) were identified as having a significant association with GBM, and 18 were significantly associated with non-GBM glioma (or lower-grade glioma). The strongest association identified to date is *CCDC26* (rs55705857), which increases risk for lower-grade glioma. This SNP is most strongly associated with oligodendroglioma, where it confers an odds ratio (OR) >4.[22]

Though BTs are known to be heterogeneous, most analyses attempting to discover germline risk variants have been conducted on pooled histologies or with classification based on histologically assigned type and grade. Due to their rarity, BT case cohorts are usually ascertained at multiple centers over extended periods. Results from molecular tests may not be available on all cases, though many groups are attempting to reclassify these cases as technologies and classifications evolve, which is now part of standard of care for glioma diagnosis.

In a subset of molecularly characterized glioma cases with matching data from GWAS, Labreche et al estimated the OR associated with the 25 previously identified risk loci by molecular subtypes (Fig. 1).[23] While some single SNPs were significantly associated with all molecular subtypes (eg, 17p13.1/*TP53*), most varied in their association. SNPs previously associated with non-GBM glioma were significantly associated with isocitrate dehydrogenase 1 and 2 (*IDH1/2*) mutant subtypes, including associations at 8q24.21/*CCDC26* and 11q23.3/*PHLDB1*. SNPs previously found to have strong association with GBM, such as those at 5p15.33/*TERT* and 20q13.33/*RTEL1*, showed the strongest association with *TERT*-mutant tumors. Due to limitations in their sample size, further research is necessary in order to characterize the association between glioma risk SNPs and somatic variation.

Germline genetic factors associated with risk for BTs other than glioma have not been well studied. A recent meta-analysis GWAS for meningioma showed genome-wide significant associations in regions 10p12.31 (associated with *MLLT10*) and 11p15.5.[17] The identified SNP in 11p15.5 (rs2686876) is in strong linkage disequilibrium (LD) with *RIC8A,* which is involved in development of the meninges.[17] A GWAS of sporadic pituitary adenoma conducted in a Chinese population identified 3 genome-wide significant associations in regions 10p21.31 (near *NEBL*), 10q21.1 (*PCDH15*), and 13q12.13 (*CDK8*).[19] A recent meta-analysis of 2 studies of primary CNS lymphoma identified 2 genome-wide significant associations in regions 3p22.1 (*ANO10*) and 6q25.3 (between *EXOC2* and *IRF4*), as well as associations in 6p25.3 (in the *IRF4* promoter) and 8q24.21 (*MYC*) that did not reach genome-wide significance.[20]

Common genetic variants in childhood brain tumors

To date, few genetic association studies have been conducted in childhood brain tumors (CBTs), and there are no published GWAS in CBTs. As a result, the contribution of common genetic variants to CBT risk is largely unknown. There have been several candidate gene studies conducted, many of which have been conducted in pooled datasets including multiple subtypes. These studies have identified risk variants associated with CBTs in *CYP1A1*, *GSTT1*, *GSTM1* (genes of xenobiotic detoxification), [24,25] *NOS1* (involved in several pathways including inflammation), *XPD* (involved in DNA repair pathway), [24] *AICDA, CASP1* (genes involved in cell cycle pathway),[26] as well as genes involved in folate metabolism. Dahlin et al found that of the 10 genes known to be somatically altered in medulloblastoma, 8 variants in 3 genes (*CCND2*, *PTCH1*, and *GLI2*) are nominally associated with risk of medulloblastoma.[27] Associations have also been identified between SNPs in *IRS2* and *CDKN2A/B*, involved in cell cycle pathway, and medulloblastoma.[28,29] Adel Fahmideh et al investigated whether genetic variants identified in adult glioma are related to CBT risk and found that variants in *EGFR*, *ERCC1*, *CHAF1A*, *XRCC1, EME1*, *ATM*, *GLTSCR1*, *XRCC4, CDKN2BAS,* telomerase reverse transcriptase (*TERT*), regulator of telomere elongation helicase 1 (*RTEL1*), and *CCDC26*, involved in either DNA repair or cell cycle pathways, may also be associated with CBTs.[30,31] These findings may suggest that CBTs and adult BTs share common genetic risk factors. These candidate gene studies are based on small samples and have not been replicated. These were issues which plagued candidate gene studies in adult glioma.[32] As most validated genetic associations for adult BTs have been identified by GWAS, it is necessary to conduct GWAS in CBTs, and such efforts are currently under way.

Telomere Length

GWAS of leukocyte telomere length (LTL) have identified multiple germline variants which can be used to build a polygenic risk score (PRS) to estimate individual telomere length.[33] Longer LTL estimated using this PRS has been associated with increased risk of glioma and meningioma (reviewed by Walsh et al[34]).[35,36] Similarly, longer relative LTL (measured by quantitative PCR) has been associated with increased glioma risk in a Swedish case-control study.[37] Multiple common variants associated with glioma through GWAS are located near telomere-associated genes, including *TERT* and *RTEL1*.[35] Analysis of glioma tumor samples has demonstrated longer telomere length compared with other cancers.[38]

Genetic Ancestry

Malignant brain tumor incidence is highest in countries with primarily European ancestry populations.[39] To date, most GWAS in glioma and all in meningioma have been conducted in primarily individuals of European ancestry, while 1 GWAS of pituitary adenoma has been conducted in an East Asian population. [19] One recent GWAS of glioma in a Chinese population confirmed associations near *TERT*, *PHLDB1*, and *RTEL1*, and identified 2 new variants, but strong statistical signal in the human leukocyte antigen region suggests this analysis may be biased by population stratification.[40] Previous analyses have attempted to compare allele frequencies of previous GWAS hits within

reference datasets by ancestry groups, but these have failed to identify new risk variants in non–European ancestry populations.[41] Several candidate SNP studies have been conducted in East Asian populations, which have found novel association loci as well as validated associations previously discovered in European ancestry populations, including loci in *TERC*, *TERT*, *EGFR*, and *PHLDB1*.[42,43] Analysis of patterns of continental ancestry in African Americans and Hispanics with glioma has identified increased overall European ancestry in glioma cases compared with controls.[44]

Demographic Factors Associated with Brain Tumor Incidence

Age

Incidence of BTs overall increases with age (Fig. 2A).[1] For malignant glioma in particular, the incidence is bimodal, with highest incidence in the youngest and oldest ages. The age distribution also varies by histologic type. Embryonal tumors, a group that includes medulloblastoma and primitive neuroectodermal tumors, occur most frequently in children <10 years old (Fig. 2B). Incidence of pituitary tumors is also bimodal, with peaks in adolescence/young adulthood, and again in older adulthood (Fig. 2C). The most common BTs, such as GBM, vestibular schwannoma, and meningioma, have the highest incidence in individuals in their late 60s and early 70s, with a decreasing incidence thereafter. This may be due to competing causes of mortality, different diagnostic patterns in the oldest age group, or true differences in BT incidence.

Sex

Incidence of BTs varies by sex, with malignant tumors occurring much more frequently in males and non-malignant tumors generally occurring more frequently in females (Fig. 2D).[1] This sex difference varies significantly by histology, with some histologies showing little or no variation in incidence by sex. The largest sex difference is observed in non-malignant meningioma (which is nearly twice as common in females), and high-grade gliomas (particularly GBM, which is ~60% more common in males). Sex differences are smaller or nonexistent in many tumors that are common in children, such as pilocytic astrocytoma and medulloblastoma.

Race/Ethnicity

Incidence of different histologies of BTs varies by race/ethnicity (Fig. 2E).[1] Neuroepithelial tumors, including gliomas, are much more common in individuals of European ancestry (white non-Hispanics) compared with other groups. Meningiomas and pituitary adenomas occur more frequently in black non-Hispanics compared with other groups. Nerve sheath tumors and germ cell tumors have the highest incidence in Asian/Pacific Islanders.

Socioeconomic Status

Individuals of higher socioeconomic status (SES) are at higher risk of developing malignant BTs compared with those of low SES.[45–51] SES is associated with many cancers, often due to its correlation with causal risk factors or increased case ascertainment associated with better access to health care and screening.[52–58] For BTs, the causal factors underlying differential incidence in SES strata have not yet been determined. Although some of the trends of higher incidence in areas of high SES are explained by racial differences, studies that adjusted for race also demonstrated a higher incidence in areas of higher SES.[59] Using census tract level data, analyses have shown a 45% higher incidence rate of GBM comparing highest versus lowest SES after adjustment for self-reported race,[45] with a dose-response relationship for increasing quartiles of SES.[49] A 2016 cohort study showed higher incidence of BT among the highly educated (≥3 y university education) as well as an association with higher income in males only.[46] Highly educated women also had a higher risk of meningioma. Other non-malignant BTs, such as vestibular schwannoma, showed similar trends. For malignant BTs, these findings are unlikely to be the result of ascertainment bias alone, as these BTs have an aggressive clinical course and are often fatal and likely to be universally diagnosed in countries with high-functioning medical systems.[5,45,47] Given that studies adjusted for race show higher incidence among those in high SES areas, there appears to be some independent effect of SES beyond its association with race that may cause higher incidence of malignant BT. For other tumors, such as meningioma, acoustic neuroma, and pituitary tumors, however, improved access to medical care may lead to higher rates of incidental imaging, leading to ascertainment bias.[60] Future studies should assess these associations further, with stratification by possible confounders (eg, rural/urban status and health care–seeking behavior).

Validated and Potential Non-Genetic Risk Factors

Allergies

Studies of large and diverse groups of cases and controls have consistently shown that history of atopic conditions (including asthma, hay fever, eczema, and allergies) leads to reduced glioma risk (Supplementary Table 1).[61] History of allergies has been shown to decrease risk of glioma by ~30%, and histology-specific analyses have suggested that the protective effect conferred by allergy may vary by glioma histology.[62] Allergies and atopic disease, as well as early life exposure to infections, have also been associated with reduced risk of CBT.[3,63] The underlying mechanism through which allergy protects against development of BTs is unknown, but the primary hypothesis is that allergic conditions may lead to a heightened state of immune-surveillance, discouraging abnormal cell growth, leading to development of a brain tumor.[61,64,65]

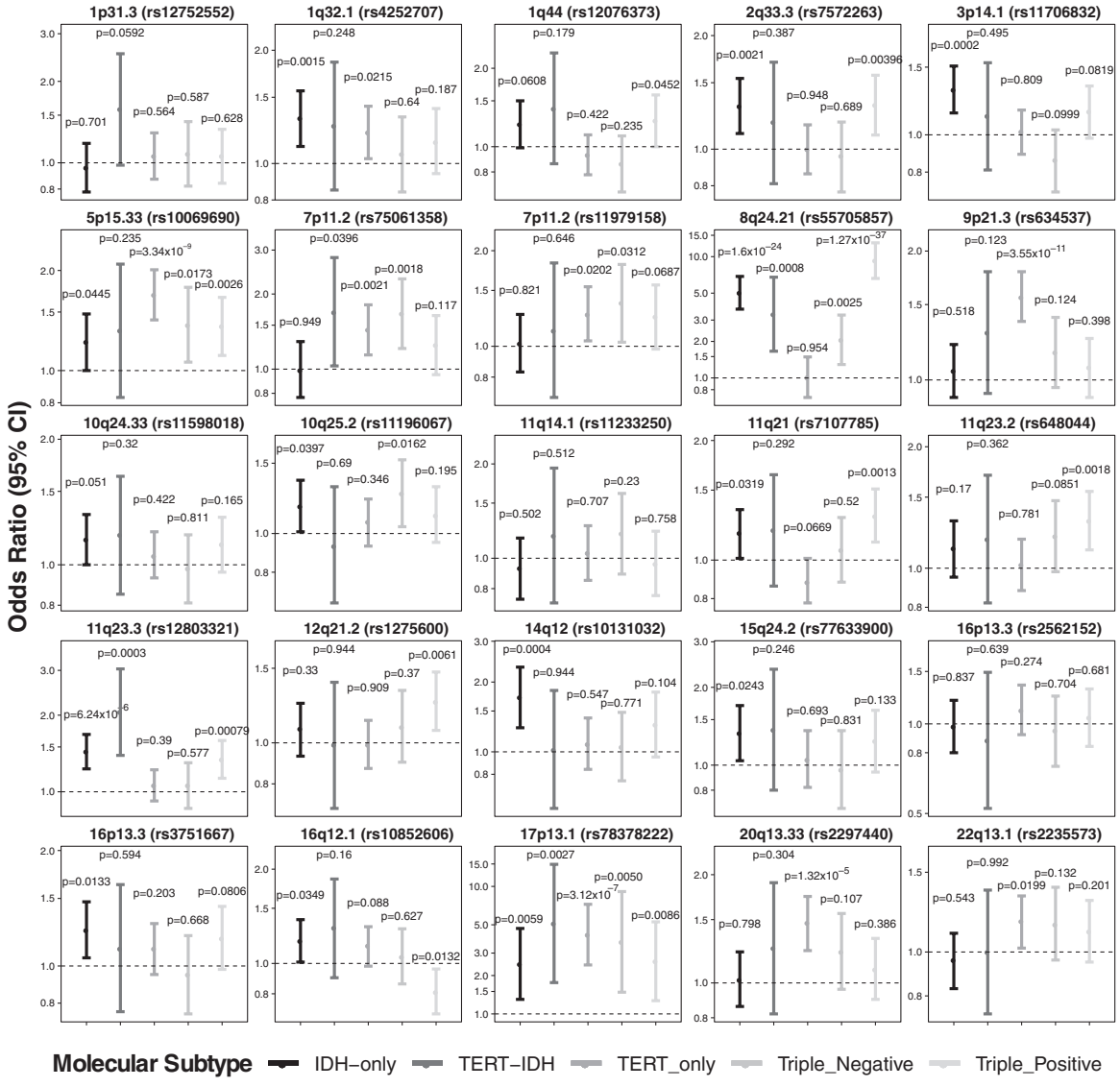

Fig. 1 ORs, 95% CIs, and *P*-values for previously identified glioma risk SNPs by molecular subtype (data from Labreche et al[23]).

Recently, a Mendelian randomization (MR) analysis was published using GWAS summary statistics to assess whether a causal association exists between allergy and glioma. These studies identified no relationship between germline variants associated with asthma, hay fever, immunoglobulin E levels, and/or self-reported allergy, but did identify a weak association between genetic predisposition to atopic dermatitis and reduced risk of glioma.[66]

Medications

Aspirin and non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) act by inhibiting prostaglandin production via suppression of the cyclooxygenase enzymes. The association of these drugs, including aspirin, has been investigated in multiple solid cancers, including glioma and meningioma (Supplementary Table 2).[67,68] A recent meta-analysis found that regular use of aspirin was associated with significantly decreased risk of all glioma (WHO grades II/III glioma) and GBM.[68] There was no significant association between use of non-aspirin NSAIDs and glioma risk. Further studies are necessary to elucidate the mechanisms through which aspirin may confer decreased risk of glioma.

Statins

Hydroxy-methylglutaryl-coenyzme A reductase inhibitors, or statins, are widely used to treat hypercholesterolemia.

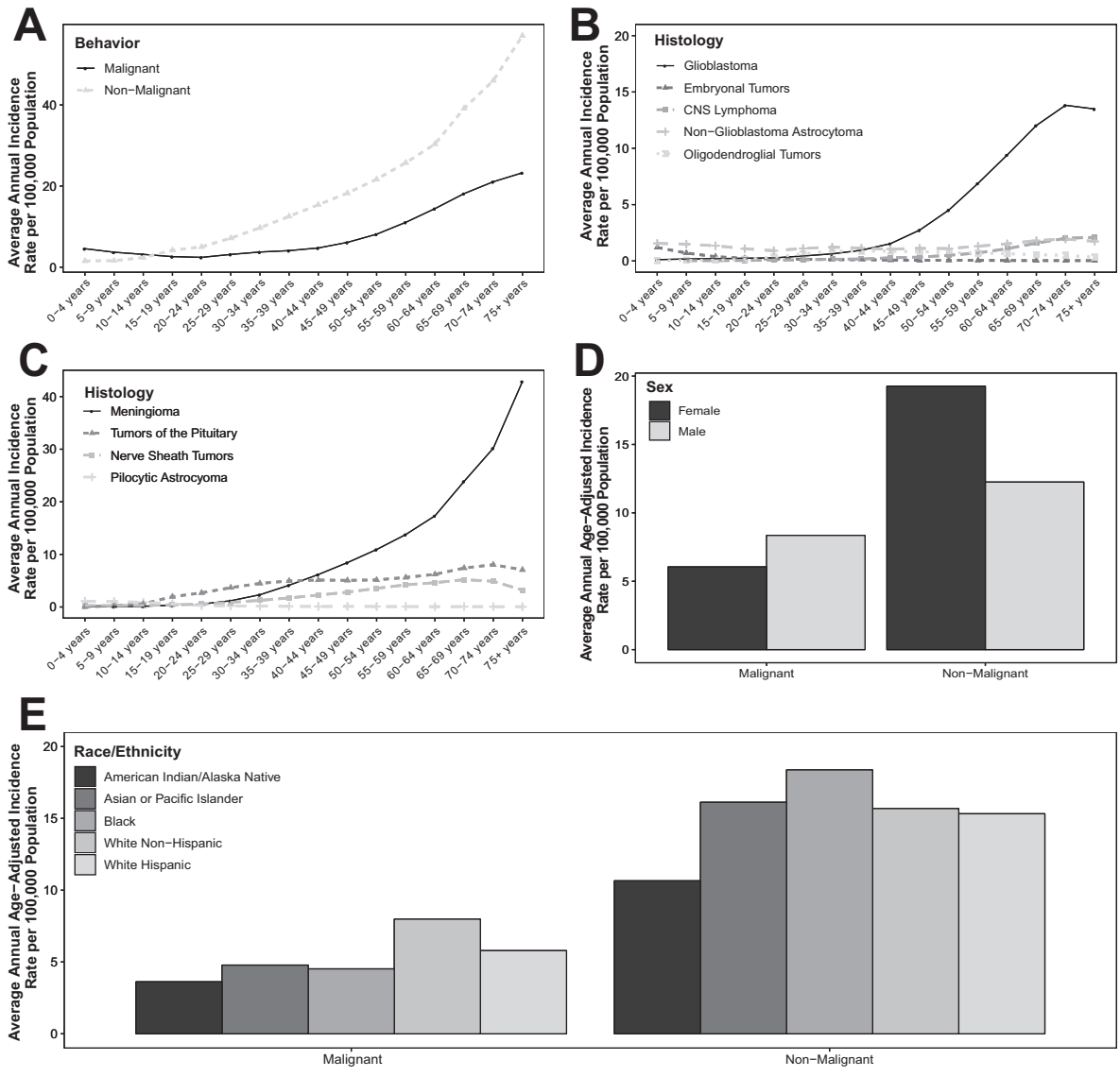

Fig. 2 Average annual incidence of primary brain and CNS tumors in the United States by age and (a) behavior, (b) selected malignant histologies, and (c) selected non-malignant histologies, and average annual age-adjusted incidence by behavior and (d) sex and (e) race/ethnicity (Central Brain Tumors Registry of the United States [CBTRUS], 2011–2015).[1]

Much research has investigated the possibility that statins may lower the incidence of neurological disease.[69,70] Some statins can penetrate the blood–brain barrier, and may specifically reduce brain inflammation, which may result in lower risk of malignant transformation.[71–73] Statin use and subsequent risk of glioma has been investigated in 3 major case-control studies: 2 using self-report data and 1 using pharmacy linkage (Supplementary Table 2). All 3 of these studies reported similar point estimates, suggesting that regular statin use may be associated with a 25% reduction in glioma risk.[74–77]

Endogenous and Exogenous Hormone Exposure

Previous analyses have examined the impact of exogenous and endogenous sex hormone exposure as a potential environmental risk factor for BTs (Supplementary Table 3).[78] The lower incidence of glioma in females has led some to hypothesize that increased lifetime estrogen exposure may act as a protective factor against developing these tumors, while increased incidence of meningioma among females suggests that this hormone exposure may be a risk factor. Lifetime hormone exposure can be difficult to accurately measure, and analyses have focused on surrogates for endogenous exposure (eg, age at menarche, parity, age at menopause) and use of supplemental estrogen or progesterone (eg, hormone replacement therapy, oral contraceptives). While some studies have found negative associations between glioma and estrogen exposure, results have generally been conflicting or null.[79] Positive associations between meningioma and estrogen exposure have also been identified, and hormone exposure remains one of the strongest risk associations identified to date in

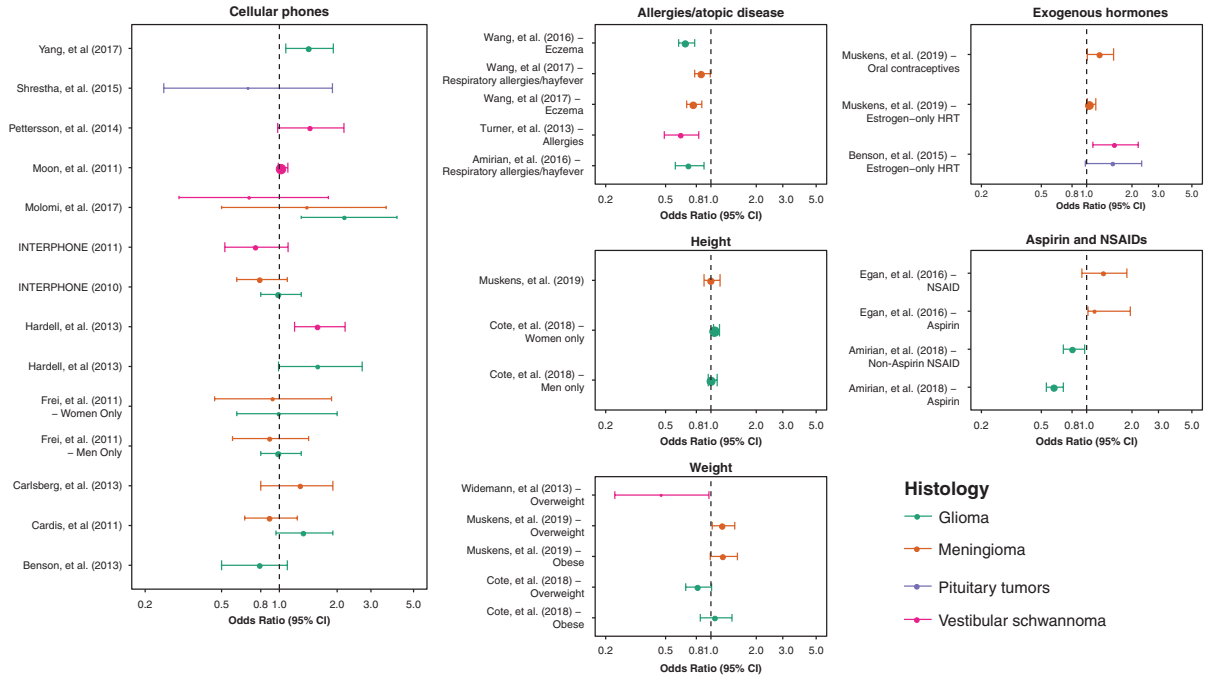

Fig. 3 ORs and 95% CIs selected potential risk factors for primary brain tumors for glioma, meningioma, vestibular schwannoma, and pituitary tumors (See Supplementary Note 3 for data sources).

these tumors.[80] Due to the difficulty in accurately assessing lifetime hormone exposure, it is not possible to definitively state if these exposures are associated with BT risk.

Anthropometric Factors

Anthropometric factors, including height and body mass index (BMI), have been repeatedly studied in relation to BT risk (Supplementary Table 4). As shown for other cancers in several prospective studies, taller adult height has been identified as a glioma risk factor, with ~20% increase in risk for every 10 cm increase in height.[81,82] In the National Institutes of Health–AARP cohort, Moore et al found significant associations between taller height and increased risk of glioma (relative risk = 2.12 comparing those >1.9 m with those <1.6 m).[83]

While taller adult height appears to be a consistent risk factor for glioma, there is less evidence for an effect of adult BMI on glioma incidence. Studies into the association between BMI and glioma risk have mostly been null.[81,84–89] A recent meta-analysis did not identify an increased risk of glioma for overweight and obese individuals,[86] although a separate meta-analysis reported an association in women only.[85] Higher BMI has been associated with increased meningioma risk in multiple large prospective cohort studies, while associations between meningioma, and height, daily activity, and waist circumference were less consistent across these studies.[88,90–92]

Recently, GWAS summary statistics have been leveraged to perform MR analyses to assess whether a causal association exists between obesity and BT. These analyses found no association between germline variants associated with BMI, waist-to-hip ratio, lipids, type 2 diabetes, hyperglycemia, and/or insulin resistance and glioma.[93] When the same analysis was performed for meningioma, significant associations were found for BMI (OR = 1.27; 95% CI = 1.03–1.56; P = 0.028) and body fat percentage (OR = 1.28; 95% CI = 1.01–1.63; P = 0.042).[94] These analyses support the results of epidemiological studies that have repeatedly identified associations between BMI and meningioma. There are many mechanisms through which excess body fat is thought to increase predisposition to cancer,[95] and for meningioma in particular it is hypothesized that the increased levels of circulating estrogen created by adipose tissue may be one pathway through which risk is increased.[96,97]

Diet

Studies of diet and BT risk are limited, in part due to the rarity of BTs and the well-known limitations of case-control studies in assessing diet. Although cohort investigations may be generally more unbiased, the number of accumulated BT cases in prospective cohorts tends to be small. Nevertheless, a recent investigation using 3 large prospective cohorts included 2313 glioma cases and did not demonstrate an association between major food groups, nutrients, or healthy dietary patterns and glioma incidence, particularly after excluding the first 5 years of follow-up. This study suggests that diet may not play a role in glioma incidence.[98] Several other studies have examined diet in relation to glioma risk, with publications on a variety of dietary exposures that have been previously reviewed by Kyritsis et al and are included in Supplementary Table 5.[99] The associations between processed meats, nitrites, and glioma risk have been previously examined, with largely null results, while an inverse association has been

suggested for both meningioma and glioma with higher intake of vegetables.[100–103] Recent meta-analyses have shown inverse associations between glioma risk and dietary vitamins C and A.[104,105] A recent MR study of vitamin D and glioma showed no evidence for a causal association.[106] Coffee and tea intake have been associated with lower risk of several cancers, and has also been studied in relation to glioma risk, but associations have largely been null or borderline inverse.[107–111]

Ionizing Radiation

Moderate-to-high doses of radiation are the strongest and most consistently documented environmental risk factor for BTs, having been independently observed in atomic bomb survivor studies, therapeutic radiation cohorts (both for treatment of prior cancer and for benign conditions), and occupational and environmental studies (Supplementary Table 6). The carcinogenic effects of ionizing radiation are stronger in children, as they are more radiosensitive and have more years of potential life to express the risk. Some studies have shown that radiation therapy for childhood cancers is associated with development of BTs later in life, particularly those being treated for acute lymphoblastic leukemia (reviewed by Davis et al[62]). Estimated risk was higher for younger children, and the latency between irradiation and BT occurrence has been estimated at 7–9 years,[112] with meningiomas and gliomas being the predominant induced tumor types.[113]

Maternal diagnostic radiation during pregnancy has been found to be related to an increased risk of BT,[114] and increasing use of diagnostic techniques such as CT and PET have raised health concerns. A recent article reviewed the research to date and concluded that for children exposed to one or more head CT scans, the excess relative risk of developing a BT was 1.29.[115] However, these findings might be confounded by reverse causation, as children with higher cancer susceptibility and preexisting cancer are more likely to undergo head CT scans.[115] These studies indicate an elevated risk of CBTs related to radiation dose, with increased risk with a younger age at exposure.[116]

Non-Ionizing Radiation

Cellular phones

Cellular phone technology was introduced in the 1980s and has rapidly increased so that the vast majority of people globally now use cellular phones (Supplementary Fig. 1). Cellular phones emit radiofrequency fields, and, when used against the head, the brain absorbs the largest dose. Due to public health concerns, the association between risk of BTs and cellular phone use has been investigated extensively. In 2011, the International Agency for Research on Cancer (IARC) classified radiofrequency fields as a possible carcinogen, based largely on preliminary epidemiological findings of an increased risk of glioma and vestibular schwannoma in heavy cellular phone users.[117] Since publication of the results of the INTERPHONE consortium case-control study[118,119] and the IARC Monograph in 2010–2011, there have been at least 13 published epidemiological studies reporting on BT risk in relation to cellular phone use (Fig. 3). Case-control studies of cellular phone use and BTs have suffered from previously described methodological issues[120,121] and have often included the same population across multiple analyses. The majority of these have found no significant association between cellular phone use and risk of any type of BT.

Analyses of time trends of age-standardized BT incidence rates from high-quality registration data are an important source of data to examine the possible association between cellular phone use and BTs. Since 2011, there have been at least 16 studies examining incidence trends during the period of increasing cellular phone use (Supplementary Table 7). The majority of these analyses have found little to no change in incidence of specific BT histologies, with the exception of some analyses of Israeli and UK data that found increased incidence of GBM.[122,123] Two studies assessed the US and Australian data and found that small observed increases in incidence were not compatible with the magnitude of risks reported by case-control studies.[124,125] An analysis by de Vocht comparing actual incidence to models based on earlier incidence data before widespread cellular phone use indicated that site-specific incidence of GBM did exceed these but was most significantly associated in the oldest populations: those least likely to have been heavy cellular phone users.[126]

The epidemiological evidence published since the IARC Monograph in 2011 does not support an association between cellular phone use and risk of BT. If an association exists, the latency period for this exposure is unknown, and monitoring of incidence trends data is advisable.

Low frequency electromagnetic fields

A number of studies have also examined the association between extremely low frequency magnetic fields (ELFs) and BT risk (Supplementary Table 8).[5] In 2002, despite some observed positive associations, particularly in case-control studies, the IARC concluded that the summation of existing data was insufficient to classify ELFs as a risk factor for BT.[127] Recently, published results from the INTEROCC consortium did not find an association with lifetime cumulative occupational exposure to ELF.[128]

Non-Radiation Occupational Exposures

Possible associations between specific occupations and/or non-radiation occupational exposures and BTs have been studied extensively (Supplementary Table 9).[5] However, to date, no occupational exposures have been consistently associated with risk of BTs.

Smoking

Although smoking remains one of the most common and well-understood causes of cancer worldwide, its association with BTs is mixed. Smoking has consistently been found to have a null association with incidence of malignant BTs. A 2016 meta-analysis reviewed 19 case-control and 6 cohort studies, reporting a summary risk ratio of 0.98 (95% CI = 0.92–1.05) for ever smokers compared with never smokers.[129] Across multiple cohorts, as well as studies from

geographically diverse regions, cigarette smoking has consistently been shown to be unrelated to glioma risk.[129–133] For non-malignant BTs, smoking appears to have a protective effect. Claus et al reported significantly decreased risk of meningioma among female smokers compared with non-smokers (OR = 0.8; 95% CI = 0.7–0.9), but no significant differences for men.[134] Other studies did not identify a significant association between smoking and meningioma, even when women were analyzed separately.[82,90,91] Similarly, the Million Women Study demonstrated reduced risk of acoustic neuroma (vestibular schwannoma) among women who were ever smokers compared with non-smokers (OR = 0.41; 95% CI = 0.24–0.70).[135,136] The reasons for these unexpected inverse associations have yet to be explored.

Birth Weight and Other Birth Characteristics

Relatively consistent evidence has been provided by large studies and meta-analyses revealing positive associations between CBTs and both advanced parental age[3,137] and birth characteristics.[138,139] A recent meta-analysis including 41 articles concluded that high birth weight (>4000 g) is associated with increased risk of CBT, particularly for astrocytoma and embryonal tumors.[138] These findings were supported by another meta-analysis indicating an elevated risk of astrocytoma and embryonal tumors related to high birth weight.[139] In contrast, a relatively smaller study based on pooled data from 2 French case-control studies could not detect any association between birth weight and risk of CBTs.[140] Despite the potential important role of maternal genetics in the initiation and progression of CBT, knowledge on the role of maternal genetic variants in CNS etiology is limited.

Structural Birth Defects

Non-chromosomal structural birth defects (excluding trisomy and other chromosomal disorders) are among the strongest and most consistent risk factors for childhood cancer, and the percentage of CBTs attributable to birth defects is about 7%.[141,142] Several large, population-based studies have recently assessed the association of any major non-chromosomal birth defect with CBT risk. These studies suggest that diagnosis of a birth defect is associated with ~2-fold increased risk of CBT.[143–146]

While considerable work remains to be done in characterizing specific birth defect–CBT associations, some patterns have emerged. Specifically, greater increases in CBT risk are seen among children with a birth defect of the CNS or with a neurological anomaly.[145–151] In addition, multiple studies reported increased prevalence of rib anomalies among CBT patients compared with controls or population norms, with only astrocytoma patients demonstrating a statistically significant excess of these anomalies,[152–154] as well as increased risk associated with oral clefts, or defects of the ear, face, and neck.[146,150,155] Studies which have investigated childhood cancer risk as a function of age suggest that hazard functions for cancer overall and CBTs specifically converge to those of unaffected controls by ~5 years of age.[143,144,147] Ascertainment biases are unlikely to fully explain these associations. Cancer surveillance is not routine in children with structural birth defects.[143] To address the possibility that birth defects may be identified incidentally during evaluation of children with cancer, one study restricted analyses to children diagnosed with cancer >1 year of age, and the maximum age at which participating registries recorded birth defects. Associations between CNS defects and CBTs remained statistically significant.[151]

This field has benefited immensely from the propagation of population-based birth defects and cancer registries; however, the identification of birth defect–childhood cancer associations remains challenging owing to the rarity of co-occurring cases. Consequently, studies have had limited power to investigate the associations of specific birth defects with CBTs or the major subgroups, and further identification of specific birth defect–BT associations will require extremely large sample sizes, such as by meta-analysis or by pooling data across multiple registries. In a recent systematic review, Johnson et al stressed the need for future studies to use standardized systems when classifying birth defects in order to facilitate such research.[141]

In addition to the previously discussed factors, many other environmental exposures have been investigated in relation to CBT development with conflicting results, including: non-ionizing radiation, maternal medications, N-nitroso compounds, maternal nutrition and vitamins, parental smoking and alcohol use, pesticides, infectious agents, allergic conditions, parental occupational exposures, parental age, and other birth characteristics.[3]

Where Do We Go from Here in Brain Tumor Epidemiology?

Significant progress has been made in identifying and confirming potential risk factors for BTs, including numerous heritable genetic factors, allergic/atopic diseases, and ionizing radiation exposures. Numerous other exposures have yielded promising results—including aspirin use for glioma, BMI for meningioma, and birth characteristics for CBTs—and many others are currently under study. Large, well-annotated datasets have now been collected for many BT subtypes, and continued analysis of these in multi-institutional collaborations will potentially lead to further understanding of the interaction of genes and environment in development of primary BTs. Several developments are critical to the future of understanding risk factors for BTs, particularly: (i) refining risk factor measurements, (ii) "omic" approaches for both germline risk and tumor phenotyping, (iii) expanding risk factor and genomics research to broader and more diverse populations, and (iv) applying novel approaches to both existing and new datasets.

Risk Factor Measurement

Johansen et al recently reviewed the state of the literature in glioma risk factor research and found substantial variability in the results derived from case-control studies as opposed to cohort study designs.[120] In evaluating the evidence present by case-control studies of medical ionizing radiation exposure and exogenous hormone exposure (relying on retrospective self-report) as opposed to those from cohort studies with prospective self-report (or prescribing records where available), they concluded that studies based on self-report resulted in estimates further from the null compared with associations reported by analyses using prescription data. The inability to replicate these case-control findings in cohort designs suggests that these case-control studies may be affected by bias and emphasizes the importance of using validated and tested instruments or pre-diagnostic records for collecting risk factor data. In comparison, glioma GWAS using cohort (Rajaraman et al[10]) or case-control designs (all others to date) have identified the same genetic loci associated with glioma risk, demonstrating that these associations should be concordant when reliable instruments (eg, germline genotyping) are used. BT epidemiology has benefited significantly from the data available within large databases, including but not limited to national cancer registry systems, institutional or national prescribing databases, birth defect registries, and administratively collected risk factor data. As these data are often collected for non-research purposes, it is critical to approach them systematically and with understanding of their limitations.

Molecular Classification

Accurate classification of disease and exposure status is critical in case-control studies, as misclassification of these factors causes poorly estimated or incorrect associations and significant decreases in power. This unmeasured phenotyping error likely contributes to both "missing heritability" and difficulties in replicating associations. Historically, most BT epidemiology studies have classified phenotype based on histologic criteria only. The advancement of high-throughput technologies that have allowed for full molecular classification of BTs, particularly glioma and medulloblastoma, has resulted in refinement of histologic classification and the creation and elimination of histologies with the 2016 WHO revision.[4] While many of these molecular markers have been used consistently at large academic medical centers for years, they did not become components of the WHO criteria until the 2016 revision, and therefore are absent from many datasets.[4] BT subtypes have distinct lineages of acquisition of malignant behavior, even when they arise within the same tissue site, for example: *IDH1/2* mutation is a precipitating event in gliomagenesis, and delineates between 2 distinct glioma phenotypes. In addition to the development of medulloblastoma subclassification based on gene expression,[156–158] incorporation of molecular characteristics into classification of other pediatric tumors is ongoing, including rare histologies such as diffuse intrinsic pontine glioma.[159] The development of molecular classification is even more critical in these pediatric phenotypes, as precise phenotype will increase the power to detect both genetic and non-genetic risk factors for these extremely rare tumors.

In order to improve risk prediction models, it is essential to fully understand associations between exposures, germline variants, and somatic characteristics of tumors. Replicating previously discovered findings within these subsets of individuals with molecular classification is an important step for more precisely targeted discovery as well as beginning to refine these associations. In addition, development of molecular classification, by integrating germline and somatic variations, leads to a better understanding of brain tumorigenesis.

Risk Factor Research in Diverse Populations

BT research to date has largely been conducted in pooled sex and primarily white/European ancestry populations. Recent research has begun to focus on differences by sex and has preliminarily identified sex-specific differences in germline risk factors as well as age at onset, somatic features, and tumor behavior.[160–162] Due to the rarity of BTs overall, there have been limited analyses done to identify genetic variants associated with BT risk in non-European populations as it is often difficult to obtain sample sizes that are appropriately powered to identify associations that reach genome-wide significance. Candidate gene analyses in glioma have demonstrated that tagged risk variants may vary by ancestry population,[42–44] and studies of non-genetic risk factors in diverse populations have demonstrated that these associations may vary by race/ethnicity,[90,163] perhaps pointing to the importance of examining gene–environment interactions in epidemiologic studies. Limited analysis of somatic alterations in tumors also suggests that initiating mutations and pathways of gliomagenesis may vary by race/ethnicity or ancestry.[164] Future research should incorporate these known population-based differences, as research both within and between specific populations has the potential to reveal information about BT risk and etiology applicable to the population at large.

Novel Computational Approaches

Decades of BT epidemiological research has generated large amounts of existing data, including both "omic" and risk factor data that can be leveraged using newly developed statistical and computational techniques that may not have been available at the time these data were collected. Techniques that use publicly available summary statistics generated from GWAS, such as MR, which uses genetic predictors of risk factors to assess whether a causal association exists between these and an outcome, can be used to further interrogate associations identified by case-control or other epidemiological studies.[66,94,106,165,166] These methods can also be used to assess relationships between risk factors that may have not been included on questionnaires but for which there may be suggestive evidence, such as age at menarche or menopause. Machine learning and other artificial intelligence approaches can also be applied to combinations of risk factor and genetic data, and can be used to assess not only direct relationships but also the extent to

which these factors interact to contribute to BT risk. Artificial intelligence methodologies such as natural language processing could also be used to further enhance existing datasets through extraction of additional risk factor or other clinical data from electronic health records.

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

Keywords

epidemiology | glioma | meningioma | pediatric brain tumors | risk factors

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