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Why Primary Tumours/Malignancies of the Nerve Cells are so rare?

Eliza Roche*
Department of Biosciences and Biomedical Sciences, Cardiff University, Cardiff, Wales
**Address for Correspondence:* *Eliza Roche, Department of Biosciences and Biomedical Sciences, Cardiff University, Cardiff, Wales, Tel: 7975894441; E-mail: elizaroche01@gmail.com*

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Supplementary

Database: Medline (*via* OVID)		
Search number:	**Search terms:**	**Number of results**
#1	(tumor OR tumour)	2046342
#2	#1 AND (CNS OR central nervous system)	27773
#3	#1 AND (PNS OR peripheral nervoussystem)	4131
#4	(cell cycle reentry) AND (DNA repair)	22
#5	#4 AND neuron	0
#6	(tumor suppressor gene OR tumoursuppressor gene)	21408
#7	PTEN AND development AND mutation	887
#8	#6 AND #7	116
#9	#6 AND #7 AND (#2 OR #3)	3
#10	Lymph AND lymphatic vessel	1465
#11	#10 AND (#2 OR #3)	1
#12	Rare AND syndrome AND mutation ANDgermline	1199
#13	#12 AND #1	686
#14	#12 AND #1 AND (glioma OR glioblastoma)	21
#15	(Brain AND (#1 OR cancer)) AND (“incidence rate” OR “mortality rate”) ANDrare	90
#16	#5 OR #9 OR #11 OR #14 OR #15	115

Database: Scopus

Search number:	Search terms:	Number of results
#1	TITLE-ABS-KEY (tumor OR tumour)	3667636
#2	#1 AND (CNS OR "central nervous system")	71952
#3	#1 AND (PNS OR "peripheral nervoussystem")	10597
#4	TITLE-ABS-KEY ("cell cycle re-entry" AND "DNA repair")	25
#5	#4 AND neuron	9
#6	TITLE-ABS-KEY ("tumor suppressor gene"OR "tumour suppressor gene")	83581
#7	TITLE-ABS-KEY (PTEN AND development AND mutation)	1691
#8	#6 AND #7	471
#9	#6 AND #7 AND (#2 OR #3)	22
#10	TITLE-ABS-KEY (Lymph AND lymphaticvessel)	18585
#11	#10 AND (#2 OR #3)	55
#12	TITLE-ABS-KEY (Rare AND syndrome ANDmutation AND germline)	2000
#13	#12 AND #1	1469
#14	#12 AND #1 AND (glioma OR glioblastoma)	62
#15	TITLE-ABS-KEY ((Brain AND (#1 OR cancer)) AND ("incidence rate" OR "mortality rate")AND rare)	331
#16	#5 OR #9 OR #11 OR #14 OR #15	477

Appendix 1. Search terms generated into a search strategy using key terms mentioned.

Database: Web of Science		
Search number:	**Search terms:**	**Number of results**
#1	(tumor OR tumour)	2009822
#2	#1 AND (CNS OR "central nervoussystem")	38582
#3	#1 AND (PNS OR "peripheral nervous system")	1646
#4	"cell cycle re-entry" AND "DNA repair"	20
#5	#4 AND neuron	7
#6	"tumor suppressor gene" OR "tumoursuppressor gene"	32868
#7	PTEN AND development AND mutation	1481
#8	#6 AND #7	554
#9	#6 AND #7 AND (#2 OR #3)	14
#10	Lymph AND lymphatic vessel	4671
#11	#10 AND (#2 OR #3)	10
#12	Rare AND syndrome AND mutation ANDgermline	1952

#13	#12 AND #1	1218
#14	#12 AND #1 AND (glioma ORglioblastoma)	32
#15	(Brain AND (#1 OR cancer)) AND ("incidence rate" OR "mortality rate") AND rare	103
#16	#5 OR #9 OR #11 OR #14 OR #15	165

Appendix 2. Search strategy generated in order to perform literature search.

(Cell cycle re-entry AND DNA repair AND neuron) OR ((pten AND development AND mutation AND (tumor suppressor gene OR tumour suppressor gene)) AND (((tumor OR tumour) AND (cns OR central nervous system)) OR ((tumor OR tumour) AND (pns OR peripheral nervous system)))) OR ((lymph AND lymphatic AND vessel) AND (((tumor OR tumour) AND (cns OR central nervous system)) OR ((tumor OR tumour) AND (pns OR peripheral nervous system)))) OR ((rare AND syndrome AND mutation AND germline) AND (tumor OR tumour) AND (glioma OR glioblastoma)) OR ((Brain AND (tumor or tumour OR cancer)) AND (incidence rate OR mortality rate) AND rare)

Theme: Regeneration and proliferation ability of nerve cells							
Author and year	**Name of paper**	**Study design**	**Aim of paper**	**Methods**	**Key findings**	**Contribution in current study**	**Critical analysis (+/-)**
Tomashevski, et al. 2010	Cyclin C-dependent cell cycle entry is required for activation of nonhomologous end joining DNA repair in postmitotic neurons	Retrospective non-randomised cohort study	Understand the mechanisms underlying DNA repair in terminally differentiate d neurones. Alongside the stimulatory factors triggering cell-cycle re- entry of these postmitotic neurones to undergo DNA damage response.	Cortical neurone cell cultures were obtained from E18 Sprague-Dawley rats, cells were seeded onto dishes. Cortical neurones were treated with hydrogen peroxide (H_2O_2) to induce DNA damage.	H_2O_2 induces repairable double-strand DNA breaks in terminally differentiated neurones. ·Neurones transitioning from G0 to G1 exposes them to double-strand DNA	The ability of postmitotic neurons to repair damaged DNA by re-entering the cell-cycle without producing two daughter cells indicates adaptations to avoid oncogenic mutations in developing in neurones.	Strengths: Saw consistent results with DNA repair using NHEJ. Positive and negative controls were used in immunoblotting analysis. Specific neuronal markers were used to identify

				Cells were fixed stained with DNA-binding dye to calculate number of apoptotic nuclei.Neuronal markers were used to see sites of non-homologous end joining (NHEJ) pathway activation in neurones. This was seen using immunofluorescence analysis. Immunoblotting measures expression of Cyclins following exposure of neurones to H_2O_2 and transfected with either cyclin or control siRNA in order to detect cell-cycle progression.	breaks where proteins involved in regulating cell cycle are activated too early.	Repairing DNA damage using NHEJ	areas of DNA repair taking place *via* NHEJ. Limitations: Using rat models may not be translatable results into human studies. Non-randomised retrospective study increases risk of bias. Study was only focused on postmitotic neurones and could have benefited from
Tomashevski, et al. 2010	Cyclin C-depende	Retrosp	Understand the mechanism	• Cortical neurone cell cultures were	• H_2O_2 induces repairable	• The ability of postmitotic	Strengths: Saw consistent

	nt cell cycle entry is required for activation of nonhomologous end joining DNA repair in postmitotic neurons	ective non-randomised cohort study	s underlying DNA repair in terminally differentiated neurones. Alongside the stimulatory factors triggering cell-cycle re- entry of these postmitotic neurones to undergo DNA damage response.	obtained from E18 Sprague-Dawley rats, cells were seeded onto dishes. • Cortical neurones were treated with hydrogen peroxide (H_2O_2) to induce DNA damage. • Neuronal markers were used to see sites of non-homologous end joining (NHEJ) pathway activation in neurones. This was seen using immunofluorescence analysis. •Immunoblotting measures expression of Cyclins following exposure of neurones to H_2O_2 and transfected with either cyclin or control siRNA in	double-strand DNA breaks in terminally differentiated neurones. • Neurones transitioning from G0 to G1 expose them to double-strand DNA breaks where proteins involved in regulating cell cycle are activated too early. • Terminally differentiated neurones can induce NHEJ following detection of double-strand DNA breaks. • Post-mitotic neurones forced G1 entry induces NHEJ activation regardless of DNA damage.	neurons to repair damaged DNA by re-entering the cell-cycle without producing two daughter cells indicates adaptations to avoid oncogenic mutations in developing in neurones. • Repairing DNA damage using NHEJ machinery enables neurones to stay plentiful in their abundance due to lack of regenerating abilities.	results with DNA repair using NHEJ. Positive and negative controls were used in immunoblotting analysis. Specific neuronal markers were used to identify areas of DNA repair taking place *via* NHEJ. Limitations: Using rat models may not be translatable results into human studies. Non-randomised retrospective study increases risk of bias. Study was only focused on postmitotic neurones and could have benefited from

				order to detect cell-cycle progression. • Cells were fixed stained with DNA-binding dye to calculate number of apoptotic nuclei.			experimenting alongside different differentiated levels of neurones to see full effect of DNA repair mechanisms. Did not provide understanding of the reasons behind cells undergoing DNA repair or undergoing apoptosis following DNA damage detection.
Gimm, et al. 2000	Expression of the PTEN tumour suppressor protein during human development	Retrospective cohort study	To explore PTEN expression throughout human development using monoclonal antibodies. As well as examining the relationship with germline PTEN mutations with the genetic	• Tissues were taken from whole human embryos (5) and foetuses (2) (following abortion), fixed, and mounted. • Specific monoclonal antibodies recognising PTEN were created and Western Blotting was	• High PTEN expression was seen in tissues directly involved in CS and BRR diseases such as the skin, thyroid, and CNS. • The highest expression of PTEN was seen in	• Explanation of the roles that PTEN plays in normal neuronal tissues in development and its involvement in regulation of the cell-cycle, migration, and apoptosis. • High expression	Strengths: their results in high expression of PTEN in the CNS and PNS have been supported by RNA in situ hybridisation experiments. Specific monoclonal antibodies to PTEN show clear

			conditions Cowden's syndrome (CS) and Bannayan-Riley-Ruvalcaba (BRR) syndrome.	performed to indicate bands of PTEN expression. This was compared against controls. • Further immunohistochemistry was performed to classify expression as absent, weak, moderate or strong.	the CNS and PNS which was maintained throughout the development process. • PTEN is highly expressed in the gastrointestinal system and thyroid gland. • Moderate-high expression of PTEN in thymus	in nerve plexus and enteric nerves were seen to show involvement of PTEN in peripheral nerves.	areas and tissues with high or low expression. Explored different systems among the body for examining different expression levels. Foetuses and embryos are reasonable for examining developmental expression of PTEN in embryogenesis. Limitations: Small sample size (7 samples) meaning data may not be representative of population. Samples were embryos and foetuses, expression may not be representative into adult form.

							Retrospective non-randomised study
Crocetti, et al. 2012	Epidemiology of glial and non-glial brain tumours in Europe	Prospective cohort study	Collectively analyse data to determine incidence, prevalence, and survival rate of a group of rare CNSTs.	• Establishment of categories of tumours depending on clinical management and patient referral structure. • Glial tumours were categorised depending on WHO classification. • Data was extracted from 44,947 rare types of CNSTs diagnosed between 1995- 2002 from different countries in Europe.	• 27,700 new "rare" CNS cases are estimated to be diagnosed every year in EU27. • Rare CNSTs were marginally more frequent in men than women. • Astrocytoma's were the most common CNST at a rate of 4.8 per 100,000 and their location was most prevalent in UK and Ireland.	from this study to compare three types of nerve cell tumours (astrocytoma's, oligodendroglioma's and ependymal tumours) to compare the prevalence of these tumours in gender as well as age. This supported the statements that the tumours appear more commonly in the elder population in certain CNSTs.	Strengths: This paper combined data from numerous different registries across Europe to provide representative data on incidence and prevalence rates of CNSTs. They achieved their aim and separated the types of CNSTs into sub-categories depending on their malignancies. Limitations: Only European not worldwide. Not all CNSTs, only a selected few of glial tumours to compare

							against non-glial CNSTs. Greater numbers of astrocytic tumours (86.9%) were examined in comparison to choroid plexus carcinomas (0.1%).
Hu, et al. 2020	Meningeal lymphatic vessels regulate brain tumor drainage and immunity	Retrospective cohort study	Exploring the role of meningeal lymphatic vessels (MLVs) in drainage of brain tumours.	• Retroviral vectors were created overexpressing GFP and VEGF-C in GL261 and B16 (glioma and melanoma markers) cells for detection. • Tumour cells were transplanted into mice, located 2 mm lateral to bregma and 3 mm deep to dura. • Deep and superficial lymph nodes were removed following ligation of collecting	• Dorsal MLVs undergo vast remodelling following glioma infiltration and are essential for dendritic cell trafficking towards deep cervical lymph nodes • Basal MLVs are susceptible to damage with increasing age • Dendritic cells showed reduced trafficking	Understanding the contribution of the lymphatic vessels and lymph nodes in harbouring immune cells to destroy tumour cells in the CNS. In particular dendritic cell role in stimulating immune responses following activation in MLVs.	Strengths: provide prospects for therapeutic opportunities targeting MLVs and cervical lymph nodes. Studying both basal and dorsal MLVs allowed differences to be seen rather than assuming the similar responses to tumour cell infiltration. Limitations: Mice models were used where

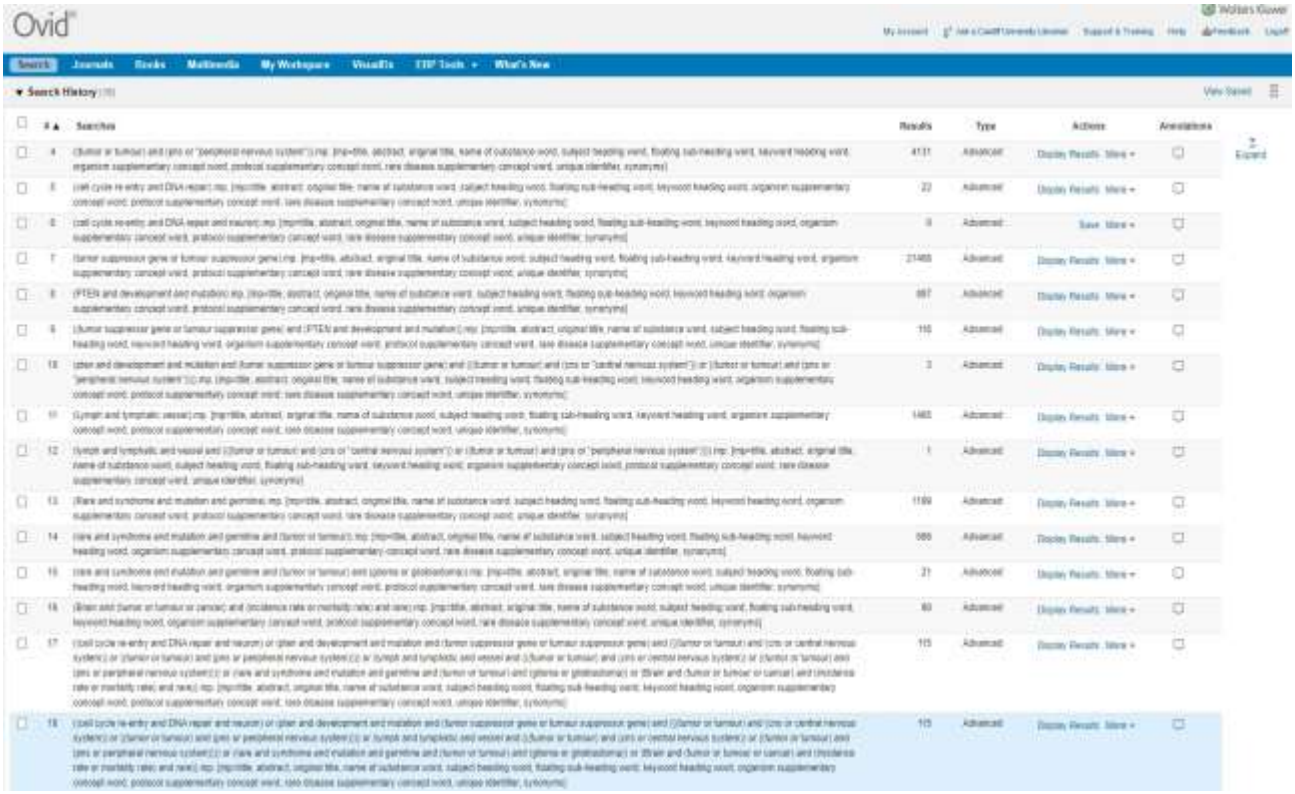
				lymphatic vessels. • MRI and immunostaining were performed to detect tumour growth	ability from tumour tissue to deep cervical lymph nodes where dorsal MLVs were deformed.		conclusions in human model may be inconsistent with these results and the data may be incomparable.
Castriconi, et al. 2009	NK Cells Recognize and Kill Human Glioblastoma Cells with Stem Cell-Like Properties	Prospective cohort study	To explore the differentiation ability, tumorigenicity and expression of neural stem cell markers in stem- cell cultured GBM cells. In addition, exploring stem- cell cultured GBM cell susceptibility to lysis by autologous and allogenic NK cells.	• Tumour cells were separated from 9 patients with GBM. • These GBM cells were cultured *in vitro* in stem cell medium and were tested for neural stem cell markers and susceptibility to lysis by NK cells. tumorigenicity. • Flow cytofluorimetric	• Stem cell cultured GBM cells tested positive for neural stem cell markers but only 45% of cells showed differentiation properties compared to normal neural stem cells. • Stem cell cultured GBM showed tumorigenic potential where further injection of these cells developed gliomas in new mice. • Stem cell cultured GBM cells are	Understanding the ligand-receptor interactions between NK cells and GBM cells. This aided in understanding the role of the immune system in controlling tumour growths and destroying them using NK cells. Provided an understanding of the roles of various ligands on the surface of NK cells in responding to pathogens and tumours. In particular	Strengths: Only GBM patients with typical characteristics of GBM were included, this reduces the chance of anomalous data inclusion. Provides opportunities for therapeutic approaches to be created using activated NK cells against GBM. Limitation: Small sample size (9 patients, 7 males, 2 females), might be unrepresent

					vulnerable to NK lytic abilities (both autologous and allogenic NK cells). • Key receptors were analysed for specific ligand interactions with stem cell cultured GBM cells	the role of NKp46 and DNAM-1 receptors in the efficient killing of GBM cells. This is important because DNAM-1 is frequently detected in most cancer cell lines including GBM and neuroblastomas.	ative of the population of GBM patients. Portions of this study were performed *in vitro* where results are less likely to be transferable to in vivo experiments. Only studies GBM rather than other types of CNSTs such as astrocytomas. No financial contributions or conflicts of interest.
Malmer, et al. 2001	Microsatellite Instability, PTEN and p53 Germline Mutations in Glioma Families	Retrospective cohort study	To investigate the presence of germline mutations in p53 and PTEN in related family members where two or more members suffer from	• Paraffin-embedded tumour DNA and blood DNA samples were taken from 25 families (3 patient samples per family) who suffer from gliomas. • PTEN analysis was	• No MSI was found in association with any of the 35 tumours. • A repeated polymorphism was detected at exon 4 codon 7 in eight patients. •	Contributed to the fact that nerve cell tumours are so rare due to the fact that germline mutations which increased prevalence of nerve cell tumours have not	Strengths: Mentioned that their results were corresponding to similar literature. All groups were treated with the same treatment

			glioma tumours. Exploring whether microsatellite instability (MSI) is associated with glioma sufferers.	achieved with PCR with primers to PTEN • p53 exons were screened in blood DNA for exon mutations (exons 2-9) *via* temporal temperature gradient electrophoresis. • MSI was tested with two markers: BAT 25 and BAT 26.	Mutations were not shown associated with PTEN in any of the cases.	been detected in any of these patients. Also indicates the varying presentation associated with nerve cell tumours in terms of types of genetic mutations. Showed the types of syndromes associated with gene mutations in *TP53, PTEN and NF1* genes.	to detect mutations in the genes mentioned. Limitations: Tumour samples were paraffin-embedded which doesn't represent fresh tissue which could have displayed different results. No controls were used to compare mutation levels in gliomas to.
Khazaei, et al. 2020	The association between incidence and mortality of brain cancer and human development index (HDI): an ecological study	Prospective case study	Investigate the relationship of brain tumours morbidity and mortality rates with the socioeconomic development of countries by measuring their human development index (HDI).	• Data for the morbidity and mortality rates for brain cancer were taken from the World Bank for Cancer. • Morbidity rates to relate age and gender were calculated using the incidence rates reported in four separate cancer	• The total number of cancer cases found for both sexes are 18,078,957 in which brain tumours represented 296,851 (1.64% of total types of cancer). • The continent with the highest incidence	Provided information for whether brain tumours have increased likelihood of developing depending on ethnicity, gender, age, availability to healthcare.	Advantages: Using four different cancer registries allowed the researchers to get the most accurate incidence rates of brain tumours in countries. Prospective study Limitations: Certain

				registries of countries until 2018. • Mortality rates were estimated using four separate registries. • HDI was calculated using an index depending on three criteria: education, life expectancy and good standards of living. This created a scale for measuring HDI for the countries used in this study.	rate was seen in Asia and the lowest seen in Oceania.		lower income countries do not have the healthcare facilities to report the incidence rate of brain tumours. This means that not all of the data here is representative of "worldwide trends". Averages were assumed in the methods section.

Appendix 3: Results following a detailed search strategy creating a shortlist of papers to analyse in the literature synthesis. Various categories have been identified to give detailed explanations as to why each research paper has been included in this literature review. Search strategies on different databases performed between 14/03/22 – 18/05/22



Appendix 3. Results from literature search on Medline (Ovid) and Scopus to generate publications to undergo criteria-based selection process and critical analysis.