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Brain Tumor Epidemiology: Updates from the USA, UK and Australia.

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Abstract:

A brain tumor is an abnormal mass of tissue found inside the brain that consists of cells that grow and multiply without any control and unchecked by the mechanisms that regulate normal cell growth. It is one of the leading causes of death in many different regions worldwide, affecting various ages, sex, race, or ethnicities. Besides being a life-threatening condition, it can also disrupt normal brain function leading to severe cognitive morbidity. Additionally, the cost associated with active treatment and palliative care of the brain tumor most often proves to be out of reach for many people. Over the past decades, even though we have several published literature showing the epidemiology and characteristics of brain tumors, up-to-date epidemiological data is yet to be published. This review will provide comparable recent statistics regarding the incidence of brain tumors in 3 different regions; - the USA, the UK, and Australia. Also, a focus will be given to brain tumor's key characteristics, classifications, and treatment protocol.

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1. Introduction:

Brain tumor still is a major health concern across the globe. It is one of the leading causes of death. Globally, approximately 300,000 men and women are diagnosed with cancer of the brain and nervous system every year, and more than 240,000 deaths are caused by the consequence of the disease[1]. Brain tumors do not discriminate in ages, genders or ethnicities[2]. The survival rate of primary brain tumors varies significantly by age, geographical location, tumor type and grading, tumor location, and molecular markers. There are about 150 types of brain tumors, but all tumors can broadly be classified as Primary and Metastatic tumor[3]. Although significant advancements have been achieved to understand the characteristics and epidemiology of brain tumors, further studies and research are required to know more about its nature. This review will focus on the updated epidemiology and characteristics of brain tumors in the USA, UK, and Australia.

2. Anatomy of the brain:

The brain and the spinal cord are the two components of the central nervous system (CNS). The brain is considered the most vital and critical organ in the human body. All body functions are precisely regulated by the brain. The treatment of brain tumors mostly depends on the location of the tumor. Hence detailed anatomy of the brain is so vital. The average weight of an adult's brain is about 3 pounds. 60% of the brain is composed of fat and 40% of water, protein, carbohydrates, and salts. The grey matter is the outer portion of the brain, while the white matter is the inner section. While the grey matter mainly does processing and interpreting of information, the white matter transmits that information to other parts of the

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nervous system. There are mainly 3 parts of the brain: cerebrum, brainstem, and cerebellum. There are 4 lobes of the brain. They are frontal, parietal, temporal, and occipital. The brainstem is divided into midbrain, pons, and medulla[4]. The covering of the brain is called meninges which have 3 layers. From outside to inside the dura mater, arachnoid mater, and pia mater. Besides these, there are also deeper structures of the brain called- Pituitary Gland, Hypothalamus, Amygdala, Hippocampus, Pineal Gland, and Ventricles. The ventricles are four open spaces with passages between them. The cerebrospinal fluid (CSF) is produced by the choroid plexus located in the ventricular wall. CSF surrounds the brain, and the spinal cord predominantly works as a cushion. Besides its mechanical function, it washes out waste products and impurities and delivers nutrients to the brain and spinal cord.

3.Risk factors of brain tumor:

There are many factors responsible for brain tumors. The main 2 factors are

3.1. Genetic factors - Only 5% of brain tumors are caused by hereditary genetic factors or conditions, including Li-Fraumeni syndrome, neurofibromatosis, nevoid basal cell carcinoma syndrome, and tuberous sclerosis, Turcot syndrome[5].

3.2. Environmental factors- these include i) Age- Brain tumors are more commonly found in children and older adults, though people of every age can develop a brain tumor. ii) Gender- Though men are more likely to develop a brain tumor, meningioma is commonly found in women[6]. iii) Exposure to chemicals- Exposure to different solvents, oil products, rubber, or vinyl chloride may increase the risk of developing a brain tumor. However, further research is required to understand the level of contribution for developing a brain tumor. iv) Exposure to infections, viruses, and allergens- Infection with the Epstein-Barr virus (EBV) and cytomegalovirus (CMV) can cause brain tumors[7]. Further research is ongoing to find the

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more intimate relationship between viral infection and the development of brain tumors. v) Other factors include ionizing radiation, including radiation therapy used to treat cancer and radiation exposure caused by nuclear research and atomic bombs[8].

4. Signs and Symptoms:

Symptoms can vary from case to case. General symptoms include 4.1. Headaches- they can be severe and get worse with activity or in the morning. 4.2. Seizures- Types of seizures vary from person to person. Certain drugs can help prevent or control seizures. Motor seizures, which are also called convulsions, are termed as sudden involuntary movements of the muscles. Seizures can also be described as Myoclonic seizure, which involves single or multiple muscle twitches, jerks, and spasms[9]. Another form of seizure is Tonic-Clonic seizure (Grand Mal). Which can be presented as loss of consciousness and body tone followed by twitching and relaxing muscles[10]. During the Tonic-Clonic seizure, a person's breathing can be arrested for a brief period, and skin may turn blue, purple, gray, or white in color. Following a Tonic-Clonic seizure, a person may feel sleepy and may experience headache, confusion, weakness, numbness, and soreness of muscles. The sensory function can also be changed, which involves changes in sensation, vision, smell, and/or hearing without losing consciousness[11]. A complex partial seizure can cause a loss of awareness or a partial or total loss of consciousness. 4.3.Personality or memory changes. 4.4. Nausea and/or vomiting. 4 5. Fatigue. 4.6. Drowsiness. 4.7. Sleep disturbances. 4.8. Memory loss and confusion.4. 9. Inability to walk or perform daily activities.

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5. Diagnosis of brain tumor:

Many tests are performed to diagnose brain tumors. The most specific and sensitive test is the Computed Tomography (CT) scan. CT scan is a series of X-ray images taken from different angles around the body and uses computer processing to create cross-sectional images (slices) of the bones, blood vessels, and soft tissues inside the body[12]. Another helpful test is Magnetic Resonance Imaging (MRI). MRI is a type of scan that uses strong magnetic fields and radio waves to produce detailed images of the internal organs of our body [13].Both CT scans and MRI prove to be very helpful not only to diagnose the tumor but also to formulate the treatment protocol. It guides surgeons to determine the level of tumor invasion to the surrounding structure and to determine to which extent the tumor needs to be resected. Magnetic resonance spectroscopy (MRS) is used to analyze the tumor's chemical profile and determine the nature of the lesions seen on the MRI[13]. Positron emission tomography (PET) scan can help detect recurring brain tumors. The definitive test for diagnosis of a brain tumor is biopsy followed by histopathology and cytology[7].

6. Incidence of brain tumor in the USA:

Over 700,000 Americans are living with brain tumors today[14]. Approximately 70% of all brain tumors are benign, while almost 30% are malignant[15]. About 58% of all brain tumors occur in females and 42% in male[16]. The incidence frequency for different age groups varies (Table 1). National brain tumor society has estimated that more than 84,000 people will be diagnosed with a primary brain tumor in 2021[16]. This year approximately 18,000 people will die as a result of a primary malignant brain tumor[17]. The overall 5+ years and 10+ years

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survival rate of people with malignant brain tumors are 36% and 31% respectively[6]. The survival rate varies among different age groups. Five years survival rate and incidence frequency in different age group are shown in Table 1. Table 2 represents the most common form of brain tumor in different age group.

Malignant brain tumors cause an average of 20 Years of Potential Life Lost (YPLL) for individuals diagnosed as adults, which exceeds most common cancers. Among children ages 0-19 years, brain tumors represent the largest cause of YPLL due to cancer, with a mean YPLL of approximately 80 years[18].

The Age Factor on Incidence and Survival Rate

Age	Incidence Frequency (2013-2017)	5+years survival Rate (%)
0-14 years	most common cancer	82.5% for Benign 75.4% for Malignant
15-39 years	3rd most common cancer	97.3% for Benign 72.5%for Malignant
40+ years	8th most common cancer	90.2% for Benign 21.5% for Malignant

Table 1: - Table 1 represents the incidence frequency and survival rate of brain tumors in the USA in specific age groups[19].

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Age Range	Most Common Brain Tumor
0-14 years	Medulloblastoma
15-39 years	Pituitary tumors, meningiomas, and nerve sheath tumors
40+ years	Meningiomas Gliomas (malignant)

Table 2: Table 2 represents the most common type of brain tumor occurring in different age groups in the USA[16].

Brain tumor incidence, types, survival rates depend on age, sex, and ethnicity.

In the USA, African American people have slightly higher incidence rates of primary brain tumor compared to other races (at 23.88 per 100,000 persons in black people compared to 23.83 per 100,000 persons in white people[16]. Among Hispanic /Latino/Asian and Pacific Islander populations, the incidence rate is 21.48 per /100,000 people and 15.04 per 100,000[16]. Brain tumor incidence rate is the lowest among Indian American and Alaskan Native (AIAN) (14.23/ per 100,000 people)[16].

Brain tumors are the highest among other tumors, with an annual mean net cost approaching $US150,000[20]. The yearly net cost during the terminal year of treatment is $US135,000 to $US210,000[20].

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7. Incidence of brain tumor in the UK:

More than 11,000 people are diagnosed with a primary brain tumor in the UK each year, of which about half are malignant in nature[21]. Many others are diagnosed with a secondary brain tumor. 51% of the tumors affect women, compared to 49% men. In contrast to most cancer types, brain, other CNS, and intracranial tumors occur more frequently at younger ages. Age-specific incidence rates remain relatively stable from infancy to around age 25-29 before increasing steadily. The peak age for females is between 85-89 years and for males is between 80-84 years. Incidence rates are similar between females and males in most age groups. The gap is widest at age 35 to 39 when the age-specific incidence rate is 1.2 times higher in females than males[13]. In terms of ethnicity, age-standardized rates for white males range from 8.2 to 8.7 per 100,000 people. Incidence rates for Asian and Black males are significantly lower (ranging from 4.0 to 6.5 per 100,000 and ranging from 2.9 to 5.4 per 100,000 people respectively)[13]. There is a similar pattern for females - the age-standardized rates for White females range from 5.3 to 5.6 per 100,000 people. The rates for Asian and Black females range from 2.4 to 4.3 per 100,000 and 2.1 to 4.1 per 100,000 respectively[13].

Ranges are given because of the analysis methodology used to account for missing and unknown data. For malignant brain and CNS tumors, 19,012 cases were identified; 17% had no known ethnicity. 40.2% of males survive brain malignancy for at least one year. This percentage falls to 11.1% for five years survival. One year and five years survival rate for female is 39.7% and 13.8% respectively. Five-year survival is highest in the youngest men and women and decreases with increasing age. A study conducted during 2009-2013 showed that five-year net survival in men ranges from 57% in 39 years old to 1% in 80-99 years old[13]. Whereas in women, five-year survival ranges from 62% to 1% in the same age groups[13].

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Brain tumors reduce life expectancy by an average of 27 years[22]. Though significant efforts had already been taken, incidence rates for brain tumors are projected to rise by 6% in the UK between 2014 and 2035[13].

8. Incidence of brain tumor in Australia:

The brain tumor is the leading cause of death in children and adults aged under 40 in Australia. In 2018, brain tumors caused 1,410 deaths in Australia (845 males and 565 females) [23], which made brain tumors the 10th most common cause of cancer death in Australia[23]. In 2020, the Australian Government documented that 1113 males and 767 females were newly diagnosed with brain tumor[23]. And sadly, 1,518 deaths (921 males and 597 females) were reported in 2020[23]. On average, 5 years survival rate of brain tumors is 22% (21% for males and 24% for females)[21]. In most malignant brain tumors, 5 years survival rate reduces significantly. In Australia, glioblastoma the most common form of malignant brain tumor in adults, which has a five year survival rate of 4.6% only[24].

9. Treatment protocol:

9.1. Surgery -Surgical protocol includes removal of the tumor with or without removal of the surrounding tissue. It is generally the first-line treatment of a brain tumor. Most often, it is the only treatment required for a low-grade brain tumor. Removal of tumors may improve the neurological symptoms and provide tissue for histopathological examination and genetic analysis. Therefore, surgery not only works as a treatment option but also a tool for diagnosis

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and prognosis. 9.2. Radiation therapy- Radiation therapy uses high-energy x-rays or other particles to destroy tumor cells, given after surgery and possibly along with chemotherapy. 9.3. Therapies using drug medication- The therapies used to treat brain tumors include Chemotherapy and Targeted therapy. These types of therapies are given through the bloodstream to reach tumor cells and subsequently destroy the tumor cells. If the primary site of cancer is outside the brain which spreads to the brain or CNS is called metastatic tumor. For metastatic tumor treatment plans may include a combination of surgery, radiation therapy and targeted therapy[25] .

10. Prognosis of brain tumor:

10.1. Tumor histology: Grading of a tumor describes certain features that are linked with specific outcomes. The World Health Organization (WHO) described the grades in 4 stages. Grade I tumors are those (also called benign tumors) which are non-cancerous, slow growing tumors. Their cells look almost normal under a microscope and are usually associated with long-term survival. They are rare in adults[26] . Grade II tumors can be described as relatively slow-growing, which sometimes spread to nearby normal tissue and come back (recurring). Their cells look slightly abnormal under a microscope. Sometimes they can come back as a higher-grade tumor[26]. Grade III tumors (malignant) are termed as cancerous tumors. They actively reproduce abnormal cells and spread into nearby normal parts of the brain. Likewise the Grade 2 tumors, their cells look abnormal under a microscope. They also have a tendency to come back as a higher-grade tumor[26] . Lastly, the Grade IV tumors are the mostly malignant, fast growing tumors which easily spread into nearby normal parts of the brain. They can actively reproduce abnormal cells. Their cells look very abnormal under a microscope. These tumors form new blood vessels to maintain rapid growth. They have areas of dead cells in their centre (called necrosis)[26] . For most tumors, the lower the grade, the

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better the prognosis. 10.2. Age: A person's age and functional status during the diagnosis of a brain tumor are some of the best ways to predict a patient's prognosis. In general, younger adults have a better prognosis than older people[7]. 10.3. Symptoms: Patient's symptoms can be an important factor in determining prognosis.10.4. The extent of tumor residual: Residual means how much of the tumor remains in the body after surgery. A patient's prognosis is better if all of the tumors can be surgically removed. 10.5. Tumor location: A tumor can form in any part of the brain. Some tumors can cause more damage than others depending on their location.10. 6. Molecular features: Some genetic mutations can help prognosis. Including- IDH1, IDH2, MGMT, and a 1p/19q co-deletion 7 [27] . 10.7. Functional neurologic status: a functional assessment scale, such as the Karnofsky Performance Scale (KPS), can be used to help in prognosis of brain tumors[28] . The higher the score, the better the functional status. 10.8. Metastatic spread of a tumor can also predict the prognosis. A tumor that rarely spreads to other parts of the body, has a better prognosis. On the other hand, a tumor that spreads to other parts of the brain or spinal cord can lead to a poorer prognosis. 10.9. Recurrent tumor: A recurrent tumor is one that comes back after treatment. If the tumor returns, there will be another round of tests to learn the extent of the recurrence[10] .

11. Options for incurable and terminal patients:

Like any other tumor, a brain tumor does not recover up to 100 percent. If the tumor cannot be cured or controlled, it leads to advanced disease. People with advanced brain tumors and/or whose life expectancy is less than 6 months are advised to consider hospice care[7]. Hospice care is given to provide the highest possible quality of life for people near the end of life[15]. It can be given at home, in a hospice care center, or a hospital setting. It is different

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from palliative care as it doesn't include any active treatment anymore, rather making sure the best possible quality of life.

12. Conclusion:

It is clearly visible that the number of cases, deaths and survival rates associated with brain tumors may vary across the continents. Incidence and survival rate are dependent on age, sex and ethnicity. Therefore, getting access to accurate statistics on the brain tumor incidence is vital to enable overall knowledge of the disease, assist with designing clinical trial study and support research efforts to combat brain tumors.

Conflict of interest :

None to declare.

Authors Contribution:

Sumit Chatterjee wrote the first draft of the manuscript. Ranjan Roy provided the required guidance, supervision and edited the subsequent drafts of the manuscript.

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