

*Ministry of Defence*

## **Synopsis of Causation**

# **Primary Intracranial Tumours**

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## **Disclaimer**

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This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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# 1. Definition

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- 1.1. Primary tumours affecting the brain may arise within the brain itself or from nerves and other structures within the skull (intracranial) cavity.
- 1.2. In the adult brain, nerve cells (neurons) do not divide and do not give rise to tumours. Other cell types, which insulate and nourish the neurons, called astrocytes and oligodendrocytes, are the source of the vast majority of adult malignant brain tumours. Collectively, astrocytes and oligodendrocytes are called glial cells, leading to the term glial tumour or glioma.
- 1.3. When a nerve process (axon) leaves the brain, it is insulated by a cell called a Schwann cell. Particularly in the vestibular (balance) nerve, these cells can give rise to a very slowly growing benign tumour called a schwannoma.
- 1.4. The membranous coverings of the brain (meninges) can give rise to slowly growing benign tumours called meningiomas.
- 1.5. Other cell types within the cranial cavity, such as the cells of the pituitary gland, may also produce benign tumours.
- 1.6. **Incidence.**
  - 1.6.1. The worldwide incidence of primary malignant brain and central nervous system tumours, age-adjusted using the world standard population, is 3.6 per 100,000 person-years in males and 2.5 per 100,000 person-years in females. The incidence rates are higher in more developed countries (males: 5.9 per 100,000 person-years; females: 4.1 per 100,000 person-years) than in less developed countries (males: 2.8 per 100,000 person-years; females: 2.0 per 100,000 person-years). This discrepancy may partly be a reflection of poor facilities for diagnosis and reporting bias, as well as a true difference in the incidence.<sup>1</sup>
  - 1.6.2. The incidence of malignant brain tumour in the UK is higher than the world average for both men (8.1 per 100,000), and women (5.3 per 100,000). There has been no significant change in these rates over the past 10 years.<sup>2</sup>
  - 1.6.3. In the USA, the rate is 7.6 per 100,000 for men and 5.3 per 100,000 for women. American men have a 1 in 149 lifetime risk of being diagnosed with a primary malignant brain tumour and a 1 in 204 chance of dying from a brain tumour. Women have a 1 in 200 lifetime risk of being diagnosed with a primary malignant brain tumour and 1 in 256 chance of dying from this cause.<sup>3</sup>
  - 1.6.4. The annual incidence of meningioma in the USA is 1.2 per 100,000 for men and 2.6 per 100,000 for women.<sup>4</sup>
  - 1.6.5. The annual incidence of pituitary tumour is 1.6 per 100,000 per year, with no sex difference.

## 2. Clinical Features

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- 2.1. Tumours within the cranial cavity produce symptoms and signs from brain dysfunction, or produce effects from increased pressure within the rigid skull cavity. The most common symptom is headache (46%), although by the time of presentation to hospital 86% of patients have additional neurological symptoms. A seizure can be the first symptom in 21% of cases.<sup>5</sup>
- 2.2. The exact symptoms and signs depend on the site of the tumour and often help to localise it. The two cerebral hemispheres have slightly differing functions, with the dominant hemisphere (the left in right-handed people) responsible for speech production and understanding, and the non-dominant hemisphere concerned more with visual-spatial functions. Each cerebral hemisphere is subdivided into 4 lobes. The cerebellum, lying beneath the cerebrum, also has 2 lobes and co-ordinates movement.
- 2.3. **Frontal lobe.** Tumours within, or compressing, the frontal lobe can cause impairment of planning, judgement, organisation and attention. There may be personality change, with disinhibition or apathy. The posterior part of the frontal lobe is called the motor cortex and can cause a weakness in the opposite arm, leg and face. Speech problems, such as naming and word-fluency (so-called expressive dysphasia), are affected by tumours in the lower part of the frontal lobe. Loss of the sense of smell (anosmia) may result from tumours affecting the undersurface of the frontal lobes. Particularly in the non-dominant frontal lobe, tumours may reach a considerable size before the patient notices any symptoms.
- 2.4. **Parietal lobe.** This lobe integrates the perception of touch with body image. Loss of spatial (three-dimensional) awareness may result from tumours in this area, along with loss of the lower field of vision due to interruption of part of the visual pathway.
- 2.5. **Temporal lobe.** Memory loss, poor concentration and learning, difficulty understanding spoken and written language (so-called receptive dysphasia), and loss of the upper field of vision may result from tumours affecting this lobe.
- 2.6. **Occipital lobe.** This contains the visual cortex. Tumours within this area cause loss of the field of vision on the side opposite the affected lobe.
- 2.7. **Cerebellum.** Disordered function will cause arm and leg incoordination, with slurred speech and unsteadiness on attempting to walk (ataxia).
- 2.8. Epileptic seizures may be produced by tumours affecting any area of the cerebral hemispheres, but particularly from tumours affecting the frontal and temporal lobes.
- 2.9. Pituitary gland tumours may compress the normal pituitary tissues leading to reduction of pituitary hormone production, or the tumour may oversecrete a specific hormone, e.g. acromegaly due to a growth hormone secreting tumour. The optic nerves cross above the pituitary gland and these can be compressed with a resultant loss in the field of vision.
- 2.10. Acoustic neuroma (vestibular schwannoma) compress the acoustic (hearing) nerve. Ringing in the ear (tinnitus) and deafness come on gradually over

months to years. If the tumour is large, then it will press on the trigeminal nerve producing unilateral facial numbness; the facial nerve, producing weakness of the facial muscles; the cerebellum, producing unsteadiness; or the brain stem, producing weakness and/or hydrocephalus (excessive cerebrospinal fluid collection within the brain).

- 2.11. Any tumour within the cranial (skull) cavity will produce a rise in intracranial pressure, unless there is a reduction in the size of the rest of the brain, or a reduction in the amount of blood volume or cerebrospinal fluid (CSF) within the head. As tumours grow, they distort and displace the soft brain and, initially, the pressure within the cranial cavity does not rise. Eventually, the capacity to absorb the increased volume produced by the tumour is lost, producing the symptoms of headache, nausea and vomiting. As the pressure increases, headache becomes more severe, followed by unconsciousness and, eventually, death. With the increased availability of brain imaging, some tumours are being detected as incidental findings.

### 3. Aetiology

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- 3.1. Glial tumours form about 50% of all primary intracranial tumours. They rarely spread (metastasise) outside the brain but kill by local spread throughout the brain.
- 3.2. The World Health Organisation has classified astrocytomas and oligodendrogliomas using histological criteria. The more malignant the tumour, the higher the grading number.<sup>6</sup>
  - Astrocytoma Grade I (pilocytic astrocytoma).
  - Astrocytoma Grade II (diffuse astrocytoma).
  - Astrocytoma Grade III (anaplastic astrocytoma).
  - Astrocytoma Grade IV (glioblastoma).
  - Oligodendroglioma Grade II.
  - Anaplastic Oligodendroglioma Grade III.
- 3.3. Astrocytoma WHO Grade IV (glioblastoma) is the commonest glial tumour in the adult population. Recently genetic analysis has suggested there may be 2 variants of this tumour. So-called “secondary” glioblastomas arise in patients in whom a pre-existing lower grade astrocytoma becomes progressively more malignant over a period of years due to mutations in the genes that regulate cell growth, division and the removal of abnormal cells by “programmed” cellular death. Histologically, these tumours are indistinguishable from “primary” glioblastomas which can erupt over as little as 3 months in a previously unaffected patient. These “primary” glioblastomas have a different set of genetic mutations leading to their more rapid growth and resistance to treatment.<sup>6</sup> Young adults, forming the majority of service personnel, are more likely to present with lower grade tumours. The “primary” glioblastoma is the usual glial tumour type in adults over 45 years of age. The poorer outcome in older patients with this tumour is due to the fact that it is extremely resistant to treatment.
- 3.4. Oligodendrogliomas also show specific genetic abnormalities in their progression between Grade II and Grade III. Tumours where the short arm on chromosome 1 and the long arm on chromosome 19 are both lost seem to have a significantly better response to chemotherapy treatment and a better outcome.<sup>7</sup>
- 3.5. **Genetic factors.** There are a few rare genetic conditions which predispose individuals to intracranial tumours:<sup>8</sup>
  - **Li-Fraumeni syndrome** These patients have a mutation in the p53 tumour suppressor gene and develop astrocytomas as young adults. There is a family history of breast cancer, leukaemia, and soft tissue tumours
  - **Neurofibromatosis type 1** Patients may develop astrocytomas and meningiomas

- **Neurofibromatosis type 2** Patients develop bilateral vestibular schwannomas
  - **Von Hippel-Lindau** Patients develop haemangioblastomas in the brain
  - **Turcot syndrome** Patients develop medulloblastoma or astrocytoma
  - **Gorlin syndrome** May predispose to medulloblastoma
- 3.6. **Environmental factors within the general civilian population** Many studies have tried to link occupation and risk of central nervous system tumour based on job titles and the likelihood of chemical or radiation exposure. There are problems in correlating job histories with specific exposures,<sup>9</sup> and in the estimation of dose of such exposure, with a tendency to underestimation.<sup>10</sup> Quantitative measurements of chemical exposure and electromagnetic field strength are lacking in many studies. There is a lag time between exposure to a carcinogenic insult and the development of brain tumour which may be up to 30-40 years, making the follow-up of large prospective cohort studies difficult. Epidemiological studies have been able to identify only a very small sub group of brain tumour patients for whom environmental factors are clearly responsible. A different approach will be required to identify possible environmental factors as a cause for the remainder.
- 3.6.1. **Chemicals** A study of 12,980 American women who died from central nervous system malignancy showed a trend in occupational exposure to solvents and petroleum products, but this was neither dose-dependant nor statistically significant.<sup>11</sup> A very small case-control study in Sweden again showed a very modest increase in glioma in men potentially exposed to solvents, pesticides and plastics.<sup>12</sup> However further review suggested that no clear-cut risk can be linked solely to pesticides.<sup>13</sup> A slight excess of deaths from potential exposure to lead has also been reported.<sup>14</sup> Studies of oil refinery workers have produced conflicting data, with some studies showing a slightly increased risk of brain tumour,<sup>15,16</sup> while others have failed to confirm an association.<sup>17-20</sup> A recent meta-analysis of studies involving 350,000 petroleum industry workers in North America and Europe has shown no increase in their risk of brain tumour.<sup>21</sup>
- 3.6.2. **Diet, alcohol and tobacco** A clear relationship between dietary factors and brain tumour has not been proven.<sup>22</sup> Similarly, there is no evidence to implicate alcohol consumption in the causation of brain tumour.<sup>23-26</sup> Data for tobacco smoking are controversial. There are reports of a slightly increased incidence of glioma in middle-aged female, but not male, smokers.<sup>26</sup> However, this is at odds with another study which found the risk to be higher in women who had recently stopped smoking compared to lifetime smokers.<sup>27</sup>
- 3.6.3. **Low frequency electromagnetic fields (LFEMF)** Exposure to LFEMF from radio and microwave sources has vastly increased over the past 50 years. Many studies have tried to address whether this has led to an increased risk of brain tumour within the civilian population, and the results remain contentious. Nearly all studies are flawed with methodological problems from lack of dosimetry (often by extrapolation of data rather than direct measurement), short periods of follow-up or statistical variation.

- 3.6.3.1. LFEMF is measured in micro-Tesla ( $\mu\text{T}$ ), with exposure estimates extrapolated from dosimeters carried for short periods by selected workers from various occupations.<sup>28</sup>
- 3.6.3.2. Studies apparently showing an increased risk of brain tumour with exposure to electromagnetic radiation have not shown a consistent dose-response relationship.<sup>29,30</sup> An analysis of more recent studies failed to show any association between LFEMF and brain tumour.<sup>10,31</sup>
- 3.6.3.3. A recent study showed an increase in gliomas, but not meningiomas, in workers concurrently exposed to chemical solvents, pesticides or lead and low frequency electromagnetic fields. Electromagnetic fields alone had no effect.<sup>32</sup> A suggested hypothesis was that LFEMF was acting as a tumour promoter but could not induce carcinogenesis on its own.
- 3.6.3.4. The World Health Organization established the International EMF project in 1996 to register and collate the many studies worldwide (<http://www.who.int/peh-emf/project/en/>). In the UK an Adult Brain Tumour Study Group has been set up to investigate potential causes of brain tumour in a prospective group of 1,000 patients using newly-acquired dosimetry measurements from UK companies.<sup>28</sup> Meantime, the current data do not clearly support a causal relationship between LFEMF and brain tumour generation.
- 3.6.4. **Mobile Phones** There are more than 1 billion mobile phones in use worldwide, with over 75% of UK households regularly using one.<sup>33</sup> They have only become popular in the past 10 years, hence there has been little time for long term studies regarding their safety. Mobile phones transmit and receive energy at a frequency just higher than microwaves. The international energy limit for mobile phones (specific absorption rate - SAR) is 2W/kg of tissue, although most mobile phones operate at energy levels well below 1W/kg.<sup>34</sup> The majority of epidemiological studies so far have failed to show a statistically significant link between mobile phone use and either glioma or acoustic neuroma formation, although there have been methodological problems with almost all of these studies.<sup>35-38</sup> Longer-term prospective studies such as the European Interphone study are awaited.<sup>39</sup> However, some early results from this continue to show selection and recall bias.<sup>40</sup>
- 3.6.5. **High Frequency (Ionising) Electromagnetic Radiation:** The annual UK background dose of radiation is 2.7 mSv per person, 84% of which is due to natural sources from radon gas, ground radiation and cosmic rays.<sup>41</sup> The largest producer of artificial radiation is medical diagnostic radiology. A chest x-ray produces a dose of 0.02mSv, lumbar spine x-ray 1mSv, CT scan of head 2mSv and CT scan of spine 4mSv. There is no biological threshold dose for the carcinogenic effect of ionising radiation and it has been estimated that the fatal cancer risk in adults is 1:20,000 per mSv of annual radiation absorption.<sup>41</sup>

3.6.6. **Therapeutic radiotherapy** In contrast to LFEMF, a causal link for ionising radiation in the production of astrocytic tumours has been clearly proven from studies of children who received prior therapeutic radiotherapy for the treatment of leukaemia or malignant brain tumours. The radiation dose was between 3 and 50 Gray, with an average latency of 16 years, although some patients developed astrocytic tumours within 10 years of treatment.<sup>42-45</sup> Meningiomas can also be induced by therapeutic radiotherapy (ionising radiation). Low dose radiation treatment (3 Gray) for scalp ringworm and higher dose treatment of intracranial tumours have led to cases of meningiomas arising within the radiotherapy treatment field 1 year to 63 years following exposure.<sup>46-50</sup> These meningiomas have tended to be atypical, with a more aggressive growth pattern and higher recurrence rate than normal. The relative risk for the development of a central nervous system tumour after low dose radiation (2-3 Gray) in childhood is 9.5 for meningiomas and 2.6 for glioma.<sup>51</sup>

### **Studies in Military Personnel and Persons of Similar Occupation Groups**

3.6.7. **Chemicals** Herbicides were used extensively by the US Army Chemical Corps in the Vietnam War. Follow-up of 2,872 veterans did not show any increase in the risk of central nervous system tumours.<sup>51</sup> In a British study of 51,721 First Gulf War veterans potentially exposed to pesticides and depleted uranium, matched with 50,755 non-deployed service personnel, no difference was found in the incidence of brain tumour or cancer in general between the 2 groups over an initial 10 year follow-up.<sup>53</sup>

3.6.8. **Cosmic radiation** Persons flying at high altitude are exposed to a higher than normal exposure to ultraviolet and cosmic radiation, with an average excess of 2mSv of extra radiation per annum for commercial aircrew.<sup>41</sup> Cohort studies in commercial pilots and flight crew in Scandinavia,<sup>54</sup> Greece,<sup>55</sup> Britain<sup>56</sup> and even combined European studies<sup>57,58</sup> have failed to show any significant effect of flying on the development of intracranial tumours. A meta-analysis of some earlier studies had shown a non-significant trend towards brain tumour in pilots, although there were methodological problems in the contributing studies.<sup>59</sup> A cohort study of the US Air Force between 1975 and 1989 has shown no difference in the incidence of brain or intracranial tumours between aircrew (532,980 man-years of observation) and ground staff (1,084,370 man-years of observation).<sup>60</sup>

3.6.9. **Low frequency electromagnetic fields (LFEMF).** US Air Force service personnel on active service between 1970 and 1989 were assessed for exposure to non-ionising electromagnetic radiation (radio, radar and microwave) and brain tumour risk. This study had a considerable observation time from a study base of 880,000 personnel (11,174,248 person-years of observation) and showed a very small excess of brain tumours in men exposed to non-ionising radiation which was just statistically significant (odds ratio 1.39; 95% confidence interval 1.01-1.90). There was no association between ionising radiation and brain tumour risk, although dosimetry data were available for only 3% of the study subjects. When all confounding factors were analysed, the strongest association with brain tumour was with military rank. Senior officers were significantly more at risk than

all other US Air Force members (odds ratio 2.11; 95% confidence interval 1.48-3.01). This was not due to length of service or age alone, as these were not statistically significant, and appeared to suggest that higher socioeconomic status was a risk factor.<sup>61</sup> Two small studies in the Brazilian navy suggested a slightly increased risk of brain tumour.<sup>62,63</sup> A much larger British study of 15,138 submariners serving between 1960 and 1989 has shown no increase in brain tumour risk within that population. Indeed, the risk of death from cancer in general was much lower in submariners.<sup>64</sup> These results were replicated in a 40 year follow-up of 20,021 Korean War veterans with high potential exposure to high-intensity radar. Again the overall cancer risk was lower than in the general population and, specifically, there was no increase in brain tumours.<sup>65</sup>

- 3.6.10. **High frequency (ionising) electromagnetic radiation** Military personnel may be exposed to ionising radiation through nuclear testing, working on nuclear powered submarines or during warfare. The NRPB reports on motability and cancer incidence amongst the participants shows no increase rates of brain tumour.<sup>67,67,68</sup> Thirty year follow-up of Canadian personnel exposed to nuclear tests has shown no increase in brain tumours.<sup>69</sup> Studies of American personnel also produced similar results.<sup>70,71</sup> Service and contract personnel working at nuclear submarine bases have an average excess of only 0.25mSv due to their occupational exposure.<sup>41</sup>
- 3.6.11. **Depleted Uranium** The extreme density of depleted uranium has been used in non-explosive armour-piercing shells during the 1991 Gulf War and the Balkans conflict.<sup>72</sup> Only in crews of military vehicles hit by depleted uranium shells have body levels higher than background been found. However, extra risk of death from any cancer has been predicted to be undetectable.<sup>72,73</sup>

## 4. Treatment

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- 4.1. **Surgery.** All intracranial tumours require surgery for accurate diagnosis. Unlike many tumours elsewhere in the body, the eventual prognosis for cure is dependent on both tumour site within the intracranial cavity and its biological properties. Some benign tumours are not operable because they are in a critical part of the brain or involve the blood supply or venous drainage of the brain. These tumours will eventually prove fatal, although histologically, they are benign. Malignant tumours of the brain are incurable by surgery alone.
- 4.2. **Radiotherapy.** Conformal external beam radiotherapy to a total dose of 60 Gray is usually given in 30 treatments (fractions) over 5-6 weeks. This doubles the survival time in Grade III or Grade IV astrocytoma compared to no radiotherapy.<sup>74</sup> Other methods for the delivery of radiotherapy (stereotactic,<sup>72</sup> interstitial,<sup>75</sup> ultra fractionated<sup>76</sup>) have not produced significantly superior results to conventional external beam radiotherapy. Newer techniques using proton<sup>77</sup> or neutron beams,<sup>78</sup> while theoretically attractive, have yet to show any benefit in patients with Grade III or Grade IV astrocytic tumours. Radiotherapy may also be used for other malignant brain tumours and recurrent benign tumours.
- 4.3. **Chemotherapy.** All glial tumours, apart from some oligodendrogliomas, are highly resistant to chemotherapy. Current chemotherapeutic agents include procarbazine in combination with vincristine and CCNU (PCV) and temozolomide. At best, only 20% of patients with glioblastoma show a response and even the most recent trial of temozolomide in glioblastoma only improved median survival from 12.1 months post diagnosis to 14.6 months.<sup>79,80</sup>

## 5. Prognosis

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- 5.1. The median survival from WHO Grades II, III or IV astrocytic tumours fully treated with surgery, radiotherapy and chemotherapy is 5 years, 2 years and 12 months respectively. Age at presentation and performance status are the only statistically proven prognostic factors for astrocytic tumours, with older patients faring worse.<sup>81</sup> Younger patients are more likely to have secondary glioblastoma, which is slightly more responsive to radiotherapy and chemotherapy. Median survival for older patients with glioblastoma is less than 12 months. The 2 year survival rate is less than 4%.<sup>81</sup>
- 5.2. Improved genetic analysis may identify subgroups of tumours which respond better to current treatments. Novel treatments (photodynamic, gene, viral, convection-enhanced drug delivery and immunotherapy) are under trial. (None of these is likely to significantly alter the outcome for patients with Grade III or Grade IV astrocytoma within the next 5 years).
- 5.3. Meningiomas are generally benign but location and histological grade may lead to recurrence. The degree of surgical resection is dependent on the site of the tumour. Fully excised tumours will have a recurrence rate below 10% over 5 years.<sup>82</sup>
- 5.4. Acoustic neuroma (or correctly vestibular schwannoma). Recent studies have failed to show any clear effect of non-ionising radiation on the production of these tumours.<sup>83,84</sup> They are benign and very slow-growing. Recurrence following surgical excision is rare.

## 6. Summary

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- 6.1. Tumours of the brain and its coverings are uncommon in the age group of active service personnel.
- 6.2. There is no conclusive evidence from current epidemiological studies that they are any more common in service personnel than in the general population, or that an uncontrolled environmental factor is at work.
- 6.3. The only specific factor clearly identified in the production of malignant brain tumours and benign tumours within the cranial cavity is prior therapeutic radiotherapy, especially during childhood.
- 6.4. All glial tumours, except pilocytic astrocytoma, should be regarded as malignant and are ultimately fatal, despite treatment.

## **7. Related Synopses**

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Cancers

Stroke

## 8. Glossary

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astrocytes	Star-shaped cells providing support functions in the central nervous system.
astrocytoma	An intracranial tumour derived from astrocytes. They can have narrow or diffuse zones of infiltration.
glioblastoma	A rapidly growing astrocytic tumour with aggressive and malignant features .
haemangioblastoma	A brain tumour composed of a proliferation of capillaries and disorganised clusters of capillary cells or angioblasts, usually occurring in the cerebellum.
histological	The microscopic appearance of cells, their pattern of arrangement and properties following chemical or biological staining.
intracranial pressure	The adult cranium (skull) is a rigid box filled with the brain, its supplied blood and cerebrospinal fluid (CSF). A tumour will cause an increase in the pressure within the cranium if there is no compensatory reduction, (or the capacity for such a reduction is exhausted), of the volume of the brain, blood or CSF.
oligodendrocytes	Glial cells that populate the central nervous system (CNS) and produce CNS myelin.
medulloblastoma	A malignant, highly radiosensitive cerebellar tumour composed of undifferentiated neuroglial cells. They are almost always found in children or young adults.
meningiomas	Tumours that originate from the arachnoidal layer of the meninges, thin membranes that cover the brain and the spinal cord. These slow-growing tumours rarely become malignant or spread.

schwannoma	A type of benign brain tumour that begins in the Schwann cells that produce the myelin which protects the vestibular nerve (the nerve of balance).
tumour suppressor gene	A gene which, normally, controls the rate of cell growth and division. There are normally 2 copies of each gene in each cell. Both copies must be inactivated to allow the cell to grow and divide unchecked.

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