The incidence of major subtypes of primary brain tumours in adults in England 1995-2017

Hiba A. Wanis¹, Henrik Møller¹,², Keyoumars Ashkan³, Elizabeth A. Davies¹

1. Cancer Epidemiology, Population and Global Health, King’s College London, Bermondsey Wing, 3rd floor, Guy’s Hospital, Great Maze Pond, London SE1 9RT
2. Danish Centre for Health Services Research, Aalborg University, Denmark
3. Department of Neurosurgery, King’s College Hospital NHS Trust, Denmark Hill, London SE5 9RS

Author for correspondence
Hiba A. Wanis
Cancer Epidemiology, Population and Global Health
King’s College London
3rd floor Bermondsey Wing
Guy’s Hospital
Great Maze Pond
London SE1 9RT
Tel: +44 (0)20 718 88414
Email: hiba.wanis@kcl.ac.uk

Funding: This work was partly supported by a donation from Mrs Julia Chappell in memory of her husband.

Conflict of Interest: None declared

Authorship: HAW, HM and EAD conceived and designed the study, HAW analysed the data, and all authors were involved in the interpretation of the results and in drafting and reviewing the manuscript.
Background: Primary brain tumours are a complex heterogenous group of benign and malignant tumours. Reports on their occurrence in the English population by sex, age, and morphological subtype and on their incidence are currently not available. Using data from the National Cancer Registration and Analysis Service (NCRAS), the incidence of adult primary brain tumour by major subtypes in England will be described.

Methods: Data on all adult English patients diagnosed with primary brain tumour between 1995 and 2017, excluding spinal, endocrinal and other CNS tumours, were extracted from NCRAS. Incidence rates were standardised to the 2013 European Standard Population. Results are presented by sex, age, and morphological subtype.

Results: Between 1995 and 2017, a total of 133,669 cases of adult primary brain tumour were registered in England. Glioblastoma was the most frequent tumour subtype (31.8%), followed by meningioma (27.3%). The age-standardised incidence for glioblastoma increased from 3.27 per 100,000 population per year in 1995 to 7.34 in men in 2013 and from 2.00 to 4.45 in women. Meningioma incidence also increased from 1.89 to 3.41 per 100,000 in men and from 3.40 to 7.46 in women. The incidence of other astrocytic and unclassified brain tumours declined between 1995 and 2007 and remained stable thereafter.

Conclusion: Part of the increase in the incidence of major subtypes of brain tumours in England could be explained by advances in clinical practice including the adoption of new diagnostic tools, classifications and molecular testing, and improved cancer registration practices.

Key words: Brain tumours; Incidence; Epidemiology; Cancer Registry
Key Points

Between 1995 and 2017, the incidence for glioblastomas and meningiomas increased in England. Primary CNS lymphoma also showed a notable increase. Other astrocytic and unclassified brain tumours declined.

Importance of the Study

This is the first study to report the incidence of brain tumour subtypes in England. The information presented will enable us to better understand their burden in the population and, ultimately as registration data becomes more detailed, to use this data to improve cancer services for these patients.
1. Introduction

Primary brain tumours are an uncommon and complex group of benign and malignant neoplasms. These tumours are diverse in terms of their morphology, topography, molecular biology and clinical behaviour. The World Health Organisation (WHO, 2016) Classification of Tumours of the Central Nervous System (CNS WHO) grouped these tumours into multiple histologic subtypes. Estimating the burden of brain tumours in the population and evaluating their incidence requires consideration of their heterogeneity according to morphological subtype, sex and age, as their prognosis varies by these factors.

Brain, spinal and central nervous system (CNS) tumours are relatively uncommon with 11,444 new cases being recorded in 2016 in the United Kingdom (UK). CNS tumours include those of the brain, spinal cord, meninges, intracranial endocrine glands and other parts of the CNS. These tumours accounted for 3% of all cancer cases in the UK in 2016, and are more frequent in men than women. These UK statistics are provided by Cancer Research UK which gathers data directly from the health systems or governments in England, Scotland, Wales and Northern Ireland.

Between 1970 to 1990, the incidence has most often been reported overall for CNS tumours combined or for gliomas alone. Results from large-scale cohort and population-based studies in the United States, Japan and Europe, have found variable patterns of incidence trends for brain tumours. Some studies, particularly those in the Far East countries have shown the incidence of brain tumours is either slightly decreasing or levelling-off, while others, mostly in Northern Europe have found an increasing incidence.

So far reports on the epidemiology of brain tumours in England are few and lack detail on tumour type, particularly when compared with those from the United States and other European countries. Using the English Cancer Registry and other established databases, this study aims to describe the incidence of primary brain tumours for the main morphological subtypes, including benign and malignant tumours, in adults between 1995 and 2017.
2. Materials and Methods

2.1. Data

In this analysis, primary brain tumours were defined as neoplasms that originate from intracranial tissues and the meninges, varying in their behaviour. Data on spinal tumours, endocrinal tumours, tumours of the CNS external to the brain, and metastatic tumours were excluded. Data on meningiomas and primary brain lymphomas were included, as they are considered as significant primary brain tumour subtypes.

Data on all adult patients (aged 18 years or over) diagnosed with primary brain tumours in England between January 1, 1995 and December 31, 2017 were extracted from the Cancer Registry – the National Cancer Registration and Analysis Service (NCRAS) within Public Health England (PHE) in England. Patients were identified as diagnosed with primary brain tumours using the International Classification of Diseases [version 10] (ICD-10) tumour sites C70, C71, D32, D33, D42 and D43. For those diagnosed with primary CNS lymphoma, ICD-10 code site was used along with the morphology codes for lymphoma. Other inclusion criteria were patients being resident in England, having a complete tumour registration and known sex. The brain tumour morphological subtypes considered in this study were based on the 2016 WHO Classification of Tumours of the Central Nervous System, and by most common types: glioblastoma, other astrocytoma (excluding glioblastoma), meningioma, oligodendrogliaoma, embryonal tumours, ependymomal tumours, oligoastrocytoma, primary CNS lymphoma, malignant glioma, unclassified malignant, unclassified benign, unclassified uncertain and other. The subtype ‘other’ includes brain tumour morphologies that could not be assigned to any of the above. These brain tumour subtype groups were based on morphology and not tumour behaviour. Categorisation of the brain tumour subtypes is shown in table 1. All tumours extracted from NCRAS were analysed irrelevant of their pathological confirmation were included. Metastatic tumours were not included in the analysis.
2.2. Incidence rates analysis

For each brain tumour subtype, the age-standardised incidence rate per 100,000 person-years were calculated to the European Standard Population (ESP 2013). This is a set of population weights that are commonly used to compare incidence rates in European populations. These weights are more similar to the European population than the World Standard Population weights which might be used in studies of other areas of the world. Male to female incidence rate ratios were calculated by year of diagnosis, age, and sex for each of the brain tumour subtypes. Age-specific incidence rates were calculated in five-year age groups in adults (aged 15 years or over) for males and females. Apart from age-standardisation we did not attempt statistical modelling of trends in incidence, aiming in this first study to describe the actual data over time.

2.3. Ethical approval

NCRAS has approval from the Confidentiality Advisory Group of the National Health Service Health Research Authority to carry out surveillance using the data they collect on all cancer patients under section 251 of the NHS Act 2006. Separate ethical approval for this study was therefore not required.

3. Results

3.1. Patient and tumour characteristics

Between 1995 and 2017, a total of 133,669 adult primary brain tumour cases, excluding spinal, endocrinal and other CNS tumours, were registered in England. There were 65,708 cases in men (49%) and 68,259 in women (51%) (Table 2). The mean age at diagnosis was 62 years. The number of diagnosed brain tumours increased gradually over the 23-year period, from 4,471 cases in 1995 to 7,580 in 2017.
Around a third of all patients were diagnosed with the most aggressive brain tumour subtype glioblastoma (WHO Grade IV) (n=42478, 31.8%), followed by the least aggressive subtype meningiomas (27.3%), and other astrocytic tumours (9.4%) (Table 3). The unclassified subtypes i.e. without a known morphology, including malignant glioma, represented 21.0% of all brain tumour diagnoses. Overall, most of the brain tumours were considered malignant (64.2%).

The number of malignant primary brain tumour diagnoses changed over time for specific tumour sites, particularly in the frontal (C70.1) and temporal lobes (C70.2) which increased by a factor of 2.6 and 3.3, respectively. Over the same period there was a decrease in the numbers recorded for unspecified site (C71.9) (Figure 1). Meningiomas can be malignant or benign, however in this cohort it can be seen in figure 1 that the vast majority were of benign tumour behaviour (site code D32 – benign neoplasms of cerebral meninges/meninges, unspecified). Also, the number of cases increased over the study period peaking at >2,000 cases in 2015. A different picture was seen for the malignant meningiomas (site code C70) where cases remained very low and below 50 cases in 2015.

3.2. Incidence analyses

Over the 23-year period from 1995, the number of primary brain tumour cases recorded in adults increased each year (Table 2). This overall increase in primary brain tumour incidence was examined further by morphological subtype, sex, and age.

3.2.1. Most common brain tumour subtypes

The most common brain tumour subtypes were glioblastoma, other astrocytoma (excluding glioblastoma), meningioma and oligodendroglioma. The age-standardised and age-specific incidence rates for these tumours are shown in figures 2 a-d and 3 a-d, respectively. The age-standardised incidence for glioblastoma increased from 3.27 per 100,000 population per year to 7.34
in men and from 2.00 to 4.45 in women (Figure 2a). By 2017, the male to female incidence ratio was 1.64:1.00. The age-specific incidence rate for glioblastoma increased continually with age, peaking at 65-74 years, and dropping after 75 years for both men and women (Figure 3a). Overall, the age-specific incidence of glioblastoma did not change over this time except to increase in the 60-74 year and over 75-year age groups.

The age-standardised incidence for other astrocytic tumours declined between 1995 and 2007 from 2.50 to 1.25 per 100,000 in males and from 1.65 to 0.79 in females, remaining stable thereafter (Figure 2b). Compared with the age-specific incidence curve for glioblastoma, other astrocytoma subtypes showed a gradual increase with age peaking at 30-39 and 65-74 years and with incidence falling after 75 years (Figure 3b).

Meningioma incidence rates also increased from 1.89 to 3.41 per 100,000 in men and from 3.40 to 7.46 in women (Figure 2c), with a sharper increase noticed in 2011. Rates were low and differed slightly in the age groups 15-29, but increased in each of the older age groups in both males and females, becoming highest in the over 75-year olds (Figure 3c).

Overall, there was a slight increase in the age-standardised incidence over time for oligodendroglioma (Figure 2d). For both sexes, the age-specific incidence curve increased sharply until 35-39 years, flattened out until 65-69 years, and then decreased with advancing age thereafter (Figure 3d). About 47% of the diagnosed adults were aged between 35 and 54 years.

### 3.3.2 Less common brain tumours subtypes

The less common brain tumours subtypes were embryonal tumours, ependymomal tumours, oligoastrocytomas and primary CNS lymphomas. The age-standardised and age-specific incidence rates for these tumours are shown in figures 2 e-h and 3e-h, respectively. These tumours were slightly more frequent in men than in women. During the period 1995-2017, there was a small
decrease in the age-standardised incidence rates for embryonal tumours (Figure 2e), and the opposite trend for ependymomal tumours (Figure 2f). The embryonal tumours were common in young adults as shown in the age-specific incidence curve where the incidence decreased with age (Figure 3e). The age-standardised incidence rate for oligoastrocytomas increased over the study years peaking at 0.23 per 100,000 population (95% CI; 0.17-0.30) for men, and 0.15 (95% CI; 0.10-0.21) for women in 2010, and the rates significantly dropped to 0.01 per 100,000 population, in 2017 (Figure 2g). Over time, there was a low incidence of primary CNS lymphomas with only a very slight increase from 0.25 per 100,000 population in 1995 to 0.32 in 2011 for men and from 0.13 per 100,000 population in 1995 to 0.29 in 2011 for women. However, from 2012, an increase in the incidence of primary CNS lymphoma was observed reaching 0.70 (95% CI; 0.58-0.81) in men and 0.59 (95% CI; 0.40-0.69) in women (Figure 2h).

3.3.3 Unclassified brain tumour subtypes

The unclassified brain tumours include malignant glioma, unclassified benign, unclassified malignant and unclassified with uncertain behaviour. The age-standardised and age-specific incidence rates for these tumours are shown in figures 2i-l and 3i-l, respectively. These subtypes were more common in men than women, except for unclassified benign where the opposite was seen. The age-standardised incidence rate of malignant gliomas showed a decrease over time, similar to that for other astrocytomas (Figure 2i), and remaining stable after 2007. The incidence for unclassified malignant and uncertain behaviour brain tumours declined slightly over time while the unclassified benign incidence remained the same (Figure 2j-l). The age-specific incidence curve for unclassified malignant gliomas, benign, malignant and uncertain, showed a similar sharp increase in the incidence increased sharply in the elderly (Figure 3i-l).
4. Discussion

4.1. Key points

This study found an overall rise in the incidence rate of primary brain tumours being diagnosed in England between 1995 and 2017. Glioblastomas were the most frequent tumour subtype, followed by meningiomas. The age-standardised incidence for glioblastomas, meningiomas and primary CNS lymphomas increased significantly over the study period. The rarer brain tumours did not show much increase during this period. Other astrocytic and unclassified brain tumours declined between 1995 and 2007 and remained stable thereafter.

4.2. Comparison with other work

Findings from our study can be compared with a recently published paper concerning brain tumour subtypes by Philips and colleagues. These authors analysed the incidence trends between 1995 and 2015 in England demonstrating an increase in the subtype glioblastoma, which was also shown in our study. However, their study focussed on malignant gliomas in patients of all ages, whereas our study concerned benign, malignant as well as uncertain tumour behaviours in adults only. Since brain tumour subtypes present differently in different age groups, analysing grouped tumours for all ages combined may be misleading and should preferably be explored independently. Although both studies might be similar due to the overlapping analysis period, our study presents more detailed findings based on grouping of each tumour subtype.

Comparing the incidence of brain tumours found in the present study with those from other Western and European countries appears to show similar increases. A French population-based registry in Gironde, showed an increase in primary CNS tumours from 2000 to 2012 although this included spinal tumours and excluded pituitary tumours and metastatic tumours. Since the crude
incidence of CNS tumours was higher in females than males and in the elderly, the overall rise was explained by the increase in meningioma incidence. For the malignant CNS tumours, which would include glioblastomas, no trend was found. In our study, it seems likely that meningiomas and glioblastomas are the main drivers of the overall increase in the incidence of brain tumours. The Spanish Girona Cancer Registry study also reported similar results with the most frequent brain tumour subtypes being meningiomas (27.6%, incidence rate = 5.11 per 100,000) and glioblastomas (22.2%, incidence rate = 4.15). However, the incidence rates over time were not presented for these subtypes. In Denmark, Finland, Norway and Sweden, the incidence rate for gliomas also increased in those aged 60-79 from 1974 to 2003, and in the same age group, an increasing incidence was observed for meningiomas in women after the 1990s. Findings from other global studies includes incidence data from Australia showing an increase in meningioma during the period 2000 to 2008, which was more pronounced in men aged 20-64 years (6.3 annual percentage change) than in women (0.6 annual percentage change). Interestingly, by contrast the age-standardised incidence rates of meningiomas in Osaka, Japan, appeared to have decreased during the period 1995-2004.

According to age distribution, brain tumour diagnoses tend to be aggregated based on biological and epidemiological aspects. Malignant brain tumours are more common in adolescents and young adults (AYA) (aged 15 to 24 years), than in children. However, the incidence rate in AYA is lower than in older adults. A recent study exploring the incidence trends in AYAs from 12 countries of Southern and Eastern Europe between 1990 and 2014. Found a high incidence in most countries except in Croatia which saw an annual decrease of 2.5%.

Data collected for the US Central Brain Tumor Register (CBTRUS), showed an increased incidence for benign CNS tumours, as a consequence of the introduction of the Benign Brain Tumor Cancer Registries Amendment Act (2002) that made collection of benign brain tumours a requirement. The UK cancer registries (including Scotland, Wales and Northern Ireland) reported an increase in the incidence of CNS tumours between 1979 and 2006, which was primarily seen in young adults (0-
24 years) and the elderly (65-84 years). Different trend patterns were seen for meningiomas where the increase was in those over 25 years old, with pilocytic astrocytomas increasing in the 0-24 age group\textsuperscript{16}.

As can be seen from these studies, differing cancer incidence rates are reported in different countries. These could be explained by structural factors such as varying cancer registration systems, the presentation of regional rather than national data, socio-economic variation between countries and access to diagnostic and treatment services. Another important issue when making between-country or between-continent comparisons is the age-adjustment procedures. Some studies present their results as crude incidence rates while others as standardised rates based on different standard populations. Finally, how these tumours are recorded in each country plays an additional role. For example, the Estonian Cancer Registry only recorded 11\% of tumours as benign\textsuperscript{17}, compared to other European registries for example the Nordic countries, which could be as high as 98\%\textsuperscript{12}. It was reported that in the earlier years of the Estonian Cancer Registry, benign cases were recorded as malignant\textsuperscript{17}.

\textbf{4.3. Limitations}

This national study used data from a 23-year period on a very large number of patients diagnosed with primary brain tumours, excluding spinal, endocrinal and other CNS tumours. As brain tumours are a heterogenous group of tumours behaving in different ways, it was necessary to investigate differences in incidence for the main morphological subtypes. Those tumours that could not be classified were grouped into ‘Other’ subtypes – a group that represent a vast range of extremely rare morphologies of brain tumours. Due to this, the incidence of this group was not analysed.

Unfortunately, English cancer registration data does not differentiate between primary and secondary glioblastomas which express different genetic features. Secondary glioblastomas are
more common in younger patients where they have transformed from diffuse (WHO grade II) or anaplastic (WHO grade III) astrocytoma. It is difficult to differentiate between primary and secondary glioblastoma histopathologically, but it is recognised that they develop through different genetic pathways\textsuperscript{18}. To investigate these tumours more deeply, detailed molecular and pathological data will be required.

To add to the complexity of brain tumour classification, some tumour subtypes that are most common in children are not common in adults, while some subtypes present in childhood, adolescence, and adulthood. This makes analysis of ‘adult-only’ types near impossible. For example, pilocytic astrocytoma, a WHO grade I tumour, is the most common primary brain tumour in children aged 5-14 and the second most common brain tumour in children aged 0-4 and 15-19\textsuperscript{5}. However, some adults are diagnosed with this brain tumour, and much of the understanding of it is based on the paediatric literature, as limited papers have been published on adult pilocytic astrocytomas.

Finally, it is necessary to consider the robustness of data within NCRAS. A UKACR agreement to the European Network of Cancer Registries (ENCR) recommendations was implemented in 2000\textsuperscript{19}. This recommendation was adopted by the eight former regional registries in England to register all brain and CNS tumours, including non-malignant tumours. Data collection and completeness has improved over the study years as regional registries have applied further strategies including interrogation of the data by site specific groups and the merger of the former eight English registries into one in 2013. However, brain tumours are less common compared to other cancers and so collection of data on these complex and morphologically diverse tumours might not be as thorough as for other cancers.
4.4. Potential explanations of study findings

This study is the most comprehensive study of the incidence of brain tumours in the English population and reports a general increase in brain tumour cases in adults between 1995 and 2017. It has been recognised that brain tumour incidence has been increasing at least since 1971. Over the last five decades, there have been advances in diagnostic technologies, associated with the introduction of computed tomography (CT) scanning during the 1970s and magnetic resonance imaging (MRI) during the 1980s. Since then, neuroimaging has evolved enabling earlier diagnosis and imaging-guided therapies, hereby improving patient care. It has been hypothesised that ionising radiation exposure from early CT scans might have contributed to the increased risk of gliomas in the population, although there is no strong evidence for this.

A more plausible reason explaining the increasing incidence of brain tumours is the combination of advances in imaging and surgical procedures, their increasing availability, and clinical guidance recommending that patients with suspicious neurological symptoms should be thoroughly investigated. The National Institute for Health and Clinical Excellence (NICE) guidelines released in 2006 outlined the importance of assessing and coordinating patient care through a multidisciplinary team. This could explain the further increased incidence following 2006 for glioblastomas and meningiomas, and a stable incidence for other astrocytomas and malignant gliomas. In 2015, updated NICE guidance was published aiming to improve investigations in primary care for suspected brain and CNS tumours with progressive, loss of central neurological function. For patients experiencing these symptoms, the referral is considered very urgent and patients are given direct access to MRI or CT scan within 48 hours for children and young adults, and within two weeks for adults. These advances could have led to more patients being operated on, and as a result the number of tumours with histological confirmation increasing.

Historically benign brain tumours have had less priority compared to malignant tumours and so they were not usually included in the national statistics. However, over time, registrations of benign
tumours cases have improved. When compared to malignant tumours, histological confirmation has decreased over time with increasing incidence for benign meningiomas in women, particularly from 2011, and this could be explained by a few reasons. With increasing use of MRI and CT scans, more small, slow growing and sometimes incidental lesions suggestive of meningioma are being diagnosed. In this scenario, patients are usually followed up rather than being operated on and hence no histology is obtained. Additionally, the decreasing histology validation for benign tumours and increasing incidence in malignant tumours could possibly be a consequence of the release of a service specification encouraging the delivery of non-surgical therapies such as stereo-radiosurgery and stereo-radiotherapy for meningioma patients in order to improve their life expectancy and quality of life. This was also cited in the latest NICE guidelines in 2018 as Evidence Report for the investigation, management and follow-up of meningioma. Furthermore, non-malignant tumour registrations have improved since 2013 when the newly merged national cancer registry (now known as NCRAS) instructed the use of the Cancer Outcomes and Services Dataset (COSD).

During the analysis period, revisions to the WHO classification of CNS tumours have led to changes in diagnostic categories for some brain tumour subtypes. From the WHO classification for CNS tumours 2000 version to 2007, and more recently 2016, it is clear that the incidence of brain tumours is greatly influenced by the diagnostic coding used in any national cancer registry. The overall decline in the incidence of unclassified brain tumours over the years could be explained by the advances in neuropathology due to more defined diagnostics criteria for brain tumours morphologies. In the 2016 edition, due to the difficulty in classifying oligoastrocytomas, their use was discouraged in favour for astrocytomas and oligodendrogliomas. The impact of this change was evident in the analysis of this cohort where only 5 cases were recorded in 2017 for oligoastrocytomas (morphology code 9382/3). In addition, the use of this morphology decreased prior to 2016 with increasing use of molecular classification. Other examples of how the 2016 WHO CNS classifications impacted on the data include the introduction of diffuse midline glioma giving 7 new cases for 2016 and 2017, and no recorded cases as a result of the deletion of protoplasmic
astrocytoma. Going forward, it is expected that more genetic-based classifications will be recorded as practices are developed to converge with the WHO CNS classifications. Furthermore, changes to diagnostic coding within the Registry could be linked to improvements in procedural practices and quality assurance processes as more data is received electronically from NHS hospitals. This was evident in the incidence of primary CNS lymphomas where coding for haematological malignancies was refined from 2012 onwards.

For the most common brain tumours, gliomas and meningiomas, it is interesting to note that the incidence shows the opposite patterns for each sex. Meningioma is more than twice as common in women compared to men while gliomas are more common in men. In addition to the differences in their incidences, male and female meningiomas differ in their tumour behaviour. Meningiomas in females are mostly benign, while those in males are more commonly malignant. For glioblastomas and meningiomas, the largest increase in incidence rates were evident in both sexes for the elderly. This could be explained by the ageing of the population together with increasing availability of imaging and less invasive neurosurgical techniques. In other studies, the incidence of primary brain tumours was observed to have tripled in those over the age 70 years. For the younger age groups, incidence remained constant over the study period, with the exception of women diagnosed aged 30-59 years in whom the incidence of meningiomas somewhat increased. The increased risk of meningiomas in women is likely to be due to improved registration of benign brain tumours over the recent years.
5. Conclusion

This study has described the incidence rates of primary brain tumours, an important measure of the changing burden of cancer in a population over time. It has explored the various brain tumour subtypes based on their morphology, sex and age. Results show an overall rise in the incidence rate of these tumours being diagnosed in England between 1995 and 2017. While the incidence varied for the different brain tumour subtypes, the most common brain tumours - glioblastoma and meningioma - seem to be driving this overall increase. Explanations for the increase in the number of primary brain tumours are likely to include ageing of the population, improvements in access to neurosurgical care and diagnostic tools, and more complete and detailed records, including benign tumours, reaching NCRAS as a result of the regular updates in the coding of the WHO classification for CNS tumours. All these factors are likely to play a role in contributing to the incidence of brain tumours, particularly for glioblastomas and meningiomas.

Acknowledgements

Data for this study is based on patient-level information collected by the NHS. The data is collated, maintained and quality assured by Public Health England, National Cancer Registration and Analysis Service. We thank Sally Vernon and Victoria Coupland from Public Health England for help extracting the data. We also thank Dr Lucy Brazil, Dr Margreet Lüchtenborg and Professor Richard Sullivan for helpful comments and suggestions on these analysis.

Funding: This work was partly supported by a donation from Mrs Julia Chappell in memory of her husband.
References

1. Louis, D. N. et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. (Berl.) 131, 803–820 (2016).

2. Ohgaki, H. & Kleihues, P. Epidemiology and etiology of gliomas. Acta Neuropathol. (Berl.) 109, 93–108 (2005).

3. Cancer Research UK. Brain, other CNS and intracranial tumours statistics https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancertype/brain-other-cns-and-intracranial-tumours?_ga=2.172768099.1375741702.1600433248-1594617780.1600433248 (2016).

4. Ferlay, J. et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int. J. Cancer 136, E359–E386 (2015).

5. Ostrom, Q. T. et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. Neuro Oncol 17 Suppl 4, iv1–iv62.

6. Ho, V. K. et al. Changing incidence and improved survival of gliomas. Eur J Cancer 50, 2309–2318 (2014).

7. Nomura, E., Ioka, A. & Tsukuma, H. Trends in the Incidence of Primary Intracranial Tumors in Osaka, Japan. Jpn. J. Clin. Oncol. 41, 291–294 (2011).

8. Miranda-Filho, A., Piñeros, M., Soerjomataram, I., Deltour, I. & Bray, F. Cancers of the brain and CNS: global patterns and trends in incidence. Neuro-Oncol. 19, 270–280 (2016).

9. Philips, A., Henshaw, D. L., Lamburn, G. & O’Carroll, M. J. Brain Tumours: Rise in Glioblastoma Multiforme Incidence in England 1995–2015 Suggests an Adverse Environmental or Lifestyle Factor. J. Environ. Public Health 2018, 7910754 (2018).

10. Baldi, I. et al. Descriptive epidemiology of CNS tumors in France: results from the Gironde Registry for the period 2000–2007. Neuro-Oncol. 13, 1370–1378 (2011).

11. Fuentes-Raspall, R. et al. Descriptive epidemiology of primary malignant and non-malignant central nervous tumors in Spain: Results from the Girona Cancer Registry (1994–2013). Cancer Epidemiol. 50, 1–8 (2017).

12. Lönn, S. et al. Incidence trends of adult primary intracerebral tumors in four Nordic countries. Int. J. Cancer 108, 450–455 (2004).
13. Dobes, M. et al. Increasing incidence of glioblastoma multiforme and meningioma, and decreasing incidence of Schwannoma (2000-2008): Findings of a multicenter Australian study. Surg. Neurol. Int. 2, 176–176 (2011).

14. Georgakis, M. K. et al. Malignant central nervous system tumors among adolescents and young adults (15-39 years old) in 14 Southern-Eastern European registries and the US Surveillance, Epidemiology, and End Results program: Mortality and survival patterns. Cancer 123, 4458–4471 (2017).

15. Benign Brain Tumor Cancer Registries Amendment Act. PUBLIC LAW 107–260—OCT 29 2002 Rec. C Ed. Legis. Hist. Vol. 148., 2558. (2002).

16. Arora, R. S. et al. Age-incidence patterns of primary CNS tumors in children, adolescents, and adults in England. Neuro-Oncol. 11, 403–413 (2009).

17. Liigant, A., Asser, T., Kulla, A. & Kaasik, A.-E. Epidemiology of primary central nervous system tumors in Estonia. Neuroepidemiology 19, 300–311 (2000).

18. Ohgaki, H. & Kleihues, P. Genetic pathways to primary and secondary glioblastoma. Am. J. Pathol. 170, 1445–1453 (2007).

19. ENCR Recommendations - Tumours of the Brain and Central Nervous System. (1998).

20. Quinn MJ, Babb P, Brock A, Kirby L, Jones J. Cancer Trends in England and Wales 1950–1999. Studies on Medical and Population Subjects No. 66. Off. Natl. Stat. Lond. 2001.

21. Castillo, M. History and Evolution of Brain Tumor Imaging: Insights through Radiology. Radiology 273, S111–S125 (2014).

22. Brenner, D. J. & Hall, E. J. Computed Tomography — An Increasing Source of Radiation Exposure. N. Engl. J. Med. 357, 2277–2284 (2007).

23. National Institute for Health and Clinical Excellence. Improving outcomes for people with brain and other central nervous system tumours. (2006).

24. National Institute for Health and Clinical Excellence. Suspected cancer: recognition and referral. (2015).

25. Uthman, Fry-Smith, Routh, Moore. The clinical and cost-effectiveness of stereotactic radiosurgery and fractionated stereotactic radiotherapy for meningiomas: an evidence based review. (2010).

26. National Institute for Health and Clinical Excellence. Brain tumours (primary) and brain metastases in adults. Evidence reviews for the investigation, management and follow-up of meningioma. (2018).

27. Kleihues, P. et al. The WHO Classification of Tumors of the Nervous System. J. Neuropathol. Exp. Neurol. 61, 215–225 (2002).
28. Louis, D. N. et al. The 2007 WHO Classification of Tumours of the Central Nervous System. *Acta Neuropathol. (Berl.)* **114**, 97–109 (2007).

29. Greig, N. H., Ries, L. G., Yancik, R. & Rapoport, S. I. Increasing annual incidence of primary malignant brain tumors in the elderly. *J. Natl. Cancer Inst.* **82**, 1621–1624 (1990).

30. Legler, J. M. et al. Cancer surveillance series [corrected]: brain and other central nervous system cancers: recent trends in incidence and mortality. *J. Natl. Cancer Inst.* **91**, 1382–1390 (1999).

31. Christensen, H. C. et al. Incidences of gliomas and meningiomas in Denmark, 1943 to 1997. *Neurosurgery* **52**, 1327–1334 (2003).
Figure Legends

Table 1 - Categorisation of brain tumour subtypes based on tumour morphologies

Table 2 - Patient characteristics of 133,669 patients diagnosed with primary brain tumour in England, 1995-2017

Table 3 - General tumour characteristics of 133,669 patients diagnosed with primary brain tumour in England, 1995-2017

Figure 1 - Distribution of brain tumours based on site of neoplasm in England over time. Cases for year of diagnosis 1995, 2000, 2005, 2010 and 2015, categorised by tumour behaviour

Figure 2 - Age-Standardised Incidence Rates of brain tumour subtypes in England, 1995-2017

Figure 3 - Age-Specific Incidence Rates of brain tumour subtypes in England, 1995-2017
Table 1 - Categorisation of brain tumour subtypes based on tumour morphologies

| Brain tumour subtypes                              | Morphology codes                      |
|---------------------------------------------------|---------------------------------------|
| Glioblastoma (GBM)                                | 9440-9442, 9445                        |
| Meningioma                                        | 9530-9539                              |
| Other astrocytic tumours (excluding GBM)          | 9381, 9384, 9400-9411, 9420-9421, 9424, 9425 |
| Oligodendrogial tumours                           | 9450-9451                              |
| Primary CNS lymphoma                              | 9590-9596, 9611-9728, 9735-9766, 9970-9971 |
| Ependymal tumours                                 | 9383, 9391-9394                        |
| Oligoastrocytoma                                  | 9382                                  |
| Embryonal tumours                                 | 9470-9477, 9490, 9500-9501, 9508       |
| Malignant glioma                                  | 9380                                  |
| Unclassified Neoplasm, Malignant                  | 8000/3*                               |
| Unclassified Neoplasm/Tumour Cells, Benign        | 8000/0*, 8001/0*                       |
| Unclassified Neoplasm/Tumour Cells, Uncertain     | 8000/1*, 8001/1*                       |
| whether Benign or Malignant                       |                                       |
| Other brain tumours                               | Uncategorised morphologies with       |
|                                                   | recorded Site Code C70-71, D32-33, D42-43 |

(*behaviour coded by /0 for benign tumours, /1 for unspecified, borderline or uncertain behaviour, and /3 for malignant tumours)
| Variables               | Groups | No. of patients | (%)  |
|-------------------------|--------|----------------|------|
| Sex                     | Male   | 65,559         | (49.05) |
|                         | Female | 68,110         | (50.95) |
| Age at Diagnosis        | Mean (SD) | 62.31 (16.72) |
| Age Group               | 18-24  | 2,617          | (1.96) |
|                         | 25-34  | 7,085          | (5.30) |
|                         | 35-44  | 11,687         | (8.74) |
|                         | 45-54  | 19,000         | (14.21) |
|                         | 55-64  | 26,888         | (20.12) |
|                         | 65-74  | 31,543         | (23.60) |
|                         | 74-84  | 25,072         | (18.76) |
|                         | 85+    | 9,777          | (7.31) |
| Year of Diagnosis       | 1995   | 4,471          | (3.34) |
|                         | 1996   | 4,502          | (3.37) |
|                         | 1997   | 4,728          | (3.54) |
|                         | 1998   | 4,640          | (3.47) |
|                         | 1999   | 4,845          | (3.62) |
|                         | 2000   | 5,116          | (3.83) |
|                         | 2001   | 5,021          | (3.76) |
|                         | 2002   | 5,079          | (3.80) |
|                         | 2003   | 4,986          | (3.73) |
|                         | 2004   | 5,131          | (3.84) |
|                         | 2005   | 5,294          | (3.96) |
| Year | Number | Quintile of Deprivation |
|------|--------|-------------------------|
| 2006 | 5,355  | 1 - Least               |
| 2007 | 5,654  | 1 - Least               |
| 2008 | 6,114  | 2                       |
| 2009 | 6,129  | 3                       |
| 2010 | 6,183  | 4                       |
| 2011 | 6,325  | 5 - Most                |
| 2012 | 6,762  | 1 - Least               |
| 2013 | 7,482  | 2                       |
| 2014 | 7,221  | 3                       |
| 2015 | 7,587  | 4                       |
| 2016 | 7,464  | 5 - Most                |
| 2017 | 7,580  | 1 - Least               |

| Quintile of Deprivation | Number | Quintile of Deprivation |
|-------------------------|--------|-------------------------|
| 1 - Least               | 28,900 | (21.62)                 |
| 2                       | 29,589 | (22.14)                 |
| 3                       | 27,728 | (20.74)                 |
| 4                       | 25,051 | (18.74)                 |
| 5 - Most                | 22,401 | (16.76)                 |

| Death Certificate | Recorded | Number | (%) |
|-------------------|-----------|--------|-----|
| Recorded          |           | 4,599  | 3.44|
| Not Recorded      |           | 129,070| 96.56|
| Variables                                | Groups                                | No. of patients | (%)   |
|------------------------------------------|---------------------------------------|-----------------|-------|
| Brain Tumour Subtype                     | Glioblastoma (GBM)                    | 42,478          | (31.78) |
|                                          | Meningioma                            | 36,493          | (27.30) |
|                                          | Other astrocytic tumours (excluding GBM) | 12,506         | (9.36) |
|                                          | Oligodendroglial tumours              | 4,368           | (3.27) |
|                                          | Primary CNS lymphoma                   | 2,661           | (1.99) |
|                                          | Ependymal tumours                     | 1,368           | (1.02) |
|                                          | Oligoastrocytoma                      | 1,258           | (0.94) |
|                                          | Embryonal tumours                     | 647             | (0.48) |
|                                          | Malignant glioma                      | 11,458          | (8.57) |
|                                          | Other brain tumours                   | 3,873           | (2.90) |
|                                          | Unclassified Neoplasm, Malignant      | 8,027           | (6.01) |
|                                          | Unclassified Neoplasm/Tumour Cells, Benign | 1,589     | (1.19) |
|                                          | Unclassified Neoplasm/Tumour Cells, Uncertain whether Benign or Malignant | 6,943 | (5.19) |
| Behaviour                                      | Count | Percentage |
|-----------------------------------------------|-------|------------|
| Malignant                                      | 85,775| (64.17)    |
| Benign                                         | 35,320| (26.42)    |
| Malignant, uncertain whether primary or metastatic | 112   | (0.08)     |
| Uncertain                                      | 12,462| (9.32)     |

| Tumour Site                                      | Count | Percentage |
|------------------------------------------------|-------|------------|
| C70.0  Cerebral meninges                        | 1078  | (0.81)     |
| C70.9  Meninges, NOS                            | 511   | (0.38)     |
| C71.0  Cerebrum                                 | 4838  | (3.62)     |
| C71.1  Frontal lobe                             | 19274 | (14.42)    |
| C71.2  Temporal lobe                            | 14201 | (10.62)    |
| C71.3  Parietal lobe                            | 12110 | (9.06)     |
| C71.4  Occipital lobe                           | 2836  | (2.12)     |
| C71.5  Ventricles, NOS                          | 559   | (0.42)     |
| C71.6  Cerebellum, NOS                          | 1461  | (1.09)     |
| C71.7  Brain stem                               | 1016  | (0.76)     |
| C71.8  Overlapping lesion of brain              | 4998  | (3.74)     |
| C71.9  Brain, NOS                               | 23113 | (17.29)    |
| Code   | Description                                                                 | Count | Percentage |
|--------|-----------------------------------------------------------------------------|-------|------------|
| C72.8  | Overlapping lesion of brain and other parts of central nervous system        | 41    | (0.03)     |
| C72.9  | Nervous system, NOS                                                          | 195   | (0.15)     |
| D32.0  | Benign neoplasm of cerebral meninges                                        | 26640 | (19.93)    |
| D32.9  | Benign neoplasm of meninges, unspecified                                    | 7144  | (5.34)     |
| D33.0  | Benign neoplasm of brain, supratentorial                                     | 639   | (0.48)     |
| D33.1  | Benign neoplasm of brain, infratentorial                                     | 184   | (0.14)     |
| D33.2  | Benign neoplasm of brain, unspecified                                       | 768   | (0.57)     |
| D33.9  | Benign neoplasm of central nervous system, unspecified                      | 44    | (0.03)     |
| D42.0  | Neoplasm of uncertain behaviour of cerebral meninges                         | 2162  | (1.62)     |
| D42.9  | Neoplasm of uncertain behaviour of meninges, unspecified                     | 500   | (0.37)     |
| D43.0  | Neoplasm of uncertain behaviour of brain, supratentorial                     | 2528  | (1.89)     |
| D43.1  | Neoplasm of uncertain behaviour of brain, infratentorial                      | 1115  | (0.83)     |
| D43.2  | Neoplasm of uncertain behaviour of brain, unspecified                        | 5600  | (4.19)     |
| D43.9  | Neoplasm of uncertain behaviour of central nervous system, unspecified       | 114   | (0.09)     |

| Tumour Size | Known | Unknown |
|-------------|-------|---------|
|             | 6,590 | 127,079 |
|             | (4.85) | (95.07) |
| Basis of Diagnosis                  |       |        |
|------------------------------------|-------|--------|
| 0       Death Certificate only      | 3,546 | (2.65) |
| **Non Microscopic**                |       |        |
| 1       Clinical - Diagnosis made before death | 8,579 | (6.42) |
| 2       All clinical Investigation using diagnostic techniques without tissue diagnosis | 32,709 | (24.47) |
| 4       Specific Tumour markers     | 15    | (0.01) |
| **Microscopic**                    |       |        |
| 5       Cytology                    | 163   | (0.12) |
| 6       Histology of a metastasis  | 69    | (0.05) |
| 7       Histology of a primary tumour | 85,127 | (63.68) |
| 9       Unknown                     | 3,461 | (2.59) |
Figure 1: Distribution of brain tumours based on site of resection in England over time. Cases by year of diagnosis 1995, 2000, 2005, 2010 and 2015, categorized by tumour behaviour.
Figure 3

Figure 3 - Age-specific incidence rates of brain tumour subtypes in England, 1995-2017.