Tampereen yliopisto

Tuomas Natukka

INCIDENCE TRENDS OF ADULT MALIGNANT BRAIN TUMORS IN FINLAND, 1990–2006

Lääketieteen ja terveysteknologian tiedekunta
Syventävien opintojen kirjallinen työ
Syyskuu 2019

TIIVISTELMÄ

Tuomas Natukka: Incidence trends of adult malignant brain tumors in Finland, 1990–2006
Syventävien opintojen kirjallinen työ
Tampereen yliopisto
Lääketieteen lisensiaatin tutkinto-ohjelma
Syyskuu 2019

Useissa tutkimuksissa on havaittu pahanlaatuisten aivokasvaimien ilmaantuvuuden lisääntyneen viime vuosikymmeninä aina 1990-luvun alkuun saakka, jolloin kasvava trendi on tasaantunut. Kuitenkin jotkut tutkimukset ovat raportoineet ilmaantuvuuden kasvaneen myös 2000-luvulla. Tutkimuksemme tavoitteena on tutkia malignien glioomien ilmaantuvuustrendejä Suomessa vuosina 1990–2006 ja selvittää, onko trendeissä tapahtunut muutoksia.

Keräsimme Suomen Syöpärekisteristä tiedot 4 730:stä potilaasta, joilla oli todettu pahanlaatuinen glioома. Näistä laskimme glioomien ikävakioituja ilmaantuvuuslukuja. Lisäksi tutkimme ilmaantuvuustrendejä sekä histologisen tyypin että kasvaimen sijainnin osalta laskemalla keskimääräisiä vuosittaisia muutoksia ilmaantuvuusluvuissa.

Miehillä pahanlaatuisten glioomien ikävakioitu ilmaantuvuus oli 9,3/100 000 ja naisilla 6,3/100 000. Kaikkien malignien aivokasvaimien yhteenlaskettu ilmaantuvuus pysyi tasaisena läpi tarkastelujakson, eikä trendissä havaittu muutosta. Ikäryhmittäisessä analyysissä havaitsimme ilmaantuvuuden kasvavan ainoastaan yli 80-vuotiaiden ikäryhmässä. Histologisten alatyyppien osalta ilmaantuvuus kasvoi anaplastisissa oligodendroglioomissa, oligoastrosytoomissa ja määrittelemättömissä maligneissa glioomissa. Laskevia ilmaantuvuuksia havaitsimme astrosytoomissa ja määrittelemättömissä aivokasvaimissa. Kasvaimen sijainnin perusteella tehdyssä analyysissä ilmaantuvuus kasvoi frontaalilohkon, aivorungon ja määrittelemättömän sijainnin kasvaimissa. Sitä vastoin ilmaantuvuus laski parietaalilohkojen, isoaivojen ja aivokammioiden kasvaimissa.

Kaiken kaikkiaan emme havainneet maligneilla glioomilla nousevaa ilmaantuvuustrendiä. Vanhimmassa ikäryhmässä ilmaantuvuustrendi oli nouseva, mikä on kuitenkin havaittu aiemmin monissa muissakin väestöissä.

Avainsanat: Brain neoplasms, epidemiology, longitudinal trends, cancer registry

TABLE OF CONTENTS

INCIDENCE TRENDS OF ADULT MALIGNANT BRAIN TUMORS IN FINLAND, 1990–2006

Tuomas Natukka, BMed [1], Jani Raitanen, MSc [2,3], Hannu Haapasalo, MD, PhD [1, 4], Anssi Auvinen, MD, PhD [2]

[1] University of Tampere, Faculty of Medicine and Life Sciences, Arvo Ylpön katu 34, Arvo/Box 100, FI-33014 Tampere, Finland

[2] University of Tampere, Faculty of Social Sciences, Arvo Ylpön katu 34, Arvo/Box 100, FI-33014 Tampere, Finland

[3] UKK Institute for Health Promotion Research, Kaupinpuistonkatu 1, Box 30, FI-33501 Tampere, Finland

[4] FIMLAB Laboratories/Tampere University Hospital, Department of Pathology, Arvo Ylpön katu 4, P.O. Box 66, 33101 Tampere, Finland

Running title: Incidence trends of adult malignant gliomas

Address for correspondence:
Tuomas Natukka
Faculty of Medicine and Life Sciences, University of Tampere
Arvo Ylpön katu 34, Arvo/Box 100, FI-33014 Tampere, Finland
Phone: +358 40 417 0406
Fax: +358 3 213 4473
E-mail: tuomas.natukka@tuni.fi

This is an original manuscript / preprint of an article published by Taylor & Francis in Acta Oncologica on 15 Apr 2019, available online:
https://www.tandfonline.com/doi/full/10.1080/0284186X.2019.1603396

1 ABSTRACT

1.1 Background

Several studies have reported increased incidence trends of malignant gliomas in the late 1900's with a plateau in the 2000's, but also some recent increases have been reported. The purpose of our study was to analyze incidence trends of malignant gliomas in Finland between 1990 and 2006 by morphology and site.

1.2 Methods

Data on 4,730 malignant glioma patients were obtained from the nationwide, population-based Finnish Cancer Registry. Age-standardized incidence rates and average annual percent changes in the incidence rates were calculated by histological subtype and tumor location.

1.3 Results

The incidence rate of gliomas was 9.3 per 100,000 for men and 6.5 for women. The incidence of all gliomas combined was stable (annual percent change +0.1%; 95% CI: −0.5, +0.7), with no departure from linearity. In an analysis by age group, increasing incidence was found only for ages 80 years and older. Incidence rates were increasing in anaplastic oligodendroglioma, oligoastrocytoma and unspecified malignant glioma, with a minor increase also for glioblastoma. Correspondingly, decreasing rates were observed for astrocytoma and unspecified brain tumors. As for tumor location, incidence was increasing for frontal lobe and brainstem tumors, as well as those with an unspecified location, but decreasing for the parietal lobes, cerebrum and ventricles.

1.4 Conclusions

No increasing incidence trend was observed for all malignant gliomas combined. An increasing incidence trend of malignant gliomas was found in the oldest age group.

2 INTRODUCTION

Gliomas comprise a heterogenous group of brain tumors originating from glial cells. They are the most common malignant central nervous system (CNS) tumors (80%) (1). However, age-standardized incidence rate (adjusted to world standard population) of malignant CNS tumors in Europe is 5.5/100,000, making it only the fifteenth most common cancer type (2). Despite their rarity, malignant gliomas contribute disproportionately to cancer mortality, because of their poor prognosis (3). Although the prognosis of malignant glioma has improved during the recent decades, mortality is still very high (4, 5).

Several studies have reported increasing incidence of gliomas, especially among the elderly, until the early 1990's, when the increasing trend has leveled off (6–11). The increasing incidence rates can be partly explained by the introduction of CT and MRI during the 1970's and 1980's, resulting in detection of cases that would have remained undiagnosed earlier (12). Even though several recent studies have shown stable incidence (6–8, 11, 13–18), the findings have not been entirely consistent (4, 19–21).

Our aim is to analyze incidence trends of malignant gliomas by histological type and anatomic location using data from a well-established, high-quality cancer registry with nationwide coverage.

3 MATERIALS AND METHODS

3.1 Data sources

The data for the study were obtained from the Finnish Cancer Registry (FCR) on all primary malignant brain tumors (ICD-O-3 morphology codes 9380–9451) and unspecified malignant brain tumors (ICD-O-3 morphology code 8000) diagnosed during 1990–2006. The cancer registry data covered date of diagnosis, primary site, histological type, malignancy and any previous cancers. Sex and age of the patient were reported, but no personal identifiers (or date of birth) were obtained.

The histological (morphology) classification of brain tumors used at FCR prior to 2008 was very crude and did not comply with ICD-O. Therefore, detailed histological type, grading and location of the tumor were abstracted from the text fields in the cancer notifications (altogether 9,389 clinical notifications and 13,217 laboratory notifications on 5,638 unique cancer patients, including subsequently excluded cases). In Finland, unique personal identification codes have been widely used since the late 1960's. They allow unequivocal identification (barring errors) and are used for elimination of duplicate records and for deterministic record linkage. Based on the detailed diagnostic information in the text fields of the cancer registry notifications, tumor histological type and anatomic site were systematically reclassified according to ICD-O-3 (22). Clinical notifications were primarily used to define tumor location and laboratory notifications for morphology. Data on population size by age, gender and calendar year for calculation of incidence rates were obtained from Statistics Finland (23).

3.2 Classification and exclusion criteria

We focused on adult malignant gliomas in the brain (ICD-O-3 topography code C71). Therefore, tumors located outside the brain and all metastatic tumors were excluded. Patients younger than 20 years were also excluded, because brain tumors in children and adolescents are biologically different from adults (1, 24), and we wanted to focus on a homogenous tumor entity. Benign (grade I) brain tumors according to the 2007 WHO classification of CNS tumors were also excluded (25). If the initial histological type was subsequently reclassified as other than malignant glioma, the tumor was excluded. Table 1 shows subtypes of malignant glioma included in our

study. Unspecified brain tumors (ICD-O-3 morphology code 8000 with topography code C71) were also included as a separate category.

Primary site of origin was defined based on ICD-O-3 topography classification. Cases with two locations (for example frontotemporal) were classified as reported for the most common combinations (subsites that comprised over one percent of all tumors). If three or more locations were reported, the location was classified as overlapping. Uncommon site combinations (subsites with two locations comprising less than one percent of all tumors) were combined as 'other specified locations'.

Table 1. Brain tumor subtypes classified as malignant glioma in our study.

Glioma subtype	Morphology code
Astrocytic tumors	
Astrocytoma	9400, 9411, 9420
Anaplastic astrocytoma	9401
Glioblastoma	9440–9442
Oligodendroglial tumors	
Oligodendroglioma	9450
Anaplastic oligodendroglioma	9451
Oligoastrocytic tumors	
Oligoastrocytoma grade II and III	9382
Ependymal tumors	
Ependymoma	9391, 9393
Anaplastic ependymoma	9392
Other tumors	
Unspecified malignant glioma	9380
Other specified tumors of the brain	9381, 9390, 9424, 9430, 9470, 9471, 9473, 9505
Unspecified tumors of the brain	8000

3.3 Statistical analyses

We calculated age-standardized incidence rates (ASR) with 95% confidence intervals (CI) for all tumors combined, by gender, calendar year, histological type and anatomic location using the 2013 European standard population (26). Age-specific incidence rates were calculated for 10-year age groups.

Age- and gender-adjusted incidence trends for each histological subtype and location were analyzed using Poisson regression, with number of cases as the outcome and population size as the offset

term to estimate the average annual percent change (APC) in incidence rate. Mutually adjusted gender- and age group-specific incidence trends were also analyzed. For incidence trend analyses, we used the classification principles presented above, with the exception that we assigned cases with two locations by dividing a half case to both locations. Thereby, only ICD-O-3 codes C71.0–C71.9 were used for incidence trend analyses.

We investigated whether the incidence trend deviated from linearity by adding calendar year of diagnosis as a categorical variable to the Poisson regression model containing a linear term for year, with a significant categorical term indicating a departure from linearity. In addition, we further investigated the possible deviation from linearity by adding squared year term as a continuous variable to the Poisson regression model. We also analyzed whether the incidence trends differed significantly between subgroups defined by gender, age group, histological type or anatomic location by adding an interaction term (the product of year and gender, and in a separate analysis of year and age group, year and histological type or year and anatomic location) to the Poisson regression model, and used the likelihood ratio test to compare the goodness of fit of the two nested models. In a sensitivity analysis, we evaluated whether distributing unspecified malignant gliomas and unspecified tumors of the brain to the specific histological subtypes by the percentage of each subtype (assuming the information was missing at random) affected the incidence trends. Statistical analyses were performed using Stata (version 15.1) and Microsoft Excel (version 16.0).

4 RESULTS

Between 1990 and 2006, 4,730 malignant glioma cases in adults were reported to the FCR. The ASR of all gliomas combined was 7.7/100,000 (95% CI: 7.5–7.9/100,000) (Table 2). Gliomas were more common in men (2,542 cases, 53.7%), with an ASR of 9.3/100,000 (95% CI: 8.9–9.6/100,000). In women, the ASR was 6.5/100,000 (95% CI: 6.3–6.8/100,000). Most malignant gliomas were diagnosed in the age group 60–69 years (1,026 cases, 21.7%), but the highest age-specific incidence rate was in the ages 70–79 years (15.2/100,000; 95% CI: 14.2–16.2/100,000). Incidence increased with age at an average rate of 37.6% (95% CI: +35.4, +39.9) increment per each decade of age. Astrocytic tumors comprised 70.6% of all gliomas, and glioblastoma was the most common histological subtype (2,284 cases, 48.3%), ASR being 3.8/100,000 (95% CI: 3.7–4.0/100,000). Unspecified tumors of the brain comprised 12.5% of all tumors (590 cases).

Most malignant gliomas were located in the cerebral lobes (73.4%) (Table 3). Frontal lobe was the most common location with 1,108 cases (23.4%), ASR being 1.7/100,000 (95% CI: 1.6–1.8/100,000). Temporal lobe was almost as common with 969 cases (20.5%), and an ASR of 1.6/100,000 (95% CI: 1.5–1.7/100,000). Tumors with an unspecified location comprised 11.2% of all gliomas.

Table 2. Incidence of adult malignant brain tumors by gender, age, year and histological type in Finland 1990–2006.

	Frequency		Age-standardized incidence rate (/100,000)	
	n	%	Rate	95% CI
Total	4,730	100.0	7.7	7.5–7.9
Gender				
Male	2,542	53.7	9.3	8.9–9.6
Female	2,188	46.3	6.5	6.3–6.8
Age[a]				
20–29	268	5.7	2.4	2.1–2.7
30–39	513	10.8	4.1	3.8–4.5
40–49	705	14.9	5.2	4.9–5.6
50–59	932	19.7	8.1	7.6–8.7
60–69	1,026	21.7	12.2	11.5–13.0
70–79	909	19.2	15.2	14.2–16.2
80+	377	8.0	12.6	11.3–13.9

[a]Unadjusted incidence rates

	Frequency		Age-standardized incidence rate (/100,000)	
	n	%	Rate	95% CI
Year				
1990	249	5.3	7.3	6.4–8.3
1991	254	5.4	7.5	6.6–8.4
1992	290	6.1	8.4	7.4–9.4
1993	249	5.3	7.3	6.4–8.2
1994	251	5.3	7.1	6.2–8.0
1995	248	5.2	7.0	6.1–7.9
1996	293	6.2	8.3	7.4–9.3
1997	272	5.8	7.6	6.7–8.5
1998	277	5.9	7.7	6.8–8.6
1999	275	5.8	7.5	6.6–8.4
2000	276	5.8	7.5	6.6–8.4
2001	279	5.9	7.5	6.6–8.4
2002	318	6.7	8.5	7.6–9.5
2003	289	6.1	7.7	6.8–8.6
2004	268	5.7	7.1	6.2–8.0
2005	337	7.1	8.7	7.8–9.7
2006	305	6.4	7.7	6.8–8.6
Histology				
Astrocytic tumors				
Astrocytoma	574	12.1	0.8	0.8–0.9
Anaplastic astrocytoma	481	10.2	0.7	0.7–0.8
Glioblastoma	2,284	48.3	3.8	3.7–4.0
Oligodendroglial tumors				
Oligodendroglioma	215	4.5	0.3	0.3–0.3
Anaplastic oligodendroglioma	135	2.9	0.2	0.2–0.2
Oligoastrocytic tumors				
Oligoastrocytoma grade II and III	238	5.0	0.3	0.3–0.4
Ependymal tumors				
Ependymoma	45	1.0	0.1	0.0–0.1
Anaplastic ependymoma	16	0.3	0.0	0.0–0.0
Other tumors				
Unspecified malignant glioma	111	2.3	0.2	0.2–0.2
Other specified tumors of the brain	41	0.9	0.1	0.0–0.1
Unspecified tumors of the brain	590	12.5	1.1	1.0–1.2

Table 3. Incidence of adult malignant brain tumors by location in Finland 1990–2006.

	Frequency		Age-standardized incidence rate (/100,000)	
	n	%	Rate	95% CI
Total	4,730	100.00	7.7	7.5–7.9
Location				
Frontal	1,108	23.4	1.7	1.6–1.8
Frontotemporal	272	5.8	0.4	0.4–0.5
Frontoparietal	146	3.1	0.2	0.2–0.3
Temporal	969	20.5	1.6	1.5–1.7
Temporoparietal	231	4.9	0.4	0.3–0.4
Temporo-occipital	85	1.8	0.1	0.1–0.2
Parietal	395	8.4	0.6	0.6–0.7
Parieto-occipital	111	2.3	0.2	0.1–0.2
Occipital	152	3.2	0.3	0.2–0.3
Cerebrum	178	3.8	0.3	0.3–0.3
Ventricles	63	1.3	0.1	0.1–0.1
Cerebellum	74	1.6	0.1	0.1–0.2
Brainstem	97	2.1	0.2	0.1–0.2
Overlapping	238	5.0	0.4	0.4–0.5
Other specified	82	1.7	0.1	0.1–0.2
Unspecified location	529	11.2	0.9	0.8–1.0

Overall, the ASR of gliomas was stable during the study period (Figure 1). The APC in the incidence rate of all gliomas was close to zero (APC: +0.1%; 95% CI: −0.5, +0.7) (Table 4). In addition, there was no indication of deviation from linearity, i.e. no evidence of change in the overall incidence trend during the study period (likelihood ratio test with year as a categorical variable $p = 0.19$; likelihood ratio test with squared year term as a continuous variable $p = 0.61$). Graphical presentation of the annual incidence rates by gender showed no difference in incidence trends between genders (Figure 2), which was also confirmed using an interaction term in Poisson regression analysis (likelihood ratio test $p = 0.33$). A difference in incidence trends between the age groups was observed, when tested using an interaction term in Poisson regression analysis (likelihood ratio test $p = 0.001$). However, the only significant increase in incidence rates was in the oldest age group (80+ years), with an APC of +4.8% (95% CI: +2.6, +7.0) (Table 4).

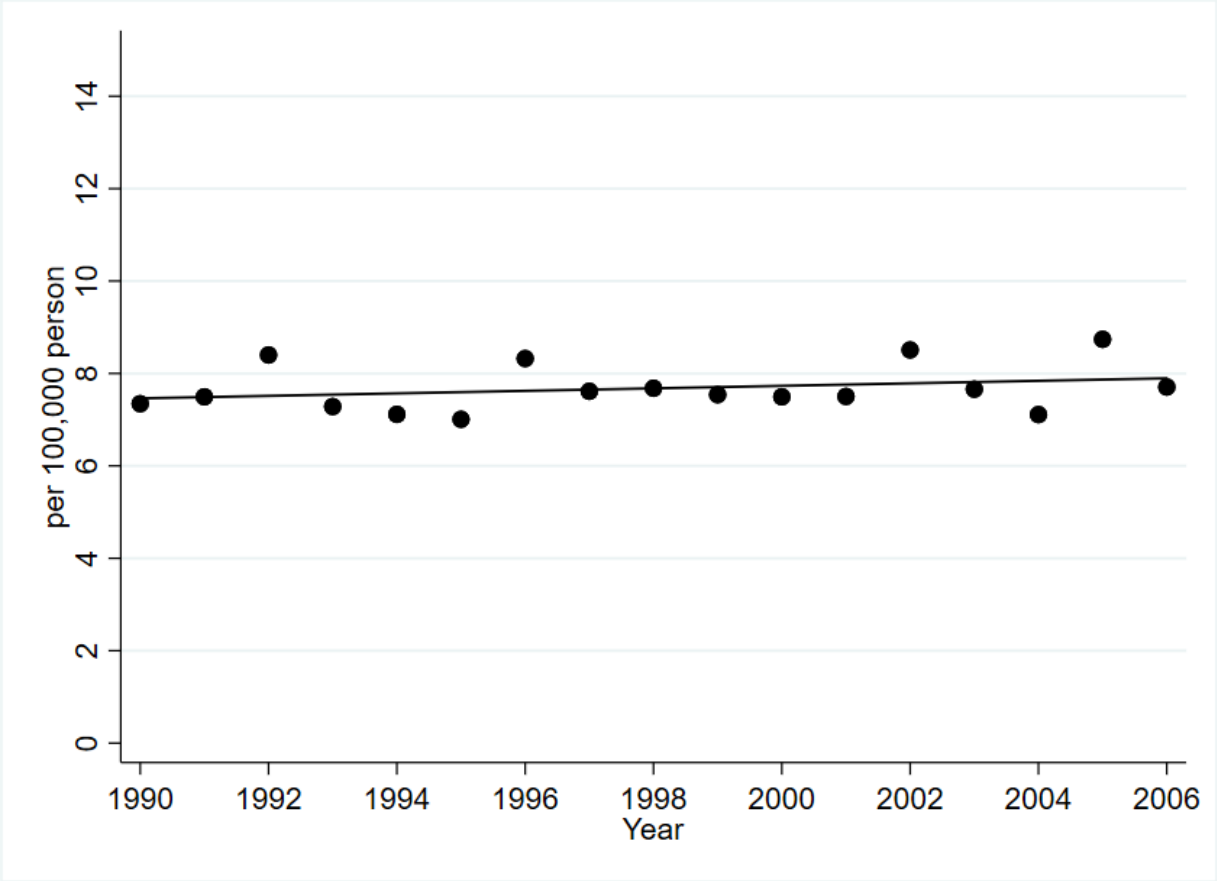

Figure 1. Incidence trend of malignant gliomas in Finland 1990–2006.

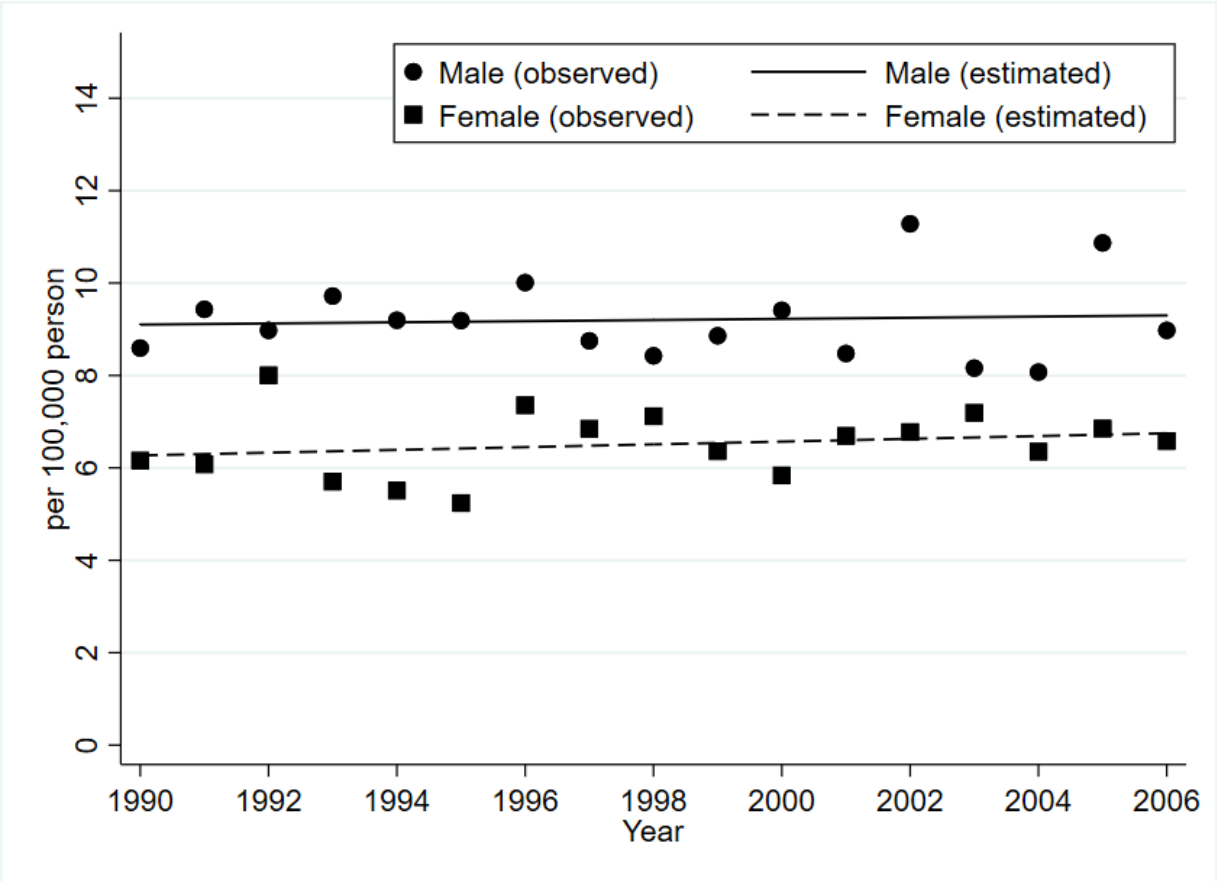

Figure 2. Incidence trends of malignant gliomas by gender in Finland 1990–2006.

A difference in incidence trends between histological types was evident (likelihood ratio test $p < 0.001$). The incidence trend of glioblastoma was slightly increasing (APC: +0.8%; 95% CI: −0.0, +1.7), while the incidence trend of astrocytoma showed a decrease of −2.8% per year (95% CI: −4.4, −1.1) (Table 4). Significant increases in ASRs were also observed for anaplastic oligodendroglioma (APC: +6.0%; 95% CI: +2.3, +9.8) and oligoastrocytoma (APC: +6.6%; 95% CI: +3.8, +9.5). A decreasing ASR was found for unspecified tumors of the brain (APC: −4.5%, 95% CI: −6.0, −2.9), whereas incidence of unspecified malignant glioma increased by +6.7% per year (95% CI: +2.6, +11.0). In addition, imputing specific histologic types (in similar proportion to those with known cell type) to unspecified tumors had no substantial effect on the incidence trends (see Supplementary Table 1).

We also found a difference in incidence trends between anatomic locations (likelihood ratio test $p < 0.001$). Incidence trends were increasing for the frontal lobe (APC: +1.7%; 95% CI: +0.6, +2.8), brainstem (APC: +5.8%; 95% CI: +1.7, +10.0) and unspecified locations (APC: +2.3%; 95% CI: +0.5, +4.1) (Table 4). Trends were decreasing for the parietal lobes (APC: −2.4%; 95% CI: −4.0, −0.9), cerebrum (APC: −3.5%; 95% CI: −6.2, −0.7) and ventricles (APC: −6.0%; 95% CI: −10.4, −1.4).

Table 4. APC in age- and gender-adjusted incidence trends of gliomas by gender, age, histological type and location in Finland 1990–2006.

	Annual percent change	
	APC	95% CI
Total	+0.1	−0.5, +0.7
Gender		
Male	−0.2	−1.0, +0.6
Female	+0.5	−0.4, +1.4
Age		
20–29	−1.0	−3.3, +1.5
30–39	0.0	−1.8, +1.8
40–49	−1.1	−2.6, +0.4
50–59	+0.3	−1.0, +1.6
60–69	−0.5	−1.7, +0.7
70–79	+0.2	−1.2, +1.5
80+	**+4.8**	**+2.6, +7.0**

	Annual percent change	
	APC	95% CI
Histology		
Astrocytic tumors		
Astrocytoma	**−2.8**	**−4.4, −1.1**
Anaplastic astrocytoma	−0.4	−2.2, +1.4
Glioblastoma[a]	**+0.8**	**−0.0, +1.7**
Oligodendroglial tumors		
Oligodendroglioma	−0.2	−2.9, +2.6
Anaplastic oligodendroglioma	**+6.0**	**+2.3, +9.8**
Oligoastrocytic tumors		
Oligoastrocytoma grade II and III	**+6.6**	**+3.8, +9.5**
Ependymal tumours		
Ependymoma	+4.2	−1.9, +10.8
Anaplastic ependymoma	−1.2	−10.6, +9.2
Other tumors		
Unspecified malignant glioma	**+6.7**	**+2.6, +11.0**
Other specified tumors of the brain	+3.0	−3.3, +9.7
Unspecified tumors of the brain	**−4.5**	**−6.0, −2.9**
Location		
Frontal	**+1.7**	**+0.6, +2.8**
Temporal	−0.6	−1.8, +0.5
Parietal	**−2.4**	**−4.0, −0.9**
Occipital	−0.1	−2.6, +2.5
Cerebrum	**−3.5**	**−6.2, −0.7**
Ventricles	**−6.0**	**−10.4, −1.4**
Cerebellum	−3.8	−8.0, +0.5
Brainstem	**+5.8**	**+1.7, +10.0**
Overlapping	+2.1	−0.6, +4.8
Unspecified location	**+2.3**	**+0.5, +4.1**

Statistically significant APC are in bold ($p < 0.05$)
[a]$p = 0.053$

5 DISCUSSION

In analyses of the incidence trends of adult malignant gliomas in Finland during 1990–2006, we found no increase for gliomas overall. Also, there was no difference in incidence trends between the genders. Incidence rates in the oldest age group (80+ years) increased throughout the study period, while younger age groups showed no such increase. Significant increases were observed for anaplastic oligodendroglioma, oligoastrocytoma and unspecified malignant glioma. In addition, there was some increase in glioblastomas. Astrocytoma and unspecified tumors of the brain, however, showed decreasing incidence trends. Incidence rates for tumors in the frontal lobe, brainstem and unspecified location increased throughout the study period. In contrast, tumor incidence decreased in the parietal lobes, cerebrum and ventricles.

Our results are consistent with most recent studies (6–8, 11, 13–18). Some studies have reported increasing trends in young adults in their 20s (6, 18), but increasing trends have been more commonly found in the oldest age groups similar to our results (6, 8, 10, 11, 13, 19–21). We also found a slightly increasing incidence trend for the most common histological subtype, glioblastoma, which is consistent with several other studies (1, 4, 6–8, 10, 16, 17). A study from United States showed an increasing incidence trend for gliomas in the frontal lobe and decreasing trends for the cerebrum, ventricles and overlapping subtypes (16). Our findings were comparable otherwise, but we also found a decreasing trend for tumors in the parietal lobes and an increasing trend for brainstem tumors.

Overall age-standardized incidence rate of all gliomas in our study was 7.7/100,000, which is relatively high compared to other studies. A Finnish study reported incidence rate of 4.7/100,000 for all gliomas, but it was based on only 331 cases, and analyses were mainly focused on anatomic locations of brain tumors (27). Incidence rates comparable to ours were reported from Northwestern England (7.2/100,000) (15). However, several studies have reported lower incidence rates, which may be partly attributable to inclusion of children or non-Caucasian ethnic groups, or incomplete case ascertainment (7, 14). A number of studies have also reported similar or higher incidence rates, but they have covered either all CNS tumors or benign brain tumors, and are therefore not comparable (4, 6, 13, 20).

One possible explanation for the increasing incidence in the oldest age group is improvement in diagnostics. Availability of MRI and CT scans has increased the use of these diagnostic methods.

Besides increasing the overall incidence, more frequent use of MRI imaging may have affected particularly the diagnosis of brain stem tumors, which are better visualized with MRI than with CT. More active treatment of brain tumors in elderly patients has probably improved the detection and diagnostic accuracy of cases in age groups older than 60–70 years, as it has likely increased both biopsies and resections, and hence specific diagnoses.

Unspecified brain tumors decreased during the study period and therefore some of the specific histological subtypes must have increased simply owing to more accurate diagnostics including modern immunohistochemistry, i.e. cases earlier assigned as unspecified were classified more accurately in more recent years. In contrast, tumors with unspecified location increased, which slightly decreased incidence rates in some specific locations.

Very few countries have a comprehensive, well-established nationwide population-based cancer registry with multiple sources of information and documented completeness of coverage. In Finland, cancer incidence data have been collected by the FCR since 1953, and notification of cancer cases to the registry has been mandatory since 1961. Case notifications are received from hospitals, health care professionals, pathology laboratories and Statistics Finland's cause of death data. The data received from different sources are then compared and double-checked to verify the accuracy of every diagnosis. Furthermore, the unique personal identification number allows elimination of duplicate records. Therefore, our data based on the FCR is very comprehensive and reliable. In addition, we abstracted information from every report for each case and reclassified histological type and anatomic site of presentation according to ICD-O-3 to improve the accuracy and comparability of the classification. (28)

Finland has centralized the treatment of malignant brain tumors into five university hospitals, which makes diagnoses very standardized and consistent, thus improving also the reliability of the data at the FCR. Also, there were no major changes in brain tumor classification during our study period, ensuring consistency of data throughout the study period.

Our study had also some limitations. Re-evaluation of the tumor slides by an experienced neuropathologist would have further improved the accuracy and reliability of the diagnoses, but this is not feasible in a large population-based study. Therefore, we could not retrospectively apply the recent 2016 WHO classification of CNS tumors. Our analysis did not cover the most recent years but focused on the time period with insufficient detail of tumor classification at the cancer registry.

Also, the number of cases in several subgroups was fairly small, limiting the precision of the estimates. We did not conduct join-point analyses, as the incidence rates were very flat.

The stable incidence rates of malignant gliomas suggest no major increase in public exposure to major risk factors. Although usage of mobile phones increased dramatically during our study period, overall incidence rates of malignant gliomas did not increase at all. Furthermore, we observed no increasing incidence rates in the temporal lobes, which are the most exposed part of the brain from the radiofrequency electromagnetic fields emitted by mobile phones.

The recently updated 2016 WHO classification of tumors of the CNS is the first to use molecular and genetic parameters besides histological features to define several CNS tumor entities including malignant gliomas. In the present study, the increase in oligodendroglial tumor incidence and the decrease of astrocytoma incidence might be due to the introduction of the chromosome 1p/19q-analysis in the diagnosis of oligodendrogliomas in the early 2000s (29).

Further studies are necessary to evaluate the impact of the new WHO classification system, and to determine the most recent incidence rates. Also, if the latency between radiofrequency field exposure and tumor development is very long, future studies with more recent data assessing longer exposure and latency periods will be needed.

In conclusion, no increase in adult malignant gliomas overall was found for Finland in 1990–2006. However, an increase in the oldest age group was observed, comparable to several other populations.

6 ACKNOWLEDGMENTS

We thank Ms. Katja Kuukka for her instrumental contribution in abstracting the data from the cancer registry notifications, Heini Huhtala, MSc, for her contribution to data analysis and Joonas Haapasalo, MD, PhD, for clinical advice. This study was financially supported by the Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital [#9U001].

7 CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest.

8 REFERENCES

1. Ostrom QT, Gittleman H, Liao P, Vecchione-Koval T, Wolinsky Y, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010–2014. *Neuro Oncol* 2017; 19(suppl_5): v1–v88. https://doi.org/10.1093/neuonc/nox158.

2. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet].
Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed 26/6/2018.

3. Rouse C, Gittleman H, Ostrom QT, Kruchko C, Barnholtz-Sloan JS. Years of potential life lost for brain and CNS tumors relative to other cancers in adults in the United States, 2010. *Neuro Oncol* 2016; 18(1): 70. https://doi.org/10.1093/neuonc/nov249.

4. Ho VKY, Reijneveld JC, Enting RH, Bienfait HP, Robe P, Baumert BG, Visser O. Changing incidence and improved survival of gliomas. *Eur J Cancer* 2014; 50(13): 2309-2318. https://doi.org/10.1016/j.ejca.2014.05.019.

5. Visser O, Ardanaz E, Botta L, Sant M, Tavilla A, Minicozzi P. Survival of adults with primary malignant brain tumours in Europe; Results of the EUROCARE-5 study. *Eur J Cancer* 2015; 51(15): 2231-2241. https://doi.org/10.1016/j.ejca.2015.07.032.

6. Arora RS, Alston RD, Eden TOB, Estlin EJ, Moran A, Geraci M, Birch JM. Are reported increases in incidence of primary CNS tumours real? An analysis of longitudinal trends in England, 1979–2003. *Eur J Cancer* 2010; 46(9): 1607-1616. https://doi.org/10.1016/j.ejca.2010.02.007.

7. Deorah S, Lynch CF, Sibenaller ZA, Ryken TC. Trends in brain cancer incidence and survival in the United States: Surveillance, Epidemiology, and End Results Program, 1973 to 2001. *Neurosurg focus* 2006; 20(4): E1. https://doi.org/10.3171/foc.2006.20.4.E1.

8. Hess KR, Broglio KR, Bondy ML. Adult glioma incidence trends in the United States, 1977–2000. *Cancer* 2004; 101(10): 2293-2299. https://doi.org/10.1002/cncr.20621.

9. Deltour I, Johansen C, Auvinen A, Feychting M, Klaeboe L, Schüz J. Time trends in brain tumor incidence rates in Denmark, Finland, Norway, and Sweden, 1974–2003. *J Natl Cancer Inst* 2009; 101(24): 1721-1724. https://doi.org/10.1093/jnci/djp415.

10. Lönn S, Klaeboe L, Hall P, Mathiesen T, Auvinen A, Christensen HC, Johansen C, Salminen T, Tynes T, Feychting M. Incidence trends of adult primary intracerebral tumors in four Nordic countries. *Int J Cancer* 2004; 108(3): 450-455. https://doi.org/10.1002/ijc.11578.

11. Nomura E, Ioka A, Tsukuma H. Trends in the incidence of primary intracranial tumors in Osaka, Japan. *Jpn J Clin Oncol* 2011; 41(2): 291-294. https://doi.org/10.1093/jjco/hyq204.

12. Helseth A. The incidence of primary CNS neoplasms before and after computerized tomography availability. *J Neurosurg* 1995; 83(6): 999-1003. https://doi.org/10.3171/jns.1995.83.6.0999.

13. J-H Kim S, Ioannides SJ, Elwood JM. Trends in incidence of primary brain cancer in New Zealand, 1995 to 2010. *Aust N Z J Public Health* 2015; 39(2): 148-152. https://doi.org/10.1111/1753-6405.12338.

14. Lin Y, Chiu H, Chiou M, Huang Y, Wei K, Kuo C, Hsu J, Chen P. Trends in the incidence of primary malignant brain tumors in Taiwan and correlation with comorbidities: A population-based study. *Clin Neurol Neurosurg* 2017; 159: 72-82. https://doi.org/10.1016/j.clineuro.2017.05.021.

15. Sehmer EAJ, Hall GJ, Greenberg DC, O'Hara C, Wallingford SC, Wright KA, Green AC. Incidence of glioma in a northwestern region of England, 2006–2010. *Neuro Oncol* 2014; 16(7): 971-974. https://doi.org/10.1093/neuonc/not301.

16. Zada G, Bond AE, Wang YP, Giannotta SL, Deapen D. Incidence trends in the anatomic location of primary malignant brain tumors in the United States: 1992–2006. *World Neurosurg* 2012; 77(3-4): 518-524. https://doi.org/10.1016/j.wneu.2011.05.051.

17. Dubrow R, Darefsky AS. Demographic variation in incidence of adult glioma by subtype, United States, 1992-2007. *BMC Cancer* 2011; 11(1): 325. https://doi.org/10.1186/1471-2407-11-325.

18. Inskip PD, Hoover RN, Devesa SS. Brain cancer incidence trends in relation to cellular telephone use in the United States. *Neuro Oncol* 2010; 12(11): 1147-1151. https://doi.org/10.1093/neuonc/noq077.

19. Dobes M, Shadbolt B, Khurana VG, Jain S, Smith SF, Smee R, Dexter M, Cook R. A multicenter study of primary brain tumor incidence in Australia (2000-2008). *Neuro Oncol* 2011; 13(7): 783-790. https://doi.org/10.1093/neuonc/nor052.

20. Etxeberria J, Román ES, Burgui R, Guevara M, Moreno-Iribas C, Urbina MJ, Ardanaz E. Brain and central nervous system cancer incidence in navarre (Spain), 1973-2008 and projections for 2014. *J Cancer* 2015; 6(2): 177-183. https://doi.org/10.7150/jca.10482.

21. Pouchieu C, Gruber A, Berteaud E, Ménégon P, Monteil P, Huchet A, Vignes J, Vital A, Loiseau H, Baldi I. Increasing incidence of central nervous system (CNS) tumors (2000-2012): findings from a population based registry in Gironde (France). *BMC Cancer* 2018; 18(1): 653. https://doi.org/10.1186/s12885-018-4545-9.

22. World Health Organization: International Classification of Diseases for Oncology: ICD-O. Available from: http://codes.iarc.fr/, accessed 2/7/2018.

23. Statistics Finland. Available from: https://www.stat.fi/index_en.html, accessed 17/7/2018.

24. Broniscer A, Baker SJ, West AN, Fraser MM, Proko E, Kocak M, Dalton J, Zambetti GP, Ellison DW, Kun LE, Gajjar A, Gilbertson RJ, Fuller CE. Clinical and molecular characteristics of malignant transformation of low-grade glioma in children. *J Clin Oncol* 2007; 25(6): 682-689. https://doi.org/10.1200/JCO.2006.06.8213.

25. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol* 2007; 114(2): 97-109. https://doi.org/10.1007/s00401-007-0243-4.

26. Eurostat. Available from: http://ec.europa.eu/eurostat/web/main/home, accessed 17/7/2018.

27. Larjavaara S, Mäntylä R, Salminen T, Haapasalo H, Raitanen J, Jääskeläinen J, Auvinen A. Incidence of gliomas by anatomic location. *Neuro Oncol* 2007; 9(3): 319. https://doi.org/10.1215/15228517-2007-016.

28. Leinonen MK, Miettinen J, Heikkinen S, Pitkäniemi J, Malila N. Quality measures of the population-based Finnish Cancer Registry indicate sound data quality for solid malignant tumours. *Eur J Cancer* 2017; 77: 31-39. https://doi.org/10.1016/j.ejca.2017.02.017.

29. Jenkins RB, Curran W, Scott CB, Cairncross G. Pilot evaluation of 1p and 19q deletions in anaplastic oligodendrogliomas collected by a national cooperative cancer treatment group. *Am J Clin Oncol* 2001; 24(5): 506-508. https://doi.org/10.1097/00000421-200110000-00018.

9 APPENDICES

Supplementary Table 1. APC in age- and gender-adjusted incidence trends of gliomas[a] by histological type in Finland 1990–2006.

	Annual percent change	
	APC	95% CI
Histology		
Astrocytic tumors		
Astrocytoma	**−1.8**	**−3.4, −0.3**
Anaplastic astrocytoma	−0.4	−2.0, +1.3
Glioblastoma	**+0.8**	**+0.1, +1.5**
Oligodendroglial tumors		
Oligodendroglioma	+0.1	−2.6, +2.8
Anaplastic oligodendroglioma	**+5.3**	**+1.9, +8.9**
Oligoastrocytic tumors		
Oligoastrocytoma grade II and III	**+7.2**	**+4.4, +10.1**
Ependymal tumours		
Ependymoma	+4.6	−1.0, +10.6
Anaplastic ependymoma	+0.0	−8.1, +8.8
Other tumors		
Other specified tumors of the brain	+4.4	−0.9, +10.0

Statistically significant APC are in bold ($p < 0.05$)
[a]Specific histologic types imputed (in similar proportion to those with known cell type) to unspecified tumors