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ORIGINAL ARTICLE

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Abstract
Time trends in the incidence of glioma may reflect changes in the prevalence of environmental risk factors for glioma. We therefore investigated trends in the incidence of childhood and adult glioma in the Netherlands from 1989 to 2003. We used population-based incidence data from the Netherlands Cancer Registry. We calculated European standardised incidence rates for glioma, and stratified for age, gender and glioma subgroups. Changes in the incidence were estimated by calculating the Estimated Annual Percentage Change. Similar to other countries, the overall incidence of glioma was fairly stable in the Netherlands during the period 1989 to 2003, for both children and adults. In adult astrocytic glioma, a significantly increasing incidence of high-grade astrocytoma was balanced by simultaneous decreases of low-grade astrocytoma, astrocytoma with unknown malignancy grade and glioma of uncertain histology. Most of these time trends can be explained by improving detection and diagnostic precision. Stable incidence rates of adult and childhood glioma suggest that no major changes in environmental risk factors have occurred, which influenced the incidence of glioma in the studied period.

Approximately 85% of all histologically verified primary cancers of the central nervous system (CNS) are gliomas [1], malignant brain tumours of neuroepithelial origin [2]. Although gliomas are the most common type of primary brain tumours they are still relatively rare. In the Netherlands, world-standardised incidence rates of glioma are 6.5 per 100 000 person-years for males and 4.4 for females with a male/female ratio of 1.5:1.8 [1]. The male predominance, which is consistently observed in different countries, remains yet unexplained [3]. Several authors reported that the incidence of glioma is stable or slightly decreasing in almost every age group since the late 1980s [4–7]. In the most recent years, an increase in incidence is particularly apparent among the elderly in Western countries [4–7], which is probably the result of better detection.

Many environmental risk factors for glioma have been studied. Only for ionising radiation has an aetiological role been established, and no other major risk factors have been identified [3]. Temporal trends can therefore not be explained on the basis of known environmental risk factors. However, the monitoring of time trends and the early detection of changing patterns in the incidence of glioma may reveal changes in the prevalence of environmental risk factors and provide new hypotheses for glioma aetiology. For example, attempts have been made to link trends in the incidence of glioma to the increasing prevalence of mobile phone users [6].

In this study we investigated trends in the incidence of childhood and adult glioma and of glioma subgroups in the Netherlands, in the period 1989 to

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2003. We compared these with the observed trends in Europe and the United States.

Material and methods

All epidemiological data were obtained from the Netherlands Cancer Registry (NCR) from the Association of Comprehensive Cancer Centres (ACCC). This population-based nationwide cancer registry records data of all malignant neoplasms. Information is available on date of incidence, histology, topography, invasiveness, grade, stage and basis of diagnosis [8]. Histology is coded according to the International Classification of Diseases for Oncology (ICD-O), first edition (until 1992), second edition (1993–2000) and third edition (since 2001) [9–11]. Pathological diagnoses were derived from the nationwide network and registry of histo- and cytopathology (PALGA) containing data of all histological, cytological and autopsy examinations in the Netherlands. Diagnoses were also derived from the Dutch Medical Register (LMR) that comprises data from all hospital admissions in the Netherlands, including discharge diagnoses. Since 1989, all hospitals in the Netherlands are linked to one of the regional cancer registries that submit their data to the NCR. During the study period there were no major changes in health care facilities in the Netherlands, nor major improvements in diagnostic methods. Neurosurgery, neuroradiology and neuropathology are concentrated in large centres with close links to radiotherapy departments. Computed tomography (CT), magnetic resonance imaging (MRI) and stereotactic biopsies were introduced and already widely available before 1989 [1].

Six histological groups were defined for analysis following a cluster scheme for CNS tumours [12]. Astrocytic gliomas were divided in low-grade tumours (ICD-O grade 1, 2), high-grade tumours (ICD-O grade 3, 4), and tumours with unspecified malignancy grade (ICD-O grade 9). Oligodendrogliomas and ependymal gliomas were analysed without considering the malignancy grade, as numbers in these groups were considered too small for subgroup analysis. A sixth group (glioma with uncertain histology) consisted of clinically diagnosed CNS tumours without histopathological confirmation. We also classified 'glioma not otherwise specified' (glioma NOS) into this group. ICD-O codes for the six groups are given in Table I. Tumours with codes 9383 (subependymal glioma), 9384 (subependymal giant cell astrocytoma), 9393 (papillary ependymoma) and 9394 (myxopapillary ependymoma) were only registered since 1999 and were therefore excluded from the analyses.

Annual incidence rates were calculated per 100 000 person-years, using the average annual population as obtained from Statistics Netherlands. Rates were age adjusted by standardisation to the European standard population (European Standardised Rates, ESR) and calculated as 3-year moving averages. Trends were estimated by calculating the Estimated Annual Percentage Change (EAPC). A regression line was fitted to the natural logarithm of the rates using calendar year as a regressor variable, i.e. $y = mx + b$ where $y = \ln(\text{rate})$ and $x = \text{calendar year}$. Then the $\text{EAPC} = 100^\star(e^m - 1)$. Testing the hypothesis that the EAPC is equal to zero is equivalent to testing the hypothesis that the slope of the line in the above equation is equal to zero. The latter hypothesis was tested two-sided using the t-distribution of m/SE_m, while the number of degrees of freedom equals the number of calendar years minus two. The standard error of m, SE_m, was obtained from the fit of the regression line [13]. This calculation assumes that

Table I. International Classification of Diseases for Oncology (ICD-O) codes for the analysed glioma groups.

Main group	Subtype	ICD-O morphology code		ICD-O grading
Astrocytic glioma	Low-grade	9400, 9410, 9411, 9420	astrocytoma	1, 2
		9421	pilocytic astrocytoma	1, 2, 9
		9424	pleomorphic xanthoastrocytoma	1, 2
	High-grade	9400, 9410, 9411, 9420	astrocytoma	3, 4
		9401	anaplastic astrocytoma	3, 4
		9424	pleomorphic xanthoastrocytoma	
		9440, 9441, 9442, 9481	glioblastoma	
	Grade unknown	9400, 9410, 9411, 9420	astrocytoma	9
		9424	pleomorphic xanthoastrocytoma	9
Oligodendroglial/mixed glioma		9382	mixed glioma (oligoastrocytoma)	1–4, 9
		9450	oligodendroglioma	1–4, 9
		9451	anaplastic oligodendroglioma	
Ependymal glioma		9391	ependymoma	1–4, 9
		9392	anaplastic ependymoma	
Uncertain histology		—	no microscopic verification	
		9380	glioma not specified	1–4, 9

the rates increase or decrease at a constant rate over the entire period.

Incidence rates and trends were calculated for males and females separately. Age was stratified into four groups: 0–14 years, 15–44 years, 45–64 years and 65+ years. Analyses were performed using Statistical Analysis System v8.2 and Microsoft Excel 2003. All data were analysed respecting the privacy legislation that applies in the Netherlands.

Results

All glioma

Between 1989 and 2003, 9290 newly diagnosed gliomas were registered in the Netherlands, 5402 in

Table II. Total number of registered glioma patients in the Netherlands during the period 1989–2003, for diagnosis groups and age categories.

Diagnosis and age (years)	Number of patients, 1989–2003	
	Males	Females
Astrocytic glioma, low-grade		
0–14	187	193
15–44	467	332
45–64	220	135
65+	71	49
Astrocytic glioma, high-grade		
0–14	30	28
15–44	559	367
45–64	1533	985
65+	1015	772
Astrocytic glioma, grade unknown		
0–14	23	21
15–44	131	83
45–64	95	79
65+	73	68
Oligodendroglial/mixed glioma		
0–14	23	23
15–44	346	265
45–64	300	249
65+	105	83
Ependymal glioma		
0–14	74	47
15–44	61	54
45–64	65	38
65+	24	17
Uncertain histology[a]		
0–14	64	48
15–44	145	106
45–64	382	259
65+	721	797
Total		
0–14	401	360
15–44	1709	1207
45–64	2595	1745
65+	2009	1786
All ages	6714	5098

[a]This category comprises clinically diagnosed tumours without histopathological confirmation (87%) and glioma not otherwise specified (13%).

males and 3888 in females. An additional 1312 males and 1210 females were registered with a clinically diagnosed tumour or a glioma NOS. The numbers of registered glioma patients per diagnosis group and age category are shown in Table II. Age-adjusted incidence rates for all glioma combined and including gliomas of uncertain histology were stable between 1989 and 2003, for males (EAPC −0.2%, p = 0.57) and females (EAPC 0.3%, p = 0.49) (Figure 1). Within age categories, small and non-significant trends in the incidence of all glioma could be seen (Figure 2). Incidence rates in the elderly (aged 65+ years) showed a small increase (EAPC 0.7%, p = 0.26 for males and EAPC 1.4%, p = 0.03 for females), whereas in children, incidence rates were slightly decreasing (EAPC −1.0%, p = 0.34 for boys and EAPC −1.3%, p = 0.26 for girls).

Astrocytoma

In an all ages analysis, age-adjusted incidence rates of high-grade astrocytoma increased significantly for males (EAPC 1.5%, p = 0.005), accompanied by a significantly decreasing trend in low-grade astrocytoma (EAPC −1.9%, p = 0.02), in astrocytoma with unknown malignancy grade (EAPC −12.5%, p < 0.001) and in glioma of uncertain histology (EAPC −1.7%, p = 0.06) (Figure 3). The incidence of astrocytic glioma in females showed a similar pattern although the accompanying decrease in low-grade astrocytoma was less pronounced (EAPC −0.8%, p = 0.46) (Figure 3). Within age categories, a significantly rising incidence of high-grade astrocytoma was seen in young adults and elderly, but not in adults aged 45–64 years (Figure 4). The incidence of low-grade astrocytoma showed no consistent pattern. A marked decrease was seen in adult astrocytoma with unknown malignancy grade (EAPC −7.0% to −16%). The incidence of glioma of uncertain histology showed
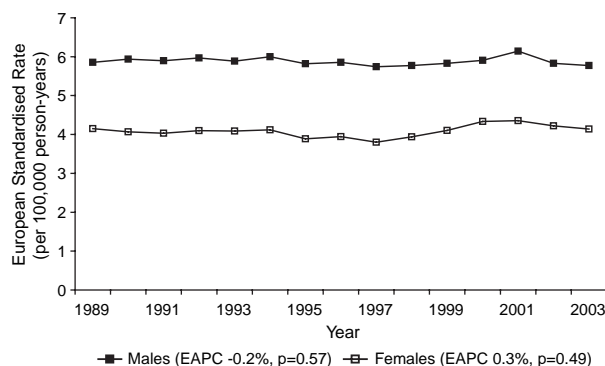

Figure 1. Incidence of all glioma according to gender, European Standardised Rates, 3-year moving average, with Estimated Annual Percentage Change (EAPC).
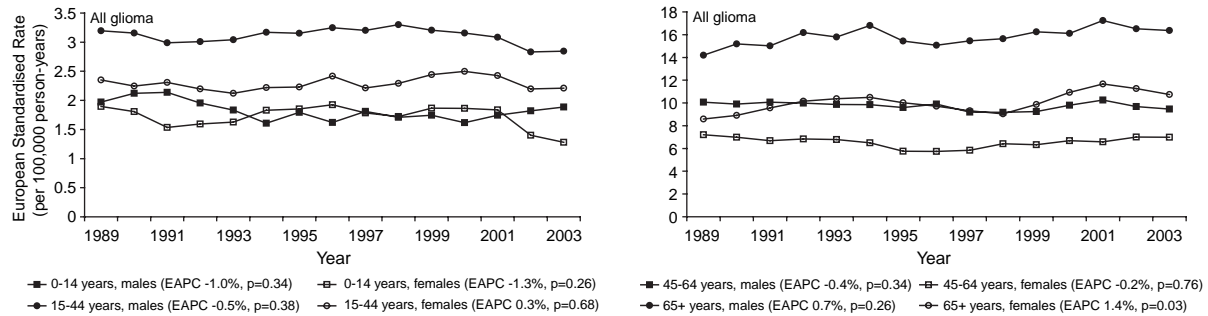
Figure 2. Incidence of all glioma according to gender and age, European Standardised Rates, 3-year moving average, with Estimated Annual Percentage Change (EAPC).

a modest and mostly borderline significant decreasing trend in all adult age categories (Figure 4).

In children aged 0–14 years, decreasing incidence was seen for all astrocytoma groups (Figure 4). This was balanced by glioma of uncertain histology (EAPC 8.0%, p = 0.05 for boys and EAPC 3.5%, p = 0.44 for girls). None of these trends were statistically significant.

Oligodendroglioma and ependymoma

The overall incidence of oligodendroglioma was stable for males (EAPC 0.4%, p = 0.71) and females (EAPC −0.2%, p = 0.84) (Figure 5). Also within age categories, no clear trends in the incidence could be seen. The overall incidence of ependymoma showed a small but non-significant increase between 1989 and 2003 (EAPC 1.5%, p = 0.53 for males and EAPC 3.4%, p = 0.12 for females). In general, incidence rates were decreasing in children and increasing in adults. None of these trends however were statistically significant and rates varied widely over the studied period, which is probably caused by the small numbers in each age category (Table II).

Male/female ratios

The male/female ratio remained constant with an average of 1.44 for all glioma, 1.41 for ependymal glioma, 1.25 for oligodendroglial glioma and 1.49 for astrocytic glioma (including low-grade astrocytoma,

high-grade astrocytoma and astrocytoma with unknown malignancy grade) (not shown). Within age groups of all glioma and astrocytic glioma, the sex-ratios were fairly constant as well. Other analyses within age groups were not performed because of small numbers of cases.

Discussion

In general, minor trends in the incidence of glioma were observed in the Netherlands during the period 1989 to 2003. Age-adjusted incidence rates were stable for all glioma combined and for oligodendroglioma/mixed glioma. In adult astrocytic glioma, a significant increase in high-grade astrocytoma was accompanied by a simultaneous decrease in low-grade astrocytoma, astrocytoma with unknown malignancy grade and glioma of uncertain histology. The incidence of astrocytoma and ependymoma in children showed a decreasing trend, which was accompanied by an increasing incidence of gliomas of uncertain histology. The overall incidence of glioma in children was stable.

Methodological considerations

The NCR is characterised by high quality incidence data and near complete ascertainment with less than 2% underregistration [14]. Completeness of registration is achieved by combining data from different sources, including PALGA and the LMR. In the
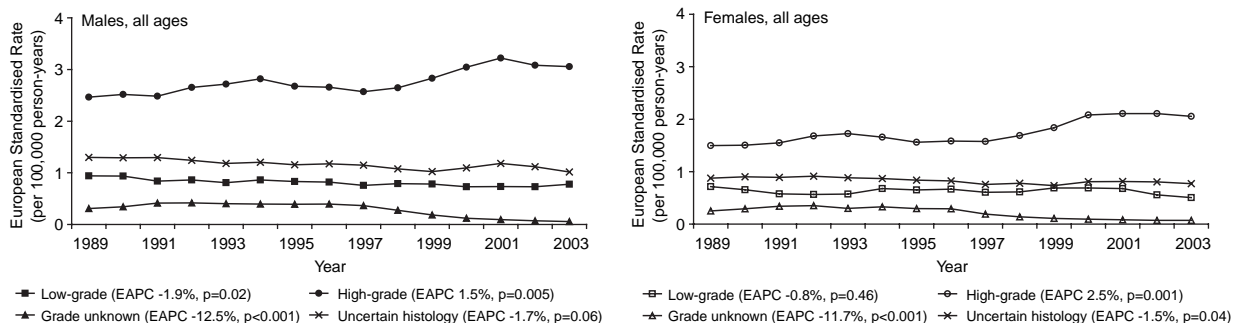

Figure 3. Incidence of astrocytic glioma and glioma of uncertain histology according to gender, European Standardised Rates, 3-year moving average, with Estimated Annual Percentage Change (EAPC).
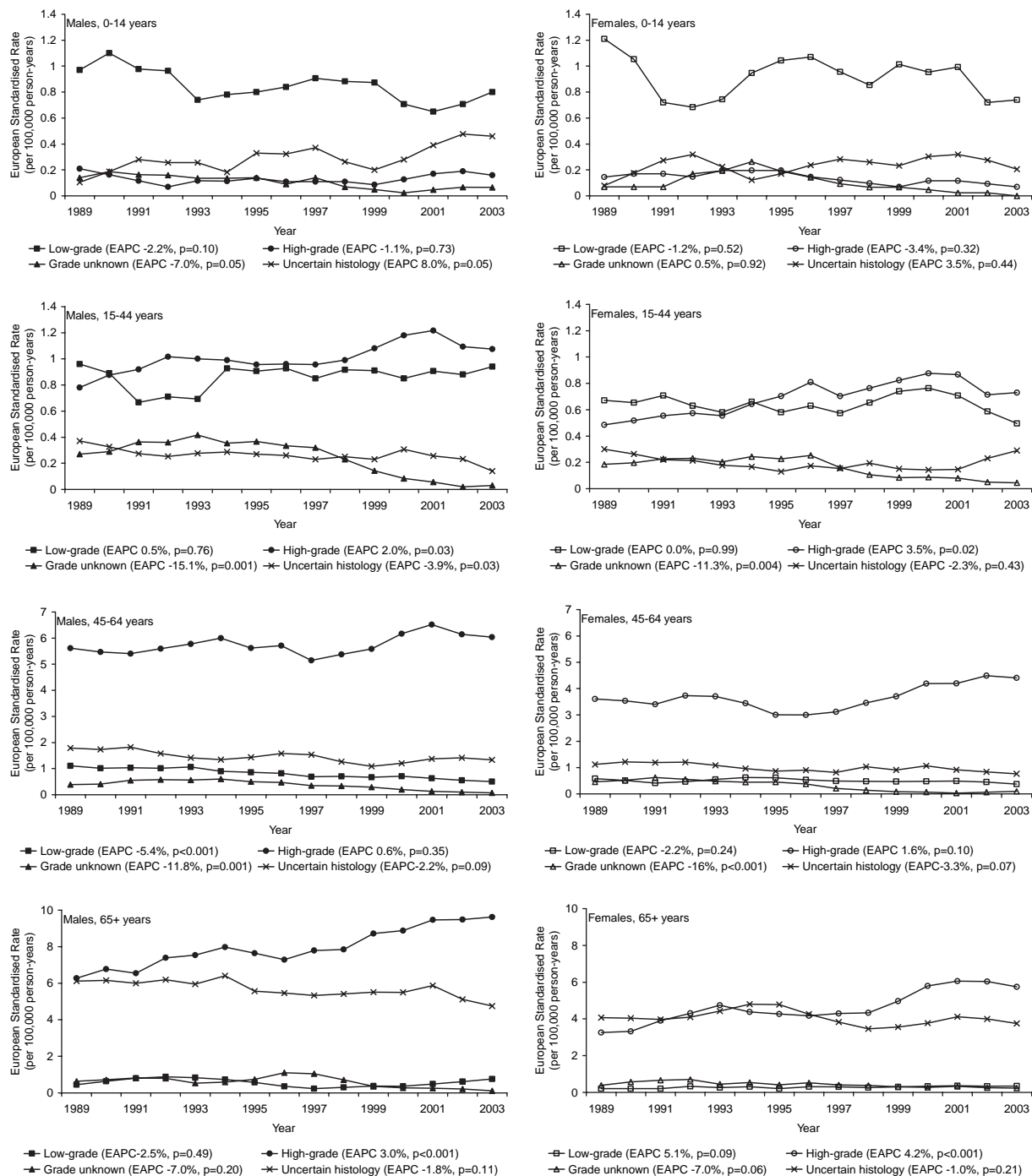
Figure 4. Incidence of astrocytic glioma and glioma of uncertain histology according to gender and age, European Standardised Rates, 3-year moving average, with Estimated Annual Percentage Change (EAPC).

studied period, access to medical care in the Netherlands was good and less than 1% of the population was uninsured [8]. We also verified registration procedures for different areas in the Netherlands, which did not change since 1989. The NCR does not have access to death records as a data source. However, patients with a clinically diagnosed tumour will be reported to the LMR. Since the cancer registry has access to the LMR, we do not

think that the unavailability of death records is a relevant source of bias. In some of the studied glioma subgroups the numbers of cases are small and trend estimation may be difficult. We therefore evaluated the general pattern of incidence trends.

Evaluation of incidence rates over time is complicated by changes in histopathological classifications [12]. We used a uniform cluster scheme for ICD-O coded primary CNS tumours [12]. In this system,
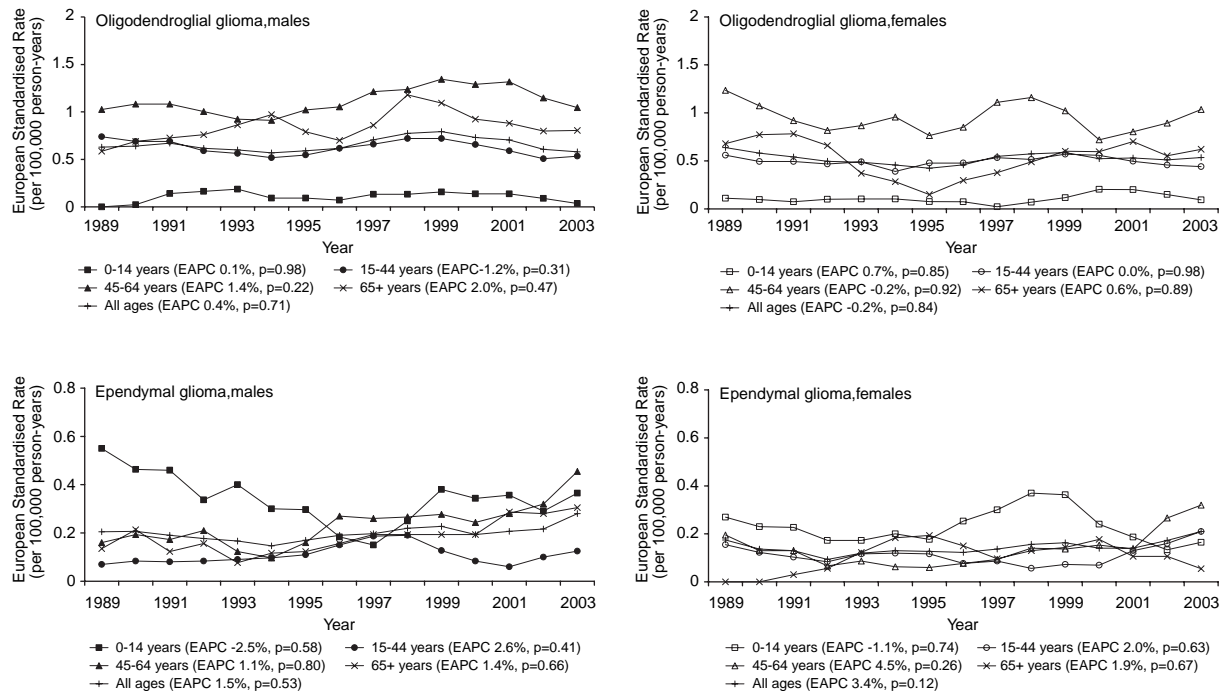
Figure 5. Incidence of oligodendroglial/mixed glioma and ependymal glioma according to gender and age, European Standardised Rates, 3-year moving average, with Estimated Annual Percentage Change (EAPC).

primary CNS tumours are clustered as clinically relevant entities, based on the second edition of the World Health Organisation (WHO) classification of CNS tumours [15]. In our opinion, no essential changes in pathological practice have occurred in the studied period that could have greatly influenced the incidence statistics. Changes in classifications may have occurred within the analysed groups, most likely in the low-grade astrocytoma group. Pilocytic astrocytomas, for example, are characterised by a very distinct histology and prognosis [16]. The recognition and classification of these tumours is improving [16], resulting in more pilocytic astrocytomas that were separately classified from other low-grade astrocytomas (data not shown). However, these shifts have occurred within the group of low-grade astrocytoma and it is therefore unlikely that this has influenced incidence rates in this study. It is possible that some of the clinically diagnosed gliomas without histopathological confirmation will in fact be a different type of tumour. This may particularly be a problem for the primary central nervous system lymphomas (PCNSL) which can be difficult to distinguish from glioma, based on neuroimaging only. The world standardised incidence of PCNSL however is less than 0.3 per 100 000 person-years [17]. This problem would also potentially apply to solitary cerebral metastases from undiagnosed primary sites. Cerebral metastases usually show characteristics that are different from gliomas:

metastases are mostly well circumscribed and show a different pattern of deposition in the brain.

Comparison with other countries

The incidence of glioma has been remarkably stable over the past decades in Europe and the United States. A temporal increase in incidence has been observed in the late 1970s and the early 1980s, but incidence was stabilising or slightly decreasing in almost every age group in more recent years [4–7]. This suggests that these increases in incidence were artifactual, probably owing to the introduction of CT and MRI in this period [7,18]. In the most recent years, increasing incidence of glioma was particularly apparent among the elderly [4–7]. This was probably the result of increasing efforts to obtain histopathological diagnosis. A simultaneous decrease in clinically diagnosed tumours and in glioma NOS is compatible with this view [6,19]. In addition, physicians treating elderly patients are increasingly willing to use more diagnostics in the elderly, revealing malignancies that otherwise would have gone undetected [5,7,20]. An observed increase in high-grade gliomas and simultaneous decrease in low-grade tumours was probably caused by improving techniques in neuroimaging and neurosurgery resulting in less sampling error and better characterisation of malignancy grade [6,7,20].

In the Netherlands, similar patterns were seen as those described in the literature. Not only was

the incidence of glioma stable, also similarly occurring shifts in astrocytoma subgroups suggests improving detection and diagnostic precision. The small increase in incidence of glioma in patients aged over 65 years is most likely the result of a changing attitude towards the elderly in which diagnosis and therapy were more persistently pursued [5,7,21]. This assumption is supported by a decreasing incidence of glioma with unknown malignancy grade and clinically diagnosed tumours. However, these trends were most marked in adults aged 15–64 years, suggesting that patients in this age category may benefit most from new techniques. The observed male/female ratios also correspond with figures previously reported in the literature.

Some authors argue that not all of the observed increases in incidence can be explained by better detection [22–25]. For example, increasing trends in the incidence of childhood astrocytoma were largely confined to girls [23], and an observed increase in the incidence of ependymoma could not be explained by diagnostic practice [19]. However, good explanations for these trends cannot be offered. In the present study, we noticed a decreasing instead of increasing trend of childhood astrocytoma. Ependymoma incidence possibly showed a modest increase in adults, but this increase was not statistically significant and numbers were small (Figure 5).

In conclusion, the incidence of glioma in the Netherlands shows only minor trends between 1989 and 2003. Most variation can be explained by better detection, improving diagnostic precision and changing attitude towards the elderly. Stable incidence rates suggest that no major changes in environmental risk factors have occurred which influenced the incidence of glioma in the studied period.

Acknowledgements

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