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Epidemiology of malignant brain tumors in Genova, Italy. 1993–2017

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We present an updated analysis on the incidence of primary brain tumors in the Metropolitan Area of Genova, the capital of the northwestern Italian region Liguria.

The number of cases and incidence rates for all malignant brain tumors, glioblastoma, malignant brain tumors other than glioblastoma, and brain tumors not otherwise specified were calculated for each of seven three-year and one-eighth four-year periods in which the quarter century 1993–2017 was divided. The rates were age-adjusted (AAR) using the 2013 European standard population, presented per 100,000 person-years and the average percentage change over the three-year period was calculated.

The number of cases of all malignant brain tumors and glioblastoma was higher in males than in females in each three-year period and in the entire quarter century 1993–2017. During the latter, the average three-year percentage change in AARs for all brain tumors was minimal [0.6 (95% C.I. = -1.0/2.1) %] while for glioblastoma there was a change of 5.3 (95% C.I. = -0.4/11.3) %. The partially concurrent decline in the incidence rates of malignant brain tumors other than glioblastoma or not otherwise specified suggests that the observed increase in the incidence rate of glioblastoma during 1993–2017 may have been at least partially linked to the improvement during the same period in sensitivity and specificity of the diagnosis of glioblastoma, depleting the reservoirs of other malignant or unspecified brain tumors. Research into possibly increased environmental risk factors (e.g., population exposure to ionizing radiation) for glioblastoma in Genova remains warranted.

Keywords Brain cancer, Incidence, Age-adjusted rate, Glioblastoma, Glioma, Non-otherwise specified

Abbreviations

3YMPV	3-year mean percent variation
AAR	age-adjusted incidence rate per 100,000 person-years (standard: Europe 2013)
AIRTUM	Italian Association of Cancer Registries
CI	confidence intervals
CNS	central nervous system
CR	crude incidence rate per 100,000 person-years
EU27	European Union at 27 countries
F	female
GB	glioblastoma
IARC	International Agency for Research on Cancer
ICD-O-3	International Classification of Diseases for Oncology
IDH	isocitrate dehydrogenase
INAIL	Italian National Institute for Insurance on Accidents at Work
ISTAT	Italian National Institute of Statistics
LCR	Liguria Cancer Registry
M	male
MGMT	O^6 methylguanine DNA methyltransferase
MVGB	microscopically-verified GB
NGB	brain malignancies other than GB
No.	observed incident cases
NOS	non-otherwise specified malignancies
SDI	Socio-Demographic Index

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SEER	Surveillance, Epidemiology, and End Results
US	United States
WHO	World Health Organization

A group of tumors with low incidence but high disabling and killing capacity affects the brain both in the glia and in other cellular components and causes important hospitalization burdens[1]. In the 27-country Europe (EU27), around 28,000 brain tumors are diagnosed every year. The mortality/incidence ratio is higher in low/middle income than in high-income countries, suggesting more difficult access to therapies and lower quality of care in the former[23] .

Brain tumors comprise 85–90% of the central nervous system (CNS) tumors https://www.cancer.net/cancer-types/brain-tumor/statistics. Exposure to ionizing radiation at a young age is the only proven environmental risk factor[4]. Some hereditary conditions, such as *HERC2* gene variants, can also predispose to some forms of these tumors[5].

Most malignant tumors arise in the glia (gliomas), neurons' supporting and trophic tissue. Gliomas are more frequent in males and white individuals [6–8]. Different mutational profiles have been observed in men and women during the progression of gliomas, suggesting that patient sex may impact the prognosis and efficacy of treatments[9]. In both sexes, younger age at diagnosis is associated with a better prognosis[10].

Among the cell types that make up glia, astrocytes are the ones in which the tumor (astrocytoma) occurs most frequently, with an incidence rate of 4.9 cases per 100,000 person-years in Italy[11]. Since the latter value remains lower than the European threshold level for the definition of rare cancer (6 cases per 100,000 person-years[12], astrocytomas are considered rare. However, they are the most frequent, aggressive and lethal of all brain tumors, with average 5-year relative survival rates of 59.0-89.1% for low-grade tumors [World Health Organization (WHO) grade I, II]; 39.6–55.4% for anaplastic astrocytoma (WHO grade III) and 14.2–23.1% for glioblastoma (GB; WHO grade IV)[13].

Among astrocytomas, GB is by far the most common and aggressive. With an incidence of 2 to 5 cases per 100,000 person-years in the EU27 and the United States (US), GB accounts for over 50% of primary malignant brain tumors[7]. Current treatment guidelines provide the broadest possible surgical resection, but this can only be performed in 50–70% of patients, depending on the brain area affected by the tumor. When resection of the tumor is not possible, a biopsy can sometimes be performed for diagnostic purposes. Subsequent therapies (the so-called "Stupp" protocol from the name of the scientist who developed it) consist of radiotherapy concomitant or followed by the alkylating drug temozolomide[14]. The effectiveness of this treatment varies depending on the biological status (methylated/mutated) of the tumor genes *O*^{6} *methylguanine DNA methyltransferase* (*MGMT*) and *isocitrate dehydrogenase* (*IDH*) *1/2*, respectively, the age of the patients and their general conditions. These treatments rarely prevent the recurrence of the tumor and its subsequent progression. In the last twenty years, no further significant progress has been made in the prevention and treatment of GB, and the therapeutic protocol used at present is essentially the Stupp's one[15]. Over the last forty years, the probability of 5-year survival has increased by only 4 − 7%, primarily linked to the introduction of temozolomide, and median survival currently remains limited to 14–16 months after diagnosis[7]. Every year in the world, approximately 200,000 people die from GB, of which almost 16,000 in Europe and 10,000 in the US. Italy is no exception in terms of incidence and survival rates of patients with malignant brain tumors, including GB[11,16].

The main aim of this work was to identify any changes in the incidence of malignant brain tumors with special reference to GB in the metropolitan area of Genova (Northwestern Italy) during the quarter of century between 1993 and 2017 using incidence cases registered by the Liguria Cancer Registry. This analysis period was selected based on the availability of complete relevant data for it.

Materials & methods

Study area

The present is a descriptive epidemiology study conducted in the Metropolitan Area of Genova. The population of the entire Area (67 Municipalities) at its administrative introduction (1 January 2015) was 853,201 inhabitants. Approximately 68% of the population (584,649 inhabitants) lives in the urban area of Genova, and 28% are over 65 years old.

Cancer registration

The Liguria Cancer Registry (LCR) is a property of the Health Councillorship of the Liguria Region and is hosted at the IRCCS Ospedale Policlinico San Martino, Genova. LCR has been active since 1986 and covers the entire population of the Genova Metropolitan Area. LCR is affiliated with the Italian Association of Cancer Registries (AIRTUM), which defines the standard rules for collecting and classifying tumor data according to the WHO-International Agency for Research on Cancer (IARC) recommendations and guidelines. The overall cancer cases of residents in the Genova Metropolitan Area are collected primarily through active consultation of the hospital discharge records provided by the Ligurian Health Information System and the pathological archive departments in the registry area. Topography and morphology of the tumors are coded according to the Third Edition of the International Classification of Oncological Diseases (ICD-O-3) https://apps.who.int/iris/bitstream/handle/10665/96612/9789241548496_eng.pdf. LCR also obtains official mortality data from the Italian National Institute of Statistics (ISTAT) and calculates mortality/incidence ratios. In the present study, the Cancer Registry data were provided in aggregate and completely anonymous form. In line with Italian legislation, since these are epidemiological surveillance evaluations that concern public health, no ethical-administrative approval from the ethics committees was necessary.

Tumor coding

All incident cases of primary brain tumors diagnosed during 1993–2017 and classified according to ICD-O-3, were considered for analysis. Pilocytic astrocytoma (9421/1) was not included in the analysis since classified as non-malignant tumor during the study period. Gliosarcoma (9442/3) is currently categorized by the WHO as a variant of GB and often grouped with GB in clinical trials. However, its peculiar histological and molecular characteristics are established and differences in clinical behavior and response to therapies with respect to GB are probably dependent on the entity of the sarcomatous component [17–20]. Since these differences might influence disease classification as well as guide targeted therapy, 9442/3 was not grouped with GB in the present study (Table 1). The inclusion or exclusion of rare gliosarcoma cases (19 total cases in 1993–2017) in the GB group did not significantly affect the results presented in the present study (Tables S2,S3 - Discussion). A few additional ICD-O-3 codes present in the Central Brain Tumor Registry of the U.S. classification table of malignant brain and other CNS tumors (Table 2 of the annual report - https://urlsand.esvalabs.com/?u=https%3 A%2 F%2Facademic.oup.com%2Fneuro-oncology%2Farticle%2F25%2FSupplement_4%2Fiv1%2F7289107%23supplementary-data&e=d1becced&h=b56b3d56&f=n&p=y) which is also based on WHO classification (ICD-O-3 third edition) are missing in our Table 1 and S1. These differences may be justified as following : (i) we have only considered the ICD-O-3 site codes C70 and C71; (ii) some morphologies have been introduced since 2018 (es. 9445/3 IDH-mutated GB) while our study period ended in 2017; (iii) some histological types are not present in our incident cases.

Table 1 reports the data quality indicators of brain tumors diagnosed in 1993–2017 and archived in the LCR. In particular, the focus has been on GB, microscopically verified GB (MVGB), other non-GB brain neoplasms (NGB), and brain tumors not otherwise specified (NOS), as well as malignant brain tumors in their entirety. 1.7% of all malignant brain tumors analyzed were known from the death certificate; 38.2% from radiological examination and 56% were subjected to microscopic verification, with a relevant percentage ranging from 83.8% of GBs to 70.1% of malignant tumors other than GB.

The age-adjusted incidence rate (AAR) trends of the benign brain tumors meningioma (MEN; 58% radiologically examined and 38.3% microscopically verified), were analyzed for comparison.

Statistical analysis

Cancer cases and population data (https://encr.eu/node/226) were stratified by sex (male, female, both sexes), age (18 five-year classes from 0 to 90 and more years) and the survey period (7 three-year periods from 1993 to 1995 to 2011–2013 plus 1 four-year period 2014–2017). The AARs per 100,000 person-years were obtained through the direct standardization method[21] using the 2013 European Standard Population as reference https://ec.europa.eu/eurostat/web/products-manuals-and-guidelines/-/ks-ra-13-028. Furthermore, changes in tumor incidence over the quarter century 1993–2017 were assessed by calculating the three-year mean percentage change (3YMPV), assuming linearity. Specifically, 3YMPV values were obtained using a weighted log-normal linear regression model applied to the log-transformed AAR. All three-year AAR and 3YMPV values were accompanied by 95% confidence intervals (95% CI). As aforementioned, the present work is essentially a descriptive epidemiological study aimed at identifying temporal trends in the incidence of malignant brain tumors in a small-to-medium sized population. In this context, statistical tests (significant vs. nonsignificant) may be poorly informative in most analyses. Rather than deciding between two alternative hypotheses, our aim was to estimate exploratory epidemiological measures of what had happened during the period under study. Brain tumors, in particular GB, are very rare health events capable of generating comparative indices (3YMPV) with very high sampling variability even in populations larger than ours. In this study this variability was taken into account through 95% CIs which can also be used to evaluate the reliability/stability of our time-

Entity	Cases (No).	Data quality indicator			ICD-O-3 codes	
		Death certificate (%)	Radiological examination (%)	Microscopic verification (%)	Topography	Morphology
All Malignancies brain tumors	2102	1.7	38.2	56		
GB	667	-	15.9	83.8	C71.	9440/3;9441/3
NGB	882	-	29.1	70.1	C71.	8802/3;9064/3;9085/3;9364/3;9380/3;9381/3;9382/3;9390/3;9391/3;9392/3;9400/3;9401/3;9410/3;9411/3;9420/3;9424/3;9425/3;9430/3;9442/3;9450/3;9451/3;9470/3;9471/3;9472/3;9473/3;9500/3;9503/3;9505/3;9508/3;9590/3;9591/3;9652/3;9671/3;9680/3;9684/3;9687/3;9698/3;9751/3
NOS	553	6.5	79.7	-	C71.	8000/3
MEN	3057	0.2	58	38.3	C70.	9530–9537/0

Table 1. Data quality indicators of intracranial tumours diagnosed 1993–2017 and archived in the [a] LCR. [a] LCR, Liguria Cancer Registry; ICD-O-3, International Classification of Diseases for Oncology; GB, glioblastoma; NGB, brain malignancies other than GB; No., observed incident cases; NOS, non-otherwise specified malignancies. The following tumors were excluded: metastases.

Period	Male				Female				Both sexes			
	No.	CR	AAR	95%CI	No.	CR	AAR	95%CI	No.	CR	AAR	95%CI
1993–1995	121	9.17	8.81	7.22–10.40	110	7.43	6.60	5.32–7.88	231	8.25	7.57	6.58–8.57
1996–1998	131	10.18	9.95	8.22–11.68	116	8.03	6.90	5.59–8.21	247	9.05	8.18	7.14–9.22
1999–2001	145	11.55	10.96	9.15–12.77	116	8.21	6.59	5.35–7.83	261	9.78	8.58	7.52–9.64
2002–2004	130	10.53	9.72	8.03–11.41	121	8.70	6.54	5.32–7.75	251	9.56	8.09	7.07–9.11
2005–2007	129	10.44	9.40	7.76–11.04	116	8.35	6.55	5.30–7.79	245	9.33	7.81	6.81–8.81
2008–2010	133	10.83	9.68	8.01–11.33	129	9.34	7.27	5.95–8.59	262	10.04	8.40	7.35–9.44
2011–2013	135	11.01	9.66	8.01–11.31	115	8.36	6.41	5.16–7.65	250	9.61	7.95	6.94–8.97
2014–2017	189	11.74	10.01	8.56–11.46	166	9.25	7.15	5.99–8.31	355	10.43	8.39	7.49–9.30
Total	1113	10.71	-	-	989	8.48	-	-	2102	9.53	-	-
3YMPV	-	-	0.3	–2.0/2.8	-	-	0.7	–1.0/2.5	-	-	0.6	–1.0/2.1

Table 2. Time trend in [a]AARs of all brain malignancies over the period 1993–2017 by sex (Standard: Europe 2013). [a]AAR, age-adjusted incidence rate per 100,000 person-years (standard: Europe 2013); CI, confidence intervals; CR, crude incidence rate per 100,000 person-years; No., observed incident cases; 3YMPV, 3-year mean percent variation.

trend estimates. Statistical analyses were performed using Stata software, version 16.1 (StataCorp. 2020. Stata Statistical Software: Release 16.1. College Station, TX) and Prism software, version 5.0 (GraphPad Software Inc., San Diego, CA).

Results

All malignancies

The global number of new cancer cases in Italy in 2022 was 232,150 for males and 204,092 for females, with a male/female ratio of 1.14 https://gco.iarc.who.int/media/globocan/factsheets/populations/380-italy-fact-sheet.pdf. The age-standardized global incidence rate of all cancers in Italy was higher in males (312.1 cases per 100,000 person-years) than in females (264.1 cases), with a male-to-female ratio of 1.18. Similarly, the total number of malignant brain tumors (2102 cases) diagnosed in Genova in the overall time period 1993–2017, whose morphologies are identified by the ICD-O-3 codes (Table 1), was significantly higher in males (1113 cases) than in females (989 cases) (male to female ratio: 1.12; Table 2; Fig. 1A). Such imbalances between men and women have been observed in every three-year period, albeit not always statistically significant. The AARs for all malignant brain tumors in Genova ranged from 7.57 (95%CI = 6.58–8.57) in 1993–1995 to 8.39 (95%CI = 7.49–9.30) in 2014–2017 with a 3YMPV of 0.6 [(95% CI = -1.0/2.1); Table 2; Fig. 1C]. AARs were higher in males [M, blue color; range 8.81 (95% CI = 7.22–10.40) in 1993–1995–10.01 (95% CI = 8.56–11.46) in 2014–2017] compared to females [F, red colour; range 6.60 (95% CI = 5.32–7.88 in 1993–1995) to 7.15 (95% CI = 5.99–8.31 in 2014–2017)] in accordance with sex differences reported worldwide [6,22]. The 3YMPV in Genova were 0.3 (95% CI = -2.0/2.8) in males and 0.7 (95% CI = -1.0/2.5) in females. These rises are not significant, but their trend agrees with the data reported for Italy by Miranda-Filho et al. for the period 1993–2007, indicating that the incidence of brain tumors increased more rapidly in females than in males[22].

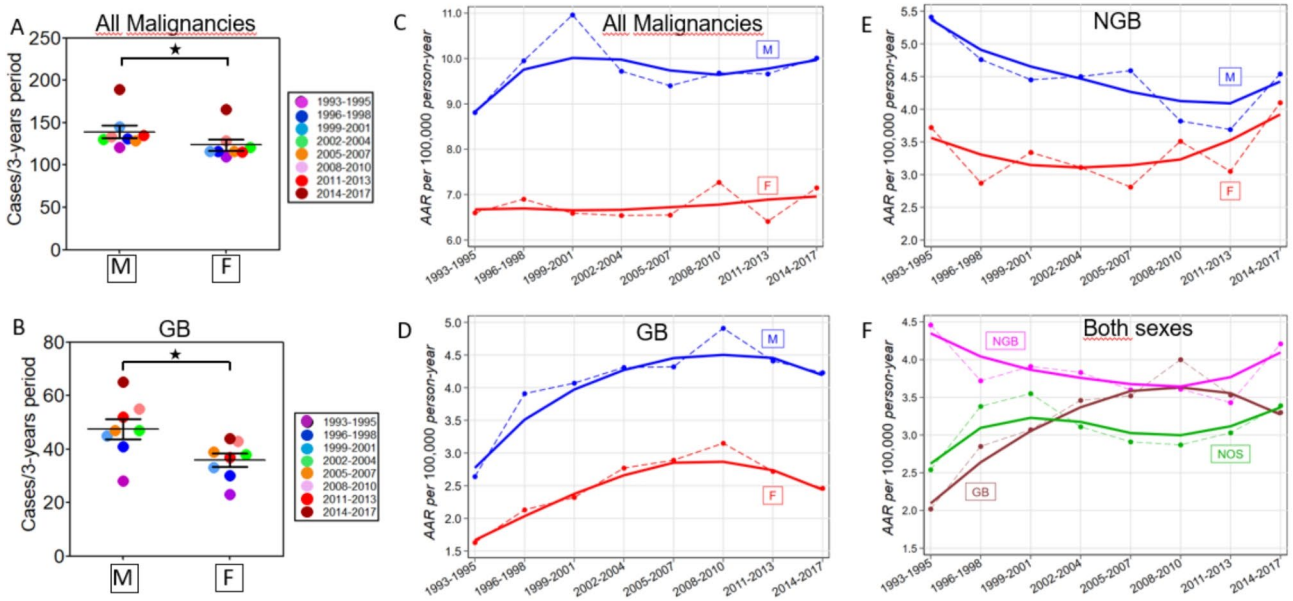

Fig. 1. Malignant brain tumors in Genova, Italy – 1993–2017. (A) The number of brain malignancies in male (M, left) and female (F, right) in each 3-years – period is shown. Brain malignancies were more common in M vs. F over each 3-year period and the whole 1993–2017 century quarter (two-tailed Mann-Whitney P value < 0.05). (B) The number of GB cases in M (left) and F (right) in each 3-years – period is shown. GB was more common in M vs. F over each 3-year period and the whole 1993–2017 century quarter (two-tailed Mann-Whitney P value < 0.05). (C) Time trend in AARs of all brain malignancies over 1993–2017 by sex. (D) Time trend in AARs of GB over 1993–2017 by sex. (E) Time trend in AARs of brain malignancies other than GB over 1993–2017 by sex. (F) Time trends in AARs of GB, NGB and NOS malignancies in both sexes.

GB

Total (diagnosed both by imaging and under the microscope) GBs (ICD-O-3 codes 9440/3-9441/3 - Table 1, S1) in Genova in the period 1993–2017 were significantly more numerous in males (380 cases) than in females (287 cases) (Table 3; Fig. 1B). Similar sex imbalances were observed for every three years. The AARs for GBs in Genova in both sexes ranged from 2.02 (95% CI = 1.45–2.59) in 1993–1995 to 3.30 (95% CI = 2.67–3.92) in 2014–2017 with a 3YMPV of 5.3 (95% CI = -0.4/11.3) indicating an increasing incidence of GB in Genova over the 25 years examined (Table 3; Fig. 1D). AARs were higher for males [range 2.64 (95% CI = 1.54–3.75) in 1993–1995 to 4.23 (95% CI = 3.19–5.28) in 2014–2017] than females [range 1.63 (95% CI = 0.96–2.31) in

Period	Male				Female				Both sexes			
	No.	CR	AAR	95%CI	No.	CR	AAR	95%CI	No.	CR	AAR	95%CI
1993–1995	28	2.12	2.64	1.54–3.75	23	1.55	1.63	0.96–2.31	51	1.82	2.02	1.45–2.59
1996–1998	41	3.19	3.91	2.60–5.22	30	2.08	2.13	1.36–2.90	71	2.60	2.85	2.17–3.53
1999–2001	45	3.59	4.07	2.81–5.33	33	2.34	2.32	1.53–3.11	78	2.92	3.07	2.38–3.76
2002–2004	47	3.81	4.31	3.03–5.59	38	2.73	2.77	1.87–3.66	85	3.24	3.46	2.71–4.21
2005–2007	47	3.80	4.32	3.03–5.61	39	2.81	2.89	1.98–3.80	86	3.28	3.52	2.76–4.28
2008–2010	55	4.48	4.91	3.59–6.23	43	3.11	3.15	2.21–4.10	98	3.76	4.00	3.20–4.79
2011–2013	52	4.24	4.41	3.20–5.63	37	2.69	2.72	1.84–3.61	89	3.42	3.53	2.79–4.26
2014–2017	65	4.04	4.23	3.19–5.28	44	2.45	2.46	1.73–3.20	109	3.20	3.30	2.67–3.92
Total	380	3.65	-	-	287	2.46	-	-	667	3.02	-	-
3YMPV	-	-	4.2	−0.9/9.5	-	-	5.1	−1.2/11.9	-	-	5.3	−0.4/11.3

Table 3. Time trend in [a]AARs of GB over the period 1993–2017 by sex (Standard: Europe 2013). [a]AAR, age-adjusted incidence rate per 100,000 person-years (standard: Europe 2013); GB, glioblastoma; CI, confidence intervals; CR, crude incidence rate per 100,000 person-years; No., observed incident cases; 3YMPV, 3-year mean percent variation.

1993–1995–2.46 (95% CI = 1.73–3.20) in 2014–2017]. Like all malignant brain tumor morphologies, 3YMPV in Genova for GB was higher in females [5.1 (95% CI = -1.2 /11.9)] than in males [4.2 (95% CI = -0.9 /9.5)].

Similar results were obtained by expressing GB as a percentage of all neoplasms, which in both sexes increased from 22.1% in 1993–1995 to 30.7% in 2014–2017, with an average value of 31.7% over the entire 1993–2017 study period (Table S4; Fig. S1 C). Again, the increase was more pronounced in males (range 23.1% in 1993–1995 to 34.4% in 2014–2017; 34.1% of all cancers in the entire study period 1993–2017) compared to females (range 20.9% in 1993–1995 to 26.5% in 2014–2017; 29.0% of all malignancies in the entire study period 1993–2017) (Table S4; Fig. S1 A-B).

Considering only MVGB diagnoses, the AARs ranged from 1.49 (95% CI = 1.00-1.98) in the three years 1993–1995 to 3.09 (95% CI = 2.49–3.70) in the three years 2014–2017 with a 3YMPV of 8.9 (95% CI = 3.0 /15.2) (Table S5). The AARs were higher for males [range 1.77 (95% CI = 0.95–2.59) in the three years 1993–1995 to 4.24 (95% CI = 3.19–5.28) in the three years 2014–2017] than for females [range 1.29 (95% CI = 0.69–1.89) in the three years 1993–1995 to 2.11 (1.43–2.79) in the three years 2014–2017] (Table S5, Fig. S2). The 3YMPV for MVGB was 9.2 (95% CI = 3.2 /15.6)] in males and 7.3 (95% CI = -1.0 /16.1)] in females.

Similar increasing trends were observed when MVGBs were expressed as a percentage of all GBs (Table S4). MVGB always constituted > 50% of all GB diagnoses for any three years and sex (Table S4).

NGB

Thirty-eight non-GB malignant brain tumor morphologies, whose ICD-O-3 codes are listed in Table 1 and S1, were included in this entity. The AARs for this group of multiple pathologies ranged from 4.46 (95% CI = 3.61–5.30) in 1993–1995 to 4.21 (95% CI = 3.51–4.92) in 2014–2017 with a 3YMPV of − 1.0 [95% CI = -4.2 /2.3 (Table 4; Fig. 1E)]. Stratifying by sex, NGB AARs were higher in males [range 5.41 (95% CI = 3.96–6.86) in 1993–1995 to 4.54 (95% CI = 3.43–5.64) in 2014–2017] than in females [range 3.72 (95% CI = 2.71–4.73) in 1993–1995 to 4.10 (95% CI = 3.07–4.95) in 2014–2017]. This sex difference progressively decreased over time due to the higher 3YMPV in females [1.6 (95% CI = -3.3/6.9)] compared to males [-3.1 (95% CI = -6.3/ 0.2)].

		Male				Female				Both sexes			
Period		No.	CR	AAR	95%CI	No.	CR	AAR	95%CI	No.	CR	AAR	95%CI
1993–1995		66	5.00	5.41	3.96–6.86	60	4.05	3.72	2.71–4.73	126	4.50	4.46	3.61–5.30
1996–1998		61	4.74	4.76	3.43–6.09	47	3.26	2.87	2.00-3.75	108	3.96	3.72	2.96–4.48
1999–2001		64	5.10	4.45	3.26–5.64	47	3.33	3.34	2.35–4.33	111	4.16	3.91	3.13–4.69
2002–2004		59	4.78	4.50	3.25–5.76	44	3.16	3.11	2.17–4.05	103	3.92	3.83	3.05–4.61
2005–2007		55	4.45	4.59	3.31–5.87	41	2.95	2.81	1.94–3.69	96	3.66	3.60	2.86–4.33
2008–2010		48	3.91	3.82	2.63–5.01	50	3.62	3.51	2.51–4.50	98	3.76	3.61	2.86–4.36
2011–2013		50	4.08	3.69	2.61–4.77	44	3.20	3.05	2.12–3.99	94	3.61	3.43	2.70–4.15
2014–2017		72	4.48	4.54	3.43–5.64	74	4.13	4.10	3.07–4.95	146	4.29	4.21	3.51–4.92
Total		475	4.57	-	-	407	3.49	-	-	882	4.00	-	-
3YMPV		-	-	−3.1	−6.3/0.2	-	-	1.6	−3.3/6.9	-	-	−1.0	−4.2/2.3

Table 4. Time trend in [a]AARs of NGB over the period 1993–2017 by sex (Standard: Europe 2013).[a]AAR, age-adjusted incidence rate per 100,000 person-years (standard: Europe 2013); NGB, brain malignancies other than GB; CI, confidence intervals; CR, crude incidence rate per 100,000 person-years; No., observed incident cases; 3YMPV, 3-year mean percent variation.

NOS

Despite the constant progress of diagnostic techniques for brain tumors between 1993 and 2017, evidenced by the periodic publication of updated editions of the WHO classification of CNS tumors[23], the classification of a significant number of neoplastic lesions remained not otherwise specified (NOS). In the period 1993–2017, the AARs for these lesions in Genova were between 2.54 (95% CI = 1.83/3.24) in 1993–1995 and 3.39 (95% CI = 2.73/4.05) in 2014–2017 with a 3YMPV equal to 0.8 (95% CI = -3.3/5.1) (Table 5). After stratification by sex, the AARs for NOS tumors ranged from 2.76 (95% CI = 1.63–3.90) in 1993–1995 to 4.58 (95% CI = 3.31–5.85) in 2014–2017 for males and from 2.26 (95% CI = 1.40–3.13) in 1993–1995 to 2.67 (95% CI = 1.91–3.43) in 2014–2017 for females (Table 5; Fig. S5). 3YMPV was 3.0 (95%CI = -4.1/10.6) in males and − 0.7 (95%CI = -4.6/3.3) in females.

Comparative analysis of neoplasms

Plots of AAR trends per 100,000 person-years of GB, NGB, and NOS in both sexes have been overlaid in Fig. 1F for ease of comparison. From the analysis of both the AARs (Tables 3, 4 and 5; Fig. 1D, E, F, S3 A, B) and the percentages of GB on all tumors (Table S4; Figs. S1, S4) it can be seen that the increase in values of GB incidence between 1993 and 2010 were partially reflected by corresponding decreases in NGB and NOS (the latter limited to 2004–2010), with greater evidence in males than females (Fig. 1F, S1, S3). In 2011–2017 the incidence of GB reached a plateau and reversed the trend. Complementary trends occurred for NGB (magenta) and NOS (green) as their incidence progressively increased in the same period 2011–2017.

Period	Male				Female				Both sexes			
	No.	CR	AAR	95%CI	No.	CR	AAR	95%CI	No.	CR	AAR	95%CI
1993–1995	27	2.05	2.76	1.63–3.90	27	1.82	2.26	1.40–3.13	54	1.93	2.54	1.83–3.24
1996–1998	29	2.25	4.02	2.43–5.63	39	2.70	3.04	2.06–4.02	68	2.49	3.38	2.54–4.22
1999–2001	36	2.87	4.65	2.97–6.34	36	2.55	2.87	1.91–3.84	72	2.70	3.55	2.70–4.41
2002–2004	24	1.95	3.01	1.71–4.32	39	2.80	3.13	2.14–4.12	63	2.40	3.11	2.32–3.90
2005–2007	27	2.19	3.24	1.88–4.60	36	2.59	2.75	1.84–3.66	63	2.40	2.91	2.17–3.66
2008–2010	30	2.44	3.23	1.99–4.47	36	2.61	2.59	1.72–3.45	66	2.53	2.87	2.15–3.58
2011–2013	33	2.69	3.78	2.43–5.12	34	2.47	2.52	1.67–3.37	67	2.58	3.03	2.30–3.76
2014–2017	52	3.23	4.58	3.31–5.85	48	2.68	2.67	1.91–3.43	100	2.94	3.39	2.73–4.05
Total	258	2.48	-	-	295	2.53	-	-	553	2.51	-	-
3YMPV	-	-	3.0	−4.1/10.6	-	-	−0.7	−4.6/3.3	-	-	0.8	−3.3/5.1

Table 5. Time trend in [a]AARs of NOS over the period 1993–2017 by sex (Standard: Europe 2013). [a]AAR, age-adjusted incidence rate per 100,000 person-years (standard: Europe 2013); NOS, non-otherwise specified malignancies; CI, confidence intervals; CR, crude incidence rate per 100,000 person-years; No., observed incident cases; 3YMPV, 3-year mean percent variation

Effect of patients' age at diagnosis

The percentages of GB, NGB, and NOS in all tumors were stratified into patients aged ≤ 49 years, 50–69 years, and ≥ 70 years (Tables S6, S7, S8; Fig. S4). These age groups were chosen considering that the threshold-values (50 and 69 years) permitted defining categories discernibly different by age and at the same time with reasonable sample sizes. Other choices would have strongly reduced the number of cases in the younger group (for instance, 40 instead of 50 years) or attenuated the age differences between adjacent groups (for instance, 79 instead of 69 years).

In younger patients (≤ 49 years) of both sexes, NGBs represented the most frequent neoplasms with a mean value of 75.8% over the entire study period 1993– 2017 (Table S6, Fig. S4 C). Stratification by sex led to similar results, with 76.4% and 75.0% NGB in male and female patients, respectively, during the entire study period 1993–2017 (Table S6, Fig. S4 A-B). The morphologies that most frequently affected those young patients were: 9380/3 Glioma, malignant (19.65% of cases); 9400/3 Astrocytoma, NOS (17.19% of cases); 9401/3 Astrocytoma, anaplastic (13.68% of cases) (Table S1).

In patients aged between 50 and 69 years of both sexes, GB represented the most frequent neoplasm, with an average value of 44.3% over the entire study period 1993– 2017 (Table S7, Fig. S4 F). Stratification by sex showed a higher frequency in males than females, with 47.4% and 39.9% of GBs, respectively, over the entire study period 1993–2017 (Table S7, Fig. S4 D-E). NGB closely followed GB with an average value of 41.6% over the entire study period 1993–2017 (Table S7, Fig. S4 F). Stratification by sex showed similar percentages of NGB in males and females, with 40.4% and 43.4%, respectively, over the entire study period 1993–2017 (Table S7, Fig. S4 D-E).

In older patients (≥ 70 years) of both sexes, NOS represented the most frequent neoplasms, with a mean value of 43.9% in the entire study period 1993– 2017 (Table S8, Fig. S4 I). Stratification by sex showed similar percentages in males and females, with 41.9% and 45.6% NOS over the entire study period 1993–2017, respectively (Table S8, Fig. S4 G-H).

Therefore, different tumors characterized patients with different ages at diagnosis, with NGB, GB/NGB, and NOS representing the most frequent entities in patients aged ≤ 49 years, 50–69 years, and ≥ 70 years, respectively.

MEN

MENs are the most common benign intracranial tumors https://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Meningiomas. Their morphologies are identified by the ICD-O-3 codes listed in Table 1 and S1. We wished to compare the epidemiology of MEN with that of malignant brain tumors in Genova. Contrary to the malignant brain tumors, the total number of MEN (3057 cases) diagnosed in Genova in the entire study period 1993–2017 was significantly more numerous in females (2206 cases) than in males (851 cases) (Table S9). Such sex imbalances between females and males were observed in every three-year period. The AARs for MEN in patients of both sexes in Genova ranged from 9.11 (95% CI = 7.78–10.44) in 1993–1995 to 14.70 (95% CI = 13.35–16.05) in 2014–2017 with a 3YMPV of 1.9 [(95% CI = -7.4/12.3); Table S9, Fig. S6]. AARs were higher in females [range 11.08 (95% CI = 9.25–12.91) in 1993–1995 to 17.83 (95% CI = 15.88–19.79) in 2014–2017] than in males [range 6.87 (95% CI = 4.68–9.06) in 1993–1995 to 10.93 (95% CI = 9.05–12.80) in 2014–2017] in accordance with sex differences reported globally [22,6]. The 3YMPV in Genova were 3.2 (-3.7/10.6) in males and 1.6 (-8.5/12.9) in females (Table S9).

Discussion

We queried the Liguria Cancer Registry database to analyze changes in the incidence of primary malignant brain tumors in the metropolitan area of Genova (northwestern Italy) between 1993 and 2017. To our knowledge, this type of analysis has never been carried out over such a long period on the Genoese population which has specific demographic properties such as a high average age[24].

Two factors that are likely to impact the overall incidence of brain tumors are ionizing radiation (which may increase the risk)[25–27] and a history of allergies (which may decrease the risk)[28,29]. An association between ageing and immunosuppression in the CNS has been reported, particularly in older age[30]. However, the role of the immunological system in the control of brain cancer is far from clear[31]. Likewise, the potential effect of cell phone use has been extensively studied, but the results remain inconclusive[32–34]. The socio-demographic index (SDI) is a composite indicator of *per capita* income, average education level and fertility rate of a population[6,35]. An inversely proportional relationship between SDI and brain cancer incidence in the population has been suggested[36,37]. The origin of most malignant tumors of the brain, as well as most other organs, remains undetermined as multiple mechanisms are likely involved.

The AARs of all malignant brain tumors examined in Genova without distinction of sex [range 7.57 (95% CI = 6.58–8.57) in 1993–1995 to 8.39 (95% CI = 7.49–9.30) in 2014–2017; Table 2; Fig. 1C] are in line with those reported in 2019 by Fan and collaborators for the Western Europe population [7.73 (95% C.I. = 5.05–9.52)][37] and slightly higher than those estimated by Leece et al. in Southern Europe [6.89 (95% CI = 6.78–6.99) cases/10^5 people][38]. The latter difference, although not significant, could be favored by a higher SDI in Genova compared to some of the Southern Europe countries examined by Leece et al. (Malta, Portugal, Spain, Italy, Croatia, Serbia, and Slovenia). Although the socioeconomic conditions of large portions of the Genova population have progressively worsened during 1993–2017 [39], the Gross Value Added (GVA) recorded in Genova remained relatively high compared to several Southern Europe countries (including Italy) examined by Leece et al. and may have contributed to a higher incidence of tumors[24,36,37]. The global incidence of brain tumors in Genova remained essentially stable between 1993 and 2017 with a 3YMPV of 0.6 (95% CI = -1.0/2.1) (Table 2). These estimates are consistent with previous estimates of temporal trends in brain cancer incidence worldwide. Miranda-Filho et al. reported limited changes in the AARs of both male and female brain tumors in Italy during

the period 1993–2007 [22]. Additionally, zero change worldwide (95% CI = -5.6 to 5.3) in age-standardized life years lost between 2007 and 2017 due to CNS tumors has been reported[6].

In the period 1993–2017 examined here, GBs constituted 667/2102 = 31.7% of all malignant brain tumors in Genova (Tables 2 and 3), a fraction lower than the 48.6% reported in 2021 by Miller and colleagues in the US[7]. Due to the notable size difference between the populations covered by the LCR in this study ($\sim 0.8 \times 10^6$ people) and the US Central Brain Tumor Registry in the study by Miller and colleagues (the entire US population, i.e., 332×10^6 people), the difference above in the contribution of GB to all brain tumors in Genova compared to the US is statistically significant (z-test; $p < 0.001$).

The average AAR per 10^5 person-years for the GBs calculated over the eight three-year periods between 1993 and 2017 in both sexes was 3.22 ± 0.59 in Genova (Table 3). This average value is almost identical to that previously reported for the entire US population by Miller and collaborators (3.23)[7]. The mean AAR for GB was higher in Genova males (4.10 ± 0.65 cases per 10^5/person-year) than in females (2.51 ± 0.48 cases per 10^5/person-year) (Table 3; Fig. 1D)]. These values are similar to those reported for the US population (4.03 vs. 2.54 cases per 10^5/person-year for males and females, respectively)[7]. GB AARs increased from 1993 to 2010 in Genova, both in males and females (Table 3; Fig. 1D, F). The corresponding decrease recorded for NGB in 1993–2010 and NOS in 2004–2010 (Fig. 1F) suggests that the increased temporal trend of GB AAR during 1993–2010 may have been at least partially linked to the significant advances in imaging and histopathology carried out in those years for the diagnosis of GB, to the detriment of diagnoses previously left unspecified (NOS-green) or incorrectly classified (NGB-magenta)[40]. This phenomenon was more evident in males (Table 3; Fig. S3A) than in females (Table 3; Fig. S3B).

Exposure to ionizing radiation during childhood is an established environmental risk factor for brain tumors[41] while the effects of exposure during adulthood are less clear [25,42]. The possible contribution to the increase in the incidence of GB in the period 1993–2010 linked to an increase in environmental exposure of Genova residents to ionizing radiation is not currently quantifiable. However, data on similar changes in the AARs of MENs (see below) may indicate that such a contribution cannot be ruled out.

Looking in more detail at MVGBs only, their AARs (Table S5; Fig. S2) as well as their percentage of all malignancies (Table S4) grew more linearly over the period 1993–2017 compared to GBs, suggesting a possible increasing use of brain biopsy, likely linked to improving surgical techniques[43]. The development in molecular diagnostics probably had a role in the observed trends. Traditionally, GBs has been classified based on their morphological features, with a significant variability in patient survival. Over the 1993–2017 years, advances in molecular profiling have gradually changed the diagnostic approach and classification of malignant brain tumors, leading to the development of an integrated morphological and molecular classification endowed with improved diagnostic capacity[44]. This expanding knowledge of brain tumor genetics and the development of new technologies required a number of updates in diagnosis and prognosis, which were regularly published in subsequent editions of WHO classifications of CNS tumors in 1993[45], 2000[46], 2007[47], 2016[48] and 2021[49]. Merely to quote an example, in addition to classical morphological and histological analyses, the classification of astrocytoma and GB as subtypes of adult diffuse gliomas is now based on *IDH* mutation status molecular identification. An open question is whether MVGBs may represent a group of tumors with common characteristics compared to tumors that do not require microscopic confirmation. This critical question is beyond the scope of our study but deserves future attention. Currently, the LCR does not record any information regarding the reasons why a GB is submitted for microscopic confirmation. The analysis of trends by age could, however, suggest some considerations: for example, biopsies increased over time more in young people (≤ 49 years; Table S6) than in older people (50–69 and ≥ 70 years; Tables S7, S8) indicating more in-depth diagnostic investigations in younger and rarer GB patients compared to older and more frequent ones. Whether a more in-depth diagnostic activity may have contributed to the worldwide rising incidence of cancer in people under the age of 50 is beyond the aims of this article but deserves consideration for future studies[50].

AARs for NGB showed a limited reduction in 3YMPV of -1.0% (95% CI = -4.2/2.3) (Table 4; Fig. 1E and F). Our data are similar to those reported by Crocetti and collaborators, who demonstrated that the incidence trend in Europe for gliomas during the seven years 1995–2002 was essentially flat[51]. They are also similar to the results obtained in the US by Lin and colleagues, showing that during the entire study period of more than forty years 1975–2018, the incidence of glioma did not change [3YMPV = 0%][52]. Our data, however, differ from the studies reported above due to the temporal trend of AARs: while in Crocetti et al. a substantially flat temporal trend was observed in the period 1995–2002 and in Lin et al. the incidence of glioma increased from 1975 to 1987 (3YMPV = 5.4% [95% CI = 3.9–6.9%]) and decreased from 1987 to 2018 (3YMPV= -1.2% [95% CI = -1.5 / -0.9%]) in the present study pronounced decreases in NGB were observed from 1993 to 2010 with subsequent recovery in the following seven years (Table 4, S4, S6, S7, S8, Fig. 1E and F). After stratification by age (Tables S6, S7, S8; Fig. S4), patients ≤ 49 years appear to be affected by higher percentages of NGB, with predominant morphologies represented by 9380/3 Glioma, malignant; 9400/3 Astrocytoma, NOS; 9401/3 Anaplastic astrocytoma (Table S1).

The above trend differences compared to our results could be linked on the one hand, to the analysis of partially different ICD-O-3 malignant brain tumor morphologies in our study (41 morphologies: Table 1, S1) compared to the studies by Crocetti et al. (120 morphologies) and Lin et al. (20 morphologies) as well as the smaller size of the population analyzed in our study (2,102 total cases of malignant brain tumors registered in the period 1993–2017 compared to the total 44,947 cases registered in 1995–2002 analyzed by Crocetti et al. in 2012 and 62,159 cases registered in the period 1975–2018 and analyzed by Lin et al. in 2021 [51,52].

The limited variations in the temporal trend of NGB incidence between Genova, EU27 and the US could be in part due to differences in genetic susceptibility and exposure to environmental factors of the populations. Mousavi and colleagues suggested that adhering to a Mediterranean diet may be associated with a lower likelihood of contracting glioma[53]. In contrast, a systematic and comprehensive investigation of diet and glioma

risk in three large prospective studies conducted in the UK and US found weak or no associations between food groups, specific nutrients or dietary patterns and glioma risk[54]. Additional factors of variability may be linked to the different standard populations used in the present study (European standard population 2013), Crocetti et al. (European standard population 2008) and Lin et al. (US standard population 2000). In all studies, the male to female rate ratios were similar [1.31 in the present study; 1.40 in[51]; 1.47 in[52]).

In 1993–2017 in Genova, more than one in four malignant brain tumors (553/2102 = 26.3%) remained undiagnosed (NOS; Table 1). In particular, the AAR per 100,000 person-years of NOS increased from 1993 to 2001, probably due to the introduction of MRI, which made it possible to detect subtle or small brain lesions unsuitable for early biopsy techniques and to find patients with only mild symptoms (Table 5; Fig. 1F, S3, S5). Subsequently, from 2002 to 2010, the progressive improvement of biopsy techniques[43] and of histopathological and molecular characterization of brain tumor morphologies, evidenced by the regular publication of subsequent editions of the WHO classification of CNS tumors[23] may have facilitated a reduction in brain tumors remaining undiagnosed (NOS), with a corresponding increase of diagnosed GBs, the most frequent malignancies (Fig. 1F; Tables 3 and 5). The growing detection activity from 2010 to 2017 of small lesions linked to the ever-increasing availability of MRI devices (the installation of which in Italy in that period was around a hundred new devices/year https://www.statista.com/statistics/557511/magnetic-resonance-imaging-scanners-in-italy/ could explain the increase in the AAR of NGB and NOS in 2010–2017.

Compared to the above malignant tumor types, most MEN are diagnosed incidentally[55]. The AAR per 100,00 person-years of MENs increased from 1993 to 2004, then reached a plateau in 2004–2007 and decreased thereafter (Table S9; Fig. S6). This "bell-shaped" time trend in the AAR of MEN resembles the time trend in the AAR of GB, except for the well-known difference that MEN, unlike GB, are more common in females than in males[7]. Similar causes could underlie the similar time courses of GB and MEN. Like that of GBs, the increased detection capacity of MENs in the period 1993–2004 could be explained by the increasing availability of MRI in those years, followed by a plateau and decline in 2004–2017 related to improvements in the interpretative capacity of MRI imaging. In other words, not all lesions diagnosed radiologically in the period 1993–2004 as MEN and not constantly subjected to surgical removal given their benign nature could have been MEN (38.3% f MEN only were microscopically verified – Table 1). MEN classification underwent significant changes in 2004–2007 (e.g. WHO defined the histological features for atypia) and this may have contributed to the trend we report[56]. Furthermore, exposure to ionizing radiation has been recognized as an environmental risk factor for both GB and MEN[25,57]. That a fraction of the increase in the incidence of MEN in the period 1993–2004 might be attributed to greater exposure of the Genova population to ionizing radiation (for example, for medical reasons) rather than to improvements in diagnosis cannot presently be ruled out.

The investigation on GB incidence might have been limited by the exclusion of cases with tumors with sarcomatous component (9442/3 gliosarcoma). However, the incidence of such cases was very low (19 cases in Genova in 1993–2017), their exclusion did not affect significantly the results and is suggested by increasing histological and molecular evidences [17–20].

Conclusions

The incidence of total malignant brain tumors in Genova showed a limited increase [0.6 (95% CI = -1.0/2.1) % every three years] in the quarter century 1993–2017. The incidence of GB, the most common and lethal malignant brain tumor, has shown an increase of 5.3 (95% CI = -0.4/11.3) % every three years. The data suggest that a significant, albeit still undetermined, part of that GB increase may be linked to progress in sensitivity and specificity of GB diagnoses in Genova over 1993–2017. However, further research into possibly increased exposure of the Genova population to environmental risk factors for GB (e.g. ionizing radiation for medical reasons) remains warranted.

Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at Liguria Cancer Registry.

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References

1. Rosa, A., Fontana, V., Filiberti, R. A., Pronzato, P. & Mannucci, M. Descriptive epidemiology of hospitalization of patients with a rare tumor in an Italian region. *Curr. Oncol.* **29**, 9711–9721 (2022).
2. Mohammadi, E. et al. A global, regional, and national survey on burden and quality of Care Index (QCI) of brain and other central nervous system cancers; global burden of disease systematic analysis 1990–2017. *PLoS One*. **16**, e0247120 (2021).
3. Gerstl, J. V. E. et al. A national stratification of the global macroeconomic burden of central nervous system cancer. *J. Neurosurg.*, 1–9 (2022).
4. Vienne-Jumeau, A., Tafani, C. & Ricard, D. Environmental risk factors of primary brain tumors: a review. *Rev. Neurol. (Paris)*. **175**, 664–678 (2019).
5. Choi, D. et al. The genomic landscape of familial glioma. *Sci. Adv.* **9**, eade2675 (2023).
6. Global Burden of Disease Cancer Collaboration. Global, Regional, and National Cancer incidence, mortality, years of Life Lost, Years lived with disability, and disability-adjusted life-years for 29 Cancer groups, 1990 to 2017: a systematic analysis for the global burden of Disease Study. *JAMA Oncol.* **5**, 1749–1768 (2019).
7. Miller, K. D. et al. Brain and other central nervous system tumor statistics, 2021. *CA Cancer J. Clin.* **71**, 381–406 (2021).
8. Wang, G. et al. Importance of the intersection of age and sex to understand variation in incidence and survival for primary malignant gliomas. *Neuro Oncol.* **24**, 302–310 (2022).
9. Zhang, H. et al. Sex difference of mutation clonality in diffuse glioma evolution. *Neuro Oncol.* **21**, 201–213 (2019).

10. Ostrom, Q. T. et al. Age-specific genome-wide association study in glioblastoma identifies increased proportion of 'lower grade glioma'-like features associated with younger age. *Int. J. Cancer*. **143**, 2359–2366 (2018).
11. AIRTUM Working Group. Italian cancer figures–report 2015: the burden of rare cancers in Italy. *Epidemiol. Prev.* **40**, 1–120 (2016).
12. Gatta, G. et al. Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet-a population-based study. *Lancet Oncol.* **18**, 1022–1039 (2017).
13. Girardi, F. et al. Global survival trends for brain tumors, by histology: analysis of individual records for 67,776 children diagnosed in 61 countries during 2000–2014 (CONCORD-3). *Neuro Oncol.* **25**, 593–606 (2023).
14. Stupp, R. et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl. J. Med.* **352**, 987–996 (2005).
15. Weller, M. et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. *Nat. Rev. Clin. Oncol.* **18**, 170–186 (2021).
16. Chebil, C. et al. Incidence, survival and geoepidemiological analysis of meningiomas and glioblastomas in the province of Catania during the 2003–2016 period. *Environ. Res.* **200**, 111286 (2021).
17. Han, S. J. et al. Clinical characteristics and outcomes for a modern series of primary gliosarcoma patients. *Cancer*. **116**, 1358–1366 (2010).
18. Smith, D. R. et al. Clinical and molecular characteristics of gliosarcoma and modern prognostic significance relative to conventional glioblastoma. *J. Neurooncol.* **137**, 303–311 (2018).
19. Frandsen, S. et al. Clinical characteristics of Gliosarcoma and outcomes from standardized treatment relative to Conventional Glioblastoma. *Front. Oncol.* **9**, 1425 (2019).
20. Zaki, M. M. et al. Genomic landscape of gliosarcoma: distinguishing features and targetable alterations. *Sci. Rep.* **11**, 18009–18006 (2021).
21. Naing, N. N. Easy way to learn standardization: direct and indirect methods. *Malays J. Med. Sci.* **7**, 10–15 (2000).
22. 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 (2017).
23. Horbinski, C., Berger, T., Packer, R. J. & Wen, P. Y. Clinical implications of the 2021 edition of the WHO classification of central nervous system tumours. *Nat. Rev. Neurol.* **18**, 515–529 (2022).
24. Vercelli, M. & Lillini, R. Deindustrialisation, demographic decline, aging, economic crisis and social involution in a metropolitan area analysed by applying Socio-Economic and Health Deprivation Indices. *J. Prev. Med. Hyg.* **62**, E709–E717 (2021).
25. Braganza, M. Z. et al. Ionizing radiation and the risk of brain and central nervous system tumors: a systematic review. *Neuro Oncol.* **14**, 1316–1324 (2012).
26. de Berrington, A. et al. Relationship between paediatric CT scans and subsequent risk of leukaemia and brain tumours: assessment of the impact of underlying conditions. *Br. J. Cancer*. **114**, 388–394 (2016).
27. Auvinen, A. et al. Diagnostic radiological examinations and risk of intracranial tumours in adults-findings from the Interphone Study. *Int. J. Epidemiol.* **51**, 537–546 (2022).
28. Linos, E., Raine, T., Alonso, A. & Michaud, D. Atopy and risk of brain tumors: a meta-analysis. *J. Natl. Cancer Inst.* **99**, 1544–1550 (2007).
29. Zhang, C. & Zhu, Q. Allergy is associated with reduced risk of glioma: a meta-analysis. *Allergol. Immunopathol. (Madr)*. **45**, 553–559 (2017).
30. Ladomersky, E. et al. The coincidence between increasing Age, Immunosuppression, and the incidence of patients with Glioblastoma. *Front. Pharmacol.* **10**, 200 (2019).
31. Mahajan, S., Schmidt, M. H. H. & Schumann, U. The Glioma Immune Landscape: A Double-Edged Sword for Treatment Regimens. *Cancers (Basel)* 15, doi: (2024). https://doi.org/10.3390/cancers15072024 (2023).
32. Ostrom, Q. T., Gittleman, H., Stetson, L., Virk, S. & Barnholtz-Sloan, J. S. Epidemiology of intracranial gliomas. *Prog Neurol. Surg.* **30**, 1–11 (2018).
33. Choi, K. H. et al. Mobile phone Use and Time Trend of Brain Cancer Incidence Rate in Korea. *Bioelectromagnetics*. **42**, 629–648 (2021).
34. Castaño-Vinyals, G. et al. Wireless phone use in childhood and adolescence and neuroepithelial brain tumours: results from the international MOBI-Kids study. *Environ. Int.* **160**, 107069 (2022).
35. GBD 2017 Oesophageal Cancer Collaborators. The global, regional, and national burden of oesophageal cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the global burden of Disease Study 2017. *Lancet Gastroenterol. Hepatol.* **5**, 582–597 (2020).
36. Wanner, M. et al. Geographical variation in malignant and benign/borderline brain and CNS tumor incidence: a comparison between a high-income and a middle-income country. *J. Neurooncol.* **149**, 273–282 (2020).
37. Fan, Y. et al. Burden and trends of brain and central nervous system cancer from 1990 to 2019 at the global, regional, and country levels. *Arch. Public. Health*. **80**, 209–205 (2022).
38. Leece, R. et al. Global incidence of malignant brain and other central nervous system tumors by histology, 2003–2007. *Neuro Oncol.* **19**, 1553–1564 (2017).
39. Vercelli, M. & Lillini, R. Application of Socio-Economic and Health Deprivation indices to study the relationships between socio-economic status and disease onset and outcome in a metropolitan area subjected to aging, demographic fall and socio-economic crisis. *J. Prev. Med. Hyg.* **62**, E718–E727 (2021).
40. Thenuwara, G., Curtin, J. & Tian, F. Advances in diagnostic tools and therapeutic approaches for gliomas: a Comprehensive Review. *Sens. (Basel)*. **23**, 9842. https://doi.org/10.3390/s23249842 (2023).
41. Taylor, A. J. et al. Population-based risks of CNS tumors in survivors of childhood cancer: the British Childhood Cancer Survivor Study. *J. Clin. Oncol.* **28**, 5287–5293 (2010).
42. Lopes, J., Baudin, C., Leuraud, K., Klokov, D. & Bernier, M. Ionizing radiation exposure during adulthood and risk of developing central nervous system tumors: systematic review and meta-analysis. *Sci. Rep.* **12**, 16209–16207 (2022).
43. Bex, A. & Mathon, B. Advances, technological innovations, and future prospects in stereotactic brain biopsies. *Neurosurg. Rev.* **46**, 5–w (2022).
44. Frosina, G. Recapitulating the key advances in the diagnosis and prognosis of high-Grade gliomas: second half of 2021 Update. *Int. J. Mol. Sci.* **24**, 6375. https://doi.org/10.3390/ijms24076375 (2023).
45. Kleihues, P., Burger, P. C. & Scheithauer, B. W. The new WHO classification of brain tumours. *Brain Pathol.* **3**, 255–268 (1993).
46. Kleihues, P. et al. The WHO classification of tumors of the nervous system. *J. Neuropathol. Exp. Neurol.* **61**, 215–219 (2002).
47. Louis, D. N. et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol.* **114**, 97–109 (2007).
48. Louis, D. N. et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol.* **131**, 803–820 (2016).
49. Louis, D. N. et al. The 2021 WHO classification of tumors of the Central Nervous System: a summary. *Neuro Oncol.* **23**, 1231–1251 (2021).
50. Ledford, H. Why are so many young people getting cancer? What the data say. *Nature*. **627**, 258–260 (2024).
51. Crocetti, E. et al. Epidemiology of glial and non-glial brain tumours in Europe. *Eur. J. Cancer*. **48**, 1532–1542 (2012).
52. Lin, D. et al. Trends in Intracranial Glioma incidence and mortality in the United States, 1975–2018. *Front. Oncol.* **11**, 748061 (2021).
53. Mousavi, S. M. et al. Adherence to the Mediterranean dietary pattern in relation to glioma: a case-control study. *Clin. Nutr.* **40**, 313–319 (2021).

54. Kuan, A. S. et al. Diet and risk of glioma: combined analysis of 3 large prospective studies in the UK and USA. *Neuro Oncol.* **21**, 944–952 (2019).
55. Islim, A. I. et al. The management of incidental meningioma: an unresolved clinical conundrum. *Neurooncol Adv.* **5**, i26–i34 (2023).
56. Trybula, S. J. et al. The evolving classification of meningiomas: Integration of Molecular discoveries to inform patient care. *Cancers (Basel).* **16**, 1753. https://doi.org/10.3390/cancers16091753 (2024).
57. Memon, A., Rogers, I., Paudyal, P. & Sundin, J. Dental X-Rays and the risk of thyroid Cancer and meningioma: a systematic review and Meta-analysis of current epidemiological evidence. *Thyroid.* **29**, 1572–1593 (2019).

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Author contributions

G.F. conceived the study, analysed data, wrote the paper and supervised the study; C.C., A.P. and E.M. registered and analyzed data, wrote the paper; D.C. analyzed data; L.B. supervised the study; V.F. designed and performed analyses, wrote the paper.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) did not use generative AI and/or AI-assisted technologies in the writing process.

Additional information

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