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Incidence Rates of the Primary Brain Tumours in Georgia – a Prospective Population-Based Study

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ABSTRACT. To determine the incidence rate and evaluate other basic epidemiologic data of primary brain tumours in Georgia a population-based cohort study was performed between March 2009 and March 2011. Active case ascertainment was used to identify brain tumour cases by searching neuroradiology scan reports and medical records from all participating medical institutions, covering almost 100% of the neurooncology patients in the country. A total of 980 new cases were identified during the two-year period. For a population of almost 4.5 million, the overall annual incidence rate was 10.62 per 100,000 person-years, age-standardized to the year 2000 US population (ASR). Non-malignant tumours constituted about 65.5% of all tumours. Males accounted for 44% and females for 56% of the cases. Among classified tumours age-standardized incidence rates by histology were highest for meningiomas (2.65/100,000), pituitary adenoma (1.23/100,000) and glioblastomas (0.51/100,000). ASR were higher among females than males for all primary brain tumours (10.35 vs. 9.48/100,000) as well as for main histology groups except for neuroepithelial, lymphomas and germ cell tumours. The annual incidence rate of all primary brain tumours in Georgia, though comparable with some European registry data, is low in comparison with 2004-2005 Central Brain Tumor Registry of the United States (CBTRUS) database, which may reflect variations in reporting and methodology. The higher percentage of unclassified tumours (37.8%) probably affects the discrepancies between our and CBTRUS findings. However, the most frequently reported tumour was meningioma with a significant predominance in females, which is consistent with CBTRUS data. *© 2013 Bull. Georg. Natl. Acad. Sci.*

Key words: *epidemiology, incidence, primary brain tumours, Georgian brain tumour registry, meningioma, glioblastoma.*

The determination of new brain tumour cases is important to describe disease patterns and to identify the causes of the disease, and it is essential for the management, evaluation and planning of healthcare services for disease control.

Information about incidence rates of primary brain tumours in Georgia during last decades was only available from hospital-based pilot studies. According to these studies carried out in the Sarajishvili Institute of Neurology & Neurosurgery in 1996-2000, meningioma

and glioblastoma were the most frequent diagnosed tumours and accounted for approximately 2/3 of all primary brain tumours [1]. At that time, new imaging techniques, which can enhance cancer detection rate, were established and situated only at hospital departments. In past decade, the situation was changed radically. With some delay, advanced neuroimaging machines have been widely introduced in Georgia and several state-of-art 1.5 tesla MRI and multi-slice CT scanners are available both in clinical and ambulatory settings. Since imaging of the brain provides accurate information about brain structures, nowadays, a patient with suspected brain tumour is routinely examined by an imaging diagnostic tool, which is a painless, noninvasive and fast medical test. In these circumstances a review of CT and MRI results would seem to be a necessary step for obtaining accurate information about brain tumour incidence.

The present study used the database of large population-based study performed in Georgia aiming to examine an incidence and clinical and pathological features of primary malignant and non-malignant brain tumours. The first year results of the study have been reported recently [2]. We performed the analysis of two years data for increasing the statistical power. In the absence of a national population-based brain cancer registry and therefore standard tumor registration procedures and training, cases are ascertained by an active search of neurosurgery hospital records and scan reports from CT and MRI units. This method allows for a precise estimation of the proportion of patients that are diagnosed only neuroradiologically and of those that undergo surgery with further histological verification.

Materials and Methods

The cancer cases included in this study were patients diagnosed with primary brain tumour in Georgia between March 1st, 2009 and March 1st, 2011. All cases were coded following the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). The information about the patients was gained from participating medical institutions: 15 different hospitals providing neurosurgical and neuroradiological services and numerous separate ambulatory-based CT and MRI units located in three big cities: Tbilisi, Kutaisi and Batumi. According to our estimates the participating medical facilities represent almost 100% of the neurooncological activity in the country. Ethical approval was obtained from the Tbilisi State University Medical Faculty ethics committee.

The active case ascertainment was used in order to capture all cases of newly diagnosed brain tumours within the study period. Relevant information (including socioeconomic, clinical, pathological, radiological and other details) was regularly collected by representatives from the participating hospitals and neuroradiological units and using specially designed cancer case reporting form. Along with written form, all collected data was kept in electronic database. Included in the active case ascertainment were (1) medical records of all neurosurgical patients with discharge cancer diagnosis, and (2) scan reports containing any suspicion of a brain tumour. Scan reports were further reviewed by a neurosurgeon to identify incident cases of primary brain tumours and to formulate a diagnosis for each selected case. If description was limited, the tumor was qualified as 'unclassified'. All final radiological cases were matched with the surgical cases to find possible duplicates and eliminate them in favour of the surgery report. If the diagnoses of the same patient differed between the radiological and the surgical database, the case was discussed with the neurosurgeon and the neurologist to give a single final diagnosis.

To ensure the completeness of the collected data, additional sources of information were used. The surgery database of the neurosurgical departments in Tbilisi hospitals and the large pathology database in Tbilisi were searched for cases coded with a brain cancer. For further verification, data obtained from clinical and radiological sources were checked against histological database and in case of any disagreement over the diagnosis the diagnosis from pathology report was kept.

Selection criteria include all cases of intracranially located malignant or non-malignant tumours and exclude cases of recurrent brain tumour and extracranial tumour with invasion into cranium. Intracranial tumours originated from the brain itself, meninges, cranial nerves, pituitary and pineal glands and craniopharyngeal duct are included in the study, according to the internationally recognized primary brain tumour standard definition [3]. The latest WHO 2007 histological classification of tumours of the central nervous system was used to classify cases into six main histology groups: neuroepithelial tumours, tumours of cranial and paracranial nerves, tumours of meninges, lymphomas and hematopoietic tumours, germ cell tumours and sellar region tumours [4].

The following information was selected and stored in the cancer case reporting form: demographics, diagnosis details (grade, behaviour, diagnosis confirmation method and date of diagnosis), treatment (surgery, radio- or chemotherapy), vital status and possible risk factor exposure. Behaviour code (0, 1, 3) was specified according to the ICD-O-3. Non–malignant primary brain tumors include those tumors with a benign behavior code of "0" or uncertain behavior code of "1". The date of the first brain scan when cancer was detected was defined as the date of diagnosis.

STATA and Microsoft Excel were used to calculate crude incidence rates, incidence rate ratio, frequency, arithmetic means of parameters and 95% confidence intervals (CIs) within the cohort and subgroups. Groups were compared by Student's *t* test and the X^2 test for continuous variables and proportions, respectively. The denominator used for the analysis was the Georgian population in 2009 and in 2010, thus person-years at risk was calculated by summarizing of population data of both years. Age-standardization (ASR) was performed based on five-year age groups across the whole age spectrum (total of 18 groups) and standardized to the US 2000 population in order to directly compare our incidence rates to those of the US Central Brain Tumor Registry (CBTRUS), since it contains the largest compilation of population–based data on the incidence of all primary brain tumours [5]. If a particular group consisted of less than 20 patients ASR and corresponding 95% CIs were not calculated. Calculating age-standardized rates (direct standardization), standard errors, and 95% CIs of the standardized rate ratio (SRR) between groups selected by sex and histology were performed according to the method described by Boyle and Parkin [6].

Results

A total of 980 cases of newly diagnosed primary brain tumours were identified in the two-year period between March 2009 and March 2011. Males constituted 44% of the cases. According to the National Statistics Office of Georgia in 2009 there were 4.385 million inhabitants and in 2010 – 4.436 million inhabitants [7]. The crude incidence rate was 11.11 per 100,000 person-years, whereas the overall annual age-standardized incidence rate per 100,000 person-years was 10.62, with similar rates in 2009 (10.25) and 2010 (10.99). The mean age at diagnosis was 48.9 years (standard deviation [SD] 18.1). In the population below 20 years of age, only 83 cases were identified (8.5%). In 59.5% of the cases, the diagnoses were based on neuroradiological data; histological confirmation was received in 35.7%, and in the remaining 4.8% tumours were diagnosed based solely on clinical data (i.e., either the medical record did not contain a pathology report or pathology report was not available at the moment of data collection). Less than half of the patients (n=404) underwent neurosurgical intervention.

Among specified neoplasms, benign and borderline tumours accounted for 65.5% (n=291; ASR=3.15) and malignant brain tumours for the remaining 34.5% (ASR=1.67); crude incidence rates were 3.29 and 1.73, respectively. The difference in ASRs between benign/borderline and malignant tumors was statistically significant (SRR=1.88, 95% CI: 1.55-2.29). The dominance of non-malignant over malignant tumours was observed in both years. The overall ASR among females was 10.35 per 100,000 person-years and 9.48

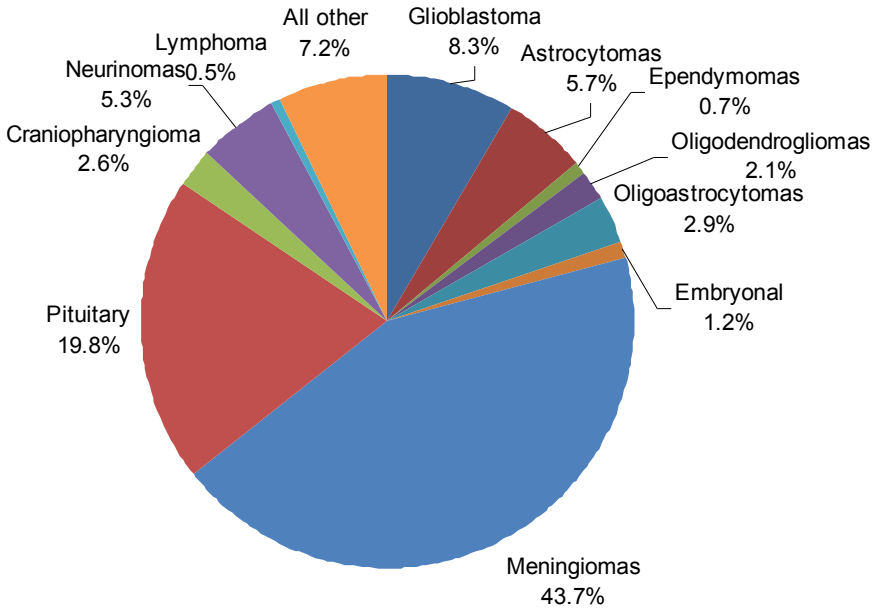

Fig. 1. Distribution of primary brain tumours by histology (n=581)

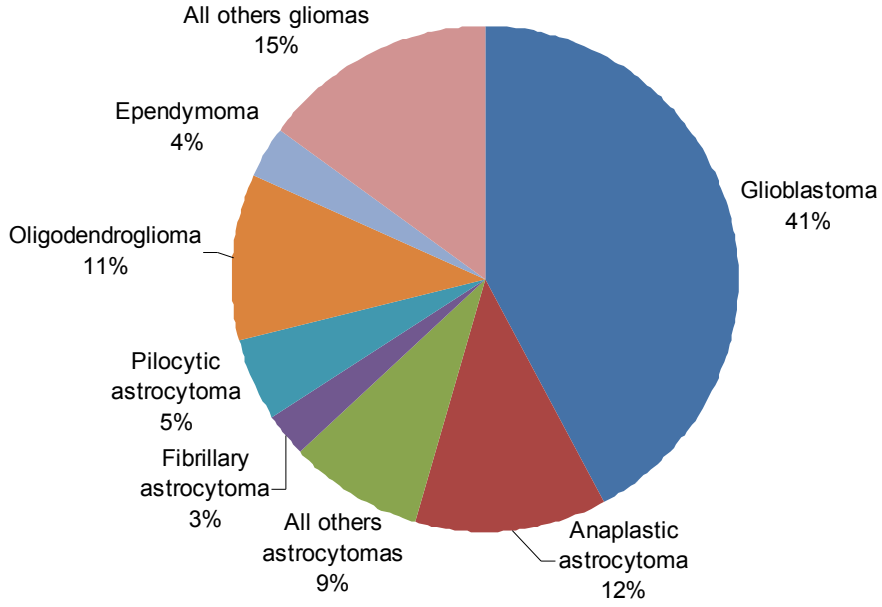

Fig. 2. Distribution of all primary brain gliomas by specific histologies (n=114).

among males. The difference is not significant (SRR=1.09, 95% CI: 0.96-1.25). Standardized incidence rates for non-malignant tumours were 3.59 for females and 2.36 for males (SRR=1.52, 95% CI: 1.19-1.93). For malignant tumours ASR were 1.46 and 1. 92 respectively (SRR=0.76, 95% CI: 0.55-1.05).

The most frequent tumours by reported histology after excluding unclassified tumours (n=399) were non-malignant meningiomas (43.7%, n=254), followed by tumours of sellar region (22.4%, n=130)

Table 1. Incidence and distribution of primary brain tumours by major histology groups and specific histologies (n=980)

Group	Histology	WHO histology code	Number	%	Incidence per 100,000	ASR per 100,000
Neuroepithelial tumours			129	13.16	1.462	1.428
	Pilocytic astrocytoma	9421	6	0.61	0.068	
	Diffuse astrocytoma	9420, 9400	11	1.12	0.125	
	Anaplastic astrocytoma	9401	14	1.43	0.158	
	Glioblastoma	9440, 9441	48	4.89	0.544	0.511
	Oligodendroglioma	9450	7	0.71	0.079	
	Anaplastic oligodendroglioma	9451	5	0.51	0.056	
	Ependymoma	9391, 9392	4	0.41	0.045	
	Other astrocytomas	9424, 9425	2	0.2	0.023	
	Oligoastrocytoma	9382	17	1.73	0.192	
	Embryonal -Medulloblastoma	9470, 9471	7	0.71	0.079	
	Neuronal - glial	9505, 9506, 9493	8	0.81	0.091	
Tumours of cranial and paraspinal nerves	Neurinoma	9560	31	3.17	0.351	0.341
Tumours of meninges			284	28.98	3.219	2.970
	Meningioma	9530, 9531, 9532, 9533, 9534, 9537, 9539	254	25.91	2.879	2.650
	Mesenchymal - lipoma, Haemangioma	8850, 9120, 9150, 9220, 9180	21	2.14	0.238	
	Haemangioblastoma	9161	9	0.92	0.102	
Lymphomas	Lymphoma	9590	3	0.3	0.034	
Germ cell tumours	Germinoma	9064, 9080	4	0.41	0.045	
Tumours of the sellar region			130	13.26	1.473	1.404
	Pituitary adenoma	8272	115	11.73	1.303	1.232
	Craniopharyngioma	9350	15	1.53	0.170	
Unclassified Tumours	Unclassified	0	339	40.71		

(Fig. 1). Gliomas, the most aggressive malignant brain tumours (astrocytic, oligodendroglial, oligoastrocytic and ependimal origin), represented 19.6% (n=114) of all brain tumours. Within this group, glioblastoma accounted for the majority of glioma, representing 42.1% of cases (Fig. 2).

Age-standardized and crude incidence rates among histology groups are shown in Table 1. The highest ASR was observed for tumours of meninges (2.97 per 100,000 person-years; crude incidence rate [IR]=3.22). Incidence rate of the sellar region tumours was 1.40 (crude IR =1.47), closely followed by neuroepithelial tumours (1.43 per 100,000 person-years, crude incidence rate=1.46). Within specific histologies, ASRs were as follows: meningiomas (2.65), pituitary adenomas (1.23), glioblastomas (0.51) and neurinomas (0.34).

For most of histology groups, primary brain tumours were more frequent in females as compared to males. The difference between age-standardized rates was statistically significant for tumors of the meninges (SRR=1.51, 95% CI: 1.18; 1.93) and of the sellar region (SRR=1.69, 95% CI: 1.16; 2.45). In contrast, among specific tumours incidence rates of glioblas-

Table 2. Crude and age-standardized incidence rates of primary brain tumours by gender

		Females				Males				
Group	Specific histology	N	%	IR	ASR (CIs)	N	%	IR	ASR (CIs)	SRR (CIs)
Neuroepithelial		62	12.1	1.33	1.26 (0.94-1.58)	65	16.1	1.55	1.56 (1.18-1.95)	0.81 (0.57-1.15)
	Pilocytic astrocytoma	2	0.4	0.04		4	1.0	0.09		
	Diffuse astrocytoma	5	1.0	0.11		6	1.5	0.14		
	Anaplastic astrocytoma	7	1.4	0.15		7	1.7	0.17		
	Glioblastoma	22	4.3	0.47	0.42 (0.24-0.60)	26	6.4	0.62	0.62 (0.38-0.86)	0.68 (0.38-1.22)
	Other astrocytomas	1	0.2			1	0.25	0.02		
	Oligodendroglioma	4	0.8	0.08		3	0.7	0.07		
	Anaplastic oligodendroglioma	2	0.4	0.04		3	0.7	0.07		
	Oligoastrocytoma	9	1.7	0.19		8	2.0	0.19		
	Ependymoma	3	0.6	0.06		1	0.25	0.02		
	Neuronal - glial	5	1.0			1	0.25	0.02		
	Embryonal -Medulloblastoma	2	0.4	0.04		5	1.2	0.12		
Tumours of cranial and spinal nerves	Neurinoma	20	3.9	0.43	0.4 (0.22-0.58)	10	2.5	0.24	0.25 (0.09-0.40)	1.61 (0.77-3.37)
Tumours of meninges		173	33.7	3.73	3.33 (2.82-3.84)	96	23.7	2.29	2.20 (1.76-2.65)	1.51 (1.18-1.93)
	Meningioma	158	30.8	3.41	3.02 (2.54-3.51)	83	20.5	1.98	1.91 (1.50-2.33)	1.58 (1.22-2.06)
	Mesenchymal - lipoma, Haemangioma	11	2.1	0.24		9	2.2	0.21		
	Haemangioblastoma	4	0.8	0.08		4	1	0.09		
Lymphomas	Lymphoma	1	0.2	0.02		2	0.5	0.04		
Germ cell	Germinoma	1	0.2	0.02		3	0.7	0.07		
Tumours of the sellar region		76	14.8	1.64	1.57 (1.21-1.93)	41	10.1	0.98	0.93 (0.65-1.22)	1.69 (1.16-2.45)
	Pituitary adenoma	67	13.1	1.44	1.36 (1.04-1.69)	36	8.9	0.86	0.82 (0.55-1.09)	1.67 (1.12-2.48)
	Craniopharyngioma	9	1.7	0.19		5	1.2	0.12		
Unclassified	Unclassified	179	34.9	3.86		187	46.3	4.46		
	Total	512	100	11.05	10.35(9.44-11.26)	404		9.64	9.47 (8.54- 10.41)	1.09 (0.96-1.25)

tomas, germinomas and lymphomas and embryonal tumours were higher in males, but not statistically significant (Table 2).

Discussion

The present population-based study performed in the Caucasus region aimed to assess an incidence and clinical and pathological features of primary brain tumours using the WHO 2007 histological classification of tumours of the central nervous system. The observed overall ASR of primary brain tumours (10.62 per 100,000) is lower than the standardized rate of primary brain and CNS tumours diagnosed in 2004-2005 in the US and reported in 2009 by CBTRUS (18.16) and also lower than ASR in 2005 received by the Austrian Brain Tumour Registry (ABTR) (18.1) [8, 9]. Lower incidence rates compared with the CBTRUS database were also observed in our study for main histology groups and specific histologies. However, in contrast to CBTRUS and ABTR data, recent publications from some European registries showed incidence rates of primary brain tumours similar to ours (8.5-14 per 100,000) [10-13].

The difference in the incidence rates may be due to several reasons. For example, a lower incidence rate in Georgia than in more affluent countries may reflect the low attention to subtle and sometimes obscure symptoms of brain tumours and as a consequence low healthcare utilization, complicated by insufficient or lack of health insurance coverage among the population. Additionally, CT and MRI imaging systems are concentrated only in big cities and therefore these diagnostic methods are too expensive and inaccessible for large parts of the rural population. A further, statistical, explanation is that a high percentage of Georgian emigrants, who are looking for a job abroad (22.9% of the total population of over 4.4. million based on 2005 report of the United Nations Population Division and the World Bank) can artificially increase the denominator (i.e., 'true' population number is less than official one) [14]. Finally, differences between countries in sociodemographic characteristics and environmental factors (so-called geographic variation factor), which may be associated with brain tumour risk, should be taken into account when interpreting ASRs of different countries.

However, the comparison of tumour distribution patterns by behaviour and histology showed a high comparability of the rates in our study with the CBTRUS statistic, in particular the predominance of non-malignant over malignant tumours, with the most common histology being meningioma, and glioblastoma representing the most frequent type of gliomas. The main difference between the registries with respect to primary brain tumour frequency is that in our study pituitary adenoma and glioblastoma account for 19.8 and 8.3%, while according to CBTRUS data glioblastoma prevailed over pituitary tumours (17.4 versus 12%). Additionally, among the main histology groups in our study, the highest incidence rate was found for tumours of meninges, whereas neuroepithelial tumours had the highest rate in CBTRUS report, followed by tumours of meninges. For the majority of tumours, incidence rates were higher among females than males, but for specific tumours the strongest differences were observed for meningiomas and pituitary adenomas (common in females) and for glioblastoma and germ cell tumours (common in males). These results are concordant with those in the CBTRUS and ABTR reports, which may indicate the validity of our data.

Our study has limitations caused by the relatively low rate of histologically confirmed tumours (36%). In contrast, histological verification rate is 69% in CBTRUS report and 80.9% in the ABTR data. In other studies, however, pathological confirmation index varied widely from 35% to 59% [11, 15, 16]. The percentage of histologically verified cases is one of the registry reliability indicators and efforts should be directed for improving this value, which is less likely to reflect bias in reporting cancer cases (the index in our study is persistently low in both years – 38% and 33.5%, respectively). There is some evidence in the literature, however, that because non-

invasive neuroimaging techniques improve and become an important diagnostic tool today, the proportion of radiologically diagnosed tumor cases has increased, especially among older patients. Indeed, 41% of the histologically unverified tumours in a population-based cancer registry of Spain province Girona were explained by easy access to sophisticated imaging tools [15]. We suggest that a limited neurosurgical activity in elderly patients, among whom nonsurgical treatment options are usually unavailable (in particular for patients in rural areas), contributes to higher number of neuroradiologically confirmed diagnoses. This can explain the significant proportion of unclassified tumours in our study.

Despite the above mentioned limitations, our data show the brain cancer diagnosing procedure quality in the country with limited economical resources and consequences of political reorientation. In this respect, regularly reported data from the brain cancer registry will help to focus on diagnostic and missing data issues for improving the validity of the data. Additionally, population-based epidemiologic data provide important information for the development of proper national healthcare strategies in relation to neurooncological patients. Regardless of the quality of currently available data, the current report of the Georgian brain tumour registry is the only opportunity to assess the impact of cancer in the community and cancer registration should be regarded as a priority in the nationwide health policy.

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ამოცანა. თავის ტვინის პირველადი სიმსივნეების ავადობისა და სხვა საბაზისო ეპიდემიოლოგიური მაჩვენებლების შეფასება პოპულაციურ კოჰორტულ კვლევაში, რომელიც ჩატარდა საქართველოში 2009 მარტიდან 2011 წლის მარტამდე. მეთოდები. გამოვიყენეთ შემთხვევების გამოვლენის აქტიური მეთოდი, რაც გულისხმობდა ნეირორადიოლოგიური კვლევის დასკვნებისა და ნეიროქირურგიული განყოფილებების სამედიცინო ისტორიების მოძიებას კვლევაში ჩართულ

ყველა პარტნიორი სამედიცინო დაწესებულებიდან, რომლებიც პრაქტიკულად ასახავდა რესპუბლიკაში ნეიროონკოლოგიური პაციენტისადმი სამედიცინო აქტივობის 100%-ს. შედეგები. ორი წლის მანძილზე გამოვლინდა 980 ახალი შემთხვევა. 4,5-მილიონიანი მოსახლეობისათვის ავადობის საშუალო წლიური მაჩვენებელი იყო 10.62 100,000 ადამიან–წლებზე კორექციით აშშ-ს 2000 წლის სტანდარტულ პოპულაციაზე (აკმ). სიმსივნეების 65.5% წარმოადგენდა არაავთვისებიანი სიმსივნეები. მამაკაცები შეადგენდნენ შემთხვევათა 44% და ქალები – 56%. კლასიფიცირებულ სიმსივნეთა შორის ავადობის მაღალი მაჩვენებელი გამოვლინდა მენინგიომებისათვის (2.65/100,000), პიტუიტარული ადენომებისათვის (1.23/100,000) და გლიობლასტომებისათვის (0.51/100,000). ავადობის აკმ ქალებში უფრო მაღალი იყო, ვიდრე მამაკაცებში ყველა სიმსივნეების სახეობებისათვის (10.35 vs. 9.48/100,000), გარდა ლიმფომების, ნეიროეპითელური და ჩანასახოვან-უჯრედოვანი სიმსივნეებისა. დასკვნა. ავადობის წლიური მაჩვენებელი სიმსივნეების ყველა სახეობისათვის საქართველოში, თუმცა შესატყვისია ევროპულ მაჩვენებლებთან, დაბალია 2004–2005 წლების აშშ-ს თავის ტვინის ცენტრალური რეესტრის მაჩვენებლებზე. არაკლასიფიცირებული სიმსივნეების მაღალი პროცენტი (37.8%) ჩვენს კვლევაში საგარაუდოდ ახდენს გავლენას ამ სხვაობაზე, მაგრამ მენინგიომების სიჭარბე გამოვლენილი სიმსივნეების სხვა სახეობებზე და მათი დომინირება ქალებში სრულად შეესატყვისება აშშ-ს ცენტრალური რეესტრის შედეგებს.

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