RESEARCH ARTICLE

Transition over 35 Years in the Incidence Rates of Primary Central Nervous System Tumors in Shanghai, China and Histological Subtyping Based on a Single Center Experience Spanning 60 Years

Fang Shen[1&], Chun-Xiao Wu[2&], Yu Yao[1&], Peng Peng[2], Zhi-Yong Qin[1], Yin Wang[3], Ying Zheng[2]*, Liang-Fu Zhou[1]*

Abstract

Background: Only few epidemiological data on primary central nervous system (CNS) tumors in Shanghai have been reported. Methods: All cases of primary CNS tumors that were registered at Center for Disease Control and Prevention (CDC) were collected (1973-2007: urban Shanghai; 2003-2007: whole Shanghai city). Trends were analyzed using joinpoint analysis and rates were stratified by age, gender and region. Histological data were collected from both CDC and Huashan Hospital. Results: From 1973 to 2007, the five-year average incidence rate in urban Shanghai increased in both genders, especially in the elderly population. Joinpoint analysis showed the age-adjusted incidence rate for males increased first but then plateaued, whilst rates for females continued increasing over the 35 years. For the five-year status quo (2003-2007), rural had a higher age-adjusted incidence rate than urban populations, and females higher than males, especially those with advanced age. According to CDC (2003-2007) and Huashan Hospital (1951-2011), the two most common histological subtypes were neuroepithelial tumors (with male predominance) and meningiomas (with female predominance). Conclusions: In Shanghai, a steadily increased incidence rate of primary CNS tumors was observed in general, and in the elderly and female population in particular.

Keywords: Primary central nervous system tumors - incidence - trends - histological subtypes - Shanghai

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Introduction

Although central nervous system (CNS) tumors are relatively uncommon as compared with other neoplasms, they are associated with a high mortality rate, especially in children (Porter et al., 2010). Intracranial tumors constitute the majority of the CNS tumors and they could be further divided into primary (de novo) and secondary (metastatic) ones in terms of site of origin or malignant and benign variants based on histopathological traits. Specifically, the most common type of malignant and benign primary intracranial tumors are those of neuroepithelial (gliomas) and meningothelial (meningiomas) origin respectively (Kleihues et al., 1993), while lung cancer and breast cancer are most likely to lead to intracranial metastasis (Cordera et al., 2002). Moreover, as compared with their male counterparts, females are reported to be at a higher risk of developing meningioma, whereas lower risk of developing glioma (Kleihues et al., 1993). The heterogeneity of brain tumors is further denoted by the fact that even histologically benign tumors could jeopardize the survival of the patients and cause severe neurological dysfunction due to their space occupying effects and, occasionally, malignant transformation (Wrensch et al., 2002).

CNS tumors seemed to have increased in incidence over the past 40 years (Fisher et al., 2007) and their incidence rates are reported to be highest in those developed countries in North America and Europe (men, 5.8 per 100,000; women, 4.1 per 100,000), and found to be lowest in Africa (men, 3.0 per 100,000; women, 2.1 per 100,000) (Shin et al., 2010). However, except for ethnic related susceptibility (Fan and Pezeshkpour, 1992) and environmental risk factors (Gurney and Kadan-Lottick, 2001), this discrepancy might also relate to improved accessibility of advanced neuroimaging facilities (Modan et al., 1992; Hoffman et al., 2006) and better CNS tumor registration practices in those developed continents (Davis et al., 1996). For example, based on data from Central Brain Tumor Registry of the United States, the overall

[1]*Department of Neurosurgery, Huashan Hospital, Fudan University,* [2]*Department of Cancer Control and Prevention, Shanghai Municipal Center for Disease Prevention and Control,* [3]*Department of Neuropathology, Institute of Neurology, Huashan Hospital, Fudan University, Shanghai, China* [&]*Equal contributors *For correspondence: lfzhouc@126.com, yzheng@scdc.sh.cn*

incidence rate for primary brain tumors was reported to be 18.1 per 100 000 person-years (Porter et al., 2010).

In China, the first report on the general incidence, age distribution, and preferential sites of CNS tumors in China was published in 1982 (Cheng, 1982), which showed that neuroepithelial and meningeal tumors occurred first and second in terms of frequency, and the age distribution of Chinese patients with CNS tumors was lower than that of Caucasians. Located at the east coast of China, Shanghai is divided into 16 districts and one county. In 1993, a pioneering study (Jin et al., 1993) on cancer incidence trends in urban Shanghai (1972-1989) revealed that the most dramatic increases in incidence rates from 1972-1974 to 1987-1989 were observed for cancers of the gallbladder, colon, and brain/other nervous system and the authors believed these changes could be partially explained by improvements in cancer diagnosis and completeness of the cancer registry. More recently, another two cancer incidence studies reported that, for the period of 1973-2005 in urban Shanghai, brain and spinal tumor was the second most common cancer among children aged 0-14 (Bao et al., 2009) and its incidence rate increased significantly in adolescents and young adults (15 to 49 year-olds) (Wu et al., 2012).

Shanghai has experienced dramatic socioeconomic developments in the past 35 years and this fast modernization is expected to have fundamental impact on the public health of the regional residents. Therefore, given the scarcely available data regarding the incidence, as well as the histological subtypes, of primary CNS tumors in Shanghai, we present here a population based incidence trend analysis between 1973-2007 in urban Shanghai and five-year status quo (2003-2007) analyses in whole Shanghai city (including both urban and rural areas) for age-, gender- and region-specific incidences. Transverse comparison with other parts of the world was also made by using data from GLOBOCAN 2008. Moreover, we also provide the first detailed report on the histological subtypes of CNS tumors by collecting both the population based data (2003-2007) and single center based data (1951-2011).

Materials and Methods

Data source

Population-based data: A resident was defined as any individual registered as permanent resident in Shanghai. All population data (anonymous individual cancer patient registration data) were obtained from the Office for Cancer Prevention at Shanghai Municipal Center for Disease Control & Prevention (CDC) on all CNS tumors (brain, meninges, spinal cord, cranial nerves and other parts of the central nervous system) that were newly diagnosed from 1973 to 2007 (urban Shanghai) or from 2003 to 2007 (the whole city including rural areas). Cancer registration data include basic demographic survey (e.g. date of birth, sex, area of residence) and tumor data (e.g. tumor site, histological diagnosis). Demographic information such as population size and population composition were obtained from the annual reports by Shanghai Municipal Bureau of Public Security. Before 2002, registration data were reported to Shanghai Cancer Institute and tumors were only classified by their locations according to the 9th edition of the International statistical classification of diseases, injuries and causes of death (ICD-9) topography codes. After 2002, registration data were reported to Shanghai Municipal CDC and tumors were classified by both ICD-9 and the second edition of the international classification of diseases for oncology (ICD-O-2, histology codes). Therefore, histological data were only available after 2002. Since it is mandatory for local hospitals to report all residents who suffered from brain tumors to CDC, theoretically, this population based data has 100% coverage.

From these database, we extracted all newly diagnosed cases of primary CNS tumor from 1973 to 2007 (ICD-9): meninges (C70.0–C70.9), brain (C71.0–C71.9), cranial nerves and other parts of the central nervous system (CNS) (C72.0–C72.9). Histology subtyping was categorized as follows (ICD-O-2): (1) tumors of neuroepithelial tissue [astrocytic tumors (9384/1, 9400/3, 9401/3, 9410/3, 9411/3, 9420/3, 9421/1, 9442/1, 9444/1, 9421/3, 9422/3, 9423/3, 9424/3, 9430/3, 9440/3, 9441/3, 9442/3, 9443/3, 9481/3); oligodendroglial tumors (9450/3, 9451/3, 9460/3); ependymal cell tumors (9383/1, 9391/3, 9392/3, 9393/1, 9393/3, 9394/1); tumors of the choroid plexus (9390/0, 9390/1, 9390/3); neuronal and mixed neuronal-glial tumors (9490/0, 9491/0, 9492/0, 9493/0, 9412/1, 9413/0, 9505/1, 9505/3, 9506/0, 9506/1, 9507/0, 8680/1); neuroblastomas (9500/3, 9503/3, 9504/3, 9522/3, 9523/3); embryonal tumors and other neuroepithelial tumours (9470/3, 9471/3, 9472/3, 9473/3, 9480/3, 9392/3 9501/0, 9501/3, 9502/0, 9502/3, 9474/3, 9490/3, 9500/3, 9508/3)], (2) tumors of the meningothelial cells [meningioma, atypical meningioma and anaplastic meningioma (9530/0, 9530/1, 9530/3, 9531/0, 9532/0, 9533/0, 9534/0, 9535/0, 9536/0, 9537/0, 9538/1, 9538/3, 9539/1, 9539/3, 9150/1)], (3) tumors of cranial and spinal nerves [schwannoma (9560/0, 9560/1, 9560/3, 9562/0); neurofibroma (9540/0, 9540/1, 9541/0, 9550/0, 9570/0); perineurioma (9571/0, 9571/3) and malignant peripheral nerve sheath tumor (9540/3, 9561/3)], (4) germ cell tumors [germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, teratoma, mixed germ cell tumors (9064/3, 9070/3, 9071/3, 9080/0, 9080/1, 9080/3, 9084/3, 9085/3, 9100/3)], (5) chordomas (9370/3, 9371/3, 9372/3, 9373/0), (6) hemangioblastomas (9161/1), (7) unspecified (8000-8001) and (8) others. To be in accordance with 2007 World Health Organization (WHO) classification of CNS tumors (Louis et al., 2007), pituitary tumors were excluded from this study. Other rare primary CNS tumors, such as pineal tumors, craniopharyngiomas, primary CNS lymphomas, soft tissue tumors and spinal cord tumors were also excluded. The study did not involve patients' personal information and, therefore, patient consent and ethical approval was not required.

Single center based data: This study also included all cases of patients who underwent surgical resection or biopsy for primary CNS tumors in the Department of Neurosurgery, Huashan Hospital from 1951 to 2011. Every case was confirmed with pathological examination at the Department of Neuropathology,

Table 1. Annual Percentage Changes (APC) for Age-adjusted Incidence Rate of Primary Central Nervous System Tumors in Urban Shanghai Between 1973 and 2007

Gender	Stage	Time frame			Rate *	APC%	Z	*P*
Male	Total	1973	-	2007	3.98 - 6.08	1.91	7.62	0
	Stage 1	1973	-	1990	3.98 - 5.36	3.47	4.77	0
	Stage 2	1990	-	2007	5.36 - 6.08	0.8	1.45	0.156
	Stage 2- Stage 1				1.38 - 0.72		-2.91	0.007
Female	Total	1973	-	2007	3.34 - 6.89	3.16	15.69	0

*Incidence rate was expressed as per 100,000 population (data from Shanghai Municipal Center for Disease Control & Prevention)

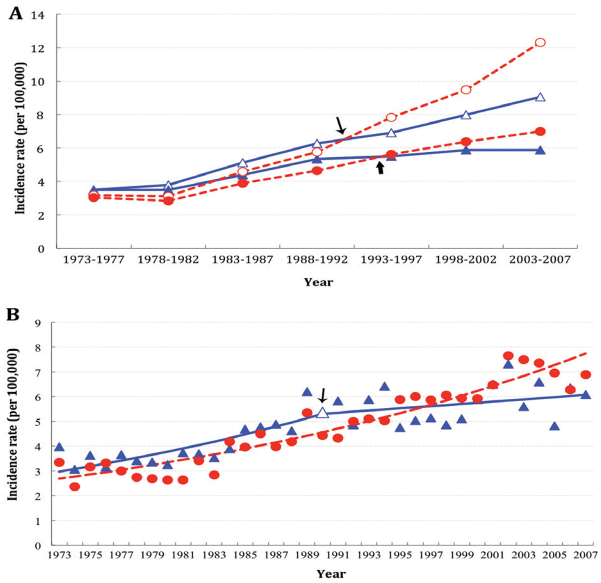

Figure 1. The Crude and Age-adjusted Incidence Rate (per 100,000 population) of Primary CNS Tumors (A) and Joinpoint Regression Analysis for the Trends (B) in urban Shanghai from 1973 to 2007. A: There was generally a steady increase in the five-year average crude and age-adjusted incidence rate in both males (blue solid line) (△ crude; ▲ adjusted) and females (red dotted line) (○ crude; ● adjusted). Moreover, females surpassed males in terms of five-year average crude and age-adjusted incidence rate since 1992 (→) and 1995 (➡). B: Joinpoint regression showed the incidence rate for males (▲: observed value; blue solid line: fitted value) increased first (1973-1990), then plateaued (1991-2007) and a joinpoint (△) was found in 1990 (→). While the rate for female (●: observed value; red dotted line: fitted value) remained increasing throughout the 35-year period (1973-2007) and no joinpoint (○) was detected

Institute of Neurology, Huashan Hospital, while those with uncertain or ambiguous pathological diagnosis were excluded. For the period of 1951-1999, the first (1979) and second edition (1993) of WHO classification of CNS tumors were successively adopted in our hospital. Since 2000 and 2007, the third edition (2000) and fourth edition (2007) were used instead (Louis et al., 2007). Moreover, in an attempt to correspond the hospital based histological subtyping data to the ICD-O codes adopted in CDC based population data, we included: 1) tumors of neuroepithelial tissue; 2) tumors of meningothelial cells; 3) tumors of cranial & spinal nerves; 4) mesenchymal tumors; 5) lymphomas & haematopoietic tumors; 6) germ cell tumors; 7) hemangioblastomas; 8) chordomas. While pituitary tumors, pineal tumors, craniopharyngiomas and spinal cord tumors were excluded.

Methods

Five-year average age-adjusted incidences were calculated by using the direct method, standardized to the 1966 world standard population and presented in per 100,000 population figures. Data regarding incidence rates were stratified by gender (male/female), region (urban/rural), and age groups (in five-year groupings: from 0- to 85+). Unless otherwise stated, reporting of the incidence rates was limited to world-standardized rates for ease of comparison. Trends were expressed as annual percentage change (APC) over the 35-year period by using the joinpoint regression program software (version 3.5.1). A positive or negative APC corresponds to an increasing or decreasing trend, respectively. Statistical analysis was performed by using IBM SPSS Statistics 20.0 for Windows. Categorical variables were analyzed with the Pearson χ^2 test, and continuous variables with the Student's t test. Multiple comparisons of the mean values of continuous variables were first performed with one-way analysis of variance (ANOVA), followed by Fisher's least significant difference (LSD) or Dunnett's post hoc test where appropriate. A P value <0.05 was considered statistically significant.

Results

Population based incidence trends analysis and five-year status quo

Incidence trends analysis: 1973-2007: All patients newly diagnosed with primary CNS tumors, including both benign and malignant tumors of varying histologies and biological behaviors, in urban Shanghai from 1973 to 2007 were recruited for the purpose of analyzing the incidence trends. There was generally a steady increase in both the five-year average crude and age-adjusted incidence rate in both males (crude: 3.5 to 9.05; adjusted: 3.5 to 5.88) and females (crude: 3.17 to 12.32; adjusted: 3.03 to 7) during this period. Specifically, the five-year average crude incidence rate was mildly greater in males before 1992, but surpassed by females since then. Likewise, the mild dominance of males over females in terms of age-adjusted incidence rate was reversed after 1995 (Figure 1A). Trends in age-adjusted incidence rates and the results of the joinpoint analysis were shown in Figure 1B and Table 1. Notably, the incidence rate for males increased significantly between 1973 and 1990 (3.98-5.36, APC=3.47%, P<0.01), but no significant increase was observed between 1991 and 2007 (5.83-6.08, APC=0.80%, P>0.05). A joinpoint was found at the year of 1990 (APC=-2.91%, P<0.01). In contrast, incidence rate

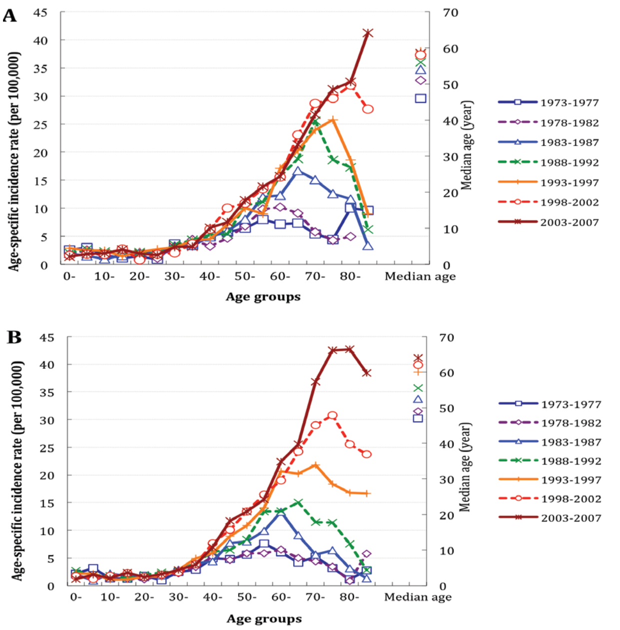

Figure 2. The Age-specific Incidence Rate (per 100,000 population) and Median Age (expressed in years) of the Males (A) and the Females (B) in Urban Shanghai Between 1973 and 2007. During this period, the five-year average incidence rate (left Y axis) increased markedly in the 40-, 50-, 60-, 70- and 80- age groups in both genders. The median age (right Y axis) also increased from 46 to 58.5 in males and 47 to 64 in females

for females remained stable increasing throughout the 35-year period (3.34-6.89, APC=3.16%, $P<0.01$) without any detectable joinpoint. Further analysis of the age-specific incidence rate and patients' median age in urban Shanghai suggested that the driving force behind this increasing trend could be largely attributed to the dramatically increased incidence rates in patients of middle aged (>40 years old), especially the elderly aged (>60 years old), groups (Figure 2). Specifically, the incidence rate of the 40-, 50-, 60-, 70- and 80- age groups increased from 4.94 to 6.5, 6.45 to 11.38, 7.15 to 15.69, 5.43 to 26.69, 10.05 to 32.48 in males and, more evidently, from 4.92 to 6.93, 5.58 to 13.42, 6.01 to 22.38, 5.23 to 36.86, 1.11 to 42.71 in females. In accordance with this soaring incidence rate in the elderly population, the median age (expressed in years) also increased from 46 to 58.5 in males and from 47 to 64 in females.

Five-year status quo: 2003-2007: During this five-year period, a total of 7166 new cases of primary CNS tumors were registered in whole Shanghai city (3174 in males vs. 3992 in females), with 3297 from urban districts (1408 in males vs. 1889 in females), and 3869 from rural areas (1766 in males vs. 2103 in females). At the same period, primary CNS tumors ranked as the 8th most common cancer type (9th in males vs. 7th in females) and accounted for 3.05% of all newly diagnosed cancers (2.48% in males vs. 3.73% in females), with a median age of 59 years old (57 in males vs. 60 in females) and a mortality/incidence ratio of 0.47 (0.58 in males vs. 0.39 in females). During this five-year, the crude incidence rate was 10.58 in whole city (9.33 in males vs. 11.85 in females), 10.67 in urban districts (9.05 in males vs. 12.32 in females) and 10.51 in rural areas (9.56 in males vs. 11.45 in females). After

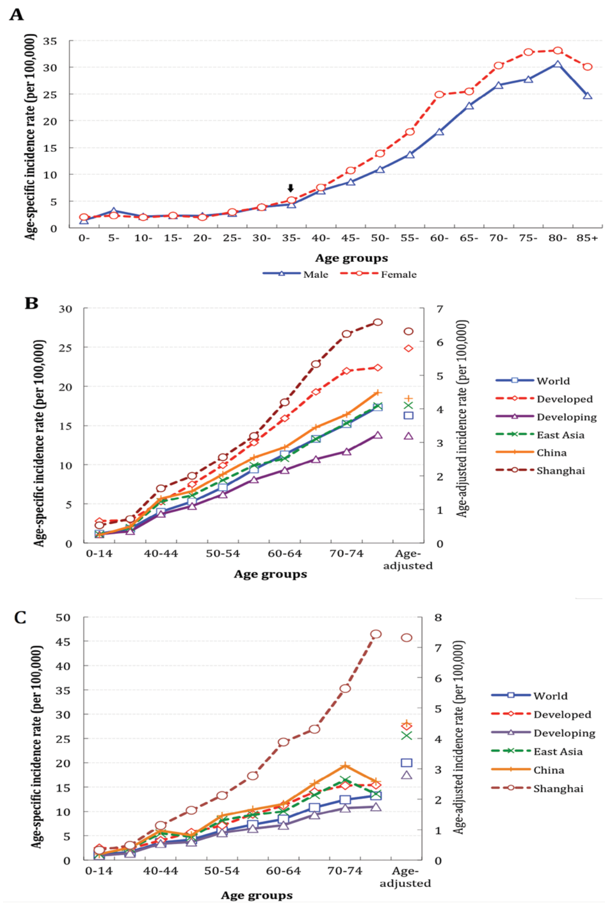

Figure 3. The age-specific incidence rate (per 100,000 population) of primary CNS tumors during 2003-2007 in whole Shanghai city (A) and its transverse comparison, together with age-adjusted incidence rate (per 100,000 population), with that of the China, East Asia, developing countries, developed countries, and World in 2008 (B: in males; C: in females). A: The age-specific incidence rate increased with ages. It became marked higher in females than in males when their ages were over 35 (➡) and reached the peak values in the age group of 80 to 84. Compared with data from GLOBOCAN 2008, in Shanghai, a larger proportion of elderly patients as indicated by age-specific incidence rate (left Y axis) and a higher adjusted incidence rate (right Y axis) were found in males (B) and females (C)

standardization to the 1966 world population, the age-adjusted incidence rate was 6.81 in whole city (6.30 in males vs. 7.31 in females), 6.45 in urban districts (5.88 in males vs. 7.00 in females) and 7.12 in rural areas (6.66 in males vs. 7.57 in females). Moreover, in whole city, the male/female ratio was 0.79 for crude incidence rate (0.73 in urban vs. 0.83 in rural) and 0.86 for age-adjusted incidence rate (0.84 in urban vs. 0.88 in rural). Similarly, for the whole population, the urban/rural ratio was 1.02 for crude incidence rate (0.95 in males vs. 1.08 in females) and 0.91 for age-adjusted incidence rate (0.88 in males vs. 0.92 in females). Statistical analysis revealed females had a significantly higher incidence rate than males (both crude and age-adjusted, $P<0.01$), and rural areas were significantly higher than urban areas in terms of age-adjusted incidence rate ($P<0.01$ or <0.05). However, as for the crude incidence rate of the female population, urban areas were significantly higher than rural areas ($P<0.05$).

From 2003 to 2007, the age-specific incidence rate increased with ages: it was greater than 1.00 ever

Table 2. Population Based Histological Subtyping of Primary Central Nervous System Tumors in Shanghai from 2003 to 2007

Histological subtype	Male		Female		Both genders		M/F*
	No.	%	No.	%	No.	%	
Astrocytic tumors	889	28.01	650	16.28	1539	21.48	1.37
Oligodendroglial tumors	47	1.48	37	0.93	84	1.17	1.27
Ependymal cell tumors	33	1.04	32	0.8	65	0.91	1.03
Tumors of choroid plexus	4	0.13	4	0.1	8	0.11	1
Neuronal and mixed neuronal-glial tumors	6	0.19	7	0.18	13	0.18	0.86
Neuroblastomas	7	0.22	9	0.23	16	0.22	0.78
Embryonal tumors	38	1.2	32	0.8	70	0.98	1.19
Tumors of the meningothelial cells	588	18.53	1561	39.1	2149	29.99	0.38
Tumors of Cranial and Spinal Nerves	315	9.92	301	7.54	616	8.6	1.05
Germ cell tumors	15	0.47	6	0.15	21	0.29	2.5
Chordomas	11	0.35	19	0.48	30	0.42	0.58
Hemangioblastomas	39	1.23	18	0.45	57	0.8	2.17
Others	104	3.28	104	2.61	208	2.9	1
Unknown/Unclassified	1078	33.95	1212	30.35	2290	31.95	0.89
Total	3174	100	3992	100	7166	100	0.8

*M/F= Male/Female ratio (data from Shanghai Municipal Center for Disease Control & Prevention)

Table 3. Single Center Based Histological Subtyping of Primary Central Nervous System Tumors in Patients Treated at the Department of Neurosurgery, Huashan Hospital from 1951 to 2011

Histology/Year	1951-1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Subtotal
Neuroepithelial	6097	470	530	650	655	714	744	765	1041	1050	1151	1174	1289	16330
Meningothelial	4205	411	461	489	564	637	545	690	886	942	1101	1141	1265	13337
Cranial & Spinal Nerves	2658	162	185	208	220	227	192	248	362	409	449	465	469	6254
Mesenchymal	180	30	41	67	115	87	71	101	206	204	196	259	207	1764
Lymphomas & Haematopoietic	266	27	22	32	31	33	34	44	59	52	72	69	73	814
Germ cell	82	15	19	17	41	34	46	34	50	40	57	33	27	495
Subtotal	13488	1115	1258	1463	1626	1732	1632	1882	2604	2697	3026	3141	3330	38994

Data from Department of Neuropathology, Institute of Neurology, Huashan Hospital

since birth (1.39 in males vs. 2.00 in females), became markedly higher in females than in males when ages were over 35 (4.38 in males vs. 5.21 in females) and reached the peak values in the age group of 80 to 84 (30.62 in males vs. 33.13 in females) (Figure 3A). When compared with data from GLOBOCAN 2008 (published by International Agency for Research on Cancer, IARC, http://globocan.iarc.fr/) on the age-specific incidence rate and age-adjusted incidence rate of the World, Developed countries, Developing countries, East Asia and China, we found both males (Figure 3B) and females (Figure 3C) in Shanghai were more likely to be diagnosed with primary CNS tumors [adjusted rate in males: Shanghai (6.3) > Developed countries (5.8) > China (4.3) > East Asia (4.1) > World (3.8) > Developing countries (3.2); adjusted rate in females: Shanghai (7.3) > China (4.5) > Developed countries (4.4) > East Asia (4.1) > World (3.2) > Developing countries (2.8)]. Moreover, as indicated by the slope of the curves (incidence rates plotted against age groups) in Figure 3 B & C, Shanghai population, more prominently in females, was characterized with a larger proportion of elderly patients (>60 years old) when compared with other regions.

Histological subtyping

Shanghai population (2003-2007): Since histological data from Shanghai Municipal CDC (registered by ICD-O histology codes) were available only between 2002 and 2009, the five-year period of 2003 to 2007 was analyzed to keep in accordance with the the aforementioned "five-year status quo" section. Because it is mandatory for local hospitals to report all residents who suffered from brain tumors to CDC, our population based data has, in theory, 100% coverage. The histological verification rate (%) increased from 43.12 to 51.85 in males (1973-1977 vs. 2003-2007, $P<0.01$), and from 48.17 to 49.55 in females (1973-1977 vs. 2003-2007, $P>0.05$). Specifically, the three most commonly diagnosed histological subtypes in Shanghai population during 2003-2007 were tumors of the meningothelial cells (29.99%), neuroepithelial tissue (25.05%: including 21.48% astrocytic tumors, 1.17% oligodendroglial tumors and 0.91% ependymal cell tumors), and cranial and spinal nerves (8.60%) (Table 2). However, a high fraction of 31.95% was "unknown/unclassified" subtypes. In addition, for males, neuroepithelial tumors (32.27%, including 28.01% astrocytic tumors) were more common than meningothelial tumors (18.53%). This was in sharp contrast with females, who manifested a predominance of meningiomas (39.10%) but fewer neuroepithelial tumors (19.32%, including 16.28% astrocytic tumors) (Table 2).

Huashan Hospital (1951-2011): In view of the low

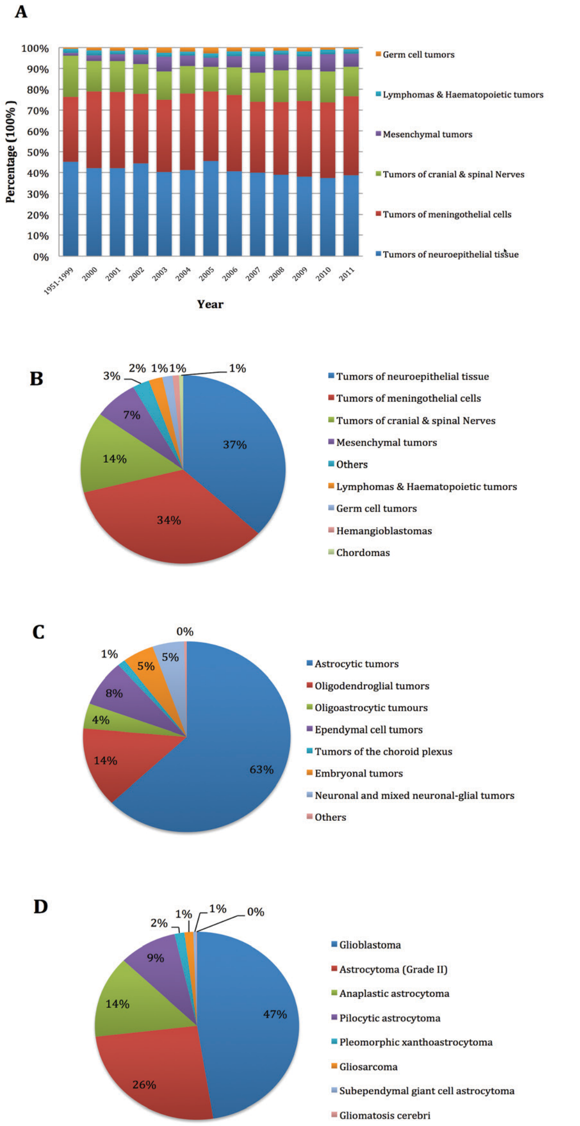

Figure 4. Histological Subtyping of Primary CNS Tumors in Patients Treated at the Department of Neurosurgery, Huashan Hospital for the Past 60 Years (1951-2011) (A) and in the Recent Five Years (2007-2011) (B-D). A: Tumors of neuroepithelial tissue, meningothelial cells, and cranial and spinal nerves were the three most common histological subtypes during the past 60 years. B: In the recent five years, 36.86% were tumors of neuroepithelial tissue, 34.20% were tumors of meningothelial cells, and 13.92% were tumors of cranial and spinal nerves. C: 62.86% of the neuroepithelial tumors were astrocytic, 13.53% were oligodendroglial and 7.86% were of ependymal cell. D: Astrocytic tumors were composed of 47.44% glioblastoma, 25.69% diffuse astrocytoma, 14.10% anaplastic astrocytoma, and 9.22% pilocytic astrocytoma

histological verification rate (>30% were unclassified) and short time period (available between 2002 and 2009) of the population based data, we then attempted to gain more precise histological information by employing neuropathological data (1951-2011, with 100% histological verification rate) from Huashan Hospital, whose neurosurgical department is the largest center in Asia-Pacific (Shi et al., 2012). Patients in Shanghai are generally referred to Huashan Hospital for neurosurgical operations (Wang et al., 2008). According to this single center based data, a total of 38994 cases of patients received surgical resection or biopsy for primary CNS tumors during 1951-2011. Neuroepithelial tumors (16330 cases, 41.13±2.68%), meningothelial tumors (13337 cases, 35.33±1.92%), and tumors of cranial and spinal nerves (6254 cases, 14.43±1.84%) were the three most common histological subtypes during the past 60 years (Table 3, Figure 4A). Moreover, within the past 10 years (2000-2011), the annual patients' number increased markedly from 1115 to 3330 (470 to 1289 for neuroepithelial tumors, 411 to 1265 for meningothelial tumors, and 162 to 469 for tumors of cranial and spinal nerves) (Table 3). Compared with the 60-year period, the percentage of neuroepithelial tumors decreased to 36.86% in the recent five years (2007-2011), while that of the meningothelial tumors (34.20%) and tumors of the cranial and spinal nerves (13.92%) remained relatively stable (Figure 4B). Unlike the population data that only use ICD-O histology codes, the WHO classification system adopted by the hospital allowed for more detailed subtyping of the tumors. Specifically, from 2007 to 2011, 62.86% of the neuroepithelial tumors were astrocytic, 13.53% were oligodendroglial and 7.86% were of ependymal cell (Figure 4C). In addition, astrocytic tumors were composed of 47.44% glioblastoma (GBM, WHO grade IV), 25.69% diffuse astrocytoma (WHO grade II), 14.10% anaplastic astrocytoma (WHO grade III), and 9.22% pilocytic astrocytoma (WHO grade I) (Figure 4D).

Discussion

Because Shanghai has many national top-level medical hospitals and medical insurance for urban residents in Shanghai only covered the cost for Shanghai hospitals, patients prefer to be diagnosed and receive neurological surgery locally. And it is mandatory for local hospitals to report all residents who suffered from brain tumors to CDC. Generally speaking, a steadily increasing trend was observed between 1973 and 2007 for both genders, which seemed to be driven mainly by escalating incidence rate in patients of the middle and elderly aged groups. Specifically, females surpassed males in terms of increasing trend since 1990s, and, at present (2003-2007), had a higher incidence rate and median age than males, but with lower M/I ratio. Besides, rural areas had a higher age-adjusted incidence rate than urban areas, while, for females, urban areas had a higher crude incidence rate. Moreover, residents in Shanghai were more likely to be diagnosed with primary CNS tumors when compared with population of the World, Developed countries, Developing countries, East Asia and China. Histological data from both the population (2003-2007) and Huashan Hospital (1951-2011) further revealed tumors of neuroepithelial tissue and meningothelial cells were the two most common histological entities, with male predominance in the former and female predominance in the latter. To our knowledge, this is the single largest and most comprehensive report on the incidence and histological subtypes of primary CNS tumors in Shanghai.

Shanghai Cancer Registry was the first established cancer registry in China. Until today, there is still not much report on the incidence of primary CNS tumor in both China and Shanghai. The first study in China was published in 1982 (Cheng, 1982) and a recent study (Ding and Wang, 2011) showed the age-adjusted incidence rate of brain tumors in urban Shanghai increased from 3.7 to 6.1 in males and 2.9 to 6.9 in females (1983-2007). But this latter report simply collected data from "Shanghai Cancer Report", which is published by Shanghai Municipal CDC annually, and lacks information on the whole city and histological subtypes. Another study (Jiang et al., 2011) reported the prevalence rate for primary brain tumors to be 24.56 per 100,000 in five cities of China (including Shanghai) in the year of 2006. However, in that study, the representative region for Shanghai is Baoshan district, which belongs to the rural part of Shanghai, and patients there have a strong tendency to be referred to Huashan hospital, which is located at the urban district, for diagnosis and surgery. Therefore, our present study incorporates the epidemiological data from both the urban and rural districts and may depict a more "actual" picture of the incidence rate in Shanghai.

The remarkably much higher incidence of CNS tumors reported in North America (Zada et al., 2012) and Europe (Caldarella et al., 2011) when compared with that of Asian (Jiang et al., 2011; Manoharan et al., 2012) and African countries (Olasode et al., 2000; Afolayan, 2004; Zalata et al., 2011) may be related to factors including, but not limited to, ethnic, genetic, and epigenetic backgrounds. For instance, improvements in modern medical care system, availability of advanced diagnostic facilities, and even the quality control for the practices of caner data registration would influence the "observed" incidence rate (Ohgaki, 2009; Shin et al., 2010). In this present study, we have identified a steady increase in the age-adjusted incidence rate of primary CNS tumors in both males and females in urban Shanghai (1973-2007). Within these 35 years, Shanghai has underwent a dramatic socioeconomic development. Economic boost is also accompanied by dramatic demographic changes. For example, the life expectancy of Shanghai residents in 2011 reached 82.51 years (80.23 for men and 84.80 for women), the highest in mainland China and higher than all but a few countries in the world (City setting records as life expectancy tops 82, http://www.shanghaidaily.com/). Economic prosperity also markedly facilitated the availability of modern medical facilities for Shanghai local residents.

In addition to improvements in life expectancy, availability of advanced diagnostic facilities, and cancer registration practice et al, the increased incidence in Shanghai may also be related to more exposure to risk factors that come along with economic growth, i.e. low frequency electromagnetic fields emitted from mobile phones (Repacholi et al., 2012), bacterial or virus infections (Davis, 2007), and various environmental pollutants (Wrensch et al., 2002). A recent study analyzed the survival of patients after glioma diagnosis in relation to the use of wireless phones and found decreased survival of glioma cases with long-term and high cumulative use of wireless phones (Hardell and Carlberg, 2013). Shanghai was among the first to adopt the use of mobile phones in China (since 1982), and cordless communication has increased rapidly since 1990s and gradually overtaken telephones connected to landlines. By May 2012, an estimate of 20 million mobile phone subscriptions has been reported in Shanghai (http://newspaper.jfdaily.com/). Concerns over adverse health effects have been increasingly discussed with the expansion of this technology. For instance, on 31 May 2011, The WHO/IARC has classified radiofrequency electromagnetic fields as possibly carcinogenic to humans (Group 2B), based on an increased risk for glioma associated with wireless phone use (http://www.iarc.fr/). However, since the only established risk factor for brain tumors is ionizing radiation exposure, more evidences were needed to establish the relationship between exposure to microwaves emitted from mobile phones and development of brain tumors.

We also attempted to make a transverse comparison of Shanghai five-year status quo (2003-2007) with that of the World, Developed countries, Developing countries, East Asia and China in 2008. Surprisingly, we found both genders in Shanghai are more likely to be diagnosed with primary CNS tumors when compared with their counterparts in other regions. Besides, residents in Shanghai, especially for females, were featured by a larger proportion of senior patients than other regions. Why females surpassed males in both incidence rate and median age might be explained by the longevity of the women and the fact that elderly population are at a much higher risk of developing cancer. And the difference in histological subtype distribution between the two genders might also explain why men had a higher M/I ratio than women. For example, population data from CDC showed females were more likely to be afflicted with meningioma, which are mostly benign and curable, than males, while males were more likely to have gliomas, which are largely malignant and incurable.

Although this identification of female predominance of meningioma and male predominance of astrocytic tumors from the population data was in accordance with previous report (Wang et al., 2013), the observed higher percentage of meningiomas than gliomas was inconsistent with previous literatures (Kleihues et al., 1993). We think this might be caused by the relatively low histological verification rate of the population data. This high fraction of "unknown/unclassified" tumors (31.95%) were largely diagnosed on the basis of clinical investigation and, therefore, making it impossible to accurately calculate the incidence rate or analyze the trend for each histological subtypes. Besides, population based histological data were only available between 2002 and 2009. Therefore, in an attempt to complement the population data, we then adopted neuropathological data from Huashan Hospital (with 100% histological verification rate) as an alternative source for histological subtyping. Because the neurosurgical department of Huashan Hospital is one of the largest neurosurgery centers in the world (Shi et al., 2012), Shanghai residents who suffered from brain tumors were generally referred to Huashan Hospital for diagnosis and surgery. In contrast with the population data, we found this center treated more neuroepithelial tumors than meningiomas over the past 60 years. Moreover, during the past five years (2007-

2011), neuroepithelial tumors were mostly astrocytic (half of them were GBM), followed by oligodendroglial and ependymal tumors. These single center based data were generally in accordance with previous report (Ohgaki and Kleihues, 2005), which showed gliomas of astrocytic, oligodendroglial, and ependymal origin account for more than 70% of all primary brain tumors, and GBM accounts for approximately 65% of all gliomas. To our knowledge, this is the first report providing such a detailed profiling on the histological subtypes of primary CNS tumors in patients from Shanghai and Huashan Hospital. In addition, the number of patients diagnosed with gliomas and meningiomas increased steadily from 1951 to 2011. This increasing trend might result from higher detection rate for asymptomatic gliomas and meningiomas through more frequent use of CT and MRI, as well as the expansion of the elderly population who are at the highest risk of developing brain tumors (Arora et al., 2010).

Because this present report is not an etiological epidemiologic study, it is beyond our goal to provide any concrete explanation for the observed increases in tumor incidence. Nevertheless, the incidence patterns and trends presented here might provide indications or clues for future epidemiologic studies. These future epidemiologic studies (either case-control or cohort studies) could investigate the possible etiology and mechanisms underlying the changes in trend and distribution patterns. In addition, this study also harbored several limitations. For example, due to drawbacks such as incomplete ICD-O coding and low histological verification rate in the population data, especially in early years, it was only possible, and also appropriate, to report percentages, instead of incidence rates, for Shanghai population, making direct comparisons to other reports difficult. Besides, though our single center data is quite valuable, we could not ensure the representativeness of the hospital based data for the population and deny the existence of diagnostic/referral bias. For example, difficult cases, such as glioma located within eloquent brain regions, meningioma at the skull base, or schwannoma at the cerebellopontile angle, are more likely to be referred to our hospital for surgery, while children with brain tumors would be suggested to be treated at specialized pediatric hospitals.

In conclusion,we presented evidences of an overall increasing incidence of primary CNS tumors over the past 35 years in Shanghai residents. The strength of this paper is the coverage of such a long time period and use of multiple sources to gain insight into histological subtypes. Improved life expectancy, better medical services and cancer registration practices, and more frequent exposure to potential risk factors may all contribute to the observed increases in incidence rate. Future epidemiologic studies are needed to investigate the underlying reasons for the changes in rate trend or pattern and examine the etiology (e.g. environments, genetics, gene-environment interactions).

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