

## Mortality of Brain Tumors During Childhood in Japan

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### ABSTRACT

**BACKGROUND:** In general, the leading cause of death due to malignant neoplasms during childhood is leukemia. The next one is brain tumors. In Japan, this situation has continued for a long time. Recently, however, it is changing, with a decrease in the mortality rate of leukemia and increase in that of brain tumors.

**METHODS:** Data on neoplasms of the brain in 5-year age categories were obtained from the 1960 to 2013 vital statistics of Japan (e.g., C71 in ICD 10). The data for subcodes from C71.0 to C71.9, which indicate the original site, and the data on leukemia were employed as well. Populations and the number of live births were obtained from the census and vital statistics of Japan.

**RESULTS:** (1) Mortality rate: Not only the age-adjusted mortality rate of brain tumors for all ages but also each of the crude mortality rates at 0-4, 5-9 and 10-14 years of age has been increasing. (2) Site of the tumors: The correlation coefficient between the crude mortality rate of tumors in the brain stem and the year was significantly positive (0.751). That of tumors in the cerebral ventricles was also significantly positive (0.534). However, that for tumors in the cerebellum was negative (-0.448). (3) Mortality rate by birth cohorts: The crude mortality rate by birth cohorts at 0-4 years of age as a whole has been increasing since 1960. (4) Comparison with leukemia: At 0-14 years of age the crude mortality rate for brain tumors has been higher than for lymphoid and myeloid leukemia since 1999 and 1990, respectively.

**CONCLUSION:** In Japan, the age-adjusted mortality rate of brain tumors and the crude mortality rates during childhood have been increasing, though the causes remain unidentified. Their incidence

may be increasing. The recent increase in the crude mortality rate of brain tumors during childhood cannot be explained by the progress in diagnostic methods, the use of a mobile phone or parental smoking. It is speculated that the incidences of pontine glioma and ependymoma are increasing. The leading cause of death at 0-14 years, as well as at 0-9 years of age, will be brain tumors in the near future.

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**Key words:** Brain tumor; Children; Epidemiology; Mortality; Vital statistics

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### INTRODUCTION

In Japan, the frequency of adulthood cancers has greatly changed according to changes in lifestyle, including eating habits<sup>[1]</sup>. The influence of the changes in the lifestyle may not be so large on the occurrence of childhood cancer, but due to the contributions of other factors its incidence and mortality rate may change.

In general, the primary cause of death due to malignant neoplasms during childhood is leukemia. The second leading cause is brain tumors. This situation has continued in Japan for a long time. Recently, however, it is changing, along with a decrease in the mortality rate of leukemia and increase in that of brain tumors.

In this article, the changes in the mortality rate of brain tumors and related matters are described from the viewpoint of descriptive epidemiology.

### METHODS

Data on neoplasms of the brain from 1960 to 2013 in 5-year age categories were obtained from the vital statistics of Japan. The codes 193a (ICD 7), 191 (ICD 8-9) and C71 (ICD 10) stand for neoplasms of the brain.

Malignant neoplasms of the cerebral meninges, olfactory nerve, optic nerve, acoustic nerve, pituitary gland, craniopharyngeal duct

and pineal gland are classified by subcodes (in the ICD10, e.g., C70.0, C72.2, C72.3, C72.4, C75.1, C75.2 and C75.3, respectively). Since the data of subcodes in 5-year age categories began to be published in 1999, and there were few children who died of neoplasms of these sites, the data on tumors in these sites were not employed. (From 1999 to 2013, the total number of deaths due to malignant neoplasms of these sites was 43, i.e., 2.87 cases per year on average.)

The data of the subcodes from C71.0 to C71.9 (Table 1), which indicate the original sites in the brain from 1999 to 2013 were employed as well.

To compare the mortality rate of brain tumors with that of leukemia, data for leukemia were obtained from 1960 to 2013. The codes B18e (ICD 7), B19h (ICD 8), 36 (ICD 9) and 02119 (ICD 10) stand for leukemia. Data concerning lymphoid leukemia (204 in ICD 8-9 and C91 in ICD 10) and myeloid leukemia (205 in ICD 8-9 and C92 in ICD 10) are available for the period from 1968 to 2013.

Population statistics and the number of live births were obtained from the census and vital statistics data of Japan.

For the statistical test of correlation coefficients (Pearson), t-distribution was employed.

**Table 1** Subcodes of C71.

Subcode	Site
C71.0	Cerebrum, except lobes and ventricles
C71.1	Frontal lobe
C71.2	Temporal lobe
C71.3	Parietal lobe
C71.4	Occipital lobe
C71.5	Cerebral ventricle (excl. fourth ventricle)
C71.6	Cerebellum
C71.7	Brain stem, fourth ventricle
C71.8	Overlapping lesion of brain
C71.9	Brain, unspecified

## RESULTS

### Age-adjusted mortality rate of brain tumors for all ages

To calculate the age-adjusted mortality rate from 1960 to 2013, the model population in 1985 in Japan (0-4, 5-9, 10-14, etc., to 80-84 and 85 years of age or older) was employed. Figure 1 shows the age-adjusted mortality rate of brain tumors. It has been increasing.

### Mortality rates of brain tumors of children

In 2013, for children aged 0-14 years, there were a total of 84 deaths due to neoplasms of the brain (C71).

**Mortality rates at 0-4, 5-9 and 10-14 years of age:** Figure 2 shows the crude mortality rates ("mortality rate" in this article) of brain tumors at 0-4, 5-9 and 10-14 years of age. In all 3 of these age groups, the mortality rate has been increasing. The correlation coefficients between the mortality rate and the year were 0.781 ( $P<0.05$ ), 0.828 ( $P<0.05$ ) and 0.798 ( $P<0.05$ ), respectively.

**Mortality rate by original site:** Table 2 shows the correlation coefficients between the mortality rate and the year from 1999 to 2013. The correlation coefficient of the tumors in the brain stem was significantly positive (0.751; Figure 3). That of the tumors in the cerebral ventricles was also significantly positive (0.534), but that of the tumors in the cerebellum was negative (-0.448; Figure 3).

**Mortality rates by birth cohorts at 0-4 years of age:** Every year the Japanese Government publishes the numbers of deaths at the ages of 0, 1, 2, 3, 4, 5-9, 10-14, etc., up to 95-99, and 100 years of age or older. Using these data, birth cohorts can be made. For example,

those who died at 0 years of age in 2000, at 1 year of age in 2001, at 2 years of age in 2002, at 3 years of age in 2003, and at 4 years of age in 2004 belonged to a birth cohort whose birth year was 1999 or 2000. (In figure 4, the year of this cohort is indicated as "1999".) The number of live births in this cohort was estimated to be "the number of live births in 1999 $\times$ 0.5 + that in 2000 $\times$ 0.5". Using the numbers of deaths and live births, mortality rates (per 100,000 live births) were calculated (Figure 4).

Though the mortality rate had a tendency to decrease from 1993 to 2004, it has been increasing as a whole since 1960. Its correlation coefficient was 0.762 ( $P<0.05$ ).

**Number of CT scanners per 1,000,000 population:** The increased use of CT scanners is reported to have led to an increase of brain tumors diagnosed<sup>[2]</sup>. Figure 5 shows the number of CT scanners per 1,000,000 population in Japan. It has been increasing continuously. (<http://www.oecd.org/els/health-systems/OECD-Health-Statistics-2014-Frequently-Requested-Data.xls>)

**Comparison with leukemia:** In 2013, the mortality rate for all types of leukemia was still higher than that of brain tumors at 0-14 years of age. However, when we compare the mortality rate of brain tumors with those of lymphoid leukemia and myeloid leukemia separately, the mortality rate of brain tumors is higher than for each of the two kinds of leukemia now. Figure 6 shows the mortality rates of lymphoid and myeloid leukemia, and brain tumors at 0-14 years of age. The mortality rate of brain tumors has been higher than those for lymphoid and myeloid leukemia since 2004 and 1994, respectively.

Figure 7 shows the mortality rates of leukemia and brain tumors at 0-9 years of age. In 2011, the mortality rate per 100,000 of leukemia was 0.458 and that of brain tumors was 0.486. In that year brain tumors were the leading cause of deaths due to malignant neoplasms at 0-9 years of age in Japan.

**Table 2** Correlation coefficients of subcodes (mortality rate vs year).

Subcode	Correlation coefficient
C71.0-71.4 (Cerebrum)	0.239
C71.5	0.534 <sup>1</sup>
C71.6	-0.448
C71.7	0.751 <sup>1</sup>
C71.8	-0.325
C71.9	0.405

<sup>1</sup>  $P<0.05$ .

## DISCUSSION

In Japan, not only the age-adjusted mortality rate for all ages but also the mortality rate of children with brain tumors has been increasing. The increases in both the mortality rate of children and the age-adjusted mortality rate in the 1980s might be partly accounted for by the increased use of CT scanners, since in the 1960s and 1970s, CT scanners were rarely used. However, the mortality rate for brain tumors of the cerebellum at 0-14 years of age had a tendency to decrease from 1999 to 2013, though in this period CT scanners continued to be more widely used. The survival rate of patients with medulloblastoma, which is one of the representative tumors in the cerebellum, is increasing, but has not dramatically improved<sup>[3]</sup>. During the period from 1991 through 2002, the 5-year survival rate of those aged 0-14 years who had the disease did not largely change<sup>[4]</sup>. Consequently, the decrease in the mortality rate during this period was not due to the progress in therapeutic methods, but rather to a decrease in its incidence. If the increased use of CT scanners led to an increase in detection, and thus the incidence of the disease, the mortality rate would increase, as well. Therefore, as far as the recent

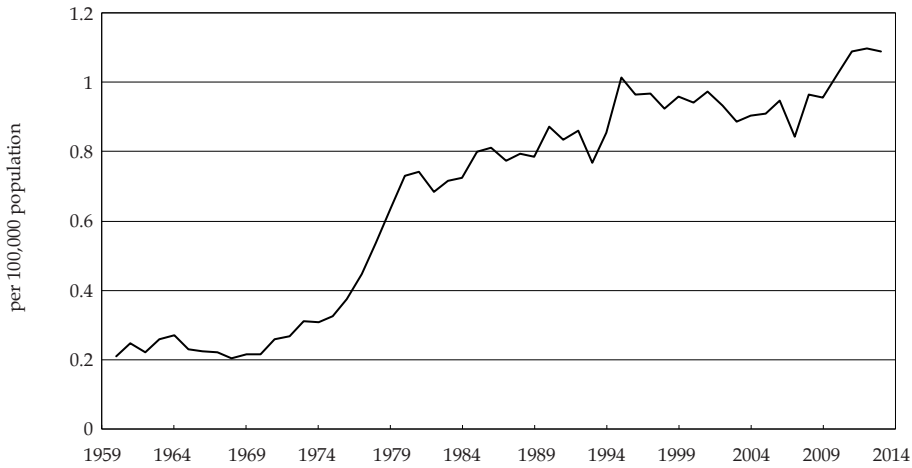


Figure 1 Age-adjusted mortality rates of brain tumors in Japan (for all ages).

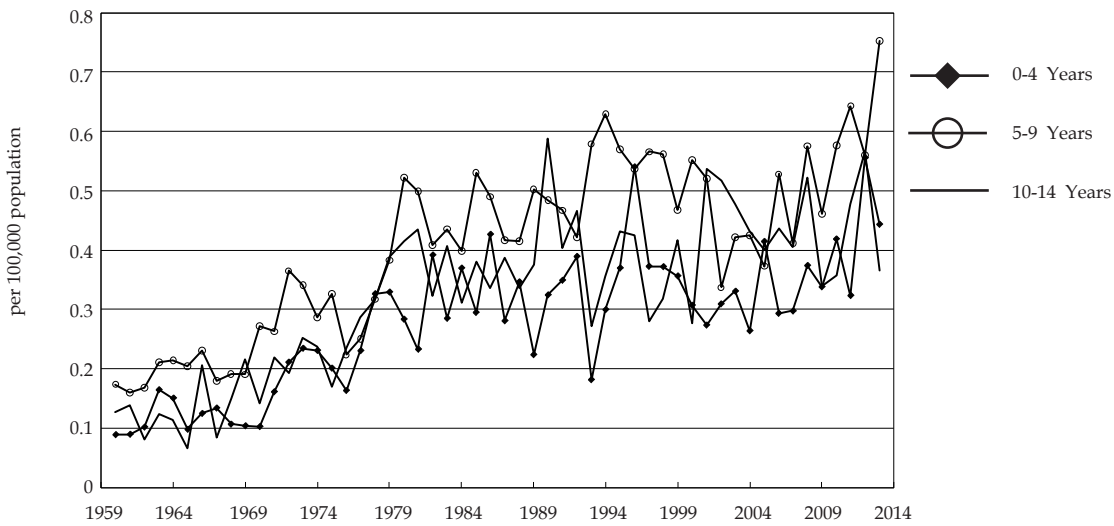


Figure 2 Mortality rates of brain tumors during childhood in Japan.

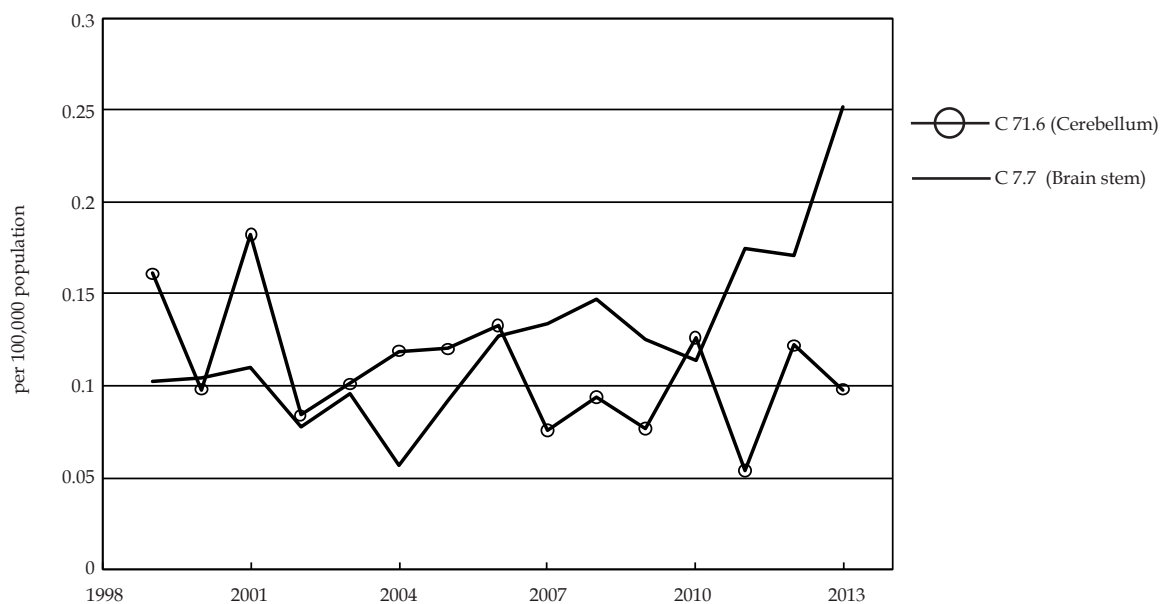


Figure 3 Mortality rates of brain tumors (subcodes C71.6 and C71.7) at 0-14 years of age.

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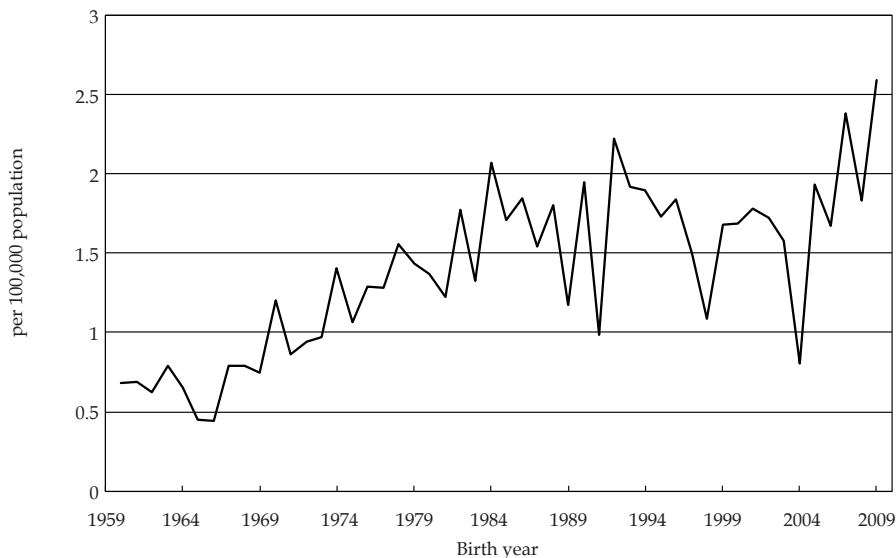


Figure 4 Mortality rates of brain tumors by birth (0-4 years of age).

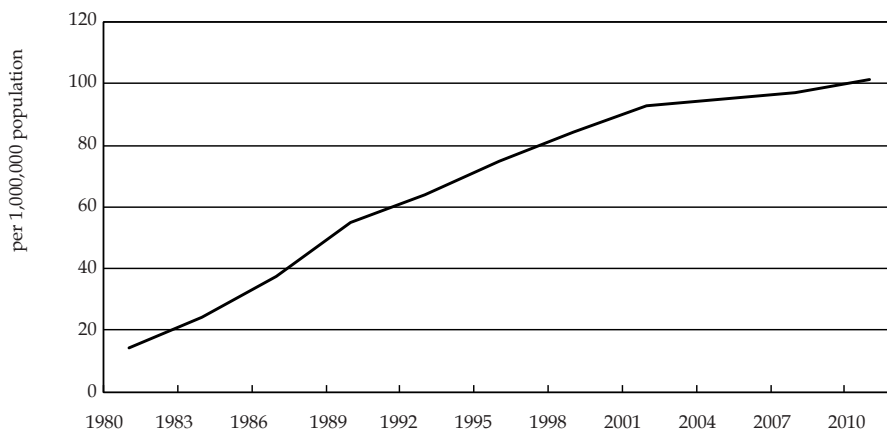


Figure 5 Numbers of CT scanners in Japan.

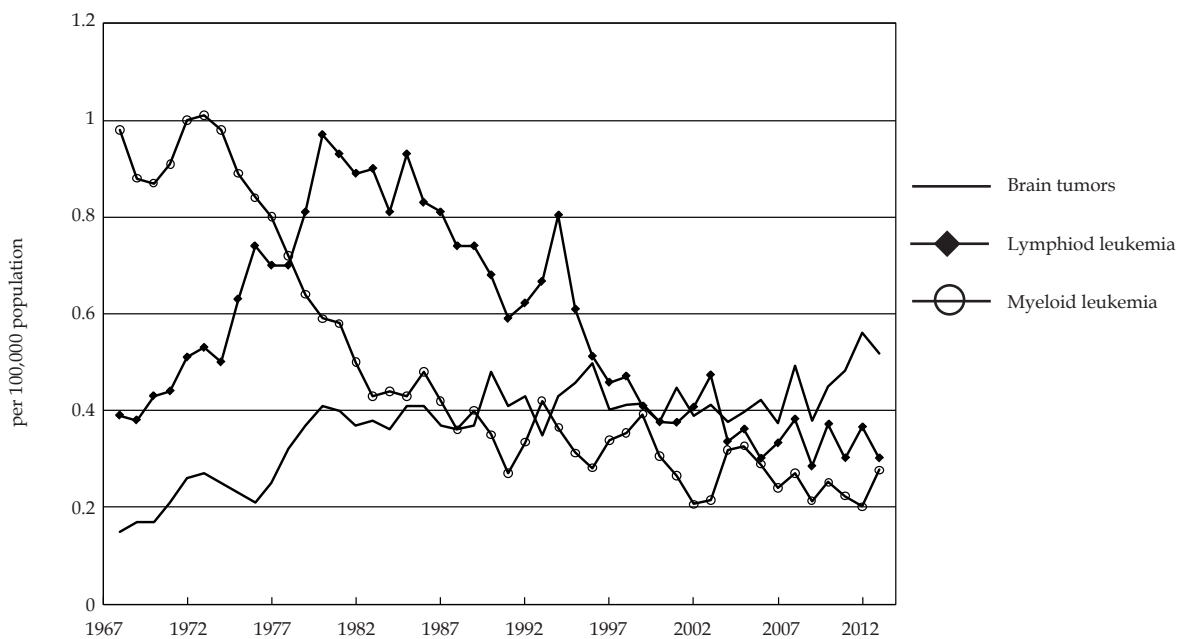


Figure 6 Mortality rates of brain tumors, lymphoid and myeloid leukemia at 0-14 years of age.

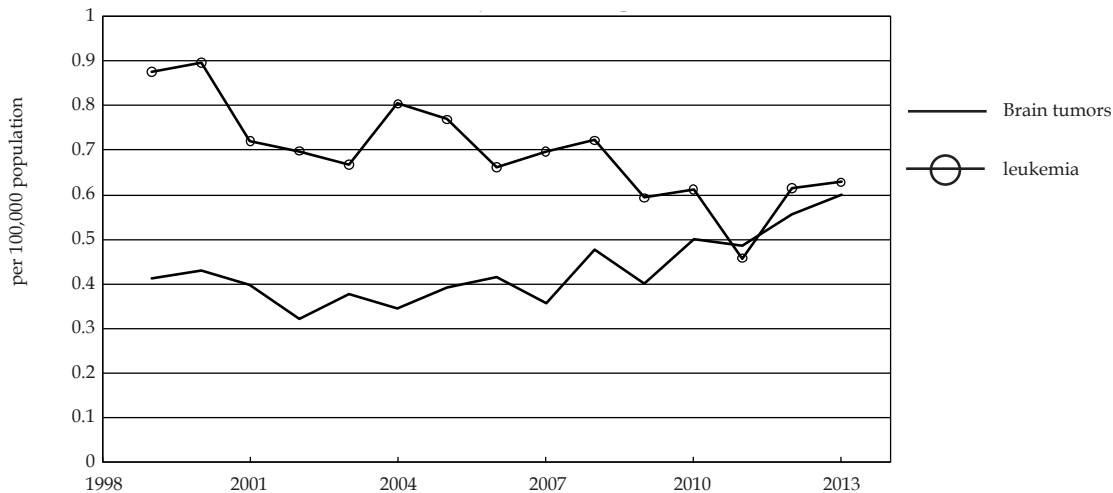


Figure 7 Mortality rates of brain tumors and leukemia at 0-9 years of age.

increase in the mortality rate of brain tumors at 0-14 years of age is concerned, the contribution of the increased use of CT scanners is small. As written in a previous article<sup>[5]</sup>, mass screening for a disease in the preclinical stage may increase the incidence of the disease through detection of silent tumors. However, CT has hardly been used for the purpose of screening for brain tumors in Japan. The use of CT might even decrease the incidence of "brain tumors" that are in fact non-cancerous diseases (e.g., brain abscesses and hemangioma).

Since there are no reliable nationwide registries of brain tumors in Japan, their precise incidence is not known. The coverage rate of the Brain Tumor Registry of Japan (BTRJ) is only about 30-40%<sup>[6]</sup>. The increase in the mortality rate is not accounted for by the increase in the cases diagnosed through the progress in diagnostic methods, but is explained by an increase in incidence.

From the present data, the pathological frequency of tumors cannot be determined, but many tumors whose original site is the brain stem during childhood are "pontine glioma". Since this tumor has one of the worst prognoses<sup>[7]</sup>, its incidence and mortality rate are almost parallel. Therefore, it is speculated that the incidence of this tumor is increasing. Similarly, since the mortality rate for the tumors of C71.5 (cerebral ventricle) is increasing, it is possible that the incidence of ependymoma is also increasing.

There is an interval from the diagnosis of a brain tumor to death. Progress in therapeutic methods prolongs the survival period and, as a result, the age at death becomes older. From 1993 to 2004, the mortality rate at 0-4 years of age in the birth cohorts decreased, which might be a result of a prolongation in the survival rate.

The leading cause of deaths due to malignant neoplasms at 0-14 years of age was, for a long time, leukemia. At 0-9 years of age, too, it was leukemia. However, in 2011, brain tumors were the leading cause, though in 2012 and 2013, leukemia again became the primary cause. The mortality rate of leukemia has been decreasing. If the mortality rate of brain tumors continues to increase, the leading causes at 0-14 and at 0-9 years of age will be brain tumors in the near future.

The etiology of brain tumors is still unknown. Microwaves are one possible cause, but the INTERPHONE study concluded that their contribution was small<sup>[8,9]</sup>. In Japan, the mortality rate of children with brain tumors at 0-4 years of age has been increasing both longitudinally and cross-sectionally. Since children of these ages do not use mobile phones, they have nothing to do with their brain tumors. In any case, considering the latent period of brain tumors

from their occurrence to the appearance of clinical symptoms, the contribution of the use of mobile phones would be small for the brain tumors occurring at the ages of 14 years or younger.

According to previous studies, parents' smoking is related to the occurrence of children's brain tumors, but its influence is, in general, not so large<sup>[10-14]</sup>. In Japan, the smoking rates of both males and females have been decreasing almost continuously since 1966<sup>[1]</sup>. If smoking made a large contribution to the occurrence of children's brain tumors, their incidence and mortality rate should have decreased.

Thus, in Japan, the age-adjusted mortality rate of brain tumors and the crude mortality rates during childhood have been increasing, though the causes remain unidentified. Their incidence may be increasing. In Japan, women's age at their first marriage and their first delivery has been increasing<sup>[1]</sup>. At the same time, the number of siblings is becoming smaller, which may lead to a decrease in the occasion of contracting infectious diseases. Such changes might have something to do with the increase in the incidence and mortality rate of brain tumors.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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