

Time Trend in Incidence of Malignant Neoplasms of the Central Nervous System in Relation to Mobile Phone Use Among Young People in Japan

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The aim of this study was to examine whether incidence of malignant neoplasms of the central nervous system from 1993 to 2010 has increased among young people in Japan, and whether the increase could be explained by increase in mobile phone use. Joinpoint regression analysis of incidence data was performed. Subsequently, the expected incidence rate was calculated assuming that the relative risk was 1.4 for those who used mobile phones more than 1640 h cumulatively. Annual percent change was 3.9% (95% confidence interval [CI], 1.6–6.3) for men in their 20s from 1993 to 2010, 12.3% (95% CI, 3.3–22.1) for women in their 20s from 2002 to 2010, 2.7% (95% CI, 1.3–4.1) for men in their 30s from 1993 to 2010, and 3.0% (95% CI, 1.4–4.7) for women in their 30s from 1993 to 2010. Change in incidence rates from 1993 to 2010 was 0.92 per 100,000 people for men in their 20s, 0.83 for women in their 20s, 0.89 for men in their 30s, and 0.74 for women in their 30s. Change in expected incidence rates from 1993 to 2010 was 0.08 per 100,000 people for men in their 20s, 0.03 for women in their 20s, 0.15 for men in their 30s, and 0.05 for women in their 30s. Patterns in sex-, age-, and period-specific incidence increases are inconsistent with sex-, age-, and period-specific prevalence trends, suggesting the overall incidence increase cannot be explained by heavy mobile phone use. *Bioelectromagnetics*. 37:282–289, 2016. © 2016 Wiley Periodicals, Inc.

Keywords: epidemiology; ecological study; cell phone; brain tumor; correlation

INTRODUCTION

Mobile phone use in Japan started in 1979 with an automobile telephone system [NTT docomo, 2014]. A compact-sized mobile phone (about 250 g) was first introduced around 1990, followed by the start of digital mobile phone service in 1993. After a major price cut on initial costs and usage fees in 1994, mobile phone use began to spread throughout Japan. The number of mobile phone subscribers in Japan was 8 million in 1996, 54 million in 2000, 90 million in 2005, 115 million in 2010, and 137 million at the end of January 2014, with one or more phones per capita [Telecommunications Carriers Association Japan, 2014].

Almost 20 years have passed since the spread of mobile phone use throughout Japan, and epidemiological studies attempting to reveal the relationship between mobile phone use and brain tumors are proceeding. Several studies on mobile phone use and brain tumors have been published in Japan [Takebayashi et al., 2006, 2008; Sato et al., 2011]. The INTERPHONE study, coordinated by the International

Agency for Research on Cancer (IARC), is the biggest epidemiological study of mobile phone use [Cardis et al., 2007; INTERPHONE Study Group, 2010, 2011]. This study is an international cooperative case-control study of 13 countries, including Japan. In the analysis of brain tumors, odds ratio for mobile phone use was 0.81 (95% confidence interval [CI], 0.70–0.94)

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for glioma, and 0.79 (95% CI, 0.68–0.91) for meningioma. However, in the 10th decile of cumulative call time (≥ 1640 h), odds ratio was 1.40 (95% CI, 1.03–1.89) for glioma, and 1.15 (95% CI, 0.81–1.62) for meningioma.

In 2011, IARC of the World Health Organization (WHO) published a carcinogenicity evaluation of radiofrequency electromagnetic fields (RF-EMF) [Baan et al., 2011; IARC, 2013]. This report stated that there is limited epidemiological evidence showing that RF-EMF increase the risk of developing glioma or acoustic neuroma, and that there is also limited evidence in laboratory animal studies. Herewith, IARC classified RF-EMF as “possibly carcinogenic to humans” (Group 2B). This result indicates that there is a need for additional epidemiological evidence on biological effects of mobile phone use.

Mobile phone use spread throughout Japan in the 1990s and 2000s, and devices became a highly popular method of communication among people aged 10–39 [Ministry of Internal Affairs and Communications, Japan, 2015]. If mobile phone use increases the risk of brain tumors, then incidence of brain tumors may have increased in these age groups over the last 20 years.

The aim of the present study was to analyze the time trend of the incidence rate of malignant neoplasms of the central nervous system among young people (aged 10–39 years) in Japan in association with the increasing trend of mobile phone use in this age group. Although such an analysis cannot determine if there is a causal relationship, results may suggest a direction for future research.

MATERIALS AND METHODS

Data

For incidence data on malignant neoplasms of the central nervous system in Japan, we used data from a nationwide estimation of cancer incidence by regional cancer registries [Matsuda et al., 2014; National Cancer Center Japan, 2014]. Target age groups were people aged 10–39. Incidence data from 1993 to 2010 were analyzed, since mobile phone use increased substantially during this period. Target diseases were categorized in the 9th revision of international classification of disease (ICD-9) codes 191–192 from 1993 to 1994, and the 10th revision of international classification of disease (ICD-10) codes C70–C72 from 1995 to 2010.

We extracted data on mobile phone usage from a cohort that we established using a nationwide Internet

survey for mobile phone use. We developed an epidemiological survey system where data are uploaded by participants via the Internet. Using this system, we registered participants, and conducted baseline and follow-up surveys on the website. Survey participants were people born before 2005 (≥ 6 years old in 2012). Legal guardians completed the survey for elementary and junior high school students, while high school students and older participants completed the survey themselves. Participants were recruited by distributing leaflets with a description of the survey at elementary schools, junior high schools, high schools, universities, and colleges across Japan. Participants accessed the survey website via personal computer or mobile phone. This cohort was operated as an open cohort. Participant registration and the baseline survey were conducted continuously between July 2008 and December 2012, and follow-up continued until March 2013. This cohort study was carried out with approval of the Ethics Committee of Tokyo Women's Medical University (Japan). Informed consent from study participants or legal guardians was obtained at the time of registration for the survey.

Number of participants in this cohort was 7,550. In the present study, we used sex, date of birth, year starting mobile phone use, average number of calls per day, average duration of one call, and last reply date from this cohort.

Analysis

According to results from the INTERPHONE study, there is no increase in risk by the 9th decile of cumulative call time; whereas, an increase in risk was observed in the 10th decile for the use of mobile phones for more than 1640 h cumulatively. In the present study, we assumed that relative risk of malignant neoplasms of the central nervous system was 1.4 for those who used mobile phones more than 1640 h cumulatively. Duration of mobile phone use is not a risk factor for malignant neoplasms of the central nervous system, but we used this index as a proxy of RF-EMF exposure.

First, we carried out a joinpoint regression analysis of incidence data of malignant neoplasms of the central nervous system using the Joinpoint Regression Program (version 4.0.4) of the National Cancer Institute [Kim et al., 2000; National Cancer Institute, 2014]. We performed the analysis by sex and 10-year age groups. Ages were adjusted using the 1985 model population in Japan with the software's age adjustment function.

Second, we calculated the proportion of users who used mobile phones 1640 h or more cumulatively. We calculated the average call time using

average number of calls per day and the average duration of one call. In each year for each age group from 1990 to 2010, the person who did not use a mobile phone was given a score of 0, and the person who used a mobile phone was given a cumulative call time up to that point. We subsequently calculated the proportion of those who had used mobile phones for calling more than 1640 h by sex and 10-year age groups. Ages were adjusted so that the population of each 1-year age category was equal in 10-year age groups.

Third, we calculated expected incidence rates from 1993 to 2010 by sex and 10-year age groups, assuming that the incidence rate increased with the relative risk of 1.4–12.0 among exposed persons with a cumulative call time of more than 1640 h in the population. We considered the point estimates of the joinpoint regression model for 1993 as the incidence of the non-exposed group.

RESULTS

Table 1 shows results of the joinpoint regression analysis. Annual percent change (APC) during the period from 1993 to 2010 did not show any significant increase or decrease among those aged 10–19 years: 1.6% (95% CI, –0.3 to 3.4) for men and 1.8% (95% CI, –0.4 to 4.0) for women. The APC for men aged 20 to 29 years showed a significant increase during the period from 1993 to 2010: 3.9% (95% CI, 1.6–6.3). For women aged 20 to 29 years, however, APC showed an increasing trend from 1993 to 1997, and a decreasing trend from 1997 to 2002, but neither trend was statistically significant. The APC for this group of women then showed a significant increasing trend from 2002 to 2010: 12.3% (95% CI, 3.3–22.1). The APC for those aged 30 to 39 years showed a statistically

significant increase: 2.7% (95% CI, 1.3–4.1) for men, and 3.0% (95% CI, 1.4–4.7) for women. The incidence rate and best-fitting joinpoint regression model are shown in Figure 1. The observed incidence rate per 100,000 people in 1993 was 1.22 for men in their 20s, 0.53 for women in their 20s, 1.76 for men in their 30s, and 1.15 for women in their 30s. The estimated incidence rate per 100,000 people in 1993 was 1.00 for men in their 20s, 0.69 for women in their 20s, 1.55 for men in their 30s, and 1.12 for women in their 30s. The estimated incidence rate per 100,000 people in 2010 was 1.92 for men in their 20s, 1.52 for women in their 20s, 2.44 for men in their 30s, and 1.86 for women in their 30s. The change in incidence rates from 1993 to 2010 was 0.92 per 100,000 people for men in their 20s, 0.83 for women in their 20s, 0.89 for men in their 30s, and 0.74 for women in their 30s.

Figure 2 shows the change in the proportion of heavy users who used mobile phones for calling more than 1640 h from 1990 to 2010 by sex and 10-year age groups. For men in their 20s, the proportion of heavy users started increasing from 1994, and reached 21.0% in 2010 ($n = 75$). For women in their 20s, the proportion of heavy users started increasing from 1996, and reached 12.0% in 2010 ($n = 97$). For men in their 30s, the proportion of heavy users started increasing from 1990, and reached 24.8% in 2010 ($n = 234$). For women in their 30s, the proportion of heavy users started increasing from 1999, and reached 12.3% in 2010 ($n = 275$).

The change in expected incidence rates of malignant neoplasm of the central nervous system is shown in Figure 3. The expected incidence rate per 100,000 people with the relative risk of 1.4 in 2010 was 1.08 for men in their 20s, 0.72 for women in their 20s, 1.70 for men in their 30s, and 1.17 for women in their 30s. The change in

TABLE 1. Annual Percent Change in Incidence Rates for Malignant Neoplasms of the Central Nervous System in Japan, Estimated With the Best-Fitting Joinpoint Model

Age (year)	Period	Men			Women			
		APC	95% CI		APC	95% CI		
			Lower	Upper		Lower	Upper	
10–19	1993–2010	1.6	–0.3	3.4	1993–2010	1.8	–0.4	4.0
20–29	1993–2010	3.9 ^a	1.6	6.3	1993–1997	19.7	–5.2	51.0
					1997–2002	–15.8	–31.8	3.9
					2002–2010	12.3 ^a	3.3	22.1
30–39	1993–2010	2.7 ^a	1.3	4.1	1993–2010	3.0 ^a	1.4	4.7

APC, annual percent change; 95% CI, 95% confidence interval.

^aSignificantly different from zero at $\alpha = 0.05$.

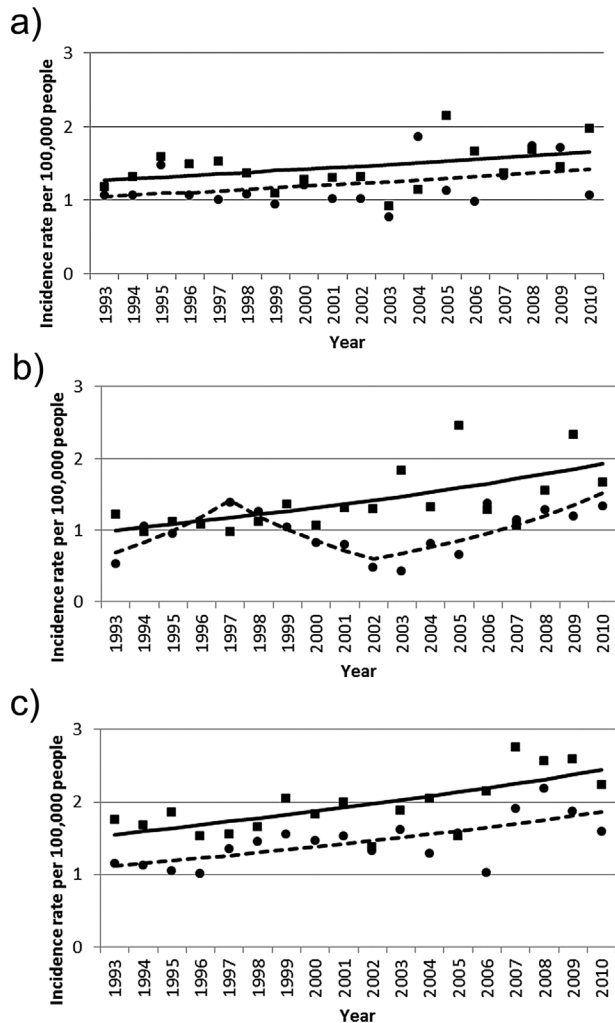


Figure 1. Incidence rates of malignant neoplasms of the central nervous system by age and sex with best-fitting joinpoint regression model (a) 10–19 years old; (b) 20–29 years old; and (c) 30–39 years old. Squares, observed values for men; Circles, observed values for women; Solid line, fitted values for men; Dashed line, fitted values for women.

expected incidence rates with the relative risk of 1.4 from 1993 to 2010 was 0.08 per 100,000 people for men in their 20s, 0.03 for women in their 20s, 0.15 for men in their 30s, and 0.05 for women in their 30s. These changes in expected incidence rates were found to be much lower than changes in estimated incidence rates using joinpoint regression analysis. Figure 3 shows expected incidence rates for the relative risk ranging from 2.0 to 12.0. The simulated incidence rate was found to be closest to the joinpoint estimate in 2010, when the relative risk was assumed to be 6.0 for men in their 20s, 12.0 for women in their 20s, 4.0 for men in their 30s, and 7.0 for women in their 30s.

DISCUSSION

In our study, the incidence of malignant neoplasms of the central nervous system for 18 years from 1993 to 2010 was found to have significantly increased in both men and women in their 20s and 30s. On the other hand, the incidence rate did not show any significantly increasing trend in men and women aged 10–19 years. If this increase in incidence was caused by a certain exposure, the effect of exposure on the incidence rate should also have increased in the last 20 years among young people aged 20–39 years, especially in men. In light of an increased risk being reported for mobile phone users with cumulative call time exceeding 1640 h, this study attempted to examine whether the observed increase in the incidence rate of malignant neoplasms of the central nervous system could be explained by an

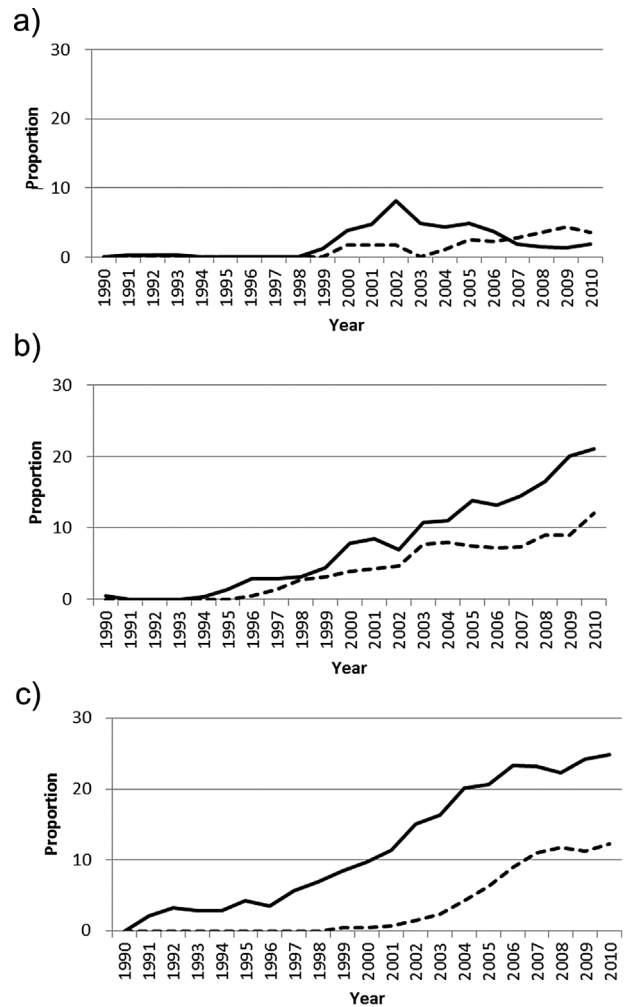


Figure 2. Proportion of those surveyed using mobile phones for more than 1640 h cumulatively by age and sex. (a) 10–19 years old; (b) 20–29 years old; (c) 30–39 years old. Solid line, men; Dashed line, women.

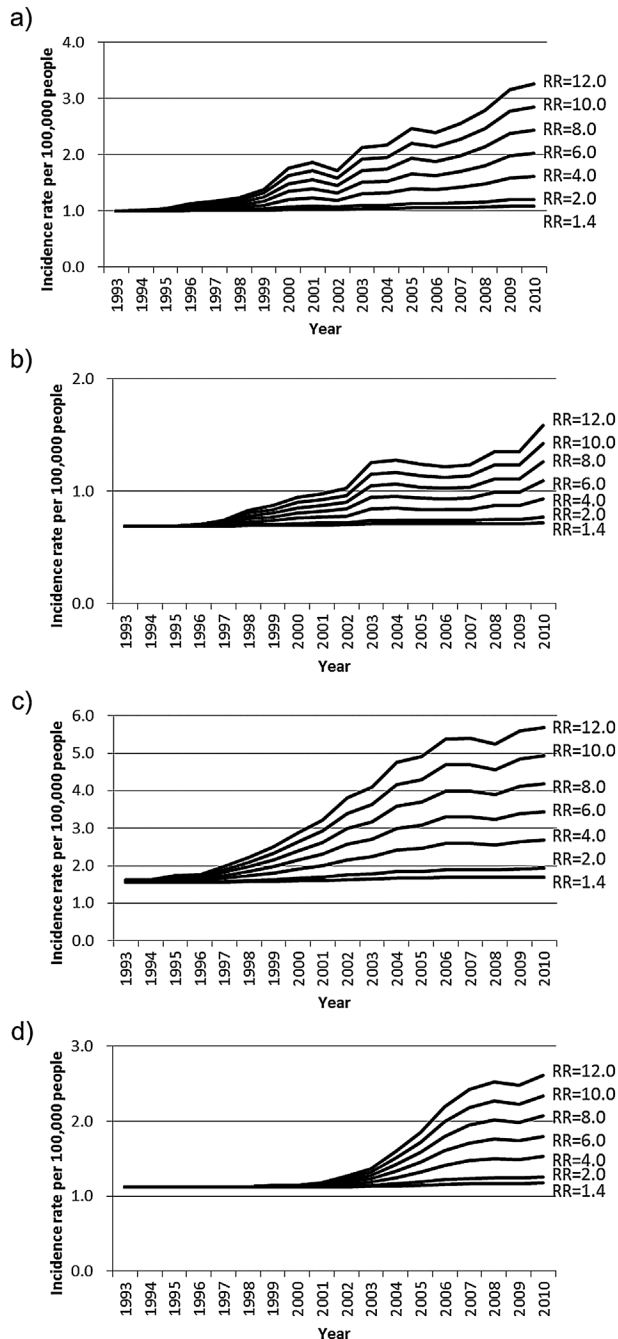


Figure 3. Change in expected incidence rates of malignant neoplasms of the central nervous system by age and sex. Expected incidence rates were calculated assuming that relative risk is 1.4, 2.0, 4.0, 6.0, 8.0, 10.0, or 12.0 among exposed persons with a cumulative call time of more than 1640 h in the population. (a) 20–29 years old, men; (b) 20–29 years old, women; (c) 30–39 years old, men; (d) 30–39 years old, women.

increase in the proportion of heavy mobile phone users.

There are consistent tendencies in the comparison between sex and age groups of time trends in

the proportion of heavy mobile phone users and the incidence of malignant neoplasms of the central nervous system. Proportion of heavy users was found to be consistently higher in men than women (Fig. 2b and c), and so was the incidence of malignant neoplasms of the central nervous system, with the exception of the years 1996–1997 among women who were 20–29 years old (Fig. 1b and c). Proportion of heavy users was found to be higher among men aged 30–39 years as compared to men aged 20–29 years (Fig. 2b and c), and so was the incidence rate (Fig. 1b and c). For women, the proportion of heavy users was higher since 2006 for those aged 30–39 years compared to those aged 20–29 years (Fig. 2b and c), and the incidence rate was higher for those aged 30–39 years compared to those aged 20–29 years, with an exception in 2007 (Fig. 1b and c).

When comparing the magnitude of change, however, there are certain discrepancies. When we assumed the relative risk to be 1.4 for mobile phone users with a cumulative call time exceeding 1640 h, the expected incidence rate (Fig. 3) was found to be much lower than the estimated incidence rate based on the joinpoint regression analysis (Fig. 1). Our simulation analysis showed that to explain the magnitude of increase in the incidence rate among heavy users, relative risk has to be between 4.0 and 12.0, given that the risk increased when the cumulative call time exceeded 1640 h (Fig. 3). Furthermore, in the joinpoint regression analysis, changes in incidence rates were bigger in males in their 20s. On the other hand, changes in expected incidence rates were bigger in males in their 30s. Although the comparison of sex was consistent, the comparison of age groups was not consistent.

The increase in incidence rate started in 1993 for both men and women in their 20s and 30s. The incidence of malignant neoplasms of the central nervous system precedes heavy mobile phone use with the cumulative call time exceeding 1640 h. This trend was remarkable in women in their 30s. The present study does not take into account the latency period between mobile phone use and the incidence of malignant neoplasms of the central nervous system. If we assume that there is a latency period of 5 years, the incidence of malignant neoplasms of the central nervous system preceded by heavy mobile phone use is more significant.

If we assume that the change in incidence of malignant neoplasms of the central nervous system was caused by a change in the proportion of heavy users, we need to account for the discrepancy between the reported relative risk and results of our simulation

analysis. One possibility is that the reported relative risk potentially underestimated the real risk, if any. Another possibility might be that the threshold of increased risk might be lower than the assumed value of 1640h.

On the other hand, if we assume that the change in incidence of malignant neoplasms of the central nervous system was not caused by a change in the proportion of heavy users, we need to account for the observed increase in incidence rate. One possibility is that the chance of detecting asymptomatic malignant neoplasms of the central nervous system increased because of improved diagnostic procedures or because of an increased likelihood that individuals underwent computed tomography (CT) or magnetic resonance imaging (MRI) scanning as part of mass screening programs, which are becoming more popular in Japan [The Japan Brain Dock Society, 2014]. Detection of asymptomatic malignant neoplasms of the central nervous system in young people might have also increased because of the increasing availability of CT and MRI scanners in Japan [OECD, 2014]. It is less likely that the observed increase in incidence rate could be explained by increased early detection by brain mass screening because such screening programs have been popular among middle-aged and older generations, but not among younger people. In the joinpoint regression analysis of those aged 40 years or older, a statistically significant increase was observed only for men in their 50s. The APC was 8.7% (95% CI, -0.3 to 18.4) from 2005 to 2010. This increase might be explained by early detection by brain mass screening (data not shown).

In Japan, a nationwide registration of brain tumors is also operated by an academic society [The Committee of the Brain Tumor Registry of Japan, 2009, 2014]. Although this registry collects detailed information on treatment and prognosis, registered patients cannot be regarded as representative of all brain tumor cases in Japan because registered patients are restricted to those diagnosed and treated in specialized centers. Nevertheless, data of this registry might offer some insight into this increase in incidence rate. According to this report, the proportion of gliomas in total primary brain tumors increased from 23% during the period of 1993–2000 to 28.3% during the period of 2001–2004. When change in proportion is examined by age group, the proportion of gliomas increased from 25.0% to 31.4% for those aged 20 to 29 years and from 26.8% to 31.8% for those aged 30 to 39 years. Proportion of gliomas in total primary brain tumors increased during the period of 1993–2004, and a greater increase was observed for men. If the observed increase in incidence rate in the present

study is caused solely by detection effects, the proportion of gliomas is not likely to increase, because a tumor with a longer latency period, not a rapidly growing tumor like glioma, is more likely to be detected by such screening. The increased proportion of gliomas should be interpreted with caution, however, because the proportion of gliomas could have changed due to a change in the number of non-glioma tumors as well.

Deltour et al. [2012] reported that changes in glioma incidence (APC) in people 20–39 years old in four Nordic countries were -0.7 (95% CI, -1.4 to 0.1) from 1987 to 2008 in men, and 0.3 (95% CI, -0.2 to 0.8) from 1979 to 2008 in women. Little et al. [2012] reported that the change in glioma incidence (APC) in non-Hispanic whites from the Surveillance, Epidemiology, and End Results (SEER) Program registry in the US was -0.02 (95% CI, -0.28 to 0.25) from 1992 to 2008. Barchana et al. [2012] reported that changes in high-grade glioma incidence in Israel were 0.007 in men and 0.13 in women from 1994 to 2009. There was a statistically significant increase among women. Ding and Wang [2011] reported that changes in brain and nervous system tumor incidence (APC) in Shanghai, China were 1.2 (95% CI, 0.4 – 1.9) in men and 2.8 (95% CI, 2.1 – 3.4) in women from 1983 to 2007; both increases were statistically significant. In Western countries, the incidence of glioma has not increased in these 20 years. However, in East Asian countries, such as China and Japan, a statistically significant increase was observed in incidence of malignant neoplasms of the central nervous system. The cause of this increase in incidence in East Asia remains unclear.

Three major limitations of this study should be mentioned with regard to the analyzed data. First, national estimates of incidence rate, on which the present study relied, are based on regional cancer registries because a nationwide population-based registration system has yet to be established in Japan. National estimates were results from the Monitoring of Cancer Incidence in Japan (MCIJ) project [Hori et al., 2015; Matsuda et al., 2009, 2010, 2011, 2012, 2013, 2014]. Research teams of the Ministry of Health, Labour and Welfare Japan collected data for MCIJ. The Center for Cancer Control and Information Services of the National Cancer Center Japan developed a surveillance system, performed quality control of the data, and aggregated the data. Finally, results were published on the website of the Cancer Information Service of the National Cancer Center Japan [2014]. These results are currently the only available statistics on nationwide cancer incidence in Japan.

National estimates are obtained from regional registries with better accuracy [National Cancer Center Japan, 2015]. Registries that meet the following criteria are used in the nationwide estimation: death certificate only percent (DCO%) is less than 25%, death certificate notification percent (DCN%) is less than 30%, and the incidence to mortality (I/M) ratio is more than 1.5. If there is a turnover in selected regions for estimation, regional disparities in cancer incidence are minimized by adding a correction to the estimated value using cancer mortality statistics. In 2003, average values of DCN%, DCO%, and I/M were 22.8%, 16.8%, and 2.01, respectively, and the number of cases for estimation was 180486. In 2010, average values of DCN%, DCO%, and I/M were 18.1%, 11.8%, and 2.23, respectively, and the number of cases for estimation was 380,337. Geographical areas used for the estimation have expanded and regional cancer registration has been promoted, thereby increasing accuracy of the data. In light of these changes, cases that had been overlooked previously may have been counted in the recent registration. In the present study, the incidence of malignant neoplasms of the central nervous system increased in both men and women in their 20s and 30s. We could not exclude the possibility that the increase was observed due to this bias.

Second, mobile phone usage was obtained from a cohort that was created on the Internet by sending a survey to schools throughout Japan. Therefore, mobile phone usage in the cohort is considered to differ from that in the general population. When focusing on the ownership curve for mobile phones, the change observed in our cohort is likely to be similar to the general population [Ministry of Internal Affairs and Communications Japan, 2015]; the rapid spread of mobile phone use since 1993 was an S-shaped curve. A Communications Usage Trend Survey also shows mobile phone ownership rate by 10-year age groups since 2001 [Ministry of Internal Affairs and Communications Japan, 2015]. The mobile phone ownership rate for people in their 20s was 75.9% ($n = 1672$) in 2001, 86.9% ($n = 1599$) in 2003, 99.0% ($n = 1530$) in 2005, 96.7% ($n = 1507$) in 2007, and 97.3% ($n = 1664$) in 2009. The mobile phone ownership rate for people in their 30s was 69.2% ($n = 1667$) in 2001, 85.8% ($n = 1768$) in 2003, 97.6% ($n = 1813$) in 2005, 94.3% ($n = 1690$) in 2007, and 95.0% ($n = 2116$) in 2009. In our cohort, the mobile phone ownership rate for people in their 20s was 92.1% ($n = 466$) in 2001, 96.4% ($n = 411$) in 2003, 97.2% ($n = 323$) in 2005, 98.5% ($n = 271$) in 2007, and 98.3% ($n = 229$) in 2009. The mobile phone ownership rate for people in their 30s was 77.4% ($n = 575$) in 2001, 88.4%

($n = 601$) in 2003, 95.2% ($n = 629$) in 2005, 97.0% ($n = 609$) in 2007, and 97.8% ($n = 537$) in 2009. There is a slightly higher trend in the ownership rate of mobile phones in our cohort. Thus, the estimated percentage of mobile phone users with a cumulative call time exceeding 1640 h is likely high in the present study. However, this overestimation does not weaken the conclusion of the present study.

Third, the cumulative call time used in this study was calculated from the average talk time and the use period. Change in talk time over the entire period was not investigated. Cumulative call time in the present study shows a rough trend and does not reflect real usage accurately. This is another drawback of the present study.

CONCLUSIONS

The incidence rate of malignant neoplasms of the central nervous system has increased significantly in men and women aged 20–29 years and 30–39 years from 1993 to 2010 in Japan. However, patterns in sex-, age-, and period-specific incidence increases are inconsistent with sex-, age-, and period-specific prevalence trends, suggesting the overall incidence increase cannot be explained by heavy mobile phone use. Further epidemiological research is warranted, especially a study with a more accurate estimate of the cumulative exposure level.

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