tumor development in other cancers such as gastric cancer [8], pancreas cancer [9], and breast cancer [10].

The Hh proteins, Sonic hedgehog (Shh), Desert hedgehog, and Indian hedgehog, act as ligands for the receptor Patched 1 protein (Ptch1) that is located on the cell membrane [11]. Hedgehog signal transduction is initiated by the binding Hh proteins to Ptch1. Ptch1 inhibits the activity of a transmembrane protein (smoothened; SMO) that activates factors downstream of Hh signaling pathway when those ligands are not bound to Ptch1. SMO stimulates a signaling cascade that results in the activation of the transcription factors Gli proteins (GLI1, GLI2, and GLI3) [12] when ligands are bound to Ptch1. GLI1 is amplified in glioma [5] and is a strong positive activator of downstream target genes in the nuclear, and GLI1 is a transcriptional activator of Hh signaling itself [13]. Therefore, GLI1 staining in the nucleus by immunohistochemistry is a marker of activation for Hh signaling [8,10].

Neuroblastoma (NB) is the most common solid malignant tumor in children arising from neural crest cells and usually occurs in the adrenal medulla. Neuroblastomas showed various clinical courses, and many studies have found both clinical and biological markers associated with the prognosis. *MYCN* gene amplification occurs in approximately 25% of primary NBs, and this factor is one of the most unfavorable prognostic factors in NB [14-16].

Hh signaling activation is associated with the development of neural crest cell, but there has been no evidence of a role in NB development. The aim of this study is to determine whether Hh signaling activation is associated with differentiation or tumorigenesis in NB.

1. Materials and methods

1.1. Clinical data of patients and biological data of NB samples

Patients were diagnosed with NB between April 1988 and March 2008. Eighty-two NB samples and 10 ganglioneuroblastoma samples were obtained. The tumor was staged according to the International Neuroblastoma Staging System (INSS). All of the parents of the patients provided informed consent for tumor preservation and the biological analysis before surgery. This study was performed according to ethical guidelines for the clinical studies by Ministry of Health, Labour, and Welfare of Japan in July 30, 2003. The patients included 56 males and 36 females; and 33 were INSS stage 1, 9 were stage 2, 16 were stage 3, 29 were stage 4, and 5 were stage 4S. Fifty-eight had been diagnosed when they were younger than 12 months. Forty-six patients were identified by a mass screening program in Japan at 6 months of age. Immunohistochemical analyses were performed in all 92 cases, and evaluated for *MYCN* gene amplification using Southern blotting or quantitative polymerase chain reaction as described previously [17,18]. *MYCN* amplification was defined as an *MYCN* gene copy of 2 or more in Southern blotting and a corrected *MYCN* gene dosage of more than 4.00 in quantitative polymerase chain reaction.

1.2. Immunohistochemistry

The immunohistochemical study was performed using the streptavidin-biotin-peroxidase method (Histofine; Nichirei, Tokyo, Japan). Samples were fixed in 10% formalin and embedded in paraffin. The primary antibodies used in this study were anti-SHH (1:100, N-19, sc-1194, Santa Cruz Biotechnology, Santa Cruz, Calif), anti-GLI1 (1:100, N-16, sc-6153, Santa Cruz Biotechnology), and anti-PTCH1 (1:100, H-267, sc-9016, Santa Cruz Biotechnology). All primary antibodies were incubated 2 hours at room temperature. Secondary antibodies were applied for 1 hour at room temperature. The results were visualized with diaminobenzidine. Slides were counterstained by hematoxylin. A number of cytoplasmic-positive cells or cell membrane–positive cells in neuroblasts were counted. The staining was judged as negative if the intensity of staining was similar to that of background staining. Three hundred cells were counted, and the percentage of positive cells was calculated for each section. The immunoreactivities were classified into 3 categories: −, 0% to 50% tumor cell positive; +, 50% to 90%; ++, 90% to 100%. The sample was judged to be "positive" if more than 50% of the tumor cells were positive. We determined the percentage of neuroblasts showing nuclear staining of GLI1 strongly in relation to the total number of neuroblasts. The NB component was used to judge the cases of ganglioneuroblastoma nodular. The specimens were determined by an independent pathologist who knew neither staging nor the status of *MYCN*.

1.3. Statistical analysis

Mann-Whitney U test and χ^2 test were used for statistical analysis. The survival curve was estimated using the Kaplan-Meier procedure and then it was statistically evaluated by the log-rank test. Results were considered to be significantly different when $P < .05$.

2. Results

2.1. Association of expression of Shh, GLI1, and Ptch1 proteins and the status of MYCN gene

The Shh and Ptch1 staining was observed in the cell membrane strongly, and GLI1 was localized in the cytoplasm in neuroblasts with ganglionic differentiation in GNB samples (Fig. 1A). The Shh, GLI1, and Ptch1 staining intensity of GNBs was higher than that of NBs, and most

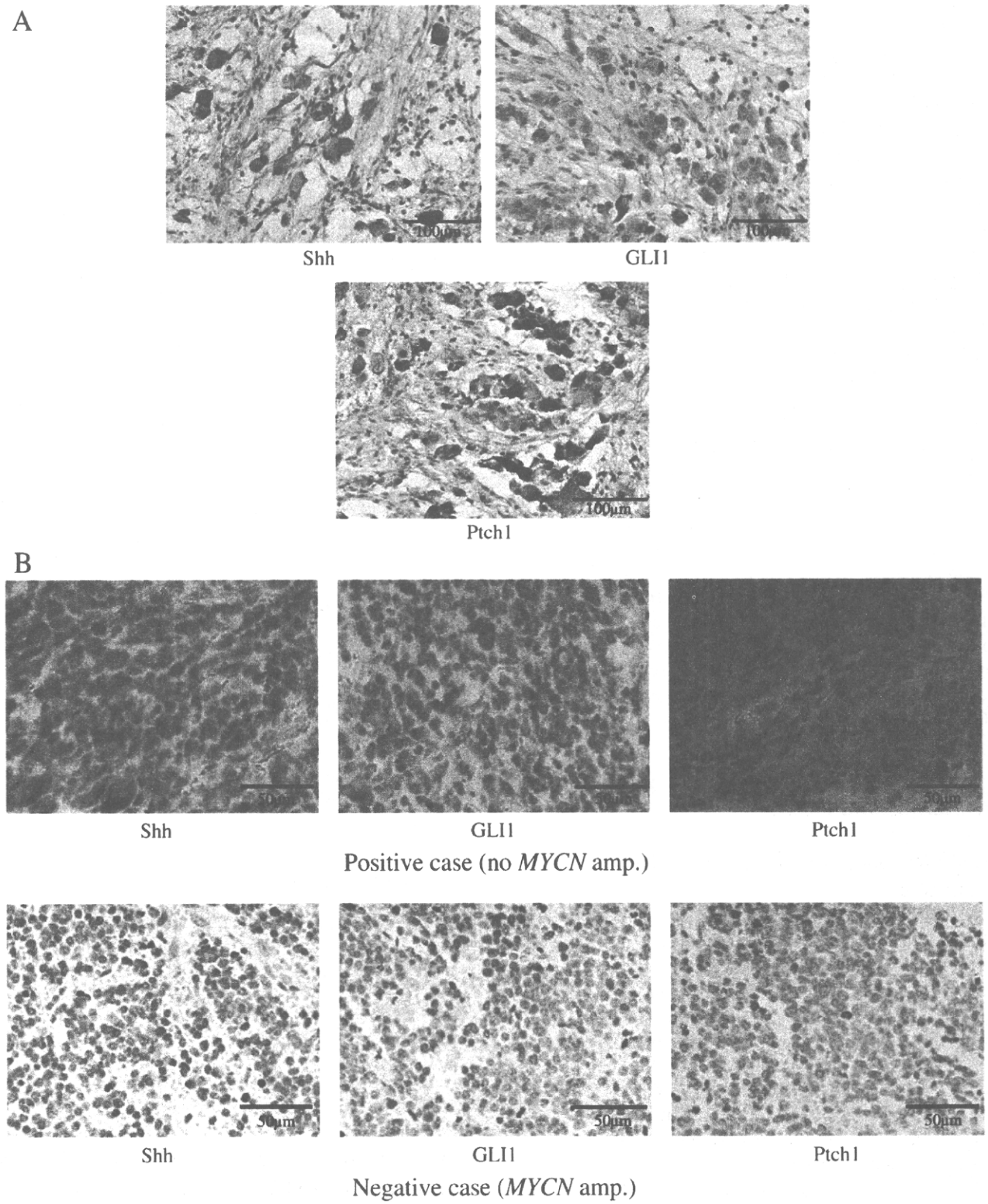

Fig. 1 A, Shh and Ptch1 staining was observed in the cell membrane strongly and GLI1 was localized in the cytoplasm of neuroblast with differentiation in ganglioneuroblastoma. No cells showed GLI1 nuclear stain (original magnification ×200). The cells demonstrating a positive expression cells are brown in color. The nuclei were stained with hematoxylin (purple). B, Shh-, GLI1-, and Ptch1-positive cases in NB without *MYCN* amplification and negative cases with *MYCN* amplification. No cells showed GLI1 nuclear stain in GLI1-positive case (top center panel) (original magnification ×400). The cells demonstrating a positive expression are brown in color. The nuclei were stained with hematoxylin (purple).

Table 1 Expression of Hh signal proteins (Shh, GLI1, Ptch1) in 92 samples

	Positive		Negative
	++	+	−
Shh	64	3	25 (27%)
	67(73%)		
GLI1	53	9	30 (33%)
	62(67%)		
Ptch1	70	3	19 (21%)
	73(79%)		

Schwann cells were negative for Shh, GLI1, and Ptch1 (Fig. 1A, B).

The result of immunohistochemistry of 92 samples is shown in Table 1. Sixty-seven of 92 samples (73%) were positive for Shh, 62 (67%) for GLI1, and 73 (79%) for Ptch1. Of 46 samples identified by mass screening system in Japan, 43 samples (93%) were positive for Shh; 39 (85%), for GLI1; and 45 (98%), for Ptch1. As shown in Table 2, only 2 (10%) of 20 samples with *MYCN* amplification were positive for Shh and GLI1, respectively, and 4 samples (20%) were positive for Ptch1. On the other hand, 65 (90%) of 72 samples without *MYCN* amplification were positive for Shh, 60 samples (83%) for GLI1, and 69 samples (96%) for Ptch1. There was a significant association between Hh signal proteins (Shh, GLI1, and Ptch1) and the status of *MYCN* gene ($P \leqq .01$).

2.2. Correlation of the expression of GLI1 and clinical stage (INSS) in the 72 NBs without MYCN amplification

Fig. 2 shows the correlation of the percentage of GLI1-positive cells and clinical stage (INSS) in the 72 cases without *MYCN* amplification. GLI1 is located downstream of the Hh signaling pathway, and it is a strong positive activator of target genes. The percentage of GLI1-positive cells in the cases with stage 1 was significantly higher than that with stage 4 (92.5 ± 21.3% vs 69.6 ± 38.8%; $P = .04$). However, there were no significant difference between stage 1 and stage 2 ($P = .23$), stage 1 and stage 3 ($P = .15$), or stage 1 and stage 4S ($P = .57$), respectively.

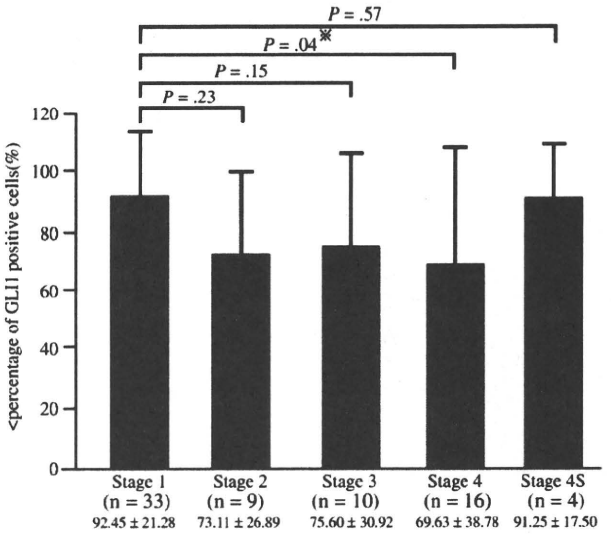

Fig. 2 Correlation between the percentage of GLI1-positive cells and clinical stage (INSS) in the 72 cases without *MYCN* amplification. The percentage of GLI1-positive cells in stage 1 cases was significantly higher than that in stage 4 (92.5 ± 21.3% vs 69.6 ± 38.8%; $P = .04$).

2.3. Association of the outcome of patients and the expression of GLI1 protein

Fig. 3 shows the survival curves of the patients with GLI1-positive cases (n = 60) and GLI1-negative cases (n = 12) in 72 NBs without *MYCN* amplification. The 5-year overall survival rate (OS) of GLI1-positive patients (93.7 ± 3.5%) was significantly higher in comparison to that of GLI1-negative patients (70.0 ± 14.5%; $P = .015$). On the other hand, 5-year OS of the patients with *MYCN*

Table 2 Associations of the expression of Hh signal proteins and the status of *MYCN* amplification in NBs

		Positive		Negative		
		++	+	−		
Shh	*MYCN* amplification	2	0	18	20	$P \leqq .01$
	No *MYCN* amplification	62	3	7	72	
		64	3	25		
GLI1	*MYCN* amplification	2	0	18	20	$P \leqq .01$
	No *MYCN* amplification	51	9	12	72	
		53	9	30		
Ptch1	*MYCN* amplification	4	0	16	20	$P \leqq .01$
	No *MYCN* amplification	66	3	3	72	
		70	3	19		

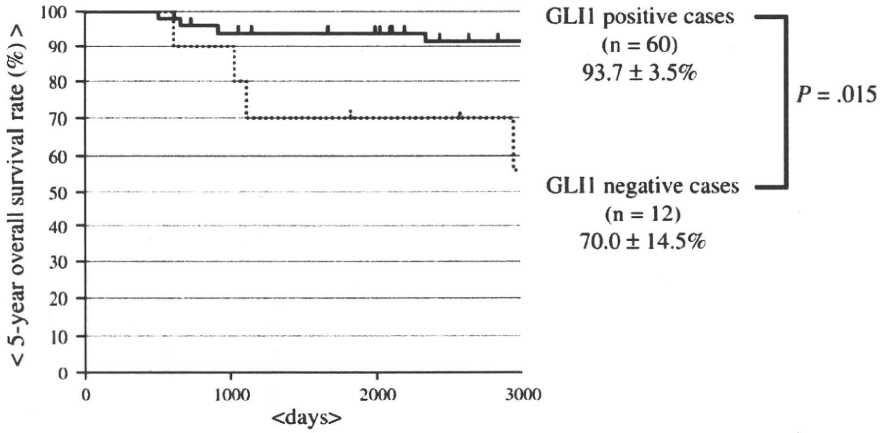

Fig. 3 Survival curves of the GLI1-positive patients (n = 60) and GLI1-negative cases (n = 12) in 72 NBs without *MYCN* amplification. The 5-year overall survival rate of GLI1-positive patients (n = 60, 93.7 ± 3.5%) was significantly higher in comparison to that of GLI1-negative patients (n = 12, 70.0 ± 14.5%).

amplification (n = 20) was 36.1 ± 11.2% and the 2 GLI1-positive cases with *MYCN* amplification are alive without disease after treatment.

2.4. GLI1 nuclear staining in NBs

The percentage of GLI1 nuclear staining was very low in all 92 cases (1.98% ± 3.83%, 0%-15%; Fig. 1A, B) and only 2 of 92 samples were higher than 10%.

3. Discussion

The current study showed that Hh signaling pathway–associated proteins such as Shh, GLI1, and Ptch1 were expressed in most NB cases, especially cases without *MYCN* amplification. Moreover, a number of positive cases show "++", whereas "+" cases are rare. As a result, most of the positive cases tended to be easy to distinguish as positive cases. The percentage of GLI1-positive cells in early-stage samples was higher than that with advanced stage. The 5-year OS rate of GLI1-positive cases without *MYCN* amplification is significantly higher than that in GLI1-negative cases. Only 2 of all 92 samples showed more than 10% of GLI1 nuclear staining.

The proteins of Hh signaling pathway such as Shh, Ptch1, and GLI1 are highly expressed in various pediatric malignant tumors such as NB [19,20], rhabdomyosarcoma [21], and clear cell sarcoma [22]. This study is the largest series evaluated for the Hh signal activation of the primary NB samples.

Mao et al [20] reported that 48% to 70% of primary NBs were positive for Hh signal–associated proteins and the ligand-dependent Hh pathway was activated in NB cell lines. These results are consistent similar with the current results. The current study found that 67% to 79% of NB samples showed expression of Shh, GLI1, and Ptch1. Only 2 of 92 cases were GLI1-positive, Shh-negative, and Ptch1-negative (data not shown). Therefore, the Hh signal activation of NB may be via the ligand-dependent pathway, and may not be a mutation or amplification of the transactivator on the Hh signal pathway as observed in medulloblastoma [6] and basal cell carcinoma [7]. Oue et al [19] reported that early-stage NBs highly express GLI1 in comparison to advanced-stage NBs. Our data also show that not only early-stage samples but also samples without *MYCN* amplification tended to be positive for Hh signal–associated proteins.

Some studies have suggested an association between Hh signaling activation and NB in vitro, although these results remain controversial. GLI1 transduction of an NB cell line inhibits proliferation and it induces a pattern of gene expression that resembles the gene expression of ganglioneuroma and the transcriptional response of treatment with the retinoic acid [23]. Therefore, Hh signal activation may be associated with the differentiation of NB. On the contrary, the inhibition of Hh signaling of NB cell line by cyclopamine, inhibitor of SMO, induces apoptosis and the Hh signal stimulates the tumorigenicity of NB cells [20]. Further examination will be necessary for NB primary samples to reveal the association between NBs development and Hh signaling.

The GLI1 nuclear staining with the immunochemistry examination has been reported to be observed in gastric cancer [8] and breast cancer [10], strongly suggesting the activation of Hh signaling. Although a large number of NBs and GNBs cases were positive for GLI1, there were very few cases with nuclear staining of GLI1 in the current study. This result might be associated with the good prognosis of the GLI1-positive cases in NB in contrast to that in adult cancers.

In conclusion, most of NBs without *MYCN* amplification were positive for Shh, GLI1, and Ptch1. In contrast, most of NBs with *MYCN* amplification were negative for Shh, GLI1, and Ptch1. In the cases without *MYCN* amplification, the high expression of GLI1 was significantly associated with early clinical stage and a good prognosis of the patients. In contrast to adult cancers, these findings may show that the activation

of the Hh signaling pathway in NB is associated with the differentiation of the NB and a good prognosis of the patients.

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Epidemiology Note

Trends in the Incidence of Primary Intracranial Tumors in Osaka, Japan

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We analyzed the trends in the age-standardized incidence rates of 10 460 cases of primary intracranial tumors diagnosed during 1975 and 2004, Osaka, Japan using the Joinpoint regression analysis. During the period 1975–2004, the age-standardized incidence rates of total intracranial tumors increased until 1987 at 3.1% per year and then decreased significantly at −1.8% per year. The time trends were different according to the age groups. In the age group 0–19, the rate did not exhibit substantial increase or decrease. In the age group 20–74, the rates increased significantly until 1988 and then leveled off until 1999 and finally decreased. Whereas in the age group 75 and over, the rates increased drastically until 1984 and then leveled off. During the recent 10 year period 1995–2004, the age-standardized incidence rates of meningioma decreased significantly, but those of glioblastoma did not.

Key words: brain tumor – trends in incidence – population-based cancer registry

INTRODUCTION

Intracranial tumors are not common in adult, although they have drawn wide attention because of the fear inspired by their organ and the accompanying generally poor prognosis. In children, it is the second most common malignancy (1), next to leukemia.

A number of reports (2–9) from North America and Europe indicated that the increasing trends in incidence rates were confined from the late 1970s to mid-1980s, coinciding with the introduction and widespread use of improved diagnostic methods. For recent time trends in the incidence, some papers reported continuous increasing (2), whereas others reported leveling off or decreasing (3–6).

We described trends in the incidence of intracranial tumors in Osaka, Japan using Osaka Cancer Registry's (OCR) data and examined the effect of wide spread use of computed tomography (CT) on these incidence rates and how they are progressing now. This study was done for all intracranial tumors, regardless of their behavior, since several intracranial tumors may have both benign and malignant subtype entities, or progress from benign to malignant.

PATIENTS AND METHODS

We used data from the OCR, which is a population-based cancer registry started in 1962 that covers Osaka prefecture, with a population of 8.8 millions (2005 census). From the OCR database, we identified 10 465 newly reported cases of intracranial tumor (ICD Tenth Revision), meninges (C70.0–C70.9), brain (C71.0–C71.9), spinal cord, cranial nerves and other parts of the central nervous system (CNS) (C72.0–C72.9), as well as pituitary gland, craniopharyngeal duct and pineal gland (C75.1–C75.3) diagnosed from 1975 to 2004. Five cases were excluded from the analysis because of uncertain age at diagnosis. Incidence rates were age-adjusted with the World Standard Population. Histological group was categorized based on WHO Classification of Tumors of the Nervous System, Lyon, 2000 (10), although it was partly modified.

The histology was subcategorized as follows, with corresponding ICD-O (Third Edition) four-digit histology cords; Glioblastoma (9440–9442), Astrocytoma, total excluding glioblastoma (9384, 9400, 9401, 9410, 9411, 9420, 9421, 9424), Oligodendroglioma (9450, 9451), Ependymoma, total (9383, 9391–9394), Glioma NOS (9380), Embryonal tumors (9470–9474, 9490, 9500–9501, 9508), Nerve sheath (9540–9560, 9571), Meningioma (9530–9534, 9537–9539), Germ cell tumors (9064, 9070–9071, 9080, 9084–9085, 9100), Craniopharyngioma (9350), Pituitary (8140–8323), Unspecified (8000–8001) and Others. Of the tumors, 74.6% were classified as malignant (ICD-O, behavior codes: 3), while 21.3% were benign (behavior codes: 0), and the rest were uncertain (behavior codes: 1).

Joinpoint regression analysis software (version 3.3.1) was obtained from the web site of the Statistical Research Applications Branch of the National Cancer Institute, USA (11,12). We set the number of joints in each cancer trend to a minimum of 0 and maximum of 3 to find best fit model using permission test method and assumed constant variance and uncorrelated errors in the calculation. The independent variable was time, expressed as year of tumor diagnosis and coded as a continuous variable. Predictors were analyzed by age and histological group. Age group was coded as a categorical variable for the broad age groups of 0–19 years old (children and adolescents), 20–74 years old (adults) and 75 years old or more (the elderly).

To compare recent time trends according to age and histological subgroup, an average annual percent change (AAPC) with a 95% confidence interval (CI) was calculated by fitting a linear term on the logarithmic scale to the trend in the age-standardized rates. An annual percent change (APC) was used to describe trends in the cancer incidence, and joinpoints were estimated where trends in the incidence changed significantly over the period.

RESULTS

The final data set included 10 460 (male 5183; female 5277) primary intracranial tumors diagnosed from 1975 to 2004 (1272 cases in 1975–1979, 1462 in 1980–1984, 1966 in 1985–1989, 1780 in 1990–1994, 2069 in 1995–1999 and 1911 in 2000–2004).

In Table 1, the histological classifications of primary intracranial tumors diagnosed in Osaka from 1995 to 2004 are illustrated according to sex and age at diagnosis. Proportion of unspecified histology was 40%. In the elderly 70% of the tumors were unspecified neoplasms. When histological unspecified neoplasm and pituitary tumors were excluded, most (33%) were glioblastoma and 24% were meningioma and 13% were astrocytoma. Embryonal and germ cell tumors occurred mainly in children and adolescents. Large sex difference in the incidence was observed for meningioma (sex ratio 3.0) and germ cell tumors (sex ratio 0.3).

The results of Joinpoint regression analysis for trends of all primary intracranial tumors from 1975 to 2004 are presented in Fig. 1 and Table 2 according to age groups and tumor characteristics. In all intracranial tumors, a joinpoint was estimated at 1987. The incidence rates increased

Table 1. Histological classification of primary intracranial tumors diagnosed in Osaka, 1995–2004

Histology	Total			Male	Ratio	Age at diagnosis (*n*)		
	n	*a* (%)	*b* (%)	*n*	F/M	0–19, *n* (%)	20–74, *n* (%)	75≤, *n* (%)
Glioblastoma	713	18	33	388	0.8	19 (5)	590 (22)	104 (11)
Astrocytoma, total	287	7	13	155	0.9	48 (12)	224 (8)	15 (2)
Oligodendroglioma, total	30	1	1	17	0.8	1 (0)	28 (1)	1 (0)
Ependimoma, total	46	1	2	24	0.9	25 (6)	20 (1)	1 (0)
Embryonal tumor	51	1	2	30	0.7	42 (11)	7 (0)	2 (0)
Glioma, NOS	159	4	7	88	0.8	42 (11)	91 (3)	26 (3)
Nerve sheath	114	3	5	46	1.5	7 (2)	101 (4)	6 (1)
Meningioma	513	13	24	127	3.0	11 (3)	409 (15)	93 (10)
Germ cell tumors	77	2	4	58	0.3	52 (13)	24(1)	1 (0)
Craniopharingioma	57	1	3	25	1.3	18 (5)	36(1)	3 (0)
Others	111	3	5	65	0.7	29 (7)	69 (3)	13 (1)
Pituitary	249	6		100	1.5	12 (3)	221 (8)	16 (2)
Neoplasm, unspecified	1,573	40		747	1.1	85 (22)	845 (32)	643 (70)
Total	3,980	100		1,870	1.1	391 (100)	2665 (100)	924 (100)

a (%), % of all intracranial tumors; *b* (%), % of all intracranial tumors exclude neoplasm, unspecified and pituitary

significantly until 1987 then decreased significantly (from 3.1 to −1.8% per year). In the 0–19 age group, the incidence rates did not exhibit substantial increase or decrease. In the 20–74 age group, joinpoints were estimated at 1988, 1993 and 1999: the incidence rate increased significantly until 1988 at 2.9% per year, decreased until 1993 at −5.7% per year, then increased again until 1999 at 3.0% per year, although the estimated APC from 1988 to 1999 was not statistically significant and finally decreased significantly at −10.4%. In those 75 years or older, a joinpoint was estimated at 1984: the incidence rate increased significantly at 28.7% per year from 1975 to 1984, and then leveled off.

In the most recent decade from 1995 to 2004, the age-standardized incidence rates of all intracranial tumors decreased significantly by −1.8% per year (95% CI −2.6, −0.9). The rate of meningioma also decreased (AAPC −2.9%, 95% CI −5.1, −0.5), but the rates of glioblastoma was not observed substantially decreasing tendency (AAPC −1.3%, 95% CI −2.8, 0.2).

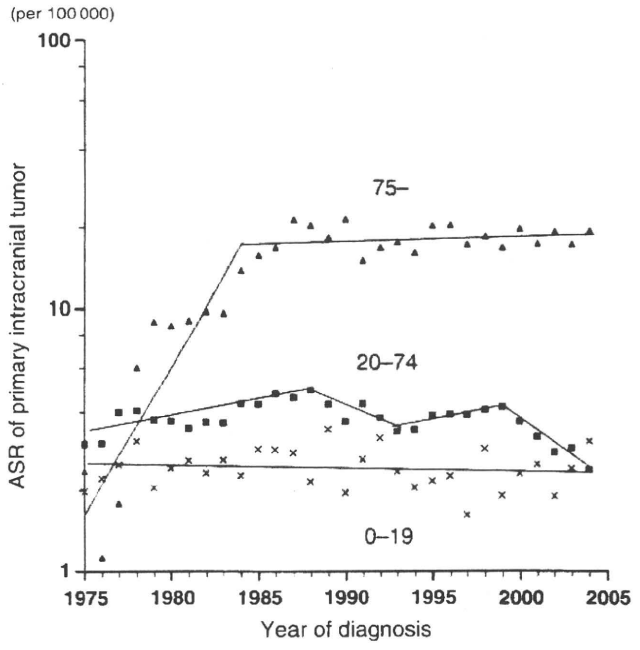

Figure 1. Trends in the age-standardized incidence rates by age groups.

DISCUSSION

The time trends were different according to age group as showed Fig. 1. In the age group 0–19, the rate did not exhibit substantial increase or decrease. In the age group 20–74, the rates increased significantly until 1988 and then leveled off until 1999 and finally decreased. Although in the age group 75 and over, the rates increased drastically until 1984 and then leveled off.

A large part of the increase in the incidence until the mid-1980s seemed to be due to an improvement in diagnostics. CT for head was used for the first time in a university hospital in Tokyo, 1975 (13) and soon came to be used in a lot of hospitals. According to the reports every 3 year from Health and Welfare Statistics, the number of CT increased 107 in 1978, 138 in 1981, 254 in 1984, 372 in 1987 and 511 in 1990 in Osaka (14). This improvement in diagnostics especially had a large influence on the elderly. Some reports (3,7,8) showed the incidence of intracranial tumor increased steeply until the mid-1980s in elderly people. Helseth et al. (9) reported that the increase is due to changing attitudes to investigation of elderly people and Asplund et al. (15) showed the frequency CT scanning in elderly has increased.

Table 2. Trends in the incidence rates of primary intracranial tumors in Osaka, 1975–2004, Joinpoint regression analysis

Age/ Behavior	Number of cases	Joinpoint	Estimate	Segment	Lower endpoint	Upper endpoint	APC (%)	Lower CI	Upper CI
All tumors	10 460	1	1987	1	1975	1987	3.1[a]	1.5	4.7
				2	1987	2004	−1.8[a]	−2.6	−0.9
0–19	1584	0			1975	2004	−0.2	−0.9	0.6
20–74	7207	1	1988	1	1975	1988	2.9[a]	1.5	4.2
		2	1993	2	1988	1993	−5.7	−12.8	2.0
		3	1999	3	1993	1999	3.0	−2.6	8.8
				4	1999	2004	−10.4[a]	−15.2	−5.3
75–	1669	1	1984	1	1975	1984	28.7[a]	19.8	38.4
				2	1984	2004	0.3	−1.8	2.5
Malignant	7807	1	1986	1	1975	1986	3.5[a]	1.8	5.3
				2	1986	2004	−1.4[a]	−2.2	−0.6

APC, Annual percent change.
[a]APC is significantly different from zero.

We found that the age-standardized incidence rates of all intracranial tumors decreased significantly by −1.8% per year during most recent decade (1995–2004). On the basis of the SEER, Legler et al. (3) and Deorah et al. (4) reported the incidence rates for total brain cancer have leveled off or decreased. Johannesen et al. (5) also reported a trend of leveling off in incidence using data from the Norwegian Cancer Registry from 1970 to 1999. Contrary to those reports Hoffman et al. (2) showed that the overall incidence rates for all brain/CNS tumors were modestly increasing using data compiled by the Central Brain Tumor Registry of the United States from six population-based state cancer registries from 1985 to 1999. It is necessary to clarify why these differences in the recent trend in the incidence were observed.

Before accepting the results, several limitations of this study should be considered. First, negative trends might be due to reporting delays from hospitals. AAPC was −1.7% in 1993–2002 whereas it was −1.8% in 1995–2004. Thus, effect of the reporting delay seemed to be small in our study. Secondary, our study was done for all intracranial tumors, regardless of their behavior. It is more likely there were the tumors diagnosed benign not to report. Proportion of benign tumor was around 20% during the study period. The percentage of cases registered by death certification only, which is often regarded as an index for the completeness, for brain and CNS (C70–C72), were 6% for male and 9% for female in 1988–1992 (16), 16% for male and 23% for female in 1993–1997 (17) and 7% for male and 11% for female in 1998–2002 (18) in Osaka. We consider that the change in the completeness influenced the trends, but it is unlikely to explain the observed trends by this factor.

In sum, the age-adjusted incidence rates of intracranial tumor in Osaka increased until the mid-1980s, especially among the elderly, with the improvement and the wide spread use of diagnostic procedures such as CT, and then recently decreased. Despite some possible limitations, this analysis contributed important information to the debate over trends in the intracranial tumor incidence rate.

Conflict of interest statement

None declared.

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Epidemiology Note

Cancer Incidence and Incidence Rates in Japan in 2004: Based on Data from 14 Population-based Cancer Registries in the Monitoring of Cancer Incidence in Japan (MCIJ) Project

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The Japan Cancer Surveillance Research Group estimated the cancer incidence in 2004 as part of the Monitoring of Cancer Incidence in Japan (MCIJ) project, on the basis of data collected from 14 of 31 population-based cancer registries. The total number of incidences in Japan for 2004 was estimated as 623 275 (C00–C96). The leading cancer site according to the crude and age-standardized incidence rates was the stomach for men and breast for women. The apparent increase in age-standardized incidence rates in 2003 was calmed down in 2004.

Key words: cancer incidence – incidence estimates – cancer registry – Japan

The Japan Cancer Surveillance Research Group is involved in cancer monitoring in Japan since 2000 (1–4). This group estimated the cancer incidence in 2004 as part of the Monitoring of Cancer Incidence in Japan (MCIJ) project, on the basis of data collected from 14 of 31 population-based cancer registries: Miyagi, Yamagata, Chiba, Kanagawa, Niigata, Fukui, Shiga, Osaka, Tottori, Okayama, Hiroshima, Saga, Kumamoto and Nagasaki. If data from all 31 registries were used, this would have led to a large underestimation of national cancer incidence because of under-registration. The methods of registry selection, estimation of incidence and the limitations of these methods have been explained in previous studies (5–7). As is mentioned in the last article, there were two major methodological changes in the MCIJ2003, and we maintained these changes in the present study: (i) we invited all 31 population-based cancer registries in Japan to participate, and from these, we selected the 14 cancer registries with high-quality data in order to estimate the national incidence, and (ii) we used 2004 data alone for the national estimation. For this year, Kumamoto prefecture was newly selected as one of the registries with high-quality data for the national estimation, but the other registries remained since the previous estimations.

The number of incidences, crude rates, age-standardized rates and completeness of registration in 2004 are shown in Table 1, and the age-specific number of incidences and the rates according to sex and primary site are shown in Tables 2 and 3. The total number of incidences in Japan for 2004 was estimated as 623 275 (C00–C96). The time trends of age-standardized incidence rates for the five major sites and male- and female-specific sites in 1975–2004 are shown in Fig. 1 (standard population: the world population) and in Fig. 2 (standard population: the 1985 Japanese model population). The leading cancer site according to the crude and age-standardized incidence rates was the stomach for men and the breast for women, as shown in Figs 1 and 2. The apparent increase in age-standardized incidence rates in 2003 because of development of hospital-based cancer registry in designated cancer care hospitals was calmed down in 2004. The estimated cancer incidence data in Japan by sex, site, 5-year age group and calendar year during the period 1975–2004 are available as a booklet and as an electronic database on the website (only available in Japanese, http://ganjoho.jp/professional/statistics/monita.html).

Table 1. Incidence, completeness of reporting and accuracy of diagnosis in Japan according to sex and primary site, 2004

Primary sites	ICD-10th	Number of incidence	Crude rate[a]	Age-standardized rate[a]		Completeness of reporting		Accuracy of diagnosis
				World population	Japanese 1985 model population	DCO/I (%)	I/M	MV/I (%)
Male								
All sites (incl. CIS)	C00–C96, D00–D09	372 913	598.6	282.3	400.4	17.1	1.93	73.8
All sites	C00–C96	362 149	581.3	273.9	388.6	17.6	1.88	73.2
Lip, oral cavity and pharynx	C00–C14	7136	11.5	6.0	8.1	14.1	1.77	79.7
Esophagus	C15	15 215	24.4	11.8	16.4	15.4	1.62	78.8
Stomach	C16	73 950	118.7	56.4	79.6	14.1	2.25	82.1
Colon	C18	35 657	57.2	26.7	38.1	12.4	2.68	82.4
Rectum	C19–C20	20 954	33.6	16.7	23.1	10.9	2.46	83.8
Liver	C22	28 172	45.2	21.5	30.2	25.6	1.20	33.7
Gallbladder etc.	C23–C24	9234	14.8	6.3	9.4	27.7	1.24	48.3
Pancreas	C25	13 128	21.1	9.6	13.9	31.3	1.10	33.8
Larynx	C32	3210	5.2	2.5	3.4	9.4	3.33	86.2
Trachea, bronchus and lung	C33–C34	55 984	89.9	38.9	58.1	24.3	1.27	70.2
Melanoma of skin etc.	C43–C44	4298	6.9	3.2	4.6	6.2	7.61	92.7
Prostate	C61	39 321	63.1	26.6	39.7	10.9	4.45	83.6
Bladder	C67	12 012	19.3	8.6	12.6	10.9	3.15	83.5
Kidney, renal pelvis, ureter etc.	C64–C66, C68	9358	15.0	7.5	10.5	15.4	2.43	76.1
Brain and nervous system	C70–C72	2352	3.8	2.6	3.1	29.4	2.58	63.4
Thyroid	C73	1933	3.1	1.8	2.4	8.3	4.53	86.9
Malignant lymphoma	C81–C85, C96	9436	15.1	8.0	10.8	17.4	1.96	82.0
Multiple myeloma	C88, C90	2723	4.4	1.9	2.8	29.4	1.37	64.9
All leukemias	C91–C95	5282	8.5	5.3	6.5	25.3	1.28	85.6
Female								
All sites (incl. CIS)	C00–C96, D00–D09	275 578	421.4	198.7	266.2	17.1	2.17	73.6
All site	C00–C96	261 126	399.3	183.5	247.2	18.0	2.05	72.4
Lip, oral cavity and pharynx	C00–C14	2980	4.6	2.1	2.8	14.7	1.94	78.1
Esophagus	C15	2600	4.0	1.6	2.2	22.4	1.47	70.2

Continued

Table 1. *Continued*

Primary sites	ICD-10th	Number of incidence	Crude rate[a]	Age-standardized rate[a]		Completeness of reporting		Accuracy of diagnosis
				World population	Japanese 1985 model population	DCO/I (%)	I/M	MV/I (%)
Stomach	C16	35 822	54.8	21.5	30.2	17.8	2.02	78.2
Colon	C18	29 070	44.5	16.9	23.8	16.6	2.21	76.5
Rectum	C19–C20	11 585	17.7	7.7	10.5	14.4	2.30	80.6
Liver	C22	13 343	20.4	7.1	10.3	30.4	1.20	29.7
Gallbladder etc.	C23–C24	10 457	16.0	4.7	7.0	33.3	1.18	40.2
Pancreas	C25	11 314	17.3	5.7	8.4	33.8	1.10	30.3
Larynx	C32	224	0.3	0.1	0.2	13.4	2.87	71.6
Trachea, bronchus and lung	C33–C34	24 122	36.9	13.7	19.5	25.3	1.51	67.3
Melanoma of skin etc.	C43–C44	4326	6.6	2.2	3.2	8.5	7.55	90.7
Breast (incl. CIS)	C50, D05	50 549	77.3	48.1	62.0	5.4	4.80	91.1
Uterus (incl. CIS)	C53–C55, D06	24 422	37.3	26.0	32.6	7.2	4.42	89.7
Uterus (only invasive)	C53–C55	17 603	26.9	16.6	21.4	9.5	3.19	86.9
Cervix uteri	C53	9252	14.1	9.5	12.2	6.8	3.71	89.6
Corpus uteri	C54	7253	11.1	6.5	8.4	5.2	5.05	91.8
Ovary	C56	8655	13.2	8.1	10.3	13.5	1.96	79.3
Bladder	C67	4039	6.2	2.0	2.9	16.9	2.32	74.7
Kidney, renal pelvis, ureter etc.	C64–C66, C68	4374	6.7	2.8	3.8	19.5	2.11	70.2
Brain and nervous system	C70–C72	2220	3.4	2.1	2.4	29.5	3.23	56.5
Thyroid	C73	7062	10.8	6.8	8.5	6.6	7.03	87.7
Malignant lymphoma	C81–C85, C96	8063	12.3	5.8	7.6	17.2	2.22	80.4
Multiple myeloma	C88, C90	2247	3.4	1.2	1.7	31.8	1.17	62.5
All leukemias	C91–C95	3726	5.7	3.3	3.9	25.7	1.28	85.0

ICD-10th, International Classification of Disease, 10th Revision; DCO/I, proportion of cases with the death certificate only to incident cases; I/M, number of incidence/number of deaths; MV/I, proportion of microscopically verified cases to incident cases; CIS, carcinoma *in situ*.
[a]Per 100 000 population.

Table 2. Age-specific incidence in Japan according to sex and primary site, 2004

Primary sites	ICD-10	All ages	Age group (years)																	
			0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
Male																				
All sites (incl. CIS)	C00–C96, D00–D09	372 913	388	171	210	282	535	1073	1727	2567	3891	8273	18 354	31 956	44 998	57 595	70 712	64 723	36 908	28 550
All sites	C00–C96	362 149	388	171	210	271	527	1056	1674	2438	3752	7980	17 771	30 896	43 301	55 799	68 663	63 034	36 053	28 165
Lip, oral cavity and pharynx	C00–C14	7136	0	0	0	16	15	33	63	58	124	290	602	812	1174	1176	1211	745	460	357
Esophagus	C15	15 215	0	0	0	0	0	1	5	8	65	328	863	1789	2633	2856	2744	2123	1198	602
Stomach	C16	73 950	0	0	5	6	10	154	243	369	739	2004	4117	7271	9433	11 844	14 072	12 063	6418	5202
Colon	C18	35 657	0	0	11	5	25	66	90	260	444	643	1762	2987	4635	5565	6765	6133	3462	2804
Rectum	C19–C20	20 954	0	0	0	0	1	31	61	235	305	558	1480	2740	3137	3508	3543	2808	1388	1159
Liver	C22	28 172	14	5	0	0	1	5	52	150	195	598	1450	2843	3811	5205	6061	4464	1952	1366
Gallbladder etc.	C23–C24	9234	0	0	4	0	0	3	28	39	32	122	292	446	733	1279	1668	1736	1447	1405
Pancreas	C25	13 128	0	1	0	0	0	9	16	31	133	274	765	1129	1555	1845	2340	2276	1535	1219
Larynx	C32	3210	0	0	0	0	0	0	0	8	11	80	166	348	548	555	630	474	228	162
Trachea, bronchus and lung	C33–C34	55 984	0	0	0	6	29	22	77	139	383	857	1952	3779	5646	7304	11 128	12 366	7287	5009
Melanoma of skin etc.	C43–C44	4298	10	0	0	7	20	35	33	51	77	108	179	270	336	520	739	820	522	571
Prostate	C61	39 321	0	0	0	0	0	0	0	21	19	96	549	1533	3952	7200	9284	8525	4534	3608
Bladder	C67	12 012	0	0	1	3	2	20	25	48	97	255	628	884	1171	1341	2224	2293	1668	1352
Kidney, renal pelvis, ureter etc.	C64–C66, C68	9358	20	2	0	0	22	21	53	82	151	442	715	1044	1039	1298	1736	1400	794	539
Brain and nervous system	C70–C72	2352	64	45	44	30	45	67	46	137	144	79	168	186	181	262	320	264	132	138
Thyroid	C73	1933	0	1	4	10	23	36	92	59	102	110	199	233	172	320	189	232	97	54
Malignant lymphoma	C81–C85, C96	9436	22	32	56	49	114	135	96	139	206	335	660	887	902	1296	1361	1392	1010	744
Multiple myeloma	C88, C90	2723	0	0	0	1	0	0	2	17	30	20	119	190	305	348	531	547	324	289
All leukemias	C91–C95	5282	127	71	41	53	67	131	119	165	187	140	334	504	562	611	611	775	462	322
Female																				
All sites (incl. CIS)	C00–C96, D00–D09	275 578	269	147	185	363	741	2395	4846	7321	10 069	13 866	20 044	24 791	27 244	29 778	34 370	34 462	29 140	35 547
All site	C00–C96	261 126	269	147	185	349	493	1514	3227	5874	8633	12 798	19 073	23 745	26 090	28 541	33 221	33 528	28 422	35 017

Continued

Table 2. *Continued*

Primary sites	ICD-10	All ages	Age group (years)																	
			0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
Lip, oral cavity and pharynx	C00–C14	2980	0	8	0	4	18	57	42	47	80	127	172	269	314	272	450	438	294	388
Esophagus	C15	2600	0	0	0	0	0	12	10	8	9	40	167	261	336	341	375	299	320	422
Stomach	C16	35 822	0	0	1	0	52	40	204	411	568	1161	1940	2747	3156	4000	5368	5409	4764	6001
Colon	C18	29 070	0	0	0	5	15	28	124	216	310	591	1507	2040	3161	3338	4365	4558	3966	4846
Rectum	C19–C20	11 585	0	0	0	0	4	10	75	206	194	483	813	1003	1363	1565	1602	1491	1273	1503
Liver	C22	13 343	14	1	0	3	0	4	30	10	45	80	353	624	1049	2066	2710	2558	1924	1872
Gallbladder etc.	C23–C24	10 457	0	0	0	0	0	0	6	15	31	87	247	380	625	967	1286	1796	2070	2947
Pancreas	C25	11 314	0	0	0	0	0	1	12	30	83	131	310	617	804	1350	1725	1936	1990	2325
Larynx	C32	224	0	0	0	0	0	0	0	0	1	0	5	22	21	17	53	55	28	22
Trachea, bronchus and lung	C33–C34	24 122	0	0	1	1	6	27	50	92	300	499	1080	1779	2288	2912	3811	3902	3156	4218
Melanoma of skin etc.	C43–C44	4326	0	2	2	4	7	31	55	55	30	61	126	215	307	340	535	673	659	1224
Breast (incl. CIS)	C50, D05	50 549	1	0	1	0	19	253	1039	2397	4204	6181	6635	6965	6556	5073	4060	3338	2104	1723
Uterus (incl. CIS)	C53–C55, D06	24 422	0	0	2	23	251	1168	2430	2605	2465	1909	2752	2636	1973	1737	1355	1256	788	1072
Uterus (only invasive)	C53–C55	17 603	0	0	2	12	32	334	900	1334	1433	1269	2397	2319	1738	1531	1267	1196	773	1066
Cervix uteri	C53	9252	0	0	0	8	27	297	759	1139	1094	673	994	878	753	645	528	592	385	480
Corpus uteri	C54	7253	0	0	2	4	5	37	134	172	321	560	1323	1371	927	827	657	478	209	226
Ovary	C56	8655	1	1	28	53	91	199	150	404	519	792	1202	1202	917	773	734	697	446	446
Bladder	C67	4039	0	0	0	1	4	0	0	30	22	72	101	248	298	366	628	579	683	1007
Kidney, renal pelvis, ureter etc.	C64–C66, C68	4374	25	6	3	4	2	5	35	29	71	141	244	303	445	508	676	701	560	616
Brain and nervous system	C70–C72	2220	43	22	58	58	11	57	48	68	67	76	180	177	122	265	231	307	197	233
Thyroid	C73	7062	0	0	8	43	130	191	297	327	402	562	761	1155	762	815	602	459	277	271
Malignant lymphoma	C81–C85, C96	8063	8	30	21	40	29	117	101	107	247	292	540	720	889	930	1042	1020	929	1001
Multiple myeloma	C88, C90	2247	0	0	0	0	0	0	3	6	10	19	60	183	163	235	375	522	346	325
All leukemias	C91–C95	3726	91	34	36	74	35	83	60	113	104	162	163	251	364	456	367	515	385	433

Table 3. Age-specific incidence rate per 100 000 population in Japan according to sex and primary site, 2004

Primary sites	ICD-10	All ages	Age group (years)																
			0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
Male																				
All sites (incl. CIS)	C00–C96, D00–D09	598.6	13.2	5.6	6.8	8.1	13.5	24.1	34.8	58.9	97.9	210.2	396.2	671.1	1073.2	1653.1	2396.2	2985.4	3266.2	3693.4
All sites	C00–C96	581.3	13.2	5.6	6.8	7.8	13.3	23.7	33.8	55.9	94.4	202.7	383.6	648.8	1032.7	1601.6	2326.8	2907.5	3190.5	3643.6
Lip, oral cavity and pharynx	C00–C14	11.5	0.0	0.0	0.0	0.5	0.4	0.7	1.3	1.3	3.1	7.4	13.0	17.1	28.0	33.8	41.0	34.4	40.7	46.2
Esophagus	C15	24.4	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	1.6	8.3	18.6	37.6	62.8	82.0	93.0	97.9	106.0	77.9
Stomach	C16	118.7	0.0	0.0	0.2	0.2	0.3	3.5	4.9	8.5	18.6	50.9	88.9	152.7	225.0	340.0	476.9	556.4	568.0	673.0
Colon	C18	57.2	0.0	0.0	0.4	0.1	0.6	1.5	1.8	6.0	11.2	16.3	38.0	62.7	110.5	159.7	229.2	282.9	306.4	362.7
Rectum	C19–C20	33.6	0.0	0.0	0.0	0.0	0.0	0.7	1.2	5.4	7.7	14.2	31.9	57.5	74.8	100.7	120.1	129.5	122.8	149.9
Liver	C22	45.2	0.5	0.2	0.0	0.0	0.0	0.1	1.0	3.4	4.9	15.2	31.3	59.7	90.9	149.4	205.4	205.9	172.7	176.7
Gallbladder etc.	C23–C24	14.8	0.0	0.0	0.1	0.0	0.0	0.1	0.6	0.9	0.8	3.1	6.3	9.4	17.5	36.7	56.5	80.1	128.1	181.8
Pancreas	C25	21.1	0.0	0.0	0.0	0.0	0.0	0.2	0.3	0.7	3.3	7.0	16.5	23.7	37.1	53.0	79.3	105.0	135.8	157.7
Larynx	C32	5.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.3	2.0	3.6	7.3	13.1	15.9	21.3	21.9	20.2	21.0
Trachea, bronchus and lung	C33–C34	89.9	0.0	0.0	0.0	0.2	0.7	0.5	1.6	3.2	9.6	21.8	42.1	79.4	134.7	209.6	377.1	570.4	644.9	648.0
Melanoma of skin etc.	C43–C44	6.9	0.3	0.0	0.0	0.2	0.5	0.8	0.7	1.2	1.9	2.7	3.9	5.7	8.0	14.9	25.0	37.8	46.2	73.9
Prostate	C61	63.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.5	0.5	2.4	11.8	32.2	94.3	206.7	314.6	393.2	401.2	466.8
Bladder	C67	19.3	0.0	0.0	0.0	0.1	0.1	0.4	0.5	1.1	2.4	6.5	13.6	18.6	27.9	38.5	75.4	105.8	147.6	174.9
Kidney, renal pelvis, ureter etc.	C64–C66, C68	15.0	0.7	0.1	0.0	0.0	0.6	0.5	1.1	1.9	3.8	11.2	15.4	21.9	24.8	37.3	58.8	64.6	70.3	69.7
Brain and nervous system	C70–C72	3.8	2.2	1.5	1.4	0.9	1.1	1.5	0.9	3.1	3.6	2.0	3.6	3.9	4.3	7.5	10.8	12.2	11.7	17.9
Thyroid	C73	3.1	0.0	0.0	0.1	0.3	0.6	0.8	1.9	1.4	2.6	2.8	4.3	4.9	4.1	9.2	6.4	10.7	8.6	7.0
Malignant lymphoma	C81–C85, C96	15.1	0.7	1.1	1.8	1.4	2.9	3.0	1.9	3.2	5.2	8.5	14.2	18.6	21.5	37.2	46.1	64.2	89.4	96.2
Multiple myeloma	C88 C90	4.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.8	0.5	2.6	4.0	7.3	10.0	18.0	25.2	28.7	37.4
All leukemias	C91–C95	8.5	4.3	2.3	1.3	1.5	1.7	2.9	2.4	3.8	4.7	3.6	7.2	10.6	13.4	17.5	20.7	35.7	40.9	41.7
Female																				
All sites (incl. CIS)	C00–C96, D00–D09	421.4	9.6	5.1	6.3	11.0	19.7	55.8	99.7	170.1	256.0	353.9	429.5	508.2	611.0	771.7	977.8	1176.2	1384.3	1811.8
All site	C00–C96	399.3	9.6	5.1	6.3	10.6	13.1	35.3	66.4	136.5	219.5	326.6	408.7	486.8	585.1	739.6	945.1	1144.3	1350.2	1784.8

Continued

Table 3. *Continued*

Primary sites	ICD-10	All ages	Age group (years)																
			0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+
Lip, oral cavity and pharynx	C00–C14	4.6	0.0	0.3	0.0	0.1	0.5	1.3	0.9	1.1	2.0	3.2	3.7	5.5	7.0	7.0	12.8	14.9	14.0	19.8
Esophagus	C15	4.0	0.0	0.0	0.0	0.0	0.0	0.3	0.2	0.2	0.2	1.0	3.6	5.4	7.5	8.8	10.7	10.2	15.2	21.5
Stomach	C16	54.8	0.0	0.0	0.0	0.0	1.4	0.9	4.2	9.6	14.4	29.6	41.6	56.3	70.8	103.7	152.7	184.6	226.3	305.9
Colon	C18	44.5	0.0	0.0	0.0	0.2	0.4	0.7	2.6	5.0	7.9	15.1	32.3	41.8	70.9	86.5	124.2	155.6	188.4	247.0
Rectum	C19–C20	17.7	0.0	0.0	0.0	0.0	0.1	0.2	1.5	4.8	4.9	12.3	17.4	20.6	30.6	40.6	45.6	50.9	60.5	76.6
Liver	C22	20.4	0.5	0.0	0.0	0.1	0.0	0.1	0.6	0.2	1.1	2.0	7.6	12.8	23.5	53.5	77.1	87.3	91.4	95.4
Gallbladder etc.	C23–C24	16.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.3	0.8	2.2	5.3	7.8	14.0	25.1	36.6	61.3	98.3	150.2
Pancreas	C25	17.3	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.7	2.1	3.3	6.6	12.6	18.0	35.0	49.1	66.1	94.5	118.5
Larynx	C32	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.5	0.5	0.4	1.5	1.9	1.3	1.1
Trachea, bronchus and lung	C33–C34	36.9	0.0	0.0	0.0	0.0	0.2	0.6	1.0	2.1	7.6	12.7	23.1	36.5	51.3	75.5	108.4	133.2	149.9	215.0
Melanoma of skin etc.	C43–C44	6.6	0.0	0.1	0.1	0.1	0.2	0.7	1.1	1.3	0.8	1.6	2.7	4.4	6.9	8.8	15.2	23.0	31.3	62.4
Breast (incl. CIS)	C50, D05	77.3	0.0	0.0	0.0	0.0	0.5	5.9	21.4	55.7	106.9	157.8	142.2	142.8	147.0	131.5	115.5	113.9	100.0	87.8
Uterus (incl. CIS)	C53–C55, D06	37.3	0.0	0.0	0.1	0.7	6.7	27.2	50.0	60.5	62.7	48.7	59.0	54.0	44.2	45.0	38.5	42.9	37.4	54.6
Uterus (only invasive)	C53–C55	26.9	0.0	0.0	0.1	0.4	0.8	7.8	18.5	31.0	36.4	32.4	51.4	47.5	39.0	39.7	36.0	40.8	36.7	54.3
Cervix uteri	C53	14.1	0.0	0.0	0.0	0.2	0.7	6.9	15.6	26.5	27.8	17.2	21.3	18.0	16.9	16.7	15.0	20.2	18.3	24.5
Corpus uteri	C54	11.1	0.0	0.0	0.1	0.1	0.1	0.9	2.8	4.0	8.2	14.3	28.3	28.1	20.8	21.4	18.7	16.3	9.9	11.5
Ovary	C56	13.2	0.0	0.0	0.9	1.6	2.4	4.6	3.1	9.4	13.2	20.2	25.8	24.6	20.6	20.0	20.9	23.8	21.2	22.7
Bladder	C67	6.2	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.7	0.6	1.8	2.2	5.1	6.7	9.5	17.9	19.8	32.4	51.3
Kidney, renal pelvis, ureter etc.	C64–C66, C68	6.7	0.9	0.2	0.1	0.1	0.1	0.1	0.7	0.7	1.8	3.6	5.2	6.2	10.0	13.2	19.2	23.9	26.6	31.4
Brain and nervous system	C70–C72	3.4	1.5	0.8	2.0	1.8	0.3	1.3	1.0	1.6	1.7	1.9	3.9	3.6	2.7	6.9	6.6	10.5	9.4	11.9
Thyroid	C73	10.8	0.0	0.0	0.3	1.3	3.4	4.4	6.1	7.6	10.2	14.3	16.3	23.7	17.1	21.1	17.1	15.7	13.2	13.8
Malignant lymphoma	C81–C85, C96	12.3	0.3	1.0	0.7	1.2	0.8	2.7	2.1	2.5	6.3	7.5	11.6	14.8	19.9	24.1	29.6	34.8	44.1	51.0
Multiple myeloma	C88 C90	3.4	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.3	0.5	1.3	3.8	3.7	6.1	10.7	17.8	16.4	16.6
All leukemias	C91–C95	5.7	3.3	1.2	1.2	2.2	0.9	1.9	1.2	2.6	2.6	4.1	3.5	5.1	8.2	11.8	10.4	17.6	18.3	22.1

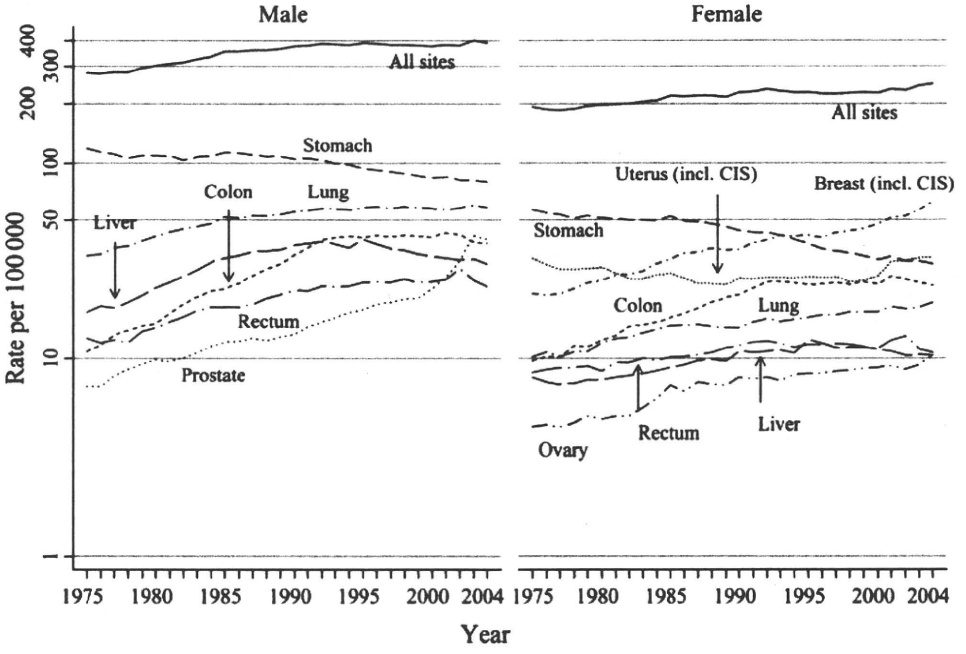

Figure 1. Trends of age-standardized cancer incidence rates for five major sites and specific sites for each sex (standard population: world population). CIS, carcinoma *in situ*.

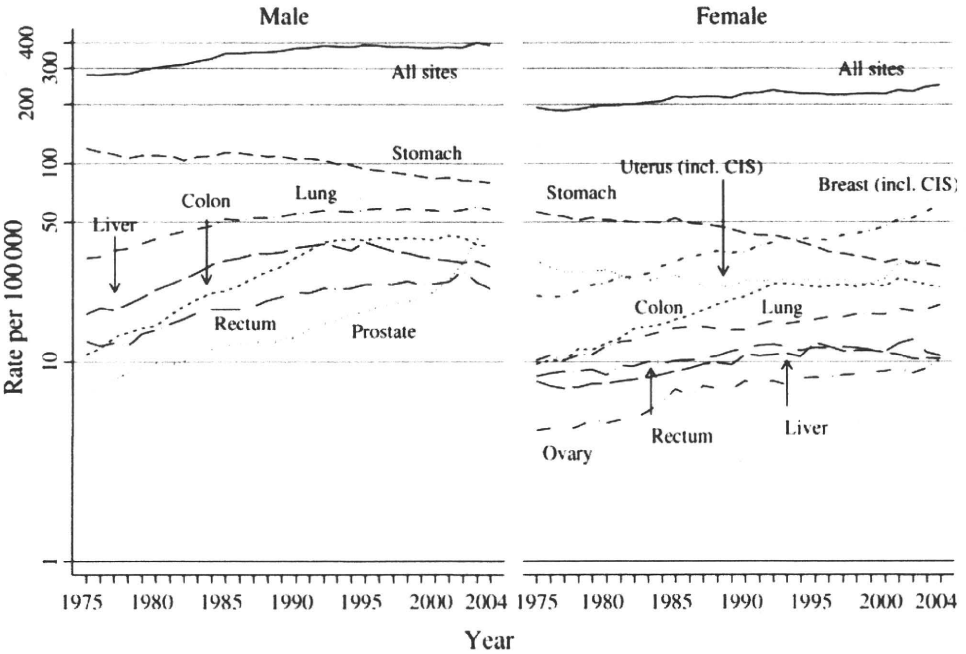

Figure 2. Trends of age-standardized cancer incidence rates for five major sites and specific sites for each sex (standard population: 1985 Japanese model population).

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Conflict of interest statement

None declared.

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—Original—

Early Detection of Subclinical Anthracycline Cardiotoxicity on the Basis of QT Dispersion

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Abstract

Background: We examined whether dobutamine-stress QT dispersion (QTd) and heart-rate corrected QT dispersion (QTcd) are useful for detecting subclinical anthracycline cardiotoxicity.

Methods: The subjects were10 control subjects and 37 patients divided into 4 groups according to cumulative anthracycline dose: non-anthracycline group (group N), 7 patients; low anthracycline cumulative dose group (group L), 8 patients (<200 mg/m^2); medium anthracycline cumulative dose group (group M), 16 patients (200 to <400 mg/m^2); and high cumulative group (group H), 6 patients (≥400 mg/m^2). Standard 12-lead electrocardiograms were recorded. QTd and QTcd were measured and calculated at rest and after administration of dobutamine at 5 or 30 μg/kg/min. We also estimated cardiac function and cardiac reserve function at rest and after administration of dobutamine at a dose of 5 or 30 μg/kg/min.

Results: At rest, QTd and QTcd were significantly greater in groups M and H. After administration of dobutamine at 30 μg/kg/min, QTd and QTcd were significantly greater in groups L, M, and H. There was good correlation between QTd and the cumulative anthracycline dose; the correlation formula was $y=0.051x + 42.2$ ($r=0.81$, $p<0.001$). The cumulative anthracycline dose of 152.9 mg/m^2, calculated from the correlation formula, was the cut-off for detection of electrophysiological cardiac abnormalities. Cardiac performance data at rest and dobutamine stress by echocardiography and pulsed Doppler echocardiography are less sensitive for detecting cardiac abnormalities than are QTd and QTcd.

Conclusions: Dobutamine-stress QTd and QTcd are useful for detecting anthracycline cardiotoxicity and subclinical cardiac abnormality at low cumulative anthracycline doses. We must be aware of the possibility of subclinical myocardial abnormalities in patients with a cumulative anthracycline dose of ≥150 mg/m^2.

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Key words: anthracycline cardiotoxicity, QT dispersion, heart-rate corrected QT dispersion, dobutamine, malignancy

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Introduction

Anthracyclines, such as daunorubicin and doxorubicin, are highly effective antineoplastic agents in the treatment of solid tumors and hematological malignancies and form an important component of many antineoplastic chemotherapeutic regimens. Unfortunately, because anthracycline have acute and chronic effects on the myocardium, their use is limited by their cardiotoxicity. Acute anthracycline cardiotoxicity causes electrocardiographic abnormalities, such as sinus tachycardia, ST depression, and arrhythmias, during administration or several hours to several days after administration. However, most of the acute cardiotoxic effects of anthracycline are transient and reversible[1]. In contrast, chronic anthracycline cardiotoxicity causes irreversible cardiomyopathies and congestive heart failure that can restrict physical activity. The incidence of chronic anthracycline cardiotoxicity depends on the cumulative anthracycline dose administered. For example, the incidence of congestive heart failure is 0.01% to 0.27% for cumulative anthracycline doses $<550\ mg/m^2$, and is >30% for cumulative anthracycline doses $>550\ mg/m^2$ [2,3]. Even at low doses, anthracyclines can cause subclinical myocardial damage with late fibrosis of the myocardium, as seen in biopsy specimens[4]. Therefore, effective monitoring of the cardiotoxic effects of anthracycline requires early assessment of both cardiac function and cardiac reserve function. This form of assessment may involve an exercise test. We previously performed exercise-stress echocardiography using a supine bicycle for asymptomatic patients receiving anthracycline therapy, and detected cardiac dysfunction even in children who received low-dose anthracycline therapy ($175\ mg/m^2$)[5]. For patients with a low tolerance for physical exercise, such as infants and small children, monitoring of cardiac function requires an alternative exercise test, such as a drug-induced exercise test.

QT dispersion is defined as the difference between the maximum and minimum QT interval durations on 12-lead standard electrocardiography (ECG), and is considered to reflect local differences in the repolarization of the myocardium. QT dispersion, which reflects cardiac autonomic imbalance[13], increases in various cardiac diseases, such as heart failure[6], cardiomyopathy[7], ischemic heart disease[8], hypertension[10], long-QT syndrome[11,12], and after myocardial infarction[9]. QT dispersion is useful for determining prognosis in these diseases.

We hypothesize that dobutamine-stress QT dispersion (QTd) can be used to detect the ventricular spatial heterogeneity of repolarization, which is a sign of anthracycline cardiotoxicity at lower cumulative doses in long-term survivors after early-stage treatment for childhood malignancies. This study presents data to test this hypothesis.

Patients and Methods

Subjects

The subjects were 37 long-term survivors of childhood malignancies who underwent anthracycline therapy from 1998 through 2003 at our hospital (17 female and 20 male; present age range, 3 years 7 months to 28 years 3 months), and 10 volunteer healthy control subjects (control group; age range, 17–28 years). Of the 37 patients, 24 had had acute lymphoblastic leukemia, 5 had had acute non-lymphoblastic leukemia, 2 had had Ewing sarcoma, 3 had had non-Hodgkin's lymphoma, 1 had had neuroblastoma, 1 had had Wilms tumor, and 1 had had Langerhans cell histiocytosis. The cumulative anthracycline doses of the patients ranged from 0 to $840\ mg/m^2$ (**Table 1**). None of the patients had symptoms of congestive heart failure. The patients were divided into 4 groups according to their cumulative anthracycline dose, based on our previous findings[14]. The groups were the non-anthracycline (group N, 7 patients); the low cumulative anthracycline dose group (group L, $<200\ mg/m^2$; 8 patients); the middle cumulative anthracycline dose group (group M, $200-<400\ mg/m^2$; 16 patients); and the high cumulative anthracycline dose group (group H, $\geq 400\ mg/m^2$; 6 patients) (**Table 1**). Informed consent was obtained for all subjects.