

Clinical and Epidemiologic Characteristics of First Primary Tumors of the Central Nervous System and Related Organs among Atomic Bomb Survivors in Hiroshima and Nagasaki, 1958–1995

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BACKGROUND. Analysis conducted in the Life Span Study (LSS) cohort of atomic bomb survivors in Hiroshima and Nagasaki found a significant dose-related excess of tumors of the central nervous system (CNS) and the pituitary gland. The objective of the current study was to evaluate clinical and epidemiologic characteristics of first primary tumors of the CNS and the pituitary gland in this cohort and to compare them with characteristics among other populations.

METHODS. CNS and pituitary gland tumors that were diagnosed between 1958 and 1995 among 80,160 LSS cohort members were ascertained through Hiroshima and Nagasaki tumor registries, autopsy reports, and other sources. Pathologists reviewed all available records and slides to verify histologic diagnoses. Poisson regression analysis was used to model background incidence rates allowing for radiation effects.

RESULTS. Meningioma was the most common tumor among clinically diagnosed tumors, followed by neuroepithelial tumor, schwannoma, and pituitary tumor. The overall incidence of these tumors increased initially with age but declined among the elderly. For all age groups and for both genders, incidence increased over time. By contrast, when tumors diagnosed at autopsy were included, incidence rose continuously with age and was stable over time.

CONCLUSIONS. The main characteristics of CNS and pituitary gland tumors diagnosed in the LSS cohort were consistent with the characteristics of "spontaneous" tumors observed in other population-based studies. The predominance of meningiomas over neuroepithelial tumors in the Japanese population was noteworthy and warrants further investigation. The secular rise in incidence of all clinically diagnosed CNS and pituitary gland tumors is most likely to be attributable to the increased use of new imaging techniques. *Cancer* 2004;101:1644–54.

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Ionizing radiation is one of the few established causes of neural tumors.^{1–4} The evidence is especially convincing for children who are treated with low-to-moderate doses of radiation for a variety of benign conditions of the head and neck^{5–9} or with high doses of

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radiation for first primary malignancies, particularly acute lymphoblastic leukemia.¹⁰ An analysis based on the Life Span Study (LSS) cohort of atomic bomb survivors in Hiroshima and Nagasaki found a significant dose-related excess of tumors of the central nervous system (CNS), cranial and spinal nerves, and pituitary gland combined (excess relative risk per sievert [Sv] [ERR_{Sv}] = 1.2; 95% confidence interval, 0.6–2.1).¹¹ Greater than 50% of the cohort members were age \geq 20 years at the time of exposure, and only 3% had estimated brain doses in excess of 1 Sv. In addition, the dose response was significant when the analysis was limited to the cohort members who received brain doses $<$ 1 Sv; thus, these results add to the evidence of effects of low-dose ionizing radiation on the adult CNS. Given the dose distribution in this cohort, it was estimated that \approx 36 of 263 (14%) first primary tumors of the CNS and the pituitary gland could be attributed to radiation exposure.¹¹ Therefore, it may be expected that the majority of the observed tumors will have the characteristics of “spontaneous” tumors.

Epidemiologic data concerning brain tumors in Japan are limited.^{12,13} The overall incidence of brain tumors, particularly malignant tumors, is low, around 2 per 100,000 population (age-standardized to the world population), compared with 6–8 per 100,000 population in North America and Europe.¹⁴ In addition, the distribution of major histologic subtypes is different.^{12,13} However, the reasons for these differences are unknown. The main objective of the current report was to provide descriptive information on clinical and pathologic characteristics and epidemiology of the CNS and pituitary gland tumors diagnosed within the LSS cohort and to compare them with other populations.

MATERIALS AND METHODS

Tumor Ascertainment

Tumors were ascertained within the full LSS cohort of atomic bomb survivors from Hiroshima and Nagasaki.¹¹ Establishment of the LSS cohort and its characteristics has been described elsewhere.¹⁵ The current analysis was limited to a subcohort of 80,160 LSS members who were in Hiroshima and Nagasaki at the time of the atomic bombings, for whom organ dose estimates could be computed, and who were alive and not known to have cancer when population-based tumor registries in Hiroshima and Nagasaki were established (January 1, 1957, and January 1, 1958, respectively).^{16,17}

Tumors initially were identified through Hiroshima and Nagasaki tumor registries and supplemented with information and tissue slides obtained

from pathology-based tissue registries for histologically diagnosed malignant and benign tumors (since 1973); relevant autopsy, surgical, and other clinical records of the Radiation Effects Research Foundation (RERF) and major medical institutions in Hiroshima and Nagasaki; and death certificates. The autopsy program conducted at RERF strived to enhance ascertainment of tumors and was particularly active from the late 1950s through 1977.¹⁸ The selection of potential tumors was not limited to tumors of the CNS, including the brain and spinal cord, but also included tumors in neighboring organs, such as the cranial and spinal nerves, the pituitary gland, sellar and parasellar regions, and the pineal gland. The date of diagnosis was taken as the date when the patient first saw a physician to receive medical treatment as a result of symptoms, the date when the patient first was diagnosed by a physician despite being free from symptoms, or the date of death for tumors identified at autopsy. Clinical information of interest, including symptoms around the time of diagnosis, tumor location, size, and use of imaging techniques (computed tomography [CT] or magnetic resonance imaging [MRI]), was abstracted from individual records archived on all the patients at RERF. Information regarding tumor laterality and size was incomplete and is not presented herein. Cases that were first discovered postmortem are defined further as diagnosed incidentally at autopsy; otherwise, these are considered clinically diagnosed, including 10 incidental findings in asymptomatic patients during clinical examinations for unrelated reasons.

Pathology Review

All materials, including tissue slides, pathology and clinical records, and death certificates for all eligible patients, were reviewed independently by four members of a pathology panel.¹¹ The pathology panel classified tumors by anatomic site (topography), histologic type (morphology), and tumor behavior according to World Health Organization (WHO) criteria.¹⁹ In case of a discrepancy, the pathology panel met again to reach consensus.

Radiation Terminology and Dose Estimation

Gray units (Gy) are used to refer to doses of radiation in which no allowance is made for the biologic effectiveness of different types of radiation. If allowance is made for the different effectiveness of various types of radiation, then the resulting dose equivalent is expressed using Sv. An absorbed dose of 1 Gy is equal to 100 rad, and 1 Sv is equal to 100 rem.

The estimation of radiation doses to the brain was based on the DS86 dosimetry system.²⁰ The current

analysis cohort included 234 individuals with shielded kerma estimates ≥ 4 Gy. Because survival after such exposures is implausible, shielded kerma estimates for these survivors were truncated to 4 Gy with a proportional reduction of the brain dose. Individual-weighted brain doses (dose equivalents, Sv) were computed as the sum of the γ -ray dose plus 10 times the neutron dose, allowing for the greater biologic effectiveness of neutron radiation. The dose estimates incorporated a correction to reduce bias arising as a result of random errors in individual dose estimates.²¹

Statistical Analysis

Population rates were computed using the AMFIT program for Poisson regression of grouped survival data.²² Person-years (PYs) of observation were computed from January 1, 1958, until the date of diagnosis of the tumor, the date of death, or December 31, 1995, whichever occurred first. Because tumors diagnosed outside the catchment area were excluded from the analysis, PYs were adjusted for immigration and emigration rates based on data of the Adult Health Study.¹⁷ This adjustment reduced the total number of PYs by approximately 15%, with larger reductions for those who were exposed as children (20%) compared with those who were exposed later in life (5%). In addition, we limited our analysis to first primary tumors of the CNS and pituitary gland, because a prior malignancy or its treatment could increase the chances of development or diagnosis of a subsequent malignancy. Overall, 1,989,297 PYs were accumulated (745,157 PYs in males and 1,244,140 PYs in females), for a mean of approximately 25 years per person.

We modeled background incidence rates allowing for radiation effect using the general excess relative risk (ERR) model: $\lambda(s, a, t, b) * [1 + \pi(d)]$, in which $\lambda(s, a, t, b)$ describes a background rate as a function of gender (s), log-attained age (a_1), or log-attained age plus squared log-attained age (a_2) for clinically diagnosed tumors (to allow for a downturn in incidence among the elderly), calendar year (t_1) or a stepwise increase from 1975 to 1985 (t_2), and birth cohort (b); $\pi(d)$ is a linear function for radiation dose response. We used the model-adjusted incidence rate for a man age 60 years in 1980 with a brain dose = 0 mSv as the basic summary measure of baseline risks. Separate analyses both including and excluding autopsy data are presented. All reported P values are two-sided and are based on likelihood ratio tests.

RESULTS

Four hundred sixty-seven primary tumors of the CNS and pituitary gland in LSS cohort members were accepted by the pathology panel from the initial screen-

ing. We excluded 73 tumors in individuals who were not in Hiroshima or Nagasaki at the time of the bombings, 35 individuals who did not have available organ dose estimates, and 27 individuals who died or were diagnosed before January 1, 1958. We also excluded 11 tumors that occurred in cohort members outside the tumor registry catchment area and 58 tumors that were diagnosed after first primary tumor(s). This resulted in 263 tumors for inclusion in the current analysis.

Selected characteristics of first primary tumors of the CNS and pituitary gland are presented in Table 1. For the purpose of further analysis, we grouped tumors in several categories: meningioma ($n = 88$ tumors), schwannoma ($n = 55$ tumors), glioma and other neuroepithelial tumors ($n = 44$ tumors), pituitary tumors ($n = 35$ tumors), and miscellaneous tumors ($n = 41$ tumors), which included not otherwise specified (NOS) tumors ($n = 27$ tumors) without histologic material or with incomplete records and a mix of uncommon tumors ($n = 14$ tumors). The proportion of histologic confirmation for all tumor types, with the exception of miscellaneous tumors, was high and ranged between 84% and 92% (Table 1). Because of the heterogeneous nature of miscellaneous tumors and the absence of histologic data for NOS tumors, we do not emphasize findings for this group. However, the group was included in all analyses that were based on the total case series.

Clinical Characteristics of Tumors by Histologic Type

Meningiomas

The proportion of meningioma diagnosed incidentally either at autopsy (36%) or at clinical examination (11%) was second only to that for pituitary tumors, reflecting the relatively benign nature of the majority of meningiomas (Table 1). There were three (3%) malignant meningiomas (Table 1). All occurred in females and had a calvarial location; 2 patients were individuals with a brain dose = 0 mSv, and 1 patient had a brain dose = 800 mSv. The remaining histologic types of meningioma were fibrous (34%), transitional/mixed (32%), meningothelial (15%), and other (16%). In addition, there were 3 double meningiomas (3%), 2 of which were diagnosed incidentally at autopsy (data not shown). The ratio of calvarial to basal skull meningiomas was 2.3:1.0 (Table 1). The convexity, particularly the parietal region (24%), was the most common site of calvarial meningioma. Among the basal meningiomas, approximately 54% were within the sphenoid region. A wide variety of symptoms were observed in the patients with clinically diagnosed meningioma, the most common of which were headache, motor deficits, and dizziness (Table 1).

TABLE 1
Selected Clinical Characteristics of First Primary Tumors of the Central Nervous System and Pituitary Gland Identified in the Life Span Study Cohort, 1958–1995

Tumor type	No. of tumors	ICDO-2 codes	Reviewed by pathology panel ^a	No. of tumors (%)			Tumor location (no.)	Prevalence of clinical symptoms (%) ^c
				Diagnosed incidentally		Malignant behavior ^a		
				At autopsy ^a	During clinical examination ^b			
Meningioma	88	9530, 9531, 9532, 9533, 9534, 9537	81 (92)	32 (36)	6 (11)	3 (3)	Cranial (88): calvarial (61), basal (26), unknown (1)	Headache (38), motor deficits (17), dizziness (10)
Schwannoma	55	9560	49 (89)	13 (24)	1 (2)		Cranial (33): acoustic (27), other cranial (6) Spinal (22): C1–L5 level (15), cauda equina (7)	Hearing loss/tinnitus (62), sensory deficits (15), gait disturbances (12) Gait disturbances (38), sensory deficits (12), motor deficits (12)
Glioma and other neuroepithelial tumors	44	9384, 9400, 9401, 9411, 9380, 9382, 9390, 9392, 9394, 9440, 9442, 9451, 9503	37 (84)	10 (23)	1 (3)	42 (95)	Cranial (41), spinal (3)	Motor deficits (45), seizures (23), headache (19)
Pituitary tumor	35	8140, 8270, 8280, 9350	30 (86)	17 (48)	2 (11)		Pituitary gland (34), craniopharyngeal duct (1)	Motor deficits (14), headache (8), visual disturbances (57)
Miscellaneous tumor	41		13 (32)				Cranial (35), spinal (6)	Headache (31), hearing loss/tinnitus (15), visual disturbances (15)
NOS	27	8000		4 (10)		10 (24)		
Other	14	9121, 9150, 9370, 9590	13 (93)	4 (28)		10 (71)		

ICDO-2: International Classification of Diseases for Oncology (ICDO-2), second edition, 2000 (morphology codes); C1–L5: cervical vertebrae 1 through lumbar vertebrae 5; NOS: not otherwise specified.

^a Relative to the overall number of tumors within the particular group.

^b Relative to the number of clinically diagnosed tumors (excluding autopsy diagnoses) within the particular group.

^c The top three of the most prevalent symptoms around the time of diagnosis for clinically diagnosed tumors.

Schwannomas

Although the craniospinal nerve roots are considered to be a part of the peripheral nervous system rather than the CNS, we treated tumors arising from cranial and spinal nerve roots along with the CNS tumors in accordance with the WHO classification system.^{2,3} All neoplasms in this group were benign schwannomas, and none were associated with clinical neurofibromatosis. Twenty-four percent of schwannomas were diagnosed first at autopsy (Table 1). All the cranial schwannomas were located within the cerebellopontine angle area. The most prevalent symptoms at onset, as expected, were hearing loss or tinnitus, followed by sensory deficits, and gait disturbance (Table 1). Among 22 spinal schwannomas, 15 were located between the cervical first and lumbar fifth spinal levels, and the remaining 7 spinal schwannomas were within

the cauda equina. Gait disturbance was the most common symptom at the time of diagnosis, followed by sensory and motor deficits.

Glioma and other neuroepithelial tumors

A relatively high percentage of neuroepithelial tumors was diagnosed at autopsy (23%) (Table 1), despite the aggressive nature of these tumors (6 of 10 tumors were glioblastoma; 7 tumors were diagnosed before 1976 in individuals age ≥ 65 years). Overall, tumors of neuroepithelial origin were intracranial (Table 1), with the exception of two spinal ependymomas and one spinal neuroepithelioma. The most common subtypes were glioblastoma (*n* = 13 tumors), followed by anaplastic astrocytoma (*n* = 11 tumors). These tumors typically were manifest by motor deficits or seizures (Table 1).

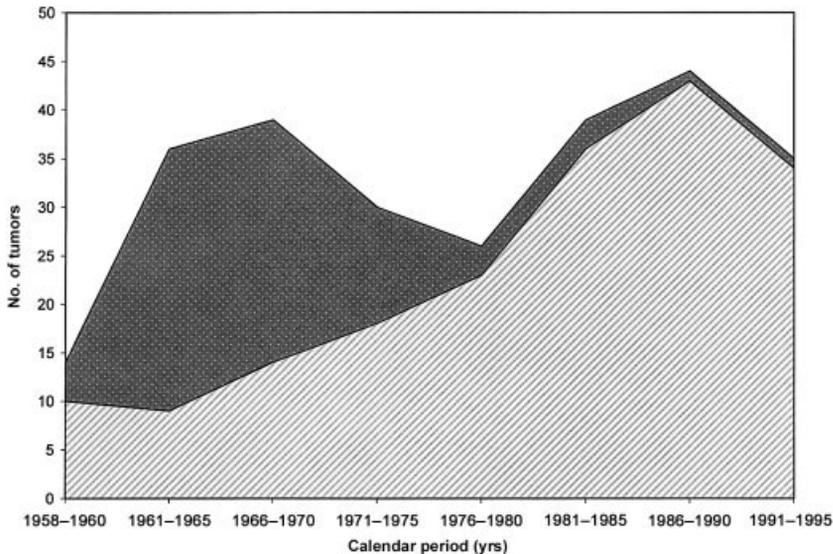


FIGURE 1. This chart illustrates the distribution of first primary tumors of the central nervous system and pituitary gland by calendar period and method of ascertainment in the Life Span Study cohort, 1958–1995. Dotted area: tumors that were diagnosed at autopsy; slashed area: clinically diagnosed tumors.

Pituitary tumors

There were 34 pituitary adenomas and 1 craniopharyngioma in the current study population. This group had the largest proportion of tumors that were diagnosed incidentally, either at autopsy (48%) or at clinical examination (11%) (Table 1). Among 18 clinically diagnosed tumors, there were 4 functional adenomas (2 prolactinomas, 1 plurihormonal adenoma, and 1 growth hormone adenoma) and 5 nonfunctional adenomas; the remaining 9 tumors were not classified according to immunohistochemical subtype because of poor quality or inadequate preservation of tissue specimens. The most common symptom at the time of diagnosis was visual disturbance, reflecting the close proximity of the pituitary gland to the optical chiasm.

Incidence Rates

Overall, 29% of tumors were identified incidentally at autopsy. Figure 1 presents the distribution of 263 tumors by calendar period and method of ascertainment. It is evident that the early peak corresponds to tumors that were identified by the autopsy program (late 1950s through 1977). Because autopsy-diagnosed tumors could influence the analysis of background incidence rates, particularly with respect to age and time trends, we present data both including (Table 2) and excluding (Table 3) tumors that were identified at autopsy.

Our previous analysis showed,¹¹ and Tables 2 and 3 demonstrate, that the incidence rate of first primary CNS and pituitary gland tumors increased with radiation dose, overall and for clinically diagnosed tumors; thus, throughout this article, we report model-adjusted background incidence rates for individuals

with a brain dose = 0 mSv. In females, meningioma was the most common clinically diagnosed tumor and was observed 2.5 times more frequently than in males ($P = 0.004$) (Table 3). It was followed by neuroepithelial tumor, schwannoma, and pituitary tumor. In males, the incidence of clinically diagnosed neuroepithelial tumor was at least as frequent as meningioma (Table 3). When clinically diagnosed and autopsy diagnosed tumors were considered together, the incidence rate tended to increase continuously with attained age for all tumor types combined (Table 2). By contrast, the incidence of clinically diagnosed tumors tended to decrease (meningioma, schwannoma, and pituitary tumor) or flatten (glioma and other neuroepithelial tumors) among individuals age ≥ 65 years, resulting in a widening incidence gap with age in the elderly (Table 3). Unlike all tumors combined (Table 2), clinically diagnosed tumors exhibited a strong secular trend irrespective of tumor type (Table 3). After taking into account a calendar-period effect that was included as a continuous variable in log-linear terms, there was little evidence of a birth cohort effect on the incidence rate of clinically diagnosed tumors of any type (Table 3).

We took a closer look at secular trends in incidence of clinically diagnosed tumors by gender and attained age (Table 4). The 3 calendar periods—before 1976, 1976–1985, and 1986–1995—were chosen to correspond roughly to the pre-CT era, the era of rapid introduction of CT and MRI, and the era of routine use of CT and MRI in neurologic practice. In both males and females, the incidence rate during 1986–1995 was approximately 3.5 times greater than before 1976. During the same period, the incidence rate in individ-

TABLE 2
Adjusted Incidence Rates for All First Primary Tumors of the Central Nervous System and Pituitary Gland by Selected Characteristics in the Life Span Study Cohort, 1958–1995

Characteristic	Meningioma		Schwannoma		Glioma ^a		Pituitary		Total	
	No.	IR	No.	IR	No.	IR	No.	IR	No.	IR
Brain dose (mSv)										
<5	35	2.5 ^b	18	3.1	20	4.2	6	1.1	92	14.4
5–100	29	2.2	10	1.8	14	3.2	19	3.8	89	15.1
100–500	14	2.7	11	5.4	5	3.0	5	2.6	42	18.4
500–1000	5	3.4	7	11.9	2	4.2	2	3.6	17	26.1
≥ 1000	5	4.6	9	18.5	3	7.5	3	6.5	23	44.1
<i>P</i> value ^c		0.07		<0.001		0.23		0.18		<0.001
Gender										
Male	14	2.3 ^d	23	2.5	21	3.5	16	2.3	94	14.5
Female	74	6.0	32	1.9	23	2.0	19	1.5	169	13.7
<i>P</i> value		<0.001		0.36		0.08		0.21		>0.50
Attained age (yrs)										
<35	0	0.0 ^e	3	0.6	2	1.2	4	1.2	9	2.6
35–49	8	0.8	14	2.0	9	2.5	9	1.9	53	9.4
50–64	33	2.6	19	2.4	14	3.0	8	1.5	88	13.4
65–79	38	4.2	12	2.3	15	5.0	11	3.2	84	19.2
≥ 80	9	3.8	7	5.7	4	4.6	3	3.6	29	26.2
<i>P</i> value		<0.001		0.009		0.03		0.01		<0.001
Calendar period (yr)										
<1976	35	2.1 ^f	28	2.5	17	2.6	18	2.5	119	13.6
1976–1985	21	1.9	14	2.4	12	3.4	8	2.1	65	13.0
1986–1995	32	2.9	13	2.5	15	4.8	9	2.6	79	16.7
<i>P</i> value		0.32		>0.50		0.006		>0.50		0.21
Year of birth										
1936–1945	7	0.7 ^g	13	2.1	9	2.2	5	1.1	41	7.8
1926–1935	20	1.9	13	1.8	12	3.0	11	2.4	60	10.9
1906–1925	26	1.7	13	1.6	16	3.7	7	1.3	75	11.1
≤ 1905	35	6.6	16	4.1	7	4.0	12	4.4	87	30.1
<i>P</i> value		<0.001		0.007		0.07		0.01		<0.001

No.: the number of tumors; IR: adjusted incidence rate per 100,000 person-years.

^a Includes glioma and other neuroepithelial tumor.

^b Dose group-specific adjusted incidence rate for a male age 60 years in 1980.

^c Test of homogeneity or trend, when appropriate.

^d Gender-specific adjusted incidence rate for unexposed individual age 60 years in 1980.

^e Age-specific, adjusted incidence rate for unexposed males in 1980.

^f Calendar period-specific adjusted incidence rate for unexposed males age 60 years.

^g Birth cohort-specific, adjusted incidence rate for unexposed males in 1908.

uals age < 50 years, ages 50–69 years, and age ≥ 70 years increased by 5.2 times, 3.6 times, and 4.2 times, respectively; and the incidence trends were not significantly different by age. Comparison of the incidence of all clinically diagnosed first primary tumors of the CNS and pituitary gland with the tumors for which diagnosis involved CT or MRI in 5-year intervals (Fig. 2) clearly indicates that the rising use of CT or MRI paralleled the overall increase in incidence. On the same note, 10 of 187 clinically diagnosed tumors (Table 1) were incidental findings, and 9 of those tumors involved CT or MRI during the early 1990s. Additional analyses aimed at describing a secular rise in incidence in terms of a stepwise increase from 1975 to

1985 demonstrated that the model fit was no better than that obtained using log-linear trend and that there was little evidence for the residual birth-cohort effect (data not shown).

DISCUSSION

The main objective of the current study was to evaluate clinical and epidemiologic characteristics of first primary tumors of the CNS and pituitary gland diagnosed in the LSS cohort of atomic bomb survivors. Based on the low doses of most cohort members and the estimated proportion of radiation-related tumors,¹¹ we anticipated that the CNS and pituitary gland tumors would have characteristics resembling

TABLE 3
Adjusted Incidence Rates of Clinically Diagnosed First Primary Tumors of the Central Nervous System and Pituitary Gland by Selected Characteristics in the Life Span Study Cohort, 1958–1995

Characteristic	Meningioma		Schwannoma		Glioma ^a		Pituitary		Total	
	No.	IR	No.	IR	No.	IR	No.	IR	No.	IR
Brain dose (mSv)										
<5	22	2.4 ^c	12	1.6	17	2.8	2	0.2	65	10.0
5–100	14	1.6	8	1.2	9	1.6	10	1.0	55	9.1
100–500	13	4.0	11	4.4	4	2.0	3	0.8	38	16.9
500–1000	4	4.1	3	4.1	1	1.7	1	1.0	10	15.3
≥ 1000	3	4.0	8	13.5	3	6.2	2	2.4	19	35.8
<i>P</i> value ^d		0.07		<0.001		0.19		0.15		<0.001
Gender										
Male	10	2.2 ^e	15	1.5	14	2.2	5	0.6	62	9.8
Female	46	5.5	27	1.6	20	1.8	13	1.0	125	11.3
<i>P</i> value		0.004		>0.50		>0.50		0.30		0.37
Attained age (yrs)										
<35	0	0 ^f	2	0.6	2	1.6	2	1.0	6	2.8
35–49	7	0.8	14	1.9	8	1.9	7	0.9	49	8.7
50–64	29	1.8	17	1.7	12	1.8	7	0.5	77	9.5
65–79	19	1.5	8	1.2	9	2.1	2	0.2	45	8.2
≥ 80	1	0.2	1	0.5	3	2.1	0	0	10	6.0
<i>P</i> value		<0.001		0.41		>0.50		0.19		<0.001
Calendar period										
<1976	5	0.5 ^g	15	0.8	10	1.3	3	0.1	51	5.0
1976–1985	19	3.2	14	1.8	9	2.3	7	0.7	59	11.0
1986–1995	32	5.8	13	2.2	15	4.6	8	1.3	77	17.3
<i>P</i> value		<0.001		0.004		<0.001		0.005		<0.001
Year of birth										
1936–1945	7	0.6 ^h	13	1.8	8	1.7	5	0.7	40	6.7
1926–1935	19	1.5	12	1.4	11	2.3	7	0.9	53	8.4
1906–1925	25	1.5	13	1.3	14	2.6	5	0.5	70	9.1
≤ 1905	5	1.2	4	0.9	1	0.5	1	0.3	24	8.6
<i>P</i> value		>0.50		0.43		>0.50		0.17		0.34

No.: the number of tumors; IR: adjusted incidence rate per 100,000 person years.

^a Includes glioma and other neuroepithelial tumor.

^b Adjusted-incidence rate per 100,000 person years.

^c Dose group-specific adjusted incidence rate for a male age 60 years in 1980.

^d Test of homogeneity or trend, when appropriate.

^e Gender-specific adjusted incidence rate for unexposed individuals age 60 years 1980.

^f Age-specific adjusted incidence rate for unexposed males in 1980.

^g Calendar period-specific adjusted incidence rate for unexposed males age 60 years.

^h Birth cohort-specific adjusted incidence rate for unexposed males in 1980.

those of “spontaneous” tumors. To make the data comparable with those from other population-based studies and to avoid potential biases when considering age and time trends, we emphasized findings concerning clinically diagnosed tumors and compared them with findings based on all tumors, including those diagnosed incidentally at autopsy.

Tumor-Specific Findings

The distribution of main histologic types of clinically diagnosed tumors of the CNS and pituitary gland in the LSS cohort was similar to that observed in the

study of residents of Kumamoto prefecture, Japan,¹³ and estimates from the Brain Tumor Registry of Japan.¹² Specifically, the most common tumor type was meningioma, followed by tumors of neuroepithelial origin. The predominance of meningioma that is observed consistently in Japanese studies^{12,13} is noteworthy because tumors of neuroepithelial origin account for the majority of all primary CNS tumors in North America and Europe.^{14,24–26}

Similar to the LSS cohort, meningioma also was the most common tumor type in an Israeli cohort of patients who were treated with cranial radiation for

TABLE 4
Case Counts and Adjusted Incidence Rates for All Clinically Diagnosed First Primary Tumors of the Central Nervous System and Pituitary Gland by Gender, Age, and Calendar Period in the Life Span Study Cohort, 1958–1995

Characteristic	Calendar period						IRR	95% CI
	<1976		1976–1985		1986–1995			
	No.	IR	No.	IR	No.	IR		
Gender								
Male	17	5.0 ^a	19	10.8	26	17.4	3.4	1.84–6.45
Female	34	5.7	40	12.7	51	19.8	3.5	2.22–5.49
<i>P</i> value ^b							>0.50	
Attained age (yrs)								
≤ 49	22	2.5 ^c	23	9.8	10	13.1	5.2	2.45–10.94
50–69	24	4.9	47	10.1	48	17.2	3.5	2.15–5.72
≥ 70	5	3.2	5	6.5	19	13.0	4.1	1.53–11.01
<i>P</i> value ^d							0.14	

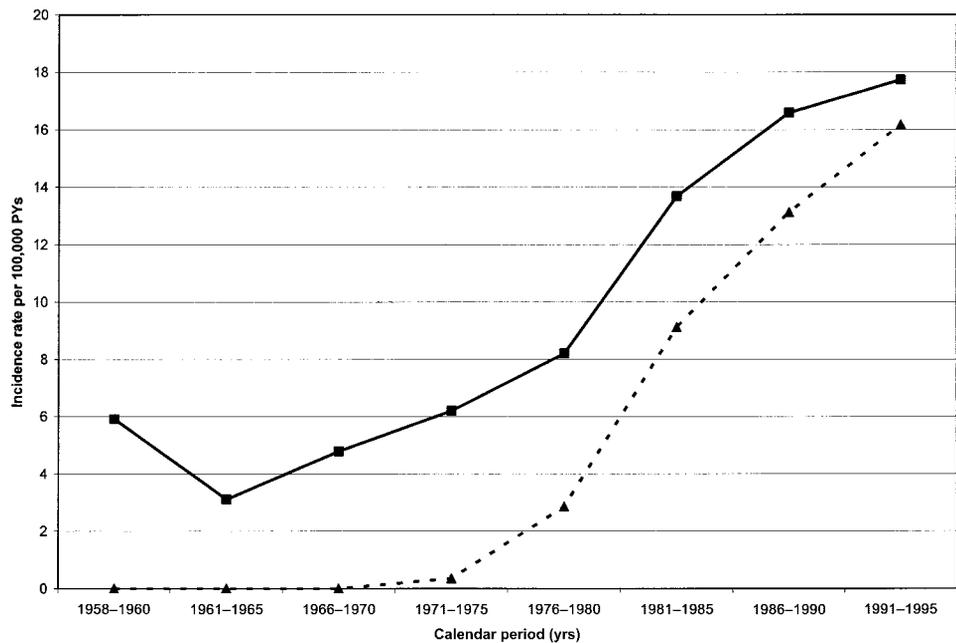
No.: the number of tumors; IR: adjusted incidence rate per 100,000 person-years; IRR: incidence rate ratio, the ratio of the 1985–1995 IR to the IR for 1958–1975; 95% CI: 95% confidence interval.

^a Gender-specific adjusted incidence rate for unexposed individuals age 60 years.

^b Test of homogeneity of incidence trends.

^c Age-specific adjusted incidence rate for unexposed males.

FIGURE 2. This chart illustrates the secular trend in the incidence of all clinically diagnosed first primary tumors of the central nervous system and pituitary gland in the Life Span Study cohort, 1958–1995, according to the calendar period-specific adjusted incidence rate for unexposed males age 60 years. Triangles: tumors that were diagnosed with the use of computed tomography or magnetic resonance imaging; squares: clinically diagnosed tumors. PY: person-years.



tinea capitis during childhood.⁵ However, unlike “radiation-induced” meningiomas found in exposed patients in the tinea capitis cohort, patients with clinically diagnosed meningiomas in the LSS cohort had a higher mean age at the time of diagnosis (61 years vs. 44 years²⁷), although patients in the tinea capitis cohort were aged only between 18–62 years at time of the latest analysis, had a lower ratio of calvarial-to-

basal meningioma (2.3:1.0 vs. 6.0:1.0²⁷), a lower proportion of malignant meningiomas (3% vs. 14%²⁸), a lower proportion of multiple meningiomas (3% vs. 16%²⁷), and a normal male-to-female incidence ratio (1.0:2.5 compared with the reduced ratios reported by Soffer et al. and Rubinstein et al.^{28,29}); thus, the characteristics of meningiomas in the LSS cohort more closely resemble the characteristics of “spontaneous”

tumors. All irradiated patients in the Israeli cohort were age < 16 years at the time of exposure, had a mean brain dose of approximately 1.5 Gy, and had the highest dose within the brain at the front of the upper plane.⁵

In agreement with the findings worldwide,¹⁴ the most common type of clinically diagnosed neuroepithelial tumor was found to be glioblastoma, followed by anaplastic astrocytoma. These tumors usually were cranial, tended to manifest with seizures, and were more common in males than in females (although the difference was not significant). It is interesting to note that the incidence of clinically diagnosed neuroepithelial tumors in this population did not change appreciably with age. Our age-specific estimates of incidence were based on small numbers; however, in other population-based studies in Japan,¹²⁻¹⁴ it was shown that the incidence of neuroepithelial tumors increased with age, but much less rapidly than in North America or Europe, resulting in overall lower rates of neuroepithelial tumors among the Japanese.

In contrast to other studies of Japanese populations,^{12,13} the third most common type of neoplasm in the current study cohort was schwannoma rather than pituitary tumor. However, the difference in incidence between the 2 tumor types was modest and could be attributed, in part, to the fact that other studies did not consider schwannomas of the spinal nerve roots, which accounted for 38% of all clinically diagnosed schwannomas in the current series. The typical presenting symptoms of schwannomas, the average patient age at diagnosis, and the balanced ratio of incidence in males and females were comparable to observations reported in other studies of clinically apparent schwannomas.^{13,30,31}

In the current study cohort, there were 18 clinically diagnosed pituitary adenomas, which translated to a crude incidence rate of approximately 1 per 100,000 PYs, or approximately 10% of all intracranial tumors. Although these estimates are somewhat lower than in other Japanese populations, they are not greatly dissimilar.^{12,13} The incidence of pituitary adenomas, as expected, tended to be higher in females than in males, in cohort members between ages 30-60 years, and the most common clinical symptom was visual disturbance.³² The proportion of nonfunctional adenomas among clinically diagnosed tumors in the current series was larger than that reported in other population based studies (55% vs. 25%³²). However, 50% of all tumors could not be classified with certainty because of inadequate staining or preservation of tissue specimens.

Incidence of All Clinically Diagnosed Tumors by Age and Calendar Period

When we combined all clinically diagnosed first primary tumors of the CNS and pituitary gland, the incidence of tumors rose with age to a maximum among individuals ages 50-64 years and then declined in the elderly. This contrasts with the analysis that included tumors that were diagnosed incidentally at autopsy, for which incidence increased continuously with age without any evidence of a downturn. A downturn in incidence of clinically diagnosed primary brain and CNS tumors with age has been reported in other population-based studies from different parts of the world,^{25,26,33,34} including Japan,¹³ and usually has been interpreted as evidence of under-ascertainment of cases among the elderly. Approximately 92% of tumors diagnosed at autopsy in the LSS cohort were in individuals who were age \geq 50 years. This points to probable under-ascertainment of cases among the elderly, at least during the era when CT was not widely available. After 1976, the autopsy program largely was discontinued, and this coincided with the introduction of CT into clinical practice.^{35,36}

The incidence of each type of clinically diagnosed first primary CNS and pituitary gland tumors increased with calendar period, after taking into account the effect of attained age, in contrast to the pattern for all tumors, including those diagnosed at autopsy. This increase closely paralleled the increase in incidence of tumors diagnosed with use of new imaging techniques (CT or MRI). The magnitude of increase over time appeared to vary little by gender, age, or dose. Overall, this suggests that the introduction of new imaging techniques largely was responsible for the observed increase in incidence. This appears more plausible than an underlying rise in incidence of brain tumors affecting different subgroups in a similar fashion, especially given little evidence for a birth-cohort effect.

A similar increase in incidence of all CNS tumors combined was observed in many developed countries,^{25,26,37} including Japan,¹² and is the subject of ongoing debate concerning whether the higher rates are artificial or are reflective of a true increase in incidence.³⁸ It has been argued that, in the U.S., the increase in the incidence of CNS cancer among children age <15 years³⁹ and adults age \geq 70 years³⁴ is due mainly to advances in imaging technology and/or more aggressive diagnosis among the elderly. In addition, there is a suggestion that incidence rates for CNS cancer overall in the U.S. are leveling off in all age groups, which would be expected after the introduction of new diagnostic techniques.³³ However, the data regarding epidemiology of benign CNS tumors

are not readily available in the U.S. before 1985,³⁸ and the rates for all CNS tumors combined (excluding lymphomas) remained largely stable between 1985 and 1994.⁴⁰ Unlike the majority of U.S. studies, studies from Scandinavian countries considered both benign and malignant CNS tumors and suggested an increase in all age groups and both genders from the pre-CT era through the 1990s.^{25,26,37} Similarly, a report of the Brain Tumor Registry of Japan estimated that the incidence rates of all primary brain tumors combined increased approximately 3-fold from 1973 to 1993, but that the pattern of increase differed by histologic subtype.¹² Thus, the overall increase in incidence of clinically diagnosed first primary tumors of the CNS and pituitary gland observed in the current study is consistent with other Japanese and Scandinavian reports of the same period but is less consistent with reports from the U.S. It is interesting to note that the dynamics of CT and MRI spread in clinical practice in Japan follows the U.S. pattern more closely,^{35,36} but the medical system and accessibility to medical care are more similar to those seen in Scandinavian countries.

The current analysis was based on data from a large, well defined cohort with long follow-up, nearly complete case ascertainment, a high rate of histologic confirmation for both benign and malignant tumors, and central pathology review at the end of the study, resulting in standardized case definition throughout the study period. We presented tumor-specific analyses to permit comparisons of age and time trends for different tumor types. However, these analyses were based on small numbers of tumors; therefore, parameter estimates are somewhat imprecise. Therefore, we focused more on the findings for all clinically diagnosed first primary CNS and pituitary gland tumors combined.

The clinical and epidemiologic characteristics of first primary tumors of the CNS and pituitary gland diagnosed in the LSS cohort of atomic bomb survivors largely were consistent with those observed in other population-based studies in Japan. The predominance of meningioma over neuroepithelial tumors in the Japanese, compared with North American and European populations, is noteworthy and warrants further exploration, and it may provide clues regarding the etiology of these tumors. The overall incidence of clinically diagnosed first primary CNS and pituitary gland tumors was found to increase remarkably during the study period. The increase was noted in males and females and among all age groups and most likely is attributable, in large part, to the increased use of CT and MRI diagnostic imaging.

REFERENCES

- Ron E, Saftlas AF. Head and neck radiation carcinogenesis: epidemiologic evidence. *Otolaryngol Head Neck Surg.* 1996; 115:403–408.
- Inskip PD, Linet MS, Heineman EF. Etiology of brain tumors in adults. *Epidemiol Rev.* 1995;17:382–414.
- Wrensch M, Minn Y, Chew T, Bondy M, Berger MS. Epidemiology of primary brain tumors: current concepts and review of the literature. *Neurooncol.* 2002;4:278–99.
- DeAngelis LM. Brain tumors. *N Engl J Med.* 2001;344:114–123.
- Ron E, Modan B, Boice JD Jr., et al. Tumors of the brain and nervous system after radiotherapy in childhood. *N Engl J Med.* 1988;319:1033–1039.
- Schneider AB, Shore-Freedman E, Ryo UY, Bekerman C, Favus M, Pinsky S. Radiation-induced tumors of the head and neck following childhood irradiation. Prospective studies. *Medicine (Baltimore).* 1985;64:1–5.
- Sznajder L, Abrahams C, Parry DM, Gierlowski TC, Shore-Freedman E, Schneider AB. Multiple schwannomas and meningiomas associated with irradiation in childhood. *Arch Intern Med.* 1996;156:1873–1878.
- Hildreth NG, Shore RE, Hempelmann LH, Rosenstein M. Risk of extrathyroid tumors following radiation treatment in infancy for thymic enlargement. *Radiat Res.* 1985;102:378–391.
- Karlsson P, Holmberg E, Lundell M, Mattsson A, Holm LE, Wallgren A. Intracranial tumors after exposure to ionizing radiation during infancy: a pooled analysis of two Swedish cohorts of 28,008 infants with skin hemangioma. *Radiat Res.* 1998;150:357–364.
- Neglia JP, Meadows AT, Robison LL, et al. Second neoplasms after acute lymphoblastic leukemia in childhood. *N Engl J Med.* 1991;325:1330–1336.
- Preston DL, Ron E, Yonehara S, et al. Tumors of the nervous system and pituitary gland associated with atomic bomb radiation exposure. *J Natl Cancer Inst.* 2002;94:1555–1563.
- Kaneko S, Nomura K, Yoshimura T, Yamaguchi N. Trend of brain tumor incidence by histological subtypes in Japan: estimation from the Brain Tumor Registry of Japan, 1973–1993. *J Neurooncol.* 2002;60:61–69.
- Kuratsu J, Takeshima H, Ushio Y. Trends in the incidence of primary intracranial tumors in Kumamoto, Japan. *Int J Clin Oncol.* 2001;6:183–191.
- International Agency for Research on Cancer. Cancer incidence in five continents. Volume 8. Lyon, France: IARC, 2002.
- Beebe GW, Ishida M, Jablon S. Studies of the mortality of A-bomb survivors. I. Plan of study and mortality in the medical subsample (selection 1), 1950–1958. *Radiat Res.* 1962;16:253–280.
- Mabuchi K, Soda M, Ron E, et al. Cancer incidence in atomic bomb survivors. Part I: use of the tumor registries in Hiroshima and Nagasaki for incidence studies. *Radiat Res.* 1994; 137:S1–S16.
- Thompson DE, Mabuchi K, Ron E, et al. Cancer incidence in atomic bomb survivors. Part II: solid tumors, 1958–1987. *Radiat Res.* 1994;137:S17–S67.
- Ron E, Carter R, Jablon S, Mabuchi K. Agreement between death certificate and autopsy diagnoses among atomic bomb survivors. *Epidemiology.* 1994;5:48–56.
- Kleihues P, Burger PC, Scheithauer BW. Histological typing of tumours of the central nervous system. New York: Springer-Verlag, 1993.

20. Radiation Effects Research Foundation (RERF). U.S.-Japan joint reassessment of atomic bomb radiation dosimetry in Hiroshima and Nagasaki: final report. Hiroshima: RERF, 1987.
21. Pierce DA, Stram DO, Vaeth M. Allowing for random errors in radiation dose estimates for the atomic bomb survivor data. *Radiat Res.* 1990;123:275-284.
22. Preston D, Lubin J, Pierce D, McConney M. *Epicure users guide.* Seattle: Hirosoft International Corporation, 1993.
23. Kleihues P, Louis DN, Scheithauer BW, et al. The WHO classification of tumors of the nervous system. *J Neuro-pathol Exp Neurol.* 2002;61:215-225.
24. Surawicz TS, McCarthy BJ, Kupelian V, Jukich PJ, Bruner JM, Davis FG. Descriptive epidemiology of primary brain and CNS tumors: results from the Central Brain Tumor Registry of the United States, 1990-1994. *Neurooncol.* 1999;1:14-25.
25. Helseth A. The incidence of primary central nervous system neoplasms before and after computerized tomography availability. *J Neurosurg.* 1995;83:999-1003.
26. Christensen HC, Kosteljanetz M, Johansen C. Incidences of gliomas and meningiomas in Denmark, 1943 to 1997. *Neurosurgery.* 2003;52:1327-1333.
27. Sadetzki S, Flint-Richter P, Ben Tal T, Nass D. Radiation-induced meningioma: a descriptive study of 253 cases. *J Neurosurg.* 2002;97:1078-1082.
28. Soffer D, Pittaluga S, Feiner M, Beller AJ. Intracranial meningiomas following low-dose irradiation to the head. *J Neurosurg.* 1983;59:1048-1053.
29. Rubinstein AB, Shalit MN, Cohen ML, Zandbank U, Reichenthal E. Radiation-induced cerebral meningioma: a recognizable entity. *J Neurosurg.* 1984;61:966-971.
30. Howitz MF, Johansen C, Tos M, Charabi S, Olsen JH. Incidence of vestibular schwannoma in Denmark, 1977-1995. *Am J Otol.* 2000;21:690-694.
31. Hardell L, Hansson MK, Sandstrom M, Carlberg M, Hallquist A, Pahlson A. Vestibular schwannoma, tinnitus and cellular telephones. *Neuroepidemiology.* 2003;22:124-129.
32. Clayton RN. Sporadic pituitary tumours: from epidemiology to use of databases. *Baillieres Best Pract Res Clin Endocrinol Metab.* 1999;13:451-460.
33. Gurney JG, Kadan-Lottick N. Brain and other central nervous system tumors: rates, trends, and epidemiology. *Curr Opin Oncol.* 2001;13:160-166.
34. Legler JM, Ries LA, Smith MA, et al. Cancer surveillance series [corrected]: brain and other central nervous system cancers: recent trends in incidence and mortality. *J Natl Cancer Inst.* 1999;91:1382-1390.
35. Hisashige A. The introduction and evaluation of MRI in Japan. *Int J Technol Assess Health Care.* 1994;10:392-405.
36. Lavayssiere R, Cabece AE. [Marketing of MRI in the world]. *J Radiol.* 1990;71:385-399.
37. Lonn S, Klæboe L, Hall P, et al. Incidence trends of adult primary intracerebral tumors in four Nordic countries. *Int J Cancer.* 2004;108:450-455.
38. Davis FG, McCarthy BJ. Current epidemiological trends and surveillance issues in brain tumors. *Expert Rev Anticancer Ther.* 2001;1:395-401.
39. Smith MA, Freidlin B, Ries LA, Simon R. Trends in reported incidence of primary malignant brain tumors in children in the United States. *J Natl Cancer Inst.* 1998;90:1269-1277.
40. Jukich PJ, McCarthy BJ, Surawicz TS, Freels S, Davis FG. Trends in incidence of primary brain tumors in the United States, 1985-1994. *Neurooncol.* 2001;3:141-151.