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Original Paper

Computed Tomography of the Head and the Risk of Brain Tumours during Childhood and Adolescence: Results from a Case-Control Study in Japan

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Abstract

To clarify whether medical radiation exposure, especially from head computed tomography (CT), increases the risk of brain tumours in young patients in Japan, which ranks the second highest in the world in the number of paediatric CT examinations following the US. From 2011 to 2015, we performed a case-control study of 120 brain tumour patients and 360 appendicitis patients as controls. Reasons, the number of brain and head CT scans date were available from interviews. A cumulative radiation dose to the brain was calculated as a sum of doses received from head CT scans and from conventional X-rays and estimated using a reference table derived from a literature review of published studies. We performed conditional logistic regression to assess the risk of brain tumours from brain and head CT, and from conventional head X-ray procedures.

The case group received on average 1.8 CTs to the brain area and 2.2 CTs to the whole head, with a mean estimated brain dose of 32 ±13 mGy. The odds ratio for developing a brain tumour from having a brain CT was 0.93 (95% confidence interval: 0.38–1.82). This was hardly altered when adjusting for parental educational history and for other diseases (history of neurological disease and attention-deficit disorder/attention-deficit hyperactivity disorder). Neither whole head CT nor cumulative brain dose to the brain increased the risk of glioma or of all brain tumours. Although this study conducted in Japan, where ranks second in the number of CT scans conducted in the world, did not show an increased risk of brain tumours related to CT scans, it should be taken with caution due to a case-control study with limited sample size.

Keywords:

brain tumour, ionizing radiation, diagnostic X-ray, head CT, adolescence

1. Introduction

The development of medical X-ray technology has greatly improved the precision of imaging diagnostics but raised concerns about potential health hazards associated with the increasing use of computed tomography (CT) scans, particularly in children when considering paediatric radiation exposure [1]. Japan has the highest number of CT machines among Organization for Economic Co-operation and Development (OECD) countries, with reported 200 CT scans being conducted for every 1,000 individuals per year [2]. Globally, Japan ranks second after the US in the number of CT scans conducted, which is approximately double of that, for example, in the UK [3] and Netherlands. Epidemiological studies [4, 5] have demonstrated an increase in leukaemia and brain tumours owing to diagnostic CT; however, results are not entirely consistent. Since around 2000, several countries have recommended to apply lower doses for CT scans performed on children than those used for adults because the former are overly sensitive to radiation [6]. A paediatric CT guideline was published in Japan in 2004 [7], which recommends the use of a dose reduction filter and a tube setting of 100 mAs or less for children weighing 36 kg or less (approximately under 10 years old). Despite the introduction of these low-dose CT guidelines in several countries, recently, increased morbidities have been reported for leukaemia and some solid tumours in South Korea [8].

The present study aimed to clarify whether medical radiation exposure, especially that from head CTs, increases the risk of brain tumours in young patients in Japan. We conducted a case-control study in Japan, using data from the Japanese part of the Mobi-Kids international study [9], and collected data using the same questionnaire. All brain tumours and glioma were included in the study since low grade glioma has been reported as the most frequent outcome in childhood [10].

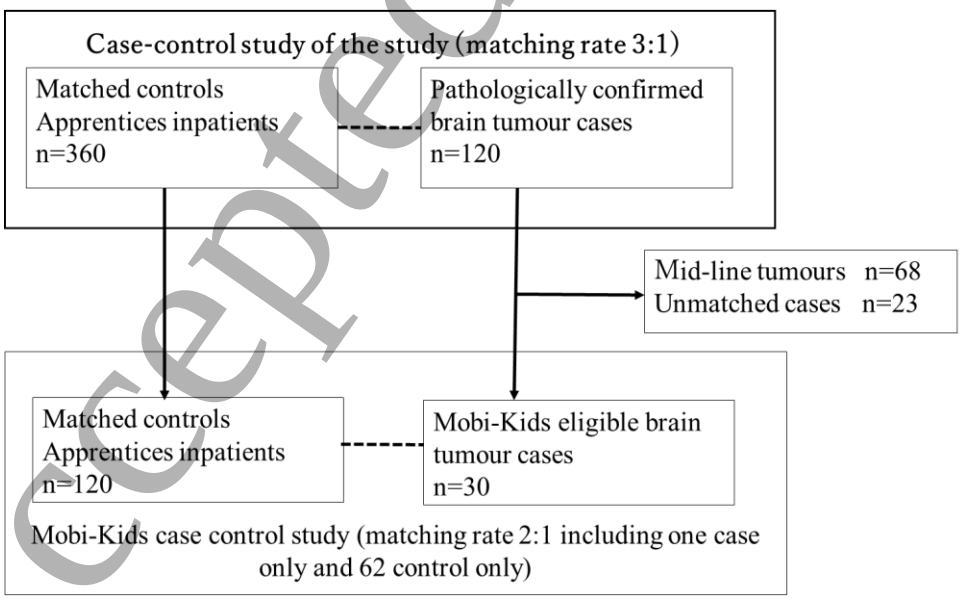
2. Materials and methods

2-1 Study design and participants

We enrolled 120 patients with primary brain tumours and 360 patients hospitalized with appendicitis between 2011 and 2015. Inclusion criteria were being aged 10–24 years at the time of diagnosis, which was defined as the reference date, and being an inpatient in the collaborating hospitals in

Tokyo metropolitan area. Only patients with pathologically confirmed brain tumours were enrolled. Exclusion criteria included having secondary brain tumours, hereditary disease, and severe mental disorders. Face-to-face interviews for patients aged 18 to 24 years were conducted by trained interviewers during the hospital stay. If the patients were aged 10 to 17 years or severely ill at any age, interviews were performed either with their parents (mothers or fathers) and the patient, or with their parents only. On the main questionnaire, social background, medical history, mobile phone, and Wi-Fi usage, and radiological exposures were collected. In addition, parental and clinical questionnaires were collected from parents and neurosurgeons, respectively. Cases were matched to controls at a 1:3 ratio based on sex and age (age difference within 2.5 years), and date of diagnosis (difference less than 1.5 years). Of these patients, 30 with brain tumours and 120 with appendicitis were enrolled in the Mobi-Kids study to evaluate the association between laterality of brain tumour and mobile phone use. Following the eligibility criteria, we excluded brain tumours which were located in the mid-line (Figure 1). The detailed protocol of MOBI-Kids was previously published [9].

Figure 1 Flowchart for patients' inclusion in the study compared to the eligibility of Mobi-Kids study



2-2 Exposure assessment

The information on CT and X-ray examination area, age at examination, and reason for examination obtained during interviews, was monitored closely. Data on three exposure variables, including "Number of brain CT (times)" and "Number of head CT (times)" were collected. A two-year lag time was applied to reduce the likelihood that the CT scan was done related to early symptoms of the brain tumour [11] leaving out the CT scans conducted within two years before the date of brain tumour diagnosis (Lag 2). "Number of brain CT was the sum of CTs that include brain area, while "Number of head CTs" was the sum of CTs conducted at the brain, neck, dental, whole body (including head and neck), and unknown sites. Third variable "Cumulative brain dose (mGy)" was estimated using a reference table (Table 1), based on a review of data published by Pasqual et al. [12], who reported the radiation dose to the brain from conventional X-ray and CT. The literatures given time-age frame [13] and an estimation of brain dose [14] were used in a reference table. Mean dose values were estimated for new-borns and other age groups for head CTs and conventional X-rays of the head and neck, including whole body and unknown sites, excluding examinations conducted within the past two years. Interviews included also information on the number of dental X-rays, including bite wing, full mouth, and panoramic X-rays in the 5-year age categories, but these were excluded from dose evaluation, given the extremely low dose to the brain from these X-ray examinations [15].

Table 1 Reference table for mean brain dose estimation from diagnostic radiation procedures by age and year of examinations [12,13,14)]

Body area	Age	CT scan			conventional X-ray		
	(years)	-1989	1990-1999	2000-	-1989	1990-1999	2000-
Dental	3 to 7			20	NA	NA	NA
	8 to 12			10	NA	NA	NA
	13 to 18			10	NA	NA	NA
	Adults			10	NA	NA	NA
Brain	Newborn		50	31	2.4	0.4	0.6

	1 to 2	62	50	31	1.5	0.9	0.4
	3 to 7		50	32		0.7	0.7
	8 to 12		50	36		0.7	0.8
	3 to 18			36			0.7
	Adults			33			1.5
Neck	Newborn					0.1	0
	1 to 2					0.1	0
	3 to 7			19		0.1	0
	8 to 12			17		0.3	0
	13 to 18			14			0
	Adults			12			
Whole body	Newborn		6	8		0.4	0.6
	1 to 2		29	22		0.9	0.4
	3 to 7		28	22		0.7	0.7
	8 to 12		28	22		0.7	0.8
	13 to 18			26			0.7
	Adults			20			1.5
Don't know	1 to 2		50			0.9	
	3 to 7		50	33		0.7	0.7
	8 to 12		2	34			0.8
	13 to 18		2	35			0.7
	Adults		8	33			1.5

NA; not applicable

2-3 Sensitivity analysis

In the present study, the equipment and imaging settings of the CT scans were unknown. Therefore, our brain dose estimates used for sensitivity analyses were based on the National Cancer Institute's dosimetry system for CT (NCICT) (https://ncidose.cancer.gov/#ncict) [16], selecting typical CT scanner models used widely in Japan [17], namely, TOSHIBA XVISION (used until 1999) and TOSHIBA Aquillion16 (used since 2000). We selected a phantom by sex and age (0 years old at the time of imaging: new-born; 1–2 years old: 1 year old; 3–7 years: 5 years old; 8–12 years: 10 years old; 13–17 years: 15 years old; 18 years and older: adult) for the dose estimation [18]. The following imaging settings were used as default: tube voltage of 120 kV, rotation time 1, Computed

Tomography Dose Index $(CTDI)_{vol}$ 6. The absorbed dose to the head was determined using the varying tube currents of 100 mAs, 200 mAs, and 400 mAs for the sensitivity analysis. In addition, we assumed 2 models: "Mix 1" determined that the tube current was 400 mAs (the same as that for adults) before the release of the paediatric low dose CT guidelines in Japan in 2004, and 100 mAs, after the release of the guidelines, if the patient was aged 10 years or less at the time of examination. "Mix 2" was set up as 400 mAs before 1999 and 100 mAs after 2000 if the subject was aged 10 years or less, to allow for the scenario that the dose lowering strategy for paediatric patients might have occurred a few years before the guideline was published.

2-4 Statistical analyses

The odds ratios (ORs) for risk of all brain tumours and histologically confirmed gliomas, and 95% confidence intervals (CIs) were calculated for all diagnostic radiation procedures and head CT scans using the chi-squared test for categorical variables with STATA16 [Stata Corp. 2015. Stata Statistical Software: Release 14. College Station, TX]. Conditional logistic regression was conducted for the main analysis. Using the Power software [19], we performed a post hoc power calculation. Planning a study with 3 matched control(s) per case, when the probability of exposure among controls is 0.3 and the correlation coefficient for exposure between matched cases and controls is 0.6, and the true odds ratio for disease in exposed subjects relative to unexposed subjects is 2, we will need to study 198 cases to be able to reject the null hypothesis that this odds ratio equals 1 with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05. The present study was approved by the Tokyo Women's Medical University ethics committee (2394 R5, November 8, 2018).

3. Results

3-1 Baseline characteristics

Table 2 shows the baseline characteristics of cases and controls one year before the reference date. Socioeconomic status (SES) was derived from parental education (mother's or father's education, whichever was higher). Main difference between cases and controls was seen in the parental

education: 30% of cases but only 16.4% of controls parental education was high school or less (p = 0.001). According to the Mobi-kids questionnaire, the past history of neurological disease, such as migraine, epilepsy, convulsions, and hydrocephalus, was collected. Prevalence of past neurological disease was significantly higher in the case group (20.0%). Among cases, 4.2% had attention-deficit disorder / attention-deficit hyperactivity disorder (ADD/ADHD) while it was only 0.8% among the control group (p = 0.034). With regard to medical radiation exposure, 24 (20%) cases and 78 (21%) controls had a history of brain or neck X-rays (p = 0.699). 13 (11%) cases and 42 (12%) controls had a history of brain CT more than one year before the diagnosis date, with the largest number of scans being 11 and 5, respectively (p= 0.964). Finally, 21 (18%) cases and 76 (21%) controls had a history of head CT. More than 80% of patient was responded by themselves in controls, where 59.2% in cases, although guardians, mostly mothers, were obligated to stay at the interviews with patients aged 17 years and younger. Glioma represented 39% of all brain tumours, but the majority of the cases were those of schwannoma, which were excluded in the Mobi-Kids international study.

Table 2 Baseline characteristic between cases and controls at one year before diagnostic date

	Cases (n=120)	Controls (n=360)	p-value
Gender, n (%)			
Male, n (%)	72 (60.0)	216 (60.0)	1.000
Age at diagnosis mean±SD	20.1±6.5	19.9±6.4	
10-14, n (%)	38 (31.7)	112 (31.1)	
15-19	23 (19.2)	69 (19.2)	
20-24	22 (18.3)	73 (20.2)	
25-29	37 (30.8)	106 (29.4)	0.971
SES（Parental education）, n (%)			
High school or less	36 (30.0)	59 (16.4)	
Vocational school and college	13 (10.8)	85 (23.7)	
University and more	67 (55.8)	201 (56.0)	
Unknown	4 (3.3)	14 (3.9)	0.001*
Past history, n (%)			
Neurological disease	24 (20.0)	24 (6.7)	0.000*

ADD/ADHD	5 (4.2)	5 (0.8)	0.034*
Psychological Disorder	2 (1.7)	12 (3.3)	0.542
Other cancers	2 (1.7)	2 (0.6)	0.511
Allergies	55 (45.8)	176 (48.9)	0.704
Mobile phone use at 1-year before reference date, yes n (%)	82 (68.3)	270 (75.0)	0.153
Head or Neck X-ray yes n (%)	24 (20.0)	78 (21.1)	0.699
Dental X-ray			
Bite wing x-ray yes n (%)	10 (55.6)	33 (55.0)	
Full mouth X ray yes n (%)	0 (0.0)	5 (8.3)	
Panoramic X ray yes n (%)	10 (55.6)	26 (43.3)	
Dental CT yes n (%)	3 (16.7)	7 (11.7)	
Number of brain CT, n (%)			
0	107 (89.2)	318 (88.3)	0.964
1	11 (9.2)	35 (9.7)	
2 and more	2 (1.7)	7 (1.9)	
Number of head CT, n (%)			
0	99 (82.5)	284 (78.9)	0.695
1	16 (13.3)	58 (16.1)	
2 and more	5 (4.17)	18 (5.0)	
Interviewee. n (%)			
patient only	71(59.2)	300(83.3)	0.001*
mother's help or mother only	61(31.7)	55(15.3)	
the other	11(9.2)	5(1.4)	
Glioma	47 (39.2)	-	
Meningioma	5 (4.1)	-	
Schwannoma	57 47.5)	-	
Other brain tumours	11 (9.1)	-	

3-2 Exposure to brain

Among all brain tumour cases, brain CTs were on average conducted 1.8±2.9 times, with the highest frequency for a single case being 11 times (Table 3). The corresponding figure was 1.3±0.9 times in the control group, with the highest frequency for a single patient being 5 times. The number of brain

CTs among glioma cases was on average 1.0, with no significant difference among the glioma and control groups (p=0.324). Further, the number of head CTs, which was the sum of CTs conducted at the brain, dental, neck, whole body, and unknown sites, was 2.2±0.7 (range 1–11) for the case group, which was higher than that for the control group (1.5±0.1) (range 1–6). Cumulative brain dose from all diagnostic radiation procedures to the head and neck (lagged by 2 years), which was computed using the reference table (Table 1), was 32 ±13 mGy (n = 36) and 22 ±5.5 mGy (n = 13) in the all cases and glioma groups, respectively, as compared to 25 ±3.0 mGy in the control group. However, there were no significant differences among these groups.

Table 3 Exposure estimation among exposed patients: numbers of brain and head CT, and radiation dose from CT + conventional X-rays derived from the reference table (lagged by 2 years)

Exposures	Exposed all brain tumours (glioma)		Controls		*p* values
	n	mean±SE	n	mean±SE	
1) Number of brain CT	12 (6)	1.8±0.2 (1.0)	38	1.3±0.1	0.324
2) Number of head CT	18 (8)	2.2±0.7 (1.1±0.1)	60	1.5±0.1	0.119
3) Cumulative brain dose (mGy)	36 (13)	32 ±13 (22 ±5.5)	114	25±3.0	0.385

1) Brain CT only

2) Brain CT (1) + the other head CTs including head, such as neck, whole body, and unknown

3) Brain dose from both CT and conventional X-rays to brain, neck, whole body, and unknown area

3-3 Brain tumour risk and medical radiation exposure

Table 4 shows the results of conditional logistic analysis conducted using three exposure measures as explanatory variables. The ORs for developing all brain tumours were 0.93 (95%CI: 0.55- 1.58)

with brain CTs and 0.97 (95%CI 0.66- 1.42) with head CTs. In addition, when the cumulative dose to the brain from all diagnostic radiation procedures was considered, the crude and adjusted OR were not significant for either all brains or gliomas. When the analysis was limited to patients with pathologically confirmed gliomas (n=47), the number of brain CTs and total number of head CTs (Lag 2) were lower than the exposure for all brain tumours reported in Table 3. Crude and adjusted OR of the number of brain CTs, number of head CTs, and cumulative radiation dose were not significant in the glioma group. Within the case group, one patient had undergone 11 brain CT examinations more than two years before the diagnosis, which were conducted to monitor the progress of hydrocephalus since infancy. However, the crude or adjusted OR for all brain tumours and glioma did not change after omitting this patient from analyses.

Table 4 Risk of all brain and glioma by exposure (lagged by 2 years)

all brain tumours	**Crude OR**	**95%CI (n=480)**	**Adjusted OR***	**95%CI (n=433)**
1) Number of brain CT	0.93	0.55- 1.58	0.77	0.44- 1.33
2) Number of head CT	0.97	0.66- 1.42	0.88	0.59- 1.32
3) Cumulative brain dose (mGy)	1.00	0.99- 1.01	1.00	0.99-1.01

Glioma	**Crude OR**	**95%CI (n=188)**	**Adjusted OR***	**95%CI (n=170)**
1) Number of brain CT	0.83	0.38-1.82	0.79	0.36 -1.72
2) Number of head CT	0.77	0.39- 1.55	0.73	0.37- 1.47
3) Cumulative brain dose (mGy)	0.99	0.97- 1.01	0.99	0.97-1.01

*Adjusted for parental education and history of neurological disease and ADD/ADHD

3-4 Sensitivity analysis

As shown in Table 5, dose to the brain estimated with the NCICT ranged from 18 mGy (18 years and older, with application of 100 mAs) to 100 mGy (new-born, with application of 400 mAs). In

Table 6, simulation analysis of exposure from brain CT (Lag 2) according to the NCICT, exposures to brain were relatively higher as compared to the control group. When we estimated them using 3 different shooting conditions, all crude ORs were not significant for the brain tumour group. When we applied "Mix 1", brain CT exposure in the case (73 ±8.5 mGy) and control (54 ±6.9 mGy) groups showed no significant differences. Further, the exposure doses using "Mix 2" senario which was low doses were applied approximately 5 year before publishing the Japanese CT guideline for children were lower than those in Mix 1. Even Decreasing of ORs was not detected, even the most optimistic scenario.

Table 5 Brain dose from head CT estimates with NICICT using different age of phantoms

Age of phantom	**Toshiba XVISION GX （～1999)**	**Toshiba Aquillion16（2000～）**	
	400mAs（mGy）	**100mAs（mGy）**	**400mAs（mGy）**
0	80	26	100
1	70	22	89
5	63	20	82
10	62	19	80
15	57	19	74
adults	55	18	70

Table 6 Brain dose from brain CT estimated with NCICT for sensitivity analysis

Tube current	Case (n=18) (mGy)	Controls (n=60) (mGy)	Crude OR	95%CI
100mAs	30±10	25±2.5	0.99	0.95- 1.02
200mAs	60±20	50±5.0	0.99	0.98- 1.01
400mAs	120±40	100±9.9	1.00	0.99- 1.01
Mix1*	73±8.5	54±6.9	1.00	0.98- 1.02
Mix2**	51±25	31±3.0	1.00	0.96- 1.03

*Mix1 represented the scenario that was applied 400mAs before 2004 and 100mAs after 2005 if the patient was under 10 years old at the exam for the CT shooting condition.

** Mix2 represented the scenario that was applied 400mAs before 1999 and 100mAs after 2000 if the patient was under 10 years old at the exam for the CT shooting condition.

5. **Discussion**

This is the first case-control study of brain tumours in children and adolescents following medical radiation exposure in Japanese children. Similar to the sub-analysis of German INTERPHONE study [20], our results indicated that the radiation exposure from CT and X-ray procedures did not increase the risk of developing brain tumours or its common sub-type, gliomas. To evaluate exposure as accurately as possible, we confirmed the reasons for the CT and conventional X-ray examinations through interviews and eliminated examinations conducted two years before the diagnosis date. However, since this study analysed information that was primarily collected for the case-control study on the association between mobile phones and brain tumours, recall bias for medical radiation exposure in the brain tumour group is not considerably influent.

A large UK cohort [21] regarding paediatric CT scans and the risk of brain tumours using radiology information systems databases, the excess relative risk per mGy was reported 0.023 to 0.016, where incidence rate ratio was 1.24 (95% CI 1.20 to 1.29) in Australia [22]. Recently in EPICT study of the Netherlands participants aged below 18 years conducted which included 84 patients with brain tumour [23], the mean cumulative brain dose was approximately the same as observed in our exposed group (39 mGy). The excess relative risk per 100 mGy dose was significantly higher, at 0.86 (95% CI: 0.20–2.22), in the cohort study using 5-year lag. Moreover, a study of 120,000 Koreans aged 19 years or younger reported an elevated risk of leukaemia, with an incidence rate ratio (IRR) of 2.14 [95% CI: 1.86–2.46], and all cancers due to low-dose CT scan conducted more than two years before the diagnosis date. Both these studies have no information on medical reasons for conducting the CT scans, and thus, inverse causation cannot be ruled out, given the absence of data on factors such as subjective symptoms of patients [8].

In our study, the exposure from head CT and X-ray distributed extremely right skewed, such that more than 80% of the participants were not exposed. Further, average dose values in our study were lower than those reported in previous studies [8, 25-27], shown in Table 3 that cumulative brain dose was low as approximately equivalent to 1 to 2 brain CT scans. In spite of some unknown CT imaging conditions, strength of this study was focused on detailed interviews on mobile phone

history and participants were less concerned about medical radiation exposure what reduced the effects of recall bias.

One of the limitations of our study was an imbalance of cases and controls with regard to parental education, with more case families having lower educational level. This may have influenced the accuracy of recall of the numbers and types of radiological examinations among cases, if one assumes more accurate reporting among those with higher education. However, previous studies have shown that the risk of brain tumours from CT examinations was not affected by parental education, used as a proxy for SES [24,25]. Unfortunately, information on living conditions and economic inequality which are among the leading factors of SES was not collected in the study [26]. Insufficient adjustment for SES could be therefore another limitation of the study because children living in a less affluent household were reported to be more likely to be susceptible to illness and injuries [27]. We are conscious that recall bias could lead to differential misclassification in the case-control study, despite that the radiological history was asked during well-structured interview [28]. Our risk estimates have not changed after adjusting for past history of neurological disease and ADD/ADHD, [29]. In our study, past history of allergies was similar between two groups, although most studies have demonstrated inverse associations with glioma risk [30].

The small sample size is a major limitation of our study, resulting in low statistical power to detect an association between CT scans and brain tumours. The power was insufficient as we indicated in the method section, since our case sample size was 120 which was approximately 60% of the required number. Another limitation was that the present study did not consider "retakes," despite the fact that, before 2000, it was a common practice to conduct multiple scans repeatedly to obtain clear images for infants during examinations [4, 31]. Because multiphase CT scans (with contrast material and without) are still performed occasionally and we had no possibility to check this, it may be also that brain CT dose could have been underestimated in the study.

A set of paediatric CT guidelines was published in Japan in 2004, but awareness of the potential health risks from CT scanning varies across medical professions and medical institutions. In the

sensitivity analysis conducted in the present study, the application of both scenarios that weighted exposure differently before and after the adoption of the low-dose CT guidelines did not have impact on brain tumour risk. Therefore, compliance to the guidelines needs to be examined in Japan. Further, epidemiological studies using a cohort study design, not subjected to recall bias, and individual dose and uncertainty estimates based on the information collected from radiology departments allow to evaluate more precisely the association between the dose from CT scans and risk of brain tumours [32, 33].

6. Conclusion

In this matched case-control study conducted in Japan, we found that brain CT scans were not associated with brain tumours. Diagnostic X-rays are an indispensable medical procedure. Nevertheless, the risk–benefit of such diagnostic techniques should be considered in all medical settings. Given that the exposure per image is 30 mGy or more, it is essential to make every effort to keep exposure to the minimum necessary dose, especially for CT scans in children.

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Author contributions: NK was responsible for the organisation and coordination of collected data in Japan. NK and GB were responsible for the analysis. EC was the chief investigator of the international Mobi-Kids study. YT, KO, and MK supervised issues regarding radiological exposure in Japan. AK and JS revised critically for important intellectual content the analysis and manuscript writing. All authors read and approved the final manuscript.

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