Evaluation of the lifetime brain/central nervous system cancer risk associated with childhood head CT scanning in Japan

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Keywords

Brain cancer; computed tomography; ionizing radiation exposures; low doses; pediatric population

List of abbreviations

BEIR VII: Biological Effects of Ionizing Radiation VII
CI: Confidence intervals
CNS: Central nervous system
CT: Computed Tomography
CTDIvol: Volume CT dose index
DRL: Diagnostic reference level
EAR: Excess absolute risk
ERR: Excess relative risk
FR: Fractional ratio of the excess cases to the total cases
GSD: Geometric standard deviation
ICD10: International Classification of Disease 10th revision
LAR: Lifetime attributable risk
LBR: Lifetime background risk
LSS: Life Span Study
N.S.: Not specified
OECD: Organisation for Economic Co-operation and Development
REIC: Risk of exposure induced cancer incidence

Article category

Cancer Epidemiology

Novelty and Impact

Japan is one of the leading countries in use of CT scans. This is the first study to evaluate the CT-induced lifetime risk among Japanese children. While annual frequencies of CT examinations were decreasing, a small but non-negligible portion of the brain/central nervous system cancer might be attributable to childhood head CTs. The results have implications as scientific basis for future epidemiological studies and as quantitative evidence to justify the benefits of CT vs risks.

ABSTRACT

Use of computed tomography (CT) scanning has increased worldwide over the decades, and Japan is one of the leading countries in annual frequency of diagnostic CT. While benefits of CT scan are undisputable, concerns have been raised about potential health effects of ionizing radiation exposure from CT, particularly among children who are likely more susceptible to radiation than adults. This study aims to evaluate the cumulated lifetime risk of the brain/central nervous system (CNS) cancer due to head CT examinations performed on Japanese children at age 0-10 years in 2012, 2015, and 2018. The frequency and dose distribution of head CT examinations were estimated based on information from recent national statistics and nationwide surveys. The lifetime risk attributable to exposure was calculated by applying risk models based on the study of Japanese atomic-bomb survivors. In contrast to the overall increasing trend, the frequency of childhood CT, especially at age <5, was decreasing, reflecting a growing awareness for efforts to reduce childhood CT exposure over the past decade. In 2018, 138,532 head CT examinations were performed at age 0-10, which would consequently induce a lifetime excess of 22 cases (1 per 6,300 scans) of brain/CNS cancers, accounting for 5% of the total cases. More excess cases were estimated among men than among women, and excess cases could emerge at relatively young ages. These results would have useful implications as scientific basis for future large-scale epidemiological studies and also as quantitative evidence to justify the benefits of CT vs risks in Japan.

1. Introduction

The use of diagnostic computed tomography (CT) scan has been increasingly common in modern healthcare due to its rapid and versatile acquisition of detailed morphological images that can largely improve diagnosis and treatment.[1] In Japan, installation and use of CT have grown rapidly and steadily since the mid-1970s. Indeed, Japan represents among the top nations in use of CT scans, with over 28 million CT scans performed in 2014[2] and about 13,000 operational scanners identified in 2017,[3] and 2.65 per 1,000 population have received the cumulative dose of ≥100 mSv in five years, which is the second highest among 35 OECD counties in 2017.[4]

While the benefits of the medical use of CT scan are unquestionable, the potential health risks related to ionizing radiation exposure have long been controversial since the dose per a CT examination is much higher than that of a conventional X-ray, contributing 40-70% of the total dose the general population receives.[5] Although it is well agreed that moderate to high radiation doses (e.g., > 100-200 mGy) adversely affect human health, such as inducing cancer development,[6, 7] much uncertainty remains with assessment of the risks at doses below 100 mGy, which is the dose range most relevant to exposures from diagnostic CT examinations. Of more significant concern is CT exposure among children, who are considered to be more sensitive to radiation than adults for at least about 25% of cancer sites, including brain.[8] Although the expected risk per examination may be negligible, the risk at a population level could be substantial if a large number of examinations were performed.[9]

Increased cancer risks associated with CT scan have been reported in several epidemiological studies on medically exposed cohorts.[10-12] In particular, increased risks of brain/central nervous system (CNS) cancers associated with pediatric head CT scans have been reported in recent studies in the UK, Australia, France, Germany and Netherlands.[13-17] The results of these studies, however, need to be interpreted with caution due to concerns on sources of bias that may invalidate the risk evaluation, including small sample sizes, reverse causation (pre-existed but undetected malignancy), confounding by indication (those who have conditions that confer risk for cancer receive CT examinations), lack of individual dosimetry reconstruction, short follow-up, and potential confounding due to unmeasured factors.[18, 19] To address such issues, a large cohort study, including more than 1 million CT exposed children, is currently being conducted in Europe.[20]

While awaiting more reliable results from adequately designed cohort studies, an alternative approach to evaluating the health risk associated with CT exposure is to project the number of exposure-induced excess cases in an exposed population of interest. A standard approach to this is to apply a risk model estimated from one or more of epidemiological cohort studies, such as the Life Span Study (LSS) of Japanese atomic-bomb survivors,[7, 21] to the target population by the life table method.[22-25] Based on this approach, possible lifetime cancer risks associated with pediatric CT scans have been reported in several studies, more recently for populations in France, UK, US, and Spain.[26-30] These recent studies suggested non-negligible excess cases, depending primarily on the background incidence rate, dose distributions, and the number of CT examinations.

In 2004, using the risk projection approach, Berrington de Gonzales et al. estimated more than 3% of cancers in Japan to be attributable to diagnostic X-rays, which was highest of the 15 countries considered, based on the distributions of CT examinations and radiation dose obtained elsewhere.[25] While it aroused extensive attention to the need for clinical practices to optimize and justify medical radiation exposure, few attempts have been made to quantitatively evaluate the potential risks associated with CT examinations in Japan. A recent case-control study was aimed to evaluate the association between head CT scan and brain/CNS cancers in a Japanese population but did not provide convincing evidence with a limited number of cases.[31] A major obstacle in Japan is the lack of a nationwide system to collect information about CT examinations, including equipment settings, patient information, and follow-up. Although dose management and recording have just become mandatory for healthcare facilities by law since 2020 in Japan, it is unlikely that direct risk assessment will be possible in the near future. Thus, we would be much uncertain about the potential magnitude of risk associated with the current use of CT examinations in Japan, despite the fact that the overall number of CT examinations has been consistently increasing by 40% in 2010-2018.[32]

The objective of this study is to attempt an evaluation of the potential health risk associated with the recent practice of CT examinations in Japan. In particular, we focus on the risk of brain/CNS cancer associated with pediatric head CT examinations. For this, we have combined the latest available information on the number and the dose distribution of CT scans, to which an LSS risk model was applied to project the cumulated excess lifetime risk of the disease due to exposure to head CT scan among Japanese children exposed at age 0-10 years. The information obtained from this study will have implications as a scientific basis for future large-scale epidemiological studies in Japan and also as quantitative evidence to justify the benefits of CT vs risks.

2. Methods

2.1. Study population

The study population was defined to be the children who received a head CT in Japan at age 0-10 years in each single year of 2012, 2015, and 2018. The range of age at examination (0-10) was chosen following the age grouping in the available information of the dose distribution from pediatric head CT examinations (as detailed in subsection 2.3).[33, 34]

2.2. Frequency of CT examinations

The main source of information to estimate the frequency of CT examinations performed was annual statistics reported by the Japanese government,[32] which provided data for the number of CT examinations performed in Japan by 5-year age category for the single month of June each year as a representative month. In this study, the number for June was multiplied by 12 to estimate the annual number of examinations, assuming the monthly numbers uniformly distributing through the year. In addition, the age-specific number within each of the 5 year age categories (0-4, 5-9, and 10-14 years) was assumed to be uniformly distributed with a 62.3:37.7 male to female ratio.[35] Further assuming that 54% of all CT examinations were on the head,[36] irrespective of age, sex and year, we obtained estimates for the age- and sex-specific number of head CT examinations among children aged 0-10 years for each of years 2012, 2015, and 2018. In the absence of other recent information, this is considered to be the best estimate for the annual frequency of head CT examinations performed on Japanese children in recent years.

2.3. Dose distribution

The distribution of absorbed doses to the brain from head CT scan in Japan was estimated based on two sources of information; a national questionnaire survey on scanning conditions for childhood CT[33, 34] and the conversion coefficients for brain doses.[37] The survey information provided the distribution of volume CT dose index (CTDIvol) values for head CT examinations at age 0, 1-5, and 6-10 years for examinations conducted in year 2012[33] and at age 0, 1-4, 5-9, and 10 years for those conducted in 2018-2020.[34] This was used as the primary information for establishing the recent diagnostic reference levels (DRLs) for pediatric CT examinations in Japan, first in 2015, then in 2020.[34, 38] The distribution of CTDIvol values were converted to that of the brain doses by multiplying the age- and organ-specific conversion coefficients[37] for the tube voltage value of 120 kV, which was used in 90% of facilities that responded to the questionnaire.[33] Representative values of the distributions of CTDIvol values and the converted brain doses estimated for each age category are presented in Supporting Information Table S1. The resulting distribution of the brain doses was described by a log-normal distribution specific to each age category and year (2012 and 2018). The dose distribution for year 2015, for which no information was available, was estimated by averaging the dose distributions for 2012 and 2018.

2.4. Risk model

The risk model for the current risk evaluation was derived from the LSS cancer incidence data.[7] The excess relative risk (ERR) of brain/CNS cancer was modeled by the linear function of absorbed dose (d) in Gy, multiplied by a function to allow for variation of the dose effects by effect modifiers of sex, attained age (a), and age at examination (e). Following the model of Berrington de Gonzales et al.,[23] we employed a risk model of the following ERR form, which was estimated based on the LSS cancer incidence data of follow-up in 1958–1998,[7] with some modifications made according to the methodology used in the BEIR VII report.[23, 24]

$$ERR_{d,e}(a) = \begin{cases} 0.71d\exp\left\{-\dfrac{0.3(e-30)}{10} - 1.4\log\left(\dfrac{a}{60}\right)\right\} & \text{for male} \\ 0.24d\exp\left\{-\dfrac{0.3(e-30)}{10} - 1.4\log\left(\dfrac{a}{60}\right)\right\} & \text{for female} \end{cases}$$

This model implies that the ERR of brain/CNS cancer at age 60 years among males exposed to 30 mGy at age 10 would be about 3.9%, and the corresponding ERR among females be about 1.3%, one-third of the risk in males. The ERR at given dose and age at examination tends to decrease with increasing age by the power of -1.4, whereas the ERR at given dose and attained age tends to increase by about 3% per a year decrease in age at examination.

2.5. Lifetime risk projection

We evaluate the risk of radiation exposure by estimating the lifetime attributable risk (LAR).[39] The LAR is defined as the probability that an individual would be diagnosed with the target disease associated with the exposure to dose d at age e in his/her lifetime (to a sufficiently large attained age):

$$LAR_{e,d} = \int_e^\infty \{\lambda_{d,e}(a) - \lambda_0(a)\} \frac{S_0(a)}{S_0(e)} da$$

where $\lambda_0(a)$ and $S_0(a)$ are sex-specific functions of the incidence rate of the disease and the survival probability, respectively, at age a in the target population with no exposure. $\lambda_{d,e}(a)$ is the assumed incidence rate at age a given exposure to dose d at age e so that $\lambda_{d,e}(a) = \lambda_0(a)\{1 + ERR_{d,e}(a)\}$.

This may be calculated by applying the risk model to the age- and sex-specific baseline incidence rate of the target disease (brain/CNS cancer; International Classification of Disease 10th revision (ICD10) codes C70-C72) and the all-cause mortality rate (survival function) of the target population, both of which were obtained from the database of National Cancer Center Japan.[40] We averaged the age- and sex-specific rates of all-cause mortality over 2011-2018 and those of the cancer incidence over 2011-2015 for use in projection for the population exposed in 2012, 2015, and 2018, with a maximum attained age of 99 years.

A risk adjustment for the latency period (the lag time between exposure and occurrence of an excess risk) was made by the adjusting factor to be multiplied to the ERR[24]

$$F(t) = \frac{1}{1 + \mathrm{e}^{-(t-7.5)}}$$

where t is the time since exposure. This function starts departing from zero at about 5 years after exposure and reaches to 0.5 at 7.5 years and almost one at 15 years after exposure. Supporting Information Figure S1 exhibits the sex-specific excess relative risk (ERR) at 30 mGy of brain/CNS cancer incidence as a function of attained age under this latency adjustment.

The statistical uncertainty in the estimation of the risk parameters was taken into account in the risk evaluation by applying Monte Carlo simulations under the asymptotic normality of the estimates. We scrutinized the impact of other uncertainties and the sensitivity to the assumptions made in the risk modeling. All analyses were performed with R ver 3.6.

3. Results

3.1. Frequency of CT examinations

During the period between 2010 and 2018, the overall frequency of CT examinations in Japan has increased by about 40%, from about 16,060,000 to 22,600,000 examinations, or 125.4 to 178.7 per 1,000 population.[32] In contrast to the overall trend, the frequency of CT examinations performed among children shows somewhat different trends, as shown in Supporting Information Figure S2. Whereas about 30 examinations per 1,000 population were performed for all age categories (0-4, 5-9, 10-14 years) in 2010, the number of CT examinations at age 0-4 tended to decrease remarkably since then, by about 50% from 32 in 2010 to 15 per 1,000 in 2018. Over the same period (2010-2018), the frequency decreased by 10% at age 5-9 but increased by 30% at age 10-14.

Table 1-(a) presents the estimated number of CT examinations performed for the Japanese children in year 2018, with a total of 427,776 scans at age 0 to 14 years.[32] Assuming the frequency uniformly distributed over ages, with the fixed sex ratio,[35] in each of the three age categories, the age-specific number of head CT examinations for age 0-10 was estimated as shown in Table 1-(b). These estimates indicate that a total of 138,532 scans have been performed among the children exposed at age 0-10 in Japan in 2018, which corresponds to 12.5 scans per 1,000 population. Male children were estimated to have received 86,307 scans (15.2 per 1,000 population), while 52,225

scans were performed for female children (9.6 per 1,000 population). The frequency sharply increased with increasing age, with about 60% (83,181 scans) of the total scans performed at age 6-10 (15.8 scans per 1,000 population), while 55,351 scans were done at age 5 or younger (9.5 scans per 1,000 population). This procedure was also applied to years 2012 and 2015 as shown in Supporting Information Table S2. Over the years 2012- 2018, the total number of head CT examinations decreased by 26% (3.4 per 1,000 population), with a larger reduction in examinations at age < 5.

3.2. Dose distribution

Figure 1 plots the estimated lognormal distribution for the brain doses (mGy) of head CT scans performed among Japanese children by age category (0, 1-4, 5-9, 10 years) in 2018. The median, the 75-th percentile, and the geometric standard deviation (GSD) of these distributions are presented in Supporting Information Table S1. The median brain dose increased with age; 24.7 mGy for age 0, 29.1 mGy for age 1-4, 33.3 mGy for age 5-9, and 40.9 mGy for age 10. The variation of the distribution was largest for age 5-9, with GSD of 1.7, compared to 1.4 for age 0 and 10, 1.3 for age 1-4.

The dose distributions were estimated for years 2012 and 2015 as shown in Supporting Information Table S1 and Figure S3. Over the years 2012 and 2018, the median brain dose tended to consistently decrease within each of the age categories, in particular, a considerable reduction of 24% (32.3 to 24.7 mGy) was observed for examinations at age 0.

3.3. Reference data

The sex- and age-specific rates of the brain/CNS cancer incidence averaged over 2011-2015 and the all-cause mortality averaged over 2011-2018 in Japan, which were used in the risk projection of this study, are shown in Supporting Information Figure S4. The incidence of brain/CNS cancer tended to be relatively stable up to age 50 at around 3 cases per 100,000 population then remarkably increased up to the late 70s for both sexes. The incidence rate was overall higher in males than in females, with tendency increasing with age to a difference of about 6.4 cases per 100,000 at age 85. The all-cause mortality rate was higher in males than in females over most age ranges with a sharp increase after age 75 for both sexes.

3.4. Lifetime risk projection

Table 2 exhibits the estimated numbers of age- and sex-specific baseline and radiation-associated excess cases of brain/CNS cancer among the 138,532 children who received head CT scans at age 0-10 in Japan in 2018. A total of 427 cases (281.9 for males and 145.1 for females) would be diagnosed throughout a lifetime in this population, even if none of them had taken a head CT scan. Due to the differences both in the baseline incidence rate and in the number of examinations, male children were associated with about twice more lifetime baseline cases than female children. Also, reflecting the age-dependent variation in examinations, the baseline number of cases was largest for male children exposed at age 10, with 46.0 cases, while fewer baseline cases (8.6 cases) were estimated for female children who received head CT scans at age 3 or 4.

Table 2 also suggests that, in addition to the baseline cases, a total of 22 cases (95% confidence intervals (CI):

8.1, 58.5) of brain/CNS cancer would be excessively diagnosed among the study population due to their exposures to radiation from head CT scan in 2018. Most (86%) of the excess cases were from males, with a total of 19 cases (95% CI: 7.0, 50.5), accounting for 6.3% of the total cases in males. The excess cases by age at examination among males span 1.0-2.9 cases, with the largest for those exposed at age 10, reflecting their number and median brain dose of head CT examinations, both of which were highest in this population. Female children, with both fewer numbers of head CT examinations and a smaller radiation associated risk (compared to the male's risk), would be associated with much fewer excess cases, with a total excess of 3 cases (95% CI: 1.1, 8.0) accounting for 2% of the total cases. The remarkable sex difference is largely due to the difference in the ERR estimate (with a 3:1 male to female ratio) and the baseline number of cases (with an about 2:1 male to female ratio over most age ranges). The age-specific fractional ratio of the excess to the total of excess and baseline was 5.6-7.3% for males and 1.8-2.4 % for females.

The lifetime risk projection was also conducted for the childhood head CT examinations in year 2012 and 2015 in Japan (Supporting Information Table S3). Figure 2 plots the estimated number of lifetime excess brain/CNS cancer cases among children who received head CT scans at selected ages of 0, 5, and 10 years at examination in 2012, 2015, and 2018. Overall, decreasing trends in the excess cases were projected over the years for all ages. In particular, a marked decrease (about 57%) in the excess due to examinations for males at age 0 was apparent, reflecting a steady decrease in CT examinations and the median brain doses in the young age groups over the past decade (Supporting Information Table S1, Figure S2).

Table 3 presents the estimated number of the baseline and the excess cases among the study population exposed in 2018 by sex and attained age at diagnosis (-19, 20-39, 40-59, 60-79, 80+ years). While the number of baseline cases were largest at age 60-79 for both male and female, the excess cases appeared to peak at age 20-39, with an excess of 5.5 (95% CI: 2.0, 14.7) among males and with 0.8 (95% CI: 0.3, 2.0) among females. The male to female ratio of the excess cases was also largest at age 20-39 with about 6.9 (5.5 to 0.8). The fractional ratio of the excess cases was largest below age 20, with 14% among males and 5% among females, which then tended to decrease with increasing age, to 3 % in males and 1 % in females at age 80 or older.

This procedure was also applied to years 2012 and 2015 as shown in Supporting Information Table S4, which shows similar age-related patterns as observed for 2018. Over the years 2012-2018, the baseline cases, excess cases, and fractional ratio of the excess cases were predicted to be declining within each attained age category. The decline was largest below age 20 for baseline (30%) and excess cases (42%) for both sexes.

3.5. Sensitivity analysis

Sensitivity analyses were conducted to examine the impact of uncertainty related to estimation of the distributions of doses (Supporting Information table S1) and numbers of head CT examinations (Table 1, Supporting Information table S2), which was based on combined information from various sources with additional assumptions. The primary source for estimation of the dose distribution was survey data collected from a limited portion (<5 %) of all the medical facilities with multi-slice CT examinations in Japan,[33, 34] which raises a concern on possible bias due to selection of facilities with more interest in radiation protection. Increasing or decreasing the median brain dose by 15% would change the excess cases by ±3 cases in total and the fractional ratio by ±0.7%. Increasing the 75th percentile of each dose distribution by 15% to account for a wider variation in scanning practices and associated exposures[41] had a similar impact on the results. Whereas more pediatric CT examinations were assumed to be performed on males than on females, as observed in Japan and elsewhere,[28, 30, 35] changing the sex ratio (male 62.3%, female 37.7%) to the equally balanced or the opposite ratio resulted in a substantial reduction in the total excess cases by 26-37% and the ratio by 24-33%. The impact of assuming the uniformly distributed number of examinations over ages within each age category appeared to be marginal; by assuming instead a linear trend in the frequency with the youngest age having 20% more exams than the oldest within each age category resulted in a slight increase (+0.1 cases) only in total excess cases.

We also examined the impact of latency adjustment with the S-shape model centered at 7.5 years (Supporting Information figure S1). Increasing or decreasing the latency period had only marginal impacts. A shorter latency centered at 5 years would slightly increase the total excess cases from 22 to 23.7 and the corresponding fractional ratio from 4.9 to 5.3, while a longer latency at 10 years would decrease the total to 20.6 and the ratio to 4.6.

4. Discussion

While the frequencies of examinations and scanners of CT per population have been among the highest in the world, not much has been studied about the adverse health effects potentially induced by the recent CT use in Japan. This study was aimed to integrate fractional knowledge about the frequency, the dose distribution and the radiation-associated risk to draw the best estimate of the cancer risk associated with CT examinations among the Japanese population, in particular, among children, who are likely to be more sensitive to radiation exposure than adults. Our results indicate that in 2018, 138,532 head CT scans were performed on children at age 0-10 in Japan, with the median brain doses ranging 20 to 40 mGy, which would consequently induce a lifetime excess of 22 cases (1 per 6,300 scans) of brain/CNS cancers, accounting for 5% of the total cases in that population. More excess cases were projected among men than among women, and the excess cases could be emerging at relatively young ages. The associated lifetime risk may be in a decreasing trend, presumably reflecting a growing awareness for efforts to reduce CT exposure among children, especially infants, in the past decade.

To the best of our knowledge, this study is the first attempt to estimate the CT-associated lifetime risk based on information about the current situation of CT examinations in Japan. Table 4 summarizes the results of this study as well as two other recent studies that projected the brain/CNS cancer risks associated with childhood head CT scans. The percentage of head CT examinations in all CT examinations performed in Japan was 54%,[36] which was comparable to 56% in France,[28] 66% in Spain,[30] and those in the Netherlands (69%[17]), and the UK (57%,[13] 71% [29]). The median brain dose from head CT scans in Japan appeared to be consistently higher than those in other countries; e.g., it was 32.3 mGy for examinations at age 0 in Japan in 2012, which was 20-50% higher than those in France, Spain [28, 30] and the UK.[13, 29] The fractional ratio of the radiation-associated excess cases was 5.5% (sex-averaged) in the Japanese children exposed at age 0-10 in 2012, which roughly doubled that (2.6%) for the population exposed at age 0-20 in Spain in the same year. This is mainly because of the difference in the dose distribution and the proportion of males, who have both the baseline rates and the radiation-associated brain/CNS cancer risks higher than those of females. The LAR per 100,000 examinations in this study appeared to be slightly decreasing with age at examination, which was also comparable to those of the other studies in Spain and France.[28, 30]

Brain/CNS cancers are relatively rare but are generally associated with poor prognosis in patients, often requiring sophisticated diagnostic and therapeutic technology (e.g., neurosurgical treatment, radiation therapy, chemotherapy), which could result in a heavy burden of medical resources.[42] Exposure to ionizing radiation is one of the few established risk factors to brain/CNS cancers, with evidence reported in radiotherapy patients exposed to fractionated high doses,[11] and more recently, among children who received lower doses of diagnostic CT scans.[13-17] The head is the most common site of childhood CT examinations in many countries.[13-17, 30, 43] While a direct risk assessment requires a long-term follow-up of a large cohort of exposed subjects, an indirect modeling approach to predict the attributable risk allows for a timely assessment of the potential risk in a population of interest.[26-30] Given that epidemiological studies that directly quantified CT-related risks have not yet provided convinced evidence, largely owing to methodological limitations,[18, 19] our modeling approach based on the risk estimated from the LSS is considered to be one of the few reasonable and feasible options to evaluate the potential population risk associated with childhood CT examinations. Our risk evaluation by the lifetime attributable risk (LAR) measure, an approximation to the risk of exposure induced cases (REIC), seems adequate in this study since it allows for a simplified but sufficiently precise approximation of the risk in the dose range of this study.[44]

While we evaluated the risk accounting for statistical uncertainty in the parameter estimates of the risk model, there were many other uncertainties not sufficiently accounted for. The risk model used in this study was derived from evidence in the LSS cohort of Japanese atomic-bomb survivors.[7] Since the relatively small number of cases for brain/CNS cancer limited a detailed characterization of the dose-response relationship and its effect modifiers with sufficient precision, we employed an essentially equivalent ERR model of RadRAT,[23] commonly used as a standard risk assessment tool in other similar studies.[28-30] In particular, we found risk estimation using the EAR model did not allow for estimation of effect modification with sufficient precision and led to extreme consequences, so risk transfer was only conducted multiplicatively. Generally, the risk transfer with a constant EAR would lead to a fairly implausible lifetime risk projection, especially for rare events such as brain/CNS cancer, most likely resulting with a much larger number of projected excess cases. Alternatively, additive transfer would be possible using the ERR and the baselines of LSS and the target population. However, considering the relatively similar characteristics of the two populations (younger survivors and the current general Japanese population) we decided not to pursue for that.

An updated result with an extended follow-up of the brain/CNS cancer incidence in the LSS was recently reported,[45] which, however, considered effect modification by sex, attained age, and age at examination separately, but not simultaneously, unlike the model used in this study. Although a direct comparison of the risk models between the updated analysis and the current study was difficult, fairly similar estimates for the risk parameters were reported in the updated analysis, with some variations depending on the baseline adjustment and the case definitions.[45] Another concern about use of LSS risk models in this study arises with radiobiological evidence showing an increased effectiveness of low-energy photons compared to high-energy photons (as for the LSS).[46, 47] Data suggest an increase by a factor between 1-3,[48] which suggests the CT-associated cancer risks might be higher than projected from the LSS risk model. Since epidemiological evidence is limited evaluation of the impact of this issue is difficult.

A major uncertainty of this study is in estimation of the distributions of doses and numbers of head CT examinations, which was based on combined information from various sources with additional assumptions. Our sensitivity analyses showed that the potential impact of deviation from these assumptions might not be substantial, mostly within differences of a few total excess cases and of less than 1% of the fractional ratio. One exception is the assumption about the sex balance in frequency; changing the male:female ratio (1.7) could be influential due to the relatively large sex difference of the ERR (male:female ratio=3). A formal account for these additional uncertainties would result in an increased width of the confidence intervals. Another concern is related to possibility of including CT examinations performed on children who were already diagnosed or suspicious of cancer and thus would not survive long enough to develop a radiation-associated cancer, or otherwise have shorter life expectancy than the general population. If those examinations were excluded from the study, then the number of excess cases would be reduced, but the ratio of excess might not unless the doses for such examinations were substantially different from those for the others.

Our evaluations were for the lifetime risk associated with the head CT scans in a given year but not for the lifetime risk of a particular individual or group of individuals who may receive more head CT exposure during treatment. If we focus on a particular birth cohort, say those born in 2011 (about 11,957,000 people[49]), our results (with an interpolation by the results of the nearest years) imply that the cohort would suffer from 28 additional cases of brain/CNS cancer (1 per 431,977 population) due to exposure to head CT examinations at age 0-10 (Supporting Information Table S5). This number would reduce to 22 cases (1 per 511,487 population) for those born in 2017. These calculations implicitly assume one scan per person-year, which may be less realistic but would have little impact on our estimation for the population number of excess cases under the linear non-threshold dose-response models.

Despite the limitations and uncertainty, we believe that our study would provide meaningful evidence to understand the plausible size of the lifetime cancer risk associated with recent CT practices in Japan, where direct assessment of the risk remains impossible or extremely difficult due to the lack of nationwide information at present. Our estimates indicate that while the number of pediatric CT examinations per year was in a decreasing trend, a small but non-negligible portion of the brain/CNS cancer to be diagnosed in the exposed population might be attributable to head CT examinations. Identification of ages with higher risks would have implications for patient protection and provide important information for planning a future large-scale epidemiological study. Our results are also expected to provide scientific basis to establish commonly agreed clinical guidelines for justification of the use of CT and to improve imaging procedures for optimization of CT parameters. Further studies are anticipated to investigate the risk-benefit balance of CT scans to assess potential consequences of reductions in examinations and dose as well as to assist decision makings in clinical practices.

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Conflict of interest

No conflicts of interest to declare.

Data availability

This data used for the analysis that are minimally required to replicate the study outcomes will be made available by authors upon reasonable request.

Ethics statement

The data used in this study has been publicly available and aggregated and has not been individually identifiable; therefore, ethical committee approval was not needed.

Figure legend

Figure 1. The probability density functions of the estimated distribution of the brain doses (mGy) from head CT scan by age at examination (0, 1-4, 5-9, 10 years) in Japan in 2018.

Figure 2. Estimated number of the lifetime excess brain/CNS cancer cases attributable to head CT scans performed among Japanese children at age 0, 5, and 10 years in 2012, 2015, and 2018.

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Tables

Table 1. Estimated distributions for the total number of (a) CT examinations and (b) head CT examinations by sex and age at examination in Japan, in 2018.

(a)		**(b)**				
			Number of head CT exam			
Age at exam	**Total Number of CT exam**	**Age at exam**	**Male**	**Female**	**Total**	
			N	**N**	**N**	**%**
0-4	74,700	**0**	5,026	3,041	8,067	5.8
		1	5,026	3,041	8,067	5.8
		2	5,026	3,041	8,067	5.8
		3	5,026	3,041	8,067	5.8
		4	5,026	3,041	8,067	5.8
5-9	139,032	**5**	9,355	5,661	15,016	10.8
		6	9,355	5,661	15,016	10.8
		7	9,355	5,661	15,016	10.8
		8	9,355	5,661	15,016	10.8
		9	9,355	5,661	15,016	10.8
10-14	214,044	**10**	14,402	8,715	23,117	16.7
Total	427,776	Total	86,307	52,225	138,532	100.0

Table 2. Estimated number of the lifetime baseline and excess cases of brain/CNS cancer attributable to head CT scans performed among Japanese children at age 0-10 in 2018.

Age at exam	**Male**				**Female**				**Total**			
	Baseline case	**Excess case (95%CI)**		**FR (%)**	**Baseline case**	**Excess case (95%CI)**		**FR (%)**	**Baseline case**	**Excess case (95%CI)**		**FR (%)**
0	16.9	1.3	(0.5-3.4)	7.0	8.7	0.2	(0.1-0.5)	2.3	25.6	1.5	(0.5-3.9)	5.4
1	16.9	1.3	(0.5-3.6)	7.3	8.7	0.2	(0.1-0.6)	2.4	25.6	1.5	(0.6-4.1)	5.7
2	16.8	1.2	(0.5-3.3)	6.8	8.7	0.2	(0.1-0.5)	2.2	25.5	1.4	(0.5-3.8)	5.2
3	16.7	1.1	(0.4-3.0)	6.3	8.6	0.2	(0.1-0.5)	2.0	25.3	1.3	(0.5-3.5)	4.9
4	16.6	1.0	(0.4-2.8)	5.9	8.6	0.2	(0.1-0.4)	1.9	25.2	1.2	(0.4-3.2)	4.6
5	30.8	2.3	(0.8-6.1)	6.9	15.8	0.4	(0.1-0.9)	2.2	46.6	2.6	(1.0-7.0)	5.3
6	30.6	2.1	(0.8-5.7)	6.5	15.7	0.3	(0.1-0.9)	2.1	46.3	2.5	(0.9-6.6)	5.0
7	30.4	2.0	(0.7-5.3)	6.2	15.6	0.3	(0.1-0.8)	2.0	46.0	2.3	(0.9-6.2)	4.8
8	30.2	1.9	(0.7-5.0)	5.8	15.5	0.3	(0.1-0.8)	1.9	45.8	2.2	(0.8-5.8)	4.5
9	30.1	1.8	(0.7-4.7)	5.6	15.4	0.3	(0.1-0.8)	1.8	45.5	2.1	(0.8-5.5)	4.3
10	46.0	2.9	(1.1-7.8)	6.0	23.6	0.5	(0.2-1.2)	1.9	69.6	3.4	(1.3-9.0)	4.7
Total	281.9	19.0	(7.0-50.5)	6.3	145.1	3.0	(1.1-8.0)	2.0	427.0	22.0	(8.1-58.5)	4.9

FR: fractional ratio of the excess cases to the total cases (baseline + excess)

Table 3. Estimated number of the baseline and excess brain/CNS cancer cases by sex and attained age among the Japanese population exposed to head CT scans at age 0-10 in 2018.

Attained age	**Male**			**Female**			**Total**		
	Baseline case	**Excess case (95%CI)**	**FR (%)**	**Baseline case**	**Excess case (95%CI)**	**FR (%)**	**Baseline case**	**Excess case (95%CI)**	**FR (%)**
-19	19.9	3.3 (1.2-8.9)	14.3	9.2	0.5 (0.2-1.3)	5.0	29.0	3.8 (1.4-10.2)	11.6
20-39	37.5	5.5 (2.0-14.7)	12.8	15.6	0.8 (0.3-2.0)	4.6	53.1	6.2 (2.3-16.7)	10.5
40-59	52.8	3.6 (1.3-9.6)	6.4	26.2	0.6 (0.2-1.6)	2.2	79.0	4.2 (1.5-11.1)	5.0
60-79	104.5	4.4 (1.6-11.7)	4.0	51.9	0.7 (0.3-1.9)	1.4	156.4	5.1 (1.9-13.7)	3.2
80+	68.8	2.2 (0.8-5.7)	3.0	42.6	0.4 (0.2-1.2)	1.0	111.4	2.6 (1.0-6.9)	2.3

FR: fractional ratio of the excess cases to the total cases (baseline + excess)

Table 4. Comparison of the results of lifetime risk projections of brain/CNS cancer associated with childhood head CT scans.

Study	Journy et al., 2014	MagdaBosch de Basea et al., 2018	This study	
Population, Year	France, 2004-2009	Spain, 2013	Japan, 2012	Japan, 2018
Age range at exam	< 10	0 to 20	0 to 10	
Male to female ratio in CT examinations (%)	57.6:42.4	55.3:44.7	62.3:37.7	
Percentage of head CTs for all CT types (%)	55.76	Male 66.3 Female 66.2	54.0	
Age at exam (Left), Median brain dose (mGy) (Right)	<1 21.0 1-10 27.0	<1 23.6 1-4 27.0 5-9 27.9 10-14 33.4 15-20 37.9	<1 32.3 1-5 30.8 6-10 39.9	<1 24.7 1-4 29.1 5-9 33.3 10 40.9
Risk models used	Preston, Ron and UNSCEAR	Extended BEIR VII	Extended BEIR VII	
LBR† (per 100,000 exam subjects)	500	790.7	310.6	308.2
Age at exam (Left), LAR† (per 100,000 exam subjects) (Right)	1mo. 12.0 1yr 11.0 5yrs 8.0 10yrs 6.0	<1 34.2 1-4 28.3 5-9 22.2 10-14 18.8 15-20 16.7	<1 24.1 1-4 18.7 5-9 17.4 10 15.4	<1 18.3 1-4 16.9 5-9 15.5 10 14.7
Age at exam (Left), FR†(%) (Right)	1mo. 2.3 1yr 2.2 5yrs 1.6 10yrs 1.2	<1 4.1 1-4 3.5 5-9 2.7 10-14 2.3 15-20 2.1	<1 7.2 1-4 5.7 5-9 5.3 10 4.7	<1 5.6 1-4 5.2 5-9 4.8 10 4.5

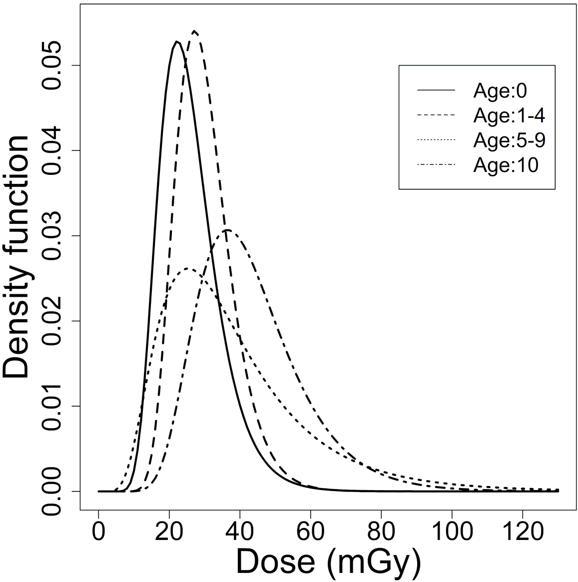
N.S.: Not specified

†Sex-averaged

LBR: lifetime background risk

LAR: lifetime attributable risk

FR: fractional ratio of the excess cases to the total cases (baseline + excess)


Density function
0.00
0.01
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Dose (mGy)
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20
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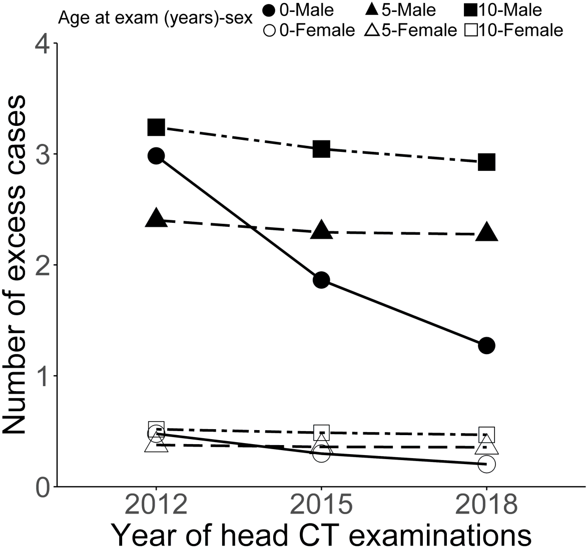
60
80
100
120
Age:0
Age:1-4
Age:5-9
Age:10


Age at exam (years)-sex
● 0-Male
○ 0-Female
▲ 5-Male
△ 5-Female
■ 10-Male
□ 10-Female
Number of excess cases
0
1
2
3
4
2012
2015
2018
Year of head CT examinations