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Topical Review

The Risk of Developing Secondary Central Nervous System Tumors After Diagnostic Irradiation From Computed Tomography in Pediatrics: A Literature Review

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ABSTRACT

Background: Advanced diagnostic imaging has provided tremendous benefits; however, increased use of ionizing radiation modalities such as cranial computed tomography (CT) may be associated with an increased risk of developing central nervous system tumors.
Methods: A literature review identified studies published for more than the last 50 years from 1968 to 2018 that explored the association between head CT scans and developing central nervous system tumors in pediatrics. We reviewed seven studies that described and analyzed the risk of brain tumors.
Results: A positive correlation between exposure to CT scans and developing central nervous system tumors was evident in all cohorts. The strength of the association varied across the studies. Exclusion of patients with predisposing factors to central nervous system tumors was examined in four studies with a decreased risk to develop central nervous system tumors noted in three studies. Two studies reported nonsignificant reduction in the excess relative risk per milliGray of brain dose after adjusting for predisposing factors, whereas the reduction was significant in one study. The frequency of CT exposure was proportional to the risk of developing tumors in two studies although not significantly maintained in two other studies. Gender had no significant effect on the central nervous system tumor risk. The calendar year at the time of imaging showed decreasing risk in those exposed to CT in more recent years compared with prior decades.
Conclusions: Prospective epidemiologic studies are needed to examine the precise carcinogenic effect of exposure to ionizing radiation and help tailor further preventive measures.

Introduction

In the last decade, diagnostic ionizing radiation technologies such as computed tomography (CT) and positron emission technology (PET) scans have led to huge advancements in precise noninvasive diagnostics, providing immense clinical benefit. Accordingly, the use of CT scans in six integrated health systems in the United States was expanded from 52 per 1000 enrollees in 1996 to 149 per 1000 in 2010 with 7.8% annual increase.[1] A similar uptrend has been reported globally in Northern England, Great Britain, Spain, Japan, and Australia.[2-6] However, the expanding use of these advanced diagnostic modalities is coupled with increased exposure to ionizing radiation, which may be associated with an increased risk of developing central nervous system (CNS) tumors.

Ionizing radiation exposure from CT scans has become a public health concern especially after the worrisome long-term outcomes elucidated in the Life Span study of the Japanese atomic bomb survivors[7-11] and occupational irradiation exposures.[12,13] Hence, the attention was extended to include long-term survivors after radiation therapy for malignant[14-20] and benign conditions,[21,22]

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pediatric patients who underwent fluoroscopic-guided procedures,[23] and those who were exposed to radiographic diagnostic examinations.[1,24-28] The 40-year follow-up of the Life Span study showed that 117 solid cancers have affected a subgroup constituting 40% of the survivors exposed to a low to moderate dose of irradiation (0.005 to 2.0 Gray (Gy)), a dose comparable to that from advanced diagnostic imaging.[11] In addition, CNS tumors constituted 1.4% of all solid tumors.[11] With the amplified use of advanced diagnostics, it is crucial to bear in mind that CT imaging delivers much higher irradiation doses compared with conventional diagnostic X-rays with a median estimated effective dose delivery of 2mSievert (mSv) for a head CT scan and 10 mSv for a chest CT scan, equivalent to 150 and 750 chest x-rays, respectively (with a chest x-ray effective dose of 0.013 mSv).[25] The effective radiation dose concept provides a theoretical quantification of the total amount of x-ray radiation to the different exposed tissues using the Sievert metric (Sv) allowing the comparison of the biologic effects and carcinogenic risks between the different types of radiation (1 mSv = 1 mGy).[29,30] In the Life Span study an excess relative risk (ERR) to develop acute lymphocytic leukemia and CNS tumors was estimated to be 0.0103 (95% confidence interval [CI], 0.0004 to 0.025) and 0.0006 (90% CI, 0.0002 to 0.001).[9,11]

Moreover, the longer life span and the sensitivity of the growing brain tissue render children especially vulnerable to tumorigenic effects of ionizing radiation.[11,26,31]

Methods

Our objective was to identify the available evidence of an association between the exposure to diagnostic ionizing radiation and developing secondary brain tumors. We searched independently the database of the United States National Library of Medicine "PubMed" from July 1968 through December 2018 for potentially relevant articles. The search strategy used Boolean logic with Medical Subject Headings search terms including ("cancer risks" OR "brain tumors" OR "central nervous system tumors") AND ("diagnostic imaging" OR "ionizing radiation" OR "CT" OR "computerized tomography" OR "positron emission tomography" OR "PET") AND ("pediatric*" OR "child*") and non–Medical Subject Headings search terms including "external radiation." All published articles related to ionizing radiation, brain tumors, and relevant references within these articles were assessed for inclusion by us. Supplementary material for all included studies was reviewed when available.

Selection of articles was based on title and abstract. The following inclusion and exclusion criteria were used: articles were excluded if they were case reports, did not present original data, were in a language other than English, did not include pediatric population (age less than 21 years at the time of diagnostic ionizing exposure), analyzed ionizing radiation forms other than CT or PET scans, or reported on long-term effects of therapeutic radiotherapy for benign and malignant conditions. Only studies that calculated an ERR estimate for brain tumors, and reported whether the tumor is benign or malignant were included in the review. ERR is generally used as a measure of the cancer risk associated with radiation when dose information is available.

Data from included studies were extracted and summarized. Information on the characteristics of the study population, study design, including year(s) in which study was conducted and published, age groups included in the study, definition of the comparative group, length of follow-up, and study latency period. The latency period (the period during which new CNS tumors were excluded from analyses post-exposure) varied between the studies and allowed for the exclusion from the analyses the occurrence of events that cannot be associated with the exposure and could represent reverse causation from the analyses. Specific study results such as total number of cases, number of exposed individuals, number of control subjects, cross-tabulations by sex (if available), age at exposure and diagnosis, information on radiation dosage, details on observed tumors, and ERR per dose estimates, and corresponding 95% CIs from each of the studies were also extracted and summarized. If available, other risk estimates such as relative risks (RRs), incidence rate ratios (IRRs), and hazard ratios (HRs) were also reported. To standardize and compare risk estimates between studies, fixed-effects models were used to perform a *post hoc* analysis. The analysis was performed using the metafor package for the R statistical package (R Foundation for Statistical Computing, Vienna, Austria).[32]

Results

The PubMed search identified a total of 801 potentially eligible articles. Screening the titles and abstracts of these articles excluded 794 articles. The remaining original studies were retrieved in the full text for more detailed examination. The reference lists of the reviews were scrutinized for potentially eligible articles. Seven of the retrieved articles met all inclusion criteria.[33-39]

Characteristics of included studies

Table 1 summarizes the characteristics of the seven retrospective studies included in the review, two of them are for the same cohort with the second being revised data after excluding some predisposing factors (PFs) to CNS tumors. The six cohorts had considerable similarities with respect to the characteristics of the study population. Yet the included studies varied by the studied population's country of origin, gender, the definition of CNS tumors, latency period, and inclusion criteria. Six were national studies,[33,34,36-39] whereas the seventh was multi-institutional.[35]

Three studies had a short latency period of two years[34-36] and two of them had a short follow-up of four years.[35,36] Follow-up period in the remaining four studies ranged from 6.7 to 10 years after the latency period or until the child reached the age 28 years.[33,34,37-39]

The Australian and Taiwanese studies reported enough data to calculate the risks of exposed population to ionizing radiation from head CT scans only,[34,37] whereas the British, French, German, and Dutch studies had insufficient risk estimate data from head CT specifically and included the risk from all CT scan types combined or head and neck CT scans combined.[33,35,36,38,39] Pokora et al.[40] interestingly provided separate risk-estimates statistical calculations for the French and the second British studies, which we have referred to for a more comparable estimate parameters between the studies.

Only three studies excluded patients with some PFs to CNS tumors, whether it was a prior history of cancers or an underlying high-risk clinical condition.[33,35,36] On the other hand, this confounded the results of the other four.[34,37-39] Yet there was no uniformity in the excluded PF, for example, one study excluded neurofibromatosis, Li-Fraumeni syndrome, nevoid basal cell syndrome, von Hippel-Lindau, and Turcot syndrome.[33] Another excluded patients with neurofibromatosis types 1 and 2, familial adenomatous polyposis, retinocytoma, and other disorders that predispose to CNS tumors.[35] The third study selected conditions based on the suggestions of the united nations scientific committee on the effects of atomic radiation report (UNSCEAR).[36,41] The last study considered only patients with tuberous sclerosis as a highly predisposed population to brain tumors and collected their data.[39] The final analysis was performed on the whole population without

adjusting for tuberous sclerosis complex as this exclusion did not affect their results.[39]

Studies varied in their definition for CNS tumors, one included only malignant tumors,[37]whereas six included both benign and malignant tumors.[33-36,38,39] Two of the latter group did not further specify the numbers in each category.[33,36] Furthermore, five studies explored the risk of developing brain tumors only,[33,34,37-39] and the rest included both spinal and brain tumors.[35,36]

The average dose of ionizing radiation exposure was highest in the studies from earlier decades (range of cumulative dose 34.4 to 60.24 mGy).[33,36-38] The mean cumulative dose before 2001 was 60.48 mGy, which was equivalent to two to three times of its counterpart after 2001 in the British studies.[35,38]

The overall risk of secondary CNS tumors in patients exposed to CT diagnostic examinations without excluding the predisposed population

All studies included in the analysis reported a trend for higher risk to develop CNS tumors postexposure to diagnostic ionizing radiation; however, the strength of the association varied across studies (Table 2).[34-39] Four of the six studies that reported on the risk without excluding RF showed statistical significance.[34,37-39] Without adjusting for PF, the RR to develop a CNS tumor after exposure to a cumulative dose of 50 to 74 mGy in Pearce et al.[38] was 2.82 (95% CI, 1.33 to 6.03) after a five-year latency period compared with Journy et al.[35] with a RR of 1.22 (95% CI, 0.84 to 1.61) after a one-year latency period as reported by Pokora et al.[40] (including all brain tumors with or without PF). This discrepancy (and non-significance in the estimate of Journy et al.) could be a result of different interplaying factors; first the shorter follow-up with a mean of four years compared with 11.7 years in Pearce et al.[38] Furthermore, the use of lower median cumulative radiation brain dose of 18.6 mGy in Journy et al.[35] could also be behind the decreased RR to develop CNS tumors essentially to nonstatistically significance compared with the control group.

Two studies used incomparable risk estimates yet significant risk for developing CNS tumors. Mathews et al.[37] reported an IRR and an absolute excess incidence rate (EIR) to develop malignant CNS tumors of 2.02 (95% CI, 1.69 to 2.43) and 2.97 (95% CI, 2.28 to 3.66), respectively, whereas Huang et al.[34] showed an HR of 2.56 (95% CI, 1.44 to 4.54).

The last two studies used different risk estimates compared with the previous studies but comparable between those two with a significant standardized incidence risk (SIR) in Meulepas et al.[39] compared with an increased trend in Krille et al.[36] with SIR of 2.05 (1.48 to 2.83) vs 1.35 (0.54 to 2.78), which could be because of the longer follow-up in the former study.

The overall risk of secondary brain tumors in patients exposed to CT diagnostic examinations after excluding conditions that predispose to brain tumors

From the four studies (Table 2), which excluded high-risk population, the first study did not report a comparable RR to the other studies and Pokora et al. calculated the RR for that study but without excluding PF as mentioned previously.[35,40] Yet Journy et al. showed that excluding children with PF had a significantly increased risk to develop CNS tumors with a RR of 86.6 (95% CI, 33.1 to 205.9) when comparing the RR of those exposed to the nonexposed.[35] This increase was similar to that observed by Berrington de Gonzalez et al.[33] where a reduction in the ERR per mGy by 57% ($P \leq 0.0001$) and a significant RR reduction of brain tumors from 2.82 (1.33 to 6.03) to 1.1 (95% CI, 1.02 to 1.26) was noted when results were corrected for PF. On the other hand Krille et al.[36] showed a nonsignificant increase in the incidence of brain tumors after excluding those with PF, which could be attributed to the smaller sample size compared with other studies and lower brain dose exposure. The exclusion of one patient with PF from Krille et al. had a similar SIR to develop CNS tumors compared with including all children regardless of their predisposition status with a SIR of 1.20 (0.44 to 2.61) and 1.35 (0.54 to 2.78), respectively.[33,36,40] Finally,

TABLE 1.
Characteristics of Included Studies in the Literature Review

Reference	Country	Year Published	Study Population	Comparison Groups	Age Group at Exposure (Years)	Timeline (Years)	Mean Follow-up Time	Latency Period (Years)	% of Head CT	PF Excluded	Mean Dose/ CT (mGy)
Pearce et al.,[38] Berrington de Gonzalez et al.[33]	Great Britain	2012, 2016	176,587, 176,190	Exposed to <5 vs 30-75 mGy	0-21	1985-2002	Age 6.7 years or up to 28 years	5	64	No, Yes	60.42
Mathews et al.[37]	Australia	2013	334,203 exposed versus 10,219,789 control subjects	Head CT versus no head CT	0-19	1985-2005	7.3	5	100	No	40
Huang et al.[34]	Taiwan	2014	24,418 exposed versus 97,668 control subjects	Head CT versus no head CT	0-18	1998-2006	1998-2008	2	100	No	N/A
Journy et al.[35]	France	2015	67,274 exposed (65,512 no PF versus1762 with PF)	CT versus no CT PF versus no PF	<10	2000-2010	4 years	2	56.9	Yes	PF: 33, 22.4* non-PF: 23,18.6*
Krille et al. [36]	Germany	2015	39,184 exposed versus 117,552 control subjects	CT versus general population	0-15	1980-2010	4.1 years	2	1 CT: 67.6% >1 CT 47.9%	Yes	34.4*
Meulepas et al.[39]	Netherlands	2018	106,530	CT versus general population	<18	1979-2014	7.8 years	5	68%	No†	38.5

Abbreviations:
CT = Computed tomography
N/A = Not available
PF = Predisposing factor
* Median dose.
† Data on patients with tuberous sclerosis were collected from two hospitals where most Dutch patients with tuberous sclerosis have been treated since 1995. It was stated that excluding patients with tuberous sclerosis did not substantially change the risk and reported analysis on the whole population assessed without any adjustments.

after the exclusion of patients with tuberous sclerosis, Meupelas et al.[39] reported no decrease in the brain tumor risk after head and neck CT scan exposure among their cohort. Therefore they based their analyses on the whole population rather than adjusting for PF. This result could be caused by the limited inclusion for patients with tuberous sclerosis only.[39]

Types of secondary CNS tumors after exposure to diagnostic ionizing irradiation

Table 3 summarizes CNS tumors' histology reported in the included studies. There were not enough data to draw conclusions regarding the differences in tumor prevalence according to the histology.

Pearce et al.[38] found positive associations between CT scan exposure in two tumor subgroups; the gliomas with ERR per mGy of 0.019 (95% CI, 0.003 to 0.070), $P = 0.0033$ and the schwannomas as well as meningiomas with ERR per mGy of 0.033 (95% CI, 0.002 to 0.439), $P = 0.0195$. Huang et al.[34] found the HR for developing benign brain tumors to be 2.97 times higher among patients (95% CI, 1.49 to 5.93, $P < 0.01$). But he found no evidence of a significantly increased prevalence of benign tumors compared with malignant tumors with an HR of 2.97 (95% CI, 1.49 to 5.93) and 1.84 (95% CI, 0.64 to 5.29) respectively, $P = 0.54^{*}$ (based on our calculation).[34] Meulepas et al.[39] reported an insignificant increase in the RR to develop benign brain tumors but a significant risk to develop malignant CNS tumors. This study also showed a significant increase by two to four times in the RR to develop malignant brain tumors in those exposed to a cumulative dose of 120 + mGy when analyzing the exposure by different dose exposures.[39]

Effects of age on exposure and time lapse since exposure

A heterogeneous association between the age at exposure and the risk to develop a CNS tumor was noted across studies. Three studies[34,35,37] were similar in their results for both factors: age at exposure and time since exposure, which contradicted with studies from Great Britain and the Netherlands.[33,38,39] The former studies revealed that the exposure to CT scan at a younger age was associated with higher risk to develop CNS tumors.[34,35,37] The multivariate analysis of Mathews et al.[37] showed the risk to develop CNS malignant tumor was the highest for children aged less than five years at their initial exposure for head CT scan (IRR, 3.10; 95% CI, 2.12 to 4.54) and a downtrend was noted with advancing age at exposure ($P = 0.09$). Similarly, Huang et al.[34] identified those aged zero to six years at time of exposure to be at the highest risk (HR, 3.16; 95% CI, 1.18 to 8.49; $P = 0.05$) with a continued downtrend afterward. Furthermore, Journy et al.[35] showed similar results with a trend of increased risk in those aged less than five years at the time of exposure compared with those greater than five years ($P \geq 0.50$).

For the effect of the lag period since exposure, Mathews et al.[37] showed the greatest risk to develop CNS malignant tumor after head CT scan, reflected by IRR and EIR, was within the one to four years from exposure ($P < 0.001$ for IRR trend and $P = 0.05$ for EIR trend) with a downtrend afterward ($P = 06$). Likewise, Huang et al.[34] showed that the risk to develop brain tumors after head CT peaked at the fourth and fifth years postexposure (HR, 3.62; 95% CI, 1.47 to 8.91; $P = 0.01$) and trended down after the sixth year. Similarly, Journy et al.[35] demonstrated a downtrend risk with the longer the time lapse since exposure ($P = 0.21$).

Pearce et al.[38] indicated that a heterogenic significant ERR to develop brain tumors across the different age at time of exposure categories, with a proportional increase in the ERR with increasing age ($P = 0.0003$). When examining the effect of elapsed time after exposure, a trend that was not statistically significant with risk peaking at five to 10 years from exposure was noted.[38] Berrington de Gonzalez et al.[33] showed that after excluding PFs the effect of age at exposure and time since exposure both peaked at 10 to 14 years and downtrended afterward reflected by ERR per mGy for brain tumors. Meulepas et al.[39] on the other hand showed the dose-response for brain tumors did not vary according to age or time lapsed from exposure.

Effect of gender

There was no significant difference between the sexes and the risk to develop brain tumors after CT scan exposure.[34,35,37-39]

Effect of calendar years of exposure

In the Australian study, the IRR of CNS malignant tumors among children who were exposed in the recent calendar years was less than that reported in children exposed to CT scans in earlier calendar years.[37] Children who underwent CT scans between the years 1985 to 1989 had an IRR to develop CNS cancer within one to four years of exposure of 5.09 (95% CI, 3.60 to 6.99) compared with

TABLE 2.
Comparison of CNS Tumor Risk Estimates After CT Irradiation Exposure in Childhood

Reference	No. of CNS Tumors	Risk Estimated	Estimate (95% CI)
Pearce et al.[38] Berrington de Gonzalez et al.[33]	135, 107[*,†]	RR	2.82 (1.33-6.03) vs 1.1(1.02-1.26)
Mathews et al.[37]	123	IRR	2.02 (1.69-2.43)
Huang et al.[34]	19	HR	2.56 (1.44-4.54)
Journy et al.[35]	27[*]	RR	1.22 (0.84-1.61)
Krille et al.[36]	7,6[†]	SIR	1.35 (0.54-2.78) vs 1.20 (0.44-2.61)
Meulepas et al.[39]	37[‡]	SIR	2.05 (1.48 to 2.83)

Abbreviations:
CI = Confidence interval
CNS = Central nervous system
CT = Computed tomography
HR = Hazard ratio
IRR = Incidence rate ratio
PF = Predisposing factor
RR = Relative risk
SIR = Standardized incidence risk

[*] Studies included enough data to calculate RR by Pokora et al., in Journy et al. it was based on 27 total cases (with and without PF).
[†] Studies that reported RR after excluding the PFs.
[‡] SIR calculated for malignant CNS tumors only. While data on patients with tuberous sclerosis as a PF were collected, the exclusion of patients with tuberous sclerosis did not affect the brain tumor risk. Therefore the final analysis reflected the whole population without any adjustments to PFs.

TABLE 3.
CNS Tumor Behavior as Reported in the Six Cohorts for Children Exposed to CT Scans

Reference	Reported CNS Tumors	Malignant	Benign	Nonspecified
Pearce et al.[38] Berrington de Gonzalez et al.[33]	135, 107	65 (glioma), N/A	20 (meningioma and schwannoma), N/A	50, N/A
Mathews et al.[37]	123	123	N/A	—
Huang et al.[34]	19	5	14	—
Journy et al.[35]	22*,†	12	10 (meningioma, n = 2)	—
Krille et al.[36]	7†	N/A	N/A	—
Meulepas et al.[39]	84†	37	47	—

Abbreviations:
CNS = Central nervous system
CT = Computed tomography
N/A = Not available
* Number of cases after 2-year latency period.
† Total number of tumors for those with or without predisposing factors.

children who were exposed to CT scans in 2000 to 2005 who had an IRR of 2.38 (95% CI, 1.64 to 3.35, $P < 0.001$).[37]

Effect of the number of CT scan exposures

Four studies explored the association between the frequency of CT scans and the risk to develop CNS tumors.[34,36,37,39] Huang et al.[34] found that an increased frequency of head CT exposure from one to three or more scans was associated with an increased HR from 2.32 to 10.4 ($P = 0.0001$) when compared with the nonexposed population. Furthermore, children with history of two or more CT scans had double the risk to develop CNS tumors compared with children who received only one CT scan (SIR of 2.12 versus 1.08); however, the finding was not statistically significant (95% CI, 0.29 to 2.71 and 95% CI, 0.44 to 6.18, respectively).[36] On the other hand, Mathews et al.[37] and Meulepas et al.[39] did not show a significant increase in IRR and ERR per 100 mGy, respectively, with increasing number of CT scans with the latter showing increasing trend only.

Approximate ERR per unit dose of brain exposure

The ERR per mGy of brain dose for all CNS tumors without adjusting for PF ranged from 0.0086 (95% CI, 0.0020 to 0.022) to 0.23 (95% CI, 0.010 to 0.049).[35,37-39]A nonsignificant reduction in ERR per mGy of brain dose after adjusting for PF was noted in the French (reduction by half was noted) and in the Dutch studies (adjusted to tuberous sclerosis only, $P = 0.72$), whereas the decrease was significant in the British studies with ERR per mGy of 0.012 (95% CI, 0.013 to 0.037), 0.0079 (95% CI, 0.0016 to 0.021), and 0.010 (95% CI, 0.002 to 0.026), respectively[33,35,38] Comparison with the studies from Taiwan and Germany were more difficult because of the lack of dose estimation in the former and the use of HR per mGy in the latter.[34,36] Refer to Table 4.

Discussion

CT imaging delivers much higher irradiation doses compared with conventional diagnostic x-rays.[25] In addition, children may have a higher susceptibility to potential effects of ionizing radiation compared with the adults.[11] That can be attributed to the higher effective radiation dose in the pediatric population because of their smaller size, the proximity of organs, which puts adjacent organs at risk, the increased vulnerability of rapidly dividing cells, and having a longer life expectancy after irradiation exposure.[26,31] In our review, we found a trend toward developing CNS tumors after exposure to diagnostic CT scans in the pediatric population.

The effect of including patients with PF to develop CNS tumors in studies examining the risk to develop CNS cancers after head and neck CT scan is controversial. Patients with PF were reported to have a higher frequency of undergoing CT scans at a younger age, therefore the possibility of an indication bias for the apparent excess cancer risks.[42] Without excluding PF, four studies showed significant increase in the risk of developing brain tumors.[34,37-39] From the four studies that examined the risk after excluding PF,[33,35,36,39] two showed significantly decreased risk,[33,35] one showed a trend toward lower risk[36] and the last one showed a statistically insignificant effect.[39] Nonetheless, the risk was still higher than the nonexposed population in all those studies.[33,35,36,39] The studies also described the ERR to develop brain tumors for each mGy of ionizing radiation exposure with significant increase noted in all studies.[33,35-39] Worth mentioning, Meulepas et al.[42] examined the confounding role of various PF on the risk to develop brain tumors after CT scans; however, because of analytic error, they retracted their results. After the correction of the analytical error they did not find a statistically significant confounding effect of tuberous sclerosis on the risk to develop brain tumors after head and neck CT scan exposure.[42]

Journy et al.[35] reported increased RR to develop CNS tumors in the predisposed to nonpredisposed population. A later report on the same cohort interestingly reported an uptrend in CNS tumor risk with the increased cumulative dose exposure in children without PF (HR per 10 mGy of 1.07 [95% CI, 0.99 to 1.10]) whereas this risk tended to decrease in children in the predisposed group (HR per 10 mGy of 0.80 [95% CI, 0.45 to 1.06]).[43] This was attributed to an earlier noncancer mortality rate in patients with PF, which may reflect the severity of their conditions.[43]

The effect of age at exposure to CT scans and the effect of the latency period varied across the studies. All studies except the ones from Great Britain and the Netherlands showed a decreased risk to develop brain tumors with increased age at exposure.[26,44] This was paralleled with institutional[26] and national[44] studies that used CT scan utilization data from 1999 to 2003 and 1996 to 1999, respectively. On the basis of the published organ doses for common CT examinations and radiation-related cancer mortality risk estimates from studies in the Japanese atomic bomb survivors exposed to intermediate radiation doses, an estimated excess lifetime risks for cancer mortality attributed to use of CT in children and adolescents (age up to 18 years) was calculated and used in their analyses.[26,44] The estimated lifetime CNS cancer mortality risk attributable to ionizing radiation from head CT examination was inversely proportional to age at exposure.[26,44] Brenner et al.[26] predicted the lifetime cancer mortality risks attributable to pediatric CT scans' exposure to specific organ sites by age-dependent linear extrapolation of risks from intermediate to low doses analyses. They estimated highest CNS cancer mortality risk among those who were exposed to CT scan at age one year compared with those exposed at age 15 years.[26,27] Chodick et al.[44] used the methodology reported by Brenner et al.[26] and found similar results in Israel with the

TABLE 4.
Comparison of CNS Tumor Risk Estimates per Dose of Irradiation Exposure After CT Exposure

Reference	Quality Estimated	Estimate (95% CI) Without Adjusting for PFs	Estimate (95% CI) After Adjusting for PFs
Pearce et al.[38] Berrington de Gonzalez et al.[33]	ERR/mGy of brain dose	0.023 (0.010-0.049)	0.010 (0.002-0.026)
Mathews et al.[37]	ERR/mGy of brain dose	0.021 (0.014-0.029)	N/A
Huang et al.[34]	ERR/mGy of brain dose	N/A	N/A
Journy et al.[35]	ERR/mGy of brain dose	0.022 (−0.016 to 0.061)	0.012 (−0.013 to 0.037)
Krille et al.[36]	HR/mGy of brain dose	N/A	1.008 (1.004-1.013)
Meulepas et al.[39]	ERR/mGy of brain dose*	0.0086 (0.0020-0.0222)	0.0079 (0.0016-0.021)

Abbreviations:
CI = Confidence interval
CNS = Central nervous system
CT = Computed tomography
ERR = Excess relative risk
HR = Hazard ratio
N/A = Not available
PF = Predisposing factor
* ERR/mGy from head and neck CT scans only.

highest estimated excess risk for cancer mortality attributed to CT examinations being in children aged less than three years and continued to decline with increasing age. Moreover, a retrospective multi-institutional study (mean age of 59 years) estimated the lifetime attributed risks of cancer after head CT exposure at 20, 40, and 60 years with inverse proportional risk to age at exposure.[24]

Gender had no effect on the risk to develop CNS tumors after CT scan exposure. Similarly in the previously mentioned multivariate analysis by Brenner et al.,[26] the sex effect did not vary greatly. From our review the frequency of CT exposure was proportional to the risk of developing a tumor in one study but not maintained in the other three studies with insignificant trend toward increased risk, and there were limited data provided on the behavior of CNS tumors in these studies.

The calendar year at the time of imaging showed decreased risk in those exposed to CT scans in the more recent years compared with prior decades. The average brain dose was highest in the studies that included earlier decades of exposure,[33,36-39] whereas lowest in the most recent French study. Two indicators for using lower doses of radiation were probably a reflection of successfully increased awareness to the effects of ionizing radiation exposure. The first was the effect of calendar year assessed by Mathews et al., which showed the drop of CNS tumor incidence by almost 50% in the same age group of those exposed between the years 2000 and 2005 compared with those exposed between the years 1985 and 1989.[37] The other indicator for lower dose exposure was in the downtrend in average brain dose reported in the study by Journy et al. that examined exposure after the year 2000 compared with older decades in the other studies, which could have been reflected by the nonsignificant increase in CNS tumors in comparison to control subjects.[35,40]

Both indicators reflect successful continuing efforts of many initiatives that have been established to increase awareness of ionizing radiation exposure risks in the pediatric population,[45-51] and results are consistent with three more recently published pediatric studies.[3,40,52] In the first study, the estimated brain-absorbed dose decreased from 62 mGy before 1990 to approximately 30 mGy after 2000 in Great Britain.[52] The other study analyzed data from patients who were exposed to CT imaging from a German pediatric CT cohort with added data from a large health insurance provider between the years 2006 and 2012 and showed a 29% decline per year in CT scans performed.[40] The third looked into trends of CT scan utilization in Spain from the years 1991 to 2013 and interestingly showed a decrease in the relative frequency of head and neck imaging in 2012 that was attributed to the increased awareness and a shift in the use of CT scans to other nonionizing diagnostic techniques following a study published same year, which pointed out the risks of developing leukemia and brain tumors after ionizing radiation exposure.[3,53]

Our review has several limitations that may affect the significance of our findings. There was uncertainty regarding the dose estimates because of the unavailability of individual information about the received doses except for the Netherlands' study. Furthermore, the inclusion/exclusion criteria varied from one study to another. Mathews et al. and Huang et al. did not adjust for prior medical conditions with PF to develop CNS tumors. Moreover, the exclusion criteria have also varied by adjusting for different and rather some but not for an extensive list of conditions that could be associated with brain tumor development. Additional exclusions based on the pathology reports by Berrington de Gonzalez et al. were applied to the cases but not the control subjects, with possible underestimation bias for the actual risks.

The different latency period used in the studies limited our ability to compare studies, with higher chance of reporting reverse causation bias when shorter latency period was used.[34-36]Another limitation was the difference in calendar periods of exposure between the studies. It is noteworthy that in five studies there were unavailable data on the effect of exposure in the different decades.[33,34,36,38,39] Furthermore, the studies used variable risk-estimates measures, which limited comparison.

One limitation in Mathews et al. was the potential bias of misclassification, with the possibility of placing people in the nonexposed arm although they may have had an exposure before the implementation of Medicare system in Australia or had obtained their CT scans outside Australia. Similarly, those who were diagnosed with cancer before the establishment of the cancer registry in 1985 might have been included with the nonexposed population. All across the studies, there was a limited description of the tumor pathologies and behaviors, providing too little information to draw conclusions.

In summary, the growth of advanced diagnostic imaging of the brain has contributed to improved patient care but one must be conscious of the associated brain tumor risks. There remains an increased risk of developing brain tumors, although this risk is becoming less significant in the more recent studies. Decreasing the number of CT studies, using newer technologies, and different imaging modalities to reduce the CT-related dose without compromising image quality is crucial. Finally, newer studies are required to better determine the effect of the continuing efforts in reducing the exposure dose in the more recent years.

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