UCLA
UCLA Previously Published Works

Title
Risk of Brain Tumor Induction from Pediatric Head CT Procedures: A Systematic Literature Review

Permalink
https://escholarship.org/uc/item/5gv9b1cc

Journal
Brain Tumor Research and Treatment, 6(1)

ISSN
2288-2405

Authors
Sheppard, John P
Nguyen, Thien
Alkhalid, Yasmine
et al.

Publication Date
2018

DOI
10.14791/btrt.2018.6.e4

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

REVIEW ARTICLE
Brain Tumor Res Treat 2018;6(1):1-7 / pISSN 2288-2405 / eISSN 2288-2413
https://doi.org/10.14791/btrt.2018.6.e4

Check for updates

Risk of Brain Tumor Induction from Pediatric Head CT Procedures: A Systematic Literature Review

John P. Sheppard[1], Thien Nguyen[1], Yasmine Alkhalid[1], Joel S. Beckett[1], Noriko Salamon[2], Isaac Yang[1,3-7]

Departments of [1]Neurosurgery, [2]Radiological Sciences, Section of Neuroradiology, [3]Head and Neck Surgery, [4]Radiation Oncology, David Geffen School of Medicine of the University of California, Los Angeles (UCLA), Los Angeles, CA, USA
[5]Jonsson Comprehensive Cancer Center, [6]Los Angeles Biomedical Research Institute, [7]Harbor-UCLA Medical Center, David Geffen School of Medicine of the University of California, Los Angeles (UCLA), Los Angeles, CA, USA

Received February 15, 2018
Accepted March 30, 2018

Correspondence
Isaac Yang
Department of Neurosurgery, David Geffen School of Medicine of the University of California, Los Angeles (UCLA), 300 Stein Plaza, Suite 562 , Los Angeles, CA 90095, USA
Tel: +1-310-267-2621
Fax: +1-310-825-9384
E-mail: iyang@mednet.ucla.edu

Head computed tomography (CT) is instrumental for managing patients of all ages. However, its low dose radiation may pose a low but non-zero risk of tumor induction in pediatric patients. Here, we present a systematic literature review on the estimated incidence of brain tumor induction from head CT exams performed on children and adolescents. MEDLINE was searched using an electronic protocol and bibliographic searches to identify articles related to CT, cancer, and epidemiology or risk assessment. Sixteen studies that predicted or measured head CT-related neoplasm incidence or mortality were identified and reviewed. Epidemiological studies consistently cited increased tumor incidence in pediatric patients (ages 0–18) exposed to head CTs. Excess relative risk of new brain tumor averaged 1.29 (95% confidence interval, 0.66–1.93) for pediatric patients exposed to one or more head CTs. Tumor incidence increased with number of pediatric head CTs in a dose-dependent manner, with measurable excess incidence even after a single scan. Converging evidence from epidemiological studies supported a small excess risk of brain tumor incidence after even a single CT exam in pediatric patients. However, refined epidemiological methods are needed to control for confounding variables that may contribute to reverse causation, such as patients with pre-existing cancer or cancer susceptibility. CT remains an invaluable technology that should be utilized so long as there is clinical indication for the study and the radiation dose is as small as reasonably achievable.

Key Words Tomography, X-ray computed; Brain tumor; Pediatrics; Patient safety; Epidemiology; Radiometry.

INTRODUCTION

Cranial computed tomography (CT) has transformed diagnostic neuroradiology over the past half century, beginning with its first clinical use in 1971 to image a suspected frontal lobe tumor [1-3]. In the United States, an estimated 82 million CT scans were performed during the year 2016 alone [4]. Cranial imaging accounts for roughly one-third of these scans, totaling around 25–30 million head CTs annually [5]. Despite its benefits, there remains concern of neoplastic induction from the low dose ionizing radiation of head CT.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Copyright © 2018 The Korean Brain Tumor Society, The Korean Society for Neuro-Oncology, and The Korean Society for Pediatric Neuro-Oncology

Relative to other CT imaging protocols, non-contrast head CT scans are among the safest, delivering around 2 mSv in effective radiation dose to the body depending on the scanner, protocol, and patient [6,7]. By comparison, this is the approximate radiation dose incurred from 225 one-way flights from New York City to Chicago [8], slightly less than the excess radiation received annually by a typical flight crew member [9, 10], and only one tenth the occupational limit for flight crews recommended by the United States Federal Aviation Administration [8] and the International Commission on Radiological Protection [11]. For context, typical annual levels of background radiation exposure are in the range of 3–6 mSv [12,13].

The safety of head CTs is due to the small amount of radiation delivered per scan and the low susceptibility of brain tissue to cytotoxic damage from ionizing radiation relative to other organs [11]. However, certain populations may be at increased risk. Children, in particular, are markedly more susceptible to radiation-induced cancer than adults [14], and the lifetime attributable risk (LAR) of malignancy from a single head CT may be more than ten-fold higher for an infant than for a middle-aged adult patient [5,15,16]. Furthermore, patients with conditions requiring repeat CT exams (i.e., traumatic brain injury [17,18] or cerebrospinal fluid shunts [19,20]) receive cumulative radiation doses that magnify the potential risk.

Given the heightened concerns of potential cancer risks in pediatric patients undergoing CT, a comprehensive view of head CT radiation risk is needed as a basis for evidence-based guidelines and serial surveillance protocols. Here, the authors assess the current body of peer-reviewed epidemiological evidence on the incidence and risk of brain tumor induction associated with head CT exams administered to children and adolescents.

MATERIALS AND METHODS

Study eligibility criteria

Published studies that examined the incidence or attributable mortality of intracranial neoplasms observed in pediatric patients undergoing head CT imaging compared to non-exposed persons were reviewed, including: 1) studies that predicted tumor incidence attributable to head CT based on estimated radiation dose or 2) epidemiological studies that directly measured rates of neoplasms in pediatric patients undergoing no or varying numbers of head CT scans, relative to patients who had no CT radiation exposure. All full-text, English language articles were considered regardless of publication date.

Information sources & search protocol

The National Library of Medicine's MEDLINE Database (1966–Present) was queried via PubMed. The last electronic search was performed on March 13, 2017 and consisted of an intersectional search for papers containing keywords or indexed with medical subject headings related to three broad categories: 1) computed tomography, 2) radiation and radiation-induced neoplasm, and 3) risk, incidence, or epidemiology. Additional studies were identified through manual search of bibliographies. Details of the electronic search protocol are provided in Fig. 1.

Study selection

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were utilized to guide our literature review and synthesis [21,22]. Study selection was carried out by two independent authors (JPS and JSB). Studies of chest CT for lung cancer screening, radiotherapy, or other topics that clearly diverged from head CT-related radiation risks were excluded. A total of 16 relevant studies pertaining to cancer or solid tumor risks from head CT radiation exposure met our eligibility criteria (Fig. 2).

Given the small number of published epidemiological studies on cancer incidence from head CT, we considered risk assessment studies if they made a quantitative prediction of neoplasm risk based on estimated radiation doses. For inclusion, we required that studies measured or predicted the inci-

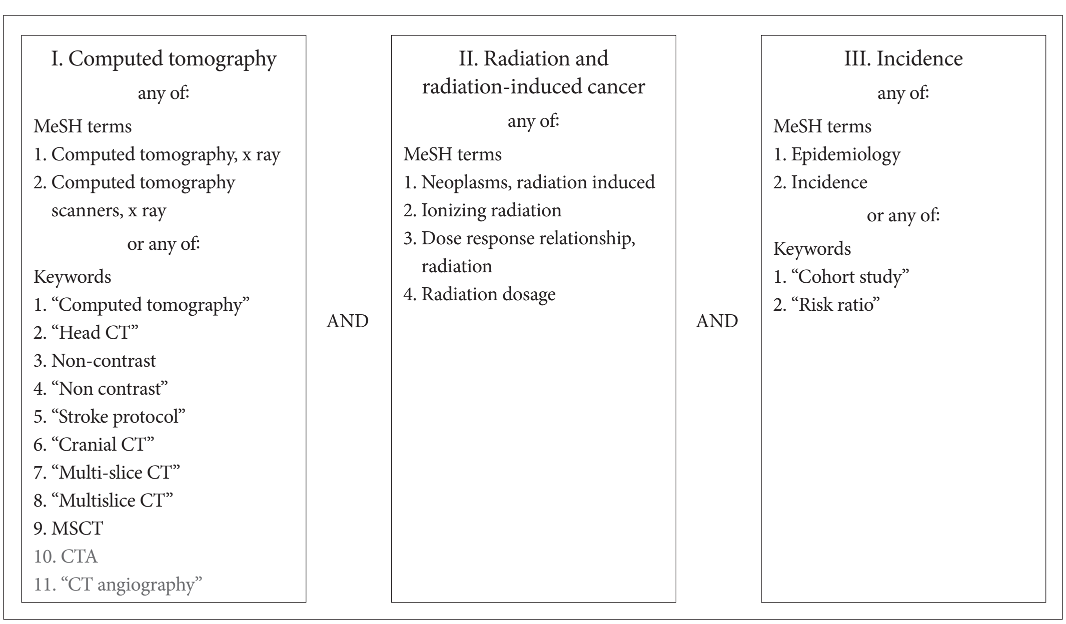

Fig. 1. Protocol used for electronic search of MEDLINE database via PubMed. Identified articles contained at least one relevant keyword or MeSH from each of three major search categories (columns). Grey terms at bottom of left column relate to CT angiography and were subsequently excluded. MeSH, medical subject heading.

dence of neoplasms attributable to one or more head CT scans in an actual or hypothetical patient population.

Data extraction

After eligibility screening, we extracted all available quantitative measures involving: population prevalence of head CT procedures, per-scan or cumulative radiation dose levels, and predicted or actual tumor incidence or mortality. Radiation dosages were reported as per-scan or cumulative administered doses reported in units of brain absorbed dose (mGy) or converted to biological effective dose (mSv). Head CT-attributable tumor incidence or tumor-associated mortality was reported using a range of epidemiological measures. Generally, these rates were reported as lifetime attributable absolute risk for predictive studies, and either absolute risk, excess relative risk (ERR), hazard ratio (HR), or standardized incidence within the defined follow-up periods for epidemiological studies. Metrics were extracted as presented in each reviewed study, tabulated, and used for pooled statistical analysis.

Statistical analysis

In addition to tabulating head CT prevalence, radiation dose, and brain tumor risk estimates, summary metrics of head CT population prevalence, absorbed or effective radiation dose, and attributable brain tumor risk were computed as cross-study averages with 95% confidence intervals (CIs). We also summarized the ERR of head CT exams observed in the epidemiological studies on a per patient, per brain dose (mGy), and per scan (assuming 60 mGy) basis. ERR metrics were directly calculated using the reported incidence data from each reviewed study. ERR per patient was calculated using the reported tumor incidence rates for exposed and un-exposed patient cohorts within each study period. ERR per mGy of absorbed brain dose was next determined by dividing the excess incidence rates by the mean cumulative absorbed brain dose (mGy) across exposed patients. Finally, a standard ERR per head scan was estimated and summarized across studies (mean and 95% CI) by multiplying the normalized ERR (ERR per mGy brain dose) by a hypothetical head CT scan delivering 60 mGy of absorbed radiation to the brain.

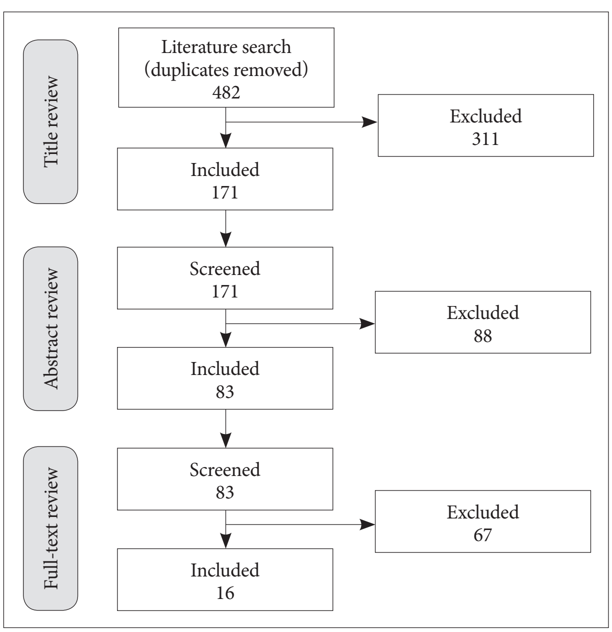

Fig. 2. Summary of article search strategy. Numbers of surviving articles at each stage of screening and review are indicated.

RESULTS

Population health burden of pediatric head CT exams

We identified four published studies that reported data on pediatric head CT incidence per capita [23-26]. Study characteristics are presented in Table 1. These studies reported an average annual incidence of 720 head CT procedures per 100,000 children, or 0.72% per capita.

Predicted tumor risk from single pediatric head CT exam

Seven studies reported projected tumor risks from single non-contrast head CT exams based on estimated absorbed or effective dose [10,23-25,27-29]. Results from studies of interest are summarized in Table 2. On average, predictive studies estimated brain doses of 55 mGy and effective doses of 1.6 mSv per head CT scan for pediatric patients. Predicted LAR of brain tumor from a single pediatric head CT scan was 0.056% (95% CI 0.009–0.102%) on average across five predictive studies [23,25,27,29,30]. This estimate corresponds to one induced neoplasm per 1,800 pediatric head CTs, but is skewed upwards by estimates for infant patients who have the highest expected susceptibility to radiation but are scanned

Table 1. Population health burden of pediatric head CT exams

Author [ref]	Population studied	Ages included	Annual scans per 100k
Chodick et al. [24]	Israel (1999–2003)	0–18	800
Pflugbeil et al. [23]	Germany (2007)	0–14	850
Miglioretti et al. [25]	United States (1996–2010)	0–14	1,070
Pokora et al. [26]	Germany (2006–2012)	0–14	120–220

Table 2. Estimated LAR of tumor induction from predictive studies of pediatric head CT exposure

Author [ref]	Patients (n)	Dose/scan	Scans/tumor (n)	LAR (%)
Journy et al. [29]	27,362	21–27 mGy	8,300–100,000	0.001–0.012
Miglioretti et al. [25]	400,000+	1–2.6 mSv	570–9,100	0.011–0.175
Pflugbeil et al. [23]	-	60 mGy	4,200	0.024
Feng et al. [30]	-	0.7 mSv	2,800–6,700	0.015–0.036
Stein et al. [27]	-	2 mSv	450–2,500	0.04–0.22
Chodick et al. [24]	570,000	30–130 mGy	2,800*	0.036*
Brenner et al. [16]	-	2 mSv	1,500*	0.067*

*Tumor-related mortality. LAR, lifetime attributable risk

less frequently than older children and adolescents in practice.

Measured brain tumor incidence in pediatric head CT-exposed populations

We identified five core epidemiological studies of neoplasm incidence in pediatric CT-exposed populations [14,31-34], which elucidated specific risks from head CT exams (Table 3), as well as a sixth article that reported methodological refinement and re-analysis of data from one of the core studies [35]. The identified studies collectively included 995,091 patients exposed to CT radiation. The cumulative estimated radiation dose delivered to the brain from head CT exams was 41±9 mGy across these studies on average.

All five studies reported increased incidence of brain tumors in patients exposed to CT exams, with a relative risk of 2.29 (95% CI 1.66–2.93) compared to patients not exposed to CT radiation. This corresponds to an ERR of 1.29 (95% CI 0.66–1.93). Normalizing these relative risks by the cumulative brain dose of radiation delivered in each study demonstrated an average ERR of brain tumor of 2.25% (95% CI 1.59–2.92%) per mGy absorbed brain dose from head CTs. Assuming a brain dose of 60 mGy per scan [31], the reviewed epidemiological studies estimated an ERR of 140%, or a 2.4-fold increase in brain tumor risk from baseline from a single head CT scan, corresponding well to prior theoretical predictions based on dosimetry [31].

Finally, we identified three published studies [19,20,36] describing specific pediatric patient populations that considered the cumulative radiation exposure and attributable tumor risks from head CTs over their course of care (Table 4).

Table 3. Risk estimates of tumor induction from epidemiological studies of pediatric head CT exposure

Author [ref]	Risk estimate
Berrington de Gonzalez et al. [35]	Pts=70,000
ERR at 0–5 yrs	0.64
ERR at 10–15 yrs	0.81–1.01
ERR at 20 yrs	0.81–0.97
Krille et al. [34]	Pts=44,584
Standardized incidence at 2 yrs	1.51
Huang et al. [32]	Pts=24,418
HR	2.32
Journy et al. [29]	Pts=7,274
ERR/mGy at 2 yrs	0.22
Mathews et al. [14]	Pts=10,939,680
Excess incidence at 0–10 yrs	0.010–0.025
Adjusted IRR	1.45–1.99
ERR	0.60–1.16
Pearce et al. [31]	Pts=178,605
AR at 0–5 yrs	0.140–0.784
AR at 10–15 yrs	1.295–1.763
ERR at 20 yrs	1.435

AR, attributable risk; ERR, excess relative risk; HR, hazard ratio; IRR, incident risk ratio; Pts, patients

DISCUSSION

This systematic review surveyed radiological studies that predicted or directly measured neoplasm incidence (or attributable mortality) related to head CT exposure in pediatric patients. Assessing tumor risks from head CT is pertinent given its high utilization rates in developed nations, which only recently plateaued after steady increases in use throughout the 1980s, 1990s, and 2000s [5].

Much published work on CT cancer risks has focused on pediatrics, because children are more sensitive to the effects of ionizing radiation than adults, and have longer life expectancy for a potential cancer to develop after exposure [37]. Despite the known vulnerability of pediatric patients, efforts to extrapolate CT-related cancer risks using epidemiological data from higher-dose exposures such as the atomic bombings [12, 38,39] (i.e., the linear no-threshold hypothesis), have been questioned or dismissed by many [40-42]. Such critiques argue that in lieu of hard epidemiological evidence, there is no basis for any assertion of cancer risk from low-dose CT radiation.

Since 2012, however, five large-scale epidemiological studies [14,31-34] have all reported increased incidence of neoplasms (predominantly brain tumors) in pediatric patients

Table 4. Predicted lifetime attributable tumor risks in scanned pediatric patients by head CT indication

Author [ref]	Indication	Pts (n)	Dose (mSv)	Mean scans per pt	Cml dose (mSv)	LAR (%)	Pts/tumor
Aw-Zoretic et al. [20]	VPS	138	-	3.1	1.4−6.2	0.011−0.074	1,350−9,100
Koral et al. [19]	VPS	182	1.1−2.5	38	-	0.43−1.03*	97−230*
King et al. [36]	Trauma	160	1.7−2.7	-	42−95	0.007−0.017*	6000−14,000*

*Tumor-related mortality. Pts, patients; Cml, cumulative; LAR, lifetime attributable risk; VPS, ventriculoperitoneal shunt

exposed to head CTs. Moreover, multiple studies reported dose-dependent effects between tumor incidence and CT exposure [14,32], the latter study specifically demonstrating a dose-dependent increase in brain tumor incidence with number of head CT exams [32]. A reasonable estimate based on convergent evidence between predictive [16] and epidemiological [14] studies is that one excess neoplasm may be expected per 3,000−10,000 head CT exams in children under age 10. However, implementation and continued refinement of dose reduction strategies for pediatric CT protocols may stand to lower these risk estimates in future studies [43-45].

Despite recent evidence of associations between CT exams and neoplasm incidence, some skepticism remains due to methodological limitations in published epidemiological studies. These limitations center around the confound of reverse causality, which posits that patients who undergo head CT are already more likely to possess pre-existing neoplasms or underlying conditions that increase their baseline risk of cancer (e.g., neurofibromatosis, occupation, or socioeconomic status). Comparing cancer incidence between scanned and unscanned populations without stringent, validated methods to account for such confounds could overestimate the risk of cancer attributed to CT. This poses a challenge for epidemiologists analyzing hundreds of thousands to millions of cases, particularly with follow-up periods of only a few years with scant incident cancers.

At least two published articles have attempted to address the issue of reverse causation effects. First, Berrington de Gonzalez et al. [35] revisited a prior pediatric cohort study from the United Kingdom [31] and re-computed cancer risk estimates after thorough review of radiology information systems (RIS) databases and death certificates. Analyses were repeated after excluding cases involving any existing or suspected brain tumor prior to CT exposure. The corrected risk estimates for brain tumor induction were reduced by approximately 30% from the original findings, but still demonstrated significantly elevated risk in CT-exposed patients [35].

Second, Huang et al. [32] also attempted to control for reverse causation effects when reporting brain tumor incidence attributable to pediatric head CT within a Taiwanese cohort. Medical records of around 24,000 cases were searched and excluded if patients had any underlying genetic disorders predisposing them to cancer, or any previous history of cancer. Even after applying these exclusion criteria, significantly increased incidence of brain tumors was observed from a single head CT exam (HR=2.32, $p<0.01$). HRs for brain tumor increased to 4.58 after two head CTs and up to 10.4 after three or more scans. After only two head CT scans, the HR for malignant brain cancer was 12.3 ($p<0.01$) [32]. These results suggest that reverse causation effects contribute to, but do not fully explain, the association between head CT and increased cancer incidence.

Despite the correlational nature of epidemiological studies, mounting empirical evidence consistently supports a small risk of tumor induction from head CT exams and has generally corroborated theoretical predictions. The strength of epidemiological evidence seems poised to grow further with ongoing studies incorporating larger cohorts and more sophisticated analyses of electronic medical records to better quantitate potential sources of reverse causality such as predisposing factors [33,35] and socioeconomic status [46].

Limitations

Several aspects of our systematic review and the available published evidence on head CT cancer risks limit the strength of our conclusions. First, attributing head CT scans to tumor incidence is inherently limited by the correlational nature of epidemiological studies and the potential for reverse causation, as it is known that patients undergoing head CT exams have higher baseline likelihood of having or being predisposed to brain tumors. Second, the risk estimates extrapolated from predictive studies rely upon the linear no-threshold model, which postulates that cancer risk is linearly proportional to absorbed radiation dose in the limit of very small radiation doses not studied epidemiologically. Nevertheless, emerging large-scale epidemiological studies report increased incidence of brain tumors even among patients receiving a single head CT exam. Third, our systematic review was limited to a single electronic database (MEDLINE). Another limitation of the reviewed literature is that the ability to establish increased risk of brain tumor induction after head CT is limited by the relatively high baseline risk of brain tumors relative to the expected attributable risk from head CT.

Conclusions

A newly emerging body of epidemiological evidence has broadly corroborated non-zero theoretical estimates for CT-associated brain tumor risk in pediatric populations. Current epidemiological evidence confirms the view that the risk of tumor induction from pediatric head CT is very small, on the order of one excess tumor per 3,000−10,000 scans [16]. The minimal estimated risk of tumor induction from pediatric head CT is heavily offset by the benefits of diagnostic imaging, given clinical indication for the study and minimization of radiation dose and tissue exposure [47]. Understanding and quantifying neoplasm risks of head CT has motivated significant dose reduction efforts for pediatric CT protocols; this push should continue and apply to all demographics. While the decision to obtain a head CT is often indisputable (e.g. trauma or suspected stroke), careful consideration is warranted as to the optimal frequency of scans in patients who require serial monitoring. In these cases, cumulative exposure from repeat scans may increase an otherwise minimal tumor risk. Larger, refined epidemiological studies are needed to more adequately elucidate these risks.

Conflicts of Interest

The authors have no financial conflicts of interest.

Acknowledgments

C.L. is supported by the Tina and Fred Segal Benign Brain Tumor and Skull Base Research Fellowship. J.P.S. and T.N. are supported by the David Geffen Medical Scholarship. I.Y. is supported by the UCLA Visionary Ball Fund Grant, Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research UCLA Scholars in Translational Medicine Program Award, Jason Dessel Memorial Seed Grant, UCLA Honberger Endowment Brain Tumor Research Seed Grant, and Stop Cancer (US) Research Career Development Award.

REFERENCES

1. Beckmann EC. CT scanning the early days. Br J Radiol 2006;79:5-8.
2. Hounsfield GN. Computerized transverse axial scanning (tomography). 1. Description of system. Br J Radiol 1973;46:1016-22.
3. Ambrose J. Computerized transverse axial scanning (tomography). 2. Clinical application. Br J Radiol 1973;46:1023-47.
4. IMV Medical Information Division I. 2016 CT market outlook report. Des Plaines, IL: IMV; 2016.
5. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. N Engl J Med 2007;357:2277-84.
6. Smith-Bindman R, Lipson J, Marcus R, et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. Arch Intern Med 2009;169:2078-86.
7. McCollough CH, Bushberg JT, Fletcher JG, Eckel LJ. Answers to common questions about the use and safety of CT scans. Mayo Clin Proc 2015;90:1380-92.
8. Friedberg W, Copeland K, Duke FE, O'Brien K 3rd, Darden EB Jr. Radiation exposure during air travel: guidance provided by the Federal Aviation Administration for air carrier crews. Health Phys 2000;79:591-5.
9. Oksanen PJ. Estimated individual annual cosmic radiation doses for flight crews. Aviat Space Environ Med 1998;69:621-5.
10. Feng YJ, Chen WR, Sun TP, Duan SY, Jia BS, Zhang HL. [Estimated cosmic radiation doses for flight personnel]. Space Med Med Eng (Beijing) 2002;15:265-9.
11. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103. Ann ICRP 2007;37:1-332.
12. United Nations. Scientific Committee on the Effects of Atomic Radiation. Sources and effects of ionizing radiation: United Nations Scientific Committee on the Effects of Atomic Radiation: UNSCEAR 2000 report to the General Assembly, with scientific annexes. New York: United Nations; 2000.
13. National Council on Radiation Protection and Measurements. Ionizing radiation exposure of the population of the United States. National Council on Radiation Protection report no. 160. Bethesda (MD): National Council on Radiation Protection and Measurements; 2009.
14. Mathews JD, Forsythe AV, Brady Z, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ 2013;346:f2360.
15. Schwartz DT. Counter-Point: are we really ordering too many CT scans? West J Emerg Med 2008;9:120-2.
16. Brenner D, Elliston C, Hall E, Berdon W. Estimated risks of radiation-induced fatal cancer from pediatric CT. AJR Am J Roentgenol 2001;176:289-96.
17. Tien HC, Tremblay LN, Rizoli SB, et al. Radiation exposure from diagnostic imaging in severely injured trauma patients. J Trauma 2007;62:151-6.
18. Salibi PN, Agarwal V, Panczykowski DM, et al. Lifetime attributable risk of cancer from CT among patients surviving severe traumatic brain injury. AJR Am J Roentgenol 2014;202:397-400.
19. Koral K, Blackburn T, Bailey AA, Koral KM, Anderson J. Strengthening the argument for rapid brain MR imaging: estimation of reduction in lifetime attributable risk of developing fatal cancer in children with shunted hydrocephalus by instituting a rapid brain MR imaging protocol in lieu of Head CT. AJNR Am J Neuroradiol 2012;33:1851-4.
20. Aw-Zoretic J, Seth D, Katzman G, Sammet S. Estimation of effective dose and lifetime attributable risk from multiple head CT scans in ventriculoperitoneal shunted children. Eur J Radiol 2014;83:1920-4.
21. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
22. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100.
23. Pflugbeil S, Pflugbeil C, Schmitz-Feuerhake I. Risk estimates for meningiomas and other late effects after diagnostic X-ray exposure of the skull. Radiat Prot Dosimetry 2011;147:305-9.
24. Chodick G, Ronckers CM, Shalev V, Ron E. Excess lifetime cancer mortality risk attributable to radiation exposure from computed tomography examinations in children. Isr Med Assoc J 2007;9:584-7.
25. Miglioretti DL, Johnson E, Williams A, et al. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. JAMA Pediatr 2013;167:700-7.
26. Pokora R, Krille L, Dreger S, et al. Computed tomography in Germany. Dtsch Arztebl Int 2016;113:721-8.
27. Stein SC, Hurst RW, Sonnad SS. Meta-analysis of cranial CT scans in children. A mathematical model to predict radiation-induced tumors. Pediatr Neurosurg 2008;44:448-57.
28. Brenner DJ, Hall EJ. Cancer risks from CT scans: now we have data, what next? Radiology 2012;265:330-1.
29. Journy N, Ancelet S, Rehel JL, et al. Predicted cancer risks induced by computed tomography examinations during childhood, by a quantitative risk assessment approach. Radiat Environ Biophys 2014;53:39-54.
30. Feng ST, Law MW, Huang B, et al. Radiation dose and cancer risk from pediatric CT examinations on 64-slice CT: a phantom study. Eur J Radiol 2010;76:e19-23.
31. Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet 2012;380:499-505.
32. Huang WY, Muo CH, Lin CY, et al. Paediatric head CT scan and sub-

sequent risk of malignancy and benign brain tumour: a nation-wide population-based cohort study. Br J Cancer 2014;110:2354-60.
33. Journy N, Rehel JL, Ducou Le Pointe H, et al. Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a large-scale cohort study in France. Br J Cancer 2015;112:185-93.
34. Krille L, Dreger S, Schindel R, et al. Risk of cancer incidence before the age of 15 years after exposure to ionising radiation from computed tomography: results from a German cohort study. Radiat Environ Biophys 2015;54:1-12.
35. Berrington de Gonzalez A, Salotti JA, McHugh K, et al. Relationship between paediatric CT scans and subsequent risk of leukaemia and brain tumours: assessment of the impact of underlying conditions. Br J Cancer 2016;114:388-94.
36. King MA, Kanal KM, Relyea-Chew A, Bittles M, Vavilala MS, Hollingworth W. Radiation exposure from pediatric head CT: a bi-institutional study. Pediatr Radiol 2009;39:1059-65.
37. Chen JX, Kachniarz B, Gilani S, Shin JJ. Risk of malignancy associated with head and neck CT in children: a systematic review. Otolaryngol Head Neck Surg 2014;151:554-66.
38. Pierce DA, Preston DL. Radiation-related cancer risks at low doses among atomic bomb survivors. Radiat Res 2000;154:178-86.
39. Chomentowski M, Kellerer AM, Pierce DA. Radiation dose dependences in the atomic bomb survivor cancer mortality data: a model-free visualization. Radiat Res 2000;153:289-94.
40. Jaffurs D, Denny A. Diagnostic pediatric computed tomographic scans of the head: actual dosage versus estimated risk. Plast Reconstr Surg 2009;124:1254-60.
41. Rosen NS. Taking care of children. AJR Am J Roentgenol 2001;177: 715-7.
42. Bertell R, Ehrle LH, Schmitz-Feuerhake I. Pediatric CT research elevates public health concerns: low-dose radiation issues are highly politicized. Int J Health Serv 2007;37:419-39.
43. Arrangoiz R, Opreanu RC, Mosher BD, Morrison CA, Stevens P, Kepros JP. Reduction of radiation dose in pediatric brain CT is not associated with missed injuries or delayed diagnosis. Am Surg 2010;76:1255-9.
44. Pindrik J, Huisman TA, Mahesh M, Tekes A, Ahn ES. Analysis of limited-sequence head computed tomography for children with shunted hydrocephalus: potential to reduce diagnostic radiation exposure. J Neurosurg Pediatr 2013;12:491-500.
45. Morton RP, Reynolds RM, Ramakrishna R, et al. Low-dose head computed tomography in children: a single institutional experience in pediatric radiation risk reduction: clinical article. J Neurosurg Pediatr 2013;12:406-10.
46. Bosch de Basea M, Pearce MS, Kesminiene A, et al. EPI-CT: design, challenges and epidemiological methods of an international study on cancer risk after paediatric and young adult CT. J Radiol Prot 2015;35: 611-28.
47. Strauss KJ, Kaste SC. The ALARA concept in pediatric interventional and fluoroscopic imaging: striving to keep radiation doses as low as possible during fluoroscopy of pediatric patients--a white paper executive summary. AJR Am J Roentgenol 2006;187:818-9.