OXFORD

JNCI J Natl Cancer Inst (2019) 111(3): djy104

doi: 10.1093/jnci/djy104
First published online July 18, 2018
Article

ARTICLE

Radiation Exposure From Pediatric CT Scans and Subsequent Cancer Risk in the Netherlands

Johanna M. Meulepas, Cécile M. Ronckers, Anne M. J. B. Smets, Rutger A. J. Nievelstein, Patrycja Gradowska, Choonsik Lee, Andreas Jahnen, Marcel van Straten, Marie-Claire Y. de Wit, Bernard Zonnenberg, Willemijn M. Klein, Johannes H. Merks, Otto Visser, Flora E. van Leeuwen, Michael Hauptmann

See the Notes section for the full list of authors' affiliations.
Correspondence to: M. Hauptmann, PhD, Department of Epidemiology and Biostatistics, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands (e-mail m.hauptmann@nki.nl).

Abstract

Background: Computed tomography (CT), a strong diagnostic tool, delivers higher radiation doses than most imaging modalities. As CT use has increased rapidly, radiation protection is important, particularly among children. We evaluate leukemia and brain tumor risk following exposure to low-dose ionizing radiation from CT scans in childhood.
Methods: For a nationwide retrospective cohort of 168 394 children who received one or more CT scans in a Dutch hospital between 1979 and 2012 who were younger than age 18 years, we obtained cancer incidence, vital status, and confounder information by record linkage with external registries. Standardized incidence ratios were calculated using cancer incidence rates from the general Dutch population. Excess relative risks (ERRs) per 100 mGy organ dose were calculated with Poisson regression. All statistical tests were two-sided.
Results: Standardized incidence ratios were elevated for all cancer sites. Mean cumulative bone marrow doses were 9.5 mGy at the end of follow-up, and leukemia risk (excluding myelodysplastic syndrome) was not associated with cumulative bone marrow dose (44 cases). Cumulative brain dose was on average 38.5 mGy and was statistically significantly associated with risk for malignant and nonmalignant brain tumors combined (ERR/100 mGy: 0.86, 95% confidence interval = 0.20 to 2.22, $P = .002$, 84 cases). Excluding tuberous sclerosis complex patients did not substantially change the risk.
Conclusions: We found evidence that CT-related radiation exposure increases brain tumor risk. No association was observed for leukemia. Compared with the general population, incidence of brain tumors was higher in the cohort of children with CT scans, requiring cautious interpretation of the findings.

The use of computed tomography (CT) scans among children has increased dramatically in Western countries (1,2), including the Netherlands (3). CT scans greatly improve diagnostic capabilities but deliver higher radiation doses than many other diagnostic radiation procedures (4). Therefore, radiation protection is a concern, especially among children, who may receive higher radiation doses, are more susceptible to radiation-related malignancies than adults, and have a longer lifespan to express late effects. The most common radiogenic malignancies among children and young adults are leukemia and brain tumors (5). Although the thyroid gland is exquisitely sensitive to radiation carcinogenesis in children (5,6), background rates in children and young adults are too low to allow for detection of excess risk associated with radiation exposure from CT scans in the follow-up period that can be studied.

Epidemiological studies have demonstrated an increased cancer risk associated with pediatric CT scans (7–12). The UK-NCI study found a statistically significant positive association

Received: February 14, 2018; **Revised:** April 10, 2018; **Accepted:** May 4, 2018

between radiation dose from CT scans and brain tumors but not leukemia (excluding myelodysplastic diseases) (7,8). Australian investigators showed a higher risk of several types of cancer, including leukemia and brain tumors, for subjects with CT scans compared with unexposed persons (9). Moreover, Taiwanese children with at least one head CT had statistically significantly higher benign brain tumor risk than a matched comparison group, in particular four to five years after a first head CT scan (10). Two substantially smaller studies from France (11) and Germany (12) also suggested elevated cancer risks.

This pattern of excess cancer risk may be partly due to confounding by indication, that is, if the reason for conducting a CT is associated with cancer risk (13–15). Two main sources of confounding are of concern: subclinical tumors and cancer susceptibility syndromes (CSS). Although data from two cohort studies (8,11) and our own theoretical assessment (16) suggest that unmeasured CSS are not a major confounder for leukemia and brain tumors, little empirical information is available on slow-growing brain tumors that cause symptoms leading to CT scans (12).

We present data from the nationwide Dutch Pediatric CT Study on the association between childhood radiation exposure from CT scans and subsequent risk of leukemia and brain tumors in Dutch children and young adults (17).

Methods

Study Design

The study was conducted under the common procedures and methodology of the EPI-CT consortium. Details about the study design and the consortium are described elsewhere (17,18). In brief, this retrospective cohort includes children (aged <18 years) who received one or more electronically archived CT scans in any participating Dutch hospital. We surveyed all Dutch hospital-based radiology departments (n = 94) to ascertain eligibility and participation. We excluded 34 hospitals that conducted fewer than 10 pediatric CT scans annually. Eighteen hospitals declined participation, leaving 34 general and all eight academic hospitals (17). Individual consent requirements were waived; institutional review board review for observational studies, where required, was obtained from participating institutions (17).

Exposure Assessment

Participating hospitals queried their Radiology Information System (RIS) for CT scans among children and provided the following for each CT conducted before age 18 years among eligible patients: name, address, date of birth, sex, date of examination, and scanned body region. Patients who were scanned in different hospitals were identified by pairwise linkage of all data sets from participating hospitals. Scans were assigned to the appropriate patient, and duplicate scans were eliminated. Twenty-one hospitals (six academic) additionally queried their Picture Archiving and Communication System (PACS) for all accession numbers from the RIS query. Performance and Monitoring Server for Medical Data (PerMoS) (19) software retrieved the Digital Imaging and Communications in Medicine (DICOM) objects and extracted scanned body region, number of x-ray images (series), CT scanner manufacturer/model, tube potential, tube current-time product, pitch, and volumetric CT Dose Index ($CTDI_{vol}$). Topograms or reconstructions were identified by PerMoS and excluded.

In the absence of comprehensive organ dose surveys for children in the Netherlands, we calculated absorbed doses to the red bone marrow (RBM) and the brain for CT scans with PACS information using the program NCICT (20). We assigned CT-specific RBM and brain doses from a predictive model based on 36 944 and 25 992 CT scans with PACS information, respectively (Supplementary Methods, available online). Models for dose to the RBM and the brain explained 80% and 84% of the variation, respectively, were well calibrated (average differences of 0.4 mGy at a mean RBM dose of 4.5 mGy and 0.8 mGy at a mean brain dose of 27.5 mGy, respectively), and were similar to published estimates for the UK-NCI study (Supplementary Tables 1 and 2, available online) (21,22).

Outcome Assessment

Cancer incidence among cohort members was determined by linkage with the Netherlands Cancer Registry (NCR), which includes all malignancies since 1989, and myelodysplastic syndrome and nonmalignant brain tumors since 2001 (23). Childhood leukemia incidence before 1989 was ascertained through linkage with the Dutch Childhood Oncology Group (complete since 1973) (24). All cancer diagnoses were recoded according to the World Health Organization's International Classification of Diseases for Oncology, third edition, topography codes (Supplementary Tables 3 and 4, available online). Vital status and date of death were obtained from the Central Bureau of Genealogy.

Assessment of Potential Confounders

Six-digit postal codes (average population, 40 persons) of cohort members' residential addresses were linked with data on household income and house value from Statistics Netherlands (25). Prevalence of tuberous sclerosis complex (TSC), a brain tumor susceptibility syndrome and potential confounder as patients undergo routine brain imaging from time of diagnosis, was obtained by linkage with patient lists from two hospitals where the majority of Dutch TSC patients have been treated since 1995. We did not collect information on the (clinical) indications for the CT scans.

Statistical Analysis

To avoid inclusion of CT scans related to cancer diagnosis, accrual of person-time started two years after the first CT for analyses of leukemia incidence and five years after the first CT or 1989, whichever occurred later, for solid tumors. Follow-up ended at the first diagnosis of a registry-recorded tumor, death, or December 31, 2014, whichever came first. Cumulative radiation doses (in mGy) to the RBM (lagged by two years) and the brain (lagged by five years) were calculated time-dependently based on estimated doses for each CT scan. Standardized incidence ratios (SIRs) were calculated using sex-, age-, and calendar year–specific Dutch cancer incidence rates. Relative risks and 95% likelihood ratio confidence intervals (CIs) were estimated using ungrouped Poisson regression (26) stratified by calendar year (1980–<1985, 1985–<1990, 1990–<1995, 1995–<2000, 2000–<2005, 2005–<2010, ≥2010), age (for brain: 5–<10, 10–<15, ≥15 years; for leukemia: 2–<5, 5–<10, 10–<15, ≥15 years), and sex.

Dose–response was evaluated by categories of cumulative dose, using less than 5 mGy as the reference and equal numbers

Table 1. Patient characteristics by outcome in the Dutch Pediatric CT Study

Charateristics	No. of cases	Person-years
Leukemia*		
Overall	44	1 201 357
Sex		
Male	26	659 532
Female	18	541 825
Years since first exposure		
2 to <5	14	370 679
5 to <10	17	403 544
10 to <15	9	220 758
≥15	4	206 376
Attained age, y		
2 to <20	24	689 812
20 to <30	18	408 901
30 to <35	1	63 192
≥35	1	39 452
Birth cohort		
<1980	10	200 644
1980 to <1990	11	430 513
1990 to <1995	12	262 089
≥1995	11	307 958
Calendar year		
<1985	0	2268
1985 to <1990	1	14 675
1990 to <1995	2	45 682
1995 to <2000	3	91 148
2000 to <2005	9	174 886
2005 to <2010	12	317 837
≥2010	17	554 862
No. of CT scans		
1	26	924 523
2	11	166 093
≥3	7	110 741
Mean bone marrow dose (IQR), mGy	9.5 (2.0–11.8)	
Mean follow-up (IQR), y	8.5 (3.1–12.3)	
Brain tumors†		
Overall	84	827 261
Sex		
Male	49	456 892
Female	35	370 368
Years since first exposure		
5 to <10	41	400 126
10 to <15	24	220 758
≥15	19	206 376
Attained age, y		
5 to <20	44	365 387
20 to <30	27	359 230
30 to <40	10	90 671
≥40	3	11 972
Birth cohort		
<1980	25	172 160
1980 to <1990	31	339 872
1990 to <1995	15	160 091
≥1995	13	155 031
Calendar year		
1989 to <1990	0	1800
1990 to <1995	8	25 430
1995 to <2000	6	60 729
2000 to <2005	23	118 361
2005 to <2010	17	222 020
≥2010	30	398 920
No. of head CT scans		
0	13	176 419
1	49	527 350
2 to <4	14	96 137
≥4	8	27 354
Mean brain dose (IQR), mGy	38.5 (1.5–49.4)	
Mean follow-up (IQR), y	7.8 (2.5–11.4)	

*Follow-up started two years after the first recorded scan and included 140 612 patients. CT = computed tomography; IQR = interquartile range.
†Follow-up started five years after the first recorded scan and included 106 530 patients.

of cases in the remaining categories. The excess relative risk (ERR) per 100 mGy was estimated as RR = EXP($\sum_j \alpha_j X_j$)[1+βD], with D being cumulative radiation dose in 100 mGy, β being the ERR/100 mGy, and X_j being other covariates with corresponding log RRs α_j. Departure from linearity was evaluated by a likelihood ratio test of the null hypothesis $\gamma = 0$ in a model including dose as an exponential factor RR = EXP($\sum_j \alpha_j X_j$)[1+βD*EXP(γD)], where γ indicates downward ($\gamma < 0$) or upward curvature ($\gamma > 0$) in the ERR/100 mGy (27). Heterogeneity among ERR estimates was assessed by likelihood ratio tests. Tests were two-sided at a 5% statistical significance level.

We performed sensitivity analyses 1) excluding patients with a confirmed diagnosis of TSC (brain tumor analyses), 2) adjusting for quartiles of income and house value, 3) varying lag intervals, 4) further delaying the start of follow-up after the first CT scan (exclusion period) and evaluating the incidence of malignant tumors of the central nervous system (CNS) relative to the general population by time since first (head) CT scan, 5) starting follow-up in 2001 when nonmalignant brain tumors and myelodysplastic syndrome (MDS) were completely ascertained, 6) excluding subjects born before 1989 because of more uncertain dose estimates and potentially unknown solid—including brain—tumor diagnoses, 7) excluding children who had CT scans in participating hospitals close to Belgium or Germany because of the possibility of additional CT scans conducted there, 8) fitting a threshold model with the linear dose–response relationship starting at the threshold dose D_t, that is, ERR = β(D-D_t)$_+$, where (D-D_t)$_+$ = max(0, D-D_t), and 9) excluding the 2% person-years with the highest cumulative brain dose to eliminate outliers. SAS (version 9.2; SAS Institute Inc., Cary, NC) and EPICURE (version 2.00.02; Risk Sciences International, Metcalfe, Canada) software were used for the analysis.

Results

We collected data on 262 227 pediatric CT scans performed on 168 394 children in 42 hospitals between 1979 and 2014. After exclusions due to foreign addresses, age restrictions, incompleteness or data errors, and follow-up of less than two years (leukemia) or five years (solid tumors) after the first scan, we included 140 612 patients in the leukemia analyses and 106 530 patients in solid tumor analyses. Four percent of individuals alive two years after their first CT had CT scans in multiple participating hospitals. Patient characteristics are presented in Table 1.

Among the 208 709 CT scans eligible for leukemia analyses, 65.5% were of the head, 8.3% of the extremities, 8.1% of the chest, and 7.6% of the abdomen. For brain tumor analyses

ARTICLE

Table 2. Distribution of eligible pediatric CT scans across age and body part: the Dutch Pediatric CT Study

	Age at CT, y				
Outcome	0 to <5 No. (%)	5 to <10 No. (%)	10 to <15 No. (%)	15 to 18 No. (%)	Total
Leukemia*					
Head	37 778 (76.3)	28 866 (71.5)	37 018 (62.7)	32 958 (55.2)	136 620
Neck	1973 (4.0)	1984 (4.9)	2894 (4.9)	3714 (6.2)	10 565
Chest	4400 (8.9)	3298 (8.2)	4325 (7.3)	4882 (8.2)	16 905
Abdomen	1950 (3.9)	2521 (6.3)	4676 (7.9)	6662 (11.2)	15809
Pelvis	895 (1.8)	646 (1.6)	1426 (2.4)	1789 (3.0)	4756
Extremities	680 (1.4)	2092 (5.2)	7082 (12.0)	7551 (12.6)	17 405
Multiples	1864 (3.8)	993 (2.5)	1591 (2.7)	2201 (3.7)	6649
Total	49 540 (100.0)	40 400 (100.0)	59 012 (100.0)	59 757 (100.0)	208 709
Brain tumor†					
Head	31 884 (78.6)	23 579 (73.7)	28 888 (66.0)	24 458 (57.5)	108 809
Neck	1437 (3.5)	1383 (4.3)	1815 (4.1)	2309 (5.4)	6944
Chest	3143 (7.8)	2440 (7.6)	3100 (7.1)	3414 (8.0)	12 097
Abdomen	1632 (4.0)	2018 (16.7)	3550 (8.1)	4908 (40.5)	12 108
Pelvis	711 (1.8)	508 (1.6)	1079 (2.5)	1405 (3.3)	3703
Extremities	557 (1.4)	1452 (4.5)	4420 (10.1)	4754 (11.2)	11 183
Multiples	1200 (3.0)	603 (1.9)	938 (2.1)	1258 (3.0)	3999
Total	40 564 (100.0)	31 983 (100.0)	43 790 (100.0)	42 506 (100.0)	158 843

*Follow-up started two years after the first recorded scan. CT = computed tomography.
†Follow-up started five years after the first recorded scan.

(n = 158 843 CT scans due to the longer exclusion period), the distribution across body parts was similar (Table 2). The mean cumulative RBM dose at the end of follow-up was 9.5 mGy, and for 75% of patients it was less than 12 mGy. The mean brain dose was 38.5 mGy (Table 1).

Overall cancer incidence (starting five years after the first CT) was 1.5 times higher than expected (SIR = 1.47, 95% CI = 1.34 to 1.61, 454 observed cases) including malignant CNS tumors (SIR = 2.05, 95% CI = 1.48 to 2.83, 37 observed cases) and hematolymphoproliferative cancers (HLP; SIR = 1.39, 95% CI = 1.13 to 1.70, 93 observed cases) (Table 3). Statistically significant excesses were also noted for cancers of the colon, bone, large bowel, soft tissues, thyroid, and for nonmelanoma skin cancer.

Risk for all leukemia combined (44 cases) was not associated with bone marrow dose (ERR/100 mGy = 0.21, 95% CI = –0.12 to 2.40, P = .68) (Table 4), including all leukemia and MDS (ERR/100 mGy = 0.04, 95% CI = –0.12 to 1.61, P = .92). For all brain tumors combined, and for malignant and nonmalignant brain tumors separately, relative risks increased to between two and four for the highest dose category (≥120 mGy), with ERRs of 0.86 (95% CI = 0.20 to 2.22, 84 cases), 1.02 (95% CI = 0.01 to 4.30, 37 cases), and 0.78 (95% CI = 0.07 to 2.58, 47 cases) per 100 mGy and no evidence of nonlinearity (P = .72, .45, .92) (Table 5). The dose–response for brain tumors and for leukemia did not vary according to sex, number of CT scans, years since exposure, or age at exposure (Table 6).

Several factors potentially biasing risk estimates were assessed in sensitivity analyses, including—sometimes substantially—reduced numbers of patients, CT scans, and/or cancer cases. Adjustment for household income and exclusion of 82 patients with confirmed TSC did not materially affect brain tumor risks (Supplementary Table 5, available online) whereas they were attenuated with a 10-year lag instead of five years (Supplementary Table 6, available online). Reducing the exclusion period from five to two years did not change results, whereas increasing it to eight years somewhat attenuated radiation risks. Consistent results were obtained for nonmalignant brain tumors in analyses limited to the post-2001 period with complete registration of nonmalignant brain tumors. Further, results were generally similar (with reduced precision) when excluding subjects with a first CT before 1989 or born before 1989 (Supplementary Table 6, available online). Incidence of CNS cancers vs the general population remained elevated 10 or more years after the first (head) CT (Supplementary Tables 7 and 8,

Table 3. Overall and site-specific standardized incidence ratios of tumors in the Dutch Pediatric CT Study*

Cancer site	Observed cases†	SIR (95% CI)
All sites (C00-96)	454	1.47 (1.34 to 1.61)
All sites excluding skin (C00-96, excl. C44)	379	1.25 (1.13 to 1.38)
Lip, oral cavity, and pharynx (C00-14)	6	1.15 (0.52 to 2.57)
Colon (C18)	13	1.95 (1.13 to 3.36)
Large bowel (C18-21)	21	2.02 (1.32 to 3.10)
Bone (C40-41)	22	2.05 (1.35 to 3.11)
Melanoma of skin (C43)	57	1.18 (0.91 to 1.53)
Nonmelanoma skin (C44)	18	3.36 (2.11 to 5.33)
Connective tissue (C47+C49)	16	2.03 (1.24 to 3.31)
Breast (C50)	38	1.11 (0.81 to 1.52)
Cervix uteri (C53)	13	1.27 (0.74 to 2.19)
Testis (C62)	56	1.22 (0.94 to 1.58)
Kidney (C64-66, C68)	6	1.94 (0.87 to 4.32)
CNS (C70-72)	37	2.05 (1.48 to 2.83)
Thyroid (C73)	17	1.64 (1.02 to 2.63)
Hematolymphoproliferative cancers (C81-88, C90)	93	1.39 (1.13 to 1.70)

*Follow-up started five years after the first CT scan. CI = confidence interval; CNS = central nervous system; SIR = standardized incidence ratio.
†Thyroid: zero medullary, 17 papillary/follicular/mixed; colon: six carcinoid, seven adenocarcinomas; nonmelanoma skin: 11 BCC/SCC, three dermatofibrosarcoma, four other skin cancers.

ARTICLE

Table 4. Relative risks for leukemia by cumulative red bone marrow dose from CT scans to the head, trunk, and lower extremities

	Red bone marrow dose, mGy*									
	<5		5 to <10		10 to <17		17+			
Outcome	RR (95% CI) ‡	Cases	RR (95% CI) ‡	Cases	RR (95% CI) ‡	Cases	RR (95% CI) ‡	Cases	ERR/100 mGy (95% CI)	P†
Leukemia without myelodysplastic diseases	1.00 (reference)	17	1.07 (0.47 to 2.43)	9	0.59 (0.26 to 1.38)	9	0.51 (0.21 to 1.28)	9	0.21 (–0.12§ to 2.40)	.68
Leukemia with myelodysplastic diseases	1.00 (reference)	20	1.41 (0.70 to 2.83)	14	0.88 (0.44 to 1.74)	16	0.62 (0.28 to 1.34)	13	0.04 (–0.12§ to 1.61)	.92
Acute myeloid leukemia and myelodysplastic syndromes	1.00 (reference)	5	3.28 (1.06 to 10.18)	8	1.52 (0.45 to 5.13)	6	1.41 (0.40 to 4.93)	7	–0.12 (–0.12§ to 2.53)	.64
Acute lymphoblastic leukemia	1.00 (reference)	10	0.54 (0.15 to 2.02)	3	0.54 (0.17 to 1.66)	5	0.74 (0.24 to 2.30)	6	1.23 (–0.12§ to 7.43)	.22
Myeloid leukemia	1.00 (reference)	6	2.23 (0.71 to 6.99)	6	0.79 (0.21 to 2.91)	4	0.35 (0.08 to 1.68)	3	–0.12 (–0.12§ to 1.86)	.60
Lymphoid leukemia	1.00 (reference)	11	0.50 (0.14 to 1.82)	3	0.49 (0.16 to 1.48)	5	0.66 (0.22 to 2.01)	6	1.07 (–0.12§ to 6.51)	.26
Hematolymphoproliferative cancers	1.00 (reference)	53	0.52 (0.28 to 0.94)	14	0.70 (0.44 to 1.13)	30	0.81 (0.50 to 1.31)	31	0.11 (–0.12§ to 1.40)	.79
Any cancer	1.00 (reference)	227	0.89 (0.69 to 1.13)	90	0.98 (0.80 to 1.19)	203	1.03 (0.84 to 1.26)	192	0.31 (–0.12§ to 0.90)	.18

*Estimated as described in the Supplementary Methods (available online). CI = confidence interval; CT = computed tomography; ERR = excess relative risk; RR = relative risk.
†Likelihood ratio test of the null hypothesis ERR = 0.
‡Including two-year cancer-free survivors of first recorded CT scan, cumulative dose lagged by two years, stratified for sex, calendar year, and attained age.
§Estimate was constrained at –1/max(dose) to avoid negative relative risk.

Table 5. Relative risks for brain tumors by cumulative brain dose from CT scans to the head and neck

	Brain dose, mGy*													
	<5		5 to <43		43 to <51		51 to <65		65 to <120		120+			
Outcome	RR† (95% CI)	Cases	RR† (95% CI)	Cases	RR† (95% CI)	Cases	RR† (95% CI)	Cases	RR† (95% CI)	Cases	RR† (95% CI)	Cases	ERR/100 mGy (95% CI)	P‡
All brain tumors	1.00 (reference)	16	0.72 (0.34 to 1.52)	13	1.18 (0.57 to 2.45)	15	0.91 (0.43 to 1.93)	13	1.23 (0.58 to 2.59)	13	3.01 (1.46 to 6.25)	14	0.86 (0.20 to 2.22)	.002
Malignant brain tumors	1.00 (reference)	6	0.88 (0.27 to 2.83)	6	1.04 (0.32 to 3.40)	6	0.93 (0.29 to 2.98)	6	1.10 (0.32 to 3.67)	5	3.90 (1.32 to 11.50)	8	1.02 (0.01 to 4.30)	.047
Nonmalignant brain tumors	1.00 (reference)	10	0.62 (0.23 to 1.66)	7	1.31 (0.52 to 3.28)	9	0.90 (0.33 to 2.42)	7	1.34 (0.52 to 3.45)	8	2.33 (0.84 to 6.47)	6	0.78 (0.07 to 2.58)	.02
Glioma	1.00 (reference)	5	1.02 (0.31 to 3.36)	7	1.08 (0.30 to 3.95)	5	0.76 (0.20 to 2.92)	4	1.65 (0.49 to 5.52)	6	4.15 (1.29 to 13.34)	7	1.17 (0.04 to 5.13)	.04
Meningioma			1.00 (reference)			4			1.29 (0.31 to 5.44)			5	0.06 (–0.035§ to 6.44)	.42
Any cancer‖	1.00 (reference)	158	0.71 (0.54 to 0.92)	88	0.83 (0.62 to 1.09)	75	0.84 (0.66 to 1.08)	120	0.84 (0.64 to 1.10)	84	1.14 (0.82 to 1.60)	45	0.07 (–0.035§ to 0.23)	.33
Any cancer except brain tumors	1.00 (reference)	142	0.72 (0.54 to 0.96)	75	0.78 (0.57 to 1.07)	60	0.84 (0.65 to 1.09)	107	0.79 (0.59 to 1.06)	71	0.90 (0.61 to 1.33)	31	–0.02 (–0.035§ to 0.13)	.79

*Estimated as described in the Supplementary Methods (available online). CI = confidence interval; CT = computed tomography; ERR = excess relative risk; RR = relative risk.
†Including five-year cancer-free survivors of first recorded CT scan, cumulative dose lagged by five years, stratified for sex, calendar year, and attained age.
‡Likelihood ratio test of the null hypothesis ERR = 0.
§Estimate was constrained at –1/max(dose) to avoid negative relative risk.
‖Including nonmalignant brain tumors.

Table 6. Linear excess relative risk per 100 mGy for leukemia and brain tumors by sex, number of CT scans, years since exposure and age at exposure

Outcome	ERR per 100 mGy*	P†
Leukemia‡		
Sex		
Male	0.40	.54
Female	–0.17	
No. of CT scans		
1	–0.12§	.31
2	3.13	
≥3	1.04	
Years since exposure		
5 to <10	–0.12§	.50
10 to <15	1.33	
15+	–0.12§	
Age at exposure, y		
0 to <10	0.44	.83
10 to <15	–0.12§	
15+	–0.12§	
Brain tumors‖		
Sex		
Male	0.68	.62
Female	1.16	
No. of head CT scans		
1	0.78	.71
2 to 3	1.09	
≥4	1.02	
Years since exposure		
5 to <10	1.56	.13
10 to <15	0.80	
15+	0.10	
Age at exposure, y		
0 to <10	0.44	.43
10 to <15	1.44	
15+	0.88	

*Stratified for sex, calendar year, and attained age. CT = computed tomography; ERR = excess relative risk.
†Likelihood ratio test of homogeneity of ERRs.
‡Without myelodysplastic diseases, including two-year cancer-free survivors of first recorded CT scan, cumulative dose lagged by two years.
§Estimate was constrained at –1/max(dose) to avoid negative relative risk.
‖Malignant and nonmalignant combined, including five-year cancer-free survivors of first recorded CT scan, cumulative brain dose lagged by five years.

Supplementary Figures 1 and 2, available online). Leukemia results did not change substantially during comparable sensitivity analyses (Supplementary Tables 9 and 10, available online). Excluding patients scanned in hospitals near the German or Belgian border did not change the results (not shown). A threshold at 20 mGy resulted in the best goodness of fit for all brain tumors combined, although the deviance was only marginally (and statistically nonsignificantly) reduced compared with the no-threshold model and any other threshold level between 5 and 120 mGy (not shown). Excluding the 2% person-years with the highest cumulative brain dose (exceeding 220 mGy) resulted in a similar and significant ERR for all brain tumors as in the main analysis (based on 78 cases).

Discussion

In the Dutch Pediatric CT study, we observed a statistically significant dose–effect relationship for brain tumors and found no association between the estimated cumulative RBM dose and incidence of leukemia.

Many published studies with empirical data have noted a positive association between radiation dose from CT scans and brain tumor (5,7,12) and leukemia (excluding MDS) risks (8,12). In these studies, radiation dose estimates were based on 1) external estimates stratified by sex, age, calendar period and body part (7–9), 2) number of CT scans (8,10,12), or 3) protocol-based doses (11). None of these studies estimated doses based on PACS data for a sizeable subset of CT scans from the cohort and predicted doses for all CT scans in the cohort, as done here.

Further strengths of our study include the representativeness and completeness of the cumulative exposure estimates. The coverage of the previously published cohorts varies from a few hospitals to a nationwide health care system. Our study includes the majority of all pediatric CT scans conducted annually in the Netherlands (42 of 60 eligible hospitals performing pediatric CT scans and 84% of all Dutch pediatric CT scans for the period 1990–2012) (3). Moreover, we had the ability to combine CT scans of the same patients in multiple hospitals for complete cumulative exposures. The average follow-up time in our study was about eight years (maximum = 21 years), which is close to the largest studies published to date (7,9).

The absence of a statistically significant association between radiation dose and leukemia in our data is not inconsistent with other studies. After exclusion of MDS, the ERR from the UK-NCI study was no longer statistically significantly elevated (ERR/100 mGy: 1.9, 95% CI = –1.2 to 7.9) (7). Smaller studies from France and Germany also observed statistically nonsignificantly elevated risks (11,12). We chose not to include MDS in the main leukemia outcome definition because only 3%–7% of MDS progress to acute myeloid leukemia (28).

The ERR/100 mGy of 1.02 (95% CI = 0.01 to 4.30) for brain cancer observed in our data is compatible with the estimate for a comparable sample of atomic bomb survivors (<20 years of age at exposure, during ≤20 years of follow-up: 0.61, 95% CI = 0.012 to 6.39) (29), and also similar to the corrected estimate from the UK-NCI study (1.3 per 100 mGy) (8).

Our study has some limitations. Most importantly, we did not have information on the (clinical) indications for the CT scans to, for example, limit analyses to children with trauma.

Although pediatric CT scans are not performed outside hospitals in the Netherlands, we might have missed some CT scans, for example, CT scans in one of the 18 nonparticipating hospitals, or CT scans in radiology practices or hospitals across the border in Germany or Belgium, or CT scans in participating hospitals before electronic recording was introduced. However, excluding children with CT scans performed in Dutch border-region hospitals or excluding children born before electronic recording was available yielded similar results.

Socioeconomic status is associated with childhood leukemia incidence (30,31) and with the likelihood of having a CT scan (2,32), but it did not confound our results. Excluding TSC patients did also not change the results. For other syndromes, we were not able to obtain individual information. We showed in a theoretical assessment that CSS are unlikely to be major confounders for brain tumor and leukemia risks (16). The brain tumor dose–response in the UK-NCI study was attenuated after exclusion of subjects with a previous cancer diagnosis, that is, patients for whom the cancer ascertained in the study, in fact, was a subsequent primary tumor. After exclusion of subjects born before 1989, the first year that solid cancer registration was complete in the Netherlands, our results were based on a

substantially smaller database and were attenuated, although still generally consistent with the results of the main analyses.

It has been questioned whether epidemiological cohort studies of children who received CT scans for medical reasons can provide unbiased insights into the low excess risks expected from the relatively low CT-related radiation doses, particularly if the reasons for the CT scans are unknown (13,14,33). These concerns are more relevant for brain tumors than for leukemia because CT scans are not routinely used for diagnosing leukemia, and the onset of predominantly acute leukemias among children and young adults is generally rapid. For brain tumors, concerns raised include slow-growing tumors in the brain leading to symptoms for which CT scans are used long before clinical diagnosis, or accidents leading to head CT scans while brain trauma might increase long-term brain tumor risk (34). The critics did not provide any data, however, to support their claims. To address the issues, we, and others, started follow-up five years after the first CT scan and included only children without a cancer diagnosis at that time (two years for leukemia). Results changed relatively little when the period was extended. However, the interpretation of small radiation-related excess risks is complicated by two observations. Brain cancer incidence in the study population is twofold higher than expected, even 10+ years after a first head CT, although the numbers are small. Also, the absence of clearly increased risks for leukemias is puzzling because these malignancies originate in the RBM, a tissue more radiosensitive than the brain. At the same time, the risk estimates for leukemias are likely less affected by indication bias and reverse causation. These considerations necessitate a cautious interpretation of the brain tumor findings. The observed general excess cancer risk (SIR = 1.47) is unlikely to be radiation-related but, rather, due to an over-representation of young patients who had diagnostic/screening CT scans for disorders related to genetic syndromes (eg, bone/soft tissue sarcoma, CNS tumors, nonmelanoma skin cancer) or other underlying medical conditions (eg, colon carcinoid detection during abdominal imaging for other reasons).

In summary, our results indicate that the relatively high brain doses from head CT scans (20–50 mGy) may increase brain tumor risk, whereas RBM doses generally under 10 mGy per CT and often under 5 mGy do not lead to an observable risk increase (Supplementary Tables 1 and 2, available online, for CT scans after 2001). The brain tumor findings may reflect a causal relationship because 1) our study is large and has almost nationwide coverage, 2) the exposure assessment is based on a large internal sample of CT scans with dosimetric information, 3) cancer registration in our study goes back to 1973 (leukemia) and 1989 (solid cancer) with high completeness, 4) the brain cancer results are very similar to those in the Life Span Study, 5) we could rule out confounding by TSC, the most common brain tumor susceptibility syndrome for which children have been exposed to CT scans, and 6) adjustment for socioeconomic status in our study is one of the most detailed ones so far. Nevertheless, the results need to be interpreted with caution because 1) the RBM is known to be more radiosensitive than the brain, 2) leukemia risk estimates are less prone to reverse causation and indication bias in CT studies than brain tumor risk estimates, 3) the number of cases in our study is too small for subgroup analyses, and 4) the increased brain tumor risk in our study is observed earlier after low-dose radiation exposure than current knowledge on latency for solid tumors suggests.

From a clinical perspective, we observed an excess absolute risk for all brain tumors of 1.3 (95% CI = 0.4 to 2.2) per 100 000 person-years per 20 mGy, the average brain dose among head CT scans during 2012–2014 in our study. This means that during the decade after the first head CT scan, one excess case per 10 000 head CT scans is estimated to occur. We estimate the number of annual head CT scans among Dutch children to be around 10 000 (3), leading to one brain tumor case annually attributed to radiation. In the Dutch population, nearly 120 pediatric brain tumors are diagnosed annually (35).

CT scans (for children) represent a potentially life-saving and quality of life–improving technique for many patients. In addition, the tumors evaluated here are associated with small absolute excess risks. Nonetheless, careful justification of pediatric CT scans and dose optimization, as are customary in many hospitals, are essential to minimize risks.

Funding

This work was supported by the European Community Seventh Framework Programme (grant number FP7/2007-2013) under grant agreement number 269912-EPI-CT ("Epidemiological study to quantify risks for paediatric computerized tomography and to optimize doses") and by Worldwide Cancer Research, formerly known as the Association for International Cancer Research (grant number 12-1155). Dr. Cecile Ronckers is supported by the Dutch Cancer Society.

Notes

Affiliations of authors: Department of Epidemiology and Biostatistics, Netherlands Cancer Institute, Amsterdam, the Netherlands (JMM, PG, FEvL, MH); Department of Paediatric Oncology, Emma Children's Hospital (CMR, JHM), and Department of Radiology (AMJBS), Academic Medical Center Amsterdam, Amsterdam, the Netherlands; Dutch Childhood Oncology Group, the Hague, the Netherlands (JHM); Department of Radiology (RAJN) and Department of Internal Medicine (BZ), University Medical Center Utrecht, the Netherlands; Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Rockville, MD (CL); Luxembourg Institute of Science and Technology (LIST), Esch-sur-Alzette, Luxembourg (AJ); Department of Radiology and Nuclear Medicine, Erasmus MC Rotterdam, the Netherlands (MvS); Department of Neurology and Paediatric Neurology, Erasmus MC, Sophia Children's Hospital, Rotterdam, the Netherlands (MCYdW); Department of Radiology and Nuclear Medicine, Radboud University Medical Center, Nijmegen, the Netherlands (WMK); Department of Registration, Netherlands Comprehensive Cancer Organisation, Utrecht, the Netherlands (OV).

The funders had no involvement in the study design, data collection, analysis and interpretation, writing of the report, or the decision to submit the paper for publication.

We sincerely thank the staff members, clinicians, and boards of directors of all hospitals who provided data for our study (AMC Amsterdam, Amphia Ziekenhuis, Albert Schweitzer Ziekenhuis, Bethesda Ziekenhuis, Canisius-Wilhelmina Ziekenhuis, Diaconessenhuis Leiden, Isala Diaconessenhuis Meppel, Diakonessenhuis Utrecht, Elkerliek Ziekenhuis, Erasmus MC, Flevoziekenhuis, Groene Hart Ziekenhuis, Medisch Centrum Haaglanden, HagaZiekenhuis, Ikazia Ziekenhuis, Isala Ziekenhuis, Jeroen Bosch Ziekenhuis, Kennemer Gasthuis, Streekziekenhuis Koningin Beatrix, Leids Universitair Medisch Centrum, Medisch Centrum Alkmaar, Medisch Centrum Leeuwaarden, Meander Medisch Centrum, Medisch Spectrum Twente, Onze Lieve Vrouwe Gasthuis,

ARTICLE

Radboudumc, Rijnland Ziekenhuis, Rijnstate, Rivas Beatrix Ziekenhuis, Saxenburgh groep Röpcke-Zweers Ziekenhuis, Sint Franciscus Gasthuis, Slotervaartziekenhuis, St. Antonius Ziekenhuis, St. Elisabeth Ziekenhuis, Sint Maartenskliniek, Maastricht UMC, UMC Groningen, UMC Utrecht, Het Van Weel-Bethesda Ziekenhuis, VUMC Amsterdam, Ziekenhuisgroep Twente, ZorgSaam Zeeuws-Vlaanderen). This study would not have been possible without the dedicated support of numerous professionals in the participating radiology departments.

References

1. Pearce MS, Salotti JA, McHugh K, et al. CT scans in young people in Northern England: Trends and patterns 1993-2002. *Pediatr Radiol*. 2011;41(7):832–838.
2. 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 Pediatrics*. 2013;167(8):700–707.
3. Meulepas JM, Smets AMJB, Nievelstein RAJ, et al. Trends and patterns of computed tomography scan use among children in the Netherlands: 1990-2012. *Eur Radiol*. 2017;27(6):2426–2433.
4. Rehani MM, Berry M. Radiation doses in computed tomography. The increasing doses of radiation need to be controlled. *BMJ*. 2000;320(7235):593–594.
5. National Research Council, Committee to Assess Health Risks from Exposure to Low Level of Ionizing radiation. *Health Risks From Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2*. Washington, DC: National Academies Press; 2006.
6. Lubin JH, Adams MJ, Shore R, et al. Thyroid cancer following childhood low-dose radiation exposure: A pooled analysis of nine cohorts. *J Clin Endocrinol Metab*. 2017;102(7): 2575–2583.
7. 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(9840):499–505.
8. Berrington de Gonzalez A, Salotti JA, McHugh K, et al. The relationship between pediatric CT scans and subsequent risk of leukemia and brain tumors: Assessment of the impact of underlying conditions. *Br J Cancer*. 2016;114(4): 388–394.
9. 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.
10. Huang WY, Muo CH, Lin CY, et al. Paediatric head CT scan and subsequent risk of malignancy and benign brain tumour: A nation-wide population-based cohort study. *Br J Cancer*. 2014;110(9):2354–2360.
11. 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(1):185–193.
12. 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):1–12.
13. Walsh L, Shore R, Auvinen A, et al. Risks from CT scans – what do recent studies tell us? *J Radiol Prot*. 2014;34(1):E1–E5.
14. Boice JD Jr. Radiation epidemiology and recent paediatric computed tomography studies. *Ann ICRP*. 2015;44(1 Suppl):236–248.
15. Hauptmann M, Meulepas JM. CT scans in childhood and risk of leukaemia and brain tumours. *Lancet*. 2012;380(9855):1736–1737.
16. Meulepas JM, Ronckers CM, Merks J, et al. Confounding of the association between radiation exposure from CT scans and risk of leukemia and brain tumors by cancer susceptibility syndromes. *J Radiol Prot*. 2016;36(4):953–974.
17. Meulepas JM, Ronckers CM, Smets AM, et al. Leukemia and brain tumors among children after radiation exposure from CT scans: Design and methodological opportunities of the Dutch Pediatric CT Study. *Eur J Epidemiol*. 2014; 29:293–301.
18. 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(3):611–628.
19. Jahnen A, Kohler S, Hermen J, et al. Automatic computed tomography patient dose calculation using DICOM header metadata. *Radiat Prot Dosimetry*. 2011; 147(1-2):317–320.
20. Lee C, Kim KP, Bolch WE, et al. NCICT: A computational solution to estimate organ doses for pediatric and adult patients undergoing CT scans. *J Radiol Prot*. 2015;35(4):891–909.
21. Kim KP, Berrington de González A, Pearce MS, et al. Development of a database of organ doses for paediatric and young adult CT scans in the United Kingdom. *Radiat Prot Dosimetry*. 2012;150(4):415–426.
22. Lee C, Pearce MS, Salotti JA, et al. Reduction in radiation doses from paediatric CT scans in Great Britain. *Br J Radiol*. 2016;89(1060):20150305.
23. Karim-Kos HE, Kiemeney LA, Louwman MW, et al. Progress against cancer in the Netherlands since the late 1980s: An epidemiological evaluation. *Int J Cancer*. 2012;130(12):2981–2989.
24. Coebergh JW, Van der Does-Van den Berg A, Van Wering ER, et al. Childhood leukaemia in The Netherlands, 1973-1986: Temporary variation of the incidence of acute lymphocytic leukaemia in young children. *Br J Cancer*. 1989; 59(1):100–105.
25. Van Duin C, Keij I. *Sociaal-Economische Status Indicator op Postcodeniveau. Maandstatistiek van de Bevolking* 50, 32–35 [in Dutch]. Voorburg, Netherlands: Statistics Netherlands; 2002.
26. Breslow NE, Day NE. Statistical methods in cancer research. Volume II – the design and analysis of cohort studies. *IARC Sci Publ*. 1987:1–406.
27. Ronckers CM, Sigurdson AJ, Stovall M, et al. Thyroid cancer in childhood cancer survivors: A detailed evaluation of radiation dose response and its modifiers. *Radiat Res*. 2006;166(4):618–628.
28. Hoffman R,, Benz EJ, Silberstein LE, et al. *Hematology, Basic Principles and Practice*. Elsevier Health Sciences; 2013
29. Preston DL, Ron E, Tokuoka S, et al. Solid cancer incidence in atomic bomb survivors: 1958-1998. *Radiat Res*. 2007;168(1):1–64.
30. Kroll ME, Stiller CA, Murphy MF, et al. Childhood leukaemia and socioeconomic status in England and Wales 1976-2005: Evidence of higher incidence in relatively affluent communities persists over time. *Br J Cancer*. 2011; 105(11):1783–1787.
31. Poole C, Greenland S, Luetters C, et al. Socioeconomic status and childhood leukaemia: A review. *Int J Epidemiol*. 2006;35(2):370–384.
32. Pearce MS, Salotti JA, McHugh K, et al. Socio-economic variation in CT scanning in Northern England, 1990-2002. *BMC Health Serv Res*. 2012;12:24.
33. National Council on Radiation Protection and Measurements (NCRP). Uncertainties in the estimation of radiation risks and probability of disease causation: Recommendations of the National Council on Radiation Protection and Measurements. NCRP report no. 171; 2012; Bethesda, MD.
34. Preston-Martin S, Pogoda JM, Schlehofer B, et al. An international case-control study of adult glioma and meningioma: The role of head trauma. *Int J Epidemiol*. 1998;27(4):579–586.
35. Reedijk AMJ, Van der Heiden-Van der Loo M, Visser O, et al. Site of childhood cancer care in the Netherlands. *Eur J Cancer*. 2017;87:38–46.