Brain cancer after radiation exposure from CT examinations of children and young adults: results from the EPI-CT cohort study

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Summary

Background The European EPI-CT study aims to quantify cancer risks from CT examinations of children and young adults. Here, we assess the risk of brain cancer.

Methods We pooled data from nine European countries for this cohort study. Eligible participants had at least one CT examination before age 22 years documented between 1977 and 2014, had no previous diagnosis of cancer or benign brain tumour, and were alive and cancer-free at least 5 years after the first CT. Participants were identified through the Radiology Information System in 276 hospitals. Participants were linked with national or regional registries of cancer and vital status, and eligible cases were patients with brain cancers according to WHO International Classification of Diseases for Oncology. Gliomas were analysed separately to all brain cancers. Organ doses were reconstructed using historical machine settings and a large sample of CT images. Excess relative risks (ERRs) of brain cancer per 100 mGy of cumulative brain dose were calculated with linear dose-response modelling. The outcome was the first reported diagnosis of brain cancer after an exclusion period of 5 years after the first electronically recorded CT examination.

Findings We identified 948 174 individuals, of whom 658 752 (69%) were eligible for our study. 368 721 (56%) of 658 752 participants were male and 290 031 (44%) were female. During a median follow-up of 5·6 years (IQR 2·4–10·1), 165 brain cancers occurred, including 121 (73%) gliomas. Mean cumulative brain dose, lagged by 5 years, was 47·4 mGy (SD 60·9) among all individuals and 76·0 mGy (100·1) among people with brain cancer. A significant linear dose-response relationship was observed for all brain cancers (ERR per 100 mGy 1·27 [95% CI 0·51–2·69]) and for gliomas separately (ERR per 100 mGy 1·11 [0·36–2·59]). Results were robust when the start of follow-up was delayed beyond 5 years and when participants with possibly previously unreported cancers were excluded.

Interpretation The observed significant dose-response relationship between CT-related radiation exposure and brain cancer in this large, multicentre study with individual dose evaluation emphasises careful justification of paediatric CTs and use of doses as low as reasonably possible.

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Introduction

CT among children and young adults has increased substantially since the 1990s, although rates have stabilised or even decreased since approximately 2010.[1–3] CT examinations are undoubtedly beneficial for countless patients because they provide valuable diagnostic information. Despite ongoing efforts such as ImageGently and recommendations of the International Commission of Radiological Protection,[4] evidence suggests that many CT examinations are done unnecessarily[5] and dose reductions are possible without compromising diagnostic accuracy.[6] Brain cancer is of concern in this context because it is a frequent paediatric cancer[7] and the head is the most commonly examined body part of paediatric patients.[1,8] Several epidemiological studies showed increased brain tumour risk after paediatric CT examinations.[9–12] Most of these studies included a relatively small number of

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See Online for appendix

Research in context

Evidence before this study

Associations between external exposure to ionising radiation in childhood and the risk of brain tumours have been observed in several studies, including studies of patients who underwent CT scans. Using the search terms ("brain cancer" OR "brain tumour" OR "intracranial tumour") AND ("CT scan" AND "ionizing radiation") AND ("children" OR "adults"), without language restrictions, we identified ten studies published in PubMed between database inception and June 25, 2022, related to the risk of developing benign or malignant brain tumours following CT scans administered to paediatric or young adult patients. Five cohort studies and one case-control study reported significant increases in the risk of brain tumours (malignant, benign, or both) associated with exposure to CT scans. Two studies yielded imprecise estimates and were based on few cases. The associations reported in CT studies have been questioned because of the absence of individual dose reconstruction, reverse causation, indication bias, small numbers of cases, and other methodological limitations. A study in Norway addressed reverse causation by reviewing radiology reports to identify previously unreported meningioma cases at the time of the first CT scan. Upon their exclusion, the effect of CT-related radiation exposure was attenuated. In the UK study, re-analysis of the cohort excluding patients with previously unreported previous malignancies reduced the risk of brain tumours from exposure to CT radiation by 30%, although estimates remained significant. Very few studies used individualised dose reconstruction approaches based either on substantial amounts of picture archiving and communication system information; external published data stratified by sex, age, calendar period, and body part scanned; or hospital-specific scanning protocols. Many of the risk estimates were derived using crude comparisons of exposed versus non-exposed patients or between the numbers of CT scans administered.

Added value of this study

The EPI-CT study results for all malignant brain tumours combined and for gliomas separately suggest a linear increase in the relative rate of cancer with increasing radiation dose to the brain from CT examinations. These results are robust in sensitivity analyses addressing factors potentially biasing risk estimates that were subject to the criticism in previous studies. Methods used for dose reconstruction and its uncertainty in EPI-CT, the largest multinational CT study so far, were state-of-the-art and surpassed the amount of detail in all previous studies. The study adds important evidence that exposure to low doses of radiation from any source is associated with increased cancer risk.

Implications of all the available evidence

Our study findings emphasise the need to adhere to the basic principles of radiological protection in the medical setting; namely, the need for justification of diagnostic procedures involving ionising radiation (that the procedure is appropriate and in accordance with national and international guidelines) and optimisation of scanning protocols (that the dose should be as low as reasonably achievable). Despite various efforts for dose reduction, CT remains the main contributor to the population diagnostic medical radiation dose, particularly in middle-income and high-income countries.

cases or did not assess individual organ doses. EPI-CT is a large, European cohort of children and young adults exposed to ionising radiation during CT examinations.[8] The study quantifies cancer risks, overcomes shortcomings of previously reported studies, and motivates optimisation strategies for reducing exposures. Here, we present results from EPI-CT on the risk of brain cancer from CT examinations.

Methods

Study design and participants

In this cohort study, we pooled individual patient data from Belgium, Denmark, France,[13] Germany,[14] the Netherlands,[11] Norway, Spain, Sweden,[15] and the UK.[8,10,16,17] Individuals with at least one CT examination before age 22 years (depending on country; appendix p 15), and documented between 1977 and 2014 were identified through the Radiology Information System in 276 radiology departments of participating hospitals.[8] Individuals were linked with national or regional registries of cancer (all countries), vital status (Denmark, Norway, Sweden, the UK, Spain, the Netherlands, Belgium, and some parts of France), and emigration status (Denmark, Norway, Sweden, and the UK). Individuals were included if they were alive at least 1 year after the first documented CT examination and if no previous cancer or non-malignant brain tumour was recorded.[8]

Eligible cases were patients with brain tumours according to WHO International Classification of Diseases for Oncology (third edition, revision 1)[18] topographic codes for meninges (except spinal), brain, cranial nerves, and other parts of the CNS except spinal tumours, and a malignancy behaviour code 3 (fifth digit in the morphology code; appendix p 1). We separately examined gliomas because they are the most common type of malignant brain tumour at all ages. Individuals with registered brain tumours of benign or unknown behaviour were excluded if diagnosis was before entry, and otherwise censored because of increased surveillance, possibly using CT. We excluded 13 individuals with brain cancer from the UK cohort because they were found, upon a review of additional records, to be second malignancies with an unknown date of first primary cancer.[12] This registry linkage study did not involve direct contact with patients and patients were not required to give written informed consent. The protocol (IARC

IEC 12–35) was approved by the Ethics Committee of the International Agency for Research on Cancer and by all appropriate national, regional, and hospital ethics committees of all participating countries.

Procedures

A complex dose reconstruction approach was designed to estimate the absorbed radiation dose to the brain.[17] Available historical information on CT machine settings, questionnaire data, and Digital Imaging and Communication in Medicine (DICOM) header metadata from a sample of 378 000 CT scans extracted from the Picture Archiving and Communication System of participating hospitals were used to derive scanning protocols by body region, gender, age, and machine type representative of technology evolution. We calculated absorbed organ doses to 33 organs and tissues, including the brain, for all cohort members and for each examination recorded in the Radiology Information System, entering the sampled x-ray machine parameter values in the National Cancer Institute Dosimetry System for CT software.[19] Dose uncertainties due to missing data were addressed by Two-Dimensional Monte-Carlo simulation (ie, the mean of 200 realisations sampled for each examination was used as estimated examination brain dose).[17]

Outcomes

The outcome was the first reported diagnosis of brain cancer and gliomas separately after an exclusion period of 5 years after the first electronically recorded CT examination. A 5-year exclusion period was chosen to prevent reverse causality (ie, CT scans administered because of present but undiagnosed malignancies at baseline).

Statistical analysis

Person-years were accrued from 5 years after the first recorded CT examination or the start of cancer registration (2004 in Belgium, 1943 in Denmark, 2000 in France, 1980 in Germany, 1989 in the Netherlands, 1953 in Norway, 1980–2006 in Spain [depending on region), 1958 in Sweden, and 1985 in the UK], whichever was later, until the first of: diagnosis of a malignant or non-malignant brain tumour, diagnosis of other malignancy than brain, death, emigration (if data were available), or end of follow-up (2010 in Germany; 2012 in Belgium, France, and Norway; 2013 and Denmark, Spain, and the UK; 2014 in Sweden and the Netherlands). In France and Germany, follow-up ceased at 15 years of age because paediatric registries were used for case ascertainment. The 5-year exclusion period after the first recorded CT examination was chosen because we consider it unlikely that a brain cancer is undiagnosed 5 or more years after symptom onset, even if it is initially missed.

Relative risks (RRs) and 95% likelihood-based CIs were estimated using Poisson regression[20] stratified by country, sex, calendar year (1980 to <1995, 1995 to <2000, 2000 to <2005, 2005 to <2010, and 2010 to <2015), and attained age (5 to <6, 8 to <10, 10 to <12, 12 to <14, 14 to <16, 16 to <18, 18 to <20, 20 to <25, 25 to <30, 30 to <35, 35 to <40, and 40 to 54 years). The number of head or neck CT examinations and associated cumulative brain dose were calculated as time-dependent variables by summing examination-specific doses lagged by 5 years. The excess relative risk (ERR) per 100 mGy brain dose (ie, the percentage increase [or decrease if negative] of the risk per 100 mGy) was estimated by linear dose–response modelling:

$$RR=EXP(\Sigma_j \alpha_j X_j)[1+\beta D]$$

in which D is continuous cumulative brain dose per 100 mGy, β the ERR per 100 mGy, and X_j stratification variables with corresponding log RRs α_j. Tests of trend and heterogeneity were based on the likelihood ratio of the ERR. We aimed to include 1 100 000 children and young adults, which provides at least 80% power to detect a RR of 1·75 for 10 CT examinations.

In prespecified analyses, departure from linearity of the dose–response relationship was evaluated by a likelihood ratio test of the null hypothesis $\gamma=0$ in the model:

$$RR=EXP(\Sigma_j \alpha_j X_j)[1+\beta D*EXP(\gamma D)]$$

in which γ indicates downward curvature ($\gamma<0$) or upward curvature ($\gamma>0$). We assessed whether sex, age at exposure (0 to <6, 6 to <12, or ≥12 years), attained age (5 to <18, 18 to <25, or ≥25 years), and time since exposure (5 to <10, 10 to <15, or ≥15 years) modified the dose-response by adding interaction terms between dose and potential modifiers. Tests were two-sided at a 5% significance level. EPICURE software (version 2.00.02) was used for the analysis.

For post-hoc sensitivity analyses, we left out one country at a time; delayed start of follow-up after the first CT examination by each whole-number value in the range 6–10 years (exclusion period) to further assess potential reverse causation; lagged cumulative brain dose by 10 years; excluded individuals with a first CT examination before 1990 because of high uncertainty in dose estimates and the possibility of non-reported previous cancers; excluded person-years corresponding to older attained ages (above 20, 25, 30, 35, and 40 years) to limit consequences of possibly unknown exposures at older ages; excluded older individuals (birth years <1980, <1990, and <1995); excluded less recent calendar years (<1995, <2000, <2005, and <2010) to reduce the consequences of unascertained cancers due to cancer registry incompleteness; excluded extreme doses by censoring individuals when their cumulative dose reached a specific value that ranged from 40–200 mGy; and excluded the 1%, 2%, and 3% person-years with highest cumulative brain dose to eliminate outliers. We

	All individuals (N=658 752)	Cases (n=165)	Person-years (n=4 536 716)
Sex			
Male	368 721 (56%)	95 (58%)	2 524 786 (56%)
Female	290 031 (44%)	70 (42%)	2 011 930 (44%)
Country			
Belgium	3244 (<1%)	0	8915 (0%)
Denmark	9289 (1%)	1 (1%)	30 349 (1%)
France	63 994 (10%)	3 (2%)	201 760 (4%)
Germany	21 890 (3%)	1 (1%)	71 472 (2%)
Netherlands	107 034 (16%)	29 (18%)	831 615 (18%)
Norway	50 770 (8%)	9 (5%)	277 060 (6%)
Spain	36 439 (6%)	0	102 447 (2%)
Sweden	98 415 (15%)	28 (17%)	812 508 (18%)
UK	267 677 (41%)	94 (57%)	2 200 590 (49%)
Time since first CT exposure, years			
5 to <10	304 818 (46%)	89 (54%)	2 471 097 (54%)
10 to <15	187 896 (29%)	50 (30%)	1 258 461 (28%)
≥15	166 038 (25%)	26 (16%)	807 157 (18%)
Attained age, years			
5 to <20	266 371 (40%)	78 (47%)	2 038 328 (45%)
20 to <30	273 031 (41%)	64 (39%)	1 908 730 (42%)
30 to <40	104 116 (16%)	22 (13%)	548 887 (12%)
≥40	15 234 (2%)	1 (1%)	40 771 (1%)
Year of birth			
<1980	64 480 (10%)	46 (28%)	972 233 (21%)
1980 to <1990	219 575 (33%)	65 (39%)	1 837 084 (40%)
1990 to <1995	138 993 (21%)	35 (21%)	802 363 (18%)
≥1995	235 704 (36%)	19 (12%)	925 037 (20%)
Calendar year of first CT exposure			
<1995	90 403 (14%)	66 (40%)	1 535 303 (34%)
1995 to <2000	120 208 (18%)	52 (32%)	1 274 904 (28%)
2000 to <2005	222 691 (34%)	35 (21%)	1 306 348 (29%)
≥2005	225 450 (34%)	12 (7%)	420 030 (9%)
Cumulative number of head or neck CT examinations (lagged by 5 years)			
0*	177 220 (27%)	24 (15%)	1 089 643 (24%)
1	390 920 (59%)	102 (62%)	2 828 828 (62%)
2–3	74 681 (11%)	24 (15%)	505 152 (11%)
≥4	15 931 (2%)	15 (9%)	113 092 (2%)
Cumulative brain dose (lagged by 5 years), mGy			
Mean	47·4 (60·9)	76·0 (100·1)	..
Median	44·0 (11·9–56·9)	53·8 (39·0–66·3)	..
Maximum	4719·7	964·9	..
Follow-up duration after 5 years since the first CT examination, years			
Mean	6·9 (5·5)	5·4 (4·4)	..
Median	5·6 (2·4–10·1)	4·2 (1·9–8·0)	..
Maximum	29·6	20·4	

Data are n (%), mean (SD), or median (IQR). Time dependent variables (years since first exposure, attained age, number of head or neck CTs, follow-up duration, and cumulative brain dose) are reported at the end of follow-up. *Cohort members with no head or neck CT examinations entered the cohort with a CT examination of another body part

Table 1: **Cohort characteristics**

fitted an excess absolute risk model to estimate the absolute excess number of brain cancers as a whole associated with CT examinations.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We identified 948 174 individuals with at least one CT examination who were alive and cancer-free 1 year or more after the first CT examination, of whom we included 658 752 (69%) people who were alive and cancer-free (including free from known brain tumours of benign or unknown behaviour) 5 years after their first CT examination with a total of 4 536 716 person-years (table 1). 539 402 (82%) of 658 752 individuals were younger than 30 years old at the end of follow-up, 368 721 (56%) were male and 290 031 (44%) were female, and data on race or ethnicity were not collected. Median follow-up duration (starting 5 years after the first CT examination) was 5·6 years (IQR 2·4–10·1). 165 cases of brain cancer were reported during follow-up (table 1), including 121 (73%) gliomas and the rest being a variety of different morphologies (appendix p 1). In the analytic cohort, 481 532 (73%) of 658 752 individuals received at least one head or neck CT examination. The study from the UK contributed 2 200 590 (49%) of 4 536 716 person-years and 94 (57%) of 165 brain cancer cases, the Netherlands contributed 831 615 (18%) person-years and 29 (18%) brain cancer cases, and Sweden contributed 812 508 (18%) person-years and 28 (17%) brain cancer cases (table 1). Mean cumulative brain dose, lagged by 5 years, was 47·4 mGy (SD 60·9) among all individuals and 76·0 mGy (100·1) among people with brain cancer (table 1). Mean brain dose per head or neck CT examination increased from 1984 until about 1991, following the introduction of multi-slice CT scanners at which point thereafter the mean dose decreased and then stabilised around 2010 (appendix p 4).[17]

We observed a significant positive association between the cumulative number of head or neck CT examinations and the risk of all brain cancers combined (p<0·0001), and of gliomas separately (p=0·0002; table 2). The ERR per 100 mGy of brain dose for all brain cancers was 1·27 (95% CI 0·51–2·69), for glioma separately was 1·11 (0·36–2·59), and for all brain cancers excluding gliomas was 2·13 (0·25–13·6; appendix p 3). Linearity was not rejected (p=0·85 for all brain cancers, p=0·37 for gliomas, and p=0·26 for all other brain cancers excluding gliomas).

In prespecified analyses, the RR of all brain cancers for doses ranging from 41 mGy to less than 47 mGy was 2·1 (95% CI 1·1–3·8) and for doses equal to or exceeding 150 mGy was 5·0 (2·5–9·7), with the reference being cumulative doses less than 5 mGy (table 2; figure). The RR

	All brain cancers		Glioma	
	Cases	RR* (95% CI)	Cases	RR* (95% CI)
Number of head or neck CT examinations				
0	24	1·0 (ref)	18	1·0 (ref)
1	102	1·6 (1·0–2·5)	76	1·6 (0·9–2·7)
2–3	24	2·1 (1·2–3·6)	16	1·9 (0·9–3·7)
≥4	15	5·9 (3·1–11·2)	11	5·9 (2·8–12·6)
p value†	<0·0001	..	<0·0001	..
Cumulative brain dose, mGy				
0<5	18	1·0 (ref)	16	1·0 (ref)
5 to <41	27	1·4 (0·8–2·6)	18	1·1 (0·5–2·1)
41 to <48	26	2·1 (1·1–3·8)	21	1·9 (1·0–3·7)
48 to <56	23	1·2 (0·6–2·2)	17	1·0 (0·5–2·0)
56 to <65	27	2·2 (1·2–4·1)	18	1·7 (0·9–3·4)
65 to <150	27	1·9 (1·0–3·4)	19	1·5 (0·8–3·0)
≥150	17	5·0 (2·5–9·7)	12	4·1 (1·9–8·8)
p value‡	<0·0001	..	0·0002	..
ERR per 100 mGy§ (95% CI)	1·27 (0·51–2·69)	..	1·11 (0·36–2·59)	..

RR=relative risk. ERR=excess relative risk. *Poisson regression stratified for calendar year of follow-up, attained age, gender, and country. †p value of coefficient for continuous number of head or neck CT examinations in linear model. ‡p value of coefficient for continuous dose in linear model. §No evidence of non-linearity, p=0·85 for all brain cancers and p=0·37 for glioma.

Table 2: **Relative risks for all brain cancers and for glioma separately by cumulative number of head or neck CT examinations and categories of brain dose (5-year exclusion period, 5-year lag)**

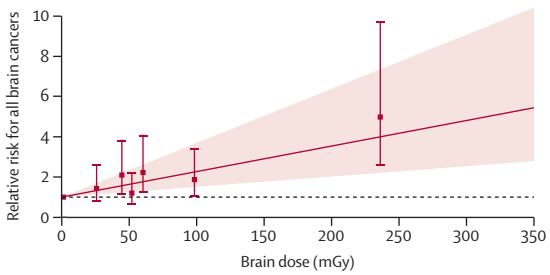

Figure: **Relative risks for all brain cancers by cumulative brain dose (lagged by 5 years and with a 5-year exclusion period)**
Bars show 95% CIs. The solid line represents the fitted linear dose–response (ERR of 1·27 per 100 mGy). Shaded areas represent the upper and lower 95% CIs (0·51–2·69). The dotted line represents the reference value (1). ERR=excess relative risk.

	All brain cancers		Glioma	
	ERR per 100 mGy (95% CI)	Homogeneity p value	ERR per 100 mGy (95% CI)	Homogeneity p value
Sex				
Male	1·76 (0·52–5·27)	..	1·37 (0·26–4·97)	..
Female	0·89 (0·13 to 2·65)	0·40	0·91 (0·10 to 2·89)	0·66
Age at CT exposure, years				
0 to <6	0·40 (<–0·40 to 1·79)	..	0·21 (<–0·52 to 1·62)	..
6 to <12	1·98 (0·60 to 4·48)	..	1·67 (0·34 to 4·22)	..
≥12	1·62 (0·40 to 4·09)	0·16	1·67 (0·27 to 4·73)	0·17
Attained age, years				
5 to <18	3·30 (0·87 to 16·07)	..	2·59 (0·56 to 13·17)	..
18 to <25	1·33 (0·11 to 5·30)	..	1·64 (0·08 to 7·94)	..
≥25	0·33 (–0·19 to 1·75)	0·12	0·16 (<–0·38 to 1·49)	0·14
Time since exposure, years				
5 to <10	1·84 (0·78 to 3·76)	..	1·45 (0·53 to >2·66)	..
10 to <15	1·34 (0·26 to 3·23)	..	1·76 (NA)	..
≥15	–0·12 (<–0·91 to 1·12)	0·020	–0·29 (NA)	0·010

ERR=excess relative risk. NA=not available.

Table 3: **Modification of radiation-related brain cancer risk (5-year exclusion period, 5-year lag)**

of developing brain cancer from a brain dose of 38 mGy, which was the average dose per head or neck CT in 2012–14, was 1·5 (95% CI 1·2–2·0) compared with a brain dose of 0 mGy. The excess absolute risk per 38 mGy brain dose per 100 000 person-years was 1·1 (95% CI 0·6–1·6; ie, for every 10 000 people who received a single head CT examination, approximately one person is expected to develop brain cancer attributable to radiation exposure in the period 5–15 years following the CT examination.

In prespecified analyses, we observed decreasing ERR per 100 mGy for brain cancer with time since exposure (homogeneity p value=0·020; table 3). The ERR per 100 mGy did not significantly change with attained age (p=0·12) or age at exposure (p=0·16). There was no significant difference in ERR per 100 mGy between sexes (homogeneity p value=0·40). Results were similar for glioma (appendix p 3).

In sensitivity analyses, the ERR per 100 mGy changed little when leaving out Spain, Germany, Belgium, France, Denmark or Norway (appendix p 1). When leaving out the Netherlands the ERR slightly increased to 1·41 (95% CI 0·52 to 3·23) and when leaving out Sweden the ERR slightly increased to 1·53 (0·59 to 3·48). ERR decreased to 0·91 (0·12 to 2·83) when leaving out the UK. ERR per 100 mGy in the UK was 1·65 (95% CI 0·50 to 4·58), in Sweden was 0·38 (<0 to 3·17), and in the Netherlands was 0·82 (–0·09 to 4·50; appendix p 1). Similar patterns were observed for glioma (appendix p 1). Lagging cumulative brain dose by 10 years shifted cases towards lower dose categories than those lagging by 5 years. The association was no longer significant (p=0·35) and the ERR per 100 mGy decreased to 0·19 (95% CI <–0·20 to 0·79) for all brain cancers and to 0·34 (<–0·17 to 1·13) for glioma (appendix p 2).

Delaying the start of follow-up after the first CT examination by 6 to 10 years decreased the ERR per 100 mGy of cumulative dose for brain cancer gradually although it remained significant, except for an exclusion period of 10 years, which resulted in an ERR of 0·37 (95% CI –0·056 to 1·40) based on 76 individuals (appendix p 2).

When analyses were limited to younger attained age groups, more recent calendar year periods, or more recent birth year periods, the ERR remained significant and of

similar magnitude as in the unrestricted analysis, although the CI broadened due to the fewer person-years (appendix p 2). When restricting analyses to patients with cumulative brain doses lower than specified levels, the ERR per 100 mGy for brain cancer remained stable and significantly elevated until exclusion of doses exceeding 50 mGy (appendix p 2).

The ERR per 100 mGy was comparable to unrestricted analyses when 45 367 (1%) of 4 536 716 person-years with highest cumulative brain doses were excluded from the analysis, and remained significantly elevated when individuals with doses greater than the 98th and 97th percentile or with two or more head or neck CT examinations were excluded (appendix p 2). Excluding 26 536 (4%) 658 752 of patients with the first CT examination before 1990 had little effect on ERRs (appendix p 2). Results for cumulative dose among UK patients resembled the UK study,[12] due to a good agreement of the dose reconstruction approaches used in both studies.[17]

Discussion

First results of EPI-CT after a median follow-up of 5·6 years (IQR 2·4–10·1) show a strong dose–response relationship between the brain radiation dose and the relative risk of all brain cancers combined and glioma separately; a finding that remains consistent for doses substantially lower than 100 mGy. Despite some heterogeneity in magnitude, the direction of effect is not influenced by one specific country.

Associations between childhood exposure to ionising radiation and the risk of benign and malignant brain tumours have been observed in several studies, including those of childhood cancer survivors after cranial radiotherapy[21,22] and Israeli children treated with radiation for tinea capitis who were followed for 40 years.[23] In the latter study, the ERR per 100 mGy for brain cancer was 0·20 (95% CI 0·07–0·47; 31 individuals) whereas the ERR per 100 mGy in our study was 1·27 (95% CI 0·51–2·69; 165 cases). However, the mean brain dose was much higher (1500 mGy) in the Israeli study than in our study (49·3 mGy). For a dose range similar to our study, the pooled Swedish cohort study of patients with haemangioma treated with radiotherapy (mean absorbed intracranial dose 70 mGy) reported an ERR per 100 mGy of 0·27 (95% CI 0·10–0·56; 86 cases) for malignant and benign brain tumours combined.[24] Among atomic bomb survivors younger than 20 years of age at exposure and within 20 years of follow-up, the ERR per 100 mGy for brain cancer was 0·61 (95% CI 0·01–6·39;) with wide CIs.[10]

These results indicate that ERRs per 100 mGy in CT cohorts, such as ours, are generally higher than in cohorts of individuals who are irradiated for other reasons, raising questions about the potential role of the reasons for the CT examination. However, a comparison of these previous study results with our own needs to consider that the previous studies have much longer follow-up; exposure characteristics, including uncertainties of reconstructed doses, were heterogeneous; and they include smaller proportions of brain cancers diagnosed in childhood and adolescence (mean age at end of follow-up in the EPI-CT study is only 22·1 years). The observed decline of risk by increasing attained age in EPI-CT supports consistency. Despite differences in exposure assessment and analytical approach, the observed ERR per 100 mGy of 1·27 (95% CI 0·51–2·69) in our study, albeit lower, is similar to the large Australian paediatric CT cohort (ERR per 100 mGy 2·1 [95% CI 1·4–2·9]).[9] A recent meta-analysis also found significantly elevated risks for brain cancer after exposure to low and moderate doses in childhood.[25]

A substantial portion of patients in our analysis were included in other published studies.[10–14] However, some of these studies (from France and the UK) included additional patients, extended follow-up, modified eligibility criteria, and used different dose reconstruction. Additionally, precise outcome definitions (eg, inclusion of brain tumours of uncertain or benign behaviour) and analytical choices (lagging of cumulative brain dose, exclusion period after first CT examination) differed. Nevertheless, country-specific EPI-CT results were generally similar to those published separately.

The higher risk of brain cancer with increasing age at exposure observed in our study is comparable with findings for CNS tumours among survivors of atomic bombs, in which only one CNS tumour type (schwannoma) showed a significantly decreasing trend in ERR with increasing age at exposure.[26] Long-term childhood cancer survivors who received 18–50 Gy of cranial radiotherapy showed the strongest glioma dose-response relationship for those exposed before the age of 5 years.[21,22] However, glioma incidence in the general population only increases substantially after about 30 years of age, depending on the grade. This age period offers the greatest power to observe a radiation-related excess but is not covered yet by paediatric cohorts exposed to medical diagnostic radiation.[9–15,21,22] The main reason we and others studied children and young adults is that they are generally more sensitive to the carcinogenic effects of ionising radiation than adults and they have a longer life span to express any effect. Extending follow-up time is necessary to study age effects in more detail, particularly for slow-growing tumour types (eg, meningioma).

Strengths of our study are the large number of exposed patients providing greater statistical stability and narrower CIs than smaller cohorts; use of long-standing and high-quality cancer registries for case ascertainment; multinational analyses providing a comparison of results across countries; and the most comprehensive dose reconstruction approach for CT studies available to date. Sensitivity analyses assessed several factors potentially biasing risk estimates.

A potential limitation of our study is reverse causation. All participants had suspected or real medical problems

for which a CT examination was indicated. These problems could, in theory, be early symptoms of subsequently diagnosed brain cancer. A 2017 study[15] reported an attenuation of the increased risk of intracranial meningioma following head CT examination after exclusion of participants with prevalent meningioma or brain tumour at the first CT examination following a review of radiology reports. A similar effect on our brain cancer results is unlikely because most meningiomas are benign and not part of this study. In contrast, we observed a dose-response relationship for gliomas, which are more common and generally rapidly progressing tumours. EPI-CT results did not change substantially when analyses were limited to more recent calendar periods of case ascertainment to avoid inclusion of children and young adults with malignancies unreported due to incomplete cancer registration.

It has been suggested that some head or neck CTs were done because of initial, very early symptoms, possibly related to brain tumours of small size that, in certain localisations, might have been undetectable by CT.[27] However, there is little credible evidence for this theory to date. Since we do not have data on medical history and reasons for the CT, we used other means to address this issue. When we excluded cases of brain cancer diagnosed 6–10 years after the first CT examination, findings did not change considerably. These periods appear sufficiently long to eliminate the possibility of CT examinations having been done for symptoms of undetectable brain cancer. Data from a large-scale multinational study of 899 paediatric patients with brain tumours support this finding.[28] A systematic review also supports these observations.[29] Finally, a recent simulation study showed no upward bias of the risks of brain cancer estimated from realistic data of a CT study that included latent cancer associated with increased frequency of head CT examinations.[30]

A related potential limitation is confounding by indication (ie, the examination is related to an underlying condition associated with an increased risk of brain cancer). Some studies included in EPI-CT had individual information on congenital syndromes predisposing children to brain tumours, but found no major effect on the ERR after excluding such children or adjusting for the syndromes.[11,13] A direct evaluation of indication bias in a study of CT-related cancer risk showed that the reason for a CT examination does not considerably bias risk estimates, although the endpoints were adult colorectal and lung cancer, and female breast cancer.[29] In summary, internal (different exclusion periods) and external evidence suggests that indication bias and reverse causation are unlikely to explain the observed association between CT scans and brain cancer in the absence of a radiation effect.[11–13,30,32] Nevertheless, some upward bias could be possible.

Country-specific results were somewhat heterogeneous, with relatively high ERRs in the UK versus the Netherlands and Sweden. UK patients were older at first CT examination and end of follow-up, and were followed for, on average, two more years compared with other countries.[8] The fraction of CTs done before 2000 was larger in the UK than in Sweden and the Netherlands.[8] However, whether these differences caused the heterogeneity is unclear.

Dose estimates harboured uncertainty since they were obtained retrospectively on the basis of various data sources. Completeness of CT examination ascertainment is mixed, with some countries including only a few hospitals versus almost nationwide coverage of all paediatric CT examinations in others.[10–12] Detailed technical information for dose estimation was particularly scarce for years before 1990. [17] Conversely, the fact that a CT examination was done and the part of the body that was examined was electronically recorded for all CT examinations, lends credibility to the dose estimation process. The EPI-CT dose reconstruction is state-of-the-art and surpasses the amount of detail in all previous studies.[17] We potentially underestimated patient doses because we did not have information on imaging procedures other than CT, such as x-ray or nuclear imaging. However, given the higher frequencies and doses of paediatric head CT examinations than with other modalities, their contribution is probably minor. An ongoing evaluation of US health insurance data will address this issue in the future.[33] Finally, although CT examinations in this study were done before 2015, current doses are probably similar because EPI-CT data showed that brain doses per examination decreased until 2010 and then stabilised,[17] possibly because the necessary skull penetration limits brain dose reduction.

The results of this EPI-CT brain cancer study agree with recent reviews concluding that epidemiological data support the linear no-threshold model for cancer risk from low-dose radiation exposure.[34] Translation of our risk estimates to the clinical setting indicates that per 10 000 children who received one head CT examination, about one radiation-induced brain cancer is expected during the 5–15 years following the CT examination. To put this finding into context, the number of paediatric head CT examinations per year during the past decade probably exceeds 1 million in the EU and 5 million in the USA.[1,35] Only a small fraction of the attributable brain cancers might be preventable (ie, those with unnecessarily high doses during CT examinations or the presumably larger group with clinically unjustified CT examinations). Nevertheless, these figures emphasise the need to adhere to the basic radiological protection principles in medicine, namely justification (procedures are appropriate and comply with guidelines) and optimisation (doses are as low as reasonably achievable).

EPI-CT provides a novel and unique contribution to the evidence on cancer risks from low doses of radiation to which large numbers of the global population are

exposed. As follow-up is updated, the study will continue to provide unique and tangible evidence for radiation protection in the context of medical radiation exposure.

Contributors

MH, AK, EC, IT-C and MK were responsible for the study design. AK and JS were responsible for the overall coordination and conduct. IT-C and SLS developed the exposure reconstruction strategy. IT-C, SLS, JD, TSI, LLC, AJ, JF, CM, RWH, and CL participated in development and validation of the exposure reconstruction approach. MH, CR, EC, M-OB, MB, JD, HE, CJ, MK, KK, NJ, JF, JMM, LLC, RP, TSI, MBdB, AN, AJ, ABdG, and RWH were responsible for patient accrual and obtaining and processing the data, including data on exposure. EC, MH, AK, and GB wrote the statistical analysis plan. MH, MM, and AK had full access to, and verified, the data. MH analysed the data and produced the results and figures. All authors had access to, and interpreted the data, and approved the draft and final version of the manuscript. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

CJ reports honoraria from Pfizer, Janssen, and Astellas, and owns stocks in Y-mAbs, Novo Nordisk, Novozymes, Hansa, Zealand, Bavarian Nordic, and BioCryst Pharmaceuticals. MK reports grants from Stockholm County for clinical research within the frame of employment as a radiologist at the Karolinska University Hospital. CR reports a grant from the Dutch Cancer Society for Junior Group Leaders. All other authors declared no competing interests.

Data sharing

EPI-CT study data are not freely available because of ethical and data protection constraints. The anonymised data are stored at the International Agency for Research on Cancer (IARC), WHO, for a limited time period defined in data sharing agreements and cannot be sent outside the Agency. Proposals for possible collaborations in further analyses of the data should be addressed to Ausrele Kesminiene (KesminieneA@iarc.who.int) and will be reviewed by the EPI-CT steering committee. Study procedures are available in the appendix.

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References

1 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:** 2426–33.
2 Smith-Bindman R, Kwan ML, Marlow EC, et al. Trends in use of medical imaging in US health care systems and in Ontario, Canada, 2000-2016. *JAMA* 2019; **322:** 843–56.
3 National Council on Radiation Protection and Measurements. Medical Radiation Exposure of Patients in the United States: report number 184. 2019. https://ncrponline.org/shop/reports/report-no-184-medical-radiation-exposure-of-patients-in-the-united-states-2019/ (accessed Nov 22, 2022).
4 Vañó E, Miller DL, Martin CJ, et al. ICRP publication 135: diagnostic reference levels in medical imaging. *Ann ICRP* 2017; **46:** 1–144.
5 Hendee WR, Becker GJ, Borgstede JP, et al. Addressing overutilization in medical imaging. *Radiology* 2010; **257:** 240–45.
6 Smith-Bindman R, Wang Y, Chu P, et al. International variation in radiation dose for computed tomography examinations: prospective cohort study. *BMJ* 2019; **364:** k4931.
7 WHO International Agency for Research on Cancer. Comparative tables. https://iicc.iarc.fr/results/comparative-tables/ (accessed Nov 22, 2022).
8 Bernier MO, Baysson H, Pearce MS, et al. Cohort profile: the EPI-CT study: a European pooled epidemiological study to quantify the risk of radiation-induced cancer from paediatric CT. *Int J Epidemiol* 2019; **48:** 379–381g.
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 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.
11 Meulepas JM, Ronckers CM, Smets AMJB, et al. Radiation exposure from pediatric CT scans and subsequent cancer risk in the Netherlands. *J Natl Cancer Inst* 2019; **111:** 256–63.
12 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.
13 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.
14 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.
15 Nordenskjöld AC, Bujila R, Aspelin P, Flodmark O, Kaijser M. Risk of meningioma after CT of the head. *Radiology* 2017; **285:** 568–75.
16 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.
17 Thierry-Chef I, Ferro G, Le Cornet L, et al. Dose estimation for the European epidemiological study on pediatric computed tomography (EPI-CT). *Radiat Res* 2021; **196:** 74–99.
18 WHO. International classification of diseases for oncology '(ICD-O)', 3rd ed., 1st revision. https://apps.who.int/iris/handle/10665/96612 (accessed June 29, 2022).
19 Lee C, Kim KP, Bolch WE, Moroz BE, Folio L. NCICT: a computational solution to estimate organ doses for pediatric and adult patients undergoing CT scans. *J Radiol Prot* 2015; **35:** 891–909.
20 Breslow NE, Day NE. Statistical Methods in Cancer Research. Volume II - The design and analysis of cohort studies. *IARC Sci Publ* 1987; **82:** 1–406.

21 Taylor AJ, Little MP, Winter DL, et al. Population-based risks of CNS tumors in survivors of childhood cancer: the British Childhood Cancer Survivor Study. *J Clin Oncol* 2010; **28:** 5287–93.

22 Neglia JP, Robison LL, Stovall M, et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2006; **98:** 1528–37.

23 Sadetzki S, Chetrit A, Freedman L, Stovall M, Modan B, Novikov I. Long-term follow-up for brain tumor development after childhood exposure to ionizing radiation for tinea capitis. *Radiat Res* 2005; **163:** 424–32.

24 Karlsson P, Holmberg E, Lundell M, Mattsson A, Holm LE, Wallgren A. Intracranial tumors after exposure to ionizing radiation during infancy: a pooled analysis of two Swedish cohorts of 28,008 infants with skin hemangioma. *Radiat Res* 1998; **150:** 357–64.

25 Little MP, Wakeford R, Bouffler SD, et al. Review of the risk of cancer following low and moderate doses of sparsely ionising radiation received in early life in groups with individually estimated doses. *Environ Int* 2022; **159:** 106983.

26 Brenner AV, Sugiyama H, Preston DL, et al. Radiation risk of central nervous system tumors in the life span study of atomic bomb survivors, 1958-2009. *Eur J Epidemiol* 2020; **35:** 591–600.

27 National Council on Radiation Protection and Measurements. Uncertainties in the estimation of radiation risks and probability of disease causation: report number 171. 2012. https://ncrponline.org/shop/reports/report-no-171-uncertainties-in-the-estimation-of-radiation-risks-and-probability-of-disease-causation/ (accessed Nov 22, 2022).

28 Zumel-Marne A, Kundi M, Castaño-Vinyals G, et al. Clinical presentation of young people (10-24 years old) with brain tumors: results from the international MOBI-Kids study. *J Neurooncol* 2020; **147:** 427–40.

29 Brasme JF, Morfouace M, Grill J, et al. Delays in diagnosis of paediatric cancers: a systematic review and comparison with expert testimony in lawsuits. *Lancet Oncol* 2012; **13:** e445–59.

30 Little MP, Patel A, Lee C, Hauptmann M, Gonzalez AB, Albert P. Impact of reverse causation on cancer risk estimates associated with radiation exposure from computerized tomography exposure: a simulation study modeled on brain tumor. *Am J Epidemiol* 2021; **191:** 173–81.

31 Meulepas JM, Hauptmann M, Lubin JH, Shuryak I, Brenner DJ. Is there unmeasured indication bias in radiation-related cancer risk estimates from studies of computed tomography? *Radiat Res* 2018; **189:** 128–35.

32 Meulepas JM, Ronckers CM, Merks J, Weijerman ME, Lubin JH, Hauptmann M. 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:** 953–74.

33 Kwan ML, Miglioretti DL, Bowles EJA, et al. Quantifying cancer risk from exposures to medical imaging in the Risk of Pediatric and Adolescent Cancer Associated with Medical Imaging (RIC) Study: research methods and cohort profile. *Cancer Causes Control* 2022; **33:** 711–26.

34 Hauptmann M, Daniels RD, Cardis E, et al. epidemiological studies of low-dose ionizing radiation and cancer: summary bias assessment and meta-analysis. *J Natl Cancer Inst Monogr* 2020; **2020:** 188–200.

35 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:** 700–07.