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Cohort Profile

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Cohort Profile: the EPI-CT study: a European pooled epidemiological study to quantify the risk of radiation-induced cancer from paediatric CT

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Why was the cohort set up?

Medical diagnostic examinations, although delivering low doses of ionizing radiation, are the main man-made source of ionizing radiation exposure for the general population. The number of procedures performed has grown dramatically in high-income countries in recent decades.[1] Among

these examinations, the use of computed tomography (CT), a highly informative medical imaging technique, has dramatically increased, partly as a result of the ease and speed of image acquisition improvements over the years. These trends are also observed in paediatric CT, which currently represents approximately 11% of all CT examinations.[1]

CT results in much higher doses of ionizing radiation than conventional radiography. CT represents 5% to 10% of all imaging procedures, but 40% to 70% of the collective medical dose.[1,2] There are concerns about potential health impacts of the radiation exposure from these procedures, particularly cancer in exposed paediatric patients. According to the epidemiological results from A-bomb survivors and from patients undergoing radiotherapy and/or radiological examinations, exposure to ionizing radiation at a young age is associated with a higher relative risk of several forms of cancer than exposure later in life.[3] Moreover, children have a longer life expectancy than adults, and hence a longer time in which to express radiation-induced cancers.

Increased cancer risk has been reported after medical diagnostic procedures associated with much higher doses than those reported nowadays.[4,5] However, recent epidemiological studies, focusing on CT exposure during childhood or early adulthood, have also reported increased risks of central nervous system (CNS) tumours, leukaemia and other cancer types in relation to CT doses.[6–12] The causal interpretation of some of these results has been questioned because of the lack of individual dose reconstruction, small sample size and potential methodological biases linked to confounding by indication and reverse causation.[13,14]

Because the risk associated with low doses is estimated to be small,[1] only large studies can achieve adequate statistical power to quantify this risk accurately. The international 'EPIdemiological study to quantify risks for paediatric Computerized Tomography and to optimize doses' (EPI-CT) was set up in 2011 to provide an estimation of the radiation-related risks of cancer after CT exposure in childhood and adolescence. The study is coordinated by the International Agency for Research on Cancer (IARC) and partially funded by the European Community. This European collaborative study pools nine European national cohorts. It takes advantage of pre-existing cohorts from three countries (France, Germany and the UK, all of which were extended as part of this study) and of new studies in six countries, based on a common core protocol[15] including a specific effort to provide individual organ dose estimation for the subjects in the cohort.[16] The EPI-CT study comprises four main parts: an epidemiological cohort study assessing cancer risks following radiation exposure from CT; a dose-reconstruction model to estimate organ doses with associated uncertainties for each individual in the cohort; a pilot study regarding biological mechanisms involved[17]; and recommendations for optimization of paediatric CT protocols.

Who is in the cohort?

EPI-CT is a retrospective European multinational cohort of children and young adults subjected to CT at least once before the age of 22 years, and who have not been diagnosed with cancer either before or at the time of the first recorded CT nor within 1 year after it. The study aimed to establish or expand existing cohorts in the following countries: Belgium, Denmark, France, Germany, The Netherlands, Norway, Spain, Sweden and the UK (Table 1). Patients were identified from the electronic records of the participating hospitals, which were mainly large paediatric hospitals or hospitals with a large paediatric patient population. Ethical agreements were obtained in each country before data collection. The study protocol[15] and detailed procedures adopted by each country are described elsewhere.[6,9,10,12,18]

Of the 1 170 186 patients for whom information was collected, 948 174 (81%) had a follow-up of at least 1 year after the first recorded CT and had no previous cancer recorded in the cancer registry (Table 1). Table 2 summarizes the number and characteristics of patients included in EPI-CT by country. There were slightly more males (56%) than females in the cohort. The median age at the first recorded CT varied between countries, reflecting differences in the age range inclusion criteria. The main age range was 0–21 years, but the age range was restricted to 0–9 and 0–14 years, respectively, in France and Germany because only paediatric and adolescent cancer registries are available at the national level in these countries. Accordingly, the median age at first exposure was lower, 2.9 years and 6.8, respectively, in France and Germany, compared with 10.7 years for the whole cohort.

How often have they been followed up?

Follow-up started at the date of the first recorded CT and ended at the earliest of: date of death; date of cancer diagnosis; or end of follow-up at the regional/national level. Cancer diagnoses and deaths were obtained through linkage with national or regional cancer registries, mortality registries and other available national/regional registries, depending on the country (Table 1). The follow-up period for cancer incidence ends usually 1 to 3 years before mortality follow-up, due to the delay in reporting cancer cases

Table 1. Description of the selection criteria and available data in the participating countries

	Belgium	Denmark	France	Germany	The Netherlands	Norway	Spain	Sweden	UK	Total
Age range of patients at inclusion, years	0 to 18	0 to 18	0 to 9	0 to 14	0 to 17	0 to 20	0 to 20	0 to 17	0 to 21	0 to 21
Number of eligible patients at national level[a]	14 002	21 649	121 101	63 998	158 130	80 225	171 336	128 748	410 997	1 170 186
Exclusion criteria										
Inconsistent/incomplete data[c]	404	12						4	111	531
Out of age range		517				15		164	34	730
No CT in the follow-up period	2083	507	7	5222	78	286	11 778	2223	4697	26 881
No cancer follow-up							60 860[d]		51 837	112 697
Follow-up less than 1 year	1074	1666	1611	6607	3962	1103	12 072	1564	16 973	46 632
Cancer diagnosed within 1 year after first CT	367	1251	84[e]	5073	5955	1569	2034	2988	15 220	34 541
Number of patients included in the international cohort[b]	10 074	17 696	119 399	47 096	148 135	77 252	84 592	121 805	322 125	948 174

[a]Initial number of patients included (before application of exclusion criteria).
[b]Final number of eligible patients.
[c]Errors in date of birth, unknown date of cancer diagnosis.
[d]In progress.
[e]Exclusion of patients with diagnosis of cancer within the first 6 months of follow-up at national level before sending the data for the pooled analysis.

Table 2. Distribution of study subjects by sex, country and age at the first CT examination

	Belgium	Denmark	France	Germany	The Netherlands	Norway	Spain	Sweden	UK	Total
Sex, *n* (%)										
Male	5292 (52.5)	9836 (55.6)	69 544 (58.2)	27 617 (58.6)	79 897 (53.9)	42 452 (55.0)	47 813 (56.5)	66 773 (54.8)	180 953 (56.4)	530 177 (55.9)
Female	4782 (47.5)	7860 (44.4)	49 855 (41.8)	19 428 (41.3)	68 218 (46.1)	34 800 (45.0)	36 779 (43.5)	55 032 (45.2)	139 680 (43.6)	416 434 (43.8)
Unknown				51 (0.1)	20 (0)				1492 (0.5)	1563 (0.2)
Median (mean) age, in years, at first examination										
Median (mean)	11.5 (10.4)	12.9 (11.3)	2.9 (3.5)	6.8 (6.8)	11.5 (10.3)	14.5 (12.8)	13.5 (12.0)	11.3 (10.3)	13.5 (12.0)	10.7 (10.2)
Age at first CT examination, *n* (%)										
<1 year	831 (8.2)	1340 (7.6)	34 732 (29.1)	5590 (11.9)	13 752 (9.3)	4118 (5.3)	6377 (7.5)	9723 (8.0)	32 873 (10.2)	10 933 (11.5)
1 to 4 years	1717 (17.0)	2262 (12.8)	47 056 (39.4)	12 938 (27.5)	21 034 (14.2)	7291 (9.4)	10 949 (12.9)	15 754 (12.9)	42 128 (13.1)	161 129 (17.0)
5 to 9 years	1824 (18.1)	2820 (15.9)	37 611 (31.5)	14 171 (30.1)	28 997 (19.6)	11 156 (14.4)	13 216 (15.6)	26 600 (21.8)	43 515 (13.5)	179 910 (19.0)
10 to 19 years	5702 (56.6)	11 274 (63.7)		14 397 (30.6)	84 352 (56.9)	51 074 (66.1)	47 576 (56.2)	69 728 (57.2)	158 637 (49.2)	442 740 (46.7)
>= 20 years						3613 (4.7)	6474 (7.7)		44 972 (14.0)	55 059 (5.8)
Total by country	10 074	17 696	119 399	47 096	148 135	77 252	84 592	121 805	322 125	948 174

in cancer registries. In two countries, vital status was partially (France) or completely (Germany) unavailable.

The earliest year of first recorded CT varied between 1977 in Sweden and 2001 in Belgium, and depended on the availability of data, i.e. complete cancer registration to exclude ineligible patients and electronic radiological information. Cancer incidence follow-up ended in 2014 in The Netherlands and Sweden, and between 2010 and 2013 in all other countries (Table 3). Median duration of incidence follow-up was 7.8 years for the whole cohort, ranging from 4.1 years in Belgium to 11.3 years in the UK (Table 3). The total incidence follow-up accounted for more than 8.7 million person-years (PY). The largest cohorts in terms of PYs were the UK (3.7 million PY), the Dutch (1.5 million PY) and the Swedish cohorts (1.4 million PY), due to the large number of children included but also due to the long follow-up. Only 1.3% of the participants had died by the end of follow-up. The median age at the end of follow-up ranged from 9.4 years in France to 24 years in the UK.

What has been measured?

For each individual CT, all computerized data were retrieved from the Radiological Information System (RIS) of the radiology department in participating hospitals. This includes patient-identifying information, patient sex, date of birth and basic variables about the examination (body part scanned, examination date and, in certain instances, indication for CT and referring hospital service). For more recent time periods, estimation of doses took advantage of data from the Picture Archiving and Communication System (PACS) (a system for storage, retrieval and distribution of images). The time periods when PACS data were available, together with the percentage of CT dosimetric data extracted from PACS for each country, are presented in Table 4. The percentage of data originating from the PACS system, extracted through a dedicated software tool (PerMoS,[19] used to automatically collect technical parameters of each scan from the header of the image in PACS), differed between the countries since the system was only implemented relatively recently in hospitals and not all participating hospitals were willing to query their PACS in addition to RIS.

From a combination of PACS data and information on radiological protocols used in the participating hospitals, individual doses to specific relevant organs, including red bone marrow and brain for respectively leukaemia and CNS cancer risk estimation, were then estimated for each CT scan for each child, using National Cancer Institute Dosimetry System for CT (NCICT) software[20] and taking into account uncertainties in dose estimates.[16] The dose

Table 3. Follow-up of the cohort

	Belgium	Denmark	France	Germany	The Netherlands	Norway	Spain	Sweden	UK	Total
Mortality follow-up period	2001 to 2015	1999 to 2015	2000 to 2013		1979 to 2015	1980 to 2013	1991 to 2014	1977 to 2014	1985 to 2015	1977 to 2015
Total of person-years	66 002	138 046	458 298	0	1 620 981	614 360	607 557	1 396 397	4 186 666	9 088 308
Vital status, *n* (%)										
Alive	10 033 (99.6)	17 413 (98.4)	75 483 (63.2)	0 (0)	146 910 (99.2)	76 109 (98.5)	84 199 (99.5)	116 276 (95.5)	307 826 (95.6)	834 249 (88.0)
Deceased	41 (0.4)	134 (0.8)	558 (0.5)	0 (0)	1225 (0.8)	673 (0.9)	393 (0.5)	1568 (1.3)	7565 (2.3)	12 157 (1.3)
Lost to follow-up	0 (0)	149 (0.8)	0 (0)	0 (0)	0 (0)	470 (0.6)	0 (0)	3961 (3.3)	6734 (2.1)	11 314 (1.2)
Unavailable	0 (0)	0 (0)	43 358 (36.3)	47 096 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	90 454 (9.5)
Cancer incidence follow-up period[a]	2001 to 2012	1999 to 2013	2000 to 2013	1980 to 2010	1979 to 2014	1980 to 2012	1991 to 2013	1977 to 2014	1985 to 2013	1977 to 2014
Median (mean) age at end of follow-up (years)	16.2 (15.1)	18.1 (17.1)	9.4 (9.3)	14.2 (12.2)	20.1 (20.4)	21.2 (20.8)	18.4 (17.3)	21.7 (21.7)	24.0 (23.6)	19.5 (19.5)
Median duration of (mean) follow-up	4.1 (4.7)	5.3 (5.8)	5.4 (5.7)	4.7 (5.4)	8.2 (10.2)	6.8 (7.9)	4.8 (5.3)	10.3 (11.4)	11.3 (11.6)	7.8 (9.3)
Total of person-years	47 815	102 657	685 333	252 970	1 506 728	613 390	448 475	1 393 454	3 720 888	8 771 710

[a]Shorter follow-up period for cancer incidence compared with mortality follow-up period is linked to the delay of cancer registries in reporting cancer cases (availability of cancer cases 1 to 3 years after the cancer diagnosis date).

Table 4. Number of CT scans received by child

Period with available PACS data (% of CT[a])										
	Belgium 2001 to 2004 (68)	Denmark 2005 to 2013 (10)	France 2003 to 2014 (10)	Germany 1995 to 2013 (95)	The Netherlands 1991 to 2014 (48)	Norway 2000 to 2014 (37)	Spain 2000 to 2015 (64)	Sweden 1998 to 2014 (9)	UK 2000 to 2014 (17)	Total 1991 to 2015 (25)
No. of scans performed per child (%)										
1 scan	7788 (77.3)	11 531 (65.2)	92 841 (77.8)	35 529 (75.4)	113 272 (76.5)	50 779 (65.7)	65 765 (77.7)	89 931 (73.8)	247 424 (76.8)	714 860 (75.4)
2 scans	1465 (14.5)	3125 (17.7)	15 929 (13.3)	6652 (14.1)	21 576 (14.6)	14 073 (18.2)	11 722 (13.9)	19 460 (16.0)	45 825 (14.2)	139 827 (14.7)
3 scans	410 (4.1)	1284 (7.3)	5300 (4.4)	2258 (4.8)	6458 (4.4)	5000 (6.5)	3451 (4.1)	5835 (4.8)	13 478 (4.2)	43 474 (4.6)
4 scans+	411 (4.1)	1756 (9.9)	5329 (4.5)	2657 (5.6)	6829 (4.6)	7400 (9.6)	3654 (4.3)	6579 (5.4)	15 398 (4.8)	50 013 (5.3)
Total	10 074	17 696	119 399	47 096	148 135	77 252	84 592	121 805	322 125	948 174

[a]Proportion of CTs extracted from PACS of all CTs.

reconstruction strategy which has been implemented allows accounting for missing data. Doses were therefore reconstructed for all examinations, but estimated doses were associated with large uncertainties when examinations were poorly characterized in the RIS data file, including missing information on the anatomical zone scanned. The total number of CT scans collected within the study was 1 430 454. The mean number of CT scans per patient was 1.5. The majority of patients (75%) received a single recorded CT scan (Table 4), and only 0.2% of them received more than 10 scans. The percentages of scans recorded before and after the year 2000 were 22% and 78%, respectively. Table 5 reports the distribution of CT according to the anatomical area explored. The main areas examined were 'head and neck', ranging from 49.5% in Denmark to 72.1% in Belgium, followed by 'chest'. accounting for 8.4% in Sweden to 19.3% in France. Scans of multiple body parts represented 4.9% of the total number of CT scans. Those without anatomical area mentioned represented 2.9% of all collected CT, with large discrepancies between countries reflecting the variability of data storage at hospital level.

Further information on underlying diseases was also collected from various sources including hospital diagnostic or discharge databases and rare diseases registries (in France, The Netherlands, Norway, Spain and Sweden). Socioeconomic status (SES), a potential confounder, was obtained from national census data by postal code or census track for Belgium, France, The Netherlands, Spain and the UK and from the National Education registry in Denmark, Norway and Sweden.

What has been found? Key findings and publications

Standardized Mortality Ratios (SMRs), as the ratio of observed and expected number of deaths based on national reference rates, were calculated for the eight countries for which vital status was available, using a 1-year exclusion period. Results are presented (Table 6) for two distinct periods of follow-up after the first CT: years 2 to 5 and 5 years and beyond. The percentage of deaths varied from 0.5% in Belgium to 2.6% in the UK for the whole study period. Even though the death rates were low, we observed strongly elevated SMRs in all countries, especially in the first 5 years following the first CT (Table 6). The SMRs for all-cause mortality during the 5 years following the first CT were statistically significant and greater than 1 in all countries, varying from 1.9 in Belgium to 4.9 in Denmark, France and the UK. For the time period greater than 5 years after the first CT, the SMR decreased but remained significantly raised, in all countries except Belgium and

Table 5. Distribution of CT scans according to age, calendar period and scanned region by countries

	Belgium	Denmark	France	Germany	The Netherlands	Norway	Spain	Sweden	UK	Total
Category of age at CT, *n* (%)										
0 to 4 years	3457 (24.3)	6127 (18.6)	115 857 (67.5)	27 031 (37.8)	51 127 (23.5)	18 767 (13.4)	24 754 (20.4)	37 223 (20.1)	112 135 (23.6)	396 478 (27.7)
5 to 9 years	2486 (17.5)	5422 (16.4)	55 794 (32.5)	22 011 (30.8)	42 157 (19.4)	17 988 (12.9)	18 630 (15.4)	37 547 (20.2)	66 702 (14.0)	268 737 (18.8)
10 to 14 years	3554 (25.0)	9498 (28.8)	45 (0)	22 517 (31.5)	61 985 (28.5)	29 527 (21.2)	25 597 (21.1)	59 665 (32.2)	95 744 (20.1)	308 132 (21.5)
>= 15	4707 (33.1)	11 959 (36.2)	0	0	62 530 (28.7)	73 281 (52.5)	52 132 (43.0)	51 025 (27.5)	201 473 (42.3)	457 107 (32.0)
Number of scans by calendar period, *n* (%)										
Before 1985	0	0	0	77 (0.1)	3377 (1.6)	703 (0.5)	0	1244 (0.7)	0	5401 (0.4)
1985 to 1999	0	11 (0)	0	15 414 (21.5)	45 539 (20.9)	18 843 (13.5)	2236 (1.8)	48 905 (26.4)	177 118 (37.2)	308 066 (21.5)
2000 to 2009	10 174 (71.6)	20 514 (62.2)	130 676 (76.1)	55 178 (77.1)	112 675 (51.7)	95 336 (68.3)	81 529 (67.3)	101 159 (54.5)	252 552 (53.1)	859 793 (60.1)
>= 2010	4030 (28.4)	12 481 (37.8)	41 020 (23.9)	890 (1.2)	56 208 (25.8)	24 681 (17.7)	37 348 (30.8)	34 152 (18.4)	46 384 (9.7)	257 194 (18.0)
Number of scans by anatomical region, *n* (%)										
Head and neck	10 248 (72.1)	16 332 (49.5)	117 458 (68.4)	50 854 (71.1)	152 690 (70.1)	80 562 (57.7)	77 082 (63.6)	118 684 (64.0)	319 430 (67.1)	943 340 (65.9)
Chest	1298 (9.1)	4342 (13.2)	33 108 (19.3)	8225 (11.5)	18 543 (8.5)	19 132 (13.7)	11 148 (9.2)	15 529 (8.4)	40 244 (8.5)	151 569 (10.6)
Abdomen and pelvis (%)	1820 (12.8)	5356 (16.2)	8329 (4.9)	4042 (5.6)	21 231 (9.7)	27 396 (19.6)	5965 (4.9)	31 130 (16.8)	45 037 (9.5)	150 306 (10.5)
Extremities (%)	664 (4.7)	3364 (10.2)	2590 (1.5)	2589 (3.6)	16 719 (7.7)	9784 (7.0)	6379 (5.3)	8221 (4.4)	23 160 (4.9)	73 470 (5.1)
Multiple (%)	139 (1.0)	3269 (9.9)	8592 (5.0)	3716 (5.2)	5880 (2.7)	2342 (1.7)	8166 (6.7)	7559 (4.1)	30 184 (6.3)	69 847 (4.9)
Not classified	35 (0.2)	343 (1.0)	1619 (0.9)	2133 (3.0)	2736 (1.3)	347 (0.2)	12 373 (10.2)	4337 (2.3)	17 999 (3.8)	41 922 (2.9)
Total	14 204	33 006	171 696	71 559	217 799	139 563	121 113	185 460	476 054	1 430 454

Table 6. SMRs of all cause, cancer and non-cancer mortality according to the time since the first CT (<5 years; >= 5 years)

	Time since first CT recorded													
		1-5 years						>5 years						
		All causes mortality		All cancer mortality		Non-cancer mortality			All causes mortality		All cancer mortality		Non-cancer mortality	
	PY	O	SMR (95% CI)	O	SMR (95% CI)	O	SMR (95% CI)	PY	O	SMR (95% CI)	O	SMR (95% CI)	O	SMR (95% CI)
Belgium	48 125	26	1.9 (1.2, 2.8)		-		-	53 387	22	1.4 (0.9, 2.2)		-		-
Denmark	84 443	101	4.9 (4.0, 5.9)		-		-	120 984	73	2.4 (1.9, 3.1)		-		-
France	322 247	474	4.9 (4.4, 5.3)	25	3.5 (2.3, 5.1)	357	4.0 (3.6, 4.4)	349 971	120	1.6 (1.3, 1.9)	6	0.8 (0.3, 1.6)	79	1.1 (0.9, 1.4)
The Netherlands	693 933	692	3.7 (3.4, 3.9)		-		-	1 507 572	580	1.2 (1.1, 1.3)		-		-
Norway	334 723	332	2.8 (2.5, 3.1)	14	1.3 (0.7, 2.2)	296	2.7 (2.4, 3.0)	535 107	416	1.8 (1.6, 2.0)	28	1.1 (0.7, 1.5)	331	1.6 (1.5, 1.8)
Spain	391 219	361	3.4 (3.1, 3.8)	89	6.1 (4.9, 7.5)	272	3.0 (2.6, 3.4)	521 598	167	1.1 (1.0, 1.3)	19	0.9 (0.5, 1.3)	148	1.2 (1.0, 1.4)
Sweden	573 367	506	3.3 (3.0, 3.6)	58	3.3 (2.5, 4.3)	446	3.3 (3.0, 3.6)	1 318 489	1062	2.3 (2.2, 2.4)	85	1.3 (1.1, 1.7)	975	2.4 (2.3, 2.6)
UK	1 563 679	3068	4.9 (4.8, 5.1)	177	3.0 (2.5, 3.4)	2286	4.1 (3.9, 4.3)	4 059 802	5233	2.7 (2.6, 2.7)	326	1.1 (1.0, 1.2)	4200	2.5 (2.4, 2.6)
Pooled	4 011 736	5560	4.2 (4.1, 4.3)	363	3.3 (3.0, 3.7)	3657	3.7 (3.6, 3.8)	8 466 910	7673	2.2 (2.2, 2.3)	464	1.1 (1.0, 1.2)	5733	2.3 (2.3, 2.4)

PYs, person-years of follow-up; O, observed cases within the cohort; SMR, standardized mortality ratio; 95% CI, 95% confidence interval; -, cause of death unknown.

Spain. Cancer mortality decreased to the level of the general population when time since first exposure exceeded 5 years, except in Sweden [SMR = 1.3, 95% confidence interval (CI) 1.1, 1.6). However, non-cancer SMRs remained significantly increased when considering time since exposure greater than 5 years, except in France and Spain. These results illustrate the fact that, as expected, our study population was less healthy than the general population. Indeed, children undergoing CT, particularly those with repeated scans, are likely to suffer conditions that could be associated with increased mortality. The observed decrease of SMR for cancer when considering time since first CT greater than 5 years confirms the need to apply exclusion periods in the statistical analyses to avoid reverse causation (i.e. the CT was performed because of a suspicion of cancer). Various exclusion periods will be examined in the main risk analyses. Detailed dose-response analyses for cancer incidence will be presented in later papers.

A summary of published results from national EPI-CT cohorts is provided in Table 7. Four national cohorts (the UK, France, Germany and The Netherlands) have published analyses of the relationship between CT exposure and cancer incidence. The British study reported a dose-response relationship between CT-related dose and CNS tumours and leukaemia in exposed children and young adults,[6,21] but not for Hodgkin lymphoma.[22] The German study reported a significantly increased incidence of cancer and lymphoma in exposed children compared with the general population.[9] Both the French and the German studies, based on small numbers of cases, reported a dose-related increase for leukaemia and CNS tumours, though it was statistically significant only for CNS tumours in Germany.[9–11] The Dutch study reported a dose-response relationship for cranial CNS tumours and found no association with leukaemia.[12]

Reverse causation bias has been considered by applying various exclusion periods for cancer risk analyses. Exclusion periods allowed accounting for individuals who were potentially scanned because of a suspicion of leukaemia (although CT generally is not required for the initial diagnosis of leukaemia) or CNS tumours. Extending the exclusion period from 5 to 10 years for CNS tumours in the British study did not decrease the dose-risk estimates, as would be expected in case of reverse causation bias.[6]

Potential confounding by indication for CT, meaning that children requiring CT may be at risk of cancer because of an underlying condition, has been handled in different manners in these studies. In the British study, an analysis published in 2016 took into account clinical information available in the RIS for 40% of the cohort and death certificates, to evaluate this potential bias.[21] This resulted in a slightly decreased, but still significant, dose-related

Table 7. Results from EPI-CT national cohorts

Outcome by country	Cases	Risk estimates		(IC 95%)
CNS tumour risk according to the brain dose				
UK[a] (Pearce *et al.*, 2012)	135[b]	ERR per mGy	0.023	(0.010, 0.049)
UK[a] (Berrington *et al.*, 2016)	122[b] without PF	ERR per mGy	0.019	(0.008, 0.043)
France (Journy *et al.*, 2015)	22	ERR per mGy	0.022	(−0.016, 0.061)
The Netherlands (Meulepas *et al.*, 2018)	84	ERR per mGy	0.0086	(0.0020, 0.022)
Germany (Krille *et al.*, 2015)	7	HR per mGy	1.008	(1.00, 1.01)
France (Journy *et al.*, 2016)	15 without PF	HR per 10 mGy	1.07	(0.99, 1.10)
	7 with PF	HR per 10 mGy	0.8	(0.45, 1.06)
UK[a] (Pearce *et al.*, 2012)	135[b]	RR [50-74 mGy] vs <5 mGy	2.82	(1.34, 6.03)
Leukaemia risk according to RBM dose				
UK[a] (Pearce *et al.*, 2012)	74	ERR per mGy (RBM dose)	0.036	(0.005, 0.120)
France (Journy *et al.*, 2015)	17	ERR per mGy	0.057	(−0.079, 0.193)
The Netherlands (Meulepas *et al.*, 2018)	44	ERR per mGy	0.0004	(−0.0012, 0.016)
UK[a] (Berrington *et al.*, 2016)	70 without PF	ERR per mGy	0.037	(0.005, 0.126)
France (Journy *et al.*, 2016)	12 without PF	HR per 10 mGy	1.16	(0.77, 1.27)
France (Journy *et al.*, 2016)	5 with PF	HR per 10 mGy	0.57	(0.06, 1.32)
Germany (Krille *et al.*, 2015)	17	HR per mGy	1.009	(0.98, 1.04)
UK (Pearce *et al.*, 2012)	74	RR [>30 mGy] vs <5 mGy	3.18	(1.46, 6.94)
Lymphoma risk according to RBM dose				
France (Journy *et al.*, 2015)	19	ERR per mGy	0.018	(−0.068, 0.104)
UK[a] (Berrington *et al.*, 2017)	65[c]	RR [>20] vs <5 mGy	0.92	(0.22, 2.94)

CNS, central nervous system; PF, predisposing factor; RBM, red bone marrow; ERR, excess relative risk; RR, relative risk; HR, hazard ratio; mGy, milligray.
[a]Follow-up period until 2005 only.
[b]Exclusion period 5 years instead of 2 years.
[c]Hodgkin lymphoma only.

increased risk for CNS tumours. Exclusion of previously unreported cancers reduced the Excess Relative Risk (ERR) per mGy by 15% from 0.036 to 0.033 for leukaemia and by 30% from 0.023 to 0.016 for CNS tumours, but these ERRs remained statistically significantly elevated. In the French cohort, using reliable information on predisposing factors (PF) for cancer from hospital discharge registries, 3% of the subjects were found to have a PF for CNS tumours and/or leukaemia.[10] This small percentage of individuals with PF was nevertheless much larger than expected in the general population.[23] Separate analyses showed a dose-related increase of leukaemia and CNS tumours in children with no PFs, whereas there was no evidence of an increase in those with PFs.[11] The difference in radiation-related risks observed according to the presence of PFs might be explained by much higher mortality risks in patients having PFs compared to children without PFs. Furthermore, Meulepas *et al.* calculated the magnitude of predisposing syndrome-related confounding of relative risk (RR) estimates for leukaemia and CNS tumours after diagnostic CT, under various assumptions for the association between predisposing syndromes and the frequency of CT. They concluded that these syndromes were unlikely to cause meaningful confounding as they were too , and CT frequency was only moderately elevated among these subjects.[24]

What are the main strengths and weaknesses?

With about 950 000 children included in the study, it has been calculated[14] that the EPI-CT study has sufficient statistical power to detect even small excess cancer risks in this first follow-up period, at least for leukaemia and CNS cancer. It will provide new insights into the potential cancer risk from CT exposure during childhood, allowing the study of specific issues such as effect of age at exposure, sex, exclusion period and cancer site, particularly as the population ages and further follow-up is conducted. The coordinated international analyses in EPI-CT not only increase statistical power, but also improve capacity to compare and contrast results from different countries while minimizing methodological differences, thanks to a common protocol.

Within EPI-CT, major efforts were devoted to the estimation of individualized organ doses for each scan. Details are provided in the article presenting the dosimetry reconstruction for the cohort.[15] Briefly, exposure-related data were extracted from the RIS and, for more recent time periods, from the PACS of participating hospitals, allowing examination-specific dose reconstructions. The implemented approach[15] allows quantification of uncertainties in doses due to missing data and produces a range of potential doses for each CT scan, each set suitable for use in a

dose-response as a surrogate of the true doses. Each missing parameter is represented by a probability density function (PDF) representative of the state of knowledge for the time period. For each calculation of the cohort dose set, values of parameters are selected from the appropriate PDFs while maintaining proper correlations between parameters. Recoding all examination types into one common classification, and centralized calculation of organ doses using the software NCI-CT[20] with appropriately sized phantoms for paediatric age categories, allowed a good standardization of the process. Apart from the use of doses for the main risk analysis, EPI-CT also provides the basis for a large and useful characterization of doses from CT in children in Europe, where previously only sparse information was available.

A limitation of the study is the inability to contact almost one million individuals to collect more precise information on potential confounders such as underlying predisposing conditions, other medical radiation procedures performed in the hospital (nuclear medicine procedures, other X-rays) or outside the participating hospitals. Indication for CT is also not routinely recorded, and few countries have electronic medical record systems that could provide this information for a retrospective cohort of this type. Simulation studies, based on scenarios of expected range of potential confounders based on information available in some of the participating countries or regions, will be performed to provide information on the likelihood of missing data in the risks estimates. Sensitivity analyses will be performed on cohorts with information on potential confounders to provide a basis for adjusting risk estimates. Nested case-control studies are also being conducted in several countries [http://www.medirad-project.eu/] to allow collection of data on other radiation procedures, missing scans, predisposing factors and other potential confounders of the relation between CT dose and leukaemia and CNS tumour risks.

Another limitation of the EPI-CT project is that the cohort is still relatively young, whereas many solid cancers (and non-cancer diseases) are more frequent at older ages. Further long-term follow-up of this important cohort will provide additional information and will allow a more precise quantification of the effects of exposure on different outcomes, as well as on the possible modifying effects of age at exposure and attained age on estimated risks. Supplementary funding should be provided to allow the long-term follow-up. Additional follow-up is currently under way in five of the largest countries with funding from the European Union within the MEDIRAD project [http://www.medirad-project.eu]. Funds will be sought in other countries to update the follow-up of the other cohorts in the coming years.

Can I get hold of the data? Where can I find out more?

Study data are not freely available because of ethical and data protection constraints. The anonymized data are stored at the IARC and cannot be sent outside the Agency. Proposals for possible collaborations in further analyses of the data should be addressed to Dr Ausrele Kesminiene [KesmienieneA@visitors.iarc.fr] and will be reviewed by the EPI-CT steering committee.

Profile in a nutshell

- The multinational EPI-CT study was set up in 2011 to provide direct estimates of risk of solid tumours and leukaemia among children and young adults who had undergone computed tomography (CT), and to consolidate the scientific basis for optimization of paediatric CT protocols and patient protection.
- Under a common protocol, cohort studies were conducted in Belgium, Denmark, France, Germany, The Netherlands, Norway, Spain, Sweden and the UK, coordinated by the International Agency for Research on Cancer (IARC).
- The study recruited a total of about 950 000 patients who had undergone CT at least once before the age of 22 years. A total of 8.7 million person-years of incidence follow-up were accrued between 1977 and 2014. Cohort members were followed up passively through linkage with population-based cancer and mortality registries. A methodology was developed to reconstruct individual organ doses and estimate associated uncertainties, using data available in electronic archiving systems of the radiology departments of participating hospitals. Description of the cohort and analysis of mortality risk are presented here.
- Proposals for possible collaboration in further analyses of the data should be addressed to Dr Ausrele Kesminiene [KesmienieneA@visitors.iarc.fr] and will be reviewed by the EPI-CT steering committee.

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