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Radiation exposure from computerized tomography and risk of childhood leukemia: Finnish register-based case-control study of childhood leukemia (FRECCLE)

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ABSTRACT

The only well-established risk factors for childhood leukemia are high-dose ionizing radiation and Down syndrome. Computerized tomography is a common source of low-dose radiation. In this study, we examined the magnitude of the risk of childhood leukemia after pediatric computed tomography examinations. We evaluated the association of computed tomography scans with risk of childhood leukemia in a nationwide register-based case-control study. Cases (n=1,093) were identified from the population-based Finnish Cancer Registry and three controls, matched by gender and age, were randomly selected for each case from the Population Registry. Information was also obtained on birth weight, maternal smoking, parental socioeconomic status and background gamma radiation. Data on computed tomography scans were collected from the ten largest hospitals in Finland, covering approximately 87% of all pediatric computed tomography scans. Red bone marrow doses were estimated with NCICT dose calculation software. The data were analyzed using exact conditional logistic regression analysis. A total of 15 cases (1.4%) and ten controls (0.3%) had undergone one or more computed tomography scans, excluding a 2-year latency period. For one or more computed tomography scans, we observed an odds ratio of 2.82 (95% confidence interval: 1.05 – 7.56). Cumulative red bone marrow dose from computed tomography scans showed an excess odds ratio of 0.13 (95% confidence interval: 0.02 – 0.26) per mGy. Our results are consistent with the notion that even low doses of ionizing radiation observably increase the risk of childhood leukemia. However, the observed risk estimates are somewhat higher than those in earlier studies, probably due to random error, although unknown predisposing factors cannot be ruled out.

Introduction

Leukemia is the most common childhood malignancy.[1] The incidence rates of childhood leukemia in Finland are comparable to those in other European countries and show a slight increasing trend up to the 1990s.[2] Acute lymphoblastic leukemia accounts for approximately 85% of all childhood leukemias. The major histological subtype of acute lymphoblastic leukemia is precursor B-cell acute lymphoblastic leukemia (~85%).[1]

Well-established risk factors for childhood leukemia include high doses of ionizing radiation, alkylating chemotherapy agents, as well as Down syndrome and some rare congenital syndromes such as Fanconi anemia, Bloom syndrome and ataxia telangiectasia.[1,3-6] A number of genetic variants have also been associated

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with increased risk of leukemia.[7,8] Furthermore, there is reasonably consistent evidence of a slightly increased risk associated with large birth weight relative to gestational time.[9] A higher risk has also been suggested for older parental age, delivery by Cesarean section, and paternal smoking.[10–13] However, daycare attendance, allergic diseases, maternal folic acid supplementation before birth, and early immune stimulation have been suggested to reduce the risk of leukemia.[14–17]

Although high doses of ionizing radiation increase the risk of childhood leukemia, the magnitude of any effect from low doses remains uncertain. Some studies have suggested increased risks associated with background radiation and following x-ray examinations *in utero* and post-natally.[18–22] Computed tomography (CT) imaging has been used for almost four decades and its frequency of utilization increased greatly during the 1980s-1990s. The annual number of scans peaked around year 2002; more recently CT scans have been partly replaced by magnetic resonance imaging in pediatric imaging, partly because of the risk of cancer from ionizing radiation.[23] In 2015, 5,311 pediatric CT scans were performed in the Finnish population of 1,024,000 children under 17 years old, which is a low rate compared to that in many other countries.[23,24]

Four high-quality studies have investigated the association of pediatric CT scans and childhood leukemia.[25–28] The interpretation of the findings must include an evaluation of confounding by indication, i.e. underlying conditions predisposing children to both CT scans and leukemia.[28–30] Nevertheless, the evidence is still limited and the magnitude of the risk needs to be characterized further.

In this study, we examined the magnitude of the risk of childhood leukemia after pediatric CT examinations using a nationwide case-control design with efforts to avoid reverse causation.

Methods

We used a register-based, case-control study with individually matched controls. The key characteristics of the material have been presented previously.[10] Briefly, all cases of childhood leukemia (M9800–M9948 in ICD-O-3) diagnosed in Finland during 1990–2011 (n=1,100) before the age of 15 years were identified from the Finnish Cancer Registry (Figure 1). Three controls were individually matched, by sex and year of birth, for each case from the Population Register Center. In all analyses, a 2-

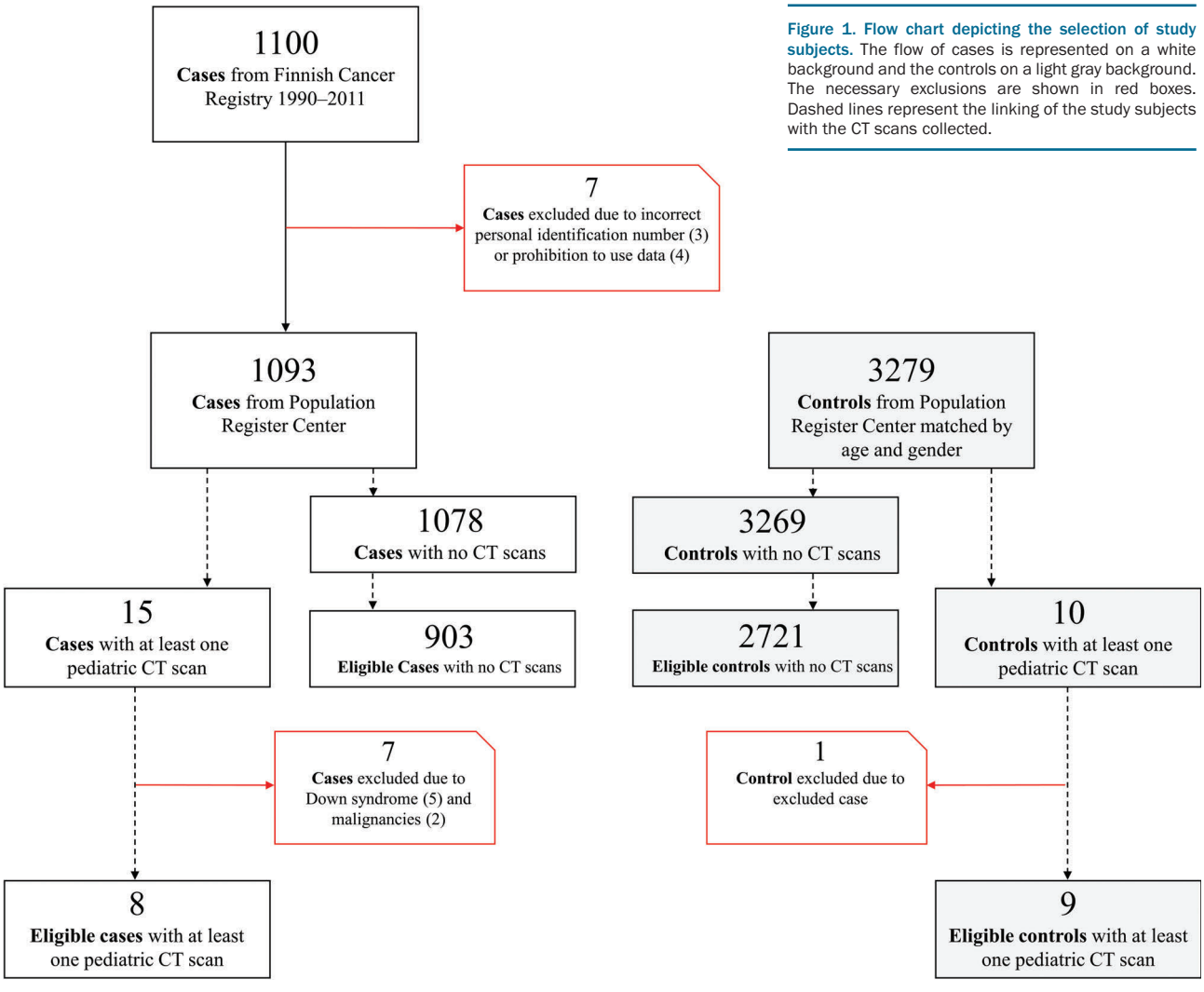

Figure 1. Flow chart depicting the selection of study subjects. The flow of cases is represented on a white background and the controls on a light gray background. The necessary exclusions are shown in red boxes. Dashed lines represent the linking of the study subjects with the CT scans collected.

year latency period was used, in part to deal with reverse causation due to confounding by indication.[31] Also, multiple predisposing factors (*Online Supplementary Table S1*) were accounted for with outpatient register data. The methods are described in more detail in the *Online Supplementary Material*.

We obtained data on all CT scans performed on pediatric patients (<15 years) from all five university hospitals and the five largest central hospitals in Finland (Table 1, Figure 2). The period of data availability varied between hospitals, because radiological databases with information on each CT scan for individual patients were introduced at different times. We estimated that the data from the study hospitals covered 87% of all pediatric CT scans performed in Finland during 1975–2011 (see the *Online Supplementary Material* for details). For each CT scan, we

Table 1. The collection and availability of electronically stored computed tomography scans.

Hospital	City	Data availability	Number of CT scans
Helsinki University Hospital	Helsinki	1990–2011	31,825
Tampere University Hospital	Tampere	1978–2011	9,236
Oulu University Hospital	Oulu	1993–2011	7,513
Turku University Hospital	Turku	1996–2011	7,360
Kuopio University Hospital	Kuopio	1996–2011	5,408
Central Finland Central Hospital	Jyväskylä	2002–2011	2,571
Satakunta Central Hospital	Pori	1995–2011	1,948
Seinäjoki Central Hospital	Seinäjoki	1999–2011	1,759
Päijänne Tavastia Central Hospital	Lahti	2000–2011	1,597
North Karelia Central Hospital	Joensuu	1993–2011	1,191
TOTAL			**80,783**

All Finnish university hospitals are listed first followed by the five chosen central hospitals.

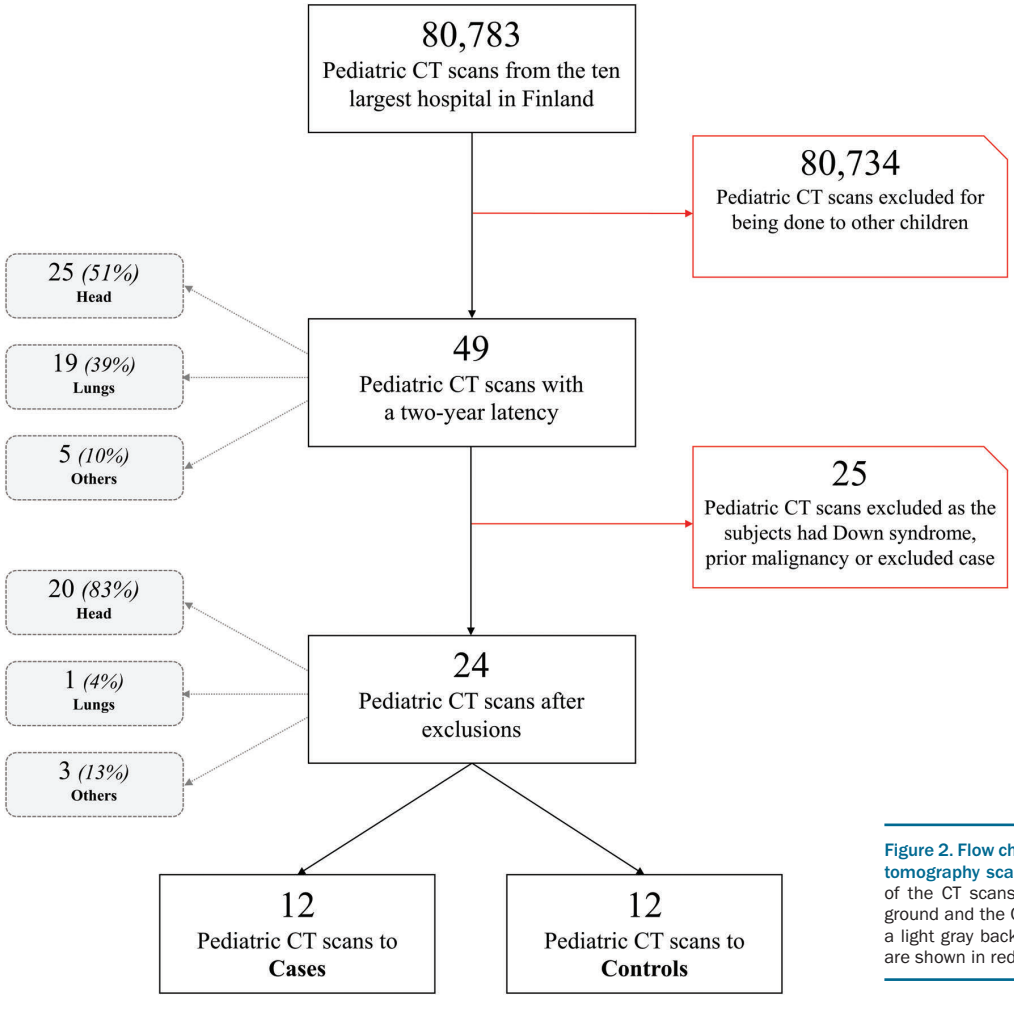

Figure 2. Flow chart linking the collected computed tomography scans to the study subjects The flow of the CT scans is represented on a white background and the CT scans to different body parts on a light gray background. The necessary exclusions are shown in red boxes.

obtained the parameters used for dose assessment including year, body part, use of contrast medium and the number of sequences. Manufacturers and models of CT scanners in each hospital were acquired from the Radiation and Nuclear Safety Authority (STUK). For dose calculations, we assumed in the main analysis that each CT scan was performed using the latest CT scanner available at the hospital.

Data on a total of 80,783 pediatric CT scans were obtained and of those, 49 CT scans were performed on the study subjects, excluding the 2-year latency period (Table 1). Half (n=25) were head scans, and 19 were lung scans. Of the CT scans, 36 were performed on 15 (1.4%) cases and 13 scans on 10 (0.3%) controls.

The CT scan parameters were obtained based on expert opinion of an experienced hospital physicist (*Online Supplementary Table S2*). The doses were estimated using the NCICT software (v1.2).[32] Age- and sex-specific pediatric software phantoms (for neonates, and children aged 1, 5, 10, and 15 years) were used. The input for dose calculation also included the scanner manufacturer and model. If data were available only on the manufacturer, a manufacturer-specific average was used. It was assumed that a head or body filter was used, based on the target body part. The cumulative absorbed red bone marrow (RBM) doses were obtained as the sums of absorbed RBM doses from all CT scans for each study subject. The dose from a scan was multiplied by 1.5 if contrast medium was used, consistent with tissue-specific coefficients suggested for other tissues.[33] Alternative dose estimates were obtained based on values reported in the literature.[34]

We identified subjects with Down syndrome (40 cases and 2 controls) from the Congenital Malformation Register and Care Register for Health Care, and those with a previous malignancy (2 cases) from the Finnish Cancer Registry. They were excluded to avoid confounding by indication (reverse causation). We also collected information on birth weight (large for gestational age) and maternal smoking during pregnancy from the Medical Birth Register, as well as socioeconomic status and education of the parents from Statistics Finland. Residential exposure to background gamma radiation, including natural terrestrial radiation and Chernobyl fallout, was estimated as described previously.[8]

Due to small frequencies, exact conditional logistic regression in SAS 9.4 was used for estimating odds ratios (OR), excess odds ratios and their confidence intervals (CI).[35] Statistical power calculations indicated that the sample size is sufficient for detecting a linear dose-response with an OR of 1.05 or greater per 1 mGy increase in cumulative RBM dose with a statistical power of 80% using asymptotic conditional logistic regression.[36]

The ethical committee of Pirkanmaa Hospital district reviewed the study protocol (tracking number R14074) and, in accordance with Finnish regulations, no informed consent was required for this register-based study. In addition, each hospital approved our study protocol before delivering the data on CT scans. We obtained permission to use data from the Finnish Cancer Registry, the Medical Birth Register, Care Register for Health Care and Congenital Malformation Register from the National Institute of Health and Welfare (1774/5.05.00/2014), as well as census data on socioeconomic status from Statistics Finland (TK-52-306-16).

Results

In our nationwide register-based study, after excluding cases with an incorrect personal identification number or prohibition to use their data, we identified 1,093 cases of childhood leukemia diagnosed in 1990-2011. Most of the cases were acute lymphoblastic leukemia (81.1%) or acute myeloid leukemia (13.0%). The median age at diagnosis among cases was 4.52 years (interquartile range, IQR 2.72 – 8.23). Of the cases and controls, 52% were male (Table 2). The criteria for large for gestational age were met by 121 (13.3%) of the cases and 275 (9.9%) of the controls.

Table 2. The characteristics of cases and controls before any exclusions.

	Cases (n=1,093)	Controls (n=3,279)	*P*
Gender			
Female	48.0% (525)	48.0% (1575)	
Male	52.0% (568)	52.0% (1704)	
Large for gestational age			
No	86.7% (788)	90.1% (2493)	
Ys	13.3% (121)	9.9% (275)	0.001
Missing	184	511	
Mother's smoked during pregnancy			
No	83.1% (742)	84.5% (2296)	
Yes	16.9% (151)	15.5% (420)	0.096
Missing	200	563	
Down syndrome			
No	96.3% (1053)	99.9% (3277)	
Yes	3.7% (40)	0.1% (2)	<0.001
Parents' education			
Mother			
Upper secondary	48.5% (530)	50.6% (1659)	ref
Bachelor's degree	22.3% (244)	23.1% (756)	0.869
Master's or doctor's degree	10.2% (112)	9.8% (321)	0.406
Missing	18.9% (207)	16.6% (543)	
Father			
Upper secondary	52.0% (568)	51.4% (1685)	ref
Bachelor's degree	15.2% (166)	16.2% (532)	0.423
Master's or doctor's degree	10.0% (110)	10.2% (334)	0.880
Missing	22.8% (249)	22.2% (728)	
Parents' socioeconomic status			
Mother			
Self-employed	7.7% (84)	8.3% (273)	ref
Upper level employee	16.1% (176)	15.7% (514)	0.477
Lower level employee	34.8% (380)	34.5% (1130)	0.521
Manual worker	21.4% (231)	20.6% (674)	0.490
Other	18.2% (199)	20.3% (664)	0.859
Missing	2.1% (23)	0.7% (24)	
Father			
Self-employed	13.9% (152)	12.0% (395)	ref
Upper level employee	17.6% (192)	18.2% (596)	0.178
Lower level employee	18.3% (197)	17.9% (587)	0.273
Manual worker	34.0% (372)	35.0% (1148)	0.170
Other	12.4% (135)	14.3% (469)	0.036
Missing	4.1% (45)	2.6% (84)	
Age at leukemia diagnosis, years			
0 – 2	14.3% (156)		
2 – 7	55.5% (605)		
7 – 15	33.4% (332)		
Leukemia type			
Pre-B-ALL	75.6% (826)		
Pre-T-ALL	5.9% (64)		
Unclassified ALL	1.8% (20)		
Acute myeloid leukemia	13.6% (149)		
Other	3.1% (34)		

The reported *P*-values are from an univariate conditional logistic regression model. The non-binary variables were treated as factors and the reference categories are marked with "ref". ALL: acute lymphoblastic leukemia.

After exclusions, eight cases (0.7%) and nine controls (0.3%) had undergone at least one CT scan. The median RBM dose was 10.1 mGy (IQR 4.79 – 13.6) for the exposed cases and 6.29 mGy (IQR 5.69 – 7.14) for the exposed controls (Figure 3). The corresponding literature-based values were 26.5 mGy and 17.6 mGy. The RBM doses calculated with NCICT from thoracic CT scans varied between 1.8 and 6.8 mGy (median 4.0 mGy) and similarly, the doses for head CT scans varied between 1.6 and 10.7 mGy (median 6.6 mGy).

The OR for any *versus* no CT was 2.82 (95% CI: 1.05 – 7.56). For two or more pediatric CT scans, the OR was 5.22 (95% CI: 0.89 – 69.9). For any head CT scans, an OR of 4.00 (95% CI: 1.39 – 11.5) was obtained.

The overall excess OR of childhood leukemia was 0.13 (95% CI: 0.02 – 0.26) per mGy of absorbed RBM dose calculated with the NCICT software (Table 3). Using the cumulative RBM dose estimates from the literature, an excess OR of 0.05 (95% CI: 0.01 – 0.10) per mGy was obtained. In an analysis by dose tertile calculated with NCICT, the excess OR relative to zero dose were 1.26 (95% CI: -0.50 – 10.1) for the first group, 0.09 (95% CI: -0.89 – 10.5) for the second, and 5.00 (95% CI: 0.10 – 31.7) for the last (Figure 4).

For the most common subtype, precursor B-cell acute lymphoblastic leukemia, the excess OR per mGy was 0.14 (95% CI: 0.02 – 0.29) using estimates from NCICT and 0.06 (0.01 – 0.11) for literature-based estimates. The excess OR for any *versus* no CT scans was 2.25 (95% CI: 0.08 – 8.75) for acute lymphoblastic leukemia and 2.88 (95% CI: 0.22 – 11.4) for precursor B-cell acute lymphoblastic leukemia. In the analysis by age at diagnosis/reference date, the excess OR for any *versus* no CT scans was 3.50 (95% CI: -0.25 – 25.9) for children aged 2 – <7 years and 1.27 (95% CI: -0.32 – 6.54) for those aged 7 – <15 years.

Covariate (confounder) adjustments (large for gestational age, maternal smoking during pregnancy, parental education and parental socioeconomic status) did not alter the OR for CT exposure by more than 0.05 units, with the exception of maternal smoking, which increased the OR related to the number of pediatric CT scans (0 *versus* 1 or more) (approximately 0.10 units). Nevertheless, we preferred the unadjusted model, as missing data on maternal smoking resulted in wider confidence intervals for the main variables.

The OR were higher when the subjects with Down syndrome were not excluded (for 1 or more CT scans OR=5.21, 95% CI: 2.19 – 12.4 and for cumulative RBM dose excess OR=0.19 per mGy, 95% CI: 0.07 – 0.32). No evidence of a different effect of the RBM doses on leukemia risk for subjects with or without Down syn-

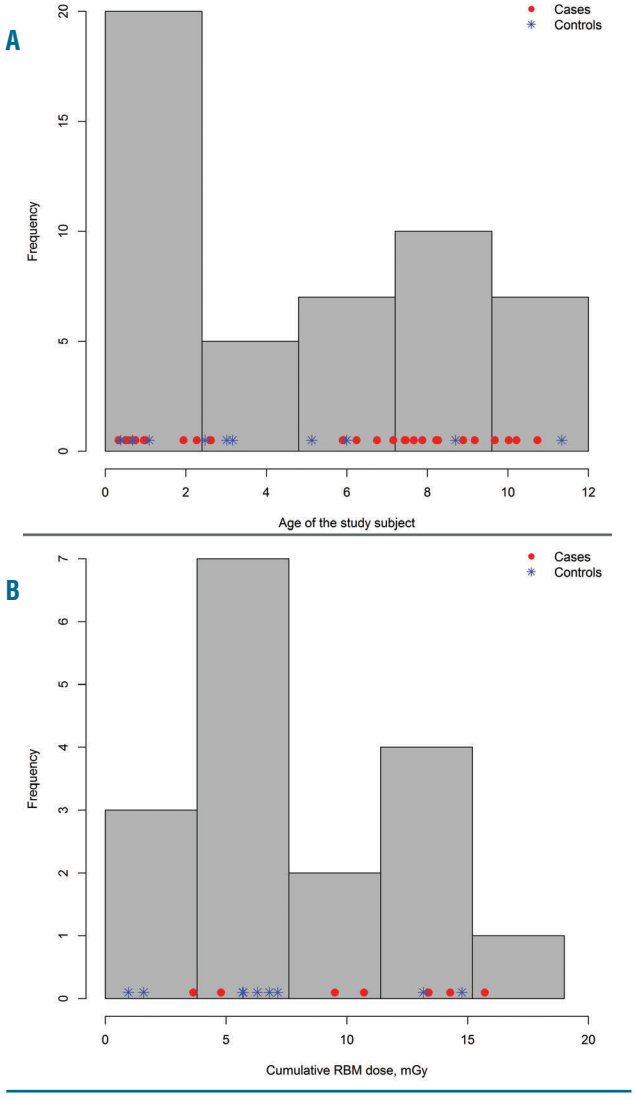

Figure 3. Histograms of (A) the ages of the subjects at the time of computed tomography scan and (B) the cumulative doses received by the subjects, calculated with NCICT.

Table 3. The frequencies of computed tomography scans for subjects >2 years old at the reference date and odds ratios calculated with exact conditional logistic regression.

	Cases	Controls	OR (95% CI)
	911	2730	
CT scans			
0	903	2721	
1	4	7	1.85 (0.39, 7.36)
2 or more	4	2	6.22 (0.89, 68.9)
by type (1 or more)			
ALL	7	7	3.25 (1.08, 9.75)
pre-B-ALL	7	6	3.88 (1.22, 12.4)
by age-group (1 or more)			
2 - <7 years	3	2	4.50 (0.75, 26.9)
7 - <15 years	5	7	2.27 (0.68, 7.54)
by dose index (NCICT/literature)			
low, 4.79[a]/11.6[b] mGy	3	4	2.26 (0.50, 10.1)
medium, 6.72[a]/19. 8[b] mGy	1	3	1.09 (0.11, 10.5)
high, 13.8[a]/33.2[b] mGy	4	2	6.00 (1.10, 32.8)
per 1 mGy (NCICT)			
TOTAL			1.13 (1.02, 1.26)
pre-B-ALL			1.14 (1.02, 1.29)
per 1 mGy (literature)			
TOTAL			1.05 (1.01, 1.10)
pre-B-ALL			1.06 (1.01, 1.11)

The reference group for all calculated odds ratio (OR) is zero CT scans for categorical variables. Study subjects with Down syndrome or cancer diagnoses were excluded. All reported OR are from an unadjusted model. The median doses for dose-index classes calculated with NCICT are marked with [a]. The respective class medians based on literature are marked with [b]. ALL: acute lymphoblastic leukemia; pre-B-ALL: precursor B-cell acute lymphoblastic leukemia.

drome was found to suggest effect modification (interaction *P*=0.99).

When the oldest possible CT scanner (at maximum, 10 years old) at the hospital was used in dose estimation instead of the most modern CT scanner, the median cumulative RBM dose for cases was 9.71 mGy (IQR 7.09 – 18.7) and for controls 7.14 mGy (IQR 5.71 – 12.6), with an excess OR of 0.11 (95% CI: 0.02 – 0.22) per mGy.

When the cumulative RBM dose from terrestrial gamma radiation and Chernobyl fallout was included in the model, the OR for cumulative RBM dose from pediatric CT scans remained unchanged. The median cumulative dose from residential gamma radiation was 1.96 mSv for cases and 1.90 mSv for controls.

The distributions of cities of the last addresses of cases and controls were analyzed to evaluate whether cases and controls belonged to catchment populations of different hospitals, which might have caused differential misclassification due to contrasting data availability. No difference in the distributions was noted (chi-squared test, *P*=0.30). The age and CT scan years of the subjects are reported in *Online Supplementary Table S3.*

Discussion

We estimated the impact of radiation exposure from pediatric CT scans on risk of childhood leukemia in a nationwide register-based case-control study in Finland. Overall, a statistically significant increase in risk per mGy of RBM absorbed dose was found. The central estimate is larger than in previous studies, but the confidence intervals overlap with earlier results, and the effect size is compatible with extrapolation from high-dose studies. The higher main point estimate is likely influenced by random error, as the dose estimates were imprecise due to lack of detail in dosimetric data, including parameter values used for the scanner. It is also possible that the typical values based on expert opinion are representative of current procedures, but may underestimate doses from older examinations, which could inflate the risk estimates per unit dose. However, our site-specific dose estimates calculated with NCICT were quite comparable with those reported in the British study.[25] We minimized the potential for systematic error by adjusting for several confounders and used consistent procedures for the cases and controls. The risk estimates were slightly higher for precursor B-cell acute lymphoblastic leukemia than for other leukemias, but the difference was not statistically significant.

Two large studies have been published on the subject prior to ours. The cohort studies from the United Kingdom and Australia reported a significant risk of childhood leukemia associated with RBM dose from pediatric CT scans.[25,26] Pearce *et al.* found an excess relative risk of 0.04 per mGy and Mathews *et al.* reported a relative risk of 1.2 for one or more CT scans with an excess relative risk of 0.04 per mGy. The Australian cohort had 211 exposed leukemia cases and the UK study 74. A smaller German cohort study reported an increased leukemia incidence following two or more CT scans, but a non-significant dose-response based on 12 exposed cases.[27] Based on the Life Span Study in Japan, the extrapolated excess relative risk for childhood exposure would be approximately 0.05 per mGy.[37]

Other major sources of ionizing radiation were taken into consideration by including cumulative RBM doses from terrestrial gamma radiation and Chernobyl fallout, and this did not affect the results. In our data, the average cumulative RBM dose from CT for the controls was only 0.002 mGy, which is approximately 0.1% of the average annual RBM dose in Finland.[38] We accounted for medical use of radiation, to which tomography scans make the largest contribution, and terrestrial gamma radiation, which accounts for nearly two-thirds of average annual radiation to the RBM in Finland.[23,39] In addition, there is little evidence to assume that other sources of ionizing radiation, such as cosmic radiation or internal exposure to natural radioisotopes, would distribute unequally among the cases and controls.

The coefficient 1.5 for incremental dose due to CT imaging with contrast medium was chosen pragmatically based on the coefficients for other body parts, as the effects on RBM dose were not reported separately.[33]

Based on limited population statistics available from the Radiation and Nuclear Safety Authority,[23] roughly 30 CT scans were expected for the controls. However, only 13 scans were recorded among them. This might partly reflect incomplete availability of data, but the estimate of the expected numbers is highly uncertain because of lack of data on pediatric CT scans prior to 2008. It is also worth noting that pediatric CT scans are performed less frequently in Finland than in several other countries.[24]

Our material consists of a comprehensive set of childhood leukemia cases and representative controls, which should eliminate selection bias by virtue of a register-based approach, which required no consent or information from the study subjects or their families. The study period covers the years in which the use of pediatric CT scans was most frequent, as the annual number of pediatric CT scans has been decreasing in Finland since the year 2000.[23] The data on CT scans were obtained from

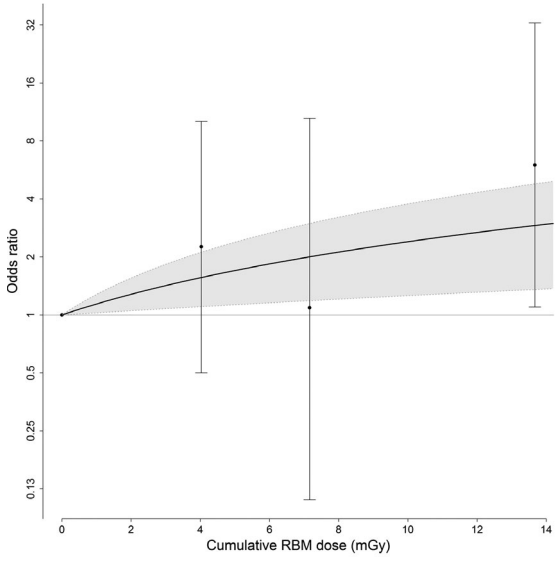

Figure 4. Dose-response curve of cumulative red bone marrow dose from pediatric computed tomography scans and childhood leukemia. The point estimates with 95% confidence intervals are for the three dose index levels and the fitted curve is for the cumulative RBM dose calculated with NCICT. The shaded area represents the 95% confidence interval for the continuous dose-response. The vertical axis is on a binary logarithm scale.

hospital databases to avoid recall bias, and also included the scanner model and use of contrast medium. As in other studies, the most common single CT scan in our analysis was a head scan.[23]

Radiation doses to RBM from the CT scans were calculated using the best available methods, employing NCICT software, with age- and sex-specific phantoms and taking into account the scanner model. The scanning parameters entered into the software were based on the settings and procedures commonly used in Finland, although data were not available for each scan. We also evaluated the effects of choosing the most modern CT scanner at each imaging site and the OR showed robust behavior.

We also had data on several important risk factors including Down syndrome, parental socioeconomic status, large for gestational age and maternal smoking. We were able to incorporate data on cancer predisposing factors, which have been shown to be of importance recently.[28,30] Inclusion of cases with Down syndrome would have increased the risk estimates, possibly because Down syndrome is associated with increased risks of both leukemia and infections.[4,40] We also explored the joint effect of Down syndrome and cumulative RBM dose and found no interaction. Subgroup analyses of exploratory nature were carried out by subtype of childhood leukemia and age at diagnosis, although these were underpowered.

Our study has some shortcomings. We were able to obtain data from all ten hospitals only after 2002, thus exposure assessment is not uniformly complete for subjects born prior to that year. Only a minor improvement in statistical power would have been reached by collecting pediatric CT scans from the rest of the imaging centers in Finland. In addition, there is no reason to assume that the missed CT scans would have been unequally distributed for the cases and controls, i.e. result in differential misclassification. For dose estimation, complete information on the scanning parameters is included in the modern picture archiving systems, but was not available before the year 2000. Use of parameters for each individual scan would have provided more accurate dose estimates. The unexpectedly lower median dose of cases for older scanners found in our sensitivity analysis may be due to random error. The number of different CT scanners in our analysis was limited and thus the estimates of average dose were imprecise.

Our results support the notion that even small doses of radiation from pediatric CT scans produce a small, but detectable increase in leukemia risk. In the subgroup analyses, we observed no substantial differences by age or leukemia subtype, although slightly higher risks were found for precursor B-cell acute lymphoblastic leukemia.

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