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

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Supplemental methods

Details of the materials and methods

We used a register-based case-control study with individually matched controls. The key characteristics of our dataset have been presented previously[12]. Briefly, all cases of childhood leukemia (M9800 – M9948 in ICD-O-3) diagnosed in Finland during 1990-2011 (N=1100) were identified from Finnish Cancer Registry (Figure 1**)**. Three controls were each individually matched by sex and year of birth for each case from Population Register Center. The controls were assigned a reference date corresponding to the diagnosis date of their case, to define a period for exposure assessment comparable with the pre-diagnostic period of the cases. In all analyses, a two-year latency period was used to eliminate reverse causation due to confounding by indication. This resulted in null exposure for study subjects aged under two years at their diagnosis/reference date.

The Finnish Cancer Register provided the data on the date and details of diagnoses (ICD-O-3 codes). We classified the diagnoses into five categories: acute B-cell lymphoblastic leukemia (B-ALL), acute T-cell lymphoblastic leukemia (T-ALL), unknown type of acute lymphoblastic leukemia (ALL, unknown), acute myeloid leukemia (AML) and other childhood leukemias using also diagnostic data collected from hospital databases. We had to exclude three cases due to incorrect personal identification number and four due to a prohibition to use their personal information at the population registry, resulting in 1093 cases in the analyses (Figure 1).

We acquired data on the diagnoses of Down syndrome from Register of Congenital Malformations by the National Institute of Health and Welfare. The gestational weeks and birth weights of the study subjects were obtained from the Medical Birth Register, though the data (birth weight, gestation weeks or both) was missing for 184 (18.6%) cases and 511 (15.6%) controls (Table 1). Large for gestational age (LGA) was defined as birth weight exceeding the 90th percentile given the gestation time. Data on maternal smoking during pregnancy was also obtained from Medical Birth Register and it was missing for 200 (18.3%) cases and 563 (17.2%) controls. Statistics Finland provided data on the level of educational attainment and socio-economic status of the study subjects' parents from multiple nationwide surveys throughout parents' lives. The first available data point prior to the reference date was used for each variable. Paternal education was missing for 249 cases (22.8%) and 728 controls 728 (22.2%); maternal education status for 207 cases (18.9%) and 543 controls (16.6%); paternal socio-economic status for 152 cases (13.9%) and 395 controls (12.0%) and mother's socio-economic status for 84 cases (7.7%) and 273 controls (8.3%). The education factor had three levels: upper secondary school/vocational school(1), bachelor's

degree(2), master's or doctor's degree (3). Socioeconomic status had five levels: self-employed(1), Upper-level employees with administrative, managerial, professional and related occupations(2), lower-level employees with administrative and clerical occupations(3), manual workers(4) and others(5).

We obtained data on outpatient visits and hospitalizations since 1996 from the Care Register to account for reverse causation due imaging for prodromal symptoms of leukemia and confounding by indication due to conditions increasing both leukemia risk and other health conditions associated with CT imaging. First, each subject's all main diagnoses of the outpatient visits or hospitalizations prior the subject's reference date were listed. Then the diagnoses were searched for conditions that could act as confounders such as other malignant diseases of the childhood.

We obtained data on all CT scans performed on pediatric patients (<15 years) from all five university hospitals (Helsinki, Tampere, Turku, Kuopio and Oulu) and the five largest central hospitals (Jyväskylä, Pori, Joensuu, Lahti, Seinäjoki) in Finland (Figure 2). We approximated that the data cover 87% of all pediatric CT scans performed in Finland during 1975-2011. The approximation is based on the real annual pediatric CT scan numbers from the largest university hospital (Helsinki University Hospital) between years 1990 and 2011.Helsinki University hospital was the second hospital, from which the CT scans were collected, allowing us to decide on the strategy fairly early. First, we assumed a linear decrease to zero CT scans towards year 1975, the year when the use of CT scanners was starting to rise in Finland. Then the annual numbers of Helsinki (1975-2011) were extrapolated by proportions to the nine other hospitals using the average of distributions of CT scans at 2008 and 2011 at different hospitals by the Radiation and Safety Authority[a,b]. Finally, the absolute estimated number of CT scans from the ten largest hospitals, covered by our approach, was compared the expected total number of CT scans from the aforementioned 2008 and 2011 surveys.

For each CT scan, data covered the year, body part, and use of contrast medium. Manufacturers and models of CT scanners in each hospital were acquired from Radiation and Nuclear Safety Authority. For dose calculations, we assumed that each CT scan was performed using the latest CT scanner of the hospital.

Data availability varied between hospitals and the whole study period was covered only from Tampere University Hospital. The radiological databases with individual patient data on each CT scan were introduced at different times (Table 1).

In total, data on 80,783 pediatric CT scans was obtained and 49 CT scans were performed on the study subjects excluding the two-year latency period (Table 1). Half (25) were head scans, and 19 lung scans. Of the CT scans, 36 scans were performed on 15 (1.4%) cases and 13 scans on 10 (0.3%) controls.

To reduce confounding by indication, we excluded subjects with Down syndrome (40 cases, 1.0%, and two controls, 0.1%). We also excluded two cases with a previous hepatoblastoma and a brain tumor. Whenever a case was excluded, his or her controls were also excluded, which resulted in the exclusion of an exposed control. After the exclusions, the material included eight (0.8%) exposed cases and nine (0.3%) exposed controls (Figure 1). Also other predisposing factors (Supplementary table 3) were searched for from outpatient registry but they did not result in any further exclusions.

The scan parameters used with each pediatric CT scan were obtained based on expert opinion of an experienced hospital physicist at the Tampere University Hospital (Supplementary table 1). These typical scan parameters for the three most common pediatric CT scans (head, thorax, abdomen) for five different years (2002, 2004, 2006, 2008, 2010) were applied for each of the 49 CT scans. The doses were estimated with NCICT software (v1.2)[13]. Age-specific and sex-specific pediatric software phantoms (newborn, and children aged 1, 5, 10, and 15 years) were used. The dose calculation input also included scanner manufacturer and model. If only the manufacturer was available, manufacturer-specific average was used. Use of a head or body filter was assumed based on the target body part. The cumulative absorbed red bone marrow (RBM) doses were obtained as the sums of absorbed RBM doses for each study subject. The dose from native scan was multiplied by 1.5 if contrast media was used, consistent with tissue-specific coefficients suggested for other tissues[14]. Alternative dose estimates were obtained based on values reported in the literature, but the primary analyses were based on dose estimates calculated with NCICT software[15]. The dose estimates from the literature were consistently approximately three times higher than the doses calculated with NCICT, probably reflecting scan parameters optimized for pediatric imaging in Finland.

Risk of leukemia was first estimated in relation to number of CT examinations (none vs. any CT scans, none vs one CT scan, none vs. ≥2 CT any scans, and no vs. any head CT scans). Second, risk was related to tertiles of cumulative RBM (including children with no CT scans with zero doses). Third, the cumulative dose was treated as a continuous variable to obtain an odds ratio per 1 mGy increase in the cumulative RBM dose.

Subgroup analyses were performed by age at diagnosis/reference date (2-6.99 vs 7-15 years) and histological subtype of childhood leukemia (pre-B-ALL and ALL).

Due to small frequencies, exact conditional logistic regression was used for estimating odds ratios and their confidence intervals[16]. Two-sided alpha with a critical value of 0.05 was used as the criterion for statistical significance. We report crude ORs unless adjustment altered the OR estimates by more than 0.05 units. Twelve analyses were conducted with a statement about statistical significance. No correction for multiple testing was used, as the main objective of our study was estimation and not hypothesis testing.

Statistical power calculations indicated that the sample size is sufficient for detecting a linear dose-response with OR 1.05 or greater per 1 mGy increase in cumulative RBM dose with a statistical power 80% using asymptotic conditional logistic regression[17]. The regression analyses were carried out using SAS 9.4 and the other statistics were computed with R 3.4.0.

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 a register-based study. In addition, each hospital approved our study protocol before delivering the data on CT scans. We obtained permissions to use data from Finnish Cancer Registry and Medical Birth Register from the National Institute of Health and Welfare.

References:

a. Tenkanen-Rautakoski P. [in Finnish] Radiologisten tutkimusten ja toimenpiteiden määrät vuonna 2005. Helsinki: Radiation and Nuclear Safety Authority; 2006.

b. Tenkanen-Rautakoski P. [in Finnish] Radiologisten tutkimusten ja toimenpiteiden määrät vuonna 2008. Helsinki: Radiation and Nuclear Safety Authority; 2010.

Supplementary table 1 – The predisposing factors from outpatient register

Predisposing factors	**Number among CT scanned study subjects**
Fanconi anemia	0
Bloom syndrome	0
Ataxia telangiectasia	0
Any heart malformation	2
Any GI malformation	1

Down syndrome or malignancies are not listed here as data on them was retrieved elsewhere. The subjects with a listed syndrome were, however, already excluded due to some other reason.

Supplementary table 2 - The scan parameters used with NCICT

	Abdomen					Head					Thorax				
	Age	**kV**	**mAs**	**pitch**	**Coll.**	**Age**	**kV**	**mAs**	**pitch**	**Coll.**	**Age**	**kV**	**mAs**	**pitch**	**Coll.**
2002	0	120	40	1	10-20	0	120	140	1	10-20	0	120	30	1	10-20
	1	120	40	1	10-20	1	120	140	1	10-20	1	120	40	1	10-20
	5	120	70	1	10-20	5	120	140	1	10-20	5	120	50	1	10-20
	10	120	90	1	10-20	10	120	200	1	10-20	10	120	70	1	10-20
	15	120	90	1	10-20	15	120	300	1	10-20	15	120	90	1	10-20
2004	0	120	40	1	10-20	0	120	140	1	10-20	0	120	30	1	10-20
	1	120	40	1	10-20	1	120	140	1	10-20	1	120	40	1	10-20
	5	120	70	1	10-20	5	120	140	1	10-20	5	120	50	1	10-20
	10	120	90	1	10-20	10	120	200	1	10-20	10	120	70	1	10-20
	15	120	90	1	10-20	15	120	300	1	10-20	15	120	90	1	10-20
2006	0	100	40	1	20 - 40	0	100	140	1	20 - 40	0	80	30	1,3	20 - 40
	1	100	40	1	20 - 40	1	100	140	1	20 - 40	1	100	40	1,3	20 - 40
	5	100	70	1	20 - 40	5	120	140	1	20 - 40	5	120	50	1,3	20 - 40
	10	100	90	1	20 - 40	10	120	200	1	20 - 40	10	120	70	1,3	20 - 40
	15	120	90	1	20 - 40	15	120	300	1	20 - 40	15	120	90	1,3	20 - 40
2008	0	100	40	1	20 - 40	0	100	140	1	20 - 40	0	80	30	1,3	20 - 40
	1	100	40	1	20 - 40	1	100	140	1	20 - 40	1	100	40	1,3	20 - 40
	5	100	70	1	20 - 40	5	120	140	1	20 - 40	5	120	50	1,3	20 - 40
	10	100	90	1	20 - 40	10	120	200	1	20 - 40	10	120	70	1,3	20 - 40
	15	120	90	1	20 - 40	15	120	300	1	20 - 40	15	120	90	1,3	20 - 40
2010	0	100	40	1	20 - 40	0	100	140	1	20 - 40	0	80	30	1,3	20 - 40
	1	100	40	1	20 - 40	1	100	140	1	20 - 40	1	100	40	1,3	20 - 40
	5	100	70	1	20 - 40	5	120	140	1	20 - 40	5	120	50	1,3	20 - 40
	10	100	90	1	20 - 40	10	120	200	1	20 - 40	10	120	70	1,3	20 - 40
	15	120	90	1	20 - 40	15	120	300	1	20 - 40	15	120	90	1,3	20 - 40

Age stands for child's age at the CT scan. The tube potential is represented with kW and the current with mAs. Collimation is abbreviated with Coll.

Supplementary table 3 – The age of subject at CT scan and year of the CT scan

Table S1A - *cases*

AGE	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	2	0	0	0	0	0	0	0	0	3	1	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0
3	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1991	**1992**	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**

YEAR

*T*able S1A - *controls*

AGE	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
2	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	1	2	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0
	1991	**1992**	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**

YEAR

There were no subjects, who have had one or more CT scans, with a reference date before 1995.