PAPER

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Second follow-up of a German cohort on childhood cancer incidence after exposure to postnatal diagnostic x-ray

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Abstract

Studies on children exposed to ionising radiation by computed tomography (CT) indicate an increased risk of leukemia and central nervous system (CNS) tumors. Evidence of the risks associated with diagnostic x-ray examinations, the most frequent examination in pediatric radiology, in which the radiation dose is up to 750 times lower compared to CT examinations, is less clear. This study presents results of the second follow-up for the risk of childhood cancer in a cohort of children (<15 years) with diagnostic x-ray exposure at a large German hospital during 1976–2003 followed for additional 10 years until 2016. With a latency period of 6 months, 92 998 children contributed 794 549 person-years. The median effective dose was 7 μSv. Hundred incident cancer cases were identified: 35 leukemia, 13 lymphomas, 12 CNS tumors, 15 blastomas, 15 sarcomas and 10 other solid tumors, consisting of six germ cells tumors, three thyroid cancers and one adrenocortical carcinoma. For all cancer

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cases combined the standardised incidence ratio (SIR) was 1.14 (95% confidence interval (CI) 0.93–1.39), for leukemia 1.15 (95% CI 0.63–1.61), for lymphomas 1.03 (95% CI 0.55–1.76), for CNS tumors 0.65 (95% CI 0.34–1.14), for blastomas 1.77 (95% CI 0.91–2.91), for sarcomas 1.28 (95% CI 0.71–2.11) and for other solid tumors 2.38 (95% CI 1.14–4.38). Dose-response analysis using Poisson regression revealed no significant trend for dose groups. Results did not differ substantially with a latency period of 2 years for all cancer entities and 5 years for solid tumors in sensitivity analyses. Overall, the null results of the first follow-up were confirmed. Although an association between radiation exposure and a risk for certain solid tumors like thyroid cancer is known, the significantly increased SIR in the group of other solid tumors must be critically interpreted in the context of the small number of cases and the very low doses of radiation exposure in this group.

Keywords: diagnostic x-ray, childhood cancer, cohort study, low dose radiation

1. Introduction

Cancer in children is a rare disease, accounting for approximately 1% of all incident malignancies, with an annual incidence of 1.4 per 10 000 live birth in Europe [1]. Nonetheless, cancer is the most common cause of disease-related death in children in industrialised countries [2]. Little is known about the etiology of childhood cancer and the rarity complicates the generation of reliable data on the causes of childhood cancer [3]. One established environmental risk factor is ionising radiation [3, 4]. Evidence for this mainly comes from studies of atomic bomb survivors in Hiroshima and Nagasaki [5, 6] and a variety of studies on medical exposure to ionising radiation [7].

In 2009 Hammer and colleagues published results from a large cohort study investigating very low exposure to radiation from diagnostic x-ray examinations, in which they did not observe any increased risk for childhood cancer [8]. Since then several cohort studies on children exposed to computed tomography (CT) with radiation doses up to 750 times higher when comparing, for example, an x-ray examination of the chest to a CT examination of the same region [9], have been published. These recent studies showed an increased risk for leukemia ranging from a relative risk (RR) of 1.19 (95% confidence interval (CI) 1.03–1.37) comparing CT versus no CT [10] to a RR of 3.18 (95% CI 1.46–6.94) comparing a cumulative radiation dose to the red bone marrow of <5 mGy versus $\geqslant 30$ mGy [11]. For brain or central nervous system (CNS) tumors a RR of 2.13 (95% CI 1.88–2.41) comparing CT versus no CT [10] to an RR of 3.32 (95% CI 1.84–6.42) comparing <5 mGy versus $\geqslant 50$ mGy of cumulative radiation dose to the brain [11] was reported.

In terms of radiation protection children are a particularly vulnerable group for mainly two reasons. First, because of a tissue radiosensitivity to radiation-induced cancer compared to adults [12] and second, because of a longer life expectancy in which a cancer can develop [13]. Although doses of ionising radiation by diagnostic x-ray are far lower compared to newer procedures like CT, they still contribute to the collective medical radiation exposure and thus potentially to the stochastic radiation risk of the population [14]. In addition, diagnostic x-ray examinations are still the most frequent examinations in pediatric radiology involving ionising radiation [15].

This study represents the second follow-up of a retrospective cohort study published in 2009 by Hammer and colleagues [8] with ten more years of follow-up of a so far unique cohort and provides an update about the risk of childhood cancer after exposure to very low doses of diagnostic x-ray.

2. Materials and methods

2.1. Study population

This is the second follow-up of a retrospective cohort study published in 2009 by Hammer and colleagues with data from about 100 000 children exposed to postnatal diagnostic x-ray in the years 1976–2003 [8]. The study material and methods have been described previously [8]. Briefly, this study was performed by linking pseudonymised cohort data of children exposed to postnatal diagnostic x-ray at the Dr von Hauner Children's Hospital, University of Munich (DvHCH) between 1976 and 2003 to the nationwide data of the German Childhood Cancer Registry (GCCR), which started registration in 1980, by stochastic record linkage with the software Merge Toolbox [16]. For this study the stochastic record linkage was done as a complete rerun of the initial record linkage for the first follow-up. Together with an experienced medical documentalist, all potential matches were reviewed in the GCCR.

Besides individual information on basic patient characteristics like sex and age, information on the examined body part, number of x-ray examinations and exposure parameters were available through the electronic documentation system of the DvHCH. Until the introduction of a new Radiological Information System (RIS) in 1998 the referral criteria and diagnosis of examinations, coded according to the International Classification of Disease, 10th revision (ICD-10), were also recorded. Since 1998, this information is not readily available as database files through RIS and therefore not available for this study.

Included patients had to be younger than 14.5 years of age at time of first examination, German residents, and without any previous diagnosis of cancer. Patients diagnosed with cancer at the time of their first examination or up to 6 months after diagnosis were excluded. The GCCR has been registering all incident cancer cases in Germany since 1980 for children aged 0 to under 15 years, with a completeness of more than 95% since 1986. Therefore, we had to restrict the cohort to children that were younger than 14.5 years at their first examination, to ensure a minimum latency period of 6 months and additionally had to exclude children older than 15 years at their first examination, because we could not follow them up regarding the occurrence of cancer due to the registration at the GCCR.

The cohort was first followed-up from 1980 to 2006 and now for 10 more years until the end of 2016 while data on exposure from the DvHCH remained the same [8]. Time under risk started 6 months after the initial x-ray examination and ended at date of cancer diagnosis, their 15th birthday, or 31 December, 2016, whichever occurred first. We chose a 6 month minimum latency period for the main analysis in accordance with the first follow-up of Hammer and colleagues for a better comparability of the results. In addition, we performed analyses with 2 years latency period for all cancer cases and sensitivity analyses with 5 years latency period for solid cancers. No mortality follow-up was done because of financial reasons. In Germany follow-up for vital status is expensive and mortality rates in children are generally low. The absence of a mortality follow-up could lead to a slight overestimation of the true person-years. Therefore, we reduced the observed person-years by the expected loss due to non-cancer mortality using rates of the general population of Germany in this cohort [17]. In addition, we did sensitivity analysis for children with a potentially high mortality risk, tagged as 'high mortality risk' (see appendix A).

2.2. Exposure assessment

Individual radiation doses were previously estimated by Seidenbusch and colleagues using the PAEDOS algorithm developed in the pediatric radiology department at DvHCH. Details on PAEDOS and general exposure assessment are described elsewhere [8, 14]. Briefly, organ doses and whole-body doses were derived from the entrance dose or the dose area product by using conversion coefficients. Conversion coefficients were determined on the basis of the Monte Carlo software PCXMC which was developed by the Finnish Radiation and Nuclear Safety Authority [18]. PCXMC simulates an irradiation to a hermaphrodite mathematical phantom. Simulations were performed for phantoms of different size. The sizes were based on individual data on age at exposure, type of examination, target organ, individual dose area product and other known exposure parameters, e.g. the direction of the beam projection, the patient's position or the distance from the source to detector [8].

For risk estimation, the individual cumulative effective dose in μSv was used for analyses on all cancer entities combined, lymphomas, blastomas, sarcomas and a combined group of other solid tumors as in the first follow-up [8]. For leukemia and CNS tumors we used individual cumulative tissue doses and organ doses. Red bone marrow dose was used for leukemia and brain dose for CNS tumors. In case of missing doses, we used the median dose of subjects with the same age, sex and year of examination.

2.3. Statistical analyses

For external analysis, standardised incidence ratio (SIR) with 95% CI were calculated for groups of all cancers (International Classification of Childhood Cancers, 3rd revision (ICCC-3) I–XII), leukemia (ICCC-3 I), lymphomas (ICCC-3 II), CNS tumors (ICCC-3 III), blastomas (ICCC-3 IV–VII), sarcomas (ICCC-3 VIII–IX) and a combined group of the remaining other solid tumors (ICCC-3 X–XII), which are composed of germ cell tumors, trophoblastic tumors, and neoplasms of gonads (ICCC-3 X), other malignant epithelial neoplasms and malignant melanomas (ICCC-3 XI) and other unspecified malignant neoplasms (ICCC-3 XII). In addition, we performed subgroup analyses for Hodgkin lymphomas (ICCC-3 IIa) and Non-Hodgkin lymphomas (except Burkitt lymphoma) (ICCC-3 IIb). We used sex-, age- and calendar year-specific cancer incidence rates of West Germany provided by the GCCR as the reference. Radiation doses were categorised as <1, $1-<5$, $5-<10$, $10-<25$, $25-<50$, $50-<100$, $100-<250$, $250-<500$ and $\geqslant 500$ μSv to ensure comparability with the first follow-up. We performed the Cochran–Armitage test for trend to investigate a possible dose-response relationship for these radiation dose categories.

We used Poisson regression modeling to investigate a possible dose-response relationship between doses of x-rays and the risk of childhood cancer. Incidence rate ratios (IRR) were adjusted for sex and age at diagnosis and 95% CI were calculated. IRR were calculated for all cancers, leukemia, lymphomas, CNS tumors, blastomas, sarcomas and other solid tumors by dose categorised as $0-<10$ μSv as reference category, $10-<50$ μSv and $\geqslant 50$ μSv. Again, these dose categories were chosen to make the results comparable to the first follow-up.

To ensure comparability with previously published case-control studies additionally the number of examinations categorised as 1, 2 and $\geqslant 3$ x-ray procedures was used as a dose proxy. The Cochrane–Armitage test for trend was also performed for the number of examinations. For all analyses, a latency period of 6 months was used. In addition, we used a latency period of 2 years for all cancer entities and of 5 years for solid tumors for sensitivity analyses and we performed subgroup analyses on children who were exposed within the first

100 days after birth, to investigate the influence of x-ray examinations very early in life on cancer incidence in childhood. Because the cohort included some heterogeneous subgroups, the following groups of patients based on available diagnostic or exposure information were defined to be able to differentiate them in analyses: 'highly exposed', 'high mortality risk', 'elevated incidence risk', 'premature'. Children were labeled as 'highly exposed' if they had a recorded CT or contrast media examination. Exposures from these examinations have not been reconstructed. These examinations, which were performed on 3.7% of the cohort, were documented. Reconstruction of doses were however not possible within this project due to the application of more complex and time-consuming methods. Children were assigned to the group of 'high mortality risk' if they had a serious disease such as AIDS or hydrocephalus. Children were marked as 'elevated cancer risk' if they were diagnosed with a syndrome that is known to be associated with an increased cancer incidence like Down's syndrome. Premature babies have an increased mortality risk and are repeatedly exposed to x-ray examinations to check the development of the lungs. Children were tagged as 'premature' when this was noted as an indication or diagnosis for an x-ray examination. A complete list of labels of ICD-10 blocks and disease for the tags 'high mortality risk' and 'elevated cancer risk' and the corresponding ICD-10 codes can be found in the supplementary material (appendix A) and in the publication of Hammer and colleagues [8].

3. Results

3.1. Study population

In total, the cohort included information on 105 847 children, who had at least one postnatal diagnostic x-ray examination at the DvHCH. Of these, 12 849 children had to be excluded from analyses: 9757 children were 14.5 or older at their first x-ray examination, and 1547 were 15 years or older at the start of follow-up. One-thousand-three-hundred-and-sixty-three children had a prevalent cancer at time of the first x-ray examination or within 6 months after the first examination, or before beginning of the follow-up, 176 children had inconsistent data on date of birth and examination and six children had an examination after 2003. Forty-one fewer children were excluded from the study compared to the first follow-up because of a rerun of the probabilistic record linkage and possible changes in the dynamic registry of the GCCR in terms of name spelling or date of birth.

The cohort consists of 92 998 children: 50 010 boys, 41 467 girls and 1521 children of unknown sex. During the analysis, we discovered a small overestimation of the total person-years in the previous analysis (4.19% of the true person-years) which led to an overestimation of the mean follow-up time of 0.3 years. Compared to the first follow-up until 2006 with corrected person-years of 696 970 and corrected mean follow-up of 7.5 years, the extended follow-up until 2016 increased the total number of person-years by 97 624 to 794 594 person-years and the mean follow-up time by 1.0 year to a mean follow-up time of 8.5 years in this study [8].

Overall 100 incident cancer cases (60 boys and 40 girls) were found by record linkage to the GCCR between 1980 and 2016 using a latency period of 6 months (table 1). The group of other solid tumors (ICCC-3 X–XII) includes four cases of intracranial and intraspinal germ cell tumors (ICCC-3 Xa), 3 cases of thyroid carcinomas (ICCC-3 XIb) and one case each of malignant extracranial and extragonadal germ cell tumors (ICCC-3 Xb), malignant gonodal germ cell tumors (ICCC-3 Xc) and adrenocortical carcinomas (ICCC-3 XIa). When using a latency period of 2 years, 71 cancer cases were observed (table 1) and 39 cases when applying a latency period of 5 years (table 1). Twenty of the incident cancer cases were tagged as

Table 1. Number of incident cancer cases occurring in the period 1980–2016, by cancer diagnosis, sex and age at diagnosis for 6 month latency period and total number of cases by diagnosis for 6 month, 2 year, 5 year latency period, in a cohort of children who underwent diagnostic x-ray procedures at Dr von Hauner Children's Hospital, Munich, Germany, in the period 1976–2003.

		Sex		Age at diagnosis of cancer				Total		
Diagnosis	ICCC-3[a]	Boys	Girls	0	1–4	5–9	10–14	6 month latency	2 year latency	5 year latency
All cancers	I–XII	60	40	0	34	32	34	100	71	39
Leukemias, myeloproliferative diseases, and myelodysplastic diseases	I	19	16	0	15	10	10	35	24	8
Lymphocytic Leukemia	Ia	14	10	0	12	5	7	24	16	4
Acute myeloid Leukemia	Ib	2	2	0	0	2	2	4	4	2
Other Leukemias	Ic–Ie	3	4	0	3	2	2	7	4	2
Lymphoma	II	12	1	0	5	6	2	13	7	3
Hodgkin lymphoma	IIa	4	0	0	1	2	1	4	1	0
Non-Hodgkin lymphoma (except Burkitt lymphoma)	IIb	7	1	0	4	3	1	8	5	3
CNS tumors	III	8	4	0	3	5	4	12	8	7
Neuroblastoma and other peripheral nervous cell tumors	IV	1	3	0	2	2	0	4	3	2
Retinoblastoma	V	1	0	0	1	0	0	1	0	0
Renal tumors	VI	5	3	0	3	5	0	8	6	4
Hepatic tumors	VII	2	0	0	1	0	1	2	1	1
Malignant bone tumors	VIII	3	0	0	0	0	3	3	3	3
Soft tissue and other extraosseous sarcomas	IX	5	7	0	4	3	5	12	10	4
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	X	3	3	0	0	0	6	6	5	4
Other malignant epithelial neoplasms and malignant melanomas	XI	1	3	0	0	1	3	4	4	3
Other and unspecified malignant neoplasms	XII	0	0	0	0	0	0	0	0	0

[a] ICCC-3: International Classification of Childhood Cancers, third revision [37].

'patients with high mortality risk', five were tagged as 'highly exposed' and one case was tagged as 'elevated incidence risk'. There was no case that was tagged as 'premature'. The most frequent cancer was acute lymphoblastic leukemia (ALL) with 24 cases (table 1). The mean age at diagnosis was 7.4 years (range 1–14, standard deviation 4.2, median 7.3). Infant cancer cases were not observed.

When restricting our analyses to children exposed to diagnostic radiation in the first 100 days after birth, we identified 11 403 children of whom 21 were diagnosed with cancer during childhood (eight leukemia, two lymphomas, four CNS tumors, four blastomas, three sarcomas).

3.2. Exposure

Most children (59%) had only one radiographic examination at the DvHCH. About 19% of the cohort had two examinations and 22% had three or more examinations. The mean age at first examination at the DvHCH was 5.6 years. About 22% of the cohort had their first examination at 0 years of age, 10% at one year of age, 21% from 2 to 4 years, about 27% at 5–9 years and 20% in the age group of 10–14 years. Of the 100 incident cancer cases, 59 children had only one radiographic examination. A further 16 patients had two, and 25 children had three or more examinations. Forty-two of all incident cancer cases had their first examination at 0 years of age, while 15 cases had their first examination at one year of age, 24 between 2 and 4 years, 14 between 5 and 9 years and five cases in the age group of 10–14 years (table 1). Individual cumulative effective doses ranged from 0 to 343 400 μSv. The median cumulative effective dose in the cohort was 7 μSv and the mean cumulative effective dose was 134.7 μSv. For the cancer cases, the median cumulative effective dose was 20 μSv and the mean cumulative effective dose was 114.5 μSv.

3.3. Statistical analysis

The SIR for all incident cancers was 1.14 (95% CI 0.93–1.39). The SIR for leukemia, lymphomas (in general and for Hodgkin lymphomas and Non-Hodgkin lymphomas), CNS tumors, blastomas and sarcomas did not differ significantly from 1.0 (table 2). In the group of other solid tumors, the SIR was 2.38 (95% CI 1.14–4.38) (table 2). For all cancers combined, the SIR generally did not differ between sexes (table 2), and in analyses for dose categories, no single SIR was significant and no trend with increasing dose was observed (table 2). The same applies to the number of examinations as a dose proxy (table 2). Subgroup analyses were carried out for patients tagged as 'high mortality risk' with 120 552 person-years and patients tagged as 'highly exposed' with 28 831 person-years (table 2). SIR were not significantly raised for these subgroups. Other subgroups had too few cases for analyses.

No overall trend of increasing cancer risk with increasing dose was observed in the IRR analyses for all cancers combined, leukemia, lymphomas, CNS tumors, blastomas, sarcomas and other solid tumors (tables 3 and 4). In IRR analyses for children excluding patients tagged as 'highly exposed', no association was observed for dose categories of 10–$<$50 μSv and $\geqslant$50 μSv compared to the reference category (tables 3 and 4). There were too few cases in the groups labeled as 'high mortality risk' 'elevated cancer risk' and 'premature', so no regression model could be fit. In sensitivity analyses with the number of examinations as a dose proxy, a dose-response relationship was not observed either.

No increased risk could be observed in an additional IRR analysis based on the 21 cancer cases with exposure to diagnostic radiation within the first 100 days after birth adjusted for sex and age at diagnosis in exposure category of 10–$<$50 μSv (IRR 1.04 CI 0.32–3.36) and of $\geqslant$50 μSv (IRR 0.79 CI 0.24–2.61) compared to the reference group of $<$10 μSv.

Table 2. Standardised incidence ratios (SIR) of incident cancer cases in a cohort of children who underwent diagnostic x-ray procedures at Dr von Hauner Children's Hospital, Munich, Germany, in the period 1976–2003 by cancer type, sex, assigned tags, cumulative effective dose and number of examinations.

	6 month latency period				2 year latency period			
	O[a]	E[a]	SIR[a]	95% CI[a]	O[a]	E[a]	SIR[a]	95% CI[a]
All cancers	100	88.0	1.14	0.93–1.39	71	72.7	0.98	0.76–1.23
Leukemia	35	30.5	1.15	0.80–1.61	24	24.3	0.99	0.63–1.47
Lymphoblastic leukemia	24	24.2	0.99	0.63–1.47	16	19.2	0.83	0.48–1.36
Acute myeloid leukemia	4	4.2	0.96	0.26–2.45	4	3.5	1.15	0.31–2.94
Lymphomas	13	12.7	1.03	0.55–1.76	7	11.4	0.61	0.25–1.26
Hodgkin lymphoma	4	6.6	0.60	0.16–1.54	1	4.8	0.21	0.01–1.16
Non-Hodgkin lymphoma	8	5.1	1.56	0.57–3.08	5	3.7	1.35	0.44–3.16
CNS tumors	12	18.4	0.65	0.34–1.14	8	15.7	0.51	0.22–1.00
Blastomas	15	8.5	1.77	0.91–2.91	10	5.3	1.89	0.91–3.47
Sarcomas	15	11.8	1.28	0.71–2.11	13	8.4	1.54	0.82–2.64
Other solid tumors	10	4.2	2.38	1.14–4.38	9	2.7	3.32	1.52–6.31
Sex (all cancers)								
Boys	60	52.5	1.14	0.87–1.47	42	43.7	0.96	0.69–1.30
Girls	40	35.1	1.00	0.81–1.55	29	29.0	1.00	0.67–1.43
Patients tagged as having 'high mortality risk'[b,c]								
No	80	73.0	1.10	0.87–1.36	55	60.1	0.91	0.69–1.19
Yes	20	14.7	1.36	0.83–2.10	16	12.6	1.27	0.72–2.06
'Highly exposed' patients[b]								
No	95	84.2	1.13	0.91–1.38	69	69.7	0.99	0.77–1.25
Yes	5	3.5	1.43	0.46–3.34	2	3.0	0.67	0.08–2.40
Effective dose category (μSv) (all cancers)								
<1	16	18.9	0.85	0.49–1.38	7	14.7	0.48	0.19–0.98
1–<5	13	11.4	1.14	0.61–1.95	12	9.3	1.29	0.67–2.25
5–<10	17	12.0	1.42	0.83–2.27	11	10.0	1.10	0.55–1.97
10–<25	15	13.7	1.09	0.61–1.80	10	11.7	0.86	0.41–1.58
25–<50	15	8.4	1.79	1.00–2.95	11	7.2	1.54	0.77–2.75
50–<100	6	7.3	0.82	0.30–1.79	4	6.3	0.64	0.17–1.63
100–<250	7	7.7	0.91	0.37–1.87	6	6.6	0.91	0.33–1.99
250–<500	5	4.0	1.26	0.41–2.93	5	3.4	1.47	0.48–3.44
⩾500	6	4.3	1.40	0.51–3.04	5	3.7	1.36	0.44–3.18
Trend test: *P* value			0.31				0.12	
Number of examinations (all cancers)								
1	59	53.0	1.11	0.85–1.44	38	44.1	0.86	0.61–1.18
2	16	16.1	1.00	0.57–1.62	13	13.3	0.97	0.52–1.67
⩾3	25	18.6	1.35	0.87–1.99	20	15.4	1.30	0.80–2.01
Trend test: *P* value			0.33				0.16	

[a] O: observed cases, E: expected cases, SIR: standardised incidence ratio, CI: confidence interval.
[b] See methods section for a definition.
[c] Excluding patients labeled as 'highly exposed'.

Table 3. Incidence rate ratios (IRR) for categories of cumulative effective dose for all cancers and lymphoma and tissue dose for leukemia adjusted for sex and age at diagnosis of cancer obtained through several multilevel Poisson regression models in a cohort of children who underwent diagnostic x-ray procedures at Dr von Hauner Children's Hospital, Munich, Germany, in the period 1976–2003.

		All cancers (I–XII)			Leukemia (I)			Lymphoma (II)		
Group	Dose category[a] (μSv)	Cases	IRR[b]	95% CI[b]	Cases	IRR[b]	95% CI[b]	Cases	IRR[b]	95% CI[b]
6 month latency period										
All patients	0–<10	46	Reference		21	Reference		6	Reference	
	10–<50	30	1.10	0.69–1.75	8	1.15	0.51–2.60	3	1.03	0.24–4.32
	⩾50	24	0.84	0.51–1.37	6	0.93	0.37–2.30	4	1.38	0.37–5.20
All patients without 'highly exposed'[c]	0–<10	46	Reference		20	Reference		6	Reference	
	10–<50	27	1.03	0.64–1.66	8	1.24	0.55–2.82	3	0.79	0.20–3.18
	⩾50	22	0.80	0.48–1.33	6	1.00	0.40–2.48	3	0.79	0.20–3.17
2 year latency period										
All patients	0–<10	30	Reference		12	Reference		3	Reference	
	10–<50	21	1.26	0.72–2.21	6	1.45	0.54–3.86	2	1.18	0.18–7.53
	⩾50	20	1.12	0.64–1.98	6	1.51	0.57–4.03	2	1.17	0.18–7.55
All patients without 'highly exposed'[c]	0–<10	30	Reference		12	Reference		3	Reference	
	10–<50	19	1.17	0.65–2.08	6	1.48	0.55–3.94	2	0.99	0.16–5.98
	⩾50	20	1.16	0.66–2.05	6	1.55	0.58–4.13	2	0.99	0.13–5.95

[a] Effective dose for all cancers and lymphoma, tissue dose for leukemia (red bone marrow dose).
[b] IRR: incidence rate ratio, CI: 95% Wald confidence interval.
[c] See methods section for a definition.

Table 4. Incidence rate ratios (IRR) for categories of cumulative effective dose for blastomas, sarcomas and other solid tumors and organ dose for CNS tumors adjusted for sex and age at diagnosis of cancer obtained through several multilevel Poisson regression models in a cohort of children who underwent diagnostic x-ray procedures at Dr von Hauner Children's Hospital, Munich, Germany, in the period 1976–2003.

		CNS tumors (III)			Blastomas (IV–VII)			Sarcomas (VIII–IX)			Other solid tumors (X–XII)		
Group	Dose category[a] (μSv)	Cases	IRR[b]	95% CI[b]	Cases	IRR[b]	95% CI[b]	Cases	IRR[b]	95% CI[b]	Cases	IRR[b]	95% CI[b]
6 month latency period													
All patients	0–<10	11	Reference		6	Reference		6	Reference		8	Reference	
	10–<50	0			4	1.00	0.28–3.57	7	2.17	0.72–6.51	2	0.57	0.12–2.71
	⩾50	1	0.95	0.12–7.40	5	1.21	0.37–3.98	2	0.57	0.12–2.84	0		
All patients without 'highly exposed'[c]	0–<10	11	Reference		6	Reference		6	Reference		8	Reference	
	10–<50	0			3	0.77	0.19–3.09	6	1.88	0.60–5.90	2	0.59	0.13–2.79
	⩾50	1	0.96	0.12–1.42	5	1.01	0.28–3.59	2	0.59	0.12–2.92	0		
2 year latency period													
All patients	0–<10	8	Reference		4	Reference		5	Reference		7	Reference	
	10–<50	0			2	0.71	0.13–3.93	6	1.95	0.58–6.48	2	0.60	0.12–2.88
	⩾50	0			4	1.35	0.34–5.44	2	0.60	0.12–3.19	0		
All patients without 'highly exposed'[c]	0–<10	8	Reference		4	Reference		5	Reference		7	Reference	
	10–<50	0			1	0.36	0.04–3.21	5	1.63	0.46–5.72	2	0.62	0.13–2.97
	⩾50	0			4	1.38	0.34–5.57	2	0.61	0.12–3.19	0		

[a] Effective dose for blastomas, sarcomas and other solid tumors, organ dose for CNS tumors (brain dose).
[b] IRR: incidence rate ratio, CI: 95% Wald confidence interval.
[c] See methods section for a definition.

A latency period of 2 years for all cancer entities observed yielded 71 incident cancer cases and 680 825 person-years in the cohort. For all cancers combined, the SIR was lower compared to a latency period of 6 months. The same applies to leukemia, lymphomas (in general, and Hodgkin lymphomas and non-Hodgkin lymphomas), and CNS tumors. In the groups of blastomas, sarcomas and other solid tumors, the SIR increased, with other solid tumors remaining significant (table 2). In sensitivity analyses with a latency period of 5 years for CNS tumors, sarcomas, and other solid tumors the SIR for other solid tumors remained significantly raised and the SIR for blastomas became significantly increased (SIR 3.57 95% CI 1.44–7.36) (appendix B). Results for IRR analyses with 2 year latency period again showed no dose-response relationship (table 3), and the same applies for analyses using a 5 year latency period on blastomas, sarcomas and other solid tumors (appendix C). However, it was not possible to perform a dose-response analyses on CNS tumors due to the low number of cases ($n = 7$).

4. Discussion

Our study is the second follow-up, adding further 10 years of follow-up and additional analyses with organ doses, extended latency periods, and subgroups of cancer entities, of a cohort of children with postnatal diagnostic x-ray and the risk of childhood cancer. Overall, 794 549 person-years with a mean of 8.5 years follow-up were observed with 100 incident childhood cancer cases under the age of 15 compared to 87 cases after the first follow-up in a cohort with an overall very low median cumulative effective dose of 7 μSv. The relatively small increase in the mean follow-up time of 14% is due to the fact that many children from the cohort already reached the maximum included age of 14.5 years in the first follow-up until 2006.

Since 2009, three case-control studies [19–21] on postnatal diagnostic x-rays cancer risk have been published. The results of our study are in line with the results of a case-control study of Rajaraman and colleagues, who observed an odds ratio (OR) of 1.16 (95% CI 0.83–1.16) for all cancers in children exposed to diagnostic x-rays in the first 100 days after birth [20]. They also found no statistically significantly increased risks for leukemia or lymphomas and a reduced risk for CNS tumors. In our additional analyses, which were limited to children with diagnostic radiation in the first 100 days after birth we also did not observe an increased risk for all cancers in children. The distribution of the occurring 21 cancer cases of children exposed in the first 100 days after birth was comparable to the distribution of all cancer cases in the cohort. The number of cases in our study was too small for further stratified analyses for cancer entities of this group. In a study of Milne and colleagues focusing on childhood brain tumors, no evidence of a positive association with diagnostic x-ray in childhood had been observed [21]. Bartley and colleagues suggest that postnatal diagnostic x-rays are associated with an increased risk for ALL (OR 1.85 CI 1.12–2.79) when exposed to three or more examinations, but no association for acute myeloid leukemia (AML) was observed [19]. When restricting our analysis on those two subgroups of leukemia patients and comparing children with one postnatal diagnostic x-ray with children with three or more diagnostic x-rays we could not observe an increased risk for ALL (IRR 0.31 95% CI 0.07–1.35) with very low numbers of cases (ten cases with one diagnostic x-ray, two cases with three or more diagnostic x-rays). For AML we found an IRR of 8.50 (95% CI 0.88–81.77), which should be interpreted with caution because of the wide CI resulting from a very small number of cases (one case with one diagnostic x-ray, three cases with three or more diagnostic x-rays).

Overall the risk estimates of this extended follow-up are in line with the null results of the first follow-up, which one would expect with the very low effective doses in this cohort. However, the observed increased risk for other solid tumors for all latency periods (6 months, 2 years, 5 years) must be interpreted with caution since the number of cases for this group ($n = 10$), mainly consisting of germ cell tumors ($n = 6$) and thyroid carcinomas ($n = 3$) is very small. Although an association between radiation exposure and the risk for certain solid tumors like thyroid cancer is well documented [22, 23] our findings could be due to chance because of the small number of cases. For this very reason no more stratified analyses with even smaller subgroups were performed. The individual cumulative effective doses in this cohort, in general, are very low. Of the ten cases of other solid tumors 8 had a cumulative exposure of <10 μSv effective dose and two had between 10 and <50 μSv. At these low doses a radiation-induced significant increased effect would not be expected. The same limitation in terms of the interpretation applies to the increased SIR for blastomas in sensitivity analyses with a 5 year latency period ($n = 7$). Although the cumulative exposure in this group was higher. Four children had a cumulative exposure of $\geqslant 50$ μSv effective dose, two children had between 10 and <50 μSv and one children had <10 μSv.

In the discussion of the recent CT-studies [10, 11, 24–26] and the observed relationship between CT and increased risks for leukemia and brain tumors, the issue of confounding by indication and reverse causation came up since CT is a commonly used technique for diagnosing cancer, particularly solid cancers [27–29]. In our study information on the indication for the x-ray examination and the resulting diagnosis were available for x-rays until 1998. Any patients with an indication of cancer as the reason for the examination were excluded from the cohort. Nevertheless, we cannot completely rule out that certain cancer susceptibility syndromes like the Li-Fraumeni syndrome for leukemia and brain tumors or the Noonan syndrome for leukemia [30] caused an increased risk for childhood cancer or lead to additional CT scans that would confound our results. However, we did not observe an increased risk for leukemia or CNS tumors in our study.

The main strength of this study is avoiding a possible recall bias compared to those case-control studies on childhood cancer after diagnostic x-ray, which use self-reported history of x-rays from the parents [19, 21]. Further strengths of our study are: absorbed doses for organs and tissues were reconstructed individually from medical records at the DvHCH [8] and the identification of incident cancer cases was performed via a registry with a completeness of above 95% of incident cancer cases in Germany and a high data quality [31].

Limitations of this study are: data on exposure was exclusively collected at the radiology department of the DvHCH and patients may have had further x-ray examinations elsewhere. In addition, children could have been exposed to further x-ray examinations before 1976, about which we had no information. Both limitations lead to an underestimation of the exposure. While CT or contrast media examinations were recorded and tagged as 'highly exposed', the corresponding doses were not reconstructed, which leads to an additional underestimation of the individual radiation dose [8]. With the introduction of the RIS at the DvHCH in 1998, information on indication and radiological examination were no longer abstracted from (often handwritten) medical files so children, who were examined to clarify possibly cancer-related symptoms, could not be identified and excluded after 1997. This could lead to a possible overestimation of the observed number of incident cancer cases in childhood. Nevertheless, the risk for a possible overestimation should be reduced by the latency period, especially by the 2 year latency period and the 5 year period in sensitivity analyses for solid tumors. In addition, we did not exclude patients born before the beginning

of the cancer registration at the GCCR in 1980. Therefore, we cannot completely rule out that children born before 1980 had a first incident cancer before 1980 and had a second neoplasm before the age of 15 after 1980, which was documented as a first incident cancer case. Although the number of these cases should be small this could lead to an overestimation of the observed number of incident cancer cases. Results of additional analyses with children born before 1980 excluded were generally in line with the results of the complete cohort and did not change the conclusion (data not shown).

Residual confounding is a further limitation of this study. Possible confounding factors could be in utero exposure to ionising radiation [32], maternal alcohol consumption [33] and smoking [34]. In addition, when calculating SIR, the observed cases in the cohort were compared to the general population that can be exposed to diagnostic x-ray examinations too. An exposure free comparison group for the external comparison would have been more informative, but was unavailable.

5. Conclusion

The analysis of Hammer and colleagues and this extended follow-up analysis suggest that exposure to very low doses of postnatal conventional diagnostic x-rays (median effective dose of 7 μSv) in childhood is not associated with an increased risk for childhood cancer under 15 years. There was no observed increased risk for leukemia, lymphomas, CNS tumors, blastomas and sarcomas compared to the general population and no dose-response relationship. The increased risk for other solid tumors must be critically interpreted in the light of the small number of cases and the very low doses of radiation exposure.

The latest published Commentary No. 27 of the National Council on Radiation Protection and Measurements (NCRP) concludes that recent epidemiologic studies support the use of the linear no-threshold (LNT) model for the purposes of radiological protection, which is in accordance with the older judgments by other national and international scientific committees [35]. In the light of this commentary of the NCRP on LNT and for reasons of radiation protection [36] an extension of this cohort with further follow-up of cancer incidence into adult age and additional dosimetry including CT could be a future goal, which would provide more insight into the risk of cancer in a cohort with very low doses of ionising radiation due to postnatal diagnostic x-ray examination during childhood.

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Appendix A

Table A1. List of ICD-10 codes used to classify patients as having 'high mortality risk' or 'elevated incidence risk' in a cohort of children who underwent diagnostic x-ray procedures at Dr von Hauner Children's Hospital, Munich, Germany, in the period 1976–2003.

Study tags and labels of ICD-10 blocks and diseases	ICD-10 Codes
Patients tagged as having 'high mortality risk' when seen at DvHCH radiology department	
Tuberculosis, Meningococcal infection, Streptococcal septicaemia, Other septicaemia	A15-A19, A39-A41
Human immunodeficiency virus (HIV) disease	B20-B24
Other coagulation defects	D68
Cystic fibrosis, Other metabolic disorders	E84, E88.0
Mental and behavioral disorders due to psychoactive substance use	F10-F19
Inflammatory diseases of the central nervous system, Systemic atrophies primarily affecting the central nervous system, Cerebral palsy and other paralytic syndromes, Other disorders of the nervous system	G00-G09, G10-G13, G80-G83, G90-G99
Acute rheumatic fever, Chronic rheumatic heart diseases, Pulmonary embolism, Endocarditis, Cardiomyopathy, Cerebrovascular diseases, Atherosclerosis, Aortic aneurysm and dissection, Other aneurysm	I00-I02, I05-I09, I26, I30, I38, I43, I60-I69, I71-I72
Acute epiglottitis, Chronic laryngitis and laryngotracheitis	J05.1, J37
Appendicitis, Diverticular disease of intestine, Fissure and fistula of anal and rectal regions, Other diseases of anus and rectum, Peritonitis, Alcoholic hepatic failure, Toxic liver disease with hepatic necrosis, Hepatic failure, Fibrosis and cirrhosis of liver	K35-K36, K57, K60, K62, K65, K70.4, K71.1, K72, K74
Mucocutaneous lymph node syndrome (Kawasaki)	M30.3
Renal failure	N17-N19
Chronic respiratory disease originating in the perinatal period, Necrotising enterocolitis of fetus and newborn, Other disturbances of cerebral status of newborn	P27, P77, P91
Congenital malformations, deformations and chromosomal abnormalities (except Down's syndrome and few other syndroms)	Q00-Q07, Q10-Q18, Q20-Q28, Q30-Q34, Q35-Q37, Q50-Q56, Q60-Q64, Q65-Q79, Q80-Q89 except Q18.1, Q52.8, Q65.8, Q66, Q67.6, Q67.7, Q69, Q70
Injury involving multiple body regions, Poisoning	T00-T07, T36-T50
Patients tagged as having 'elevated incidence risk'	
Agranulocytosis, Immunodeficiency	D70, D80-D83
Crohn's disease, Colitis ulcerosa	K50-K51
Down's syndrome, other chromosomal anomalies	Q90-Q99

[a] International Coding of Diseases, 10th revision.

Appendix B

Table B1. Standardised incidence ratios (SIR) of incident cancer cases with a latency period of 5 years in a cohort of children who underwent diagnostic x-ray procedures at Dr von Hauner Children's Hospital, Munich, Germany, in the period 1976–2003 by cancer type.

	5 year latency period			
	O[a]	E[a]	SIR[a]	95% CI[a]
CNS tumors	7	10.46	0.67	0.27–1.38
Blastomas	7	1.96	3.57	1.44–7.36
Sarcomas	7	7.31	0.96	0.38–1.97
Other solid tumors	7	2.77	2.53	1.02–5.20

[a] O: observed cases, E: expected cases, SIR: standardised incidence ratio, CI: confidence interval.

Appendix C

Table C1. Incidence rate ratios (IRR) for categories of cumulative effective dose for blastomas, sarcomas and other solid tumors and organ dose for CNS tumors adjusted for sex and age at diagnosis of cancer with a latency period of 5 years obtained through several multilevel Poisson regression models in a cohort of children who underwent diagnostic x-ray procedures at Dr von Hauner Children's Hospital, Munich, Germany, in the period 1976–2003.

		CNS tumors (III)			Blastomas (IV–VII)			Sarcomas (VIII–IX)			Other solid tumors (X–XII)		
Group	Dose category[a] (μSv)	Cases	IRR[b]	95% CI[b]	Cases	IRR[b]	95% CI[b]	Cases	IRR[b]	95% CI[b]	Cases	IRR[b]	95% CI[b]
					5 year latency period								
All patients	0–<10	7	Reference		2	Reference		3	Reference		5	Reference	
	10–<50	0			2	2.47	0.22–27.35	3	1.48	0.30–7.36	2	0.63	0.12–3.26
	⩾50	0			4	4.73	0.53–42.43	1	0.47	0.05–4.55	0		
All patients without 'highly exposed'[c]	0–<10	7	Reference		1	Reference		3	Reference		5	Reference	
	10–<50	0			1	1.26	0.08–20.25	2	1.02	0.17–6.11	2	0.65	0.13–3.35
	⩾50	0			4	4.94	0.55–44.33	1	0.49	0.05–4.74	0		

[a] Effective dose for blastomas, sarcomas and other solid tumors, organ dose for CNS tumors (brain dose).
[b] IRR: incidence rate ratio, CI: 95% Wald confidence interval.
[c] See methods section for a definition.

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References

[1] Kaatsch P 2010 Epidemiology of childhood cancer *Cancer Treat. Rev.* **36** 277–85
[2] Buka I, Koranteng S and Osornio Vargas A R 2007 Trends in childhood cancer incidence: review of environmental linkages *Pediatric Clin. North Am.* **54** 177–203
[3] Spector L G, Pankratz N and Marcotte E L 2015 Genetic and nongenetic risk factors for childhood cancer *Pediatric Clin. North Am.* **62** 11–25
[4] Belson M, Kingsley B and Holmes A 2007 Risk factors for acute leukemia in children: a review *Environ. Health Perspect.* **115** 138–45
[5] Walsh L and Kaiser J C 2011 Multi-model inference of adult and childhood leukaemia excess relative risks based on the Japanese A-bomb survivors mortality data (1950–2000) *Radiat. Environ. Biophys.* **50** 21–35
[6] Preston D L, Cullings H, Suyama A, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K, Kasagi F and Shore R E 2008 Solid cancer incidence in atomic bomb survivors exposed in utero or as young children *J. Natl Cancer Inst.* **100** 428–36
[7] Wakeford R 2013 The risk of childhood leukaemia following exposure to ionising radiation—a review *J. Radiol. Prot.* **33** 1–25
[8] Hammer G P, Seidenbusch M C, Schneider K, Regulla D F, Zeeb H, Spix C and Blettner M 2009 A cohort study of childhood cancer incidence after postnatal diagnostic x-ray exposure *Radiat. Res.* **171** 504–12
[9] Linet M S, Kim K P and Rajaraman P 2009 Children's exposure to diagnostic medical radiation and cancer risk: epidemiologic and dosimetric considerations *Pediatric Radiol.* **39** S4–26
[10] Mathews J D *et al* 2013 Cancer risk in 680 000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians *Br. Med. J.* **346** f2360
[11] Pearce M S *et al* 2012 Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study *Lancet* **380** 499–505
[12] Alzen G and Benz-Bohm G 2011 Radiation protection in pediatric radiology *Deutsches Ärzteblatt Int.* **108** 407–14
[13] Shah N B and Platt S L 2008 ALARA: is there a cause for alarm? Reducing radiation risks from computed tomography scanning in children *Curr. Opin. Pediatrics* **20** 243–7
[14] Seidenbusch M C and Schneider K 2008 Zur Strahlenexposition von Kindern in der pädiatrischen Radiologie *Fortschr. Röntgenstr* **180** 1082–103
[15] Brix G, Nekolla E and Griebel J 2005 Radiation exposure of patients from diagnostic and interventional x-ray procedures. Facts, assessment and trends *Radiologe* **45** 340–9
[16] Schnell R, Bachteler T and Reiher T 2005 Ein Record-Linkage-Programm fuer die empirische Sozialforschung *ZA-Inf.* **56** 93–103 (https://nbn-resolving.org/urn:nbn:de:0168-ssoar-131793)
[17] Becher H and Winkler V 2017 Estimating the standardized incidence ratio (SIR) with incomplete follow-up data *BMC Med. Res. Methodol.* **17** 55
[18] Tapiovaara M, Lakkisto M and Sercvomaa A 1997 *PCXMC: A PC-based Monte Carlo Program for Calculating Patient Doses in Medical X-Ray Examinations* Report No. STUK-A139 Finnish Centre for Radiation and Nuclear Safety, Helsinki
[19] Bartley K, Metayer C, Selvin S, Ducore J and Buffler P 2010 Diagnostic x-rays and risk of childhood leukaemia *Int. J. Epidemiol.* **39** 1628–37
[20] Rajaraman P, Simpson J, Neta G, Berrington de Gonzalez A, Ansell P, Linet M S, Ron E and Roman E 2011 Early life exposure to diagnostic radiation and ultrasound scans and risk of childhood cancer: case-control study *Br. Med. J.* **342** d472
[21] Milne E, Greenop K R, Fritschi L, Attia J, Bailey H D, Scott R J, Ashton L J, Smibert E and Armstrong B K 2014 Childhood and parental diagnostic radiological procedures and risk of childhood brain tumors *Cancer Causes Control* **25** 375–83

[22] Iglesias M L, Schmidt A, Ghuzlan A A, Lacroix L, Vathaire F, Chevillard S and Schlumberger M 2017 Radiation exposure and thyroid cancer: a review *Arch. Endocrinol. Metab.* **61** 180–7
[23] Han M A and Kim J H 2018 Diagnostic x-ray exposure and thyroid cancer risk: systematic review and meta-analysis *Thyroid* **28** 220–8
[24] Berrington de Gonzalez A *et al* 2016 Relationship between paediatric CT scans and subsequent risk of leukaemia and brain tumours: assessment of the impact of underlying conditions *Br. J. Cancer* **114** 388–94
[25] Huang W Y, Muo C H, Lin C Y, Jen Y M, Yang M H, Lin J C, Sung F C and Kao C H 2014 Paediatric head CT scan and subsequent risk of malignancy and benign brain tumour: a nation-wide population-based cohort study *Br. J. Cancer* **110** 2354–60
[26] Krille L *et al* 2015 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.* **54** 1–12
[27] Boice J D Jr 2015 Radiation epidemiology and recent paediatric computed tomography studies *Ann. ICRP* **44** 236–48
[28] Journy N, Rehel J L, Ducou Le Pointe H, Lee C, Brisse H, Chateil J F, Caer-Lorho S, Laurier D and Bernier M O 2015 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* **112** 185–93
[29] Walsh L, Shore R, Auvinen A, Jung T and Wakeford R 2014 Risks from CT scans—what do recent studies tell us? *J. Radiol. Prot.* **34** E1–5
[30] Meulepas J M, Ronckers C M, Merks J, Weijerman M E, Lubin J H and Hauptmann M 2016 Confounding of the association between radiation exposure from CT scans and risk of leukemia and brain tumors by cancer susceptibility syndromes *Cancer Epidemiol. Biomarkers Prevention* **25** 114–26
[31] Kaatsch P 2004 German childhood cancer registry and its favorable setting *Bundesgesundheits-blatt Gesundheitsforschung Gesundheitsschutz* **47** 437–43
[32] Linet M S, Kim K P and Rajaraman P 2009 Children's exposure to diagnostic medical radiation and cancer risk: epidemiologic and dosimetric considerations *Pediatric Radiol.* **39** 4–26
[33] van Duijn C M, van Steensel-Moll H A, Coebergh J W and van Zanen G E 1994 Risk factors for childhood acute non-lymphocytic leukemia: an association with maternal alcohol consumption during pregnancy? *Cancer Epidemiol. Biomarkers Prevention* **3** 457–60 (https://cebp.aacrjournals.org/content/cebp/3/6/457.full.pdf)
[34] Rumrich I K, Viluksela M, Vahakangas K, Gissler M, Surcel H M and Hanninen O 2016 Maternal smoking and the risk of cancer in early life—a meta-analysis *PLoS One* **11** e0165040
[35] NCRP 2018 *Implications of Recent Epidemiologic Studies for the Linear Nonthreshold Model and Radiation Protection* Commentary No. 27 Bethesda, MD: National Council on Radiation Protection and Measurements
[36] Shore R E *et al* 2018 Implications of recent epidemiologic studies for the linear nonthreshold model and radiation protection *J. Radiol. Prot.* **38** 1217–33
[37] Steliarova-Foucher E, Stiller C, Lacour B and Kaatsch P 2005 International classification of childhood cancer, third edition *Cancer* **103** 1457–67