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A Cohort Study of Childhood Cancer Incidence after Postnatal Diagnostic X-Ray Exposure

Gaël P. Hammer,[a,1] Michael C. Seidenbusch,[b] Karl Schneider,[b] Dieter F. Regulla,[c] Hajo Zeeb,[a] Claudia Spix[d] and Maria Blettner[a]

[a] Institute for Medical Biostatistics, Epidemiology and Informatics (IMBEI), Johannes Gutenberg-University, Mainz, Germany; [b] Department of Radiology, Dr. von Hauner Children's Medical Hospital, Ludwig-Maximilians-University of Munich, Germany; [c] Helmholtz Zentrum München – German Research Center for Environmental Health GmbH, Neuherberg, Germany; and [d] German Childhood Cancer Registry, Institute for Medical Biostatistics, Epidemiology and Informatics (IMBEI), Johannes Gutenberg-University, Mainz, Germany

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Ionizing radiation is an established cause of cancer, yet little is known about the health effects of doses from diagnostic examinations in children. The risk of childhood cancer was studied in a cohort of 92.957 children who had been examined with diagnostic X rays in a large German hospital during 1976–2003. Radiation doses were reconstructed using the individual dose area product and other exposure parameters, together with conversion coefficients developed specifically for the medical devices and standards used at the radiology department. Newly diagnosed cancers occurring between 1980 and 2006 were determined through record linkage to the German Childhood Cancer Registry. The median radiation dose was 7 μSv. Eight-seven incident cases were found in the cohort: 33 leukemia, 13 lymphoma, 10 central nervous system tumors, and 31 other tumors. The standardized incidence ratio (SIR) for all cancers was 0.99 (95% CI: 0.79–1.22). No trend in the incidence of total cancer, leukemia or solid tumors with increasing radiation dose was observed in the SIR analysis or in the multivariate Poisson regression. Risk did not differ significantly in girls and boys. Overall, while no increase in cancer risk with diagnostic radiation was observed, the results are compatible with a broad range of risk estimates.

INTRODUCTION

Little is known about the causes of childhood cancers. Recent reviews mention genetic disorders, infections, environmental factors and ionizing radiation as risk factors (*1, 2*). Current epidemiological knowledge on radiation risks in children, especially those exposed to low doses of ionizing radiation, is not as good as for that adults, since fewer and smaller study populations could be investigated (*3, 4*). The risk of cancer after childhood exposure to high radiation doses has been investigated in the survivors of the atomic bombs (*5, 6*) and in patients treated with ionizing radiation for either benign diseases (*7–9*) or cancer (*10–14*).

Public awareness about the potential risks of diagnostic uses of ionizing radiation in children was first raised by a publication in 1956 on the risk in children after diagnostic X-ray exposure *in utero* (the Oxford Survey of Childhood Cancers) (*15*), which resulted in major changes in medical practice (*16, 17*). Doll and Wakeford found support for the association reported by Stewart *et al.* in many case-control studies conducted in different countries and estimated the excess absolute risk (EAR) per gray for all childhood cancers to be about 6% (*16*). Similarly, Wakeford and Little compared the risk estimates from studies on persons with *in utero* exposure to the results of the Life-Span Study of atomic bomb survivors and found them to be compatible after accounting for known sources of uncertainty (*18, 19*). Controversy continues regarding the causal interpretation of the association (*20*).

The risk of childhood cancer after postnatal diagnostic irradiation has been studied less extensively (*21–23*). Studies of persons exposed in early childhood have uncertainties similar to those in persons exposed *in utero.* These are related mainly to problems of recall bias and radiation dose reconstruction (*24*).

This publication reports the risk of childhood cancer observed in a cohort of about 100,000 children who had been examined using diagnostic X rays.

MATERIAL AND METHODS

The study was performed by linking a large cohort of children exposed to X rays for diagnostic reasons at the Dr. von Hauner Children's Hospital, University of Munich (DvHCH) to the nationwide German Childhood Cancer Registry (GCCR).

[1] Address for correspondence: Institute for Medical Biostatistics, Epidemiology and Informatics (IMBEI), Johannes Gutenberg-University, Langenbeckstr. 1, D-55101 Mainz, Germany; e-mail: hammer@imbei.uni-mainz.de.

Study Population

The present study includes patients who had been examined in the DvHCH's radiology department between 1976 and 2003 and who were less than 14.5 years of age at the time of first examination. The patients had to be German residents and without any previous diagnosis of cancer. Those who were diagnosed with cancer at or up to 6 months after the first documented X-ray examination in the department were considered as prevalent cases and thus were excluded from the cohort. The referral criteria and diagnoses of examinations were coded according to the International Classification of Diseases, 10th revision (ICD-10), by trained staff.

Source of Data

An electronic documentation system for all diagnostic radiology procedures carried out in the radiology department of the Dr. von Hauner Children's Hospital, University of Munich, Germany, was set up in 1976. In addition to basic information on the individual patients, the documentation also includes information on the body part that was examined, the radiographic views done, and the exposure parameters. Until the introduction of a new Radiological Information System (RIS) in 1998, the referral criteria for the examination and the radiological diagnosis were also recorded. The RIS system does not record these latter items as readily available database fields but instead contains the complete discharge letter.

Exposure Assessment

Individual radiation doses were estimated by using the PAEDOS algorithm developed in the DvHCH's department of radiology. Based on the known exposure parameters for each individual examination, organ doses and whole-body doses were reconstructed for 96% of all examinations. Details have been described elsewhere[2] (*25, 26*).

Briefly, PAEDOS uses conversion coefficients to derive organ doses and whole-body doses from the entrance dose or the dose area product for the given examination. These conversion coefficients were determined for all combinations of examination type, target organ and patient age occurring at the DvHCH using the Monte Carlo software PCXMC developed by the Finnish Radiation and Nuclear Safety Authority (*27*). This software virtually irradiates hermaphrodite mathematical phantoms of different sizes based on the following parameters: individual records comprising age at exposure, type of examination, target organ, as well as the individual dose area product and other known exposure parameters such as the direction of the beam projection, the patient's position, the distance from source to detector, field dimensions, tube voltage and filtering. These parameters were taken from the study database, and missing parameters were reconstructed from other available data and the documentation of the radiological procedures. When available information was insufficient, no dose was estimated.

About 3.7% of the patients were diagnosed using computed tomography (CT) or contrast medium examinations. These examinations were recorded, but corresponding doses were not reconstructed. This task is much more complex and is planned for the future. As described in the Data Analysis section below, these patients were assigned a special tag. The first CT scanner was installed in the department in 1997.

In the present study, cumulative effective dose (in μSv) was used. Missing doses were replaced with the median dose of subjects of the same age and sex examined in the same year.

[2] M. Seidenbusch, *Rekonstruktion von Organ- und Effektivdosen bei konventionellen Röntgenuntersuchungen am Dr. von Haunerschen Kinderspital der Universität München mit einer Berechnung neuer Konversionsfaktoren für die pädiatrische Radiologie (Dissertation).* LMU München: Medizinische Fakultät, 2006.

Cancer Incidence

Cohort follow-up for newly diagnosed cancers occurring between 1980 and 2006 was done through the GCCR. The GCCR records all childhood cancers (under 15 years old at diagnosis) in Germany since 1980 with a high degree of completeness for most childhood cancer types; only brain tumors are somewhat under-reported, especially in Upper Bavaria. The GCCR has been used previously as a study base for several large-scale childhood cancer investigations at the national and international level (*28–30*). Pseudonymized cohort data were linked to the pseudonymized data of the GCCR using the software Merge Toolbox for stochastic record linkage (*31*). An experienced medical documentalist reviewed all matches.

Estimation of Person-Years

All persons in the cohort contributed person-years of observation starting 6 months after the date of initial attendance in the radiology department until whichever of the following came first: date of cancer diagnosis, their 15th birthday, or December 31, 2006. This method of computing person-years overestimates the true figure slightly since mortality is not taken into account. Childhood mortality rates are very low; therefore, a mortality follow-up was not done. To compensate for this, (1) patients with a high *a priori* mortality risk were tagged, and (2) person-years accumulated after the individual date of last X-ray examination were discounted for non-cancer mortality by multiplying person-years by the appropriate survival rates. For this, childhood mortality rates for West Germany (excluding Berlin)[3] were used.

Data Analysis

The analyses were restricted to the following cancer groups: all cancers, all leukemia, lymphocytic leukemia, acute myeloid leukemia, tumors of the central nervous system (CNS), lymphoma, and all other cancers.

Risks were quantified by calculating standardized incidence ratios (SIR) and incidence rate ratios (IRR) with 95% confidence intervals (CI). For the SIR calculations, the cancer incidence rates in West Germany (excluding Berlin) provided by the GCCR were used as the reference. The cumulative effective dose (in μSv) was used as exposure measure for all cancers, using a latent period of 6 months. In the SIR analyses, dose was categorized as <1, 1–4.99, 5–9.99, 10–24.99, 25–49.99, 50–99.99, 100–249.99, 250–499.99 and 500+ μSv. Additionally, the number of examinations (categorized as 1, 2, 3+) was used as a dose proxy to achieve comparability with previous studies. In the IRR analyses, Poisson regression was used to describe incidence rate ratios for all cancers, leukemia, and lymphoma and solid tumors by dose categorized as 0–9.99, 10–49.99 and 50+ μSv, adjusted by age and sex. To allow for a nonlinear effect of age at diagnosis, it was categorized as 0–4, 5–9 and 10–14 years in the regression analysis.

The cohort included some heterogeneous subgroups of patients. Individual children were labeled accordingly, based on the available diagnostic or exposure information. Each individual could be in more than one group.

1. Children were labeled as ''high mortality risk'' if their diagnoses were included in a predefined list of ICD-10 codes for serious diseases such as AIDS, complex congenital heart defects, cystic fibrosis or hydrocephalus (Table 1).
2. Likewise, children with syndromes known to be associated with elevated cancer incidence (e.g. Down's syndrome) included on a second list of ICD-10 codes were marked as ''elevated incidence risk''.
3. Premature children were tagged separately as ''premature'' when this was noted as an indication or diagnosis. These children carry an in-

[3] Since the German reunification, incidence and mortality rate are available only for Berlin as a whole instead of just West Berlin. Thus including Berlin would have led to comparability problems.

TABLE 1
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[a] 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, Necrotizing 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 a few other syndromes)	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.

creased mortality risk and repeatedly undergo X-ray examinations to check the development of the lungs.

4. Patients with recorded CT or contrast media examinations were labeled as ''highly exposed''. As noted above, exposures from these examinations were not reconstructed. Person time for such patients counted as ''high exposure'' from the date of first CT or contrast media examination onward.
5. Children for whom the indication for examination and the diagnosis were completely missing because the RIS system does not record this information could not be tagged in the same manner as other children. These children were marked as ''RIS'' patients.

Ethical Approval

The study has been reviewed and approved by the ethics committee of the German federal state of Rhineland-Palatinate.

RESULTS

Cohort

The initial cohort consisted of 105,847 patients, of whom 12,890 were excluded: 9757 were 14.5 years or older at their first X-ray examination, 1547 were 15 years or older at the beginning of follow-up, six were examined after 2003, 993 had a prevalent cancer at first examination, 395 had a cancer diagnosis within 6 months after first examination, 16 were diagnosed with cancer before 1980, and 176 had inconsistent dates of birth and examinations that could not be corrected. The net cohort consists of 92,957 children: 50,005 boys, 41,432 girls, and 1520 of unknown sex (Table 2).

On average, 3423 patients per year newly entered the cohort. The mean age of patients entering the cohort was 5.6 years, with 20,546 (22.1%) entering the cohort below 1 year of age and 9096 (9.8%) at 1 year of age. Nearly one quarter of all patients (n = 21,319, 23%) entered the cohort in 1998 or later, the ''RIS'' patients (Table 2). Among the other 71,638 patients, 14,174 (19.8%) were tagged as ''high mortality risk'', 398 (0.6%) as ''elevated incidence risk'' and 279 (0.4%) as ''premature''. A total of 3428 patients were tagged as ''highly exposed'', 442 (2.1%) among ''RIS'' patients and 2986 (4.2%) among the others.

The patients contributed a total of 726,200 person-years of observation time, of which 107,612 person-years (14.8%) were from ''RIS'' patients. The mean follow-up time was 7.8 years (Table 2).

TABLE 2
Selected Characteristics of the Cohort of Children who Underwent Diagnostic X-Ray Procedures at Dr. von Hauner Children's Hospital, Munich, Germany, in the Period 1976–2003

	All patients	Incident cancer cases
All patients	92957	87
Boys	50005	52
Girls	41432	35
Patients labeled as having ''high mortality risk''[a,b]	14174	25
Patients tagged as having ''elevated incidence risk''[a,b]	398	0
Premature children[a,b]	279	0
''RIS'' patients[a]	21319	17
Highly exposed in total	3428	4
non-''RIS'' patients	2986	3
''RIS'' patients	442	1
Age at first X-ray exposure (years) 0	20546	35
1	9096	11
2	6945	9
3	6202	7
4	6387	6
5–9	24891	14
10–14	18890	5
Number of examinations per patient 1	54605	35
2	17818	19
3	7515	9
4	4042	4
5	2341	7
6	1611	1
7	1128	1
8	737	2
9	561	1
10+	2599	6
Person-time of observation (years)	726200.6	318.4
among ''RIS'' patients	107612.2	48.3
estimated using mortality rates[a]	678218.9	0.0
Mean follow-up time (years)	7.8	3.7
Cumulative dose (μSv): median, interquartile range	7.0, 1.0–48.0	22.5, 6.0–111.0
Cumulative dose (μSv): mean ± SD	134.7 ± 2083.2	116.4 ± 353.2

[a] See Material and Methods section for definition.
[b] This tag could be assigned only for non-''RIS'' patients.

In total, 87 incident cancer cases (52 in boys and 35 in girls) were found in the GCCR's files (Table 3). Seventeen of the incident cancer cases were in ''RIS'' patients (nine boys and eight girls). No cases were found among patients marked as ''elevated incidence risk'' or ''premature''. Nine additional suspected cases were identified from hospital records. Because they would not be included in the denominator for rate comparisons, they were excluded from the main analysis.

Exposure

Most patients (n = 54,605, 59%) had only one recorded examination. A further 17,818 (19%) patients had two, 7515 (8%) had three, and 13019 (14%) had four or more examinations, the maximum being 120 for one patient. The median radiation dose per individual examination declined from 18 μSv [interquartile range (IR): 8–66 μSv] in 1976 to 3 μSv (IR: 0–8 μSv) in the year 2002, with a marked drop in 1982 due to changes in procedures. The median exposure per examination was highest (25 μSv, IR: 10–90 μSv) in 0-year-olds and lowest (<1 μSv) in 12- to 14-year-olds.

Individual cumulative dose (Fig. 1) ranged from 0 to 343.4 mSv, with a median of 7 μSv (IR: 0–48 μSv) and arithmetic mean of 135 μSv, and did not differ in boys and girls. A total of 1984, 77 and seven patients had doses ≥1, 10 and 100 mSv, respectively. In cancer cases, the median and mean cumulative dose were 22 μSv (IR: 6–111 μSv) and 116 μSv, respectively (Table 2). Two cases had cumulative doses above 1 mSv: 1.04 and 3.13 mSv.

Medical procedures involving ''high exposures'' (CT scans and or contrast media examinations) were mostly used among children with higher mortality risk: Among the 2986 non-''RIS'' cohort members classified as ''highly exposed'', 2223 (74.4%) were classified as having ''high mortality risk'', 89 as having ''elevated incidence risk'', and 260 as ''premature''.

TABLE 3
Number of Incident Cancer Cases Occurring in the Period 1980–2003, by Cancer Diagnosis, Sex and Age at Diagnosis, 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			
Diagnosis	ICCC-3[a]	Boys	Girls	0	1–4	5–9	10–14
All cancers	I–XII	52	35	0	34	28	25
Leukemias, myeloproliferative diseases, and myelodysplastic diseases	I	19	14	0	15	9	9
Lymphocytic leukemia	Ia	15	9	0	14	5	5
Acute myeloid leukemia	Ib	2	3	0	0	2	3
Other leukemias	Ic–Ie	2	2	0	1	2	1
Lymphoma	II	11	2	0	5	6	2
CNS tumors	III	7	3	0	3	4	3
Neuroblastoma and other peripheral nervous cell tumors	IV	1	3	0	2	2	0
Retinoblastoma	V	1	0	0	1	0	0
Renal tumors	VI	5	2	0	3	4	0
Hepatic tumors	VII	2	0	0	1	0	1
Malignant bone tumors	VIII	1	0	0	0	0	1
Soft tissue and other extraosseous sarcomas	IX	2	7	0	4	3	2
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	X	2	3	0	0	0	5
Other malignant epithelial neoplasms and malignant melanomas	XI	1	1	0	0	0	2
Other and unspecified malignant neoplasms	XII	0	0	0	0	0	0

[a] International Classification of Childhood Cancers, 3rd revision (*38*).

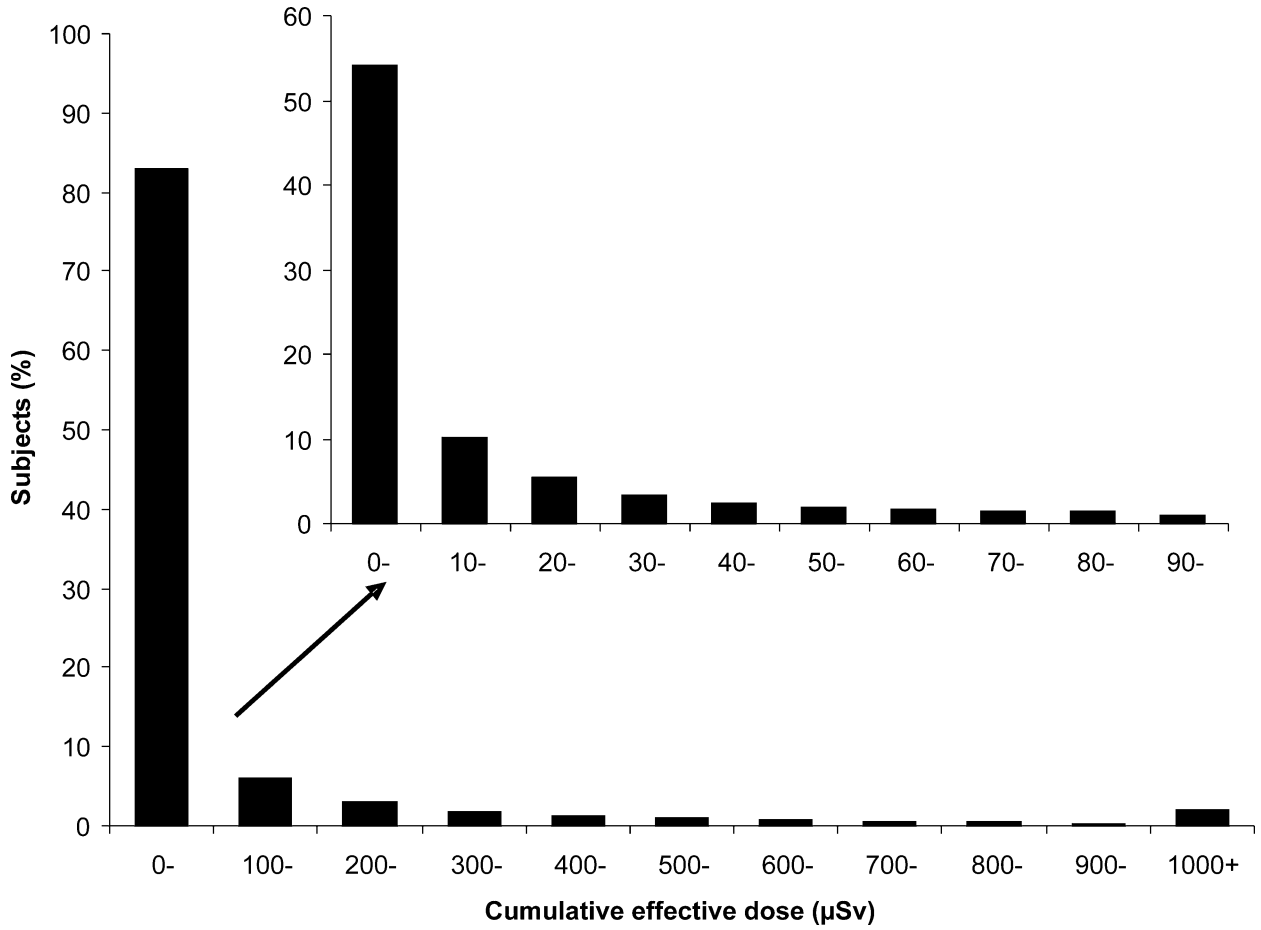

FIG. 1. Histogram of cumulative dose (in μSv) in a cohort of children who underwent diagnostic X-ray procedures at Dr. von Hauner Children's Hospital, Munich, Germany, in the period 1976–2003. The inset shows in greater detail the distribution of doses over the range of 0–100 μSv, which together comprise the first bar in the larger figure.

TABLE 4
Observed and Expected Numbers of Incident Cancer Cases and Standardized Incidence Ratios (SIR) of Cohort Members by Cancer Type, Sex, Assigned Tags, Cumulative Exposure and Number of Examinations

	O[a]	E	SIR	95% CI
All cancers	87	88.0	0.99	0.79–1.22
Leukemia, myeloproliferative diseases, and myelodysplastic diseases	33	30.5	1.08	0.74–1.52
Lymphocytic leukemia	24	24.5	0.98	0.63–1.45
Acute myeloid leukemia	5	4.3	1.16	0.38–2.70
Lymphoma	13	13.4	0.97	0.52–1.66
Tumors of the central nervous system	10	19.3	0.52	0.25–0.95
Other tumors	31	24.8	1.25	0.85–1.77
Sex				
Boys	52	52.8	0.99	0.74–1.29
Girls	35	35.2	1.00	0.69–1.38
Patients tagged as having ''high mortality risk''[b,c]				
No	52	56.1	0.93	0.69–1.22
Yes	18	16.4	1.10	0.65–1.74
Highly exposed patients[b]				
No	83	84.4	0.98	0.78–1.22
Yes	4	3.7	1.09	0.30–2.78
Exposure category (μSv) (all cancers)				
<1	16	22.2	0.72	0.41–1.17
1–	10	10.9	0.92	0.44–1.69
5–	14	10.7	1.31	0.72–2.19
10–	12	13.2	0.91	0.47–1.59
25–	11	8.2	1.35	0.67–2.41
50–	6	7.1	0.84	0.31–1.84
100–	8	7.4	1.08	0.47–2.13
250–	5	3.9	1.27	0.41–2.96
500+	5	4.5	1.12	0.36–2.62
trend test: *P* value			0.32	
Exposure category (μSv) (leukemia and lymphoma)				
<1	8	18.1	0.44	0.19–0.87
1–	5	9.2	0.55	0.18–1.27
5–	8	9.1	0.87	0.38–1.72
10–	9	11.4	0.79	0.36–1.50
25–	3	7.1	0.43	0.09–1.24
50–	4	6.1	0.65	0.18–1.67
100–	3	6.4	0.47	0.10–1.38
250–	4	3.4	1.19	0.32–3.04
500+	2	3.8	0.52	0.06–1.90
trend test: *P* value			0.26	
Number of examinations (all cancers)				
1	53	54.4	0.97	0.73–1.27
2	14	15.4	0.91	0.50–1.52
3+	20	18.2	1.10	0.67–1.70

[a] O: observed cases, E: expected cases, SIR: standardized incidence ratio, CI: confidence interval.
[b] See Material and Methods section for definition.
[c] This tag could be assigned only for non-''RIS'' patients.

SIR Analysis

The overall SIR was 0.99 (95% CI: 0.79–1.22), based on 87 cases (Table 4). SIRs generally did not differ between sexes. The SIR for all cancers was 0.99 (95% CI: 0.74–1.29) for boys and 1.00 (95% CI: 0.69–1.38) for girls. SIRs were not significantly different from 1.0 for any cancer entity except CNS tumors (all of which were brain tumors), for which it was 0.52 (95% CI: 0.25–0.95). An SIR below unity was observed for the lowest dose category (<1 μSv) and above unity for most other dose categories, although none was significant and no trend was observed (Fig. 1). The same pattern is observed for the number of examinations.

IRR Analysis

There were only four cases among the patients labeled as ''highly exposed'', so no regression model was fitted for this group. Among the other patients, IRRs adjusted for age

TABLE 5
Incidence Rate Ratios (IRR) for Categories of Cumulative Effective Dose (in mSv) 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

Group	Exposure category (μSv)	All cancers				Leukemia and lymphoma				Solid tumors			
		Cases	IRR[a]	95% CI[a]	*P* value	Cases	IRR	95% CI	*P* value	Cases	IRR	95% CI	*P* value
All patients[b,c]	0–9.9	40	1.00			21	1.00			19	1.00		
	10–49.9	21	1.02	0.60–1.74	0.93	11	1.00	0.48–2.07	0.99	10	1.05	0.49–2.27	0.89
	50+	22	1.01	0.60–1.71	0.96	12	1.04	0.51–2.12	0.91	10	0.98	0.46–2.12	0.97
Patients with "high mortality risk"[c,d]	0–9.9	3	1.00			2	1.00			1	1.00		
	10–49.9	3	0.55	0.11–2.76	0.47	1	0.26	0.02–2.93	0.28	2	1.16	0.10–12.78	0.91
	50+	9	0.61	0.16–2.26	0.46	4	0.39	0.07–2.16	0.28	5	1.05	0.12–9.03	0.97
Other patients	0–9.9	37	1.00			19	1.00			18	1.00		
	10–49.9	18	1.08	0.61–1.89	0.80	10	1.13	0.53–2.44	0.75	8	1.01	0.44–2.34	0.97
	50+	13	1.04	0.55–1.96	0.89	8	1.24	0.54–2.83	0.61	5	0.84	0.31–2.25	0.72

[a] IRR: incidence risk ratio, CI: Wald confidence interval.
[b] Excluding patients labeled as "highly exposed".
[c] See Material and Methods section for definition.
[d] This flag could be assigned only for non-"RIS" patients.

and sex did not differ from unadjusted IRR. No significant risk increase and no trend were observed for all cancers combined, for leukemia and lymphoma, or for solid tumors combined (Table 5). Patients with "high mortality risk" had IRR below unity for all cancers combined (15 cases), driven by the low IRR for leukemia and lymphoma (seven cases). In other patients, non-significant IRRs of 1.13 (95% CI: 0.53–2.44) and 1.24 (95% CI: 0.54–2.83) were observed for leukemia and lymphoma in the dose categories 10-49.9 μSv and 50+ μSv compared to <10 μSv (total 37 cases), while no elevation was seen for solid tumors (31 cases).

DISCUSSION AND CONCLUSION

This study investigated the childhood cancer risk associated with postnatal diagnostic ionizing radiation exposure in a large cohort of children who underwent diagnostic radiological procedures and were followed up through the nationwide and comprehensive childhood cancer registry in Germany.

Overall, no increase in the risk of solid tumors or leukemia in childhood associated with radiation exposure was observed in this cohort, nor was an increase in risk observed in patients labeled as having had high exposures or "high mortality risk". The apparent risk reduction for brain tumors might be explained by the documented under-reporting in Upper Bavaria and fact that, in Munich, they are often treated in hospitals other than the DvHCH, where the chance of reporting to the GCCR is even lower.

The strengths of this cohort study are the large population included in the study, the prospective assessment of detailed exposure data over a long period, the ability to reconstruct absorbed doses, and the independent case ascertainment through a cancer registry with a high degree of completeness. This avoids the problem of recall bias encountered in case-control studies. On the other hand, the use of only one source of data bears the risk of missing exposures for some children. This could be of particular relevance should the participants have had procedures which might involve high radiation doses, such as computed tomography (CT). Doses for CT or contrast media examinations were not reconstructed. However, three quarters of cohort members with such exposures were classified *a priori* as having "high mortality risk". The low radiation exposure in the cohort, with a median cumulative dose of 7 μSv, reflects the constant efforts of the DvHCH radiology department to optimize and document instruments and procedures. The DvHCH is the largest children's hospital in Munich; there is a small chance that the children seen here could have received large doses of radiation elsewhere. An underestimation of the radiation dose would most likely have led to an overestimation of risks, which does not seem to be the case here.

A further limitation lies in the practical restrictions imposed by the Radiological Information System introduced in 1998. While in principle some of the necessary information such as the indication for the radiological examination and the resulting diagnosis is available from scanned (often handwritten) medical files, abstracting this information would have meant a huge amount of manual record review. This could not be done in the framework of the current study.

Sensitivity analyses including the nine cases ascertained from hospital records generated essentially unchanged results. For four of these nine cases, there were plausible explanations why they were not reported to the GCCR: Two brain tumors and an ovarian cancer were probably treated in an adult ward, and the fourth was an HIV-positive patient

with lymphoma. Intensified manual search in the GCCR did not yield any linkable records for these cases.

To the authors' knowledge, there are no cohort studies directly comparable to the one presented here. Previous case-control studies conducted in Germany involving children exposed to postnatal diagnostic X rays did not show any increased risk for leukemia or solid tumors (*23, 32*). In recent large case-control studies, Shu *et al.* found a significant increase in the risk of total cancer with the number of postnatal exposures (*34*), and both Shu *et al.* and Infante-Rivard *et al.* reported increases in the risk of acute leukemia with the number of exposures (*21, 33*). In another study by Shu *et al.*, no such increase for acute leukemia was observed (*22*). In a recent report from the life-span study of atomic bomb survivors, Preston *et al.* found a significant excess relative risk of solid cancer in teens and adults with postnatal and *in utero* doses. The risks decline with attained age and are 1.70 per Sv (95% CI: 1.1–2.5) at age 50 (*6*). In contrast to earlier studies, a recent review of studies on prenatal and postnatal diagnostic exposures and the risk of childhood cancer (*24*) found no evidence for an increased risk of leukemia in studies published since 1990.

The results of the present large cohort study suggest that postnatal exposure to diagnostic X rays is not linked to an appreciable increase in the incidence of solid tumors or leukemia in this cohort. No trends with increasing radiation dose from diagnostic imaging were detected. It should be noted that only 2.1% of all patients, including two cases, had cumulative doses above 1000 μSv.

The relevance of the present findings needs to be assessed in the light of current trends in diagnostic imaging. There has been an increase in the use of computed tomography, including on children, which has led to a significant increase in patient exposure (*35*). These developments pose a continuous challenge for the quantification of cancer risk from diagnostic radiography and associated issues such as improved radiation protection. Recently, Brenner and Hall and Chodick *et al.* estimated the number of excess lifetime cancer cases due to CT examinations in the U.S. (*35*) and Israel (*36*), respectively, using frequency data for CT scans and cancer risk models. They concluded that CT examinations during childhood present non-negligible lifetime health risks. Their findings were criticized because they applied models used in radiation protection for adults. Clearly, more data obtained directly from observational studies among children exposed to diagnostic radiation are required, and the current large, well-documented cohort study contributes to this. It can also serve as a base for further investigations. An extension of the current study including doses from CT and contrast media is planned for the future, as is a further follow-up of cancer incidence and mortality, also into adult age.

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REFERENCES

1. C. A. Stiller, Epidemiology and genetics of childhood cancer. *Oncogene* **23**, 6429–6444 (2004).
2. M. Greaves, Infection, immune responses and the aetiology of childhood leukaemia. *Nat. Rev. Cancer* **6**, 193–203 (2006).
3. UNSCEAR, *Sources and Effects of Ionizing Radiation—Report to the General Assembly, with Scientific Annexes.* United Nations, New York, 2000.
4. National Research Council, Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, *Health Risks from Exposure to Low Levels of Ionizing Radiation (BEIR VII-Phase 2).* National Academies Press, Washington, DC, 2006.
5. R. R. Delongchamp, K. Mabuchi, Y. Yoshimoto and D. L. Preston, Cancer mortality among atomic bomb survivors exposed *in utero* or as young children, October 1950–May 1992. *Radiat. Res.* **147**, 385–395 (1997).
6. D. L. Preston, H. Cullings, A. Suyama, S. Funamoto, N. Nishi, M. Soda, K. Mabuchi, K. Kodama, F. Kasagi and R. E. Shore, Solid cancer incidence in atomic bomb survivors exposed *in utero* or as young children. *J. Natl. Cancer Inst.* **100**, 428–436 (2008).
7. E. Ron, B. Modan and J. D. Boice, Mortality after radiotherapy for ringworm of the scalp. *Am. J. Epidemiol.* **127**, 713–725 (1988).
8. R. E. Shore, M. Moseson, X. Xue, Y. Tse, N. Harley and B. S. Pasternack, Skin cancer after X-ray treatment for scalp ringworm. *Radiat. Res.* **157**, 410–418 (2002).
9. S. Sadetzki, A. Chetrit, A. Lubina, M. Stovall and I. Novikov, Risk of thyroid cancer after childhood exposure to ionizing radiation for tinea capitis. *J. Clin. Endocrinol. Metab.* **91**, 4798–4804 (2006).
10. F. Nguyen, C. Rubino, S. Guerin, I. Diallo, A. Samand, M. Hawkins, O. Oberlin, D. Lefkopoulos and V. F. De, Risk of a second malignant neoplasm after cancer in childhood treated with radiotherapy: correlation with the integral dose restricted to the irradiated fields. *Int. J. Radiat. Oncol. Biol. Phys.* **70**, 908–915 (2008).
11. J. P. Neglia, D. L. Friedman, Y. Yasui, A. C. Mertens, S. Hammond, M. Stovall, S. S. Donaldson, A. T. Meadows and L. L. Robison, Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. *J. Natl. Cancer Inst.* **93**, 618–629 (2001).
12. S. Garwicz, H. Anderson, J. H. Olsen, H. Dollner, H. Hertz, G. Jonmundsson, F. Langmark, M. Lanning, T. Moller and H. Tulinius, Second malignant neoplasms after cancer in childhood and adolescence: a population-based case-control study in the 5 Nordic countries. The Nordic Society for Pediatric Hematology and Oncology. The Association of the Nordic Cancer Registries. *Int. J. Cancer* **88**, 672–678 (2000).
13. M. C. Cardous-Ubbink, R. C. Heinen, P. J. Bakker, B. H. van den, F. Oldenburger, H. N. Caron, P. A. Voute and F. E. van Leeuwen, Risk of second malignancies in long-term survivors of childhood cancer. *Eur. J. Cancer* **43**, 351–362 (2007).
14. G. Klein, J. Michaelis, C. Spix, R. Wibbing, G. Eggers, J. Ritter and P. Kaatsch, Second malignant neoplasms after treatment of childhood cancer. *Eur. J. Cancer* **39**, 808–817 (2003).
15. A. Stewart, J. Webb, D. Giles and D. Hewitt, Malignant disease in childhood and diagnostic radiation *in utero*. *Lancet* **1**, 447 (1956).
16. R. Doll and R. Wakeford, Risk of childhood cancer from fetal irradiation. *Br. J Radiol.* **70**, 130–139 (1997).
17. M. Belson, B. Kingsley and A. Holmes, Risk factors for acute leu-

kemia in children: a review. *Environ. Health Perspect.* **115**, 138–145 (2007).

18. R. Wakeford and M. P. Little, Childhood cancer after low-level intrauterine exposure to radiation. *J. Radiol. Prot.* **22**, A123–A127 (2002).
19. R. Wakeford and M. P. Little, Risk coefficients for childhood cancer after intrauterine irradiation: a review. *Int. J Radiat. Biol.* **79**, 293–309 (2003).
20. J. D. Boice, Jr. and R. W. Miller, Childhood and adult cancer after intrauterine exposure to ionizing radiation. *Teratology* **59**, 227–233 (1999).
21. C. Infante-Rivard, G. Mathonnet and D. Sinnett, Risk of childhood leukemia associated with diagnostic irradiation and polymorphisms in DNA repair genes. *Environ. Health Perspect.* **108**, 495–498 (2000).
22. X. O. Shu, J. D. Potter, M. S. Linet, R. K. Severson, D. Han, J. H. Kersey, J. P. Neglia, M. E. Trigg and L. L. Robison, Diagnostic X-rays and ultrasound exposure and risk of childhood acute lymphoblastic leukemia by immunophenotype. *Cancer Epidemiol. Biomarkers Prev.* **11**, 177–185 (2002).
23. R. Meinert, U. Kaletsch, P. Kaatsch, J. Schuz and J. Michaelis, Associations between childhood cancer and ionizing radiation: results of a population-based case-control study in Germany. *Cancer Epidemiol. Biomarkers Prev.* **8**, 793–799 (1999).
24. R. Schulze-Rath, G. P. Hammer, M. Blettner and H. Zeeb, Are pre- or postnatal diagnostic X-rays a risk factor for childhood cancer? A systematic review. *Radiat. Environ. Biophys.* **47**, 301–312 (2008).
25. M. C. Seidenbusch and K. Schneider, Zur Strahlenexposition von Kindern in der pädiatrischen Radiologie Teil 1: Indikationen und Röntgenuntersuchungshäufigkeiten in der konventionellen radiologischen Diagnostik an einer Universitäts-Kinderklinik zwischen 1976 und 2003. *Fortschr. Röntgenstr.* **180**, 410–422 (2008).
26. M. C. Seidenbusch, D. Regulla and K. Schneider, Zur Strahlenexposition von Kindern in der pädiatrischen Radiologie. Teil 2: Der PÄDOS-Algorithmus zur rechnergestützten Dosisrekonstruktion in der Kinderradiologie am Beispiel der Röntgenuntersuchung des Schädels. *Fortschr. Röntgenstr.* **180**, 522–539 (2008).
27. M. Tapiovaara, M. Lakkisto and A. Servomaa, *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, 1997.
28. F. H. Schilling, C. Spix, F. Berthold, R. Erttmann, J. Sander, J. Treuner and J. Michaelis, Children may not benefit from neuroblastoma screening at 1 year of age. Updated results of the population based controlled trial in Germany. *Cancer Lett.* **197**, 19–28 (2003).
29. P. Kaatsch, E. Steliarova-Foucher, E. Crocetti, C. Magnani, C. Spix and P. Zambon, Time trends of cancer incidence in European children (1978–1997): Report from the Automated Childhood Cancer Information System project. *Eur. J. Cancer* **42**, 1961–1971 (2006).
30. C. Spix, D. Eletr, M. Blettner and P. Kaatsch, Temporal trends in the incidence rate of childhood cancer in Germany 1987–2004. *Int. J. Cancer* **122**, 1859–1867 (2008).
31. R. Schnell, T. Bachteler and J. Reiher, Ein Record-Linkage-Programm für die empirische Sozialforschung. *ZA-Information* **56**, 93–103 (2005).
32. J. Schüz, U. Kaletsch, P. Kaatsch, R. Meinert and J. Michaelis, Risk factors for pediatric tumors of the central nervous system: results from a German population-based case-control study. *Med. Pediatr. Oncol.* **36**, 274–282 (2001).
33. X. O. Shu, F. Jin, M. S. Linet, W. Zheng, J. Clemens, J. Mills and Y. T. Gao, Diagnostic X-ray and ultrasound exposure and risk of childhood cancer. *Br. J. Cancer* **70**, 531–536 (1994).
34. D. F. Regulla and H. Eder, Patient exposure in medical X-ray imaging in Europe. *Radiat. Prot. Dosimetry* **114**, 11–25 (2005).
35. D. J. Brenner and E. J. Hall, Computed tomography—an increasing source of radiation exposure. *N. Engl. J. Med.* **357**, 2277–2284 (2007).
36. G. Chodick, C. M. Ronckers, V. Shalev and E. Ron, Excess lifetime cancer mortality risk attributable to radiation exposure from computed tomography examinations in children. *Isr. Med. Assoc. J.* **9**, 584–587 (2007).
37. E. Steliarova-Foucher, C. Stiller, B. Lacour and P. Kaatsch, International Classification of Childhood Cancer, third edition. *Cancer* **103**, 1457–1467 (2005).