Childhood Cancer Risk From Conventional Radiographic Examinations for Selected Referral Criteria: Results From a Large Cohort Study

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OBJECTIVE. Little is known about the long-term effects of exposure to diagnostic ionizing radiation in childhood. Current estimates are made with models derived mainly from studies of atomic bomb survivors, a population that differs from today's patients in many respects.

MATERIALS AND METHODS. We analyzed the cancer incidence among children who underwent diagnostic x-ray exposures between 1976 and 2003 in a large German university hospital. We reconstructed individual radiation doses for each examination and sorted results by groups of referral criteria for all cancers combined, solid tumors, and leukemia and lymphoma combined.

RESULTS. A total of 68 incidence cancer cases between 1980 and 2006 were identified in a 78,527-patient cohort in the German childhood cancer registry: 28 leukemia, nine lymphoma, six tumors of the CNS, and 25 other tumors. The standardized incidence ratio for all cancers was 0.97 (95% CI, 0.75–1.23). Dose-response relations were analyzed by multivariable Poisson regression. Although the cancer incidence risk differed by initial referral criterion for radiographic examination, a positive dose-response relation was observed in five patients with endocrine or metabolic disease.

CONCLUSION. Overall, we observed no increase in cancer risk among children and youths with very low radiation doses from diagnostic radiation, which is compatible with model calculations. The growing use of CT warrants further studies to assess associated cancer risk. Our work is an early contribution of epidemiologic data for quantifying these risks among young patients.

Keywords: cancer, child, cohort studies, incidence, ionizing radiation, risk

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Diagnostic radiation is an indispensable tool of modern medicine. The immediate benefit to the individual patient can be great. However, the growing use of x-rays, particularly in CT procedures on children and adolescents, raises concern over long-term risks associated with medical radiologic diagnostics [1–5]. Results of studies of atomic bomb survivors and other populations exposed to ionizing radiation indicate that children are more sensitive to the health effects of radiation than adults are [6, 7]. The long-term risks of diagnostic radiation have been investigated in several epidemiologic studies [8, 9], among them only six cohort studies. A common weakness of these studies is the lack of individual dosimetry because of the tremendous difficulties of retrospective dose reconstruction. Risk estimates derived from these studies are thus associated with great uncertainty [9].

Current risk estimates for childhood exposure to diagnostic ionizing radiation are based on theoretic models derived mainly from the studies of atomic bomb survivors. For lack of better data, these models are currently used in predicting cancer risk in the population due to medical diagnostic measures and to stimulate discussion of the necessity and justification of such procedures [2, 10]. However, exposure patterns, genetic background, and lifestyle differ markedly between atomic bomb survivors and today's patients [6], and there are substantial uncertainties regarding the transfer of risk estimates between these populations [11, 12]. In addition to precautionary measures, studies performed with data on patients exposed to diagnostic radiation are needed to discern the health risks among children and adolescents [13].

We analyzed the cancer incidence risk in an epidemiologic cohort study of nearly 79,000 children who underwent diagnostic x-ray exposures between 1976 and 2003 in a large German university hospital. A special feature of this cohort was that individual

radiation exposures had been recorded since 1976. In our first analysis focusing on dosimetry [14], we did not observe a dose-response relation between increasing cancer risk and increasing radiation dose. In the current study, we sorted results separately by referral criterion. This step is important because radiation sensitivity and cancer risk may differ between groups of patients.

Materials and Methods

Ethics Approval

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

Patients

The study sample consisted of children who underwent radiography and other procedures involving ionizing radiation in the radiology department at our institution between 1976 and 2003. Only children without a previous diagnosis of cancer were included. The cases of patients with cancer diagnosed at the first documented radiologic examination or up to 6 months afterward were considered prevalence cases and were excluded from the cohort. Other inclusion criteria were that the patient be a resident of Germany and be younger than 14.5 years on the date of the first examination. Details of the methods have been described elsewhere [14]. Special risk groups were excluded from the current analysis as a homogeneous collective. These groups were children with a priori high mortality risk (such as those with AIDS or complex congenital heart defects), increased risk of cancer (such as those with Down syndrome), and premature infants. Furthermore, patients were excluded if they underwent CT or other procedures involving contrast administration, or if their cumulative effective dose was 10 mSv or more (comparable to an abdominal CT examination). Such exposures are subsumed as "high dose" hereafter.

All patients' cases were documented in the computerized database set up in our radiology department in 1976. The database contained information about the patients and the technical parameters necessary for dose reconstruction, as specified by federal regulations [15]. In 1998, the database was replaced with a radiologic information system (RIS), in which the same information except for referral criteria and radiologic diagnosis is recorded. All referral criteria and diagnoses were coded according to the International Classification of Diseases, 10th revision (ICD-10), for the purpose of this study.

Dosimetry

The PAEDOS dose reconstruction algorithm for conventional radiography was developed by one of the authors and has been described in detail elsewhere [16–21]. Briefly, PAEDOS is used to compute organ doses and an effective dose with the entrance dose or the dose area product together with a list of conversion coefficients for all combinations of examination type, target organ, and patient age. PAEDOS includes an imputation algorithm for supplementing missing data necessary for dose reconstruction. In a few cases, missing information prevented dose reconstruction. In this study, the cumulative effective dose in microsieverts and the cumulative dose to the red bone marrow were used. Missing doses were replaced by the median dose in subjects of the same age and sex examined in the same year.

Subgroups by Referral

In the analyses we differentiated the largest groups of referral criteria for the first examination according to ICD-10 chapter: injury (chapter XIX), endocrine and metabolic disease (IV), congenital malformation (XVII), respiratory disease (X), and other diseases. Referral criteria and diagnoses were not available for patients whose cases were documented in the RIS. These patients were assigned any of the foregoing labels and were considered RIS only.

Cohort Follow-Up

The individual observation periods started at the first examination and ended on December 31, 2006, the 15th birthday, or the date of cancer diagnosis, whichever came first.

Cancer Endpoints

Incident cancer cases of patients younger than 15 years in the cohort in the period 1980–2006 were detected through record linkage with the German Childhood Cancer Registry. They were restricted to the groups of all forms of cancer, leukemia and lymphoma, and solid tumors.

Statistical Analysis

Risk was quantified by calculation of standardized incidence ratio (SIR) and by estimation of incidence rate ratio with Poisson regression. The 95% CI was computed for all risk measures. Patients who received high doses were excluded from analysis. The SIR is the number of cases observed divided by the number of cases expected on the basis of the reference rates. The incidence rate ratio is the cancer incidence among children with higher exposure divided by that among children with lower exposures (used as a reference group in this study) [22]. An SIR or incidence rate ratio greater than 1.0 indicated an incidence higher than that in the general population or the reference group.

The reference for the SIR calculations was the cancer incidence in West Germany (excluding Berlin) provided by the German Childhood Cancer Registry. Multivariable Poisson regression was used to describe the incidence rate ratio for cumulative effective dose adjusted by age and sex. Individual cumulative effective radiation dose was included in the model as a categoric covariate with categories less than 10, 10–49.9, and 50 μSv or more. Because there were few cases, most of them in a narrow range of doses, regression analysis with dose as a continuous variable with the assumption of a linear dose-response relation would have led to statistical instability, partially strongly influenced by the small number of patients with the highest exposures.

Results

Cohort

The cohort consisted of 78,527 children: 42,436 boys, 34,829 girls, and 1262 of unknown sex. The initial cohort consisted of 105,847 patients, 27,320 of whom were excluded: 9757 were 14.5 years or older at the first radiographic examination, 1547 were 15 years or older at the beginning of follow-up, 993 had prevalent cancer at first examination, 395 had a cancer diagnosis within 6 months after the first examination, 16 had a cancer diagnosis before 1980, six were examined after 2003, and 176 had inconsistent dates of birth and examination. A further 12,794 patients with a priori high mortality risk, 253 with increased cancer risk, 189 premature infants, and 1194 patients with high-dose exposures were excluded.

A total of 21,103 (27%) patients were documented in the RIS only or had unspecific information, precluding detailed analysis by referral criterion. Among the other 57,424 patients, the referral criterion for the first examination was an injury for 22,016 (38%), endocrine or metabolic disease for 8554 (15%), and respiratory disease for 6909 (12%) children. In total, 68 incidence cancer cases (38 boys, 30 girls) were found in the German Childhood Cancer Registry files (Table 1). Seventeen of the cases of cancer (nine boys, eight girls) occurred in patients with records in the RIS only. According to the referral criterion for the first examination, 16 cases of cancer occurred in patients who had sustained trauma, five in patients with previous endocrine or metabolic disease, six in patients with previous respiratory disease, and 41 in other patients.

Exposure

Most (49,408, 63%) of the patients underwent only one recorded examination. A further 14,680 (19%) patients underwent two, 5967

TABLE 1: Characteristics of the Cohort

Characteristic	All Patients	Patients With Incidence Cancer
No. of patients		
All	78,527	68
Boys	42,436	38
Girls	34,829	30
No. of examinations per patient		
1	49,408	30
2	14,680	16
3	5967	7
4 or more	8472	15
ICD-10 chapter of referral criterion for first individual examination		
I, Certain infectious and parasitic diseases	242	0
II, Suspected neoplasms	576	5
III, Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	153	0
IV, Endocrine, nutritional, and metabolic diseases	8554	5
V, Mental and behavioral disorders	21	0
VI, Diseases of the nervous system	54	0
VII, Diseases of the eye and adnexa	14	0
VIII, Diseases of the ear and mastoid process	53	0
IX, Diseases of the circulatory system	270	1
X, Diseases of the respiratory system	6909	6
XI, Diseases of the digestive system	1947	0
XII, Diseases of the skin and subcutaneous tissue	238	0
XIII, Diseases of the musculoskeletal system and connective tissue	1159	0
XIV, Diseases of the genitourinary system	1095	3
XV, Pregnancy, childbirth, and the puerperium	2	0
XVI, Certain conditions originating in the perinatal period	1637	1
XVII, Congenital malformations, deformations, and chromosomal abnormalities	1251	7
XVIII, Symptoms, signs, and abnormal clinical and laboratory findings not elsewhere classified	5402	3
XIX, Injury, poisoning, and certain other consequences of external causes	22,016	16
XX, External causes of morbidity and mortality	4	0
XXI, Factors influencing health status and contact with health services	5827	4
Not recorded or insufficient context	21,103	17
Person-time of observation (y)	580,523.7	261.0
Mean follow-up time (y)	7.4	3.8
Cumulative dose (μSv)		
Median and interquartile range	5.0 (1.0–26.0)	20 (3.0–123.0)
Mean ± SE	57.9 ± 0.7	55.3 ± 14.3

Note—ICD-10 = International Classification of Diseases, 10th revision.

(8%) three, and 8472 (11%) four or more examinations, the maximum being 85 examinations of one patient. The median cumulative effective dose in all patients was 5 μSv (interquartile range [IQR], 1–26 μSv), which did not differ in boys and girls. A total of 692 (1%) patients received a cumulative effective dose greater than 1 mSv. The median cumulative effective dose per examination was highest among infants younger than 1 year (25 μSv; IQR, 10–90 μSv) and lowest among those 12–14 years old (< 1 μSv).

The median cumulative effective dose was less than 1 μSv (IQR, 1–15 μSv) in trauma patients, 1 μSv (IQR, 1–2 μSv) in patients with endocrine or metabolic disease, and 13 μSv (IQR, 6–27 μSv) in patients with respiratory disease (Fig. 1). The median cumulative

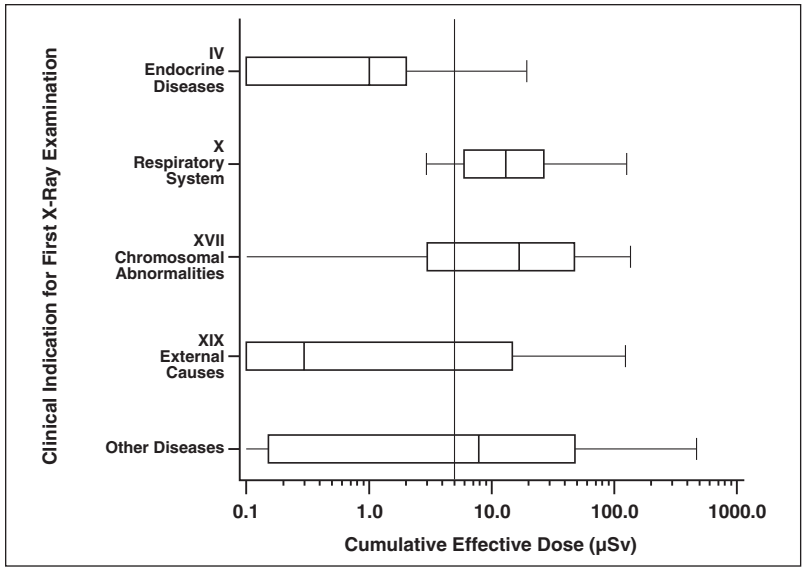

Fig. 1—Box and whisker plot shows distribution of cumulative effective dose by referral criterion for first individual examination of indication groups with 1000 or more patients. Roman numerals indicate ICD-10 chapter numbers; boxes, median and quartiles; whiskers, 90% CI; reference line, overall median.

effective dose was highest in patients with mental disorders (502 μSv; IQR, 307–650 μSv) followed by those with diseases of the genitourinary system (200 μSv; IQR, 79–474 μSv).

The procedures in the radiology department and the quality of the equipment used were constantly optimized. The median effective dose per individual examination declined from 18 μSv (IQR, 8–66 μSv) in 1976 to 3 μSv (IQR, 0–8 μSv) in 2002 with a marked decrease in 1982 due to increased beam filtration and improved procedures. A similar pattern was observed in all groups of referral criteria considered.

Cancer Risk

The SIR for all cancers was 0.97 (95% CI, 0.75–1.23). SIRs generally did not differ between the sexes: the SIR for all cancers was 0.90 (95% CI, 0.64–1.23) for boys and 1.08 (95% CI, 0.73–1.54) for girls. SIRs were not significantly different from 1.0 in any of the four referral groups considered (Table 2), for either leukemia and lymphoma or for solid tumors, except in patients examined because of congenital malformations who had not already been excluded from the analysis for having a priori increased cancer risk. In this group, the SIR was 4.10 (95% CI, 0.84–11.97) for solid tumors and 5.43 (95% CI, 1.48–13.91) for leukemia and lymphoma on the basis of three and four cases, respectively.

In the regression analysis, no overall trend of increasing cancer risk with increasing dose was observed when adjustment was made for sex and age (incidence rate ratio per microsievert, 0.81; 95% CI, 0.19–3.41). In the groups defined by referral criteria, no significant dose-response relation was observed, except in patients in the referral group with endocrine disease. Five cases of cancer were identified in this group: three in the reference category (cumulative effective dose < 10 μSv) and two in the category 50 μSv or greater (0.12 and 0.78 mSv), leading to an incidence rate ratio of 21.68 (95% CI, 3.57–131.50) (Table 3).

Discussion

To our knowledge, this study is the first epidemiologic cohort study in which cancer risk among children exposed to diagnostic radiation was investigated with a detailed individual dose history. It included nearly 79,000 children. The median individual effective radiation dose from x-ray examinations was very low (5 μSv). Between 1980

TABLE 2: Standardized Incidence Ratio by Referral Criterion for First Individual Examination and Tumor Type

Referral Criterion[a]	All Types of Cancer				Solid Tumors				Leukemia and Lymphoma			
	Cases	Expected No. of cases	Standardized Incidence Ratio	95% CI	Cases	Expected No. of cases	Standardized Incidence Ratio	95% CI	Cases	Expected No. of cases	Standardized Incidence Ratio	95% CI
All patients	68	70.22	0.97	0.75–1.23	31	35.10	0.88	0.60–1.25	37	35.11	1.05	0.74–1.45
IV, Endocrine, nutritional, and metabolic diseases	5	4.89	1.02	0.33–2.39	2	2.44	0.82	0.10–2.96	3	2.45	1.22	0.25–3.58
X, Diseases of the respiratory system	6	7.84	0.77	0.28–1.67	3	3.87	0.77	0.16–2.26	3	3.96	0.76	0.16–2.21
XVII, Congenital malformations, deformations, and chromosomal abnormalities	7	1.47	4.77	1.92–9.82	3	0.73	4.10	0.84–11.97	4	0.74	5.43	1.48–13.91
XIX, Injury, poisoning, and certain other consequences of external causes	16	20.25	0.79	0.45–1.28	8	10.06	0.80	0.34–1.57	8	10.19	0.79	0.34–1.55
All other diseases	17	15.48	1.10	0.64–1.76	10	7.89	1.27	0.61–2.33	7	7.59	0.92	0.37–1.90
Not recorded (radiology information system–only patients)	17	20.29	0.84	0.49–1.34	5	10.11	0.49	0.16–1.15	12	10.18	1.18	0.61–2.06

[a]Roman numerals are International Classification of Diseases, 10th revision, chapter numbers.

and 2006, a total of 68 incident cancer cases were observed in the cohort, which is close to the expected number of 70 cases. The results suggest that childhood exposure to diagnostic x-rays is not linked to an appreciable increase in the incidence of solid tumors or leukemia in this cohort. The dose-response analysis did not reveal a trend toward increasing cancer risk with increasing dose. The only statistically significant cancer incidence rate ratio was observed in the referral group endocrine disease, which consisted of only five cases. This result is probably spurious because a 20-fold risk increase in two patients with medical exposures of 0.12 and 0.78 mSv compared with others is highly unlikely.

Context of This Study

Direct epidemiologic observations of children exposed to low doses of ionizing radiation are scarce. Risk estimations therefore still have to rely on models published by the United Nations Scientific Committee on the Effects of Atomic Radiation [7] and the Committee on the Biological Effects of Ionizing Radiation VII [6]. To our knowledge, no other cohort study on childhood cancer in this dose range has been conducted to which the current study can be directly compared. Previous German case-control studies including children exposed to postnatal diagnostic x-rays did not show any increased risk of leukemia or solid tumors [23, 24]. In a large case-control study, Shu et al. [25] observed a significant increase in risk of cancer with the number of postnatal exposures. Both Shu et al. and Infante-Rivard et al. [26] reported increases in the risk of acute leukemia with the number of exposures, but no such increase was observed in another study by Shu et al. [27]. Preston et al. [28] analyzed data from the Life Span Study of atomic bomb survivors and found a significant excess relative risk (ERR) of solid cancer among adolescents and adults exposed to postnatal and in utero doses. The ERR was found to decline with attained age and was still significantly elevated at age 50 years, the ERR per sievert being 1.70 (95% CI, 1.1–2.5). Earlier studies of prenatal and postnatal diagnostic exposures and the risk of childhood cancer [8] showed no clear evidence of increased cancer risk after low-level intrauterine and postnatal radiation exposure and had serious limitations [9, 29].

Strengths and Limitations

The main strengths of this study were the large size of the cohort; the detailed, prospective individual exposure documentation, which enabled good dose reconstruction; the representativeness of the cohort of the population of patients of a large pediatric hospital; and the independent case ascertainment through a cancer registry with a high degree of completeness. The quality of the registry is in accordance with international standards for almost all cancer entities. It has been involved in several large-scale childhood cancer investigations at the national and international levels [30–32].

One limitation of this study was the limited information on potential confounders. We therefore used the referral criteria to identify groups of patients at high cancer or mortality risk and accounted for this factor in the regression analysis. Another limitation was the potential for systematic underassessment

TABLE 3: Incidence Rate Ratios for Cancer by Referral Criterion Adjusted for Sex and Age

Referral Criterion[a]	Cumulative Effective Dose (μSv)	No. of Cases	Person-Years	Incidence Rate Ratio	95% CI	*p*
All patients	< 10	37	332,782.0	1.00	Reference	
	10–49.9	18	138,997.4	1.08	0.62–1.90	0.78
	≥ 50	13	108,213.6	1.05	0.56–1.98	0.88
IV, Endocrine and metabolic diseases	< 10	3	41,555.2	1.00		
	10–49.9	0	3105.8	NA		
	≥ 50	2	1761.3	21.68	3.57–131.50	< 0.01
X, Respiratory system	< 10	2	29,458.5	1.00		
	10–49.9	4	28,018.5	2.23	0.41–12.20	0.36
	≥ 50	0	8723.6	NA		
XVII, Chromosomal abnormalities	< 10	5	5947.6	1.00		
	10–49.9	2	4250.1	0.64	0.12–3.38	0.60
	≥ 50	0	2217.3	NA		
XIX, External causes	< 10	11	121,692.1	1.00		
	10–49.9	2	30,802.0	0.63	0.14–2.83	0.54
	≥ 50	3	23,089.4	1.38	0.38–4.97	0.62
All other diseases	< 10	7	60,807.5	1.00		
	10–49.9	7	54,556.9	1.12	0.39–3.20	0.83
	≥ 50	3	57,083.6	0.52	0.13–2.00	0.34
Not recorded (radiology information system–only patients)	< 10	9	73,321.1	1.00		
	10–49.9	3	18,264.2	1.46	0.38–5.56	0.58
	≥ 50	5	15,338.3	2.82	0.91–8.72	0.07

Note—NA = not applicable.
[a]Roman numerals are International Classification of Diseases, 10th revision, chapter numbers.

of radiation dose, because the children might have additionally been examined elsewhere. No direct information on this point was available. However, it is reasonable to assume that further radiologic examinations, if performed in Munich, would have been performed at the university hospital where we conducted our study. Although organ doses were calculated in the dosimetry study, the effective dose was used in this study for purely practical reasons, as in many other epidemiologic studies. The concept of effective dose was conceived for radiation protection purposes, and its use in epidemiologic studies is problematic [33]. Because of the small number of observed cancer cases, it was necessary to look at large groups of cancer entities. Organ doses therefore could not be used, with the exception of the dose in red bone marrow in leukemia.

For this analysis, doses from contrast-enhanced CT examinations were not reconstructed, and patients who underwent such examinations (2.1% of all patients in the cohort) were excluded from analysis. The median cumulative effective dose to the patients whose records were analyzed was 5 μSv, and only 1% had a dose greater than 1 mSv. This dose is much less than the yearly dose from natural radiation, which is estimated to be 2.4 mSv in Germany. This finding emphasizes the importance of investigating risk among patients exposed to higher doses of ionizing radiation. Although reconstruction of doses from CT and other contrast-enhanced examinations was too demanding for the current project, such doses will be reconstructed in a future study.

Although some misclassification in the ICD coding of the referral criteria cannot be ruled out, the current analysis should not have been affected because broad ICD chapters with clearly distinct illnesses were used. More detailed analyses would have been desirable but were precluded by the small numbers of cases.

Despite the size of the cohort, only 70 cases of cancer were expected to occur until the age of 15 years. This factor limits the power of the study, which was 80% for a detection SIR of 1.36 or greater for all forms of cancer and an incidence rate ratio of 4.76 or greater in the highest exposure group at a significance level of 5%.

No cancer follow-up was conducted after the age of 15 years. Follow-up in adult cancer registries would theoretically have been possible, but because incidence rates are even lower between the ages of 15 and 40 years compared with earlier ages, one would expect few extra cases, and the cost of the necessary completion of address histories of study subjects was not justified.

Outlook

Radiation doses incurred by the patients in this cohort constantly diminished for several reasons. Improvements in equipment have constantly been sought and implemented. Internal documentation helped us to assess the techniques and doses needed to achieve the best results while adhering to the as low as reasonably achievable principle.

The experiences gathered have influenced the guidelines of the German Radiation Protection Commission on examinations involving ionizing radiation in children [34]. Our cohort study showed not only the feasibility of such a study but also that the study can be expanded in terms of longer follow-up and in terms of exposures from procedures other than conventional radiography. Investigating the health effects of high-dose procedures (such as CT) on children is one of the research needs explicitly stated by the U.S. National Academy of Sciences in its report on the Biologic Effects of Ionizing Radiation VII [6]. This type of study is especially important if the rate of high-dose procedures on children increases to the level documented for adults [2, 35]. A pilot study on CT-exposed children is underway in Germany and several other countries. The combined results will contribute currently missing epidemiologic data on children.

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References

1. Berrington de González A, Darby S. Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries. *Lancet* 2004; 363:345–351
2. Brenner DJ, Hall EJ. Computed tomography: an increasing source of radiation exposure. *N Engl J Med* 2007; 357:2277–2284
3. Herzog P, Rieger CT. Risk of cancer from diagnostic X-rays. *Lancet* 2004; 363:340–341
4. Task Group on Control of Radiation Dose in Computed Tomography. Managing patient dose in computed tomography: a report of the International Commission on Radiological Protection. *Ann ICRP* 2000; 30:7–45
5. Rehani MM, Berry M. Radiation doses in computed tomography: the increasing doses of radiation need to be controlled. *BMJ* 2000; 320:593–594
6. Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, National Research Council. *Health risks from exposure to low levels of ionizing radiation: BEIR VII phase 2*. Washington, DC: National Academies Press, 2006
7. United Nations Scientific Committee on the Effects of Atomic Radiation. *Effects of ionizing radiation: report to the General Assembly, with scientific annexes*. Vienna, Austria: United Nations, 2006
8. Schulze-Rath R, Hammer GP, Blettner M, Zeeb H. Are pre- or postnatal diagnostic x-rays a risk factor for childhood cancer? A systematic review. *Radiat Environ Biophys* 2008; 47:301–312
9. Wakeford R. Childhood leukaemia following medical diagnostic exposure to ionizing radiation in utero or after birth. *Radiat Prot Dosimetry* 2008; 132:166–174
10. Hall EJ, Brenner DJ. Cancer risks from diagnostic radiology. *Br J Radiol* 2008; 81:362–378
11. Brenner DJ. Extrapolating radiation-induced cancer risks from low doses to very low doses. *Health Phys* 2009; 97:505–509
12. Land CE. Low-dose extrapolation of radiation health risks: some implications of uncertainty for radiation protection at low doses. *Health Phys* 2009; 97:407–415
13. Kim JE, Newman B. Evaluation of a radiation dose reduction strategy for pediatric chest CT. *AJR* 2010; 194:1188–1193
14. Hammer GP, Seidenbusch MC, Schneider K, et al. A cohort study of childhood cancer incidence after postnatal diagnostic X-ray exposure. *Radiat Res* 2009; 171:504–512
15. Verordnung über den Schutz vor Schäden durch Röntgenstrahlen (Röntgenverordnung-RöV). *Bundesgesetzesblatt Teil I* 1973; 1973:173–192
16. Seidenbusch MC, Regulla D, Schneider K. Radiation exposure of children in pediatric radiology. Part 2. The PAEDOS algorithm for computer-assisted dose reconstruction in pediatric radiology and results for X-ray examinations of the skull [in German]. *Rofo* 2008; 180:522–539
17. Seidenbusch MC, Regulla D, Schneider K. Radiation exposure of children in pediatric radiology. Part 3. Conversion coefficients for reconstruction of organ doses achieved during chest X-ray examinations [in German]. *Rofo* 2008; 180:1061–1081

18. Seidenbusch MC, Regulla D, Schneider K. Radiation exposure of children in pediatric radiology. Part 6. Conversion coefficients for reconstruction of organ doses achieved during x-ray examinations of the abdomen [in German]. *Rofo* 2009; 181:945–961
19. Seidenbusch MC, Schneider K. Radiation exposure of children in pediatric radiology. Part 1. Referral criteria and x-ray examination frequencies at a university children's hospital between 1976 and 2003 [in German]. *Rofo* 2008; 180:410–422
20. Seidenbusch MC, Schneider K. Radiation exposure of children in pediatric radiology. Part 4. Entrance doses achieved during the x-ray examination of the chest [in German]. *Rofo* 2008; 180: 1082–1103
21. Seidenbusch MC, Schneider K. Radiation exposure of children in pediatric radiology. Part 5. Organ doses in chest radiography [in German]. *Rofo* 2009; 181:454–471
22. Dos Santos Silva I. *Cancer epidemiology: principles and methods,* 2nd ed. Lyon, France: IARC, 1999
23. Meinert R, Kaletsch U, Kaatsch P, Schuz J, Michaelis J. Associations between childhood cancer and ionizing radiation: results of a population-based case-control study in Germany. *Cancer Epidemiol Biomarkers Prev* 1999; 8:793–799
24. Schüz J, Kaletsch U, Kaatsch P, Meinert R, Michaelis J. Risk factors for pediatric tumors of the central nervous system: results from a German population-based case-control study. *Med Pediatr Oncol* 2001; 36:274–282
25. Shu XO, Jin F, Linet MS, et al. Diagnostic x-ray and ultrasound exposure and risk of childhood cancer. *Br J Cancer* 1994; 70:531–536
26. Infante-Rivard C, Mathonnet G, Sinnett D. Risk of childhood leukemia associated with diagnostic irradiation and polymorphisms in DNA repair genes. *Environ Health Perspect* 2000; 108:495–498
27. Shu XO, Potter JD, Linet MS, et al. Diagnostic x-rays and ultrasound exposure and risk of childhood acute lymphoblastic leukemia by immunophenotype. *Cancer Epidemiol Biomarkers Prev* 2002; 11:177–185
28. Preston DL, Cullings H, Suyama A, et al. Solid cancer incidence in atomic bomb survivors exposed in utero or as young children. *J Natl Cancer Inst* 2008; 100:428–436
29. Wakeford R. On pre- or postnatal diagnostic x-rays as a risk factor for childhood leukaemia. *Radiat Environ Biophys* 2009; 48:237–239
30. Kaatsch P, Steliarova-Foucher E, Crocetti E, Magnani C, Spix C, Zambon P. Time trends of cancer incidence in European children (1978-1997): report from the Automated Childhood Cancer Information System project. *Eur J Cancer* 2006; 42:1961–1971
31. Schilling FH, Spix C, Berthold F, et al. Children may not benefit from neuroblastoma screening at 1 year of age: updated results of the population based controlled trial in Germany. *Cancer Lett* 2003; 197:19–28
32. Spix C, Eletr D, Blettner M, Kaatsch P. Temporal trends in the incidence rate of childhood cancer in Germany 1987–2004. *Int J Cancer* 2008; 122: 1859–1867
33. Brenner DJ. Effective dose: a flawed concept that could and should be replaced. *Br J Radiol* 2008; 81:521–523
34. Gumprecht D, Hähnel S, Hahn C, Heller H; German Commission on Radiological Protection (Strahlenschutzkommission SSK). Orientierungshilfe für radiologische und nuklearmedizinische Untersuchungen, issue 51. Bonn, Germany: SSK, 2006
35. Fazel R, Krumholz HM, Wang Y, et al. Exposure to low-dose ionizing radiation from medical imaging procedures. *N Engl J Med* 2009; 361:849–857