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## Computed tomography in children: multicenter cohort study design for the evaluation of cancer risk

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► **To cite this version:**

L. Krille, A. Jahnen, P. Mildenerger, K. Schneider, G. Weisser, et al.. Computed tomography in children: multicenter cohort study design for the evaluation of cancer risk. *European Journal of Epidemiology*, 2011, 26 (3), pp.249-250. 10.1007/s10654-011-9549-6 . hal-00669206

**HAL Id: hal-00669206**

**<https://hal.science/hal-00669206>**

Submitted on 12 Feb 2012

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# **Manuscript: Brief Report Study Design KiCT (CT-Study)**

## **Submission History**

Submitted 9.12.2010 to the European Journal of Epidemiology

Accepted with minor revisions: 10.1.2011

Revised: 17.1.2011

Version: 20110117\_full\_submission\_commentary.doc

## **The manuscript**

### ***Title:***

Computed tomography in children – multicenter cohort study design for the evaluation of cancer risk

### ***Authors:***

L. Krille<sup>1</sup>, A. Jahnen<sup>2</sup>, P. Mildenerger<sup>1</sup>, K. Schneider<sup>3</sup>, G. Weisser<sup>4</sup>, H. Zeeb<sup>5</sup>, M. Blettner<sup>1</sup>

1. University Medical Centre Mainz, Germany
2. Centre de Recherche Henri Tudor, Luxembourg, Luxembourg
3. Kinderklinik und Kinderpoliklinik im Dr. von Haunerschen Kinderspital, München, Germany
4. Universitätsklinikum Mannheim, Germany
5. Institut für Präventionsforschung und Sozialmedizin, Bremen, Germany

### ***Correspondence address***

Lucian Krille M.A.

Institute of Medical Biostatistics, Epidemiology and Informatics

University Medical Centre Mainz

Obere Zahlbacher Str. 69,

D-55131 Mainz, Germany

Tel: +49 6131 17-3232

lucian.krille>>O<<unimedizin-mainz.de

### ***Abstract***

Exposure to ionizing radiation is a known risk factor for cancer. Cancer risk is highest after exposure in childhood. The computed tomography is the major contributor to the average, individual radiation exposure. Until now the association has been addressed only in statistical modeling. We present the first feasible study design on childhood cancer risk after exposure to computed tomography.

### ***Keywords***

childhood cancer

cohort study

computed tomography

ionizing radiation

## **Text**

The use of computed tomography (CT) is growing in developed countries [1]. Radiation doses from CT are around 10-100 times higher than those from conventional x-ray examinations. CT is currently the major contributor to annual medical radiation exposure and the major reason for the ongoing increase of the exposure [2]. It is well known that cancer risk after irradiation is highest after exposure in childhood as children have a higher susceptibility to ionizing radiation and a longer life span under risk [3]. Brenner et al. estimated that among the 600,000 children annually scanned in the USA, 500 will develop cancer and die in consequence of the radiation exposure from CT [4]. Until now, only model-based estimations but no primary epidemiological study data are available to estimate the cancer burden from CT exposure. In Germany, we will perform a cohort study of paediatric patients exposed to ionizing radiation through CT with prospective follow-up for cancer incidence.

Based on the electronically stored patient records from the departments of radiology of large hospitals a cohort of children who underwent a CT examination will be assembled. Our pilot study indicates that paediatric CTs are predominantly done in large hospitals. However, for the few patients who have CTs done in different centres, we will underestimate the exposure. Any available information on previous CTs will be collected. Records available in the radiology information systems (RIS) include patient identifiers like name, address, sex and date of birth, date and performed procedure. The indication for CT and the report allow identifying those individuals with cancer or other diseases associated to cancer.

Technical information for individual dose reconstruction is stored as metadata together with the image in the picture archiving and communication systems (PACS). This metadata will be abstracted by software specifically designed for this study and the effective dose will be calculated [5]. Individual organ doses will be calculated based on newly modelled conversion factors and having regard of exposed organs. The cumulative doses will be calculated.

The full cohort will be pseudonymised and linked with the database of the German Cancer Registry (GCCR). The GCCR was established 1980, registers all cancer cases in children younger 15 years and reached full coverage around 1987. The registration age range of the GCCR was recently raised to 18 years. After assembling of the cohort further follow-ups will be performed, lengthening the observation period. Due to pseudonymisation and strict data separation data privacy is assured.

Statistical analyses will include external comparison with the childhood cancer incidence of the German population from the GCCR (SIR analysis) as well as internal comparison (dose-response analysis). Patients with prevalent cancer will be excluded. Confounding by indication will be a major challenge for the analysis and the interpretation of the study results. To address it, patients will be assigned to specific risk groups based on indication, result and clinical information. Sensitivity analyses will be performed concerning the a priori higher risks of cancer development and mortality for

exposed children. Conventional x-rays will not be considered as their dose contribution is considered negligible as compared to CT. Our recent large cohort study did not detect increased cancer risks after conventional x-ray examination [6].

Based on calculations from our pilot study we expect to enrol retrospectively about 80,000 to 130,000 eligible patients in more than 40 hospitals nationwide, who underwent CT-examinations from 1980 until 2010. For the conservative power calculations, we applied the average number of annual CTs per type of hospital, applied average observation periods and reduced the number of CTs by the fraction of those expected to be prescribed for cancer therapy. The resulting number of CT examinations was converted into the number of patients by using the fraction of multiple CTs per patient. For each patient, the time under risk was halved and a lag period of six months applied. The expected cancer cases in the cohort were calculated based on the data from GCCR. Finally, we will be able to detect a SIR of 1.6 for leukaemia and a SIR of 1.3 for all cancer.

Results are expected in 2013.

Statistical power may only be enhanced by international pooling. The described design is applicable in every country with an existing nationwide cancer registry and other scientists are encouraged copying it. International pooling within a European joint project is envisaged.

The study is funded by the German Federal Ministry of Education and Research (02NUK0116A).

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### ***Authors' contributions***

LK coordinates the study and wrote the manuscript draft

HZ contributed medical experience and project guidance.

MB contributed experience and the overall project outline.

AJ programmed the software and contributed experience concerning data abstraction.

PM, GM, KS abstracted data and provided experience on PACS, RIS and dosimetry.

All authors contributed to and accepted the final version.

The correspondence has not been published or is under consideration of being published elsewhere. Corresponding author is Lucian Krille.

### ***Role of the funding source***

The study is funded by the German Federal Ministry of Education and Research. The funds will be used to finance the scientific personnel, the data abstraction and the software tools needed.

### ***Conflicting interests***

We declare that the authors and their institutions have no conflicting interests. All authors contributed to this article and take responsibility for its content.

### ***Ethics***

The study design has been approved by the ethics committee and the data protection officer.

## **Additional Information & Content**

### ***Formatting standard***

Brief Reports

Brief reports should not exceed 6 double-spaced typewritten pages and should not be divided into sections. **All brief reports must have abstracts of no more than 60 words and references.**

### ***Type:***

Brief Report

### ***Title:***

Computed tomography in children – multicenter cohort study design for the evaluation of cancer risk

## **Authors**

<b>First Name</b>	<b>Last Name</b>	<b>Academic Degree</b>	<b>Affiliation</b>	<b>E-mail Address</b>
Lucian	Krille		University Medical Centre Mainz	krille@imbei.uni-mainz.de
Andreas	Jahnen		Centre de Recherche Henri Tudor	Andreas.Jahnen@tudor.lu
Peter	Mildenberger	Prof. Dr.	University Medical Centre Mainz	milden@radiologie.klinik.uni-mainz.de
Karl	Schneider	Prof. Dr.	Kinderklinik und Kinderpoliklinik im Dr. von Hauerschen Kinderspital	karl.schneider@med.uni-muenchen.de
Gerald	Weisser	PD Dr.	Universitätsklinikum Mannheim	gerald.weisser@umm.de
Hajo	Zeeb	Prof. Dr.	Bremer Institut für Präventionsforschung und Sozialmedizin	zeeb@bips.uni-bremen.de
Maria	Blettner	Prof. Dr.	University Medical Centre Mainz	blettner@imbei.uni-mainz.de

## **Classification**

11: Cancer

28: Risk Factors