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To cite this article: Magda Bosch de Basea *et al* 2015 *J. Radiol. Prot.* **35** 611

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# EPI-CT: design, challenges and epidemiological methods of an international study on cancer risk after paediatric and young adult CT

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Received 27 February 2015, revised 4 May 2015

Accepted for publication 27 May 2015

Published 30 July 2015



CrossMark

### Abstract


Computed tomography (CT) has great clinical utility and its usage has increased dramatically over the years. Concerns have been raised, however, about health impacts of ionising radiation exposure from CTs, particularly in children, who have a higher risk for some radiation induced diseases. Direct estimation of the health impact of these exposures is needed, but the conduct of epidemiological studies of paediatric CT populations poses a number of challenges which, if not addressed, could invalidate the results.

The aim of the present paper is to review the main challenges of a study on the health impact of paediatric CTs and how the protocol of the European collaborative study EPI-CT, coordinated by the International Agency for Research on Cancer (IARC), is designed to address them.

The study, based on a common protocol, is being conducted in Belgium, Denmark, France, Germany, the Netherlands, Norway, Spain, Sweden and the United Kingdom and it has recruited over one million patients suitable for long-term prospective follow-up. Cohort accrual relies on records of participating hospital radiology departments. Basic demographic information and technical data on the CT procedure needed to estimate organ doses are being abstracted and passive follow-up is being conducted by linkage to population-based cancer and mortality registries. The main issues which may affect the validity of study results include missing doses from other radiological procedures, missing CTs, confounding by CT indication and socioeconomic status and dose reconstruction. Sub-studies are underway to evaluate their potential impact.

By focusing on the issues which challenge the validity of risk estimates from CT exposures, EPI-CT will be able to address limitations of previous CT studies, thus providing reliable estimates of risk of solid tumours and leukaemia from paediatric CT exposures and scientific bases for the optimisation of paediatric CT protocols and patient protection.

Keywords: CT scan, cohort study, epidemiological methods, cancer, leukaemia

 Online supplementary data available from [stacks.iop.org/JRP/35/030611/mmedia](http://stacks.iop.org/JRP/35/030611/mmedia)

(Some figures may appear in colour only in the online journal)

### List of abbreviations

|       |   |
|-------|---|
| CT    | Computed Tomography                                       |
| DICOM | Digital Imaging and Communications in Medicine            |
| IARC  | International Agency for Research on Cancer, Lyon, France |

|        |  |
|--------|--|
| PACS   | Picture Archiving and Communication System         |
| PerMoS | Performance and Monitoring Server for Medical Data |
| RIS    | Radiology Information System                       |
| SES    | Socioeconomic status                               |
| UK     | United Kingdom                                     |

## 1. Introduction

Computed tomography (CT) scanning is an essential imaging technique for diagnosis and follow-up of certain conditions, and its use has grown in all age groups since its introduction in the 1970s [1]. Concerns have been raised about cancer risks related to ionising radiation exposure from CTs, particularly in children, whose longer expected lifespan translates into a higher number of years at risk of developing a radiation-induced malignancy. Further, children, due to their smaller body mass, tend to receive higher organ doses than adults if the same CT protocol is not size adapted [2] or if the clinical practice at the hospital does not apply age and weight-based scanning guidelines [3]. It is also well known that exposure in childhood leads to higher risk of cancer, than similar exposure in adults [4].

Though radiation doses to specific organs from a CT scan are typically low (1–10 mGy), a small proportion of patients with repeated CT scans receives moderate doses, in the range 100–150 mGy [5] at which increased cancer risks have been demonstrated in epidemiological studies [6, 7]. Given the large number of children undergoing CTs in developed countries, the public health and radiation protection implications of this exposure are potentially important.

The most comprehensive quantitative estimates of cancer risk following low linear energy transfer (LET) radiation exposure come from studies of the atomic bomb (A-bomb) survivors [8]. This large cohort study concluded that radiation-related risk for all cancers—and particularly for leukaemia, breast, brain and thyroid cancer—is greatest for exposure in childhood and adolescence [9, 10]. Risk estimates, primarily based on this study, have been used to predict the potential health impact of CT scanning on cancer risk [11–13]. Although the A-bomb survivors study featured a large well-characterised all-ages cohort with a long large-scale follow-up for the study of health effects associated with ionising radiation, some important uncertainties remain unsolved, including: the shape of the dose-response model for doses lower than 100 mSv, particularly when received at low dose-rates in a protracted or fractionated fashion and whether the risks identified from a Japanese population can be applied to any other ethnicity with different baseline cancer risks [5, 10, 14]. Increasingly, studies of occupational exposures [15, 16] and of environmental exposures [17–19]—including studies of natural background radiation [20, 21]—are providing important complementary information on effects of low dose protracted exposure in Western populations. However, with the exception of those based on environmental exposure, these studies do not provide information about risks from childhood exposure. Careful studies of large populations with paediatric CT exposure are therefore needed to directly estimate the health effects of these exposures.

Several epidemiological studies on cancer risk related to CT-scanning in young people have recently been published [22–26]. Two of them (Pearce [22] and Mathews [23]) found increased risks for leukaemia and brain tumours associated with CT scan exposure. A third study by Huang and co-authors did not evaluate leukaemia risks but also found an increased risk of benign brain tumours associated with paediatric head CT examinations [24]. Despite the apparent consistency of results, these papers have received criticism for several reasons. In the Pearce study, based on a cohort of over 175 000 exposed young people in the

UK [22], there were concerns over potential organ-dose errors, and the possible inclusion of patients with cancer predisposing syndromes (such as Down syndrome or neurofibromatosis type 1, among others) and, benign conditions with malignant transformation potential. The Mathews study [23], comparing cancer incidence between 680 000 exposed and over 10 million unexposed Australians, used very limited dosimetric methods. The study imputed an average effective dose as well as bone marrow and brain doses for each type of CT from the published literature, scaled to the paediatric population. This could have potentially led to substantial exposure misclassification as exposures from CTs are not uniform over the whole body. The study also reported an unusual finding of increased risk for a large number of very different malignancies. Again, information on patients with tumour and leukaemia predisposing syndromes was not available, and therefore, were not excluded. As for Huang *et al* [24] they compared cancer risk between a group of over 24 000 persons with at least one brain CT and a group of 24 418 randomly selected unexposed people. The main limitations of this study were the short follow-up of the participants, the absence of any dosimetric reconstruction impeding the study of dose-response relationships and the short exclusion period of incident cases after the first exposure which may have allowed for some confounding by indication (lag period of 2 years).

The EPI-CT multinational collaborative study, which aims to estimate individual radiation organ doses and associated uncertainties from CTs in young people and to assess subsequent cancer risk, was specifically designed to address factors which can affect the interpretation of results from CT studies, including reverse causation, confounding by predisposing factors and other causes as well as possible effect modification through a number of sub-studies. These – and the results of the first of these sub-studies—will be described below.

EPI-CT builds upon some pre-existing cohort studies in France [27], the UK [22] and Germany [28], extending them and setting-up new cohorts based on a common protocol, in Belgium, Denmark, the Netherlands [29], Norway, Spain and Sweden. The current paper describes the design of the study, its methodological challenges and approaches implemented to address these.

Separate publications present the dose reconstruction approach developed within the project [30] and results of sub-studies on biomarkers of DNA damage, oxidative stress and gene expression profiling after CT exposure [31]. Additional papers will present recommendations for patient dose optimisation, based on analyses of international data collected within EPI-CT.

## 2. Methods

EPI-CT is a European multinational cohort study of patients who have undergone at least one CT scan before the age of 21 years, and for some countries 0–21 inclusive. The main objectives are the establishment of a large-scale multinational cohort of paediatric patients for long-term follow-up (subject to funding being secured); the description of patterns of use of paediatric and young adult CT over time and among countries; the improvement of individual organ-dose estimates from paediatric and young adult CTs and the evaluation of the radiation-related risk of diseases—particularly leukaemia and brain cancer (neoplasms related to radiation and the most common childhood malignancies) and non-cancer diseases (cardiovascular diseases, among others). The assessment of biological markers of CT-irradiation effects and dose optimisation in paediatric radiology in Europe are also important aims of the study.

As required in each country, ethical and other approvals must be gained, prior to commencing any epidemiological study.

Within EPI-CT, although the study methodology and its ethical implications are identical for all national cohorts, different guidelines apply in different countries to safeguard the rights and privacy of the patients in the study (table 3). These differences range from gaining a single approval from a national authority to obtaining individual ethical approval in each of the enrolled hospitals, which greatly delayed and hindered the study setting up in some countries.

## 2.1. Study methodology and challenges

### 2.1.1. The study population

Though CT scans can be performed in a large number of radiological facilities, including in some countries, private radiological clinics, it is not logistically feasible to include patients from all hospitals and clinics with a radiology department in a given region or country. The study population is therefore defined on the basis of the large paediatric hospitals and of the radiology service of hospitals with a large paediatric patient population in participating countries.

The cohort is defined retrospectively (and in some countries prospectively) from the records of participating hospital radiology departments. Eligible subjects should have at least one recorded CT scan before the age of 22 years and be cancer-free at the time of the first CT. Due to logistical aspects of follow-up (e.g. countries with only paediatric cancer registries) or cohort identification (patterns of referral of adolescent and young adults) the age range is narrower in some countries (table 1).

Only residents of the participating countries/regions are eligible for inclusion in the study population to ensure the feasibility of follow-up.

### 2.1.2. Sample size and statistical power

The risk of radiation-induced cancer following exposure to low doses is estimated to be small [1] and it is typically considered that a whole body dose of 1 Sv (which is 100 times higher than the dose in the CT scan examination involving the highest radiation exposure: an abdomen/pelvis CT scan) leads to an approximately 5% increase in the risk of fatal cancers. For children and teenagers, this risk may be 2 or 3 times higher [32]. Given the likely small carcinogenic effects, large collaborative studies are required to achieve adequate statistical power to significantly identify a potential radiation-induced increase of cancer cases [33], particularly for rare diseases such as childhood cancers (annual incidence rate about 145 per 100 000 aged 0–19 years in Europe [34]). Adequate power calculations are therefore needed prior to setting up a study to ensure that the study size is sufficient to be informative about such risks.

Table 1 describes the planned national cohorts in EPI-CT, which based on *a priori* study power calculations (included in the additional material section) ([stacks.iop.org/JRP/35/030611/mmedia](http://stacks.iop.org/JRP/35/030611/mmedia)) should ensure sufficient statistical power to evaluate the association between radiation dose from CT scans and risk of leukaemia and possibly of brain tumour within the time-frame of the current EU grant agreement (2011–2017).

Based on the data collected to date, it is foreseen that the international pooled EPI-CT cohort will include approximately 1 200 000 patients, exceeding the approximately 1 000 000 patients initially planned.

### 2.1.3. Follow-up

Within EPI-CT, cohort members are being followed-up passively through linkage to cancer, mortality and other national/regional registries (including centralised hospital discharge

**Table 1.** National contribution to the EPI-CT cohort, as initially planned.

| Country                | Study population                      | Age (years) | Planned period of cohort accrual | Targeted cohort size (N) | Targeted contribution to the European EPI-CT cohort | Current cohort size (N) |
|------------------------|---------------------------------------|-------------|----------------------------------|--------------------------|---|-------------------------|
| Belgium                | Patients from participating hospitals | 0–18        | 2001–2013                        | 30 000                   | 2.9%  | 14 500                  |
| Denmark                | Patients from participating hospitals | 0–18        | 2001–2013                        | 30 000                   | 2.9%  | 10 000                  |
| France                 | Patients from participating hospitals | 0–10        | 2000–2013                        | 90 000                   | 8.7%  | 130 000                 |
| Germany                | Patients from participating hospitals | 0–15        | 1980–2013                        | 140 000                  | 13.6%   | 51 000                  |
| Netherlands            | Patients from participating hospitals | 0–18        | 1983–2013                        | 40 000                   | 3.9%  | 150 000                 |
| Norway                 | Patients from participating hospitals | 0–20        | 1980–2013                        | 20 000                   | 1.9%  | 87 000                  |
| Spain                  | Patients from participating hospitals | 0–20        | 1991–2013                        | 200 000                  | 19.4%   | 177 000                 |
| Sweden                 | Patients from participating hospitals | 0–18        | 1984–2013                        | 95 000                   | 9.2%  | 96 000                  |
| UK                     | Patients from participating hospitals | 0–21        | 1985–2013                        | 387 000                  | 37.5%   | 405 000                 |
| Total accrued patients |                                       |             | 1980–2013                        | 1 032 000                | 100.0%  | 1 120 500               |

databases), to determine incidence and mortality from leukaemia, cancer and non-cancer causes in the cohort. Follow-up starts at the date of the first CT in a participating radiology service and ends at the earliest of data of death, incidence of a disease of interest (here leukaemia and solid cancers, in particular brain tumours), emigration (where available) or end of follow-up in the participating country/region. The population is being followed-up into adulthood in all countries except France and Germany where currently national cancer registries only include cancer diagnoses up to the age of 15.

Within the framework of the current EC grant, the cohort is still relatively young and the power to study the relation between radiation dose in young people and risk of diseases, such as cardiovascular diseases and many solid cancers which are more frequent at older ages, will be inadequate. Further follow-up will be needed for this.

**2.1.3.1. Challenges.** As in all cohort studies, emigration information is not comprehensively available in most countries. The exceptions for EPI-CT are Denmark, Norway, Sweden and part of the UK. Emigration, when not known, may challenge the adequacy of risk estimates in the study: incident cases will be lost, while person-years at risk will be overestimated, thus leading to bias in the risk estimates. A sub-study in the countries where emigration data are available will provide information on the magnitude and direction of the possible bias related to lack of emigration data. Simulation studies will be conducted based on this information and on other credible scenarios of missing data in order to evaluate the impact of missing emigration data on the magnitude of the risk estimates.

Mortality follow-up is feasible in all countries except Germany and, in part, France. In these countries, subjects who have died will not be identified and will continue to contribute person-years at risk in the analyses, leading to overestimation of person-years and biased risk

estimates. While this is generally not a major issue in studies of young people where mortality rates are low, it is of concern in a study of CT patients, who tend to have a substantially higher mortality risk than the general population (due to the inclusion of patients with severe and often life-shortening diseases). Analyses using data from the other study countries will allow the evaluation of the magnitude and direction of the possible bias related to lack of mortality data in Germany and France. Simulation studies will be conducted based on this information and on other credible scenarios of missing data in order to evaluate the impact of missing mortality data on the magnitude of the risk estimates.

#### 2.1.4. Dosimetric data collection

Proper exposure assessment is critical in any epidemiological study and especially challenging in studies in which direct measurement of exposure is not possible, due to the retrospective nature of the data collection or to elevated costs.

In EPI-CT, computerised data are being collected for every scan a cohort member underwent in any of the participating hospitals of his/her country. This includes basic radiological data from the Radiological Information Systems—RIS—including date of scan, body region scanned, sex and date of birth. In addition, for recent periods, data are being collected from the Picture Archiving and Communication System—PACS—which contains much more detail about the examination including the technical parameters used for each specific scan. This is being achieved using dedicated software, such as PerMoS (Luxembourg Institute of Science and Technology, Luxembourg) [28, 35] or Gladys (Qaelum NV, Belgium) [36], which extract information from the DICOM (Digital Imaging and Communications in Medicine header) header of the scan from the computer servers of participating radiological departments.

**2.1.4.1. Challenges.** Epidemiological studies on diagnostic ionising radiation exposure ideally demand a complete reconstruction of the radiological history of the patient. Risk estimates may be impacted by the fact that CT data are only being collected from participating hospitals, as was the case in the UK [22] and Australian [23] studies as well as in the countries participating in EPI-CT, or only collected on specific procedures (as in the Taiwanese study [24]). Estimated doses, therefore, will not include doses from scans performed in other non-participating hospitals or doses received from other irradiating medical procedures. If there is a relation between the number of scans in participating hospitals and doses from CTs conducted elsewhere and/or from other procedures, this will induce confounding.

EPI-CT is assessing the potential impact on risk estimates of unaccounted exposure sources through a number of sub-studies conducted in regions where all hospitals and/or all ionising radiation medical procedures are included. The most common ionising radiation procedure besides CT scanning is conventional radiography, which entails very low radiation doses compared to CT (typical organ doses in the range 0.005–0.15 mGy depending on body part examined [37, 38], compared to several mGy from CTs for organs in the field) and will, therefore, have little impact on risk estimates. Regarding missing doses from unaccounted CT scans, results are already available from the UK, indicating that only a small number of patients (2.3%) in the study age-range received scans in other hospitals, and hence the impact of such missing doses may be small [39]. In Belgium, information on CTs and other radiological examinations was obtained from the health insurance system for a 2.5% sample of the Belgian population. The proportion of children who had numerous imaging tests (mostly conventional radiography) was significantly higher for those who had had a CT compared to those who had not had a CT scan. In France, in a sub-study based on



health insurance data it was observed that around 80% of the annual dose received by children who already had a CT scan is due to other CT scans and therefore, additional ionising radiation doses from other radiological procedures accounted only for a small part of their total dose [40].

Population and/or hospital-based registries of radiological procedures in other countries will also provide information on missing examinations. With this information, credible scenarios will be identified and simulation studies conducted to assess the influence of missing doses on risk estimates and to correct, if possible, for a potential confounding bias.

### 2.1.5. Dose reconstruction

In studies of low-dose ionising radiation, the direct estimation of the health impact of radiation remains imprecise, and an accurate dosimetry and assessment of potential biases and uncertainties is needed. This is crucial to ensure the validity of the resulting risk estimates.

EPI-CT plans to improve the organ dose estimation methodology currently used in similar studies by combining the results of national surveys on doses from CT examinations [22]; standard examination protocols from different hospitals in different time periods and the real settings used for CT imaging recorded once PACS was implemented at the hospitals [30]. The standard examination protocols will provide information about typical machine settings that influence the delivered dose used in paediatric and young adult CT examinations when individual settings for each examination were not available (period where hospitals were managing their radiological information using RIS only, typically before the year 2000). Missing settings will be imputed through simulations, providing multiple alternative dose estimates for each subject and each scan accounting for shared errors in dosimetric model parameters [41]. Multiple realisations of the cumulative individual doses to specific relevant organs (e.g. red bone marrow for analyses of leukaemia risk) will be generated for all examinations included in the study and appropriate statistical methods (including Monte Carlo Maximum Likelihood [42, 43] and Bayesian averaging approaches) will be implemented to assess the risk of radiation induced disease in these organs taking into account the uncertainty in the dosimetric model. The methodology for dose-estimation from RIS and PACS data has been published elsewhere [30].

## 2.2. Potential sources of bias

Incorrect assessment of the association between an exposure and an effect in the studied population will invalidate results. Thus it is important to identify and characterise potential sources of bias in order to minimise them and/or take them into account in statistical analyses, as appropriate.

In EPI-CT, *a priori* potential bias factors of the association between ionising radiation exposure from CT scans and risk of leukaemia and solid tumours include socioeconomic status (SES), confounding by indication (i.e. the reason for the CT being a precursor or risk factor for the cancer, such as congenital disorders entailing a higher cancer risk) and reverse causation.

### 2.2.1. Socioeconomic status

The influence of socioeconomic status—often employed as a surrogate for unmeasured lifestyle factors—in the variation of disease burden rates is widely accepted by the scientific community. At the same time, SES can be related to exposure to certain environmental factors, thus potentially confounding any observed association between exposure and health outcome.

As SES indicators are not available in some EPI-CT countries, the potential impact of missing socioeconomic status is being assessed through sub-studies in those regions where SES data are available.

Within EPI-CT, different indicators of SES have been used in the different countries, based, as available, on parents' job title or education level from census data, or through geocoding the subjects' address from radiological records and linking with maps of geographical distribution of SES (table 2). Preliminary results are available from sub-studies that have been run in the UK, the Netherlands, Belgium and Spain, based on heterogeneous SES indicators. UK data [44] suggest that young people from deprived areas are more likely to undergo CT scans than those in more affluent areas, possibly reflecting injury rate disparities and highlighting the potential confounding effect of SES. Similarly, in Belgium, young patients belonging to the less affluent socioeconomic group had more CT scans per patient on average than those in the more affluent group (1.4 versus 1.2 CT scans per patient, respectively) (unpublished data). Results of the Dutch sub-study indicated that children from deprived SES categories, whether based on income or house value, are slightly overrepresented among children with at least one CT scan based on a sample from a large academic hospital in a poor urban area of Amsterdam, compared with a random sample from the Dutch population. Little change, however, was observed in the SES categories by number of scans [29]. Results based on 3 different autonomous communities in Spain, on the other hand, show decreasing number of CT scans associated with a lower SES level based on residence area (unpublished data). Disparities in these results may reflect differences in the healthcare systems between the countries as well as differences in the adequacy of the measure of SES. To better understand the possible confounding effect of SES and its likely magnitude where data are unavailable, a sub-study is underway comparing different SES indicators (in countries where they are available) and evaluating whether the results differ depending on the size of the geographic area on which SES is determined (which vary between countries from a few 10s of inhabitants to several thousands). Results will also be compared, where possible, for different age groups, scan types and, where available, reasons for scans.

#### *2.2.2. Confounding by indication due to cancer predisposing factors*

A number of syndromes or diseases are known to be associated with an increased risk of some tumours, including individuals with inactivation of tumour suppressor genes, alterations in DNA repair genes, or non-malignant chronic immune deficiency syndromes [45, 46]. If patients with such syndromes or diseases are also at higher risk of undergoing CT, there is the potential that these predisposing factors may bias the association between radiation dose from CT scans and risk of cancer, a criticism raised about the studies by Pearce, Matthews and Huang.

Within the EPI-CT study, where possible, centres are using available sources (including detailed reviews of clinical information, pathology reviews, and registries of congenital malformations, rare diseases and bone marrow transplants) to attempt to identify these patients, evaluate whether they confound the association and, if so, to adjust for them in the statistical analyses.

In a recent publication Journy and co-authors published results concerning the follow-up of part of the French component of the EPI-CT study, including a very thorough review of the presence of cancer predisposing factors [25]. The study included 67 000 children with a CT scan. Among these 1.7% of the children had predisposing conditions to leukaemia, and 0.5% to Central Nervous System (CNS) tumours (this proportion is quite high, probably due, as the authors indicate, to the participation of a major paediatric referral centre). Despite these small

**Table 2.** Estimators and sources of information to assess the SES confounding and confounding by indication effect.

| Country         | Socioeconomic status                            |   | Cancer cases and other high risk factors for cancer                                      |   |  |
|-----------------|---|---|--|---|--|
|                 | SES estimator (at the time of the last CT scan) | Source of information                               | Variables for identification of cancer cases and other high risk factors for cancer      | Information recorded  | Source of information  |
| Belgium         | Geographic estimate (residence postal code)     | National census data                                | (1) Cancer diagnosis;<br>(2) Descriptive statistics for a subsample                      | (1) Cancer diagnosis;<br>(2) Indication and results (findings/diagnosis) of the scans | (1) National Cancer Registry; (2) Sub-study of 680 children with CT followed for 6 months based on medical records |
| Denmark         | Parental education                              | National education registry                         | Cancer diagnoses, other relevant diagnosis identified in National registries             | Diagnoses, ICD-format, free text  | National Cancer Registry, National Hospital Discharge Registry   |
| France          | Geographic estimate (residence postal code)     | National census data                                | Medical diagnoses associated with hospitalisation, cancer diagnosis                      | Cancer / non cancer   | Medical identifying records/ paediatric cancer registry  |
| Germany         | Geographic estimate (residence postal code)     | National census data                                | Indication, results and clinical information   | Risk group  | Medical records  |
| The Netherlands | Geographic estimate (residence postal code)     | National census data                                | Cancer diagnoses, birth defects (e.g. Down syndrome), CT indication, leukaemogenic drugs | Diagnoses, ICD-format, free text  | Netherlands Cancer Registry, Perinatal Registry of the Netherlands, Bone Marrow Transplant registry                |
| Norway          | Parental education                              | National education registry                         | Cancer diagnoses, Down syndrome, birth defects   | Diagnoses, ICD-format   | Cancer Registry of Norway, Medical Birth Registry  |
| Spain           | Geographic estimate (residence postal code)     | Synthetic index of urban vulnerability <sup>a</sup> | Cancer diagnoses   | Diagnoses, ICD-format   | Medical Hospital Discharge Registry records  |
| Sweden          | Parental education                              | National census data                                | Cancer diagnoses, Down syndrome  | Diagnoses, ICD-format   | Cancer Registry of Sweden, National Inhospital Registry  |
| UK              | Geographic estimate (residence postal code)     | National census data                                | Cancer diagnoses   | Diagnoses, ICD-format   | National Health Service Central Registry   |

<sup>a</sup> Index based on % of unemployed population, % of young unemployed population, % of temporary unemployed population, % of non-skilled employed population and % illiterate population per census-tract section.

numbers, children with predisposing conditions accounted respectively for 32% and 26% of the incident cases of leukaemia and CNS tumours. Though the number of cases in the entire cohort was low (27 CNS tumours, 25 leukaemia and 21 lymphoma), and the follow-up was quite short (4 years on average), results from this study suggested a possible increased risk of leukaemia, lymphoma and brain tumours with increasing dose from CT. This effect disappeared when adjusted for the presence of predisposing factors, suggesting the results were confounded by predisposing factors.

A more in-depth analysis showed that for brain tumours and lymphoma, the risk estimates among subjects with no predisposing factors were similar to those based on the entire cohort. For leukaemia the risk estimate among subjects without predisposing factors was higher than that in the entire cohort. These findings suggest that predisposing factors do not explain the observed association between CT dose and tumour risk in the cohort but may, rather, be modifiers of the association between radiation dose and risk of disease (differentially affecting the observed effect of the exposure to doses from CT scan depending on the disease status) [47].

Results of analyses of data from the Dutch part of EPI-CT [48] also suggest that most cancer susceptibility syndromes are unlikely to confound the association between radiation dose and risk of disease. If other sub-studies in EPI-CT yield similar results, this will greatly facilitate the interpretation of results of CT studies in general and of the international EPI-CT study in particular.

Recently, however, Krille *et al* published results on the Germany component of the EPI-CT study [26]. The standardised incidence ratio (SIR) for lymphomas and solid cancers (11 and 9 cases respectively) decreased substantially when persons with medical conditions possibly associated with an increased risk of cancer were excluded. In contrast, the SIR for leukaemia changed only marginally. Based on small numbers, the authors concluded that still potential for reverse causation and confounding by indication could not be discarded when interpreting the excess of observed cancer cases compared with the expected number of cases [26].

Results of other sub-studies in EPI-CT are awaited. If results are similar to those of the French and Dutch study, this will greatly facilitate the interpretation of results of CT studies in general and of the international EPI-CT study in particular. If, however, they suggest that confounding by indication is a potential confounder, credible scenarios will be identified and simulation studies conducted to assess the influence of confounding by indication on risk estimates and to correct, if possible, for this potential bias in countries where no data are available.

### 2.2.3. Reverse causation

Epidemiological studies involving diagnostic ionising radiation exposure may suffer from confounding by indication, because the allocation of diagnostic procedures in observational studies is not randomised and may be related to the health outcome of interest for the study. Therefore, the difference in the underlying risk profile between the exposed and unexposed groups can bias the study results.

Within studies of CT patients, such as EPI-CT, scans possibly related to the cancer diagnosis or to symptoms caused by an underlying non-diagnosed cancer should be excluded in the estimation of cancer risk from CT radiation dose. However, information on the reason for the scan is often missing from radiology records. In countries where this is possible work is being conducted with hospitals and registries to ensure that information is collected to help identify and exclude from analyses those patients whose scan may be linked to their cancer. The impact of this bias is also being assessed in several countries through sub-studies,

providing results that can be used through simulation or sensitivity analyses to evaluate the potential impact of this bias and adjust for it.

The French study [25] also studied the possibility of reverse causation, first, by applying various periods of exclusion (from 1 to 4 years), and then, by removing the CT scans performed after the onset of first symptoms of cancer (for CNS tumours). The authors suggested that reverse causation potentially biased the risk estimates of CNS tumours, though the very short follow-up (average 4 years) prevents a definitive conclusion.

The German study [26] manually reviewed the available radiology reports and identified patients who had a CT scan due to signs of cancer at the time of the first CT and excluded them from analysis. Radiology reports were available for 37 cancer cases and 7 of them contained information on potential cancer signs at the time of their first CT scan. Although very rarely, delays of more than 2 years between the first signs possibly suggestive of cancer and the final cancer diagnosis were observed for seven cases and delays of more than 5 years for two cases. The potential residual reverse causation could lead to an overestimation of risks, and therefore results need to be carefully interpreted.

Analysis of medical records is also underway in several EPI-CT partner countries and will provide further information on this important topic. At the European level, moreover, analyses will exclude any scans occurring less than 2 years before diagnosis for leukaemia and 5 years for solid tumours, in order to minimise the potential for confounding by indication.

Should any of the sub-studies underway still suggest a residual effect of confounding by indication, the magnitude of such an effect will be estimated and simulation studies performed in order to assess the potential impact on the risk estimates from the study.

### 3. Discussion and impact

There is no doubt that the use of CT imaging is beneficial for millions of patients, but the potential adverse health effects related to the ionising radiation doses are a cause for concern in the radiological protection, medical and public health communities, and these effects are yet to be quantified with enough precision and certainty. Large studies of health effects of low doses of ionising radiation pose a number of important methodological challenges, particularly in the medical setting where predisposing factors and confounding by indication may affect the adequacy and interpretability of the results. EPI-CT has been designed from the start to identify and characterise the potential magnitude of factors that may affect the bias of risk estimates so that they can be taken into account in the risk analyses.

Research addressing the diverse health effects of CTs, both for cancer and non-cancer diseases, is scarce and the available evidence is based either on risk projections [11, 12] or on studies too small for detailed evaluation of specific cancer subtypes [23, 24], despite including more than 100 000 subjects. EPI-CT is the first large-scale international collaborative study to contribute not only to estimating effects of low level radiation in children following CTs, but to consolidate a European paediatric cohort for very long-term follow-up. EPI-CT has been designed to improve on earlier studies by deriving individual organ-dose estimates for each cohort member, to evaluate related uncertainties, to analyse possible biases which may affect the results of the study, and thus provide the most comprehensive and precise direct estimates of cancer risk from CT scans received at young ages. It will therefore provide important information to assess the adequacy of current radiation risk estimates (which are currently derived from studies of children with moderate to high doses received at high dose-rates from atomic bombings or radiotherapy) in relation to the generally lower doses received by CT patients.

**Table 3.** Country-specific differences in Ethical guidelines in observational follow-up cohorts, based on the EPI-CT experience.

| Country     | Requirements prior to start data collection from hospitals or medical trusts   |  |                          |  |
|-------------|--|--|--------------------------|--|
|             | National authority approval for collecting patient data  | Ethical or other approval required in each individual hospital | Patients written consent | Others   |
| Belgium     | Yes—National Privacy Protection Commission ( <i>Commissie voor de bescherming van de persoonlijke levenssfeer—Commission de protection de la vie privée</i> )                    | Yes  | No                       |  |
| Denmark     | Yes—National board of Health ( <i>Sundhedsstyrelsen</i> )  | No   |                          |  |
| France      | Yes—National Privacy protection Commission ( <i>Commission nationale Informatique et Liberté (CNIL)</i> )  | No   | No                       | Passive information (poster in radiology ward) of subjects is required |
| Germany     | No—National ethical approval gained from the Ethics Committee at the State Chamber of Physicians in the specific areas of the study  | Data protection statement is required                          | No                       |  |
| Netherlands | No   | No   | No <sup>a</sup>          |  |
| Norway      | Yes—Regional Committees for Medical and Health Research Ethics/ South-East ( <i>Regionale komiteer for medisinsk og helsefaglig forskningsetikk/Sør-Øst</i> )                    | Varying  | No                       |  |
| Spain       | No   | Yes  | Depends on the hospital  |  |
| Sweden      | Yes—Regional Ethical Review Board in Stockholm ( <i>Regionala Etkprövningsnämnden i Stockholm</i> )  | No   | No                       |  |
| UK          | Yes—Confidentiality Advisory Group (CAG) for England and Wales. For Scotland and Northern Ireland separate agreements were sought. One ethical approval covers the whole country | Yes  | No                       |  |

<sup>a</sup> Submission to local IRBs is required which generally determine that only a feasibility check by the head of the hospital is required.

This study should therefore have important implications for radiation protection and for optimising paediatric CT examination protocols.

Although the approach chosen for the study is likely to miss some radiological exposures of study subjects, it is clear that extremely low-dose procedures such as conventional radiography will have little impact on risk estimates and sub-studies to date within EPI-CT suggest

that there is little potential for confounding due to other, generally unrelated, high dose medical procedures.

Other factors that will influence the accuracy and precision of dose estimates include: missing or incomplete information on the performed scan; uncertainties on machine settings for each examination; whether information was available from PACS or only from RIS; lack of precise information on patient characteristics and on exposed organs. The impact of these factors is being investigated within the dosimetry study and will be taken into account in the risk estimation [30].

Of concern also is that paediatric CT patients may not be representative of the general paediatric population. Preliminary data from the Netherlands (unpublished), Germany [28] and France [49] suggest that a sizeable proportion of CT patients (e.g. 15% in Germany), were examined because of a suspected cancer. Information is also being collected on whether subjects with conditions predisposing them to cancer (including Down syndrome and familial syndromes) may be overrepresented among patients undergoing CTs. Sub-studies to date suggest that these are unlikely to confound the risk estimates though effect modification may be present. Should further sub-studies suggest an effect, it will be characterised and simulation studies conducted to investigate its potential impact on the risk estimates from the study.

EPI-CT will assess the importance of SES as a potential confounder, allowing adjustment of risk estimates where possible and corrections in countries where SES data might not be available for a large proportion of the cohort. Results of the association between SES and CT frequency available to date in our sub-studies suggest that this relation may differ between countries with different public healthcare systems [44]. Also, although SES has been related to risk of some cancers, the leukaemia and brain cancer literature is not conclusive regarding such associations [50] and analyses will be conducted to assess whether in fact SES confound the association between radiation dose from CT scans and risk of cancers.

Data on other potential confounding factors for specific outcomes are difficult to collect systematically in such a large cohort due to heterogeneity both in information sources and confounding factor data availability. While potential risk factors for brain tumours and leukaemia—other than those mentioned above—are unlikely to be related to CT doses, nested case-control studies are planned to address this formally. In a second phase, Spain, the Netherlands and the UK are planning nested case-control studies of specific outcomes in order to obtain detailed information of both cases and controls that cannot be addressed in the full cohort.

Denmark, Norway, Sweden and the UK will provide data to assess the impact of potential loss to follow-up due to emigration.

#### 4. Conclusion

Epidemiological studies of diagnostic radiation exposures aim to impact on clinical practice and public health and their results may have major implications for patient protection. It is very much hoped that the results of the EPI-CT study, in which major efforts are being made to evaluate and adjust for factors which may invalidate the results, as well as in the optimisation of paediatric imaging protocols, may help limit the radiation dose delivered to children and therefore reduce any potential risk arising from CT. At the same time results of EPI-CT may be an important component to empower physicians and parents for informed decision making.

## Acknowledgments

The authors gratefully acknowledge the contribution of David Richardson from University of North Carolina in the preparation of the study and thoughtful discussions, the administrative and technical assistance provided by Monika Moissonnier, Gilles Ferro and Catherine Chassin from IARC; Johannes Hermen from the Luxembourg Institute of Science and Technology (LIST), Mariette Kieft from the Netherlands Cancer Institute (NKI); Jordi Figuerola, Àlex Albert and Mariona Gil, from CREAL; the collaboration of all radiologists, medical physicists and IT specialists in the participating hospitals, and the assistance provided by staff of population-based registries used for follow-up of patients and collection of data.

## Disclosure of interests

The authors declare that they have no competing financial or non-financial interests.

## Human Participant Protection

The Ethics Committee of the International Agency for Research on Cancer approved the study protocol (IARC IEC 12–35). The protocol has also been approved by all appropriate national, regional and hospital ethics committees as detailed in table 3.

## Funding

This work was supported by the European Community's Seventh Framework Programme (FP7/2007–2013) (grant number 269912 - EPI-CT: Epidemiological study to quantify risks for paediatric computerised tomography and to optimise doses).

The International Agency for Research in Cancer (IARC) received complementary funding from the Ministry of Health, Labour and Welfare of Japan (grant agreement number 2012-02-21-01). In France, complementary funding was obtained from the French national Institute of Cancer and from the Association 'La ligue contre le Cancer'. Complementary funding was received from the German Federal Ministry of Education and Research [grant number 02NUK016] for the German KICT study. In Spain, complementary funding was received from a the Consejo de Seguridad Nuclear and M Bosch de Basea was the recipient of a fellowship of the Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP) for a short stay abroad at Newcastle University. In The Netherlands Worldwide Cancer Research, formerly known as the Association for International Cancer Research, provided partial funding [Grant 12–1155]. The original United Kingdom cohort study was funded by the United Kingdom Department of Health and the United States National Cancer Institute and further funding for the study has been obtained from Cancer Research UK. In Norway, it was funded by the Norwegian Research Council through the EURATOM programme, project no. 209096/E40

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