Potentiel cancer risk associated to CT scan: state of the art of epidemiological studies

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Abstract:

Introduction: The increasing use of computed tomography (CT) scans in paediatric population raises the question of a possible health impact of ionizing radiation exposure associated with CT scans.

Material and methods

Two large cohort studies have been recently published that assessed the risk of cancer related to CT examinations of children and young adults. Methodology and results of these studies are presented.

Results

The UK cohort included over 176,000 young people, who underwent one or more CT scans between 1985 and 2002. The Australian study compared the risk of cancer and leukaemia in a population of 680,000 young people exposed to CT scans between 1985 and 2005 to non-exposed similar age people. Both studies showed a significant dose-response relation between exposure to CT and leukaemia or brain tumour risks. These results are consistent with predictions from A-bomb survivors' data. However, uncertainties in dosimetric estimation and potential bias linked to underlying medical conditions should be considered.

Conclusion and perspectives

Further studies with more accurate dosimetry and assessment of potential bias and uncertainties are needed. Ongoing national studies and the European collaborative EPI-CT study will help to better understand the relation between low level radiation exposure and cancer and to support recommendations for patients' radiation protection.

1 BACKGROUND

Medical diagnostic is the main man-made source of ionizing radiation (IR) exposure for the population, and this part of exposure is at present growing in the developed countries (1). Computerized tomography (CT) scanning is a highly informative medical imaging technique. Over the last 20 years the ease and speed of image acquisition linked to technological developments has encouraged the proliferation of procedures and led to increased doses to patients. In the USA, the number of CT scans increased from 2 million in the year 1980 to about 70 million in 2007. In France, about 7.6 million CT scans were performed in 2007 (2).

These trends are also observed in paediatric diagnostic imaging, leading to an increase in the use of CT in paediatrics. About 11% of the CT scans are carried out in paediatric population (1). It represents an issue because CT scans are associated with much higher doses of IR than conventional radiology. Indeed, CT scans represent 5 to 10% of all imaging procedures, but 40 to 70% of the collective dose (1).

Exposure to x-rays for medical diagnosis purpose has been related to an increase of cancer risk after high cumulative doses (3;4), even in prenatal and childhood exposure (5). Nonetheless, these results have mostly been associated with very high cumulative organ doses (of about 0.1 to tens of Grays (Gy)) (6-8). Indeed, the doses that used to be involved in these examinations in the past were much higher than those reported nowadays. More recent epidemiological studies of diagnostic radiological examinations with much lower doses (less than 1 to tens of mGy) have so far provided inconsistent results and they have often been limited by inaccurate dose reconstruction (9;10).

According to the epidemiological results on the follow-up of the atomic bomb survivors but also from the follow-up of patients undergoing radiotherapy and/ or radiodiagnosis, exposure to IR at a young age is associated with an increased risk of cancer. Moreover, children benefit of a long life expectancy, which is likely to increase lifetime risks. Some authors have also suggested that the doses delivered by CT scans may be higher in children than in adults because of the failure to optimize radiological parameters relative to body size (12). Then, radiation-induced risk after CT scan exposure in childhood appears as a very important issue. Because this risk linked to low doses is estimated to be small (1), only large studies could achieve adequate statistical power to study accurately this risk.

2 EPIDEMIOLOGICAL STUDIES ON CT SCAN IN PEDIATRICS

Until now, two large cohort studies have been recently published (13;14) that assessed the risk of cancer related specifically to CT examinations of children and young adults.

2.1 Presentation of the recently published studies

2.1.1 ***The UK study (13)***

A cohort of over 176,000 young people without previous cancer diagnoses, who were first examined with CT in 81 National Health Services (NHS) centres in Great Britain between 1985 and 2002 was set up. The patients were aged 0-22 years at the first exposure to CT scan. Individual organ dose estimation has been performed taking into account the number of CT scans performed, the anatomical area explored and typical technical parameters used in Great Britain for this period. Phantoms for the age categories 0, 5, 10, 15 and 20 years were used for the dose calculation.

Over 283,000 CT scans were collected. Examinations concern the head, abdomen and/or pelvis and the chest in 64%, 9% and 7%, respectively. Organ doses, according to the age ranged between 28 and 44 mGy for the brain in case of head CT scan, and between 2 and 9 mGy for the red bone marrow for a CT scan of the pelvis or chest.

A cross linkage of the cohort with the NHS Central Cancer Registry allowed to estimate the incidence of brain tumours and leukaemia in the cohort. The analysis of the relation between organ dose and the incidence of cancer has been assessed using a Poisson relative risk model.

During the follow-up period, 74 leukaemia and 135 brain tumours were observed (Table 1). The analyses showed a significant increase of the leukaemia and brain tumor incidence with the cumulative dose. The increased risk for leukaemia and brain tumours was observed for cumulative dose up to 30 mGy to the bone marrow and up to 50 mGy to the brain, respectively. Then, according to the usual doses delivered in this period by the machine, the risk of brain tumour and leukaemia would be multiplied by 3 in case of 2 to 3 head CT scans and of 5 to 10 head CT scans, respectively.

2.1.2 ***The Australian study (14)***

A cohort of about 11 million people was extracted from the Australian Medicare Health Insurance database, available since 1985. Subjects were identified from Australian Medicare records, and were aged 0-19 years on 1 January 1985 or born there between 1 January 1985 and 31 December 2005. All exposures to CT scans funded by Medicare during 1985-2005 were identified for this cohort. About 680,000 patients were exposed to CT scans. Average effective dose per scan (in mSv) were estimated, taking into account the hospital where the CT was performed, the year of the scan and the age of the patient. Effective doses were obtained from the published literature for specific ages (new born; 1, 5, 10, 15 years; adult). Then average organ doses for brain and red bone marrow were derived from local and international published sources.

About 866,000 CT scans were performed during this period. Examinations concern the head, the facial bones, the extremities and the spine or neck in 59%, 13.1%, 9.5 and 8.6%, respectively. The mean dose to the brain was 40mGy after head CT and the mean dose to the red bone marrow was 5 mGy whatever the anatomical area scanned.

A cross linkage of the cohort with the Australian National Registry of Cancer available since 1985 was performed on the period 1985-2007.The analysis of the association between exposure to CT scan and cancer incidence has been performed with the estimation of the incidence rate ratio for exposed vs. non exposed individuals by Poisson regression.

On this period, 57 524 cancers (all solid and hematopoietic cancers) occurred among the non-exposed people and 3150 among the exposed ones (Table 1). There were 608 cancers in excess in the exposed group compared to the expected number accordingly to the non-exposed group estimation. The incidence rate ratio was 1.24 (95% Confidence Interval, CI, 1.20-1.29), with a significant dose-response relation.

2.1.3 ***Comparison of the 2 studies***

Characteristics and main results of the 2 studies are shown in Table1. The results of both studies are close regarding the risk of brain tumour and leukaemia and are consistent with the results of the follow-up of the Japanese atomic bombs survivors (15;16). Indeed, in the Life Span Study, in case of exposure between 0 and 19 years, the ERR per mGy of leukaemia was 0.045 (95% CI, 0.016-0.188) and the ERR of brain tumour 0.006 (95% CI, 0.000-0.064)

Table 1 : Characteristics and results of the 2 presented studies

	Pearce, 2012	Mathews, 2013
Size of the cohort	178,604 exposed people	10 939,680 with 680,211 exposed
Age at inclusion (yrs)	0-22	0-19
Period of inclusion	1985-2002	1985-2005
Recruitment of the cohort	Radiological departments	Australian Medicare system
Mean follow-up (yrs)	10	9.5
Maximum age at the end of the follow-up (yrs)	45	41
Number of CT scans performed	283,919	857,000
Cross linkage period with cancer registry	Jan 1, 1985- Dec 31,2008	1985-2007
Number of cancer observed	135 brain tumours	3150 cancers in the exposed group/57 524* in the non-exposed group 283 brain tumours in the exposed group

RR of brain tumor	2.82 (95% CI, 1.33-6.03) for people exposed to 50-74 mGy vs exposure < 5 mGy	2.44 (95% CI, 2.12-2.81)** for exposed vs non-exposed groups
ERR (per mGy)of brain tumor	0.023 (95% CI, 0.010-0.049)	0.029 (95% CI, 0.023-0.037)**
Number of leukemia	74	643 in the exposed group
RR of leukemia	3.18 (95% CI, 1.46-6.94) for the group exposed to at least 30 mGy/ group exposed to less than 5 mGy	1.19 (95% CI, 1.03-1.37) for the exposed vs the non-exposed group
ERR(per mGy) of leukemia	0.036 (95% CI, 0.005-0.120)	0.039*** (95% CI, 0.014-0.070)

- *all types of cancer
- **lag period 1 year, for head CT
- *** : including myelodysplasias

Limits of the studies:

Uncertainties in dosimetric reconstruction are a main limitation of both studies. Indeed, individual information of the received dose was not available for both cohort and dosimetric information derived from national or international survey were used. Moreover, medical conditions that could be associated both with an increased risk of cancer or leukaemia and with exposure to CT scan, like for example Down syndrome, were also not available. However, the bias linked to indication, i.e. the fact that the CT could be performed because of a suspicion of cancer, was taken into account by varying the lag time period between the exposure and the cancer incidence in the 2 studies. For the UK study, the lag time was 2 and 5 years for leukaemia and brain tumours, respectively (13). For the Australian study, the lag time was 1 year, but sensitive analyses were performed with longer lag time, without modifying results (14).

Additional limits are noteworthy in the Australian study. Indeed, bias of classification could be suspected both for people subjected to CT scans before 1985 (beginning of the Medicare system implementation in Australia) and for those who were subjected to CT scans outside the field of the Medicare system. Moreover, medical conditions of the exposed people could be quite different from those of individuals who had never had any CT scan and these diseases could be associated with an increased risk of cancer.

2.2 Ongoing studies

Further studies are needed to confirm the results observed by these 2 studies.
A French cohort, named “Cohorte Enfant Scanner” was launched by IRSN in 2009 in order to study the relation between exposure to CT scan and cancer incidence (17). This cohort has a special focus on very young children, who are thought to be the most radiosensitive group and for whom few information of radio-induced risk is available. A special effort was done to determine the more precisely the received dose by the children, taking into account radiological protocols used in the included radiology departments, according to the time period, CT machine and age category. The cohort includes 136,000 children who had had a CT scan between 2000 and 2011 in 21 large radiological paediatric departments in France. The patients were aged 0 to 10 years at the first CT scan. Medical diagnoses were obtained for hospitalised children (available for 73% of the cohort). A cross linkage of the cohort with the French National Paediatric registries of cancer is underway. First results should be available in 2014.
Other European cohorts are ongoing, all of them included in the EPI-CT project launched in 2011. This is a European multinational cohort study of patients who have undergone a CT scan before the age of 21 years,. The study, based on a common protocol, builds upon existing cohort studies in France (17), the UK (13) and Germany (18;19) and includes new cohorts in Belgium, Denmark, the Netherlands, Norway, Spain and Sweden. The number of included children will be over 1 million, allowing more specific statistical analyses. A specific effort will be done to take into account uncertainties for the dose reconstruction (20). Special attention will be given to issues which may affect the validity of study results, including missing doses from other radiological procedures, missing CTs, confounding by socioeconomic status and by CT indication. The results of the study are expected for 2015. This study, coordinated by the IARC (International Agency for Research on Cancer), is supported by the European Community's Seventh Framework Programme (FP7)

3 CONCLUSION AND PERSPECTIVES

Even if CT scan appears as a very useful and valuable tool for the diagnosis and the follow up of special medical conditions, concern about the potential radio-induced risk associated with this examination has been raised, especially in young people. The two first very large cohort studies on this topic published in 2012 and 2013 are in favour of an excess risk of cancer and leukaemia associated to CT exposure in childhood. Further studies are ongoing, which will allow confirming these results, taking into account more precise dosimetric information and challenging with potential bias linked to the way of building these cohorts.

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