Chapter 7

Summary, general discussion and future perspective
The research presented in this thesis aimed to study various aspects of the hypothesized association between radiation exposure from pediatric CT scans and subsequent risk of leukemia and brain tumors. This chapter summarizes the findings of our research, addresses methodological issues, links the findings to other related research and discusses the future perspectives, conclusions and recommendations.

Main results

The first empirical studies on CT-related cancer risks have been published and reported a small excess cancer risk for children and young adults. Although these studies were able to determine risks of cancer following CT procedures among children and adolescents, it is unclear whether the observed excesses can be entirely attributed to CT-related radiation exposure. Information about the reasons for the CTs and the medical history of the patients was unavailable, which might have led to confounding. Further, the dosimetry was based on external estimates stratified by variables such as age, calendar period and body part or CT protocol.

Chapter 2 presents the design of the Dutch Pediatric CT Study, a large retrospective cohort study on radiation exposure from CT scans administered in children and young adults and subsequent risk of leukemia and brain tumors. The study population consists of subjects who received at least one electronically archived CT scan under 18 years of age in a Dutch hospital conducting more than 10 pediatric CTs annually (n=168,394). The Dutch Pediatric CT Study cohort has been established through electronic data systems, RIS and PACS, which are routinely used in radiology departments of all Dutch hospitals. Information on all archived CT scans for these children were collected including date of examination, scanned body part, and machine settings. Subjects were followed until 2015 for incidence of leukemia and brain tumors, which were ascertained via record linkage with cancer registries and vital status from the Central Bureau of Genealogy (CBG). This cohort is large and has almost nationwide coverage. Besides, the exposure assessment is based on an internal sample of CTs with dosimetric information and cancer registration goes back to 1973 (leukemia) and 1989 (solid cancer) with high completeness.

The data from the Dutch Pediatric CT Study were used to provide a detailed description of past and current nationwide use of pediatric CT scanning in the Netherlands (Chapter 3), to evaluate radiation-related cancer risk among children (Chapter 4) and to examine the confounding effect of cancer susceptibility syndromes on the association between radiation exposure from pediatric CT scans and risks of leukemia and brain tumors (Chapter 5).
In Chapter 2 we describe approaches to the collection of data on archived CT scans and the estimation of radiation doses. First, we tested the feasibility of the time-consuming data collection from PACS and demonstrate that receiving large amounts of archived data from electronic radiology systems within the study time period is feasible. Second, we piloted the possibility to estimate the organ dose among 230 randomly selected patients from one hospital, based on age- and sex-specific computational human phantoms coupled with Monte Carlo radiation transport simulations. Although this provided sufficient evidence as proof-of-principle, still other approaches are needed to address incomplete dose data, e.g. imputing missing parameters. In all, the study included 42 participating hospitals which contributed a total of 262,227 pediatric CT scans performed on 168,394 patients.

In Chapter 3, data of the Dutch Pediatric CT Study were analyzed to evaluate trends and patterns in CT usage among children in the Netherlands across two decades. These trend analyses were based on 236,066 pediatric CT scans among 146,368 children performed between 1990 and 2012, including examinations conducted before and after a cancer diagnosis. Publicly available measures of socio-economic status (SES), namely household income by postal code area, were linked to patients’ residential address. For 18 non-participating hospitals and for years prior to electronic archiving in some participating hospitals, data were imputed by calendar year and hospital type. The estimated annual number of pediatric CT scans in the Netherlands has more than tripled from 7,731 in 1990 to 26,023 in 2012. A particularly steep increase by 50% was observed between 2003 and 2007. The number of scans among children aged 10 years or older at examination was substantially higher than among younger children. With 70% of all scans, the head/neck was the most commonly scanned body part. Abdomen/pelvis and chest each represented about 10% of all scans. Furthermore, children with low household income received more scans than expected because more than 20% of all scans were performed in children from households with an income exceeded by 80% of children in the general population. The percentage of pediatric CT scans performed annually in general versus all hospitals ranged from 39% in 1990 to 63% in 2012. In the period 2007-2012, the total number of pediatric CT scans performed in academic hospitals has started to decline, while the number of CT scans in general hospitals was still increasing strongly up to 2012. Because the number of CT scans is rising and CTs deliver higher radiation doses than most other diagnostic radiation procedures, risks of radiation-induced carcinogenesis due to CT scans are of great interest.

Chapter 4 describes the association between radiation exposure from CT scans and subsequent risks of leukemia and brain tumors based on data from the Dutch Pediatric CT Study. Cancer incidence, vital status and tuberous sclerosis complex (TSC) incidence were obtained by record linkage with external databases. Patients who were 2- and 5-years cancer-free after their first recorded CT were included for the leukemia and other cancer analyses, respectively. Standardized incidence ratios (SIR) were estimated using cancer incidence
rates from the general population. Relative risk per 100 mGy organ dose was calculated with Poisson regression. In this study, we observed 44 leukemia cases among 140,612 eligible patients and 87 brain tumor cases among 106,544 eligible patients. SIRs were elevated for all cancer sites. Overall cancer incidence (starting 5 years after the first CT) was 1.5 times higher than expected (SIR=1.47, 95% CI: 1.34, 1.61; 454 observed cases). This included malignant tumors of the central nervous system (CNS) (SIR=2.05, 95% CI: 1.48, 2.83; 37 observed cases) and hematopoietic and lymphoid proliferative cancers (HLP) (SIR=1.39, 95% CI: 1.13, 1.70; 93 observed cases). Mean cumulative bone marrow doses were around 10 mGy at the end of follow-up, and leukemia risk was not associated with cumulative bone marrow dose. Cumulative brain dose was on average about 40 mGy and there was a significant dose-response relationship for malignant and non-malignant brain tumors combined (ERR per 100 mGy: 0.66 (95% CI: 0.12, 1.74). For malignant brain tumors, the ERR per 100 mGy was 0.60 (95% CI: 0.10, 2.87) and for non-malignant brain tumors it was 0.70 (95% CI: 0.05, 2.25). Adjustment for SES and TSC did not change the risk.

Overall, we found evidence that CT-related radiation exposure increases brain tumor but not leukemia risk. Because of the observed increased incidence of brain tumors and cancer at other sites among children with CT scans compared with the general population, the results need to be interpreted with caution.

Concerns have been raised about a possible overestimation of radiation-related risks in studies of pediatric CT scans and cancer due to confounding by indication. Confounding by indication occurs if a factor is simultaneously associated with the probability of having CT scans and with the probability of developing a malignancy of interest. We describe in Chapter 2 a challenge of obtaining complete information on these confounders for record-linkage study designs unless such characteristics are included in the exposure or outcome data for this cohort study. These confounders can be obtained by linking with external datasets and/or radiology reports and can be controlled analytically. In this thesis, two sources of confounding by indication are addressed: cancer susceptibility syndromes (CSS) (Chapter 5) and the reason for a CT scan (Chapter 6).

Published cohort studies on the association of CT scans and cancer risk lacked data to control for CSS. CSS might be confounders because they are associated with increased cancer risk and may increase the likelihood of pediatric CT scans. In Chapter 5, a systematic literature search was done to identify CSS predisposing to leukemia or brain tumors and to summarize syndrome prevalence and cancer risk. Unfortunately, there was no quantitative data from the literature on the pattern of CT use among patients affected by specific CSS. We thus estimated confounding bias of relative risks for categories of radiation exposure based on expert opinion. For leukemia, the number of CT scans among patients with Down syndrome was estimated to be higher than among children in the general population. Based on expert opinion, children with Down may only occasionally receive just a few more CTs
during diagnosis, monitoring and treatment of Down-related comorbidity, which leads to no appreciable bias of the RR. Overall, in this assessment radiation-related RRs for leukemia were not meaningfully confounded by Down syndrome or other CSS. For brain tumors bias of the RR was below 40% because, based on expert opinion, a non-negligible fraction of TSC patients might have received a considerable number of head CTs. None of the syndromes did meaningfully confound RRs for brain tumors. In conclusion, the assessment of confounding of CT-related cancer risks described in Chapter 5 indicated that associations with leukemia and brain tumors reported in previous studies are unlikely to be substantially confounded by unmeasured CSS. As a caveat, these conclusions are based on assumptions about CT use among CSS patients and therefore robust empirical data are needed to substantiate these findings.

A second source of confounding by indication is the reason for having a CT scan. CT-related cancer risk studies were criticized because the reasons for the CT examinations were not known. If CTs were done for reasons associated with later cancer occurrence, this could lead to confounding by indication. Previous cohort studies on CT-related cancer risks were performed among children. However, studies of CT-related cancer risks among adults are also relevant, since adults receive over 10-times more CT scans than children and most radiation-induced cancers appear during middle or old age. Chapter 6 describes a hospital-based cohort study among adults (19-89 years) who received a CT scan at the Columbia Medical Center in the period 1994-2014 to examine reasons for CT scans as a confounder for CT-related radiation cancer risk. We estimated potential bias for colorectal, lung and female breast cancer. There were 212,487 CT scans among 75,968 subjects and the average duration of follow-up was 7.6 years. We did not observe evidence of significant bias of hazard ratios for colorectal and female breast cancer for any of the CT reasons. For lung cancer, significant bias was observed with CTs performed for unknown reasons, for “abnormal findings” and for cancer- or nodule-related reasons. In conclusion, indication bias was estimated to be negligible for colorectal, lung, and female breast cancer risk among adults who underwent CT scans.

**General discussion**

The research presented in this thesis reported evidence of a dose-response relationship between ionizing-radiation exposure from pediatric CT scans and the risk of brain tumors but not for leukemia in a large Dutch study. Five epidemiologic studies on cancer following radiation exposure from pediatric CT scans have shown elevated risks of leukemia and brain tumors (Table 2) [16].
With regard to leukemia, all studies presented in table 1 noted a positive association between radiation dose from CT scans and leukemia risks except the Dutch study. Nevertheless, our results are not inconsistent with even the perhaps strongest study. After exclusion of the myelodysplastic syndromes (MDS), the ERR from the UK-NCI study was no longer statistically significantly elevated (ERR/100 mGy: 1.90, 95% CI: -1.20, 0.79). A re-analysis showed a decrease by 15% for leukemia/MDS risk, although the risk for leukemia without MDS was not presented. In Chapter 4, we chose not to include MDS in the leukemia risks because only 3-7% of patients with MDS will progress to a form of cancer.
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<tbody>
<tr>
<td>Country</td>
<td>Great Britain</td>
<td>Australia</td>
<td>Taiwan</td>
<td>France</td>
<td>Germany</td>
<td>The Netherlands</td>
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<td>Person-years</td>
<td>Leukemia: 1,720,984; Brain tumors: 1,188,207</td>
<td>6,486,548</td>
<td>534,597</td>
<td>296,863</td>
<td>161,407</td>
<td>Leukemia: 1,201,357; Brain tumors: 827,261</td>
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<td>Patients</td>
<td>Leukemia: 178,604; Brain tumors: 176,587</td>
<td>680,211</td>
<td>122,086</td>
<td>67,274</td>
<td>39,184</td>
<td>Leukemia: 140,612; Brain tumors: 106,530</td>
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<td>Age at exposure</td>
<td>0-21 yr</td>
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<td>0-18 yr</td>
<td>0-10 yr</td>
<td>0-15 yr</td>
<td>0-18 yr</td>
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<td>Exposure</td>
<td>Nationwide survey</td>
<td>Number of CTs</td>
<td>Number of CTs</td>
<td>Protocols</td>
<td>Survey</td>
<td>Regression model based on own PACS data</td>
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<tr>
<td>Outcome: Leukemia</td>
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<tr>
<td>Cases</td>
<td>72</td>
<td>246</td>
<td>8</td>
<td>17</td>
<td>12</td>
<td>44</td>
</tr>
<tr>
<td>IRR/SIR (95%CI)</td>
<td>-</td>
<td>1.23 (1.08, 1.41)*</td>
<td>-</td>
<td>-</td>
<td>1.72 (0.89, 3.01)</td>
<td>1.39 (1.13, 1.70)^+</td>
</tr>
<tr>
<td>Exclusion period</td>
<td>2 yr</td>
<td>1 yr</td>
<td>2 yr</td>
<td>2 yr</td>
<td>2 yr</td>
<td>2 yr</td>
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<tr>
<td>Comparison RR</td>
<td>≥ 30 mGy vs 0-&lt;5 mGy</td>
<td>≥ 1 CT vs no CT</td>
<td>≥ 1 CT vs no CT</td>
<td>≥5-20 mGy vs 0-5 mGy</td>
<td>no CT vs ≥ 1 CT</td>
<td>≥17 mGy vs &lt;5 mGy</td>
</tr>
<tr>
<td>RR/HR (95%CI)</td>
<td>2.63 (1.09, 6.24)</td>
<td>-</td>
<td>1.90 (0.82, 4.40)*</td>
<td>0.95 (0.43, 2.15)^+</td>
<td>-</td>
<td>0.51 (0.21, 1.27)</td>
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<tr>
<td>ERR/100 mGy (95%CI)</td>
<td>1.9 (-1.2, 7.9)^++</td>
<td>3.9 (1.4, 7.0)^--</td>
<td>-</td>
<td>4.7 (-6.5, 15.9)^--</td>
<td>-</td>
<td>-0.31 (-0.90, 1.98)^++</td>
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<tr>
<td>Outcome: Brain tumors</td>
<td></td>
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<tr>
<td><strong>Cases</strong></td>
<td>128</td>
<td>283</td>
<td>19</td>
<td>22</td>
<td>7</td>
<td>87</td>
</tr>
<tr>
<td>IRR/SIR (95%CI)</td>
<td>-</td>
<td>2.44 (2.12, 2.81)</td>
<td>2.56 (1.44, 4.45)</td>
<td>2.32 (1.27, 4.26)</td>
<td>4.58 (1.10, 19.2)</td>
<td>10.4 (1.41, 76.0)</td>
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<tr>
<td>Lag period</td>
<td>5 yr</td>
<td>5 yr</td>
<td>2 yr</td>
<td>2 yr</td>
<td>2 yr</td>
<td>5yr</td>
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<tr>
<td>Comparison RR</td>
<td>50-74 mGy vs 0-&lt;5 mGy</td>
<td>≥1 head CT vs no head CT</td>
<td>≥1 head CT vs no head CT</td>
<td>&lt;5 mGy vs 50 mGy</td>
<td>CT vs no CT</td>
<td>100+ mGy vs &lt;5 mGy</td>
</tr>
<tr>
<td>RR/HR (95%CI)</td>
<td>2.82 (1.33, 6.03)</td>
<td>-</td>
<td>-</td>
<td>1.39 (0.59, 3.80)</td>
<td>-</td>
<td>1.84 (0.90, 3.75)</td>
</tr>
<tr>
<td>ERR/100 mGy (95%CI)</td>
<td>1.60 (0.60, 3.70)</td>
<td>2.10 (1.40, 2.90)</td>
<td>-</td>
<td>1.20 (-1.30, 3.71)</td>
<td>-</td>
<td>0.66 (0.12, 1.74)</td>
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**Confounders**
- Radiology records and death certificates: 40% subjects, nationwide SES data
- Discharge diagnoses
- Radiology reports: all cases and sample of non-cases
- TSC patients, nationwide SES data

yr: year; mGy: milliGray; SIR: standardized incidence ratio; RR: Relative risk; HR: Hazard ratio; ERR: Excess relative risk; CI: Confidence incidence; CT scan: Computed Tomography scan
^stratified for age, sex and year of birth.
# adjusted for age and sex.
^adjusted for gender, period of birth (1995-2001, 2002-2010), attained age (in years), time since entry into the cohort (in years), presence of predisposing factors (yes/no).
^All hematolymphoproliferative cancers (C81-88, C90).
**excluding MDS.
^including MDS.
Our results for brain tumors are consistent with the British cohort, the Australian cohort, and the Taiwan study (Chapter 4). The ERR of brain cancer observed in our data is almost exactly the same as among atomic bomb survivors under 20 years at exposure during the first 20 years of follow-up, 0.60 vs 0.61 per 100 mGy. Smaller studies such as the French and German cohorts suggested higher risks. However, both studies have a short follow-up time (4 years) as they only include cancers ascertained at childhood ages owing to the lack of nationwide cancer registration into adulthood. Confidence intervals are therefore wide and include the estimate from our own study. Furthermore, a recent multicenter case-control study among children with brain tumors and controls matched by age, sex and region showed a non-significantly increased CT-related radiation risk of brain tumors among children who had a head CT compared to children who had never had a head CT (OR: 1.68, 95% CI: 0.69-4.09). The study excluded patients with neurofibromatosis and TSC and was based on 10 exposed cases.

The incidence of cancer at all sites combined was increased in the Dutch Pediatric CT study compared with the general population. The excess is unlikely radiation-related but rather due to the medical setting of our study population, which includes diagnostic/screening procedures for symptoms of genetic syndromes (e.g., bone/soft tissue sarcoma, CNS tumors, non-melanoma skin cancer) or other underlying medical conditions (e.g., detection of carcinoid tumors of the colon during abdominal imaging for other reasons). No other study has presented incidence comparisons with the general population, except for the Australian study, which observed excesses for cancers at most sites.

Some published studies have also investigated cancers other than leukemia and brain tumors with contradictory results. In the Australian study, an increased risk of Hodgkin lymphoma (HL), a cancer of a relatively radio-insensitive tissue, was reported among those who ever had a pediatric CT scan at least a year before their cancer diagnoses. On the other side, the researchers did not observe an elevated risk for breast cancer which indicated a lack of specificity since the female breast is considered very radio-sensitive. In the UK cohort no elevated CT-related risk was observed for HL. Differences between the Australian and the UK study include an exclusion period of 2 years instead of 1 year, respectively, and the evaluation of a dose-response relationship in the UK rather than an ever-never exposed contrast in the Australian study. Unfortunately, we were not able to estimate risk of other cancers due to lack of power.

Concerns have been raised about the possibility of confounding by indication in CT scan studies. We investigated confounding by CSS and by reasons for a CT scan in Chapters 5 and 6, respectively.

With regard to CSS, three studies with some information on indication for CT scanning have been published, neither of which observed any meaningful attenuation for leukemia risks after adjusting for CSS. For brain tumors, a substantial attenuation of the risk estimates
was observed for the French and German studies, but not for the British cohort. Although the observed attenuation was substantial, it was within the width of the confidence intervals and could therefore be due to chance. The assessment presented in Chapter 5 showed no substantial attenuation of leukemia or brain tumors risks after external adjustment for CSS.

The study in Chapter 6 is the first study showing that reasons for CTs do not confound CT-related cancer risks in studies of adults. Based on 40,000 CT reports, the UK cohort investigated whether medical conditions were associated with the use of CT in children or young adults with no previous cancer diagnosis for CT. Trauma, disease of the nervous or the circulatory system were mentioned in 25-30% of scans. The study showed that patients with hydrocephalus may receive higher cumulative radiation exposure from CT in early life. However, this study does not provide direct information on confounding bias by indication for CT scans.

**Strengths and limitations of the studies included in this thesis**

An important strength of the Dutch Pediatric CT study is the comparatively long follow-up period with an almost nationwide coverage. We obtained data from the majority of Dutch hospitals where children are scanned, covering all areas of the Netherlands and the full range of hospitals, from very small general hospitals to large general and academic hospitals. Therefore we were able to present the first nation-wide report on numbers and trends in CT use among children in the Netherlands (Chapter 3).

Another strength of our study is the design, described in Chapter 2, which allows follow-up of a large cohort of children with CT scans by record-linkage, without contacting the patients or their parents. Further, data collection was not affected by the willingness to participate since all pediatric patients who received a CT scan in participating hospitals were included in the cohort. Moreover, recall bias and information bias are limited since the radiation exposure was recorded at the time the patient receives a CT scan. Exposure information is therefore independent of disease outcome and recall of the patients or their parents.

Third, this study has one of the most comprehensive exposure assessments so far. We used an internal subset of about 40,000 CT scans for which individual machine settings (PACS) were available. Those were used to calculate organ doses, and a regression model was established to predict organ dose from the information available for all CTs. All previous studies imputed doses from external surveys.

Fourth, outcome information on cancer incidence, vital status and TSC was collected by linking with external (national) databases, each with high completeness covering a large part of the study follow-up period. Cancer registration in our study goes back to 1973 for leukemia and 1989 for solid cancer and we were able to rule out confounding by TSC, the most potent
brain tumor susceptibility syndrome. Of the other studies, only the French study collected data on tumor susceptibility syndromes based on hospital discharge information.

Fifth, we performed pairwise linkage of all datasets from participating hospitals to identify patients who were scanned in different hospitals. This is crucial for complete and valid exposure assessment because a) numbers of scans and associated doses need to be appropriately summed and b) digital information on CT scans initially conducted in one hospital will often be copied to the PACS/RIS systems of the second (often academic hospital) prior to start of more diagnostic procedures and/or treatment. This common clinical practice would, if not taken into account, cause over-reporting of the true numbers of scans and doses.

The medical-ethical rationale for this study design is that the study concerns secondary use of personal and medical data from medical files. In the Netherlands, a self-regulatory Code of Conduct for the use of data in health research generally mandates that physicians need explicit written individual patient consent to release personal medical information for scientific purposes. In compliance with the Code, radiologists were nonetheless allowed to provide data without consent, because (1) the resources needed to trace large cohorts render research infeasible, (2) there is a high potential of selective participation leading to biased cancer risk and loss of statistical power, and (3) the study invitation letter would likely have caused worries among children and parents, particularly because it cannot take the individual indication (and justification) of a CT scan into account.

One of the limitations of the Dutch Pediatric CT Study is that 18 hospitals declined to participate in the study. However, our study has a high coverage of all hospitals in the Netherlands performing more than 10 pediatric CT scans annually (70% of 60 eligible hospitals and 84% of all eligible pediatric CT scans for the period 1990-2012). Further, we might have missed scans among children born before digital archiving began. However, in Chapter 4, sensitivity analyses excluding children with a CT scan performed in a Dutch border-region hospital yielded similar results.

We could only collect PACS data for a subset of the CTs from the participating hospitals and, based on this information, we were able to calculate organ doses. However, these estimations did not include individual patient characteristics such as height, weight and position. Nevertheless, dosimetry of previous studies was based on external surveys, protocols or just number of CTs. This study shows a new dosimetry method based partially on own PACS data.

Although our study is large with a comparably long follow-up, the number of cases is too small for subgroup analyses. Besides, while leukemia incidence record linkage was possible since 1973, incidence of other cancers was only known from 1989 and non-malignant brain tumors and MDS were complete since 2002. However, sensitivity analyses, presented in Chapter 4, limited to these periods yielded similar results.
Finally, we were not able to correct for some potential confounders, e.g., information regarding the reason for the CT scans. Still, the assessment in Chapter 5 and results in Chapter 6 suggest that CSS and reasons for a scan do not substantially confound the association between radiation exposure from CT scans and cancer risks. Nonetheless, we were able to link the data with publicly available data for the potential confounder SES and with those from TSC referral centers in the Netherlands. Another confounder factor could be other diagnostic imaging. If the chance of receiving a CT scan is correlated with the chance of receiving other imaging procedures involving ionizing radiation. The radiation doses from a CT scan are generally much higher compared with most other common imaging procedures, particularly X-ray. Therefore, we believe that other diagnostic procedures are not a major source of confounding.

**Implications for clinical practice**

The increased risks for leukemia and brain tumors after radiation exposure from CTs observed in most studies have enhanced awareness about potential risk of CT exposures in the medical community and, together with technological progress in CT scans, led to further radiation dose optimization in pediatrics. To put the radiation risks in a clinical perspective, we observed an excess absolute risk for all brain tumors of 1.1 (95% CI: 0.3, 2.1) per 100,000 person-years per 20 mGy, which is the average brain dose among head CTs in the period 2012-2014 in our study. This means that in the 10 years after the first head CT scan, 1 excess case per 10,000 head CT scans is estimated to occur. Based on our data (Chapter 3), we estimated the number of annual head CT scans among children in the Netherlands to be around 10,000, leading to one brain tumor case annually attributed to radiation. In the Netherlands, nearly 120 children are diagnosed annually with a brain tumor.

In the last decade, improvements in CT equipment have allowed for better images at lower doses. Improved protocols have become much more widespread, resulting in reductions of doses for children. For instance, a survey in the UK showed a dose reduction of 50% in 2000-200816, but the number of CTs in the same period increased19 due to reduction in CT times and improvements of CTs. Moreover, Brenner and Hricak20 stated that future increases are likely in imaging modalities such as positron-emission tomography CT, single-photon emission CT, and potentially CT for screening of high-risk asymptomatic patients (e.g. smokers screened for early lung cancer detection). Therefore, it is still important to develop strategies to reduce medical radiation exposure and to extend continuing education for radiographers/technologists about radiation protection. For CT use optimisation in European countries, the Euratom Council Directive 2013/59 has recommended basic safety standards with details about responsibilities for employers, referrers, and practitioners, among others11,22.
Several campaigns have been set up by radiologists to raise awareness for the reduction of radiation dose in the imaging of children. These include the Image Gently campaign which was launched in 2008\textsuperscript{11}. Other campaigns have followed\textsuperscript{14,25} and more recently the ESR Euro Safe Imaging campaign was launched to improve radiation protection across Europe\textsuperscript{16}. The aim is to reduce doses from medical imaging by (1) personalized imaging, i.e., consideration of individual differences of patients being scanned such as height and weight, and (2) more stringent justification, i.e., clinicians are conscious about their use of medical imaging\textsuperscript{27}. As a successful example an intervention study across 5 University of California medical centers assessed the impact of institution-level audit and collaborative efforts to share best practices on CT radiation doses\textsuperscript{18}. The researchers collected radiation dose metrics on all diagnostic CT exams and shared audit reports detailing the distribution of radiation dose metrics for chest, abdomen and head CTs with the centres and shared best practices. Reviewing doses and sharing dose-optimization best practices resulted in an effective dose reduction of 48% and 54% for chest and abdomen CT, respectively, and more consistent doses for the head.

Additionally, MRI or ultrasound are appropriate imaging alternatives in many clinical settings for children. However, substitution of procedures with ultrasound requires that a specialized sonographer is available and substitution of radiation-based procedures with MRI requires machine availability. Besides, the risks associated with the need for anesthesia have to be considered for infants.

Although CT remains a crucial tool for pediatric diagnoses, it is important to minimize the radiation dose to children, e.g., by always using exposure settings for children. Communication with a pediatric radiologist to determine the need for a CT is a very important aspect.
Future perspectives

One limitation of the studies conducted so far concerns the small number of events for the main outcomes. Analyses of risks for less common cancer sites require larger studies. Therefore, two approaches will be used in the future: (1) extension of follow-up and (2) pooling. First, follow-up of the Dutch Pediatric CT Study will be extended in the next few years in the within the European MEDIARAD consortium. This will be greatly facilitated by the possibilities for automatic record linkage with external databases for cancer incidence and vital status. Second, the Dutch Pediatric CT Study is participating in a European pooling initiative. The EPI-CT study is a European multinational cohort study (more than one million children and adolescents), conducted in 9 European countries, of patients who have undergone at least one CT scan before the age of 21 years. 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 to provide precise direct estimates of cancer risk from CT scans received at young ages. Results of the pooled analyses are expected in 2017/2018. Pooled cohort studies increase the statistical power but do not reduce possible confounding bias by CT scan indication which all studies might suffer from. A possible next step might be nested case-control or case-cohort studies with full information about the medical history of participating patients, although it is unclear how this information can be used to derive risk estimates unaffected by indication bias.

Furthermore, although cohort studies about CT-related cancer risk have only been done among children, a next step might be to perform studies among young adults. Adults receive over 10 times more CT scans than children and most radiation-induced cancers appear during middle or old age. We (Chapter 6) and others have shown that such studies are feasible.
Concluding remarks

In conclusion, the results of this thesis provide unique and new information on the use of pediatric CTs in the Netherlands since their introduction into clinical practice, and on the radiation risks among CT-exposed children. The results, in the context of other studies with largely similar design, leave it open whether low-dose radiation risks can be estimated reliably from clinical populations. Future studies with different design and additional levels of medical information are needed for conclusive interpretation of current results. There remains no doubt that radiation protection is essential when exposing children for diagnostic purposes, and that exposure needs to be as low as possible which can be achieved by stringent dose optimization and imaging justification.
References


