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 lymphoproliferative 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 1).