CHAPTER 9

Summary and general discussion
The general aim of this thesis was to increase the knowledge about the risk of, risk factors for, and survival of subsequent neoplasms among long-term survivors of childhood cancer. This chapter summarizes our findings and compares those with findings from other studies. Furthermore, the clinical impact of our findings is discussed as well as recommendations for directions of future research.

For most chapters in this thesis, we used data from the Dutch Childhood Oncology Group–Long-Term Effects After Childhood Cancer (DCOG-LATER) cohort for evaluation of risk of subsequent malignant neoplasms (SMNs) or subsequent benign tumors (SBTs). The cohort consisted of 6,165 5-year childhood cancer survivors diagnosed between 1963 and 2001 in any of the seven pediatric oncology and stem cell transplant centers in the Netherlands. From the DCOG-LATER cohort, detailed information on childhood cancer diagnosis and treatment was collected. SMNs were ascertained by linkages to the Netherlands Cancer Registry, the nationwide network and registry of histo- and cytopathology (PALGA), and review of medical charts. Basal cell carcinomas (BCCs) and SBTs were only ascertained by linkage to PALGA.

In chapter 2, we determined the risks of all SMNs in the DCOG-LATER cohort. We specifically focused on the risks of solid cancers associated with specific chemotherapeutic agents, since not much is known about those effects. After a median follow-up of 20.7 years since childhood cancer diagnosis, we observed 291 SMNs in 261 individuals. Childhood cancer survivors had a 5.2-fold elevated incidence of SMNs compared to the expected incidence. Twenty-five years after childhood cancer diagnosis, 3.9% (95% confidence Interval (CI): 3.4%-4.6%) of survivors were diagnosed with an SMN. SMN risk in survivors was even increased beyond 30 years since childhood cancer diagnosis. We did not observe a noticeable change in the cumulative incidence of SMNs among survivors treated in the period 1990-2001 compared to those treated in earlier periods. When evaluating treatment-related risk factors in multivariable Cox regression models, we found, aside from the expected effects of radiotherapy, dose-dependent increased risks of breast cancer ($p_{trend} < .001$) and any solid cancer ($p_{trend} < .001$) associated with doxorubicin. The hazard ratio (HR) of breast cancer for survivors in the highest tertile of doxorubicin dose compared to survivors treated without doxorubicin was 5.8 (95% CI: 2.7-12.5). Point estimates for tertiles of doxorubicin exposure were higher among survivors without chest radiotherapy ($p_{trend}$ continuous dose among survivors without chest-directed radiotherapy=0.002), so residual confounding of radiotherapy is unlikely. For breast cancer, the doxorubicin-related risk appeared to be stronger among survivors of Li-Fraumeni syndrome-associated childhood cancer types (leukemia, CNS, and non-Ewing sarcoma) than among other childhood cancer types. We also observed a dose-dependent increase in sarcoma risk...
among survivors treated with cyclophosphamide ($P_{\text{trend}} = .01$), with an HR of 3.1 (95% CI: 1.5-6.0) for those in the highest tertile of cyclophosphamide dose compared to those treated without cyclophosphamide. In conclusion, our results strongly suggest that not only radiotherapy, but also chemotherapy, increases the risk of subsequent solid cancers.

Recent findings of an increased risk of colorectal cancer among childhood and young adult cancer survivors have spurred the debate on the need for surveillance among subgroups of childhood cancer survivors who are at highest risk. In chapter 3, we systematically reviewed and appraised all literature on the risk of, risk factors for, and outcome after a subsequent gastrointestinal cancer in childhood cancer survivors. A total of 45 studies were included and showed a 3.2 to 9.7-fold elevated risk of gastrointestinal cancer among survivors compared to the general population. Only a few studies examined treatment-related risk factors for gastrointestinal cancer. Abdominal radiotherapy was found to be a risk factor for subsequent gastrointestinal cancer, and procarbazine and platinum agent-based chemotherapy were also suggested to increase the risk. Most studies included only a small number of gastrointestinal cancer cases. Therefore, no conclusion could be drawn on the survival of (specific) gastrointestinal cancers in childhood cancer survivors.

In chapter 4, we contributed to filling the apparent knowledge-gaps identified in chapter 3 by evaluating the risk of histologically confirmed colorectal adenomas and cancers in the DCOG-LATER cohort. In total, 78 survivors developed a colorectal adenoma and 13 developed a colorectal cancer after a median follow-up of 24.9 years since childhood cancer diagnosis. Survivors who were treated with abdominopelvic radiotherapy showed a higher cumulative incidence (3.6%) compared to those treated without abdominopelvic radiotherapy (2.0%; $p$ difference=0.07) and compared to a sibling comparison group (1.0%; $p$ difference=0.03). In multivariable Cox regression analyses, treatment-related adenoma risk factors included abdominopelvic radiotherapy, total body irradiation, cisplatin exposure, and procarbazine exposure. Also, we confirmed the roles of hepatoblastoma (related to the tumor predisposition syndrome familial adenomatous polyposis) and of a self-reported family history of early-onset colorectal cancer as strong predictors of colorectal adenoma risk. In conclusion, we provide new evidence for excess risk of histologically confirmed colorectal adenomas among childhood cancer survivors.

In chapter 5, we evaluated the risk of subsequent skin cancers in the DCOG-LATER cohort. In total, 259 survivors developed a BCC, 20 a melanoma, and 10 a SCC. We found the incidence of BCC (29.8-fold), melanoma (2.3-fold), and SCC (7.5-fold) to be significantly elevated compared to the expected incidence based on general population rates. Cumulative incidences were similar for consecutive calendar periods of childhood cancer diagnosis (1963-1984, 1985-1994, and 1994-2001). Using a novel method of analyzing site-specific radiation exposure in a cohort setting, we showed that radiotherapy to the compartment where the BCC developed was associated with an almost 15-fold increase in risk.
increased BCC risk (HR=14.32, 95% CI: 10.10-20.29). A new finding of our study was that BCC risk appeared to increase with increasing in-field radiation-exposed skin surface area, while prescribed radiation dose and location of BCC according to likelihood of sun-exposure were not associated with BCC risk. Of all chemotherapy groups tested, only vinca alkaloids were found to increase BCC risk (HR=1.54, 95% CI: 1.04-2.27). In conclusion, we found strongly elevated risks of BCC associated with radiotherapy, which appeared to further increase with increasing skin surface area exposed.

In chapter 6, we quantified the incidence of histologically confirmed benign tumors in the DCOG-LATER cohort based on PALGA record linkage and we evaluated treatment-related risk factors. We identified 542 childhood cancer survivors who developed at least one benign tumor; risk among survivors was two times higher than among a sibling comparison group (HR=1.9, 95% CI: 1.5-2.6). The most prevalent subtypes of benign tumors were lipomatous neoplasms (N=102), meningiomas (N=98), adenomas (N=93), and nerve sheath tumors (N=55). Our analyses showed dose-dependent increases in the risk of leiomyomas of the uterus with abdominal radiotherapy, while breast fibroadenoma was not associated with high-dose trunk radiotherapy. A remarkable finding was the high number of osteochondromas among leukemia survivors treated with hematopoietic cell transplantation and total body irradiation. These exploratory results warrant further in-depth investigations into site-specific benign tumor risk factors.

Currently, there is considerable debate on the justification for or against active screening for meningioma among asymptomatic childhood cancer survivors, in particular, after cranial radiotherapy. In chapter 7, we presented results on the risk of histologically confirmed benign meningiomas in the DCOG-LATER cohort. In total, 97 individuals developed a benign meningioma, including 94 after cranial radiotherapy. Cumulative incidence 40 years post diagnosis for those treated with cranial radiotherapy was 12.4%. We found a linear dose-response for prescribed radiation dose and prescribed dose effects did not vary significantly according to exposure age nor to cranial volume irradiated. Exposed cranial volume (full vs. partial cranium) was not significantly associated with meningioma risk. Carboplatin appeared to be associated with meningioma risk. However, we saw no carboplatin dose-response and all nine exposed cases had high-dose cranial radiotherapy. In conclusion, one in eight CCSs exposed to cranial radiotherapy develops a late meningioma 40 years after diagnosis and this risk is dose-related. Our study contributes new evidence to the key element of adequate risk stratification for surveillance recommendations by evaluating the modifying effects of exposed cranial volume and exposure age on the radiation dose-response association.

In chapter 8, we evaluated whether clinical characteristics and survival of patients with SMNs are different compared to patients having similar first malignant neoplasms (FMNs) from the general population. We compared three case series of solid SMNs in the DCOG-
LATER cohort with sex-, age-, and calendar-year matched patient groups with FMNs from the Netherlands Cancer Registry (matching ratio 1-to-10). We included 45 sarcoma SMN patients, 41 breast cancer SMN patients, and 17 melanoma SMN patients. Survival of subsequent sarcoma was significantly worse than among matched FMN sarcoma patients (multivariable adjusted HR=1.89; 95% CI: 1.26-2.83), with 15-year survival rate being 32.8% among SMN patients. Almost all deaths were sarcoma-related. Survival after breast cancer and melanoma was not significantly different between SMN and FMN patients. For sarcoma and melanoma, treatment did not differ significantly between SMN and FMN patients. However, breast cancer SMN patients were significantly more likely to be treated with a mastectomy without radiotherapy/chemotherapy compared to breast cancer FMN patients. This treatment constellation represents a deviation from standard treatment guidelines likely related to limited treatment options due to previous childhood cancer therapy (chest radiotherapy and/or anthracyclines) or possibly to preference for mastectomy over breast-conserving therapy among childhood cancer survivors. In conclusion, survival of sarcoma-SMN patients is worse than sarcoma-FMN patients, while for breast cancer, survival and tumor characteristics appear similar for breast-SMN and breast-FMN patients. However, breast cancer treatment differs as breast-SMN patients receive breast-conserving therapy less often.

OVERALL CONCLUSIONS

The following general conclusions can be obtained from this thesis:

• Risk of subsequent malignant neoplasms is increased even beyond 30 years after childhood cancer diagnosis (chapter 2).

• Cumulative incidence of subsequent malignant neoplasms is not lower for survivors treated in more recent treatment eras (chapter 2).

• Survivors of childhood cancer who were treated with doxorubicin experience increased risks of developing solid tumors, breast cancer in particular, in a dose-dependent manner. Survivors who were treated with cyclophosphamide are at increased risk of developing a sarcoma (chapter 2).

• Childhood cancer survivors are at increased risk of gastrointestinal cancer and abdominal radiotherapy treatment is a risk factor for developing gastrointestinal cancer. Procarbazine and platinum agents are suggested to also increase gastrointestinal cancer risk. However, there is a lack of studies including sufficient cases on treatment-related risk factors for gastrointestinal cancer (chapter 3).

• Compared to a sibling comparison group, childhood cancer survivors show increased risks of colorectal adenomas. Survivors treated with abdominopelvic radiotherapy,
total body irradiation, cisplatin, and procarbazine are at increased risk for colorectal adenoma, but clear dose-response relationships were not observed. Colorectal cancer risk is increased in survivors compared to the general population (chapter 4).

• There is a need for a careful evaluation of the potential benefits and harms of gastrointestinal cancer screening (colorectal cancer in particular) in childhood cancer survivors at highest risk, an effort that is currently planned by the International Guideline Harmonization Group (chapters 3 and chapter 4).

• Survivors of childhood cancer are at increased risk of skin cancer, especially a remarkably increased risk of basal cell carcinoma. Radiotherapy is an important risk factor for BCC, with higher risks when a greater skin surface area is irradiated (chapter 5).

• Childhood cancer survivors are at increased risk of benign tumors compared to siblings. Site-specific findings provide leads for further in-depth etiologic studies of potential clinical relevance and are important to raise awareness among survivors, their parents, and care-providers (chapter 6).

• Childhood cancer survivors treated with cranial radiotherapy are at increased meningioma risk. Meningioma risk increases with increasing radiation dose and is more pronounced among children who received cranial radiotherapy at the youngest ages (chapter 7).

• Patients with a subsequent sarcoma after childhood cancer face higher mortality rates than a matched sample of patients from the general population with a first primary sarcoma (chapter 8).

• For subsequent breast cancer and subsequent melanoma, survival and clinical parameters for affected childhood cancer survivors were generally comparable to those from respective matched samples of patients with primary breast cancer and melanoma. An exception is breast cancer treatment in which subsequent breast cancer patients received more often a mastectomy than primary breast cancer patients (chapter 8).
THE RESEARCH IN THIS THESIS SHOWED THAT CHILDHOOD CANCER SURVIVORS ARE AT INCREASED RISK OF DEVELOPING SUBSEQUENT MALIGNANT NEOPLASMS (SMNs) AND BENIGN TUMORS. SEVERAL OTHER LARGE COHORT STUDIES HAVE ALSO PROVIDED EVIDENCE FOR INCREASED SMN RISKS AMONG SURVIVORS. THE LARGEST SMN SERIES HAVE BEEN REPORTED BY THE NORTH AMERICAN CHILDHOOD CANCER SURVIVOR STUDY (CCSS), THE BRITISH CHILDHOOD CANCER SURVIVOR STUDY (BCCSS), AND THE NORDIC COUNTRIES (TABLE 1).1-4 ALTHOUGH THESE COHORTS ARE LARGER THAN THE DCOG-LATER COHORT, OUR STUDY HAS A NUMBER OF SPECIFIC STRENGTHS. THE CCSS INVESTIGATORS RelyED ON PATIENT-REPORTED SMN OUTCOMES, WHICH WERE SUBSEQUENTLY VALIDATED BY PATHOLOGY OR MEDICAL RECORD INFORMATION. FOR DECEASED SURVIVORS, THE CCSS USED INFORMATION FROM DEATH CERTIFICATES. SURVIVORS WHO REFUSED PARTICIPATION IN THE QUESTIONNAIRE SURVEY WERE NOT INCLUDED IN THE SMN ANALYSES, POTENTIALLY LEADING TO SELECTION BIAS. FURTHERMORE, A POSSIBLE UNDERSSESSMENT OF SMNs MIGHT HAVE OCCURRED IN SURVIVORS WHO DID NOT MENTION THEIR PREVIOUS SMN IN THE QUESTIONNAIRE. THE BCCSS AND THE NORDIC COUNTRIES USED LINKAGE WITH POPULATION-BASED CANCER REGISTRIES TO OBTAIN SMN INFORMATION, BUT HAVE THE DISADVANTAGE OF LACKING DETAILED, COHORT-WIDE DATA ON CHILDHOOD CANCER TREATMENT. THE DCOG-LATER COHORT HAS A UNIQUE COMBINATION OF DETAILED DATA ON CHILDHOOD CANCER TREATMENT AND OBJECTIVE AND COMPLETE SMN INFORMATION FROM RECORD LINKAGES TO THE NETHERLANDS CANCER REGISTRY AND THE NATIONWIDE NETWORK AND REGISTRY OF HISTO- AND CYTOPATHOLOGY (PALGA), ALSO INCLUDING ADDITIONAL MEDICAL CHART REVIEWS.

ALL THREE OTHER LARGE COHORTS STUDIES PROVIDED ELEVATED RISKS OF ANY SMN COMPARED TO THE GENERAL POPULATION, WITH SIRs BEING REPORTED BETWEEN 3.3 AND 6.0, WHICH IS IN LINE WITH THE SIR IN OUR STUDY (5.4).1,2,4 DIRECT COMPARISON OF SIRs BETWEEN STUDIES IS DIFFICULT DUE TO MULTIPLE DIFFERENCES BETWEEN THE COHORTS WITH RESPECT TO INCLUSION PERIODS, FOLLOW-UP TIME (AND THUS ATTAINED AGE), TREATMENT DISTRIBUTIONS, AND OUTCOME ASSESSMENT METHODS; RESULTS OF SUCH COMPARISONS MUST BE INTERPRETED WITH CAUTION.

IN CHAPTER 2, WE FOUND THAT THE RISK OF SMNs REMAINED ELEVATED BEYOND THAT EXPECTED IN THE GENERAL POPULATION, EVEN MORE THAN 30 YEARS AFTER DIAGNOSIS AND AFTER THE AGE OF 40 YEARS. THIS IS IN LINE WITH OTHER LARGE COHORTS, WHICH ALSO SHOWED INCREASED RISKS IN SURVIVORS BEYOND AGE 40.1,2,5 IN CONTRAST TO THE CCSS3, WE DID NOT FIND A SIGNIFICANT DECREASE IN SMN RISK IN MORE RECENT TREATMENT PERIODS. THE CCSS STUDY GROUP OBSERVED A STATISTICALLY SIGNIFICANT DECREASE IN THE 15-YEAR CUMULATIVE INCIDENCE OF SMNs BY DECADE OF CHILDHOOD CANCER DIAGNOSIS. CUMULATIVE INCIDENCES AT 15 YEARS WERE 2.1%, 1.7%, AND 1.3%, FOR SURVIVORS DIAGNOSED IN THE 1970s, 1980s, AND 1990s, RESPECTIVELY.3 OUR RESULTS IN CHAPTER 2 SHOWED NO SIGNIFICANT DECLINE IN 15-YEAR CUMULATIVE INCIDENCES OF SMNs. CUMULATIVE INCIDENCES AT 15 YEARS, IN OUR STUDY, WERE 1.4%, 1.7%, AND 1.6%, FOR SURVIVORS DIAGNOSED IN THE PERIODS 1963-1979, 1980-1989, AND 1990-2001, RESPECTIVELY. A POSSIBLE
explanation might be that the decrease in radiotherapy treatment intensity started earlier in the US. It could also be that possible selection bias in the CCSS has led to different results from our study. The CCSS used questionnaires and causes of death to ascertain SMNs and therefore only 66% of the eligible cohort was included. If the questionnaire respondents are a group with other diagnosis and treatment characteristics and another distribution of SMNs than the ones who were not included, this could under- or overestimate the risk of SMNs. In our cohort, we were able to link the entire cohort to the Netherlands Cancer Registry and we had, therefore, information on SMNs for the full eligible cohort.

### TABLE 1. Characteristics and outcomes of large childhood cancer survivor cohort studies evaluating subsequent malignant neoplasm risk

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Childhood Cancer Survivor Study</th>
<th>British Childhood Cancer Survivor Study</th>
<th>Nordic countries</th>
<th>DCOG-LATER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>United States</td>
<td>Great Britain</td>
<td>Denmark, Finland, Iceland, Norway, and Sweden</td>
<td>The Netherlands</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>&lt;21</td>
<td>&lt;15</td>
<td>&lt;20</td>
<td>&lt;18</td>
</tr>
<tr>
<td>Size</td>
<td>23,603</td>
<td>17,981</td>
<td>47,697</td>
<td>6,165</td>
</tr>
<tr>
<td>Follow-up time (years)</td>
<td>Mean: 20.5 (SD: 7.5)</td>
<td>Median: 24.3 (IQR: 17.9-32.4)</td>
<td>Mean: 10.0</td>
<td>Median: 20.7 (range: 5.0-49.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data collection</th>
<th>Treatment information</th>
<th>Outcome assessment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Detailed, including specific radiotherapy and chemotherapy dose information</td>
<td>Questionnaire plus medical validation, cause of death</td>
<td>Number of SMNs</td>
</tr>
<tr>
<td></td>
<td>Crude information on radiotherapy fields and chemotherapy yes vs. no</td>
<td>Linkage to population-based cancer registry</td>
<td>SIR any SMN (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Insufficient and incomplete treatment information</td>
<td>Linkage to population-based cancer registry</td>
<td>EAR/10,000 person years any SMN</td>
</tr>
<tr>
<td></td>
<td>Detailed, including specific radiotherapy and chemotherapy dose information</td>
<td>Linkage to population-based cancer registry</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of SMNs</th>
<th>SIR any SMN (95% CI)</th>
<th>EAR/10,000 person years any SMN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,026</td>
<td>6.0 (5.5-6.4)</td>
<td>26’</td>
</tr>
<tr>
<td></td>
<td>1,354 (in 1,222 survivors)</td>
<td>3.9 (3.6-4.2)</td>
<td>16.8</td>
</tr>
<tr>
<td></td>
<td>1,180 (in 1,088 survivors)</td>
<td>3.3 (3.1-3.5)</td>
<td>17.3</td>
</tr>
<tr>
<td></td>
<td>291 (in 261 survivors)</td>
<td>5.2 (4.6-5.8)</td>
<td>20.3</td>
</tr>
</tbody>
</table>

* Data were derived from Friedman (2010), which included only the original CCSS cohort (n=14,359 survivors, n=802 SMNs in 732 survivors).

Our findings of increased breast cancer risks after doxorubicin exposure in **chapter 2** validated a recent report by Henderson et al. in the CCSS cohort, who found a dose-dependent increased breast cancer risk associated with anthracycline exposure among
women not exposed to chest radiotherapy. The CCSS study group speculated about a possible gene-anthracycline interaction since their anthracycline dose-response was stronger among leukemia and sarcoma survivors, both childhood cancer types that are associated with Li-Fraumeni syndrome in a small proportion of those patient groups. TP53 mutations or related germ-line mutations are expected to occur in higher proportions in those with a history of leukemia or sarcoma than survivors of other types of childhood cancer. Our findings of a statistically significant stronger doxorubicin dose-response among survivors of Li-Fraumeni syndrome-associated childhood cancer types (leukemia, sarcoma (except Ewing sarcoma), and CNS tumors) is in agreement with this hypothesis and warrants further investigation including details on family history of cancer and/or TP53 status. The CCSS study group also found an increased risk of breast cancer after treatment with alkylating agents in survivors not exposed to chest radiotherapy; risk was increased 3-fold in those with ≥18,000 mg/m² compared to those without alkylating agents and they found a statistically significant dose-response. In our entire cohort of survivors, we did not find an increased risk in those with ≥18,000 mg/m² exposure to alkylating agents after adjustment for radiotherapy and we did not find a dose-response relationship.

The pathway from healthy colon tissue to colorectal cancer is well-studied in the general population and in other high-risk populations, with a prominent role for colorectal adenomas as precursors for the vast majority of malignant colorectal lesions. Colorectal cancer screening aims to detect cancer in an early stage or to detect precancerous colorectal polyps that can be removed before becoming malignant. Our findings in chapter 4 are suggestive that at least some colorectal cancer in childhood cancer survivors can follow an adenoma-carcinoma sequence: 1) we also found an excess risk of colorectal adenomas in childhood cancer survivors; 2) we found similar risk factors for colorectal adenomas in our study as for colorectal cancers in previous studies (as has been shown in chapter 3); 3) most childhood cancer survivors who developed a colorectal cancer also had a colorectal adenoma. This information lends further support for the increasing call for screening of high-risk groups of childhood cancer survivors.

Radiotherapy is a well-established risk factor for BCC, and a linear radiation dose-response has been demonstrated in childhood cancer survivors. A new aspect of our study in chapter 5 was the evaluation of the effect of the amount of estimated in-field skin surface area. We found that survivors exposed to a larger estimated skin surface area of the compartment where the BCC occurred had significantly higher risks compared to those treated with a smaller skin surface area. Prescribed radiation dose to the skin compartment where the BCC occurred was not significantly associated with BCC risk. However, prescribed dose has been shown to be a modest predictor of absorbed dose at the site of the BCC. The results in chapter 6 present, to our knowledge, the first comprehensive evaluation of benign tumor risk in long-term childhood cancer survivors. Our findings indicate that childhood
cancer survivors have a dose-dependent increased risk of uterine leiomyomas for prescribed abdominopelvic radiotherapy dose. This finding is consistent with results in female atomic bomb survivors, for which a dose-response was observed between absorbed radiation dose to the uterus and risk of uterine myoma.\textsuperscript{16} In concordance with other studies\textsuperscript{17-19}, we found a high number of osteochondromas. Almost half of the survivors had received a hematopoietic cell transplantation/total body irradiation. A high risk of osteochondromas after hematopoietic cell transplantation/total body irradiation has been reported previously.\textsuperscript{17,18}

In chapter 7, we confirmed a strongly elevated meningioma risk among childhood cancer survivors who had received cranial radiotherapy and found a linear relationship with prescribed radiation dose. A linear dose-response relation has been previously shown in two case-control studies using absorbed radiation dose at the meningioma site.\textsuperscript{20,21} The use of prescribed radiation dose might have overestimated the truly absorbed dose in those patients treated with cranial radiotherapy involving only a part of the cranium. Consistent with the two case-control studies\textsuperscript{20,21}, we did not find modifications of the radiation dose-response by age at exposure. A new aspect of our study was the evaluation of the effects of exposed cranial volume (full vs. partial) on meningioma risk and the possible modification of the radiation dose-response by exposed volume. We did not find evidence of a stronger dose-response among patients treated with full cranial radiotherapy compared to those treated with partial cranial therapy. There was a suggestive, but nonsignificant main effect of full vs. partial cranial radiotherapy.

In chapter 8, we showed that survival of childhood cancer survivors who developed a subsequent sarcoma was poor and significantly worse than survival of patients with sarcomas as first primary cancer in the general population. These results are in line with results from other studies, although these studies were not specifically focused on childhood cancer survivors.\textsuperscript{22-25} An important observation in our study was the higher proportion of breast cancer patients among childhood cancer survivors who had received a mastectomy without additional radiotherapy or chemotherapy, compared to breast cancer patients in the general population. This has also been observed in other studies on breast cancer in cancer survivors vs. the general population.\textsuperscript{26-29} A likely explanation is that previous chest radiotherapy treatment for the childhood cancer has limited the adjuvant treatment options and therefore mastectomy is chosen over breast-conserving surgery.

**Strengths and limitations**

Firstly, an important strength of the DCOG-LATER cohort is the availability of detailed information on primary childhood cancer treatment and on all treatments for recurrences for >95% of the entire cohort. Details on chemotherapy included cumulative doses for all given drugs. For radiotherapy, details on prescribed dose, field, and boost/surdosage were recorded. Furthermore, names of other drugs and details on hematopoietic cell
transplantation were collected. This allows for a comprehensive evaluation of potential risk factors for subsequent tumors.

Secondly, the studies included in this thesis are based on the DCOG-LATER cohort, which includes survivors from the seven pediatric oncology and stem cell centers in the Netherlands. For the period between 1963 and 1990 the cohort is clinic-based. Yet, most younger patients (<16 years) were treated in one of the included clinics and within clinics, the cohort is considered to be nearly complete because of our rigorous identification and eligibility protocol. For the period from 1990 onwards, the study population represents a nationwide complete cohort, except for lymphomas among 16-17 years olds treated in hematology departments, certain types of brain tumors treated by neurosurgeons, and thyroid cancer treated by endocrinologists. As such, the risk of selection bias is very low.

Thirdly, in this thesis we included highly complete data on SMNs and histologically confirmed benign tumors. SMN data were collected via record linkages to the Netherlands Cancer Registry and the nationwide network and registry of histo- and cytopathology (PALGA), and via medical follow-up. Benign tumors were identified via record linkage to PALGA. PALGA is a worldwide unique source for collecting complete and objective information on histologically confirmed basal cell carcinoma and benign tumors with nationwide coverage since 1990. The Netherlands Cancer registry obtained nationwide coverage of SMNs in 1989.

Finally, the long-term follow-up of the DCOG-LATER cohort, which allows for evaluation of long-term risks of subsequent tumors, is a unique aspect of this thesis. In all the studies in this thesis, the median follow-up time exceeded 20 years since childhood cancer diagnosis. Since many solid SMNs are usually considered to have a latency period of at least 5-10 years, a long-term follow-up is needed to accurately evaluate their risks.

The first limitation of the studies described in this thesis is the low number of events for various subgroups of second tumors, so that risk factor analyses for rare second tumor types were not possible (e.g. salivary gland tumors, male breast cancer, specific gastrointestinal tract tumors, specific genitourinary tract tumors, etc.).

A second limitation is that we did not have incidence data of benign tumors (Chapters 4, 6, and 7) and basal cell carcinomas of the skin (Chapter 5) for the period before 1990, since those outcomes were only determined by linkage to PALGA, which attained nationwide coverage in 1990. To adjust for this in the analysis, we left-truncated these specific analyses at 1/1/1990. Also, only a small percentage (<10%) of the potential follow-up time of our cohort occurred before 1990, predominantly among survivors aged <30 years, an age at which the risk of subsequent tumors is still fairly low. Therefore, although the potential impact of this methodologic characteristic cannot be ignored, we consider the impact to be rather limited. For SMNs, we had no data from linkage to the Netherlands Cancer Registry before 1989. For the short follow-up time of the cohort before 1989, we
used SMN data both from PALGA and from medical records, rendering it very unlikely to have missed SMNs, especially since many childhood cancer survivors were still under surveillance in the original treatment center in this early period of their life.

A third limitation that we encountered, with regard to studies on treatment-related risk, is the fact that we relied on prescribed radiation doses, which is the target dose intended to reach the pediatric tumor and immediately surrounding tissues in the radiation field. The actual absorbed radiation dose at the site of the subsequent tumor can be quite different from the prescribed radiation dose, depending on distance between the tumor and the organ at risk. We found a dose-dependent relation between prescribed cranial radiation dose and meningioma risk (chapter 7). However, we did not find clear dose-dependent relations for breast cancer, sarcoma, any solid cancer (chapter 2), colorectal adenoma (chapter 4), and basal cell carcinoma (chapter 5), while for most of these tumors dose-dependent associations with absorbed radiation dose have been reported.32-37

Finally, a fourth limitation is the lack of individual information on genetic syndromes. A childhood cancer survivor cohort is enriched for patients with cancer susceptibility syndromes, and among this not yet entirely identified subgroup in our cohort, such syndromes may also be the causative factor, or one of the causative factors for a subsequent cancer (i.e. Li-Fraumeni syndrome). Hence, this will likely have some impact on the validity of our treatment-specific risk estimates, as in any other study on SMNs among childhood cancer survivors. For example, if the type of childhood cancer that is associated with a given cancer susceptibility syndrome is also associated with specific therapies, then these therapies may be spuriously found to be associated with an increased risk of subsequent tumors. Also, it is not possible to disentangle main effects of treatment from joint effects of treatment and genes, e.g., if the genetic syndrome predisposes the index patient to specific treatment-related SMNs. In chapter 2 we found an increased risk of subsequent breast cancer after doxorubicin exposure, while survivors with (high-dose) doxorubicin exposure were mainly treated for a pediatric leukemia and sarcoma, childhood cancer types associated with Li-Fraumeni syndrome, which also includes breast cancer. We therefore performed a sensitivity analysis where we evaluated doxorubicin-related breast cancer risk separately for childhood cancer types associated with Li-Fraumeni syndrome and other childhood cancer types. We showed that the doxorubicin dose-response appeared to be confined to Li-Fraumeni syndrome-associated childhood cancers, although numbers of breast cancers after the other childhood cancer types were rather small.

Implications for clinical practice
The studies presented in this thesis have multiple implications for childhood cancer survivors and for newly diagnosed cancer patients.

The results in this thesis emphasize that childhood cancer survivors and health
professionals looking after childhood cancer survivors need to be aware of an increased risk of subsequent tumors, even beyond 30 years post-diagnosis and also among survivors treated in more recent treatment periods. The DCOG-LATER guideline for follow-up of childhood cancer survivors includes radiation dose-specific surveillance recommendations for breast cancer screening among asymptomatic female survivors who received ≥7 Gy chest radiotherapy. For other SMNs, the DCOG-LATER follow-up guideline does not include recommendations for active screening since the 2007-2009 based evidence summaries did not contain sufficient information on a net benefit of active surveillance (for various reasons) to warrant a screening program. In the meantime, the International Guideline Harmonization Group (IGHG), an internationally collaborative endeavor to harmonize clinical practice guidelines for long-term follow-up of chronic health problems among survivors of childhood, adolescent, and young adult cancer, has also published a breast cancer surveillance guideline for female childhood cancer survivors. In both guidelines, yearly screening of female survivors who received chest radiotherapy is recommended beginning at age 25 years or 8 years after treatment, whichever occurs last. The DCOG-LATER follow-up guideline recommends screening with a combination of mammography and MRI up to age 60 years and after that, enrollment in the population-based breast cancer screening program. Currently, the IGHG guideline for breast cancer is being updated based on new available evidence published since 2011. Recently, the IGHG has also published recommendations regarding thyroid cancer surveillance. Other SMN surveillance guideline efforts from the IGHG include CNS neoplasms (in progress) and gastrointestinal/colorectal cancers (in planning stages) (www.ighg.org). Guidelines are also frequently updated, taking into account the latest (published) evidence that becomes available. The results in this thesis can inform (IGHG) surveillance guidelines:

- The results presented in chapter 2, of an increased risk of breast cancer not only after radiotherapy, but also after doxorubicin exposure, is new evidence that will be considered in the next update of the IGHG breast cancer guideline. As the risk increase associated with high-dose doxorubicin seems to be comparable to the risk increase in survivors receiving 10-19 Gy radiation, for whom annual breast cancer screening is recommended from age 35 onwards according to the DCOG-LATER surveillance guidelines, screening may also be recommendable in the high-dose doxorubicin group.

- Results of our study on meningioma risk in chapter 7 provide new evidence that can be used in the updates for the IGHG CNS neoplasm guideline for which recommendations are currently developed. Our results suggest that irradiated cranial volume is, at present, not a suitable characteristic for risk-based stratification of childhood cancer survivors. Having had any cranial radiotherapy dose, and to a lesser extent, cranial radiotherapy dose are more suitable.
Our systematic review in chapter 3 and our results of colorectal tumor risk in chapter 4 will be useful evidence for the IGHG gastrointestinal cancer surveillance guideline, the development of which is in the planning stages at present. The results in chapter 4 suggest that colorectal cancers in childhood cancer survivors may be preceded by colorectal adenomas, like in the general population. Screening on and subsequent removal of precancerous adenomas or early-stage cancers among high-risk survivors might therefore be beneficial. However, other aspects also need to be evaluated to justify screening in high-risk survivors. A sound evaluation is warranted to assess benefits in terms of mortality, treatment-related complications, and quality of life and of harms, such as distress, potentially unnecessary follow-up diagnostic procedures and/or surgery caused by false-positive findings. Furthermore, evidence is needed on the type of surveillance modality to be used, considering age-specific diagnostic values, complication rates, and costs.

During follow-up visits at the late effect outpatient clinic, the skin is examined for abnormalities by a medical professional. This includes a full body skin examination to screen for suspicious lesions. Furthermore, survivors are educated about risks of sun exposure and how to perform self-examination of the skin. Our results in chapter 5 underscore the need for awareness of skin cancer in childhood cancer survivors, especially for BCC in survivors who have received radiotherapy. Health care professionals who take care of childhood cancer survivors should be trained in recognizing suspicious skin lesions by dermatology experts.

The results presented in this thesis also provide information that can be used in developing future treatment protocols for newly diagnosed cancer patients. The aim of new treatment protocols is to achieve a high survival of childhood cancer with less (long-term) side effects. Information on the magnitude of risk increase of long-term adverse effects associated with specific cancer treatments can be used in making a well-balanced treatment choice. Whenever possible, avoiding or reducing exposure to radiotherapy (e.g. reduced fields/lower doses) should be considered, if the chances of survival are not decreased by such changes. This is certainly not new, professionals involved in (pediatric) radiotherapy treatment planning and delivery are and have been astutely aware of this principle, and avoidance of normal tissue damage, where feasible, has been the central premise of any pediatric treatment plan. Current treatment planning systems use much more sophisticated techniques than those available for the patients treated largely in the 2D-era covered by our cohort. These techniques, such as intensity modulated radiotherapy (IMRT), allow for smart combinations of multiple beams that deliver the planned target dose to the tumor but, at the same time, find the most optimal combination of beams that spare as much of critical tissues with low threshold doses/volumes as reasonably possible (see also...
below). Effects of chemotherapy on SMN risk needs to be further evaluated. If certain chemotherapy agents appear to increase SMN risk, as our results in chapter 2 suggest, agents with similar tumoricidal effects and acute side effects/other long-term side effects, but with lower SMN risk, should be considered.

A better and more individualized prediction of SMN risk can be useful for treatment decisions of newly diagnosed patients and for individualized post-treatment surveillance strategies. For subsequent thyroid cancer, a risk prediction model has been developed based on patient and primary tumor characteristics and a history of thyroid nodules combined with primary tumor treatment information, which showed good discriminatory ability for use in monitoring thyroid cancer risk. Adding genetic profiles can be of help in predicting SMN risk better. Therefore, more information is needed on genetic predictors of SMN risk as well as on interactions of genetic variants with treatment factors. A recent pooled study of the North American Childhood Cancer Survivor Study cohort and the St. Jude Lifetime cohort identified loci that were associated with an increased breast cancer risk after treatment with chest radiotherapy. This information on genetic profiles, in combination with clinical and treatment-related risk factors, can be used in the development of an individual risk prediction model for breast cancer risk. An example of a risk prediction model combining genetic information with clinical information was derived from a case-control study among childhood cancer survivors with a subsequent CNS tumor and matched controls of childhood cancer survivors without evidence of subsequent neoplasms. In this study, genetic variants selected based on published studies in adult-onset primary CNS tumors were validated and subsequently, a risk prediction model based on both the validated genetic variants and on clinical information was developed and validated to identify survivors at high or low risk for subsequent CNS tumors. The authors found that this risk prediction model had good diagnostic accuracy and could be used to inform post-treatment surveillance.

FUTURE PERSPECTIVES

• It is important to obtain sufficiently large numbers of specific SMN cases to allow for robust risk factor analyses and assessment of treatment interactions for many subgroups of SMNs. A longer follow-up of the DCOG-LATER cohort will substantially increase SMN numbers as the cohort will then reach ages where background risks of cancer are much higher and this will enable more detailed analysis of site-specific SMN risks. Furthermore, international pooling of data between studies is necessary to obtain sufficiently large numbers of specific SMN cases that allow for robust risk factor analyses and assessment of treatment interactions for many subgroups of SMNs.
Collaborations between research groups are therefore essential. Such initiatives have already been undertaken with the pan-European PanCareSurFup study for specific SMNs. Moreover, our group recently initiated a consortium to combine data from individual patient’s observations for subsequent breast cancer from various cohorts worldwide.

- Our exploratory analyses show that survivors of childhood cancer are at increased risk of benign tumors. More in-depth analyses should be done to evaluate risk factors for site-specific benign tumors, the results of which can be used to identify high-risk groups.

- The analyses presented in this thesis are based on radiotherapy characteristics including prescribed radiation dose to body regions rather than estimated absorbed radiation exposure to the organ at risk. Cohort-wide dosimetry efforts are ongoing to get full-body dosimetry for homogeneous irradiated subgroups of childhood cancer survivors based on the principle that the resulting absorbed radiation doses of the representative survivor will be assigned to all survivors in the same subgroup (based on sex, age at radiotherapy, and radiotherapy field). Also, dosimetry efforts are underway to calculate the absorbed dose for specific disease outcomes: all patients who received upper-body radiotherapy to evaluate the radiotherapy-related risks of CNS tumors, stroke, and cataract; all patients who received abdominopelvic radiotherapy to evaluate the radiotherapy-related risks of colorectal adenoma and cancer; and all basal cell carcinoma (BCC) cases and matched controls to evaluate the radiotherapy-related risks of BCC.

- In recent decades, treatment practices have changed. For various childhood cancer types, where possible, radiotherapy has been avoided or radiotherapy fields and doses have been diminished and new radiation techniques have been incorporated. For example, newly introduced techniques like intensity-modulated radiotherapy (IMRT) and proton radiotherapy decrease the radiotherapy dose to the surrounding tissues. Interestingly, the larger volume of tissue receiving radiation exposure (albeit at low doses) with IMRT treatments has been postulated to increase SMN risk, rather than decrease. Proton therapy is thought to decrease SMN risk due to an improvement in dose distribution by reduced entrance dose and minimal to no exit dose. There are, however, concerns that secondary dose from neutron scatter might lead to an increased risk of SMN compared to photons in conventional external beam radiotherapy. The DCOG-LATER cohort and other large cohort studies (e.g. BCCSS, CCSS) have assessed SMN risks of survivors prior to the millennium, since those survivors are the ones with sufficiently long follow-up to evaluate SMN risks. It is of equal importance to carefully monitor SMN risk in survivors treated with those modern therapies. Future efforts of the DCOG-LATER cohort therefore include the evaluation of SMN risk among IMRT patients. For proton therapy,
where patient numbers in single-center studies are too small to provide a comprehensive assessment of SMN risk and other long-term outcomes, large-scale collaborative studies are needed to evaluate the long-term effects, as was proposed in a recent clarion call by an international community of clinicians and radiation researchers.\textsuperscript{55} For the Netherlands, the national Health Council has mandated standardized registration and long-term follow-up of all patients treated with proton therapy to allow for appropriate evaluation of care (specifically including side effects) in the future. The methods for and data on patient registration, follow-up, and outcome assessment, as well as the infrastructure for late effects care in the DCOG-LATER Consortium provide powerful tools to conduct such studies. Expert members of the DCOG-LATER Consortium, now based at the Princess Máxima Center for Pediatric Oncology, serve as partners in recently started initiatives led by the University of Groningen and the MAASTRO clinic to allow for joint registration and research studies among childhood cancer patients.

- Not much is known about lifestyle factors and their impact on SMN risk in childhood cancer survivors. Smoking, for example, may possibly modify treatment-related risks for SMNs. A study on lung cancer risk in Hodgkin lymphoma survivors showed that the joint effects of smoking and treatment were significantly stronger than the sum of the individual effects.\textsuperscript{56} Sun exposure might modify radiotherapy-related skin cancer risk, but good-quality information on sun exposure is difficult to obtain. Evaluating interactions between treatment and lifestyle factors solicits collaborations between research groups and needs high-quality data on lifestyle factors.

- Future studies should try to identify genetic markers that increase SMN risk or modify treatment-related SMN risks. In the DCOG-LATER study, DNA is currently being collected for survivors who participate in the clinical part of the study. This offers opportunities for research on genetic markers, such as genome-wide association studies that are planned. Data of genetic markers can then be combined with clinical data about childhood cancer diagnosis and treatment and with lifestyle factor data to obtain individualized predictions of SMN risk.

- Knowing which survivors are at highest and lowest risks of developing SMNs is very important in clinical decision making. Combining genetic information with clinical information has been proven to be potentially useful in prediction of SMN risk.\textsuperscript{44} Estimating individualized risk of SMNs and other late effects among survivors by risk prediction models can guide clinicians in what choices to make regarding surveillance.

- Risk prediction models can also be informative for guiding decisions on initial childhood cancer treatment. Besides SMNs, there are other severe long-term complications, especially cardiovascular diseases. By predicting risks for all major adverse events (including SMNs) in risk prediction models, risks and benefits between different treatment options can be considered carefully.
REFERENCES


