MAIN FINDINGS

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 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 \( (P_{\text{trend}} < .001) \) and any solid cancer \( (P_{\text{trend}} < .001) \) 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 \( (P_{\text{trend}} \text{ continuous dose among survivors without chest-directed radiotherapy}=0.002) \), 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 ($P_{trend} = .01$), 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
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,