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Dose-response relationship between chemotherapy for childhood cancer and the risk for a carcinoma or malignant melanoma as subsequent neoplasm - a scoping review of the literature and a case-control study

(Dosis-Wirkungsbeziehung zwischen Chemotherapie bei Krebs im Kindesalter und dem Risiko für ein Karzinom oder malignes Melanom als Folgeneoplasie – ein Scoping Review der Literatur und eine Fall-Kontroll-Studie)

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Meinen Eltern und meiner Schwester,
sowie meinem Partner und unserem Kleinen

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List of abbreviations

95% CI	95% confidence interval
AAS	alkylating agent score (according to Tucker et al. 1987, unless otherwise specified)
AER	absolute excess risk
AIC	Akaike information criterion
ALL	lymphoid leukemia, ICCC-3 group I(a) (Steliarova-Foucher et al., 2005)
ALL-BFM	multi-center study for the treatment of children and adolescents with acute lymphoid leukemia in Germany (Austria and Switzerland); BFM stands for Berlin, Frankfurt, Muenster; a number accompanying the name is usually the year of study start
AML	acute myeloid leukemia, ICCC-3 group I(b) (Steliarova-Foucher et al., 2005)
AT	as treated (therapy a patient received)
BC	breast cancer
BCC	basal cell carcinoma
BCCSS	British Childhood Cancer Survivor Study
C	number of cases/number of persons with outcome in study period, e.g. a disease or death
CCS	childhood cancer survivors
CCSS	Childhood Cancer Survivor Study
CCSS-US/Canada	North American Childhood Cancer Survivor Study
CED	cyclophosphamide equivalent dose (Green et al. 2014)
CI	cumulative incidence
CNS	central nervous system
COALL	Co-operative Study Group for Childhood Acute Lymphoblastic Leukemia
Cox model	Cox proportional hazards regression
CRC	colorectal cancer
CSPN	carcinoma or malignant melanoma according to ICCC-3 group XI as subsequent primary neoplasm after childhood cancer (Steliarova-Foucher et al., 2005)

CT	chemotherapy
DCOG LATER	Dutch cohort Childhood Cancer Oncology Group–Long-Term Effects After Childhood Cancer
df	degrees of freedom
E	exposed population
ENCR	European Network of Cancer Registries,
Ex	number of SPN cases expected
FP	fractional polynomial
FPN	first primary neoplasm
GCCR	German Childhood Cancer Registry
GI	gastrointestinal
GPOH	Society of Pediatric Oncology and Hematology in Germany (Gesellschaft für Pädiatrische Onkologie und Hämatologie)
Gy	Gray
H	number of persons without outcome in study period
HL	Hodgkin lymphoma
HR	hazard ratio
IARC	International Agency for Research on Cancer (World Health Organization)
IACR	International Association of Cancer Registries
ICCC	International Classification of Childhood Cancer (Kramarova et al. 1996)
ICCC-3	International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005)
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
ICD-O-3	International Classification of Diseases for Oncology, 3rd edition, (World_Health_Organization 2013)
IRR	incidence rate ratio
ITT	intention-to-treat (therapy according to protocol)
LFS	Li Fraumeni syndrome
MDS	myelodysplastic syndrome and other myeloproliferative diseases, ICCC-3 group I(d)
MFP	multivariable fractional polynomial

MOPP	mechlorethamine, vincristine, procarbazine with or without prednisone
N	number of persons at risk
n.s.	not significant
n/a	not available
NHL	non-Hodgkin lymphoma
NSI	Nucleotide synthesis inhibitors (here: only methotrexate)
O	number of observed SPN cases
OR	odds ratio
P	number of persons at risk of getting the outcome
PR	Poisson regression
pyar	person-years at risk (sum of lengths of time each person stayed at risk during the period of observation
ref.	reference category
RR	relative risk
RT	radiotherapy
SAP	statistical analysis plan
SCT	stem cell transplantation
SGC	salivary gland carcinomas
SIR	standardized incidence ratio
SPN	subsequent primary neoplasm
STATT	Second Tumour After Tumour Therapy (a case-control study by the GCCR)
TBI	total body irradiation
TOS	therapy optimization study
U	unexposed population

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1 Introduction

The survival of childhood cancer patients has improved over the last few decades. Five-year-survival probability rose from 65% in the 1980s (Gatta et al., 2005) to almost 80% in the 2000s in Europe (Gatta et al., 2014). According to the annual report of the German Childhood Cancer Registry (GCCR), 82% of children in Germany survive for at least 15 years (data from 1980-2017, (Kaatsch et al., 2019)). However, the improved survival comes at a cost: Although figures from Germany are not yet available, research from the United States suggests that about two thirds of former childhood cancer patients develop late sequelae within 30 years after treatment (Langer et al., 2017, Bhatia et al., 2015), and 40% even experience late effects which are severe, life threatening, disabling, or fatal (Landier et al., 2015).

One of the most severe late effects are subsequent neoplasms, which have a higher mortality than the first neoplasm (Blettner and Scholz-Kreisel, 2018). In Germany, 8.3% of the childhood cancer patients of the GCCR were diagnosed with a SPN within 35 years after the first cancer diagnosis (Scholz-Kreisel et al., 2018a). The risk for subsequent neoplasms is expected to increase further as patients get older (Olsen et al., 2009). The GCCR systematically registers neoplasms occurring after a first neoplasm in childhood. It generally follows the definition of the IARC/ENCR/IACR[1] Working Group which defines multiple primary cancers as cancers with different topologies and/or morphologies in a patient. Extensions, recurrences (relapses), and metastases are not included (Demaret et al., 2005). Transformations are also excluded (personal communication with “deleted in the electronic version for reasons of data protection”, 7 Jan 2020). In this thesis, the neoplasm following the first primary neoplasm (FPN) in a patient is considered and referred to as a subsequent primary neoplasm (SPN). The time between FPN and SPN is called latency period.

The therapy of the FPN is a risk factor for the development of a SPN (Turcotte et al., 2018). Radiotherapy may cause malignancies by interacting with DNA and leading to genetic and/or epigenetic changes (Travis et al., 2012). The SPN risk by radiotherapy is dose-dependent and has been studied for many cancer types (Turcotte et al., 2018, Berrington De Gonzalez et al., 2013, Kennedy, 2009, Corraini et al., 2017, Inskip et al.,

[1] IARC = International Agency for Research on Cancer (World Health Organization),
ENCR = European Network of Cancer Registries,
IACR = International Association of Cancer Registries

2016, Neglia et al., 2006, Kovalchik et al., 2013, Bhatti et al., 2010). Among CCS, dose-effect relationships are established for breast cancer (Inskip et al., 2009, Moskowitz et al., 2014), thyroid cancer (Sigurdson et al., 2005, Veiga et al., 2012b), colorectal cancer (Nottage et al., 2012), sarcoma (Hawkins et al., 1996, Berrington de Gonzalez et al., 2012, Schwartz et al., 2014, Tucker et al., 1987a), CNS tumors (Neglia et al., 2006, Taylor et al., 2010), and basal cell skin cancer (Watt et al., 2012b)). The risk usually increases with increasing dose, but may decrease at very high doses (Veiga et al., 2012b).

Chemotherapeutic substances are cytotoxic and do not discriminate between tumor cells and normal cells (Jenkins, 2013). Alkylating agents and epipodophyllotoxins in particular have been associated with an increased risk of SPNs (Jenkins, 2013), but also anthracyclines (Turcotte et al., 2018). Different chemotherapeutics have been associated with the risk for different SPNs. The best-established associations between chemotherapy and increased SPN risk are for hematologic SPNs, especially acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), occurring as early as a few months after the first neoplasm (Blettner and Scholz-Kreisel, 2018, Turcotte et al., 2018). Chemotherapeutic substances also increase the risk for solid tumors (Turcotte et al., 2018), which usually occur after a longer latency period (> two years) (Blettner and Scholz-Kreisel, 2018, Turcotte et al., 2018, Scholz-Kreisel et al., 2018a).

Several studies have shown a dose-response relationship between the cumulative dose of chemotherapeutics administered during the treatment of cancer in children and the risk for SPNs. The studies usually analyzed cumulative doses as categorical variables, applying an alkylating agent score (Tucker et al., 1987b) or categories of an cyclophosphamide equivalent dose (Henderson et al., 2016).

In Germany, the STATT study (Second Tumour After Tumour Therapy) is being carried out by the GCCR to investigate therapy-related risk factors for SPNs focusing on chemotherapy. Specifically, this nested case-control study analyzed the dose-response relationships between the cumulative dose of chemotherapeutic groups and SPNs risk.

This thesis focuses on the SPN risk posed by chemotherapy because this dose-response relationship has been less well investigated than the one with radiotherapy. A deeper understanding is especially important because the frequency of

chemotherapeutic treatment has increased whereas that of radiotherapeutic treatment has decreased over the last decades ((Teepen et al., 2017, Kenney et al., 2004, Witkowska et al., 2015), personal communication with “deleted in the electronic version for reasons of data protection”, September 2018).

Particularly, this thesis focuses on carcinomas and malignant skin cancers as SPNs (CSPNs) according to the diagnostic group XI of the International Classification of Childhood Cancer, 3rd edition (ICCC-3) (Steliarova-Foucher et al., 2005), called, “Other malignant epithelial neoplasms and malignant melanomas”. Although they constitute 33.1% of all SPNs after a childhood cancer in Germany (Kaatsch P et al., 2019), the literature on these types of SPN is relatively sparse. One reason for this may be the rather long latency period for CSPNs, which requires a long follow-up period of former childhood cancer patients. This also requires a long survival of childhood cancer patients, which rose from less than 20% before the 1950s to more than 80% today (Rossig et al., 2013). The long latency period also means that these types of SPN will still be seen in the future in cohorts of childhood cancer patients treated years ago, such as the base population analyzed in STATT. Analyses of treatments in the past are relevant today and will continue to be in the future. There are screening guidelines for several types of carcinomas, and both the general population and high-risk populations may benefit from early detection (Henderson et al., 2012a). Childhood cancer survivors (CCS) with specific chemotherapy treatment may be such high-risk populations.

This thesis investigates the dose-response relationship between the chemotherapy a patient received during cancer treatment in childhood and the risk for developing a carcinoma or malignant melanoma as SPN using two approaches with the following two **research questions**:

1. In patients who had a FPN in childhood or adolescence, what is the current evidence in original research for a dose-response relationship between (a) exposure to chemotherapeutic substances for the treatment of a first malignancy or relapse and (b) the risk of having a carcinoma or malignant melanoma according to ICCC-3 group XI (Steliarova-Foucher et al., 2005) as a SPN (CPSN)?
2. In patients registered at the GCCR who had a first malignancy before the age of 15, is there a dose-response relationship between (a) the cumulative

exposure to one of the investigated chemotherapeutic groups for the treatment of the first malignancy or relapse and (b) the risk for having a having a carcinoma or malignant melanoma according to ICCC-3 group XI as a SPN (CSPN)? What form does the dose-response relationship have?

The results of the two approaches are compared in the discussion in a quantitative and qualitative way.

The two research questions were addressed using two different **methods**, a scoping review and a case-control study:

1. For the first question, I searched the literature for relevant studies and summarized the results in the manner of a scoping review (Chapter 3.1). The review gives an overview of the currently published evidence for dose-response relationships between chemotherapeutic treatment during childhood and the risk for having a CSPN. It identified study populations, the ways in which chemotherapeutic exposure was quantified, and the statistical methods of modeling the dose-response relationship (Chapter 4.1).
2. For the second question, I analyzed the intention-to-treat (ITT) data of the STATT study (see Chapter 3.2) with chemotherapeutic dose as a continuous exposure using conditional logistic regression with the principle of fractional polynomials with spike at zero. For the analyses, chemotherapeutics were summarized into common pharmaceutical groups based on the mode of action and/or type of substance because of the large number of substances (Chapter 3.2). The results are based on a relatively large group of patients. I described the CSPN risk which is posed by chemotherapy dose as a continuous exposure variable instead of a categorical one. (Chapter 4.2.2).

The integration of the results from the literature review and the data analysis (Chapter 5.3) may serve as a starting point for the quantification of chemotherapy-related risk factors for CSPNs. However, it also reveals gaps in knowledge in this field and areas of future research.

These results and results of future research may provide information for the development of long-term screening guidelines for CCS (CCSs) and possibly the adaptation of future therapy strategies for childhood cancer patients to reduce the risk of CSPNs. Surveillance strategies are available for cancer patients (Villani et al., 2011),

for instance for breast cancer, and might be extended to other risk groups based on chemotherapeutic treatment.

In the second chapter of this thesis, background relevant to the study question, the study design, and the interpretation of results is provided. If information was available, the background focused on CSPNs, but information on other common SPNs was included as well. The chapter reports cumulative incidence of SPNs in large CCS cohorts and describes risk factors for SPNs. The results of previous case-control studies from the GCCR are reported. Next, information on childhood cancer treatment is outlined. Then, study designs and measures relevant for the interpretation of the scoping review results and the case-control study are described. Last, information is provided on follow-up guidelines for SPNs in Germany and internationally.

The third chapter describes the materials and methods used for carrying out both the scoping review and the case-control study. The scope and method of a scoping review are outlined (for details see the review protocol, Appendix II). Next, the STATT-SCAR study design and the data acquisition are related. Together, the STATT study and the SCAR (Second Cancer After Radiotherapy) study form the STATT-SCAR study. The focus is on the acquisition of ITT data, which was used for the analyses in this thesis. Data preparations and statistical analyses (detailed in the statistical analysis plan (SAP, Appendix III)) are summarized, and potential sources of biases are described.

The fourth chapter reports the results of the scoping review according to the PRISMA extension of Scoping Reviews (Tricco et al., 2018). It also describes the results of the case-control study, descriptive and explorative ones.

The fifth chapter first discusses the results of the scoping review according to the PRISMA extension of Scoping Reviews (Tricco et al., 2018). Next, results and methods of the case-control study are critically reviewed and strengths and limitations are evaluated. Last, the results of case-control study and scoping review are discussed together.

2 Background

2.1 Incidence of SPN

In Germany, 8.3% of the childhood cancer patients of the GCCR were diagnosed with a SPN within 35 years after the first cancer diagnosis (Scholz-Kreisel et al., 2018a). The risk may increase further as patients get older (Olsen et al., 2009). Compared to the general population, the risk for SPNs was six to 12-fold higher in CCS than in the general population (Scholz-Kreisel et al., 2018a, Westermeier et al., 1998, Klein et al., 2002).

Direct comparisons of the cumulative incidence of SPNs with results from international cohorts of patients of childhood cancer are difficult because the cohorts may be defined differently (e.g. 6-month-survivors vs. 5-year-survivors, different FPNs and SPNs), the included age groups and the follow-up time may differ (Appendix I.1). The heterogeneity in approaches becomes clear from the following examples: In the North American Childhood Cancer Survivor Study (CCSS-US/Canada), the cumulative incidence (CI) of SPNs up to 30 years after diagnosis was 9.3% (Meadows et al., 2009). In the British Childhood Cancer Survivor Study (BCCSS), the cumulative incidence of SPNs at an attained age of 60 years was 13.8%, whereas 8.4% had been expected from rates in the general population (Reulen et al., 2011). Analysis on data from the Dutch Childhood Cancer Oncology Group–Long-Term Effects After Childhood Cancer cohort (DCOG LATER) showed that the cumulative SPN incidence 25 years after first diagnosis was 3.9% (Teepen et al., 2017). In a British-French study, the CI of solid SPNs only was calculated; it increased between 25 and 30 years after FPN treatment from 4.9% to 7.7% (de Vathaire et al., 1999). In a cohort of Japanese CCSs, only 1.3% developed a SPN up to 20 years after FPN diagnosis (Ishida et al., 2018).

The largest SPN subgroup in Germany are CSPNs (ICCC-3 XI); they make up 33.1% of all SPNs within 30 years after childhood cancer diagnosis (1981-2013) (Kaatsch et al., 2019). These 33.1% are composed of 11.4% thyroid cancer, 10.5% other and unspecified carcinoma (of these, 4.6% breast cancer), 8.4% skin carcinoma, 2.5% malignant melanoma, and 0.2% nasopharyngeal carcinoma. The remaining 66.9% are primarily CNS tumors (23.3%, ICCC-3 III) and leukemias (20.6%, ICCC-3 I). The composition of SPNs largely depends on the time of follow-up (Chapter 2.2.2).

2.2 Risk factors in general

Risk factors for SPNs after childhood cancer are the therapy (Turcotte et al., 2018), genetic predispositions for cancer (Turcotte et al., 2018), and various demographic and clinical factors. Knowledge of these risk factors is deemed relevant for this thesis. The scoping review evaluated studies in light of whether these risk factors have been addressed. In the STATT study, possible confounding (Chapter 2.6.3) by some of the risk factors were addressed in the design or the analysis (Chapter 3.2.3).

2.2.1 Sex

Females seem to be at higher risk for having a SPN. In Germany, both the CI for any SPN and the standardized incidence ratio (SIR) compared to the general population were higher for women (CI: 9.7% (95% CI: 8.6-10.8), SIR: 7.1 (95% CI: 6.4-7.9)) than for men (CI: 7.1% (95% CI: 7.1-8.2), SIR: 5.83 (95% CI: 5.3-6.4)) within 35 years of childhood cancer diagnosis (Scholz-Kreisel et al., 2018a). In the CCSS-US/Canada, Neglia et al. (2001) also saw that female sex was associated with an increased risk for any type of SPN ($p < 0.001$), and the CI of thyroid cancer as a SPN was more than twice as high in females than males (1.3 (95% CI: 1.0-1.6) vs. 0.6% (95% CI: 0.4-0.8)) (Veiga et al., 2012a). For solid cancer, Teepen et al. (2017) report a risk increase by 70% (hazard ratio (HR): 1.7 (95% CI: 1.3-2.2)) for females compared to males in the Dutch DCOG LATER cohort study. However, in the BCCSS, the risk for any SPN was standardized for sex, and it turned out to be lower in females than in males (SIR: 3.4 (95% CI: 3.1-3.8) vs. 4.5 (95% CI: 4.1-4.9)); the absolute excess risk did not differ (Reulen et al., 2011). Differences between sexes may be due to female breast cancer, which is relatively common. After 35 years of follow-up, 10.3% of females had a secondary breast cancer (n = 65 out of 630 females with an SPN) in a study with data from the GCCR (Scholz-Kreisel et al., 2018a).

2.2.2 Age at diagnosis, attained age, time since diagnosis, calendar time

Age at first treatment may be associated with SPN risk (Turcotte et al., 2018, Moskowitz et al., 2014, Jenkins, 2013, Berrington De Gonzalez et al., 2013). The risk for breast cancer and other solid tumors may be higher with a younger age (van Leeuwen and Ng, 2016). In the CCSS-US/Canada, childhood cancer at a younger age was associated with an increased risk of? any type of SPN (p for trend <0.001) (Neglia et al., 2001). However, among women without chest radiation during childhood cancer treatment, patients aged ten to 20 years at FPN diagnosis had a higher SIR compared

to the general population (4.8 (95% CI: 3.5-6.5)) than patients up to nine years of age (1.8 (95% CI: 0.8-4.1)) (Henderson et al., 2016).

Higher **attained age** or longer **time since treatment** comes with greater risk for SPNs, including solid tumors (Teepen et al., 2017, van Leeuwen and Ng, 2016), given the increased background risk at a higher age. In the BCCSS, AER for SPNs rose from 12.2/10,000 person-years (95% CI: 10.3-14.1) in CCS younger than 20 years to 38.6/10,000 person-years (95% CI: 17.5-59.7) in survivors 50 years and above (p for trend <0.001) for any SPNs, and similarly for SPNs of the digestive tract and the genitourinary tract (Reulen et al., 2011). Some studies found decreasing SIRs for SPNs with increasing time since diagnosis even though there was still a significant increase in the SIRs, compared to the general population (for SPNs in general and for digestive subsequent neoplasms: (Reulen et al., 2011), for SPNs in general and for solid tumors: (Teepen et al., 2017)). This is because the SPN risk in the general population seemed to increase stronger with age than the SPN risk for childhood cancer patients.

The number of second primary hematologic malignancies seems to peak four to nine years after childhood cancer diagnosis; the risk for MDS or AML SPNs specifically was highest four to six years after exposure (Jenkins, 2013, Teepen et al., 2017, Scholz-Kreisel et al., 2018a).

The maximum time since treatment or attained age are rough indicators for the **calendar time of treatment** with higher attained age or longer time since treatment indicating earlier calendar years. The treatment in earlier calendar years was more aggressive than today, aiming at destroying the tumor with little consideration of possible late sequelae of the therapy ((Rossig et al., 2013) and personal communication with physicians and documentalists from therapy optimization study groups). It was the establishment and constant improvement of therapy optimization studies (TOS) which enabled fine-tuning of the therapies in order to achieve the same or a better treatment effect while decreasing side and late effects (Chapter 2.5.1).

2.2.3 Type of first cancer and genetics

SPNs occur more often after some types of FPNs. For instance, in the registry population of the GCCR, 53.1% of SPNs between 1981 and 2013 occurred after hematological malignancies even though hematological malignancies made up only

43% of all FPNs in the German Childhood Cancer Registry between 2008 and 2017 (Table 1). This may be due to the fact that there is an association between the type of FPN and the type of SPN. For instance, AML is commonly seen after lymphoid leukemia (ALL) (Scholz-Kreisel et al., 2018a). One possible reason for the association is that the survival time may differ between patients with different FPNs. For instance, Hodgkin lymphoma patients have a very good prognosis (Kaatsch et al., 2019), and thyroid cancer, skin cancer, and breast cancer were the most common SPNs after this cancer in Germany (Scholz-Kreisel et al., 2018a). In the CCSS-US/Canada, SPNs of any type were associated with Hodgkin's disease or soft-tissue sarcoma during childhood ($p<0.001$ and $p = 0.01$ respectively) (Neglia et al., 2001). In Great Britain, the largest risk for digestive SPNs were seen after Wilms tumor (SIR: 13.0 (95% CI: 8.1-20.8)) and heritable retinoblastoma (SIR: 12.5 (95% CI: 6.9-22.6)); the SIR for a breast tumor was highest after Hodgkin lymphoma (SIR: 8.9 (95% CI: 5.9-13.2)) (Reulen et al., 2011).Though these sequences may be related to the therapy and prognosis of the FPN, genetics may also play a role.

Table 1. Frequencies of first primary neoplasms (FPNs) and frequency of any second primary neoplasms (SPNs) after these FPNs in patients registered at the German Childhood Cancer Registry (Kaatsch et al., 2019).

FPN according to ICCC-3[1]	FPN distribution in 2008-2017 (%, N = 17,743)	Any SPN after the FPN from column 1 in 1981-2013 (n = 1255)	
		N	%
Hematological malignancies	**43.0**	**667**	**53.1**
I Leukemias	32.2	447	35.6
II Lymphomas	10.8	220	17.5
Solid tumors	**56.8**	**588**	**46.9**
III Brain tumors	25.3	235	18.7
IV Neuroblastoma and other peripheral nervous cell tumors	6.6	63	5.0
V Retinoblastoma	2.3	35	2.8
VI Renal tumors	5.4	49	3.9
VII Hepatic tumors	1.5	4	0.3
VIII Malignant bone tumors	4.2	66	5.3
IX Soft tissue and other extraosseous sarcomas	5.6	92	7.3
X Germ cell tumors, trophoblastic tumors and neoplasms of gonads	3.3	31	2.5
XI Other malignant epithelial neoplasms and malignant melanomas	2.5	11	0.9
XII Other and unspecified malignant neoplasms	0.1	2	0.2

[1] ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

Genetic predispositions to FPNs and SPNs exist (Choi et al., 2014), i.e. persons with mutations on certain genes or with certain gene variants are more likely to develop cancer. For example, mutations in the gene TP53 are associated with many types of cancers, among them breast cancer, colon cancer, and hematological malignancies (Choi et al., 2014). Moreover, a number of genes are strongly associated with cancer predisposition syndromes (Ripperger et al., 2017). Germline mutations of TP53 are also associated with the cancer predisposing Li-Fraumeni syndrome (Choi et al., 2014), which is characterized by various early onset tumors. To date, many (childhood) cancer types have been identified to be strongly associated with cancer predisposition syndromes (Ripperger et al., 2017). Comprehensive overviews of the genomic alterations and syndromes associated with various childhood cancer types are given in Ripperger et al. (2017) and Board (2002).

The St. Jude Lifetime Cohort (SJLIFE) study on CCS in the United States found that 11.8% (95% CI: 10.6-13.1%) of the patients carried a pathogenic or likely pathogenic germline variant of one of 156 cancer predisposition genes. This result was based on genome sequence data of 2450 survivors (Wilson et al., 2019). In a SJLIFE study specifically on breast cancer SPN, (likely) pathogenic mutations linked to breast cancer were seen in 10.6% of patients with subsequent breast cancer compared to 1.6% without (Ehrhardt et al., 2019). Genetic and family history analyses of a cohort of 525 patients (not restricted to a certain age group) showed that patients with more than one primary cancer were significantly more likely to have a TP53 mutation ($p<0.005$) (Gonzalez et al., 2009).

2.2.4 Radiotherapy

Radiotherapy is a risk factor for SPNs, especially for solid tumors like breast cancer, thyroid cancer, and skin cancer. Radiotherapy may induce mutations and breakage of DNA strands (Blettner and Scholz-Kreisel, 2018). For radiotherapy-induced SPNs, the latency is at least one decade for many cancer types, but may be as low as about five years for some entities (Berrington De Gonzalez et al., 2013, Blettner and Scholz-Kreisel, 2018).

The risk usually increases with increasing radiation dose (Finke et al., 2015, Hennewig et al., 2014) but may decrease again in higher dose-ranges, presumably due to a cell killing effect (Inskip et al., 2016, Turcotte et al., 2018, Blettner and Scholz-Kreisel, 2018, Haddy et al., 2012). Three studies on secondary breast cancer after childhood

cancer reported increasing cancer risks with increasing radiation doses (Berrington De Gonzalez et al., 2013, Travis et al., 2003, Guibout et al., 2005, Inskip et al., 2009). For instance, in a cohort study with 120 breast SPNs among 5-year CCS, the risk increased tenfold in patients having received between 30 and 60 Gray (Gy) cumulative dose compared to patients not irradiated (odds ratio (OR): 10.8 (95% CI 3.8-31)) (Inskip et al., 2009). A pooled analysis of studies on CCS from several countries (CCSS-US/Canada, Childhood Cancer Survivor Study (CCSS) France and United Kingdom, Late Effects Study Group from the US, Canada and Western Europe, and Nordic Countries CCSS) showed that the relative risk (RR) for secondary thyroid cancer increased with dose, leveled off at ten to 30 Gy, and then declined (Veiga et al., 2012b). The RR for all types of SPNs analyzed by the CCSS-US/Canada (breast cancer, glioma, salivary gland cancer, meningioma, basal cell carcinoma, sarcoma) linearly increased with radiation dose to the tumor site except for thyroid cancer, for which risk decreased with higher doses beyond 15 to 20 Gy (Inskip et al., 2016).

2.3 Chemotherapy as a risk factor

Chemotherapy was found to be associated with SPNs after childhood cancer. However, the body of evidence needs to be expanded due to several reasons:

1. Most studies investigating the SPN risk, especially for solid SPNs, focus on the effect of radiotherapy with chemotherapy mostly included as a potential confounder, e.g. in (Tucker et al., 1991, Inskip et al., 2016).
2. Chemotherapy is often investigated as a binary variable or, if doses are modeled, as a categorical variable, e.g. in (Boukheris et al., 2013, Ehrhardt et al., 2019). Residual confounding is expected (Chapter 2.6.3), and, depending on the choice of the categories, the dose-response relationship may not become clear.

The most common chemotherapeutic groups linked to SPNs are alkylating agents, anthracyclines, and epipodophyllotoxins. They are mostly associated with hematologic malignancies such as MDS and AML (Jenkins, 2013, Choi et al., 2014). For instance, the risk for leukemia in CCS of solid tumors increased in a dose-dependent fashion in a French case-control study. The risk was sevenfold in patients having received 1.2 to 6 g/m^2 epipodophyllotoxins or >170 mg/m² anthracyclines compared to those having received lower doses or none of the substances (95% CI: 2.6-19) (Le Deley et al., 2003).

An increasing body of evidence suggests associations between chemotherapy and solid tumors (van Leeuwen and Ronckers, 2016, Teepen et al., 2017). In some studies, a dose-response relationship was seen: Higher doses of alkylating agents were risk factors for solid cancers and specifically for breast cancer and sarcomas (Teepen et al., 2017), lung cancer, stomach and pancreatic cancer (van Leeuwen and Ng, 2016). The alkylating agent ifosfamide increased breast cancer and sarcoma risk (Teepen et al., 2017). Patients treated with high doses of alkylating agents showed significantly elevated relative SIRs for breast cancer in the CCSS-US/Canada (Henderson et al., 2016). On the other hand, cyclophosphamide was not associated with breast cancer in a Dutch study, but with bone sarcoma for medium and high doses (Teepen et al., 2017). There is even evidence for a reduction in breast cancer risk with high cumulative doses of alkylating agents (Ehrhardt et al., 2019, Turcotte et al., 2018).

Radiotherapy can modify the risk association between chemotherapy and SPNs and is usually a stronger predictor for solid SPNs than chemotherapy (Scottish Intercollegiate Guidelines Network (SIGN), 2013). Although there was an association between chemotherapy and thyroid cancer in the CCSS-US/Canada, the association was not seen any more in patients treated with 20 Gy or more radiation (Veiga et al., 2012a). On the other hand, the association between anthracyclines and breast SPNs remained even after survivors receiving 10 Gy or more chest radiation were excluded (Ehrhardt et al., 2019).

2.4 Results of previous GCCR studies

In the past, the GCCR has carried out two case-control studies for identifying treatment-related risk factors for SPNs. The first study included 238 cases with an SPN and 450 controls matched on year of FPN diagnosis, sex, year of birth, and type of FPN. All patients were registered between 1980 and 1998 (Klein et al., 2003). The substances and radiotherapy doses were classified into three dose categories plus dose zero as the reference. The risk for any SPN was increased for high doses of the platinum derivate cisplatin, the antimetabolites mercaptopurine and methotrexate, the alkylating agent dacarbazine, the middle dose category of the alkylating agent procarbazine, and in explorative analysis for high doses of cyclophosphamide (Table 2). None of the dose categories of radiotherapy were significantly associated with SPN risk (Klein et al., 2003). This lack of association may be due to the relatively short follow-up period and the low age, especially for more recently registered patients.

Median latency period was 5.2 years; the maximum was 16.2 years. Genetic disorders, as far as known, significantly increased the SPN risk.

Table 2. Chemotherapeutic substance ranges with a significantly increased risk for a subsequent primary neoplasm after childhood cancer in a case-control study by the German Childhood Cancer Registry with 238 cases and 450 matched controls (registered 1980-1998) (Klein et al., 2003).

Substance	Dose	Odds ratio	95% confidence interval
Cisplatin	>435 mg/m²	2.8	1.1-6.7
Mercaptopurine	>12,000	8.7	1.9-40.0
Methotrexate	>19,646	2.4	1.1-4.9
Dacarbazine	>2,688	6.7	1.0-44.3
Procarbazine	>1,148- <= 2,800	8.3	1.7-39.9
Cyclophosphamide	>12,000	8.7	1.9-40.0

The second case-control study included 328 cases with an SPN (consisting of almost all cases from the first study and additional ones) and 639 matched controls (with little overlap with controls from the first study) registered at the GCCR until 2002 (Kaatsch et al., 2009b). The latency period was only slightly higher than in the first case-control study (median 5.5 year; maximum of 18.4 years). Radio- and chemotherapy overall increased the risk for SPNs (SPN after any chemotherapy: OR: 2.5 (95% CI: 1.4-4.5), OR adjusted for radiotherapy: 1.8 (95% CI: 0.98-3.1)). The risk for a SPN was greatest for treatment with alkylating agents (after adjustment for radiotherapy and other substance groups: OR: 1.96 (95% CI: 1.15–3.33)); the risk increased in a dose-dependent fashion. The SPN risk following treatment with platinum derivates was also increased (OR: 1.77 (95% CI: 1.1–2.9)); however, there was no association with any of the other groups (epipodophyllotoxins, anthracyclines, antimetabolites, vinca alkaloids, asparaginase) (Kaatsch et al., 2009b). For a separate analysis of the effect of stem cell therapy, the SPN risk was not significantly increased after adjustment for radio- and chemotherapy (Kaatsch et al., 2009b).

Concerning subgroup analyses, the risk for developing a subsequent solid tumor (n = 167 cases) was significantly elevated following the treatment with alkylating agents and platinum derivates, though only in univariable analyses (OR: 1.77 (95% CI: 1.1-2.9) and OR: 2.0 (95% CI: 1.1-3.6) respectively) (Kaatsch et al., 2009b). The effect became insignificant after adjustment for radiotherapy and other substance groups. Treatment with anthracyclines was protective after adjustment (OR: 0.4 (95% CI: 0.2-

0.8)). Only one substance group, alkylating agents, showed significant associations with the development of a subsequent carcinoma (n = 41 cases), but this association was significant in univariable analysis only (OR: 6.00 (95% CI: 1.7-21.1)). The risk for any SPN after leukemia was pronounced after treatment with antimetabolites (OR after adjustment for radiotherapy: 17.2 (95% CI: 1.7–177)) (Kaatsch et al., 2009b).

The risk for any SPN after radiotherapy was significantly increased and yielded an OR of 2.1 (95% CI: 1.5-2.9) after adjustment for substance groups; the risk for solid tumors was even higher (OR: 4.5 (95% CI: 2.5-8.0)) and greatest for patients with carcinomas as SPN (OR: 69.0 (95% CI: 3.7-1275.0)). However, the confidence interval was very wide for carcinoma patients due to the small sample size of 45 SPN cases (Kaatsch et al., 2009b). A subgroup analysis on 190 cases with solid SPNs or lymphoma and their controls showed that radiotherapy increased the SPN risk within the region of radiation but not at other body regions including those adjacent to the SPN (Hennewig et al., 2014).Another subgroup analysis showed that irradiation of the neck or spine region increased the risk for a second thyroid cancer but radiation exposure to other regions of the body did not increase the risk. A decreasing thyroid cancer risk for very high doses was not found (Finke et al., 2015).

2.5 Childhood cancer treatment

2.5.1 Therapy optimization studies in Germany

More than 90% of childhood cancer patients are currently treated in clinical trials (TOS – therapy optimization studies) or registries according to GPOH treatment protocols (Gadner et al., 2006, Rossig et al., 2013). The GPOH is the Society of Pediatric Oncology and Hematology in Germany (Gesellschaft für Pädiatrische Onkologie und Hämatologie). TOS are similar to phase III studies in clinical trials for the development of new substances (for an example, see Appendix I.2): patients are (randomly) assigned to different therapy arms/groups; one group receives a treatment oriented towards the standard of care/gold standard, and the other group(s) receive an alternative treatment/alternative treatments; the outcome in the group(s) with the alternative treatment is compared to the outcome in the standard groups to see if the patients benefited from the alternative treatment. TOS are based on detailed treatment protocols (Gadner et al., 2006). Time intervals between therapy optimization studies are bridged by registries, in which the children receive the best standard of care (Rossig et al., 2013).

Different from phase III studies, TOS are investigator-initiated trials without profit. The aim of a TOS is to test therapy concepts and further the development of diagnostic procedures and multimodal therapeutic approaches. Today, there are treatment protocols for almost all types of tumors and hematologic malignancies in children and adolescents. The current protocol for the treatment of a cancer contains modifications to the gold standard aiming at optimizing the therapy. The goals are to improve the patients' prognosis and/or decrease toxicities while holding the prognosis constant. The treatment of childhood cancer is thus constantly being improved (Gadner et al., 2006).

The degree of protocol-conformity of treatment varies: there were usually more deviations from the protocol in earlier calendar years, and even more importantly, conformity depends on the FPN entity/the protocol with fewer deviations in the treatment of hematological malignancies (personal communication with physicians and documentalists from TOS groups), which are common FPNs.

2.5.2 Chemotherapy

Over the last decades, there seemed to be a tendency to reduce the amount of radiation and increase the use of chemotherapy for the treatment of childhood cancer (Turcotte et al., 2018, Teepen et al., 2017). Chemotherapy usually involves treatment with a combination regimen of several substances. The combination of several substances can improve rate and duration of remission in children with cancer, suppress the selection of resistant cells and improve the toxicity profile. On the other hand, there may be interactions and the timing of application may be crucial (synergistic or antagonistic effect depending on timing) (Gadner et al., 2006). In addition to chemotherapeutic substances, medications to suppress the immune system, like prednisone, and supportive therapy substances to prevent or reduce therapy side effects, like antiemetics or otoprotective drugs, are given.

Conventional chemotherapy aims at killing malignant body cells. Due to the low specificity of chemotherapeutic substances, i.e. the substances do not well discriminate between malignant and normal body cells, toxicities occur, which may be life-threatening (Gadner et al., 2006). The mode of action of the chemotherapeutic substance groups investigated in the STATT study and this thesis are summarized in this chapter (Figure 1) (Gadner et al., 2006). In many cases, the effect is based on the fact that malignant body cells proliferate, i.e. increase in number during cell division, at

a higher rate than normal body cells. If DNA replication and cell division are interfered with or interrupted, this hits the fast proliferating malignant body cells harder than the cells dividing at a normal rate, i.e. the malignant cells are killed faster.

2.5.2.1 Alkylating agents

Alkylating agents attach a chemical group, an alkyl group, to the DNA. This so-called alkylation leads to breaks in the DNA strands, and affects the ability of the DNA and thus the cell to replicate. Normal cells which divide frequently are also affected. Alkylating agents are cytotoxic and cancerogenic.

2.5.2.2 Antimetabolites

Cell division requires metabolites (e.g. essential co-factors and intermediate products of nucleic acid synthesis). Malignant cells need many metabolites because of their high cell growth rate. Antimetabolites are molecules, which are similar in structure to the metabolites, but biologically ineffective. They compete with the metabolites and thus inhibit cell division and growth.

2.5.2.3 Anthracyclines

Anthracyclines act by intercalating the DNA double helix, i.e. they are inserted into the double helix. Thus, DNA replication and the activities of DNA and RNA polymerases (which synthesize DNA and RNA) are inhibited. The substance also inhibits topoisomerase II, which is an important enzyme in cell division.

2.5.2.4 Antibiotics

Actinomycin binds to the DNA and inhibits RNA- and DNA synthesis. Bleomycin binds metal ions to the DNA and thus leads to breaks in the DNA strands.

2.5.2.5 Enzymes: asparaginase

Unlike normal cells, acute lymphoblastic leukemia cells and some other leukemic cells cannot synthesize the amino acid asparagine, which is essential for cell division. Leukemic cells rely on asparagine circulating in the body. Asparaginase catalyzes the conversion of asparagine to aspartic acid, thus depleting the circulating asparagine pool and inhibiting the cell division in the leukemic cells.

2.5.2.6 Epipodophyllotoxins

Epipodophyllotoxins act by binding to the enzyme topoisomerase II. In vivo, DNA has different forms, e.g. compact or more or less curled. This change in form is necessary

for DNA replication. Epipodophyllotoxins prevent these changes and thus DNA replication.

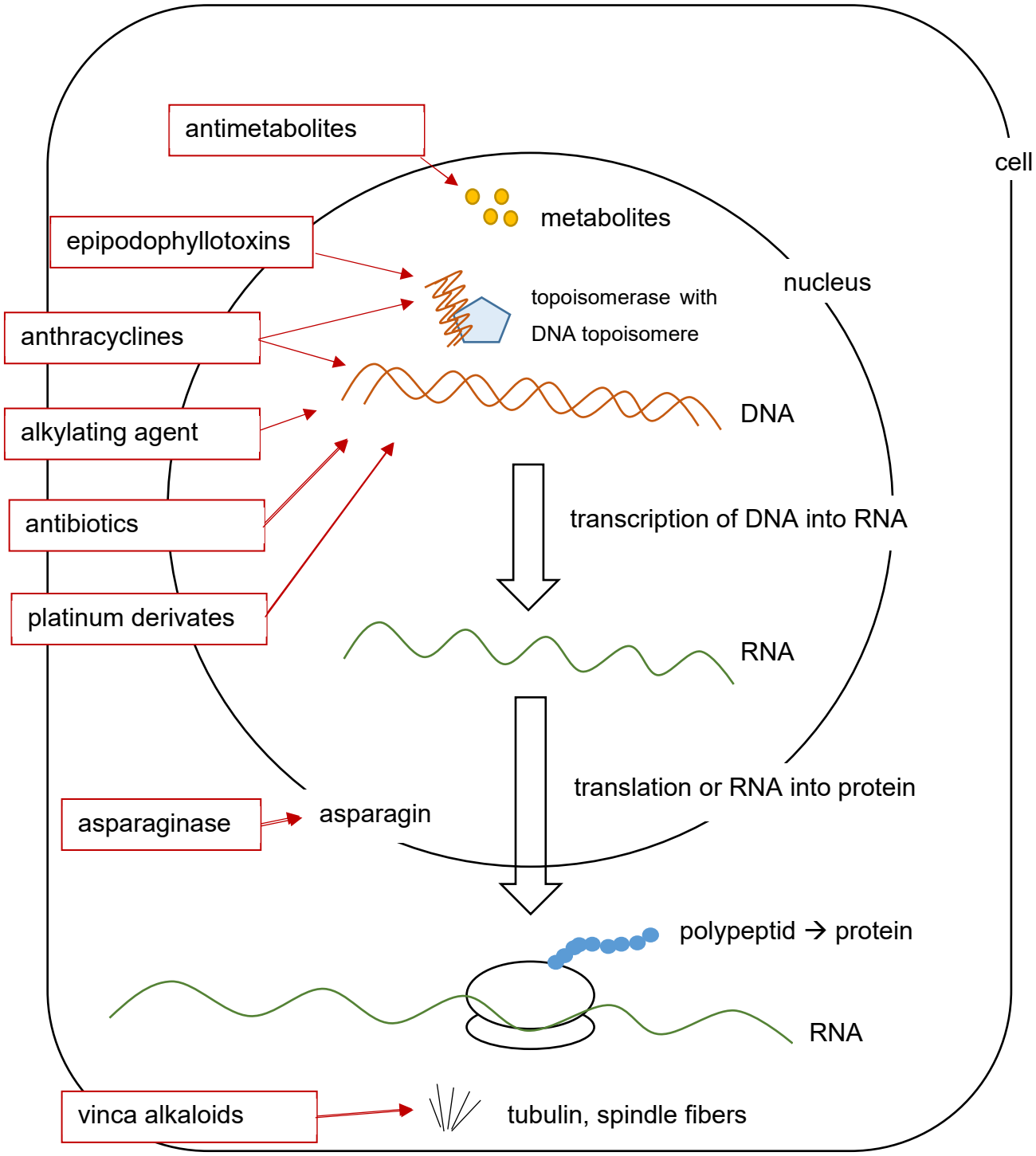


Figure 1 Chemotherapeutic groups and sites of action in body cells. Modified from Gadner et al. (2006).

2.5.2.7 *Platinum compounds*

Platinum compounds bind to DNA and thus change its structure. The cell identifies this change as irreparable and starts apoptosis, the programmed cell death.

2.5.2.8 *Vinca alkaloids*

Vinca alkaloids bind to tubulin, a protein required for cell division, which disturbs several cellular functions (e.g. alignment of the spindle structure during cell division) and inhibits normal cell division.

2.5.3 Stem cell transplantation

Another therapy, which especially leukemia patients may undergo, is a stem cell transplantation (SCT). A SCT may be indicated for two reasons: sick or inactive stem cells need to be replaced by healthy ones, or stem cells destroyed by chemo- and/or radiotherapy need to be replaced (Tallen and Kühl, 2003a).

To prepare the transplantation, patients go through a conditioning phase in which they receive high doses of chemotherapeutic substances and sometimes radiotherapy (Tallen and Yiallouros, 2003). Among other substances, cyclophosphamide, melphalan, busulfan, thiotepa (alkylating agents), etoposide (epipodophyllotoxin), and fludarabine (antimetabolite) are commonly used (Tallen and Yiallouros, 2010). The risk for a second malignancy is increased (Czyz et al., 2004, Oddou et al., 1998); the increase is higher for combined chemo- and radiotherapy than for chemotherapy alone (Baker et al., 2003, Borgmann et al., 2008). In a portion of SCTs, a chronic graft-versus-host disease arises; this disease favors the development of SPNs, especially those of the skin, due to the persistent impairment of the immune system (Tallen and Kühl, 2003b). All in all, transplant patients are a group with a special SPN risk.

2.6 Epidemiological study designs

Case-control studies and cohort studies are two common longitudinal epidemiological study designs. The studies reported in the scoping review were cohort studies and case-control studies. The aim of both study types is to infer whether an exposure is associated with an outcome (dos Santos Silva, 1999, Kreienbrock et al., 2012). Matching and risk set sampling are features of the case-control study of this thesis.

2.6.1 Cohort study

In a cohort study, a study population is followed over time. The participants must not have the outcome of interest at the beginning of the observation period. Persons

exposed to a factor (usually a risk factor, e.g., chemotherapy) are compared to persons not exposed to that factor. In both groups, the occurrence of one or more outcomes is observed over time, e.g., a SPN. The population is often followed prospectively, but a cohort study may also be retrospective. Several effect estimates may be calculated from the results of a cohort study (Appendix I.3, Table 18) (Ressing et al., 2010). The measures relevant for this thesis are the cumulative incidence (CI), the standardized incidence ratio (SIR), the incidence rate ratio (IRR), called relative risk (RR) in the studies evaluated in the scoping review, and the hazard ratio (HR). Results expressed as RR, HR, and - given the rare disease assumption – the odds ratio (Chapter 2.6.2) are comparable as they are all ratios comparing two groups in a study population. On the other hand, the SIR compares the observed number of cases in a cohort to the expected number of cases given the incidence rate of an external reference population (usually the general population), usually standardized by period, age- and sex-distribution. Thus, the SIR cannot be directly compared to the RR (Chaturvedi et al., 2008). For instance, the SIR may change in a different way by patient age than the RR because the background risk usually changes as well.

2.6.2 Case-control study and matching

A case-control study is a longitudinal observation study and usually retrospective. It involves comparing a group with an outcome, the cases, to a group without the outcome, the controls, concerning one or more previous exposures (dos Santos Silva, 1999, Kreienbrock et al., 2012). Cases and controls arise from the same source population/study base. The study may also be "nested" in a cohort study, meaning that a cohort is followed up until a number of cases develop, and controls from the cohort are matched to these cases. The STATT-SCAR study (Chapter 3.2) is carried out in this way; it is nested in the population of the GCCR. This study design is called **nested case-control study** and has the advantage over a cohort study that the exposure variable need not be collected for the entire cohort.

The three types of sampling in a case-control study are risk set sampling, case-cohort sampling, and cumulative incidence sampling (Appendix I.3, Table 19). In the STATT-SCAR study, **risk set sampling** is used, which means that the control is drawn at the time when the case becomes a case.

In the STATT-SCAR study and the studies included in the scoping review, individual **matching** was used. This means that the controls were matched to the cases based

on similarities in certain characteristics which are expected to be disease risk factors (see Chapter 2.2), called matching factors. A case and its matched control(s) are called a match group and are analyzed together, usually with a conditional logistic regression (Chapter 3.2.3.3). Sex and age are common matching factors. Since cases and controls are similar or the same in these matching factors, a difference in outcome between cases and controls cannot be attributed to differences in the matching factors (because there are no differences) (dos Santos Silva, 1999). Thus, the influence of possible confounding by these variables can be reduced or eliminated. Residual confounding may still be possible (see Chapter 2.6.3).

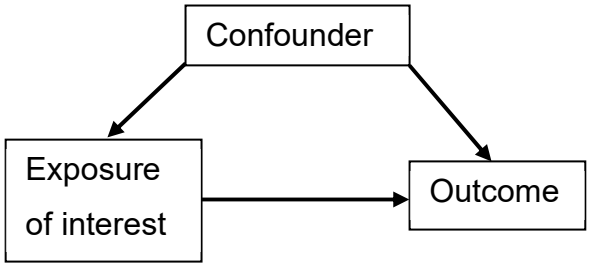
Matching must not eliminate or reduce differences in exposure between cases and controls; if it does, the effect of the exposure on the outcome cannot be properly investigated, this is called **overmatching** (Kreienbrock et al., 2012). The STATT-SCAR study did not match on type of FPN to avoid overmatching because the therapy of case and control with the same FPN may be too similar. Overmatching could occur if the type of FPN was related to the therapy (which is likely) and would not be related to SPN occurrence under the null hypothesis of "no etiologic connection between the exposure and the disease" (Miettinen, 1970). It may result in loss of estimation precision (Miettinen, 1970) and a reduction or elimination of the effect of the exposure (Kreienbrock et al., 2012).

The effect measure in case-control studies is the odds ratio (OR), which is the exposure odds of cases divided by the exposure odds of controls:

$$OR = \frac{(\text{number of exposed cases}/\ \text{number of unexposed cases})}{(\text{number of exposed controls}/\ \text{number of nonexposed})}$$

Under the rare disease assumption (Schmidt and Kohlmann, 2008), the OR can be interpreted as a risk ratio, which is a measure of cohort studies (Appendix I.3).

2.6.3 Confounding



The relationship between exposure and outcome may be mixed up by another factor and lead to bias (dos Santos Silva, 1999). The true strength of the association between exposure may be over- or underestimated, the direction of association may be inverted, or there

may be no effect. Such a factor is called confounder and has three characteristics (Rothman and Greenland, 2008, Miettinen, 2010, Rothman, 2012):

1. It must be a risk factor for the disease.
2. It must be associated with the exposure under study in the source population.
3. It must not be an effect of the exposure.

When a continuous variable is dichotomized or categorized or when an unsuitable data transformation is used, **residual confounding** may remain, i.e., confounding within the categories may not be controlled entirely (Rothman, 2012). This is a "special form of model misspecification under which the effect of the confounder is not completely removed and therefore the estimate for the effect" of the dependent variable "is not unbiased" (Becher, 1992). Dose-response-relationships cannot be correctly modeled.

2.6.4 Potential sources of bias

2.6.4.1 Information bias

Information bias may occur during data collection (Delgado-Rodriguez and Llorca, 2004) and certainly plays a role in the data used for the analysis of this thesis. One type of information bias is misclassification bias, which occurs when study subjects

- are wrongly classified as having the exposure or not (in binary variables),
- are wrongly classified into exposure categories (in ordinal variables),
- are wrongly classified as having the outcome or not (in binary variables).

The misclassification may be non-differential, meaning that the exposure is equally misclassified in cases and controls, or differential, meaning that the misclassification is different for cases and controls (Delgado-Rodriguez and Llorca, 2004).

Another type of information bias is caused by measurement errors (Rothman and Greenland, 2008); in the presented studies, study subjects may specifically have exposure values with measurement errors in continuous variables.

2.6.4.2 Selection bias

Selection biases are "distortions that result from procedures used to select subjects and from factors that influence study participation" (Rothman and Greenland, 2008). This bias may occur when the population included in the study does not represent the target population (Delgado-Rodriguez and Llorca, 2004), specifically, when the

“relation between exposure and disease is different for those who participate” and for the target population (Rothman and Greenland, 2008).

2.7 Follow-up guidelines

The German S1 guidelines for the follow-up of CCS list organs and areas possibly affected by the therapy of the various FPN groups and makes suggestions on examinations of each organ/area and therapy in case of late effects. According to the guidelines, there is a SPN risk after the treatment of virtually any FPN group (Schuster et al., 2013). The guidelines suggest regular follow-up examinations for these patients but do not specify these examinations.

Each therapy study protocol has late effects monitoring recommendations starting right after end of therapy. For instance, after therapy of Hodgkin lymphoma, a mammography or mamma-MRT for patients older than 25 years or eight years after end of radiotherapy are recommended according to the study protocol Euronet-PHL-C2 (AG Langzeitnachsorge der GPOH, 2017).

Surveillance recommendations vary internationally between guidelines. The International Late Effects of Childhood Cancer Guideline Harmonization Group was initiated in 2010 and works on evidence-based international harmonization of guidelines for the long-term follow-up of childhood and young adult cancer survivors (Mulder et al., 2013, Kremer et al., 2013). The group has provided, e.g., breast cancer surveillance recommendations for cancer survivors treated with radiation to the chest prior to 30 years of age. These guidelines are based on guidelines from the United States, the Netherlands, the United Kingdom, and Scotland.

For instance, a screening for secondary breast cancer is recommended after chest irradiation, but not after chemotherapy according to the international guidelines (Mulder et al., 2013). The International Guideline Harmonization Group did not find evidence of a protective effect of alkylating agents in cancer survivors diagnosed until the age of 20, but only in survivors between 21 and 49 years of age. Therefore, they concluded that alkylating agents “do not substantially modify the breast cancer risk” (Mulder et al., 2013). Derman (2018) gives clinical practice recommendations based on an updated review of breast cancer risk among women treated for childhood cancer. He pointed out studies which show a protective effect of alkylating agents for radiation-induced breast cancer, those which show no protective effect, and those which increase breast

cancer risk in survivors without chest radiation. These discrepancies may partly be explained by differences in the composition of the cohorts regarding FPN and age (Derman, 2018).

The UK long-term follow-up practice statement lists alkylating agents together with radiotherapy as being associated with breast cancer (Skinner et al., 2005). The US Children's Oncology Group (Children`s Oncology Group, 2018) lists cyclophosphamide as a risk factor for bladder malignancies. However, neither the UK or the US guidelines, nor the Dutch (Dutch Childhood Oncology Group, 2010) or Scottish follow-up guidelines (Scottish Intercollegiate Guidelines Network (SIGN), 2013)) recommend screening for CSPNs based on previous chemotherapy treatment (alone). The UK guidelines, however, recommend a thyroid screening for survivors having had conditioning for bone marrow transplantation based on the alkylating agent busulphan (Skinner et al., 2005).

The results of the STATT-SCAR study and this thesis are expected to contribute to the body of evidence on which decisions on long-term follow-up recommendations for CCS are based. Screening guidelines for CSPNs are important, among other things because "thyroid and breast tumors are almost symptomless in the very early stages, regular monitoring using imaging techniques is required." (Scholz-Kreisel et al. 2018)

3 Material and Methods

3.1 Scoping review

The literature review was performed in the manner of a scoping review, a method which aims at giving an overview of the available evidence in a field or on a question, including its extent, and at examining the methodology, characteristics or key concepts in studies. It may serve as a "precursor to a systematic review" (Munn et al., 2018) and identify knowledge gaps. A scoping review usually answers a broader question than a systematic review (Munn et al., 2018, Tricco et al., 2018). With the sparse evidence on dose-response relationships between chemotherapy exposure and CSPN risk in CCS, this thesis aimed at systematically extracting available evidence from original research. The evidence was synthesized, with special attention to the results of the studies which may be compared to the results of the case-control analysis of this thesis.

The method of the review was laid out beforehand in a review protocol (Appendix II), which follows the PRISMA extension of Scoping Reviews (Tricco et al., 2018). In short, the literature databases Embase, PubMed, and Scopus were systematically searched for the four concepts "childhood cancer", "second neoplasm", "chemotherapy", "dose-response relationship". Inclusion and exclusion criteria were determined, such as definition of study population, exposure, and outcome. Inclusion of articles stopped on July 15, 2019. The search results were deduplicated, titles/abstracts were screened and irrelevant papers were excluded. Next, the remaining full texts were evaluated and relevant articles were identified. In the data charting process, variables from each article such as study design, size of study population, chemotherapeutic exposure variables, covariates, analysis and results were reported in tables and compared in writing. Particularly, the results were summarized according to type of CSPN and chemotherapeutic group. Strengths and limitations of the studies were listed, which helped to interpret the study results.

There were a few deviations from the review protocol. First, articles from two sources in addition to the database searches were added: A forward and backward search of relevant recent review articles was carried out. Backward searches included scanning the reference list, forward searches meant scanning the list of articles which cite the review in question on PubMed Central (automatically listed under https://www.ncbi.nlm.nih.gov/pubmed). Moreover, references promising to be relevant from full texts, which were assessed later on, were added.

Second, an exclusion criterion in addition to the one laid out in the review protocol was deemed necessary, namely for articles which did not perform separate analyses on patients with CSPNs even though ten or more of these patients were included (exclusion item “analysis”: no separate analysis for ICCC-3 XI diagnoses even though they are included).

Thirdly, it was not feasible to restrict the SPN diagnosis strictly to the ICCC-3 group XI for selection of articles since it was common practice in studies to perform analyses based on the topology of the neoplasm, partly following the coding system for adult neoplasms, the ICD-O-3 (International Classification of Diseases for Oncology, 3rd edition, (World Health Organization, 2013)). This system is based on both topography and morphology. Topography refers to the site of the tumor in the body, such as breast (ICD-O-3 codes C50.0-C50.9) or the digestive system (C15.0-C26.9); morphology refers to the shape and structure of the tumor. Although the ICCC-3 is defined by ICD-O-3 topography *and* morphology, most articles included in the literature review reported results based on the topology *only* (without mentioning the codes explicitly), although they refered to the ICD-O-3 system in their methods. However, since most cancers of these topographies in adults are generally carcinomas from ICCC-3 group XI, the articles were included even if a few non-carcinoma cancers were included in the analyses or the diagnoses were not described in enough detail to decide if they belonged to ICCC-3 group XI.

Last, the data items for the charting process were slightly adapted. The items “Statistical Models”, “Adjusting for”, and “Outcome” were each divided to distinguish between analyses on chemotherapy dose and analyses on chemotherapy as dichotomous variable. The item “% with any chemotherapy” was added to describe what proportion of patients analyzed had received chemotherapy at all.

3.2 Case-control study

3.2.1 Study design, inclusion criteria, matching

The data analyses for this thesis were based on a subset of data collected in the STATT study. The STATT study is a nested matched case-control study carried out by the GCCR and is called “Therapy-related risk factors for second neoplasms after cancer in childhood – a population based nested case-control study. STATT: Second Tumour After Tumour Therapy.” I was the project manager for three years until October 2019 and was responsible for writing the study protocol, study registration, and data acquisition. STATT is funded by the Deutsche Krebshilfe (grant number: Bearbeitungsnummer 70112099) and runs from November 2016 to October 2020. The STATT study cooperates closely with the SCAR (Second Cancer After Radiotherapy) study, which investigates radiotherapy effects. SCAR is funded by the Bundesministerium für Bildung und Forschung (grant number: 02NUK042A). STATT and SCAR have the same study population and collect therapy data together; together they form the STATT-SCAR study. The study is registered at the German clinical trial register (DRKS) under number DRKS00017847 (Broich, 2019). Details of STATT-SCAR are laid out in the study protocol and in a design paper which was submitted (Scholz-Kreisel et al., 2020). The ethics committee of the Landesärztekammer Rheinland-Pfalz did not have any objections against the STATT-SCAR study (Bearbeitungsnummer 837.280.15 (10048)).

In brief, the basic population from which cases and controls arose, was the registry population of the GCCR. The GCCR was established in 1980 at the University Medical Center of the Johannes Gutenberg University, Mainz. At least 95% of all malignant diseases and CNS tumors in children under 15 in Germany are recorded (Kaatsch et al., 2016, Hennewig et al., 2014). As of 15 March 2016, a **base population** of 54,420 first neoplasms were registered for the time period from 1980 to 2014, which met the following inclusion and exclusion criteria.

Inclusion criteria STATT:

- primary residence of the patient at the time of diagnosis was Germany (only West Germany 1980-1990, all of Germany, including the former East, since 1991)
- diagnosis according to ICCC-3 (Steliarova-Foucher et al., 2005)

- patient's age at diagnosis was below 15 years

Cases were patients from the base population who met the following criteria:

- diagnosis with an FPN between 1 January 1980 and June 30, 2014
- SPN according to ICCC-3 by 31 December 2014
- latency period between diagnosis of FPN and SPN at least six months.

Potential **controls** were patients from the registry population of the GCCR who met the following criteria:

- diagnosis with an FPN between 1 January 1980 and 30 June 2014
- follow-up time at least six months

Exclusion criteria STATT:

- for cases: non-malignant neoplasm diagnosis between the FPN and SPN
- for controls: non-malignant neoplasm diagnosis within the latency period of their index cases (see below), before the FPN, or a diagnosis before 1980
- SPN was directly related to the FPN or an auxiliary diagnosis

The study sample for **this thesis** fulfilled the following **additional inclusion criteria**:

- cases diagnosed with a SPN according to ICCC-3 diagnostic group XI ("Other malignant epithelial neoplasms and malignant melanomas"), subsequently called CSPN, and their matched controls; the data of backup controls (see risk set sampling below) were used in the same way as that of the main controls
- intention-to-treat (ITT) therapy data from the GPOH therapy protocol database (Chapter 3.2.2) available or expected. ITT data was expected if a patient was in a therapy optimization study (TOS) whose cumulative chemotherapy doses were in the GPOH database by data closure (Chapter 3.2.2)

A case and its controls are called a **match group** with the case being the **index case** for the controls in the match group.

For the matching in STATT-SCAR, **risk set sampling with replacement** was used (Chapter 2.6.2). The controls were chosen from the set of patients in the base population "who are at risk of becoming a case at the precise time that each case was diagnosed." (Rothman, 2012) Matching on time of survival in this way allows to deal adequately with competing risks (in this case death and occurrence of SPN). Other

matching criteria were sex, age at diagnosis (max. +/- 5 years), date of birth (max. +/- 5 years), and date of diagnosis (max. +/- 5 years). The variables chosen as matching criteria may themselves influence the risk for SPNs, as outlined in Chapter 2.2. The matching eliminates this influence and allows to focus risk analysis on other variables. Matching on period of treatment accounted for secular trends in the society and in childhood cancer therapy. The type of FPN was not used as matching criterion in order to avoid overmatching (Chapter 2.6.2).

A match score was defined for all eligible controls for a case as:

Match score = (difference in age (days) + diff. in birthday (days) + diff. in diagnosis date (days)).

For each case, the two patients with the lowest score were selected as controls and the next two as backup controls. If therapy data for one or both of the controls was not obtained, an effort was made to acquire data for the backup controls. Data of both controls and backup controls was included in the analysis if available. There were 1244 cases and 4976 controls and backup controls in the dataset. As risk set sampling permits using the same person's data multiple times, there were 5596 individual patients in the dataset.

Included in the analyses for this thesis were 272 cases and 739 matched controls who had ITT data available (total n = 1011), which corresponded to 939 individual patients.

3.2.1.1 Outcome

The outcome is a binary variable with the two values:

- a case having a CSPN (subsequent neoplasm from the ICCC-3 group XI)
- a control not having any SPN within the time period after diagnosis in which an CSPN occurred in its index case.

The GCCR provided the data on SPNs. Logistics for systematically following-up survivors at the GCCR were established since 1996 in order to achieve registration of the subsequent neoplasms retrospectively and prospectively as completely as possible. This includes regular data requests to the reporting and treating hospitals, to the centralized clinical trials, and ultimately, personal inquiries to the patients or parents concerned. Patient-reported neoplasms undergo a validation with the help of the respective treating physician if the patient consents.

3.2.1.2 Exposure

For each case and control, the intention-to-treat chemotherapeutic treatment for the first neoplasm was aquired. The name of the chemotherapeutic and the cumulative dose administered with the units according to the treatment protocol were obtained. Details on the chemotherapeutics included can be found in the statistical analysis plan in Appendix III.

3.2.2 Therapy data acquisition

For the STATT-SCAR study, therapy data of the chemotherapy and radiotherapy was acquired from three data sources (Figure 2):

- from the GPOH therapy protocol database (Calaminus et al., 2013); the data was ITT data (Chapter 3.2.2.1). The majority of data came from this database.
- from hospitals; the data was as treated (AT) data
- from a previous SPN study (Kaatsch et al., 2009b, Kaatsch et al., 2009a); the data was a mixture of ITT and AT data

For this thesis, only ITT data from the GPOH therapy protocol database was used which had been acquired by the STATT-SCAR study by 1 October 2019.

3.2.2.1 ITT data from the GPOH therapy protocol database in cooperation with the TOS

More than 90% of childhood cancer patients in Germany are treated in clinical trials or registries according to GPOH treatment protocols (Rossig et al., 2013). The GPOH set up a therapy protocol database. This GPOH therapy protocol database contains ITT therapy information of 124 TOS protocols in use since 1980 (Figure 2): for every study arm of each protocol, the cumulative doses of medications and irradiation are on record. For this thesis, ITT data of 77 of these TOS protocols were relevant. For a list of these TOS with relevant study arms see Appendix I.4.

The GCCR routinely records the TOS(s) in which a patient is treated but not the study arm. For the STATT-SCAR study, the principal investigators of the TOSs were asked to provide the study arm for each patient relevant to STATT from their databases. This information was used to derive the ITT cumulative doses per patient from the GPOH therapy protocol database.

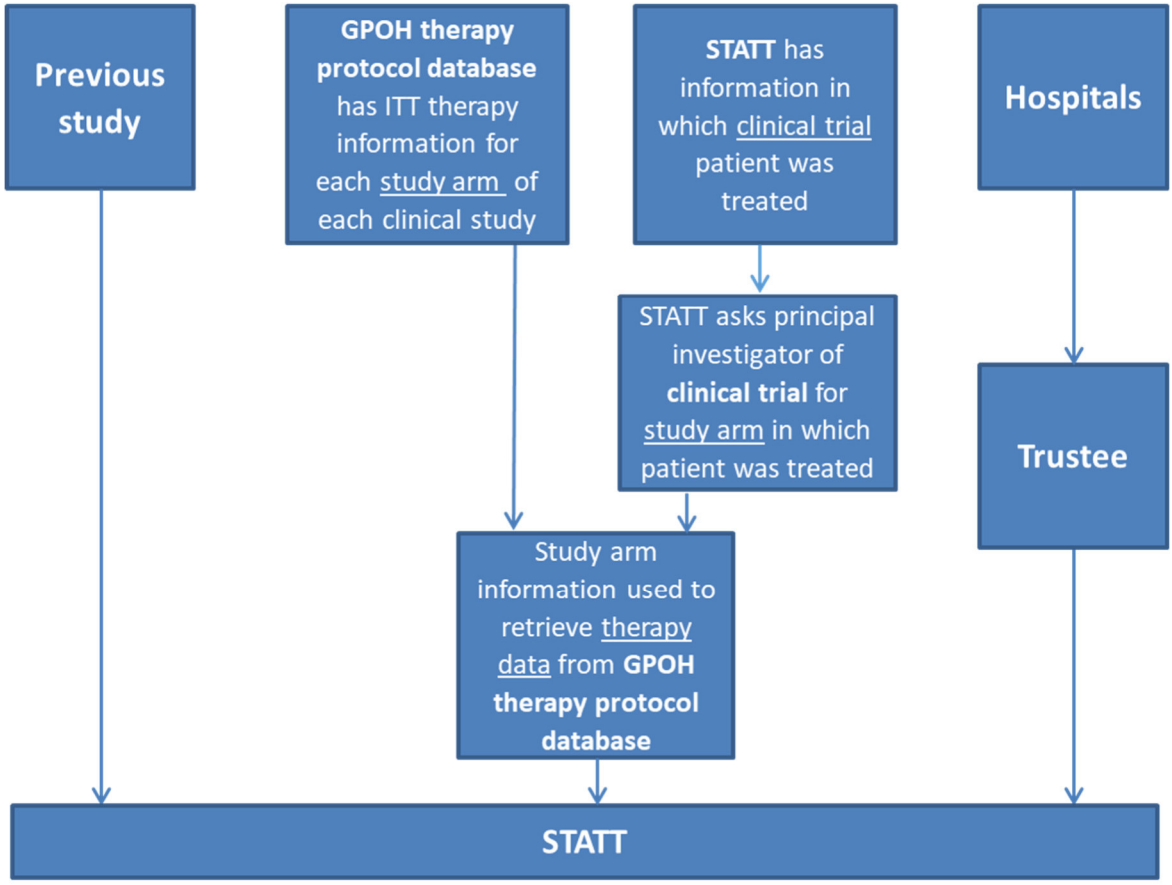


Figure 2. Sources for therapy data in the case-control study STATT on therapy-related subsequent primary neoplasms, carried out by the German Childhood Cancer Registry. Several patients have data from multiple sources.

Some patients are treated in more than one TOS. Therapy data from the second and sometimes third TOS was obtained in the same way as for the first TOS. Treatment information from relapse protocols (only available for relapses of acute lymphoblastic leukemia and brain tumors, TOS relevant to this thesis: ALL REZ 83, ALL REZ 85, ALL REZ 87, ALL REZ 90, ALL REZ 95, ALL REZ 96, ALL REZ 2002, AML REZ 93, AML REZ 2009, HIT-REZ 97) was not yet available by the closing date for data acquisition for this thesis (1 October 2019).

3.2.2.2 Data on stem cell transplantation

Through a linkage with the pediatric registry on stem cell transplantation (Pädiatrisches Register für Stammzelltransplantation), date and type of a stem cell transplantation could be obtained for the majority of patients. The registry records data of patients aged 0 to 18 years with a stem cell transplantation in Germany (Sykora, 2013). In addition, the study group for ALL relapses provided information on whether patients treated according to ALL REZ protocols had a stem cell transplantation. This concerned about 50 to 60 patients for this thesis.

3.2.3 Analyses

The SAP describes the data preparation, the variables, and the statistical analyses performed; it, can be found in Appendix III. In short, the data was prepared by grouping 36 chemotherapeutic substances and other medications (corticosteroids, cytokines, and others) into ten substance groups. This required applying equivalence ratios to make the doses of substances comparable within a group regarding assumed carcinogenic potency (Chapter 3.2.3.1). The results of the data checks according to the SAP are described in Chapter 3.2.3.2. Chapter 3.2.3.3 summarizes the statistical analyses.

3.2.3.1 Equivalence ratios of chemotherapeutic doses for group analysis

Chemotherapy was analyzed in the ten substance groups (compare Appendix I.17.1, Table 26) because there were too many single substances to analyze each single one (n = 36), and some substances were given to only a few patients. The effects of different substances are not the same at the same dose. This means one cannot simply add up the doses of different substances to have a cumulative dose per substance group, even though this approach can be seen in the literature (Allodji et al., 2019). Substance equivalence ratios for various substance groups exist. This allows for converting the dose of a substance within a substance group to the dose of a reference substance. For this thesis, I chose existing equivalence ratios (Appendix III, Chapter 2.2.1.2 in the SAP). Although this approach is used in studies (Guérin et al., 2007, Le Deley et al., 2003, Neglia et al., 2001, Veiga et al., 2012a) and for some substances in patient care to substitute one substance for another one (Children`s Oncology Group, 2018), there are several difficulties:

First, the best measure for the carcinogenic potency of a substance is not clear (Fryer, 2015). Existing equivalence ratios are based on hematological toxicity (Le Deley et al., 2003, Guérin et al., 2007, Green et al., 2014) or cardiotoxicity (Feijen et al., 2019, Feijen et al., 2015, Children`s Oncology Group, 2018, Mulrooney et al., 2009). Applying these equivalence ratios to the data analysis of this thesis is based on the assumption that the mentioned toxicities correlate with the potency of causing cancer, an assumption frequently made in studies on SPNs, e.g. by Le Deley et al. (2003).

Second, for some substances, more than one equivalence ratio exists (Feijen et al., 2015). I chose the ones reported by Green et al. (2014) who developed their cyclophosphamide equivalence dose (CED) on the basis of a literature search and the

evaluation of 17 randomized trials. I supplemented the equivalence ratios with studies by Le Deley et al. (2003), Guérin et al. (2007), and recommendations of the North American Children`s Oncology Group (2018).

Third, for some substances, no equivalence ratio is available. For these substances, I calculated data-driven conversion factors based on the mean value of available substance doses of controls from the entire STATT study population.

The substance group “other” was very heterogeneous and was included in the analysis as a binary variable.

3.2.3.2 Data check

Outliers in the continuous exposure and covariate variables were determined by visual inspection of dose histograms. As expected, multimodal distributions were seen for some substances, which is due to the fact that different therapy protocols use different dose ranges. Nevertheless, there seemed to be some extreme gaps between dose values, which I looked at more closely. I did not deem dose distributions unusual if the ranges were high but there were no obvious gaps or if there were few observations and evenly spread out gaps as seen in thioguanine (Appendix I.6).

The substance dose distributions which I deemed unusual are listed in Appendix I.7 along with the decisions I made on handling these issues. In addition, I visually inspected the dose-response-relationship of the final statistical models for potential influential points (compare Appendix I.8). I detected one influential point which substantially modified the dose-response-relationship. It was excluded for the main analysis and included in a sensitivity analysis.

3.2.3.3 Statistical analyses

The statistical analyses included descriptive analyses as well as explorative ones. The **explorative analyses** modeled the association between chemotherapy dose (independent variable) and the occurrence of a CSPN (i.e., being a case, dependent variable). One of the objectives of explorative data analyses is to describe “potential relationships (direction and magnitude) between exposure and outcome variables” (Komorowski et al., 2016). Although explorative analyses can generate hypotheses, it is different from confirmatory analyses, which are performed to test pre-defined hypotheses. In this thesis, the analyses were performed to find patterns and associations between exposure and outcome. Confidence intervals and p-values were

used to describe the results, but they cannot “prove” the post-hoc hypotheses (Kreienbrock et al., 2012). P-values should be interpreted with caution and in connection with the effect estimates. The p-values were not adjusted for multiple testing.

Exposure variables were the substance groups and substances listed in Table 3. All exposure variables were considered as both continuous dose variables and binary (yes/no) variables in the model building process except the group “other”, which was considered as binary variable only due to the heterogeneity of substances.

The method applied was **conditional logistic regression**. It is the state-of-the-art method to analyze matched case-control studies (Kreienbrock, Pigeot, and Ahrens 2012)(Allison, 2012, Krämer et al., 2018, SAS Documentation, Hosmer Jr et al., 2013). It models a function (called logit or log odds) of the odds that the outcome occurs given the exposure. The outcome is binary such as being a case (having a CSPN) or being a control (not having a CSPN). The coefficients in the logistic regression model are interpreted as log odds ratios per unit of exposure, i.e. the log of the ratio of two odds.

To model the dose-response relationship, the principle of **fractional polynomials with a spike at zero** was applied. In short, the fractional polynomials approach allows to choose the best functional form out of 44 possible models of the relationship between a continuous predictor variable (here: substance dose) and an outcome variable (here: case/control status). A closed test procedure ensures that the chosen significance level α (here: 0.1 due to the explorative character of the analyses) is preserved despite multiple testing. The option of including a “spike at zero” variable in the model allows to model unexposed versus exposed patients separately (Binder et al., 2013, Lorenz et al., 2017), which is important if we suspect that non-exposed patients differ from exposed ones in more than the dose and we do not necessarily assume that the dose response curve goes through the origin. It is possible that the final model is one with such a binary “spike at zero” variable only, which correspondes to the binary exposure model.

The final multivariable model was built in a forward selection process and with the addition of relevant covariates. Details can be found in the SAP (Appendix III). These models show a tendency to preferably fit simple dose-response relationships to data with low power (small number of cases and controls, low variation of exposure) and

vice versa. They are relatively sensitive to outliers (few or single observations of high exposure).

For all substances selected in univariable analysis, an additional univariable logistic regression with the substance as binary variable was carried out.

Table 3. Exposure variables entered into the variable selection process: therapy of a first primary neoplasm during childhood in a case-control study on subsequent primary neoplasms.1

Type	Substances
substance groups	alkylating agents anthracyclines (a type of antibiotics) antibiotics except anthracyclines antimetabolites platinum derivates vinca alkaloids enzymes corticosteroids (no chemotherapeutic substances) "others" (including chemotherapeutic and non-chemotherapeutic substances)
selected single chemotherapeutical substances (substances which 500 or more cases or controls received)	cyclophosphamide cytarabine doxorubicin methotrexate vincristine
substances complementary to the single substance of the respective substance group	alkylating agents excluding cyclophosphamide antimetabolites excluding cytarabine anthracyclines excluding doxorubicin antimetabolites excluding methotrexate antimetabolites excluding cytrabine and methotrexate vinca alkaloids excluding vincristine

[1]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

The analyses included modeling the **odds ratio** for being a case. They are interpreted as risk ratios, as CSPNs are rare events (Rodrigues and Kirkwood, 1990, Schmidt and Kohlmann, 2008). A value of one means that the odds for having a CSPN is equal to the odds for not having a CSPN; a value below one means the odds for having a CSPN is lower than the one for not having a CSPN; a value above one means the odds for a CSPN is higher than for not having a CSPN. Odds ratios (ORs) are reported with a 90% confidence interval (90% CI) in parentheses. For substances or substance

groups, which were modeled as continuous variables, the ORs are reported for specific doses against nonexposure (dose 0 mg/m²). To present clinically meaningful results, dose values which many patients had received were chosen (Appendix I.5). Higher dose values were given less often, but ORs for high dose values were reported nevertheless to present a wider range of doses.

Most of the risk factors mentioned in Chapters 2.2 and 2.3 were potential confounders because they were also associated with the exposure, i.e. the chemotherapy (Chapter 2.6.3): Differences in the effect of the chemotherapy between children of different ages and sexes even led to a stratification of the therapy in several TOS protocols, calendar time is associated with chemotherapy in so far as the therapy protocols (including application and supportive therapy) changed over time, and radiotherapy and chemotherapy doses may be mutually dependent in the treatment, chemotherapy may replace radiotherapy, and both may affect each other. Possible confounding was either eliminated through matching, or through including covariates in multivariable analysis, like radiotherapy. Though type of first cancer is associated with the therapy, it was not used for matching due to the risk of overmatching (see Chapter 2.6.2), and a subgroup analysis by FPN was not conducted due small sample sizes. Genetic predisposition may modify the effect of chemotherapy (Mutschler, 2012), but it could not be taken into account because this information is not systematically collected at the GCCR. For effect and frequency measures reported in this chapter, see Chapters 2.6.1 and 2.6.2.

A sensitivity analysis was performed in addition to the main analysis and the subgroup analyses (excluding patients with a relapse, excluding patients with a stem cell transplantation) lined out in the SAP (Appendix III). The sensitivity analysis included the data of one control with high antibiotic dose values (Appendices I.8 and I.18.2).

The data preparation was performed with the software SAS 9.4 and SAS Studio University Edition; the analyses were performed with SAS Studio University Edition 2.8 9.4 M6, Release: 3.8 (Basic Edition).

4 Results

4.1 Scoping review

4.1.1 Selection of sources of evidence

The search of the three electronic databases yielded 1202 articles for the title/abstract scan after duplicates were removed (Figure 3). Backward and forward search of eight recent review articles identified 67 articles (Appendix I.9). Seven references from full texts, which were assessed later on, were added. In addition, one article from 2019, which I found during general literature search, was included (Ehrhardt et al., 2019).

In total, I scanned titles and abstracts of 1277 articles. Articles were subsequently excluded because the age groups were irrelevant to the study question, survival in clinical trials was assessed but no SPNs, or chemotherapy were not assessed as exposure. Clinical trials usually focused on survival or were excluded due to other reasons, such as not including chemotherapeutic exposure as continuous variables or having fewer than ten CSPN cases.

A total of 102 articles remained for full text assessment. Most articles were excluded because the majority of patients included were older than 14 years at diagnosis (n = 25). Seventeen articles were excluded because SPN risk was not an outcome at all or there were fewer than ten CSPN cases; one of these articles was in Russian and was therefore evaluated by a Russian native speaker. In 13 articles, the risk for CSPN was not reported as a separate outcome (in relation to chemotherapy doses), among them the two articles of the case-control studies of the GCCR (Klein et al., 2003, Kaatsch et al., 2009b). Twenty-one studies did not evaluate chemotherapy at all or they did not evaluate chemotherapy doses. Six studies were excluded because chemotherapeutic substances were measured continuously, but they were not included into the analyses as continuous predictors or the results were not reported. Six articles were no original research articles. One of these was a summary of results of radiation-related SPNs (Inskip et al., 2016) and included an additional stratification of an analysis reported in a previous article (Veiga et al., 2012a). This previous article was included in full text evaluation; it stratified the analysis by radiotherapy exposure of 0, 0 to <20 Gy or ≥20 Gy; however, in the summary article, Inskip et al. (2016) stratified by radiotherapy exposure of 0, >0 to 5 Gy, 0-20, and ≥20 Gy. The results of the additional stratum >0 to 5 Gy are reported in Appendix I.13 together with the study by Veiga et al. (2012a).

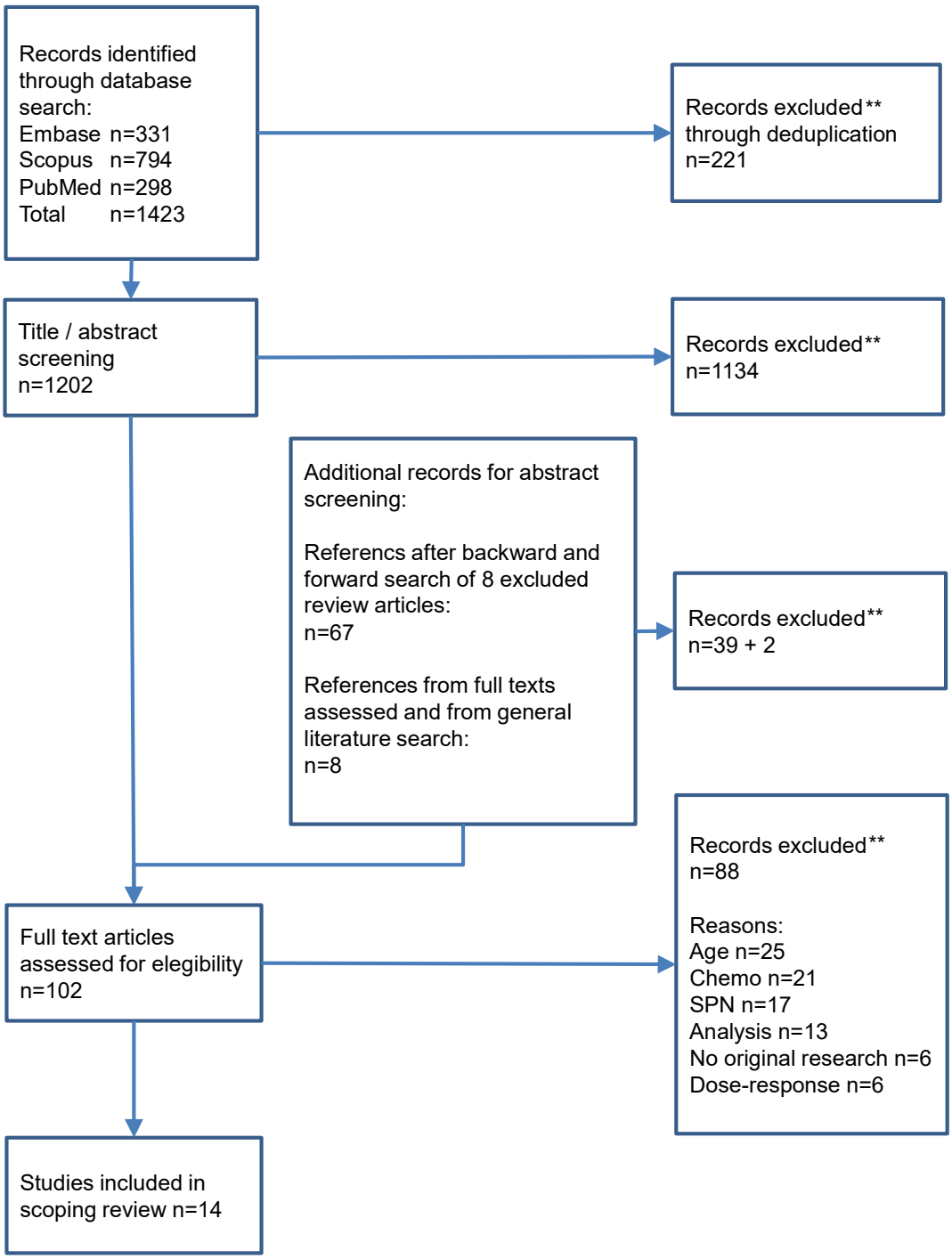


Figure 3. Scoping review: flow diagram of selection of sources of evidence. Systematic literature search of the concepts "childhood cancer", "second neoplasm", "chemotherapy", "dose-response relationship". Search of the literature databases Embase (September 2018), Scopus (February 2019), PubMed (July 2019); inclusion of articles stopped on 15 July 2019.

** Explanation of reasons for exclusion:

age	irrelevant age group, i.e. occurrence of first neoplasm for at least 50% of patients at age ≥ 15 years
chemo	no chemotherapy or no chemotherapy doses as exposure variable; dose = at least some kind of score, quantiles or similar at least some kind of score, quantiles or similar that shows variation in chemotherapy, must have been analyzed
SPN	irrelevant outcome (no CSPN) or too few cases of CSPN (<10)
analysis	no separate analysis for ICCC-3 XI diagnoses even though they are included
no original research	case study, review article, meta-analysis editorial, conference contribution (poster, oral presentation), not in peer-reviewed journal…
dose-response	no dose-response relationship established between exposure and outcome

The remaining 14 articles were considered eligible for full text evaluation (Table 4).

Table 4. Scoping review: 14 articles for full text evaluation to investigate the dose-response-relationship between chemotherapy and risk for subsequent carcinoma or malignant melanoma (CSPN) after childhood cancer.

Authors	Journal	Year of publication	Title
Cohort studies			
Boukheris et al. (2013)	Int J Radiat Oncol Biol Phys	2013	Risk of salivary gland cancer after childhood cancer: a report from the Childhood Cancer Survivor Study
Ehrhardt et al. (2019)	J Clin Oncol	2019	Subsequent Breast Cancer in Female Childhood Cancer Survivors in the St Jude Lifetime Cohort Study (SJLIFE)
Guibout et al. (2005)	J Clin Oncol	2005	Malignant breast tumors after radiotherapy for a first cancer during childhood
Henderson et al. (2016)	J Clin Oncol	2016	Breast Cancer Risk in Childhood Cancer Survivors Without a History of Chest Radiotherapy: A Report From the Childhood Cancer Survivor Study
Henderson et al. (2012a)	Ann Intern Med	2012	Secondary gastrointestinal cancer in childhood cancer survivors: a cohort study
Kenney et al. (2004)	Ann Intern Med	2004	Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study
Neglia et al. (2001)	J Natl Cancer Inst	2001	Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study
Teepen et al. (2017)	Journal of Clinical Oncology31	2017	Long-term risk of subsequent malignant neoplasms after treatment of childhood cancer in the DCOG LATER study cohort: Role of chemotherapy
Veiga et al. (2012a)	Cancer Epidemiol Biomarkers Prev	2012	Chemotherapy and thyroid cancer risk: a report from the childhood cancer survivor study
Case-control studies			
Allodji et al. (2019)	Pediatric Blood and Cancer	2019	Risk of subsequent colorectal cancers after a solid tumor in childhood: Effects of radiation therapy and chemotherapy
Inskip et al. (2009)	J Clin Oncol	2009	Radiation dose and breast cancer risk in the childhood cancer survivor study
Sigurdson et al. (2005)	Lancet	2005	Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study
Tucker et al. (1991)	Cancer Research	1991	Therapeutic Radiation at a Young Age Is Linked to Secondary Thyroid Cancer
Watt et al. (2012a)	J Natl Cancer Inst	2012	Radiation-related risk of basal cell carcinoma: a report from the Childhood Cancer Survivor Study

4.1.2 Characteristics of sources of evidence

All 14 studies included in full text evaluation were observational studies: nine cohort studies and five nested case-control studies. Nine studies were based on the North American Childhood Cancer Survivor Study (Robison et al., 2002). The remaining studies were based on European or on other US cohorts. The articles were published between 1991 and 2019.

The CSPN diagnostic groups in the 14 articles were breast cancer, thyroid cancer, colorectal cancer, gastrointestinal cancer, salivary gland cancer, and basal cell carcinoma. No article specified SPN diagnoses by a code though Guibout et al. (2005) reported using ICD-O coding. The specific diagnoses are listed in Appendix I.10 if they were available.

4.1.3 Results of individual sources of evidence

The studies are described in Appendices I.10 and I.11, therapy exposures are summarized in Appendix I.12, and the analyses and results are presented in Appendix I.13. Appendix I.14 lists strengths and limitations of the studies, which are discussed later (Chapter 5.1.2). Appendix I.16 summarizes the main results by substance (group) and SPN type and lists points important for interpretation of the results.

4.1.4 Synthesis of results

4.1.4.1 Cohort description

All studies included former childhood cancer patients who had survived for at least two years; in 11 of them, survival of at least five years was an inclusion criterion (Appendix I.10). In most studies, the earliest dates of diagnoses of childhood cancer were in the 1970s; the base cohort of one case-control study included diagnoses as early as from the 1930s (Tucker et al., 1991), and one study included primary diagnoses from as late as 2001 (Teepen et al., 2017). Most studies followed up SPNs into the 2000s with median latency times between 12 and 30 years. The number of diagnosis-specific SPN patients varied between 16 and 199, arising from cohorts of 1467 to 14,054 CCS.

Nine of the 14 studies are based on the North American CCSS cohort, in which eligible FPN diagnoses were leukemia, CNS malignancy, Hodgkin lymphoma (HL), non-HL, neuroblastoma, soft tissue sarcoma, kidney tumor, or bone cancer; patients with retinoblastoma, hepatic tumors, germ cell tumors and some other rare childhood cancer diagnoses were not included. One study was restricted to solid first neoplasms

(Allodji et al., 2019), one excluded leukemia in all study centers and retinoblastoma in part of the study centers (Guibout et al., 2005), and two did not exclude any diagnoses (Teepen et al., 2017, Tucker et al., 1991).

For the analyses with data from the North American CCSS cohort, an overlap of patients is likely among the nine studies, especially for studies on the same CSPN (breast cancer ((Kenney et al., 2004, Henderson et al., 2016, Inskip et al., 2009, Neglia et al., 2001)) and thyroid cancer ((Neglia et al., 2001, Sigurdson et al., 2005, Veiga et al., 2012a))). These studies nevertheless differed in design, inclusion period, or other inclusion criteria.

Six studies specifically investigated breast cancer as SPN, three focused on thyroid cancer, one investigated both breast and thyroid cancer, and the other studies looked at salivary gland cancer, gastrointestinal cancer, colorectal cancer, or basal cell carcinoma.

The five case-control studies matched two to four controls to each case. All studies used risk set sampling, i.e., they matched on duration of follow-up, even though only one mentioned this method explicitly (Watt et al., 2012a). All studies used age at FPN diagnosis as matching criterion; three additionally matched on sex (Allodji et al., 2019, Sigurdson et al., 2005, Tucker et al., 1991). The other two studies only included female patients. Further matching criteria were date of diagnosis (Allodji et al., 2019) and race (Tucker et al., 1991). One study explicitly matched on histology of the first neoplasm (Tucker et al., 1991); two others additionally matched on type of first neoplasm for subgroup analyses (Inskip et al., 2009, Sigurdson et al., 2005).

4.1.4.2 Exposure

Five studies explicitly reported that they included patients even if they had had another subsequent tumor before the CSPN (Appendix I.12). In Allodji et al. (2019), and Teepen et al. (2017), it was not clear whether the chemotherapeutic treatment of a preceding second tumor was included in the cumulative dose used for the analysis. From the study descriptions and the description of the North American CCSS design (Robison et al., 2002), I assume that treatment information of the intermittent neoplasm was included in the analysis of the other three studies (Henderson et al., 2016, Inskip et al., 2009, Sigurdson et al., 2005, Veiga et al., 2012a).

Most studies included the two chemotherapeutic groups alkylating agents (as AAS or CED or in mg/m²) and anthracyclines into their dose-analyses; one study investigated the effect of the groups epipodophyllotoxins and platinum compounds (Neglia et al., 2001), and one study used a different type of classification and analyzed the groups electrophilic agents, spindle inhibitors, topoisomerase II inhibitors, and NSI (nucleotide synthesis inhibitors) (Guibout et al., 2005) (Appendix I.12). Several studies analyzed the effect of frequently given single chemotherapeutic substances such as cyclophosphamide, procarbazine, or doxorubicin instead of the substance groups or in addition to the group analyses. The majority of studies classified chemotherapeutic substances into five to six groups, but most of these groups were analyzed as dichotomous variables only. Most papers included overall chemotherapy treatment as a dichotomous variable. All but one study, which used moles/m^2 as unit, measured chemotherapy doses in mg/m² or g/m² ((Guibout et al., 2005), Appendix I.12). Only one study explicitly used the cumulative dose as continuous variable in the analyses instead of categorical ones (Allodji et al., 2019).

The studies in this review used several methods for summing chemotherapeutic doses within substance groups:

1) For the analysis of alkylating agents, many studies used the score method, which was first applied to alkylating agents resulting in an alkylating agent score (AAS) (Tucker et al., 1987b). Some studies probably applied this method to other substance groups as well, even though it did not become entirely clear from the methods descriptions (Appendix I.12). The score method is specific to the cohort which received the substances in question. It is an extension of a categorical analysis. It divides the cumulative dose distribution of the entire cohort for each agent into thirds and assigns scores: 1 for the lowest third, 2 for the middle one, 3 for the highest third; 0 is assigned if a study subject did not receive this agent. The scores of all substances within a specific chemotherapeutic group are summed for each study subject. The studies reported did not specify the borders of the respective tertiles, effectively making it impossible to compare results. Only rough comparisons are possible concerning the direction of the effect estimate with increasing AAS.
2) Three studies applied the cyclophosphamide equivalent dose (CED), a method which applies conversion factors to alkylating agents which are not specific to

doses of a specific cohort (Green et al., 2014). The conversion factors were also used for the case-control study of this thesis (see Chapter 3.2.3.1 of this thesis and Chapter 2.2.1.2 in the SAP, Appendix III).

3) Three studies used anthracycline conversion factors/equivalence ratios (Neglia et al., 2001, Veiga et al., 2012a, Ehrhardt et al., 2019), which they provided or referenced (Children`s Oncology Group, 2018, Allen, 1992, Launchbury and Habboubi, 1993). The conversion factors were also used for the case-control study of this thesis (see Chapter 3.2.3.1 of this thesis and Chapter 2.2.1.2 in the SAP, Appendix III).
4) Allodji et al. (2019) was the only study which added up the doses of different chemotherapeutic substances within specific groups based “on the simple assumption that all agents share an equal carcinogenic potency”.

In six studies, radiotherapy was the main focus; nevertheless, they provided results of analyses on the risk for CSPNs associated with different chemotherapy doses. Most studies included the radiation dose to the SPN site as continuous variables in their analyses, some categorized or dichotomized radiation for the analysis or for reporting; some studies did not clearly report which of the data types they used for the analysis or for reporting.

4.1.4.3 Statistical analyses and results

All case-control studies used conditional logistic regression for the dose analyses and reported ORs as outcomes. Five cohort studies reported relative risks (RR), assuming that the number of SPNs followed a Poisson distribution. The Poisson regression usually estimates IRRs, which are sometimes called relative risks (see Chapter 2.6.1); therefore, I strongly assume that the studies actually estimated IRR instead of RR, but I take over the wording of the studies. Three cohort studies calculated HRs using Cox proportional hazards regression (Ehrhardt et al., 2019, Henderson et al., 2012a, Teepen et al., 2017). The reference group was patients with a dose of 0 mg/m² or 0 moles/m² of the substance (group) in question. One study reported relative SIRs (Henderson et al., 2016), which is a measure different from OR, RR and HR (Chapter 2.6.1). All studies but three reported 95% confidence intervals (95% CI) for the estimates of the dose-response analyses (Guibout et al., 2005, Sigurdson et al., 2005, Tucker et al., 1991). Eight studies calculated p-values for trend, thus investigating

monotone dose-response relationships. P-values were two-sided with a significance level of α = 0.05%. None of the studies adjusted for multiple testing.

Two studies did not report effect estimates for the dose-response analysis in numbers but described the results verbally (Guibout et al., 2005, Sigurdson et al., 2005), also see Appendices I.13 and I.16.

In multivariable analyses, the studies adjusted for radiotherapy (if applicable) and many of the other risk factors mentioned in Chapter 2.2, either through adjustment in multivariable analyses, through matching in case-control studies, or through subgroup or stratified analyses. In two case-control studies, it was not clear what adjustments had been made (Sigurdson et al., 2005, Tucker et al., 1991). Only three studies took genetic predispositions into account, either directly by considering cancer predisposition gene mutations (Ehrhardt et al., 2019) or indirectly through subgroup analysis of survivors with FPNs, which are known to be associated with Li-Fraumeni: sarcoma or leukemia (Henderson et al., 2016), or leukemia, CNS, and non-Ewing sarcoma (Teepen et al., 2017). Appendix I.16 lists which potential risk factors for SPNs were or were not considered by the studies.

The following chapters describe the results of multivariable analyses; results of univariable analyses are listed in Appendix I.13. Chemotherapeutic groups or agents are printed in bold if they are referred to for the first time for each carcinoma type.

4.1.4.3.1 Thyroid cancer

Three of the four studies investigating thyroid cancer as SPN did not find dose-response relationships between the SPN and **alkylating agents, anthracyclines** (see Appendix I.15, Figure 22, Figure 23), or **vinca alkaloids,** respectively, in their main analyses (Sigurdson et al., 2005, Tucker et al., 1991, Veiga et al., 2012a). The studies included between 23 and 119 thyroid SPNs. Two of these analyses were adjusted for radiotherapy; for one, it was unclear (Sirgudson et al. 2005). Neglia et al. (2001) reported a slightly elevated RR of 5.00 (1.04-23.99) for treatment with 1-1000 mg/m² epipodophyllotoxins, which two patients with thyroid SPN had received, but no significant trend across categories (Appendices I.13 and I.16).

Veiga et al. (2012a) reported significantly elevated relative risks of thyroid SPNs by alkylating agents in subgroups of patients (Table 5): in the group having received no radiation to the thyroid, the RR was significantly elevated only in the group with the

highest AAS of 3; in the subgroups having received radiation, the RR was significantly elevated in all groups having received alkylating agents.

Table 5. Cohort study on thyroid cancer as subsequent cancer after childhood cancer: dose-response relationship between alkylating agent score and odds ratio (Veiga et al., 2012a, Inskip et al., 2016).

Alkylating agent score	Odds ratio (95% confidence interval)		
	no thyroid radiation: n = 12 patients with thyroid SPN	**≤5 Gy thyroid radiation: n not reported**	**≤20 Gy thyroid radiation: n = 61 patients with thyroid SPN**
0	1 (ref.)	1 (ref.)	1 (ref.)
1-2	1.8 (0.3-10.0)	2.5[1]	**2.3 (1.3-4.5)**
3	**9.4 (1.4-56.8)**	5.5[1]	**2.8 (1.1-6.7)**

[1]p for trend = **0.02**, no 95% confidence interval reported

Concerning chemotherapy as dichotomous variable, no group (alkylating agents, anthracyclines, vinca alkaloids, or **epipodophyllotoxins**) or substance (**dactinomycin**, an antibiotic) or overall chemotherapy was significantly associated with thyroid SPN (Appendix I.13).

4.1.4.3.2 Breast cancer

Seven studies investigated subsequent breast cancer risk and included between 16 and 96 patients with breast cancer in the dose-response analyses. They yielded heterogeneous results concerning the different chemotherapeutic groups. Five studies included radiation as covariates (Ehrhardt et al., 2019, Kenney et al., 2004, Neglia et al., 2001, Teepen et al., 2017), for one study it was unclear if radiotherapy was included (Guibout et al., 2005), and in one study none of the patients had had chest radiotherapy (Henderson et al., 2016).

Only Henderson et al. (2016) reported a dose-dependent increase in breast cancer with increasing **CED** in their study with 44 breast cancer patients (test for trend of relative SIRs in multivariable analysis: p = 0.044, Figure 4, Appendices I.13 and I.16). These results are of note as they were observed in a group of women without history of chest radiation. Although the other studies adjusted for irradiation, residual confounding due to inadequate radiotherapy modeling or interaction between chemo- and radiotherapy cannot be ruled out.

In a study on 45 cases, the HR for breast cancer was significantly decreased in patients treated with the highest dose category of **alkylating agents** compared to no treatment

with the substance (≥6,000 mg/m²: 0.4 (95% CI 0.2-0.9), Figure 4, Ehrhardt et al. (2019)). If the model, however, included doxorubicin as a covariate instead of anthracyclines or if different subgroups were analyzed (women with <10 Gy chest radiation, women with pathogenic mutations excluded, women with in situ BC excluded), the low HR in patients with high dose categories was not significantly different from the patients without alkylating agent treatment (Appendices I.13 & I.16).

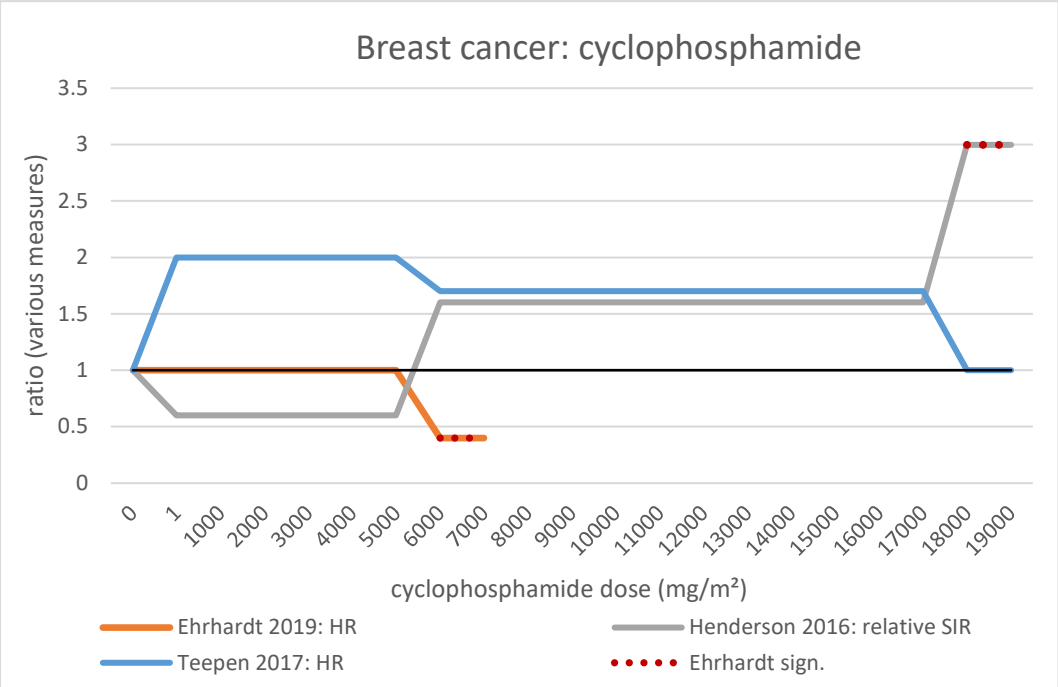


Figure 4. Breast cancer risk after childhood cancer treatment by cumulative cyclophosphamide dose (an alkylating agent). Results of articles from a scoping review on the dose-response relationship between chemotherapy and subsequent cancers according to ICCC-3 XI with original research studies published by July 2019. ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005), sign. = statistically significant

Three other studies on alkylating agents did neither see associations with breast cancer risk for any level of the AAS (Figure 5, Appendices I.13 and I.16) (Inskip et al., 2009, Neglia et al., 2001, Kenney et al., 2004) nor for mechlorethamine or procarbazine dose categories (Inskip et al., 2009). Likewise, Teepen et al. (2017) did neither find associations between breast cancer risk and any CED category nor a trend with increasing CED. These studies included between 49 and 95 breast cancer cases.

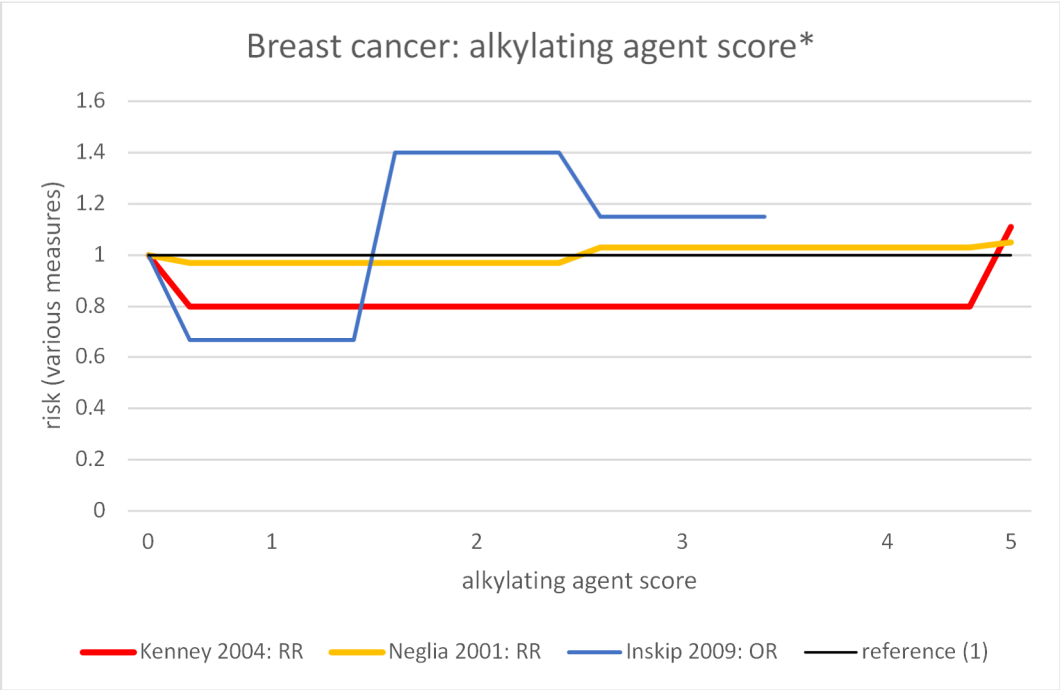


*Figure 5. Breast cancer risk after childhood cancer treatment by alkylating agent score (cohort-specific score by Tucker, Meadows, et al. (1987)). Results of articles from a scoping review on the dose-response relationship between chemotherapy and subsequent cancers according to ICCC-3 XI with original research studies published by July 2019. ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005). *The doses represented by the AAS likely differ between studies.*

For the studies which analyzed the effect of alkylating agents as dichotomous variables (Inskip et al., 2009, Ehrhardt et al., 2019, Teepen et al., 2017), the case-control study reported an elevated OR with the use of **carmustine** (**BCNU**, 3.71 (95% CI 1.12-12.30), (Inskip et al., 2009) but none of the other substances. Teepen et al. (2017) reported a HR of 3.4 (95% CI: 1.3-8.8) for the use of **ifosfamide**, but the effect could not be observed in a subgroup of patients not treated with chest radiation (HR: 2.3 (95% CI: 0.6-8.0)) (Appendices I.13 and I.16).

Five studies investigated dose-associations between breast cancer as SPN and **anthracyclines**. Three studies reported significantly higher rates of breast cancer (relative SIR or HR) in different dose categories of anthracyclines and **doxorubicin** compared to non-treatment (Henderson et al., 2016, Ehrhardt et al., 2019, Teepen et al., 2017). The risk estimates increased with higher dose categories (compare tables on anthracyclines and doxorubicin in Appendix I.16, (Henderson et al., 2016, Teepen et al., 2017)). Ehrhardt et al. (2019) reported a HR that was significantly elevated in

the anthracycline dose category of ≥250 mg/m² in the following patient subgroups: women with <10 Gy chest radiation (11.1, 95% CI: 1.8-66.3), women without pathogenic mutations (15.1, 95% CI: 6.1-37.6), and a group excluding in situ BC (24.1, 95% CI: 7.9-73.2). In addition, the cumulative incidence of breast SPN was highest in women treated with ≥250 mg/m² anthracyclines compared to women without anthracyclines treatment (p<0.001) (Ehrhardt et al., 2019). Two studies did not find significant associations between any level of doxorubicin (Inskip et al., 2009) or anthracyclines (Neglia et al., 2001) and the odds or risk for breast cancer, and there was no significant trend in the RR change across anthracycline levels (Neglia et al., 2001) (Appendices I.13 and I.16).

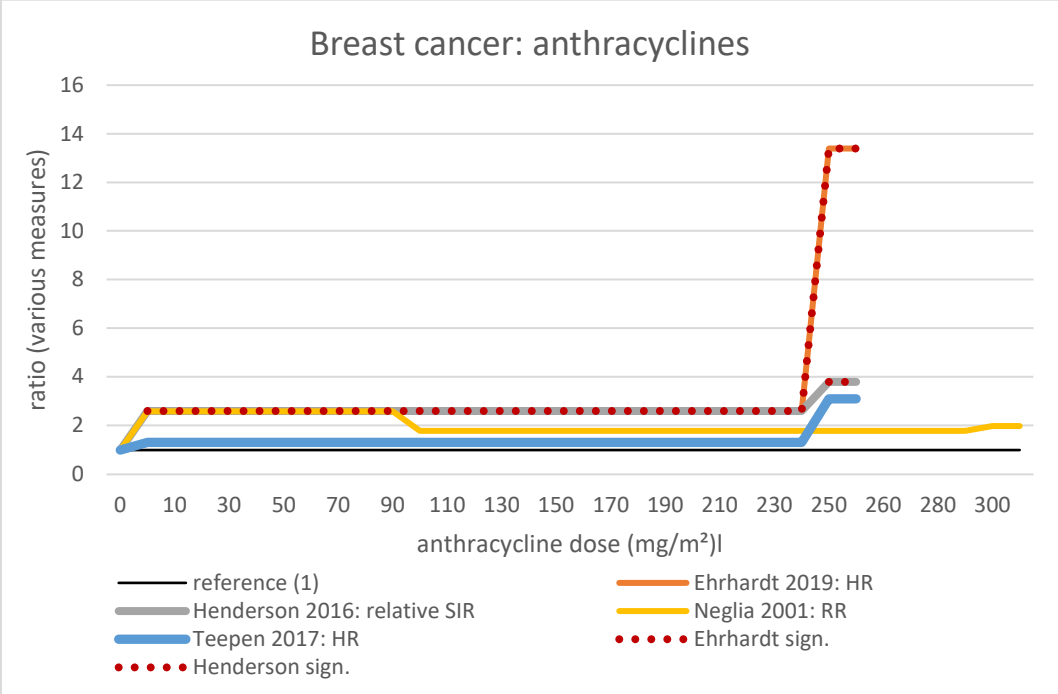


Figure 6. Breast cancer risk after childhood cancer treatment by cumulative anthracycline dose. Results of articles from a scoping review on the dose-response relationship between chemotherapy and subsequent cancers according to ICCC-3 XI with original research studies published by July 2019. ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005) , sign. = statistically significant

One study included anthracyclines as dichotomous variables into their analysis. It found a higher proportion of breast cancer cases in women having received anthracyclines than in those without this treatment (71.4% vs. 57.3%, p = 0.036) (Ehrhardt et al., 2019). Henderson et al. (2016) reported a significantly elevated SIR

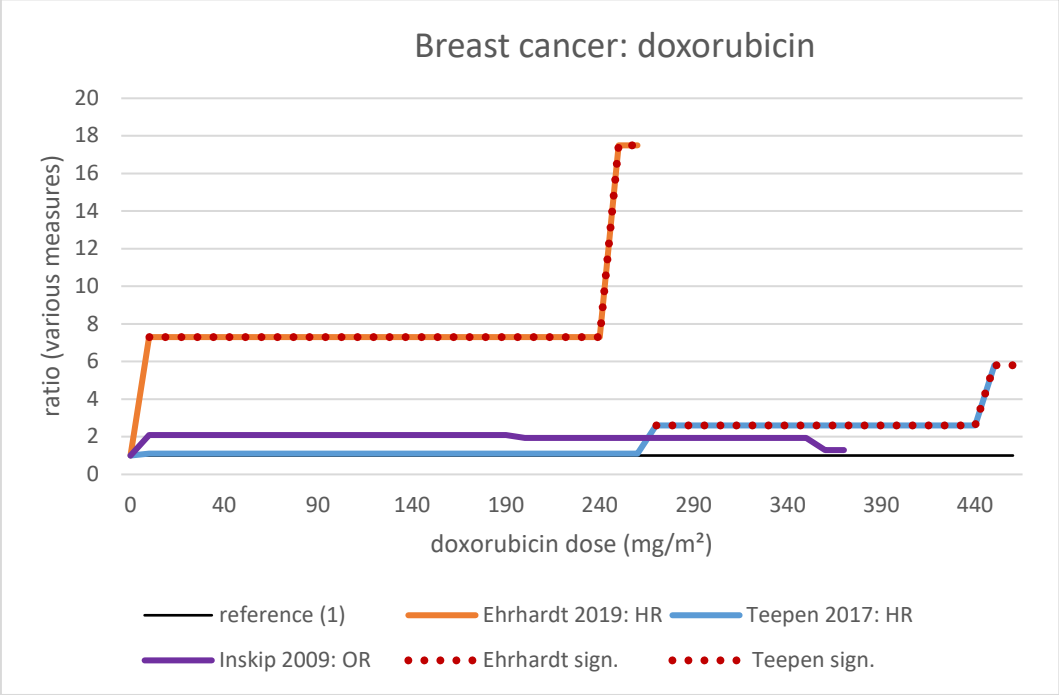


Figure 7. Thyroid cancer risk after childhood cancer treatment by cumulative doxorubicin dose (an anthracycline). Results of articles from a scoping review on the dose-response relationship between chemotherapy and subsequent cancers according to ICCC-3 XI with original research studies published by July 2019. ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005), sign. = statistically significant

for the joint treatment with anthracyclines and alkylating agents as dichotomous variable: 8.6 (95% CI: 5.7-12.8) (Appendix I.13).

Guibout et al. (2005), the only study which used moles/m² as unit, used a way of grouping chemotherapeutic substances different from the other studies, which limits comparability. The groups analyzed were **electrophilic agents, spindle inhibitors, topoisomerase II inhibitors, nucleotide synthesis inhibitors,** and other categories. They did not report effect estimates, but instead stated that there was "no evidence for a role of the number of moles per square meter for any of the substance categories or of the total number of moles per square meter administered." The RR was also not statistically significantly increased when the substances were included as dichotomous variables or when the treatment with MOPP was analyzed, a combination regimen of mechlorethamine, vincristine, procarbazine, and prednisone. The number of cases included in their analysis was low with 16.

Ehrhardt et al. (2019) reported that only 33.9% of BC patients in their cohort study were treated with **antimetabolites** whereas it was 52.6% patients without a breast SPN (p

= 0.006), but they did not find an association for **carboplatin, cisplatin, plant alkaloids** or **epipodophyllotoxins**.

4.1.4.3.3 Other types of cancer

The case-control study investigating colorectal cancer (n = 36 cases) after solid childhood cancer was nested in the French CCSS (Allodji et al., 2019). In multivariable analyses, it did not find associations between **anthracyclines** (Figure 8) or **MOPP** and colorectal cancer at any dose category or any trend on the continuous scale, neither with nor without adjustment for FPN type. This was also true for the subgroup of patients having received <30 Gy radiation (Appendices I.13 and I.16).

In the case-control study on 199 basal cell carcinomas nested in the North American CCSS, there was no evidence of an association with any dose level of **cyclophosphamide** (administered orally or intravenously) or **alkylating agents** in general (Figure 9), **procarbazine** (Figure 10), or **anthracyclines** (Figure 8). The presence or absence of **prednisone**, the only corticosteroid investigated in the included studies, was also not associated. Only patients treated with modalities which included radiotherapy had a higher risk for basal cell carcinoma (Watt et al., 2012a) (Appendices I.13 and I.16).

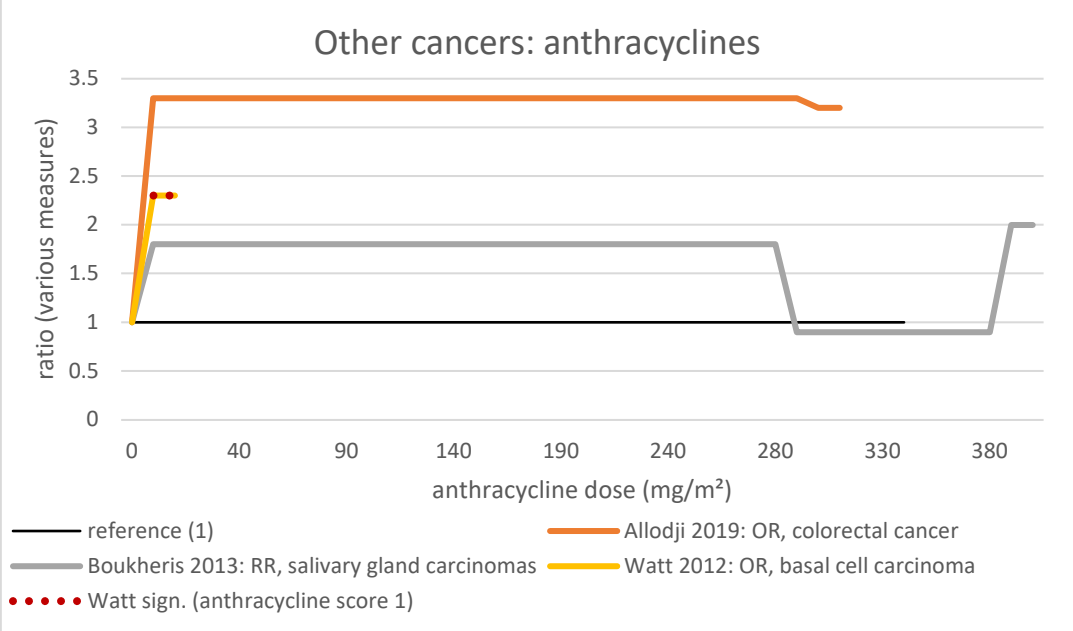


Figure 8. Colorectal cancer, basal cell carcinoma and salivary gland carcinoma risk after childhood cancer treatment by cumulative anthracycline dose. Results of articles from a scoping review on the dose-response relationship between chemotherapy and subsequent cancers according to ICCC-3 XI with original research studies published by July 2019. ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005), sign. = statistically significant

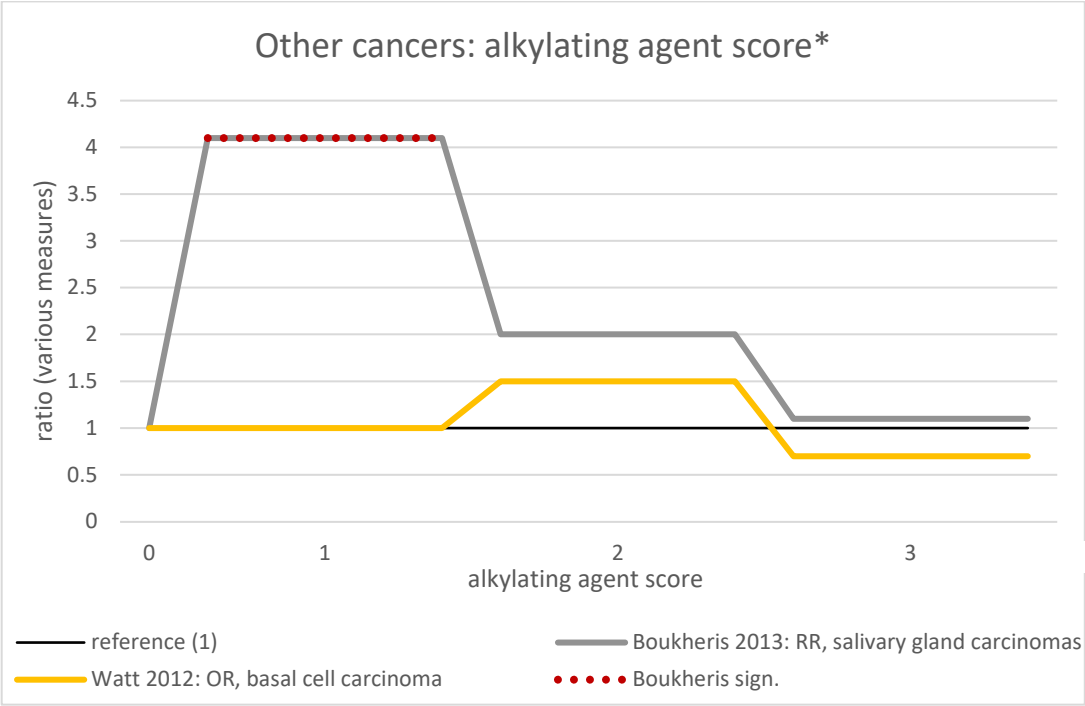


Figure 9. Basal cell and salivary gland carcinoma risk after childhood cancer treatment by alkylating agent score (cohort-specific score by Tucker, Meadows, et al. (1987)). Results of articles from a scoping review on the dose-response relationship between chemotherapy and subsequent cancers according to ICCC-3 XI with original research studies published by July 2019. ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005), sign. = statistically significant

**The doses represented by the alkylating agent score likely differ among studies*

The North American CCS cohort study did neither find any dose-response relationships between **anthracyclines** (Figure 8) nor **alkylating agents** (Figure 9) and salivary gland cancer as SPN (n = 23) nor a significant risk for the application of alkylating agents or anthracyclines (yes/no) (Boukheris et al., 2013) (Appendices I.13 and I.16).

The HR for gastrointestinal cancer (n = 45) was reported to be increased in the highest dose category of >7036 mg/m² of **procarbazine**, an alkylating agent, in a multivariable model (3.15, 95% CI 1.06-9.38, Figure 10) (Henderson et al., 2012a). In addition, the authors state in the discussion that they "did not find that procarbazine without abdominal radiation was associated with increased risk" of gastrointestinal cancer; however, it is unclear to which model this refers (Appendices I.13 and I.16).

The presence of **platinum derivates** resulted in a significantly increased HR in the multivariable model compared to an absence of platinum derivates (7.57, 95% CI 2.25-25.51).

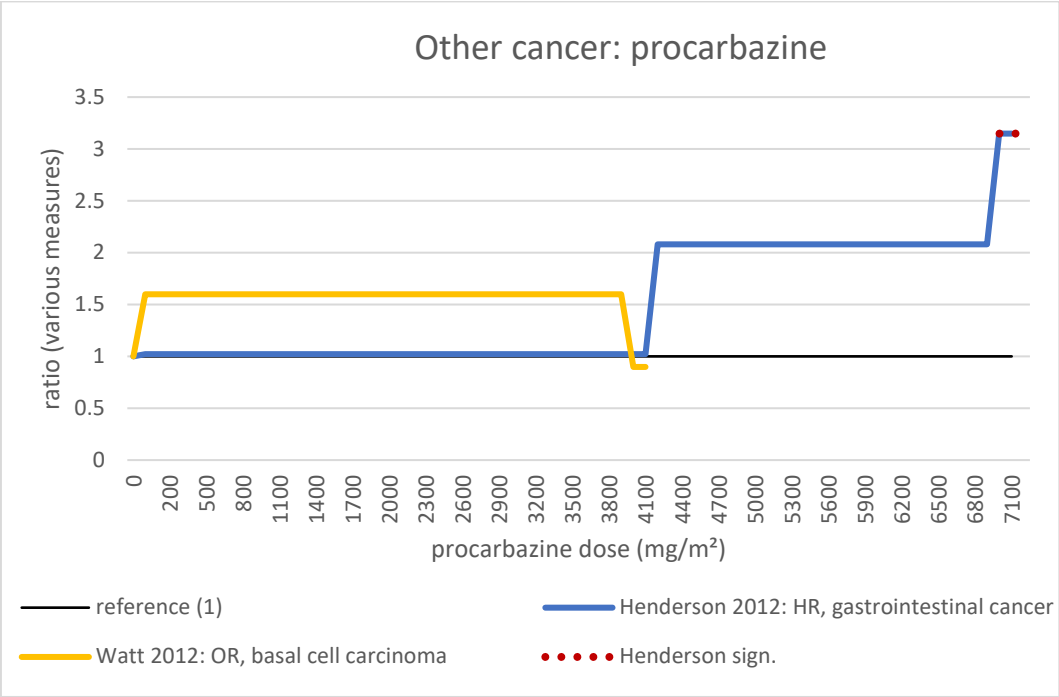


Figure 10. Basal cell and salivary gland carcinoma risk after childhood cancer treatment by cumulative procarbazine dose, an alkylating agent. Results of articles from a scoping review on the dose-response relationship between chemotherapy and subsequent cancers according to ICCC-3 XI with original research studies published by July 2019. ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005), sign. = statistically significant

4.1.4.4 Genetic predispositions

Three studies investigating breast cancer risk considered genetic predisposition as a risk factor (compare Chapter 2.2.3). One of these studies explicitly took genetic analyses into account: Ehrhardt et al. (2019) performed whole genome sequencing to identify (likely) pathogenic mutations linked to breast cancer and excluded women with these mutations in subgroup analyses. For anthracyclines, the significant association between the high dose category and breast cancer was seen in both the entire study group (HR: 13.4 (95% CI: 5.5-32.5)), and in the subgroup (HR: 15.1 (95% CI: 6.1-37.6)). Doxorubicin also remained a risk factor for BC, no matter if the predisposed group was excluded or not. However, the protective association between a high dose of alkylating agents and breast cancer seen in the entire cohort (HR: 0.4 (95% CI: 0.2-0.9)) was not significant anymore (HR: 0.4 (95% CI: 0.2-1.1)).

Other studies considered the FPN diagnosis of sarcoma or leukemia as a surrogate for a Li-Fraumeni syndrome, which is known to be associated with genetic cancer predisposition (see Chapter 2.2.3). Henderson et al. (2016) report that 85% of breast

cancer cases occurred in leukemia and sarcoma patients, although only 50-60% of patients had these types of cancer as FPN. The dose-response relationship between the chemotherapeutic groups analyzed (alkylating agents, anthracyclines) and BC was significant in both the whole cohort (CED: p = 0.044, anthracyclines: 0.004, Appendix I.13) and leukemia/sarcoma survivors only (CED: p = 0.045, anthracyclines: 0.005, Appendix I.13). Teepen et al. (2017) stratified their analyses by Li-Fraumeni-syndrome (LFS)-associated FPN diagnoses (leukemia, CNS tumor, and sarcoma except Ewing sarcoma). The HRs for breast cancer were higher for doxorubicin in survivors with LFS-associated FPN diagnoses (>443 mg/m²: HR: 5.8 (95% CI: 2.7-12.5) in the main analysis, HR: 14.8 (95% CI: 5.1-43.2) in patients with LFS-associated FPN diagnoses).

4.1.5 Conclusion

There are studies on the dose-response relationship between specific chemotherapeutic groups or substances used in childhood cancer treatment and the risk for CSPNs. Overall, the results were inconclusive. For anthracyclines, there was some evidence for an increase in breast cancer risk with increasing dose. Radiotherapy exposure might influence the effect of chemotherapy on CSPN risk.

4.2 Case-control study

4.2.1 Descriptive results

This chapter describes the availability of therapy data. The description of matching criteria, baseline characteristics, diagnoses, medical history, and exposure pertains to cases and controls whose data were included in explorative analyses. The last section compares cases and controls included in the analyses to those not included.

4.2.1.1 Data availability

ITT data for 1139 (84.5%) out of 1348 cases and controls was available. Only match groups with therapy data for the case and at least one control could be analyzed. Therefore, the data of 272 (82.4%) out of 330 match groups could be included in the analyses, totaling 1011 cases and controls (Table 6). Ninety percent of the match groups included in the analyses had at least two controls with data available (Table 7).

4.2.1.2 Matching criteria

The matching was very close. The differences between cases and controls in mean age at FPN diagnosis and mean year of diagnosis was always less than eight months.

62.9% of cases and 62.2% of controls were female; median age at first diagnosis was eight years, and median year of birth was 1980 (Appendix I.17.1, Table 23).

Table 6. Completeness of therapy data obtained for cases and their controls.1

Patient	ITT[2] data available and match group which could be analyzed[3]	ITT data available irrespective of match group	ITT data unavailable	Total[4]
Cases	272 (82.4%)	275 (83.3%)	55 (16.7%)	330
Controls	739 (72.6%)	864 (84.9%)	154 (15.1%)	1018
Total	1011 (75.0%)	1139 (84.5%)	209 (15.5%)	1348

[1]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)
[2]ITT = intention-to-treat
[3]due to risk set sampling, this corresponded to data from 939 individuals: 17 cases also served as control(s), 40 controls were controls for several cases
[4]due to risk set sampling, this corresponded to data from 1263 individuals: 18 cases also served as control(s), 52 controls were controls for several cases

Table 7. Overview of match groups included in explorative analysis: number of controls in a matchgroup.1

Number of controls in a match group	Number of match groups
1	27 (9.9%)
2	86 (31.6%)
3	96 (35.3%)
4	63 (23.2%)
Total	272 (100%)

[1]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

4.2.1.3 Baseline characteristics

Cases and controls included in the analyses hardly differed in the baseline characteristics. In general, over 60% of patients were females. More females had SPNs even when breast cancer, which is a typical cancer of females, was omitted. Around 60% of patients were diagnosed with an FPN in the 1980s, and almost 90% of SPNs occurred between 2000 and 2014 with a mean latency time of 18 years (Figure 11, Figure 12, Figure 13, Table 8).

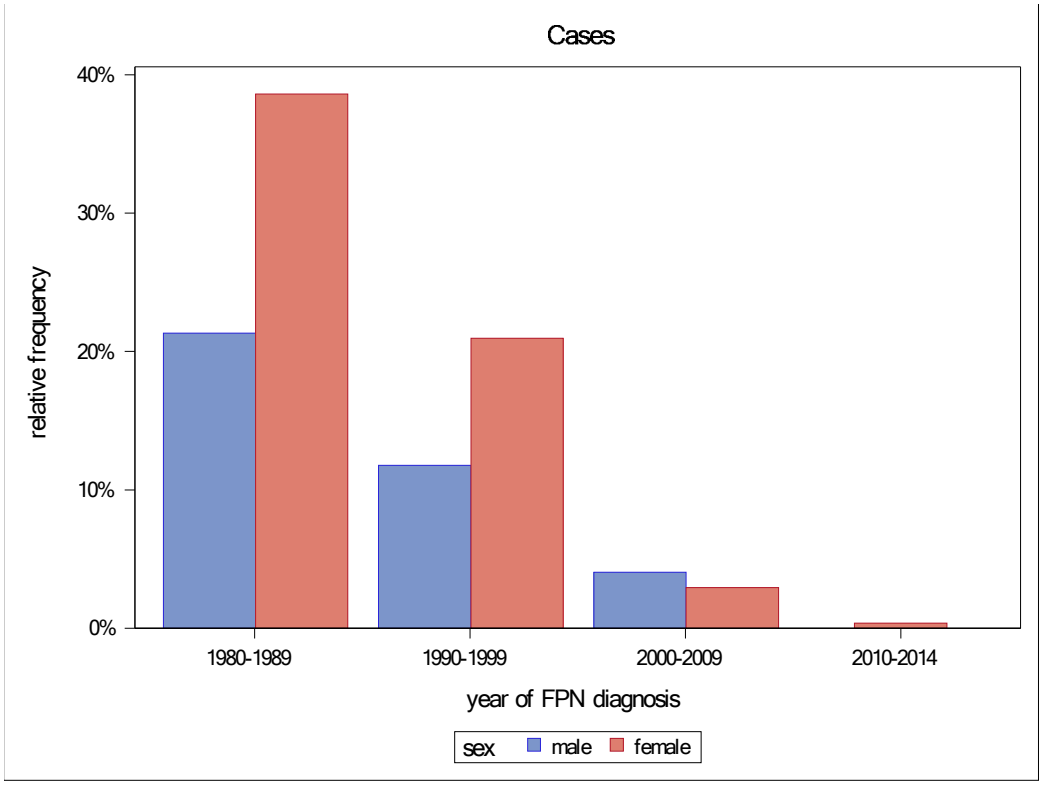
Table 8. Baseline characteristics of cases and controls.[1]

Characteristic		Cases N (%)	Controls N (%)	Total[1]
Sex	male	101 (37.13)	279 (37.75)	380
	female in match group without breast SPN	127 (46.69)	337 (45.60)	464
	female in match group with breast SPN	44 (16.18)	123 (16.64)	167
Age at FPN diagnosis	< 1 year	4 (1.47)	9 (1.22)	13
	1-4 years	59 (21.69)	150 (20.30)	209
	5-9 years	96 (35.29)	257 (34.78)	353
	10-14 years	113 (41.54)	323 (43.71)	436
Period of FPN diagnosis	1980-1989	163 (59.93)	447 (60.49)	610
	1990-1999	89 (32.72)	239 (32.34)	328
	2000-2009	19 (6.99)	49 (6.63)	68
	2010-2014	1 (0.37)	4 (0.54)	5
Period of SPN diagnosis	1980-1989	1 (0.37)	-	1
	1990-1999	28 (10.29)	-	28
	2000-2009	139 (51.10)	-	139
	2010-2014	104 (38.24)	-	104
Latency (time between FPN and SPN)	6 months to <1 year	0 (0.00)	-	
	1-4 years	9 (3.31)	-	
	5-9 years	32 (11.76)	-	
	10-19 years	128 (47.06)	-	
	20-29 years	99 (36.40)	-	
	>=30 years	4 (1.47)	-	
Total		272	739	1011

[1] due to risk set sampling, the total number of cases and controls corresponded to 939 individuals: 17 cases also served as control(s), 40 controls were controls for several cases

Characteristic in years	Cases	Controls
Median age at FPN diagnosis	8	8
Median year of FPN diagnosis	1988	1988
Median age at SPN diagnosis	26	
Median year of SPN diagnosis	2008	-
Median latency time	18	-

[1]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)



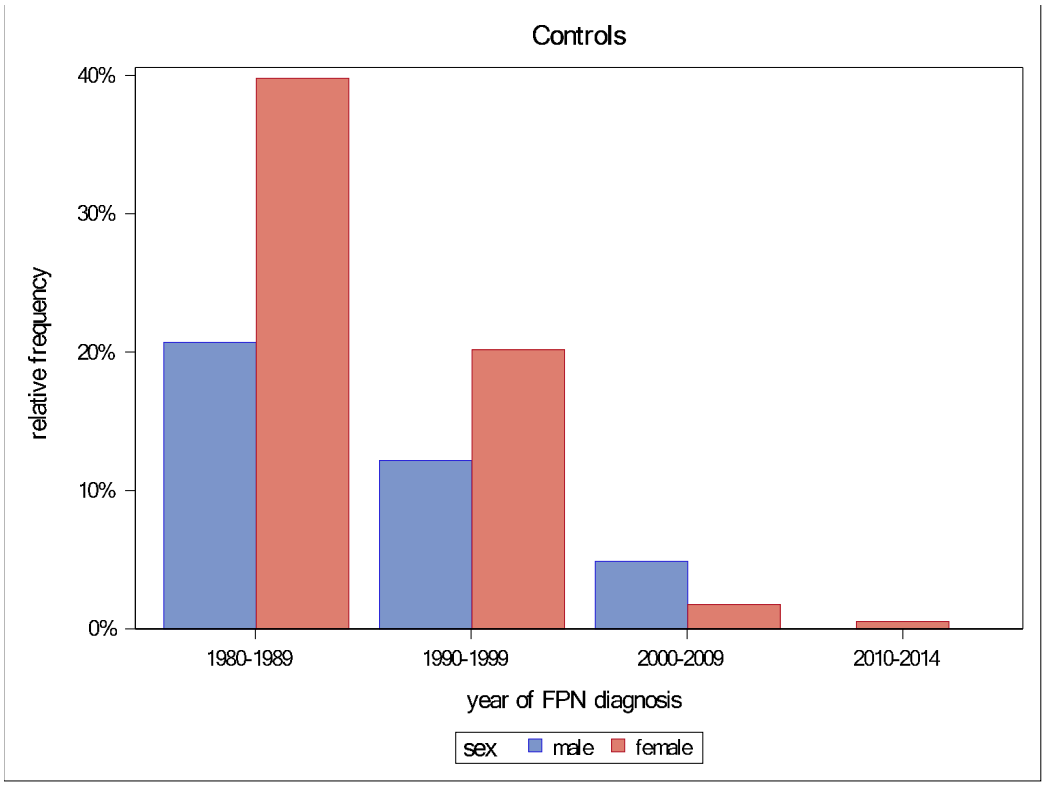


Figure 11. Year of first primary neoplasm (FPN) diagnosis of cases (left) and controls (right) by sex. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: 272 cases with CSPN diagnosis (see below) and their matched controls (n = 739); FPN diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

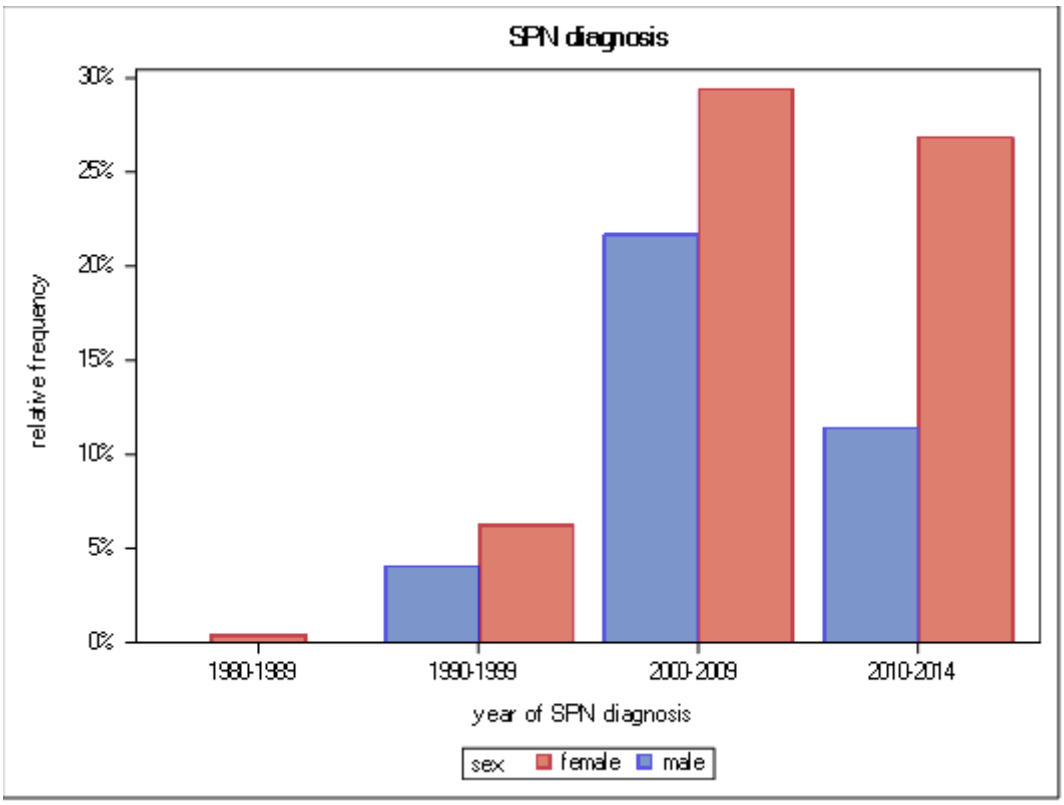


Figure 12. Year of subsequent primary neoplasm (SPN) diagnoses by sex. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: 272 cases with CSPN diagnosis (see below) and their matched controls (n = 739); first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; SPN diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

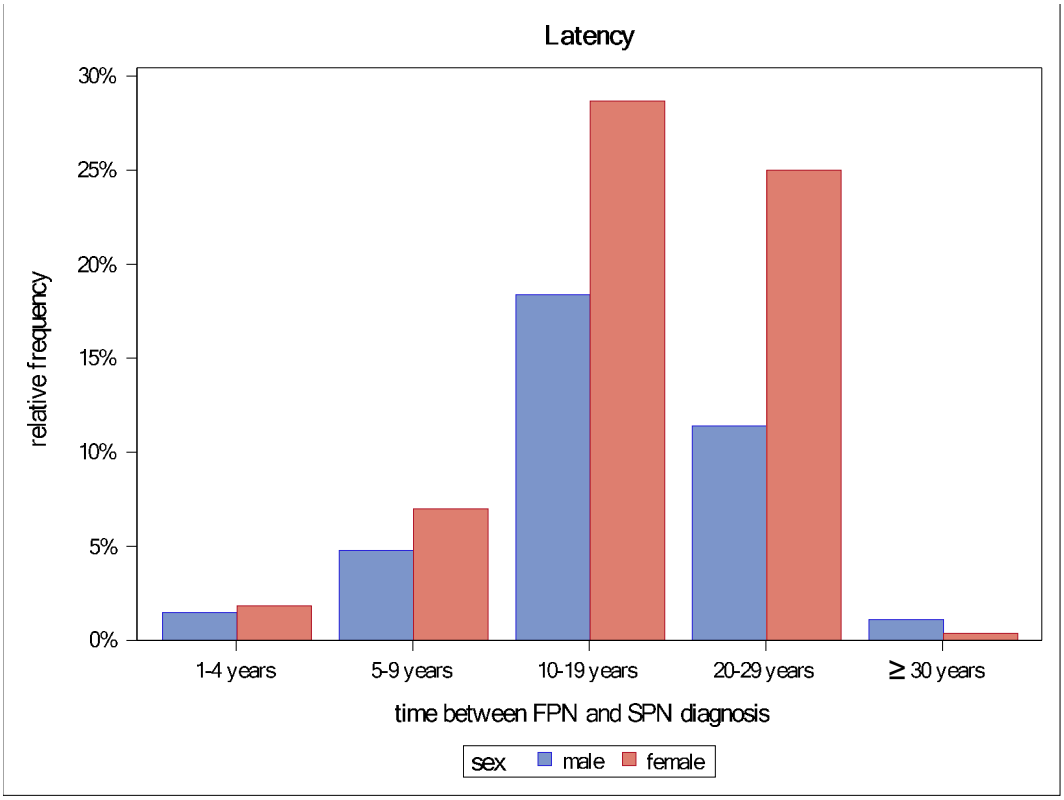


Figure 13. Latency between first primary neoplasm (FPN) and subsequent primary neoplasm (SPN) diagnosis by sex. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: 272 cases with CSPN diagnosis (see below) and their matched controls (n = 739); FPN diagnoses: ICCC-3 groups I-XII; SPN diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

4.2.1.4 FPN and SPN diagnoses

The FPN diagnosis spectrum was similar between cases and controls, with a slightly higher relative frequency of lymphoma in cases (due to Hodgkin lymphoma patients (ICCC-3 group II(a)) and a lower relative frequency of leukemia and bone tumor patients in cases than in controls (Figure 14, Appendix I.17.1, Table 24). The distribution of FPN diagnoses in the sample was 50% leukemia, 29% lymphomas, 2% CNS tumors, and 19% other solid tumors This distribution was different in the sample of *all* patients in match groups with a CSPN in the STATT-SCAR study (n = 438 cases, 2370 controls, Appendix I.17.1, Figure 24) where 32.8% (n = 953) of patients had leukemia, 22.5% (n = 653) had lymphomas, and 14.9% (n = 433) had CNS tumors. Thus, patients with CNS tumors and also other entities like neuroblastoma were underrepresented in the data analyzed. This is because availability of therapy data differed by diagnosis. The distribution also differed from all patients registered at the

GCCR where about 30% of patients have leukemia, 14% have lymphomas, and 24% have CNS tumors (Kaatsch et al., 2019). analyzed. This is because certain SPNs occur differentially after particular types of FPNs and the survival time after the FPN plays a role (Chapter 2.2.3).

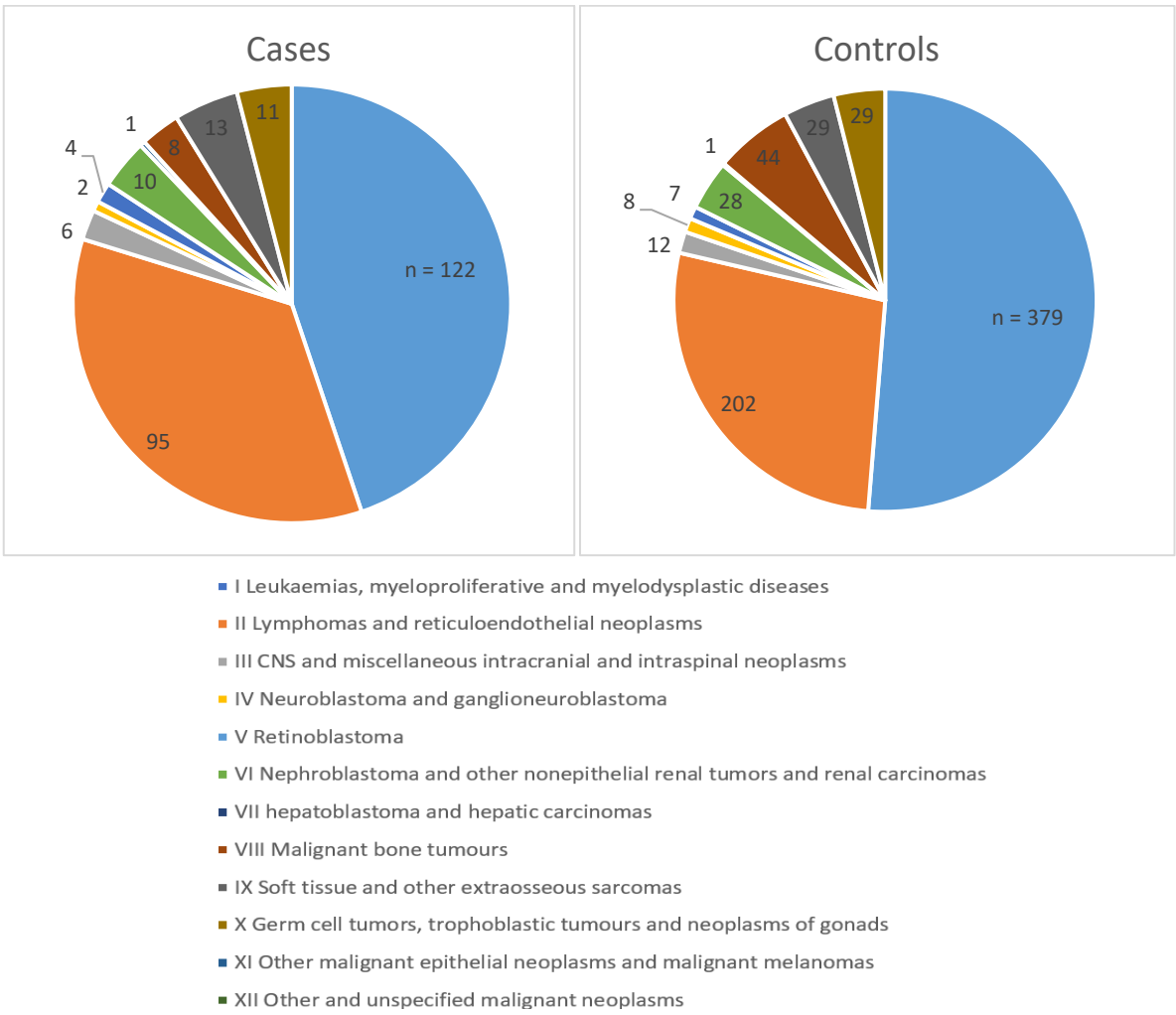


Figure 14. Number of controls and cases by diagnostic group of first primary neoplasms (FPN) according to ICCC-3. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: 272 cases with CSPN diagnosis (see below) and their matched controls (n = 739); FPN diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

The most frequent SPN was thyroid carcinoma, followed by skin carcinoma, breast cancer, and malignant melanoma (Figure 15, Table 9). A total of 30.6% (n = 22) of skin carcinomas and 40.9% (n = 18) of breast cancer followed a Hodgkin lymphoma FPN, even though only 24.6% of cases had a Hodgkin lymphoma FPN. Breast cancer is a

common subsequent cancer after Hodgkin lymphoma due to radiotherapy (van Leeuwen and Ng, 2016).

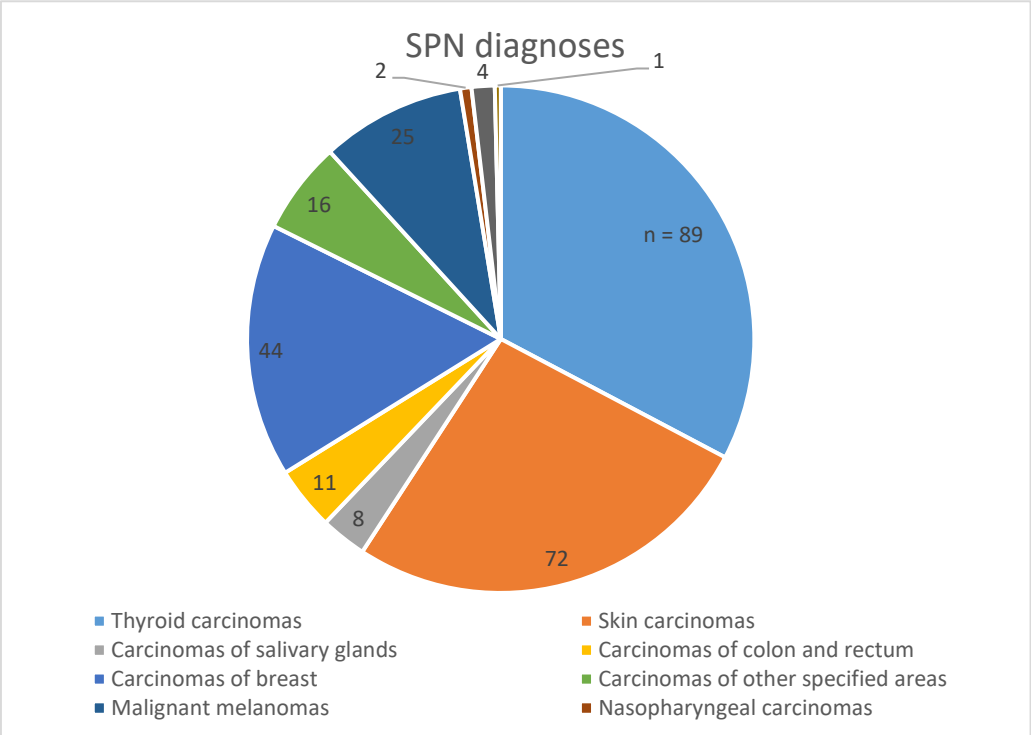


Figure 15. Number of cases by subsequent primary neoplasm (SPN) diagnosis according to ICCC. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; SPN diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005); 17 cases also served as control(s).

Table 9. Diagnoses of SPNs of cases according to ICCC-3.[1]

SPN diagnosis	ICCC-3 group	Cases[2] N (%)
Adrenocortical carcinomas	**XI(a)**	-
Thyroid carcinomas	**XI(b)**	89 (32.72)
Nasopharyngeal carcinomas	**XI(c)**	-
Malignant melanomas	**XI(d)**	25 (9.19)
Skin carcinomas	**XI(e)**	72 (26.47)
Other and unspecified carcinomas		
Carcinomas of salivary glands	**XI(f)1**	8 (2.94)
Carcinomas of colon and rectum	**XI(f)2**	11 (4.04)
Carcinomas of appendix	**XI(f)3**	-
Carcinomas of lung	**XI(f)4**	-
Carcinomas of thymus	**XI(f)5**	-
Carcinomas of breast	**XI(f)6**	44 (16.18)
Carcinomas of cervix uteri	**XI(f)7**	4 (1.47)
Carcinomas of bladder	**XI(f)8**	1 (0.37)
Carcinomas of eye	**XI(f)9**	-
Carcinomas of other specified areas[3]	**XI(f)10**	16 (5.88)
Carcinomas of unspecified site	**XI(f)11**	-

[1]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)
[2]17 cases also served as controls
[3]base of tongue not otherwise specified (NOS), border of tongue (n = 3), tongue NOS (n = 2), Mandibular gingiva, Floor of mouth NOS, esophagus NOS, stomach NOS, duodenum, ileum, small intestine NOS, head of pancreas, pudendum

4.2.1.5 Medical history

More than twice as many SPN cases had a relapse within their latency period than controls (21.7% vs. 9.5%). This refers to relapses within the latency period of the case or for controls, within the latency of the index case in a match group. Eleven point eight percent of cases had had a stem cell transplantation, but only 3.4% of controls (Table 10, Appendix I.17.1, Figure 25, Figure 26). Cases and controls with a SCT had had a relapse at similar frequencies (cases: 21 relapses in 32 SCT patients = 65.6%, controls: 17/25 = 68.0%) Eleven percent of cases and 4.7% of controls were treated in more than one TOS.

Table 10. Medical history of patients.[1]

Characteristic	Cases N[2] (%)	Controls N[2] (%)
relapse		
yes	59 (21.69)	70 (9.47)
no	213 (78.31)	669 (90.53)
stem cell transplantation		
Yes	32 (11.76)	25 (3.38)
no or unknown	240 (88.24)	714 (96.62)
relapse and stem cell transplantation		
Yes	21 (7.72)	17 (2.30)
Number of TOS[3] in which a patient was treated		
1	242 (88.97)	704 (95.26)
2	27 (9.93)	35 (4.74)
3	3 (1.10)	0 (0.00)

[1]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)
[2]due to risk set sampling, this corresponded to data from 939 individuals: 17 cases also served as control(s), 40 controls were controls for several cases
[3]TOS = therapy optimization studies

4.2.1.6 Exposure and covariate data

Overall, 97.6% of patients were treated with chemotherapy, 62.6% patients received both chemo- and radiotherapy, 0.5% radiotherapy only, and 1.9% none of these treatments. The proportion of patients treated with both chemo- and radiotherapy was higher in the group of cases (70.2%) than in controls (59.8%). Cases and controls received about the same mean number of different substances (7.4 and 7.7). Of the controls, 39.8% were not treated with radiotherapy, but only 29.0% of cases had not been irradiated (Figure 16, Appendix I.17.1, Table 25).

The dose ranges of the substance groups are displayed in Appendix I.17.1, Figure 27. There were no major differences in the mean doses between cases and controls who received the substance. Details on the number of cases and controls having received each substance and on the doses of all substances are listed in Appendix I.17.1, Table 26, along with radiotherapy doses.

Breast cancer patients were treated with cyclophosphamide and methotrexate less often than their matched controls: Only 56.8% (n = 25) of the cases had a cyclophosphamide treatment but 73.2% (n = 90) of controls; only 38.5% (n = 17) cases had a methotrexate treatment but 52.9% (n = 65) of the matched controls (data not shown).

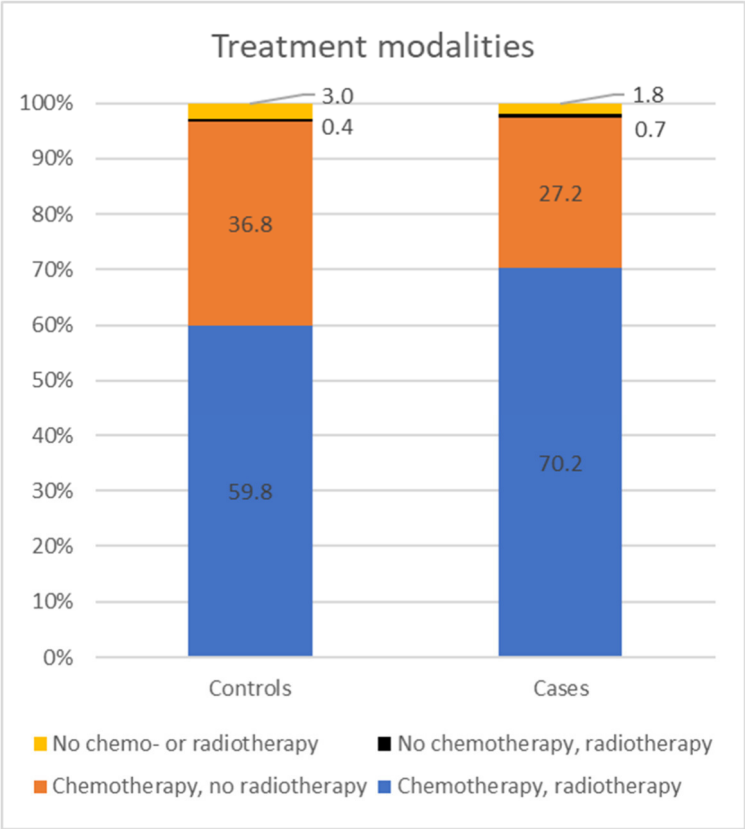


Figure 16. Chemo- and radiotherapy treatment of cases and controls. Chemotherapy treatment includes other substances (Dexamethasone, Folinic Acid, G-CSF, Interferon ALPHA, other, Prednisone). Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: 272 cases with CSPN diagnosis (see below) and their matched controls (n = 739); first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

4.2.1.7 Cases and controls not analyzed

Not included in the analyses were

- patients who did not have ITT data available and
- patients with ITT data available but who were part of a match group which could not be analyzed due to lack of data for the other patients in the group (compare Chapter 4.2.2 in Appendix III).

The demographic and diagnostic characteristics between patients included in the analyses and those not included are compared in Appendix I.17.2. Patients not included in the analyses were younger at FPN diagnosis; also, they had a lower median age at SPN diagnosis, a shorter latency period, and there was a higher percentage of cases and controls diagnosed in the years 2000-2014 compared to the group

analyzed. The latter is not surprising as not all of the most recent study protocols had been included in the GPOH database at the time of data closure, i.e. ITT data was hardly available for these calendar years. Cases and controls not analyzed had FPN diagnoses of CNS tumors, neuroblastoma retinoblastoma, renal tumors, osteosarcoma, or soft tissue sarcoma more often compared to those analyzed (Appendix I.17.2, Figure 28). This can be explained by the fact that the trial centers of these FPN diagnoses had hardly contributed ITT data at time of data closure. 22.6% (n = 26) of cases with thyroid cancer as SPN had missing ITT data (Appendix I.17.2, Table 29). Patients with and without ITT data hardly differed with respect to sex (Table 27).

4.2.2 Results of the explorative analysis

The final models included all chemotherapeutic groups or substances that were significant in univariable logistic regression. The forward selection process to build the final model is delineated in Figure 17. The best functional form of the dose response curves found in univariable analysis was applied to multivariable analysis. For a documentation of the analysis process, see Appendix I.8.

4.2.2.1 Main analysis

Four out of 20 chemotherapeutic groups or substances were statistically significantly associated with a CSPN occurrence at an α-level of 0.10 in univariable logistic regression analysis modeled with the principle of fractional polynomials with spike at zero (Table 11, Figure 17). In addition, the CPSN risk for having received each substance versus not having received it (binary variable) is described briefly.

Table 11. Association between CSPN[1] occurrence and the dose (continuous) of substances or substance groups for treatment of an FPN in childhood (n = 1010, 272 match groups).[2] The OR[1] for selected doses against nonexposure are presented (see Figure 18-Figure 20 and Figure 29-Figure 31 for association of full dose range). Only substances or substance groups were assessed which were significant at the 10% significance level in univariable analysis.[3]

Substance (group)[3]	Number of patients having received the substance	Selected doses for presentation	univariable models: OR (90% CI)[1]	multivariable model without covariates: OR (90% CI)	multivariable with covariates[4]: OR (90% CI)
cyclophos-phamide	727	0 mg/m²	reference	reference	reference
		1000 mg/m²	0.89 (0.84-0.95)	0.89 (0.83-0.95)	0.90 (0.84-0.96)
		3000 mg/m²	0.71 (0.58-0.86)	0.70 (0.57-0.87)	0.72 (0.58-0.90)
		6000 mg/m²	0.50 (0.34-0.75)	0.49 (0.32 -0.75)	0.52 (0.34-0.81)
antibiotics	135	0 mg/m²	reference	reference	reference
		6 mg/m²	0.47 (0.27-0.83)	0.36 (0.20-0.66)	0.44 (0.24-0.82)
		9 mg/m²	0.65 (0.43-0.99)	0.51 (0.32-0.80)	0.63 (0.40-1.00)
		15 mg/m²	1.23 (0.76-1.98)	1.03 (0.62-1.70)	1.28 (0.76-2.16)
		21 mg/m²	2.32 (0.99-5.46)	2.08 (0.85-5.09)	2.61 (1.04-6.54)
methotrexate	585	yes vs. no[5]	0.71 (0.55-0.93)	- [6]	- [6]
epipodo-phyllotoxins	286	0 mg/m²	reference	reference	reference
		165 mg/m²	0.64 (0.40-1.03)	0.65 (0.39-1.07)	0.60 (0.35-1.04)
		330 mg/m²	0.88 (0.63-1.22)	0.91 (0.64-1.29)	0.79 (0.54-1.15)
		1000 mg/m²	1.43 (1.05-1.96)	1.57 (1.14-2.17)	1.22 (0.86-1.72)
		3000 mg/m²	2.33 (1.35-4.02)	2.69 (1.52-4.76)	1.87 (1.02-3.43)
		6300 mg/m²	3.24 (1.54-6.80)	3.87 (1.77-8.46)	2.50 (1.09-5.74)

[1]CSPN = carcinoma or malignant melanoma according to ICCC-3 group XI as subsequent primary neoplasm after childhood cancer, ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005), FPN = first primary neoplasm OR = odds ratio, 90% CI = 90% confidence interval;

[2]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months

[3] only substance (groups) are reported which were significant at an alpha-level of 0.1 in univariable explorative logistic regression analyses with fractional polynomials with spike at zero (out of the nine substance groups alkylating agents, anthracyclines, antibiotics, antimetabolites, enzymes (Asparaginase), epipodophyllotoxins, platinum derivates, vinca alkaloids, corticosteroids, the five single substances cyclophosphamide, cytarabine, doxorubicin, methotrexate, vincristine, and their complementary substance groups alkylating agents without cyclophosphamide, anthracycline excluding doxorubicin, antimetabolites excluding cytarabine, antimetabolites excluding methotrexate, antimetabolites excluding cytarabine and methotrexate, vinca alkaloids excluding vincristine); see Appendix I.18.1, Table 31, for model details

[4] relapse, stem cell transplantation, radiotherapy

[5] for methotrexate the best model selected in univariable explorative analysis was a spike model, i.e., methotrexate as binary variable

[6] methotrexate was not selected because upon entry into the model its p-value was >0.1 and the AIC increased

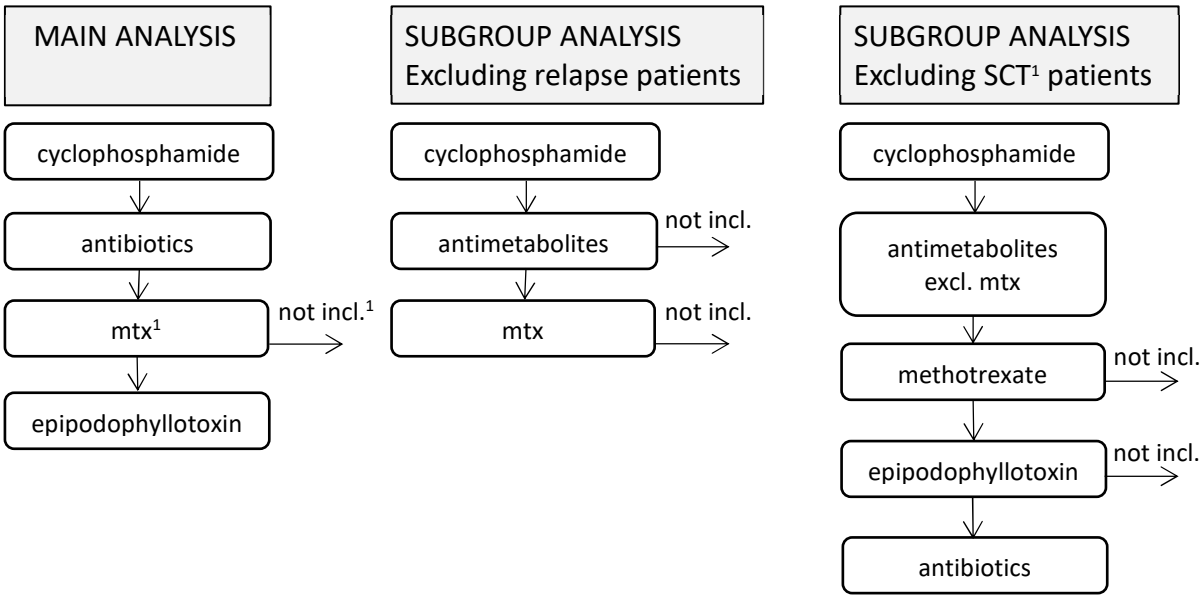


Figure 2. Forward selection process during the multivariable model building process of the dose-response-relationship between substance doses and CSPN[1] risk. The sequence of variable entry into the model is depicted from top to bottom. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months

[1]CSPN = carcinoma or malignant melanoma according to ICCC-3 group XI as subsequent primary neoplasm after childhood cancer, ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005),

[1]not incl. = not included fin the final model based on a 10% significance level, [1]mtx = methotrexate,

[1]SCT = stem cell transplantation

4.2.2.1.1 Cyclophosphamide

A total of 181 cases and 546 controls received cyclophosphamide, a type of alkylating agent, during FPN treatment with doses between 75 and 23,900 mg/m² (Appendix I.17.1, Table 26). The cyclophosphamide dose fit best when untransformed (Appendix I.18.1, Table 31). The risk for a CSPN decreased with increasing dose, e.g. the risk was by 29% significantly lower for patients having received 3000 mg/m² vs. nonexposed patients (OR: 0.71 (90% CI: 0.58-0.86), univariable model, Table 11, Figure 18). This association hardly changed when the other substances and the covariates were included into the model (Table 11, Appendix I.18.1, Figure 29).

There was also an association between cyclophosphamide as a dichotomous variable (i.e., having received cyclophosphamide or not) and CSPN occurrence (OR for having received cyclophosphamide: 0.66 (90% CI: 0.51-0.86), Appendix I.18.1, Table 32).

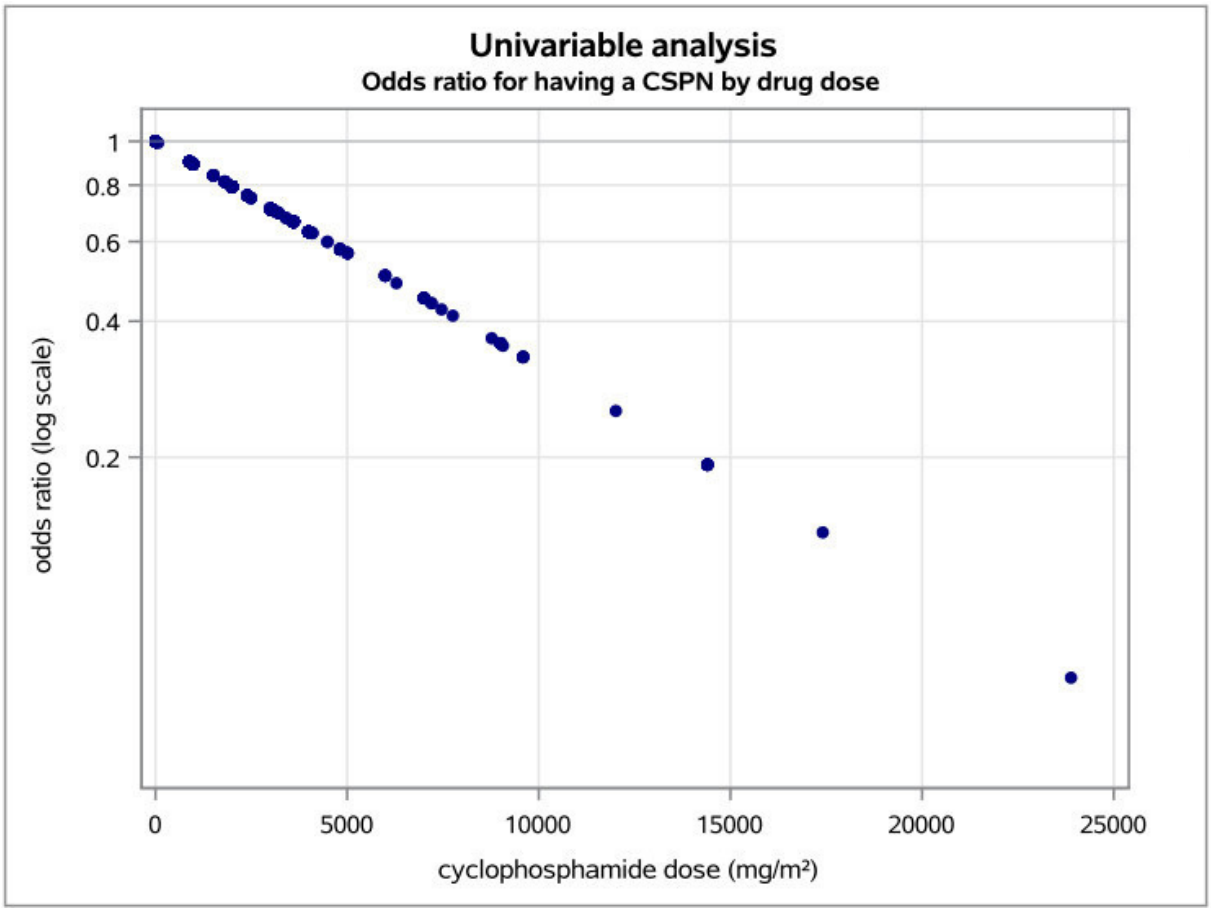


Figure 18. Univariable analysis: Odds ratio for having a CSPN by cyclophosphamide dose. CSPN = carcinoma or malignant melanoma according to ICCC-3 XI as subsequent primary neoplasm after childhood cancer. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005)

4.2.2.1.2 Antibiotics

A total of 32 cases and 104 controls received antibiotics during FPN treatment with Actinomycin D equivalent doses between 1.5 and 22.04 mg/m² (Appendix I.17.1, Table 26, influential point of 27.3 mg/m² is maximum in Table 26). Twenty-two of these patients got Bleomycin; its dose was converted to Actinomycin D equivalents (Chapter 3.2.3.1). The association between antibiotic dose and the odds for CSPN was best described by the untransformed dose and a binary indicator (spike) for having received an antibiotic or not (Appendix I.18.1, Table 31). Having received a cumulative dose of 9 mg/m² or less seemed to be protective compared to nonexposure while the risk increased with higher doses (Table 11, Figure 19, Appendix I.18.1, Figure 30). Specifically, the risk was significantly lower by more than half in patients exposed to 6

mg/m² compared to nonexposed patients (OR: 0.44 (90% CI: 0.24-0.82), multivariable analysis with covariates), while it was statistically significantly increased in patients exposed to 21 mg/m² vs. nonexposed (OR: 2.61 (90% CI: 1.04-6.54)).

The average risk for a CSPN did not differ between patients having received an antibiotic or not, as indicated by a univariable analysis with antibiotic as a binary variable (Appendix I.18.1, Table 32, OR: 0.79 (90% CI: 0.51-1.22)).

The spike in the model indicates that the baseline risk differed between patients having received antibiotics and those who did not (called no-dose group hereafter). Therefore, it is relevant to know if those groups of patients were different with respect to disease and therapy characteristics. In addition, I explored if patients having received low antibiotic doses (called low-dose group), which seemed protective, are different from patients of the no-dose group or patients with higher doses of 14 mg/m² or more (called high-dose group, compare Appendix I.18.1, Figure 30, 14 mg/m² is the dose at which the OR changed from <1 (protective) to >1 (risk factor), even though the deviation from 1 was not statistically significant at around 14 mg/m²). Two observations stuck out (Table 12): in the no-dose group, 91.0% of patients had hematological malignancies as FPN whereas in patients with antibiotic treatment, 98.5% had solid tumors as FPN. In the no-dose group, 65.6% (n = 574) of patients had a radiotherapy treatment (true for 73.3% of cases), and only 47.6% of those treated with antibiotics (53.1% of cases) received a radiotherapy treatment. In the low-dose group, only 42.9% (n = 45) had radiotherapy, in the high-dose group, 63.3% (n = 19) received radiotherapy.

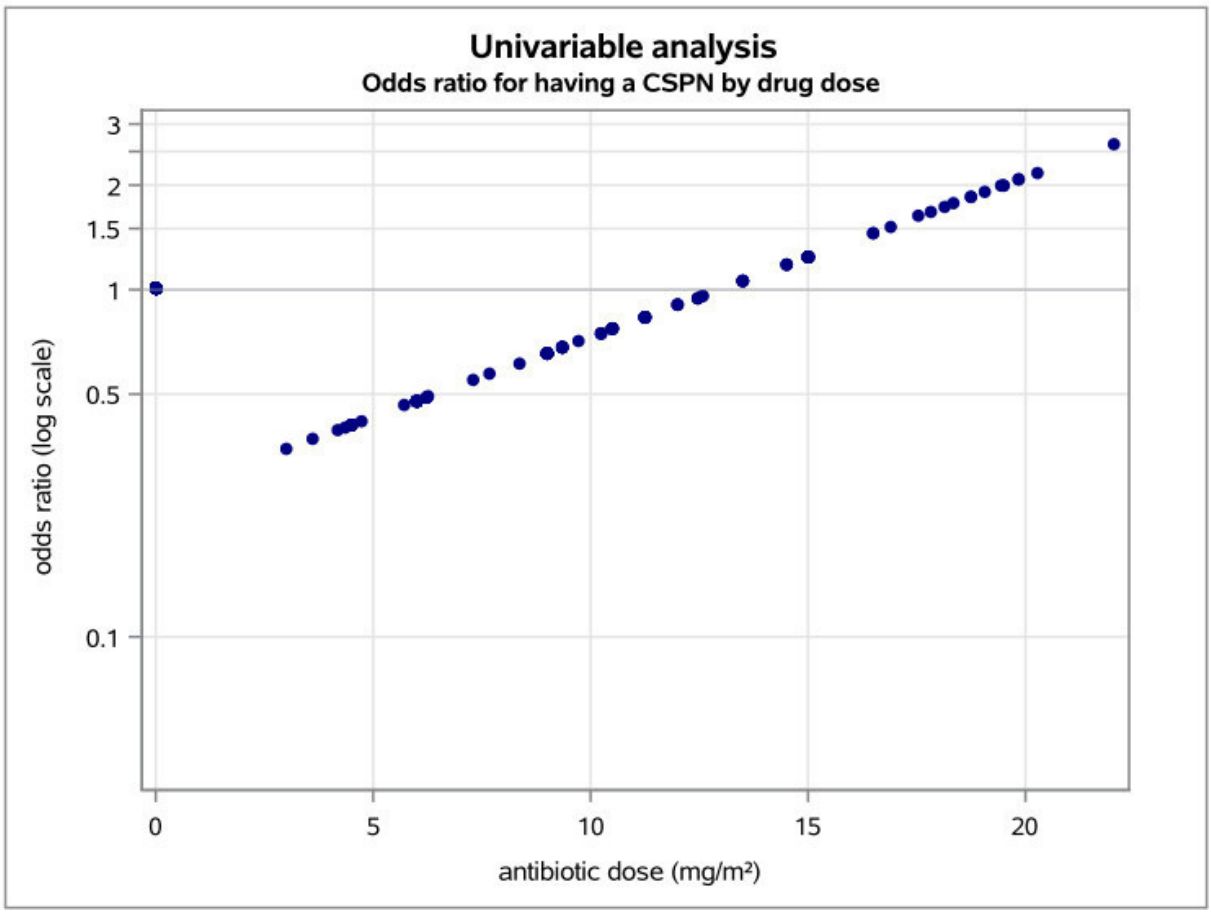


Figure 19. Univariable analysis: Odds ratio for having a CSPN by antibiotic dose. CSPN = carcinoma or malignant melanoma according to ICCC-3 XI as subsequent primary neoplasm after childhood cancer. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005)

Table 12. Comparison of patients without antibiotic treatment (no dose), with antibiotic treatment of <14 mg/m² cumulative dose (low dose), and with antibiotic treatment of ≥14 mg/m².[1]

	No dose N (%)	Low dose N (%)	High dose N (%)	Total N (%)
hematological malignancy²	796 (90.97)	2 (1.90)	0 (0.0)	798 (79.0)
solid tumors²	79 (9.03)	103 (98.10)	30 (100.0)	212 (21.0)
Total	875 (86.63)	105 (10.40)	30 (2.97)	1010 (100.0)

	No dose N (%)	Low dose N (%)	High dose N (%)	Total N (%)
any radiotherapy	574 (65.6)	81 (42.9)	19 (63.3)	638 (100.00)

[1]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005)

² hematological malignancy: ICCC-3 groups I and II; solid tumors: all other ICCC-3 groups

4.2.2.1.3 Methotrexate

A total of 146 cases and 439 controls received methotrexate, a type of antimetabolite, during FPN treatment with doses between 23.6 and 79,396.2 mg/m² (Appendix I.17.1, Table 26). The association between methotrexate and the odds for a CSPN was best described with methotrexate as binary indicator (spike) for having received methotrexate or not. In univariable analysis, methotrexate was protective (Table 11).

However, it was not selected into the multivariable model because its p-value was >0.1, the AIC (Akaike information criterion) increased upon entry during the selection process, and the OR was nonsignificant (0.86 (90% CI: 0.65-1.14) compared to 0.71 (90% CI: 0.55-0.93) in univariable analysis). The increased AIC indicated a worse model fit than without methotrexate. Some of the variance in CSPN risk, which was explained by methotrexate in univariable analysis, was explained by cyclophosphamide and epipodophyllotoxin already in the multivariable model. This explains why methotrexate was not significant anymore, though the direction of effect remained.

As Table 13 shows, methotrexate was frequently applied together with cyclophosphamide but not with epipodophyllotoxin; therapy protocols frequently stipulate the joint treatment with methotrexate and cyclophosphamide.

Table 13. Number of patients with patterns of methotrexate (yes/no) and cyclophosphamide (yes/no) treatment and methotrexate (yes/no) and epipodophyllotoxin (yes/no) treatment.[1]

other substance	**patients (n = 1010) receiving …**			
	methotrexate, other substance N (%)	**no methotrexate, no other substance N (%)**	**methotrexate, no other substance N (%)**	**no methotrexate, other substance N (%)**
cyclophos-phamide	534 (52.87)	232 (22.97)	51 (5.05)	193 (19.11)
epipodo-phyllotoxin	174 (17.23)	313 (30.99)	411 (40.69)	112 (11.09)

[1]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005)

4.2.2.1.4 Epipodophyllotoxins

A total of 82 cases and 204 controls received epipodophyllotoxins during FPN treatment with Etoposide equivalent doses between 165 and 6300 mg/m² (Appendix I.17.1, Table 26). Only 12 out of 286 patients had received doses of 3000 mg/m² or higher. One hundred and seventeen of these patients received Teniposide; its dose was converted to Etoposide equivalents (Chapter 3.2.3.1).

The association between epipodophyllotoxin dose and the odds for a CSPN was best described by the log-transformed dose and a binary indicator (spike) for having received epipodophyllotoxins or not (Appendix I.18.1, Table 31). The results hardly differed between the models (Table 11, Figure 20, Appendix I.18.1, Figure 31). Compared to nonexposed patients, patients having received a cumulative dose of 3000 mg/m² had a significantly increased CSPN risk (OR 1.87 (90% CI: 1.02-3.43)), and the risk increased with increasing dose. The odds for a CSPN did not significantly differ between patients having received the lowest dose in the dataset of 165 mg/m² compared to nonexposed patients (OR: 0.6. (90% CI: 0.35-1.04), Table 11). Compared

to the lowest dose given, 165 mg/m², doubling the dose significantly increased the CSPN risk (OR: 1.31 (90% CI: 1.04 1.65), data not shown).

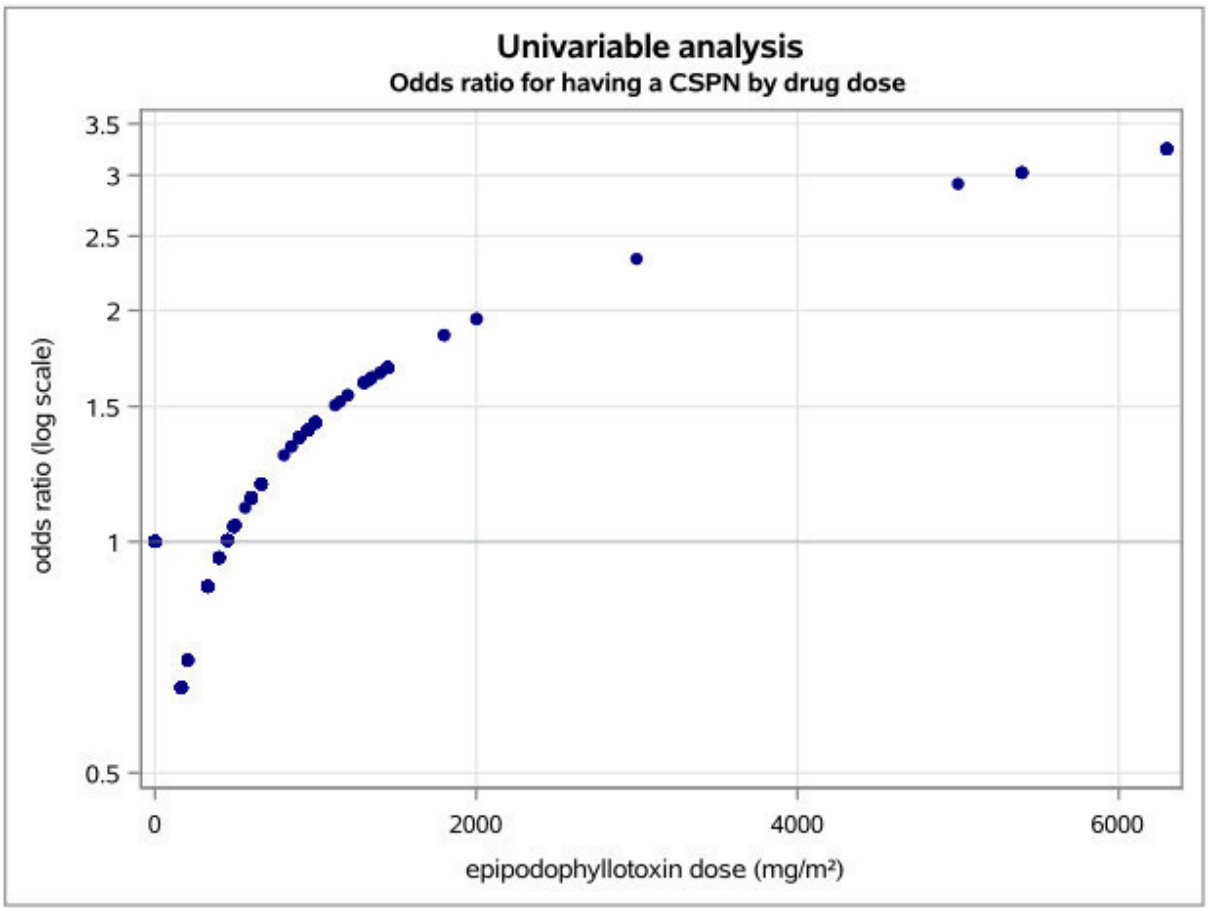


Figure 20. Univariable analysis: Odds ratio for having a CSPN by epipodophyllotoxin dose. CSPN = carcinoma or malignant melanoma according to ICCC-3 XI as subsequent primary neoplasm after childhood cancer. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005)

For the graphical representation, an offset of +1 instead of +0.1 for the cumulative epipodophyllotoxin dose was used (compare SAP, Appendix III, Chapter 4.3) because of issues in data representation. The odds ratios reported in Table 12 were calculated with the usual +0.1 offset; they hardly differed compared to the odds ratios calculated with +1 offset.

There was no association between epipodophyllotoxins as a dichotomous variable (i.e., having received epipodophyllotoxins or not) and CSPN occurrence (OR: 1.14 (90% CI: 0.87-1.49), Appendix I.18.1, Table 32)

I explored whether patients having received doses of 3000 mg/m² or above were different from the other patients. None of these twelve patients had a known SCT, whereas 40 (14.6%) with lower epipodohyllotoxin doses had had a SCT. Eleven

patients had had a radiotherapy (four of these near the site of the SPN), whereas 165 out of 274 patients with lower doses had one (60.2%). Moreover, it was striking that six patients with doses above 3000 mg/m² had bone tumors (ICCC-3 VIII) and four soft tissue sarcomas (ICCC-3 IX), whereas this was the case in none or only one patient, respectively, with lower doses.

4.2.2.1.5 Sensitivity analysis including influential point

There was hardly any difference in the results between main analysis and sensitivity analysis including the influential point except for a substantial change in the association between antibiotic dose and CSPN risk. The association between antibiotic dose and the odds for CSPN was best described by a transformed dose (FP2 with powers 3 and 3) and a binary indicator (spike = z) for having received an antibiotic or not (Appendix I.18.2, Table 33, Table 34)). The shape of the dose-response-curve is depicted in Appendix I.18.2, Figure 32, (univariable analysis) and Appendix I.18.2, Figure 33, (multivariable analysis): Low doses were protective compared to nonexposed patients (OR for 6 mg/m² vs. nonexposure: 0.30 (90% CI: 0.14-0.63)). Higher doses of 15 mg/m² increased the risk vs. nonexposure (OR: 2.17 (90% CI: 1.12-4.19), whereas the highest doses seemed to decrease the risk again (OR for 27 mg/m² vs. nonexposure: <0.001 (90% CI: <0.001-0.95)). The decrease is, however, based on the data of one single control (out of 136), the influential point (Appendix I.8).

4.2.2.2 Subgroup analyses

4.2.2.2.1 Excluding patients with relapses during latency period

Similar to the results of the main analysis, the association between methotrexate dose and the odds for a CSPN was best described by a binary indicator (spike only) for having received methotrexate or not (Table 14, Appendix I.18.3, Table 35). Methotrexate was protective, but the protective effect was not significant anymore in a model including cyclophosphamide (univariable OR: 0.69 (90% CI: 0.51-0.94); OR for model with cyclophosphamide and methotrexate: 0.87 (90% CI: 0.62-1.23)).

Unlike in the main analysis, the association between cyclophosphamide dose and CSPN odds was best described by a binary indicator (having cyclophosphamide or not) instead of the substance dose. The application of cyclophosphamide was protective; this was also true for the main analysis, but in the main analysis, the

protective effect increased with increasing dose. The association hardly changed in the multivariable model.

Unlike in the main analysis, antimetabolites were significant in univariable analysis (Figure 17); treatment with antimetabolites was protective compared to nonexposure (Table 14).

Some of the variance in CSPN risk, which was explained by antimetabolites and methotrexate in univariable analysis, was explained by cyclophosphamide already in the model. Therefore, methotrexate and antimetabolites did not significantly change CSPN risk when the cyclophosphamide effect was already accounted for.

Table 14. Subgroup excluding patients with relapse during latency period of index case: Association between CSPN[1] occurrence and exposure to substances or substance groups for treatment of an FPN in childhood (n = 748, 212 match groups). [2] The OR[1] for exposure against nonexposure are presented. Only substance (groups) were assessed which were significant at the 10% significance level in univariable analysis. [3] None of the substance (groups) were selected as continuous variables.

Substance (group)	Number of patients having received the substance	Exposure	univariable models: OR (90% CI)[1]	multivariable model without covariates[4]: OR (90% CI)[1]	multivariable with covariates[4]: OR (90% CI)[1]
cyclophosphamide	546	yes vs. no[5]	0.57 (0.42-0.77)	0.57 (0.42-0.77)	0.51 (0.37-0.69)
antimetabolites	471	yes vs. no[5]	0.68 (0.50-0.91)	- [6]	- [6]
methotrexate	428	yes vs. no[5]	0.69 (0.51-0.94)	- [6]	- [6]

[1]CSPN = carcinoma or malignant melanoma according to ICCC-3 group XI as subsequent primary neoplasm after childhood cancer, ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005), FPN = first primary neoplasm OR = odds ratio, 90% CI = 90% confidence interval;

[2]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months; only patients in complete match groups, i.e. case and at least one control

[3] only substance (groups) are reported which were significant at an alpha-level of 0.1 in univariable explorative logistic regression analyses with fractional polynomials (FP) with spike at zero (out of the nine substance groups alkylating agents, anthracyclines, antibiotics, antimetabolites, enzymes (Asparaginase), epipodophyllotoxins, platinum derivates, vinca alkaloids, corticosteroids, the five single substances cyclophosphamide, cytarabine, doxorubicin, methotrexate, vincristine, and their complementary substance groups alkylating agents without cyclophosphamide, anthracycline excluding doxorubicin, antimetabolites excluding cytarabine, antimetabolites excluding methotrexate, antimetabolites excluding cytarabine and methotrexate, vinca alkaloids excluding vincristine), the variable “other” was binary and not subject to the FP procedure; it was not significant at an alpha-level of 0.1 in univariable logistic regression; see Appendix I.18.3, Table 35, for model details

[4] stem cell transplantation, radiotherapy

[5] the best model selected in univariable explorative analysis was a spike model, i.e., the substance as binary variable

[6] methotrexate and antimetabolites were not selected because upon entry into the model their p-value was >0.1 and the AIC increased, respectively

4.2.2.2.2 Excluding patients with stem cell transplantation

Similar to the results of the main analysis, the odds for a CSPN decreased with increasing cyclophosphamide dose and increased with increasing antibiotic dose (Table 15, Appendix I.18.4, Table 36, Figure 34-Figure 37). Moreover, having received methotrexate was protective in univariable analysis and having received high doses of epipodophyllotoxins was a risk factor in univariable analysis.

Unlike in the main analysis, the substance groups antimetabolites, ‘antimetabolites excluding methotrexate’, and ‘antimetabolites excluding cytarabine’ were significantly associated with CSPN occurrence in univariable analysis (Table 15). In addition, epipodophyllotoxins were not selected in the multivariable model, but ‘antimetabolites excluding methotrexate’ were included. Besides, an antibiotic dose of 21 mg/m² was not a significant risk factor in the multivariable subgroup analysis (OR: 1.72 (90% CI: 0.65-4.56)), but it was in the multivariable main analysis (OR: 2.61 (90% CI: 1.04-6.54)).

The substance groups ‘antimetabolites excluding cytarabine’, epipodophyllotoxins, and methotrexate were not significant during the forward selection process and thus not included in the multivariable model. This was because some of the variance in CSPN risk, which was explained by these variables in univariable analysis, respectively, was explained by cyclophosphamide and ‘antimetabolites excluding methotrexate’ already in the multivariable model.

During the selection process, ‘antimetabolites excluding methotrexate’ stayed in multivariable model, but epipodphyllotoxins were excluded. In contrast, in the main analysis, epipodophyllotoxins stayed in the multivariable model. This is due to the selection process and the fact that the first two substances in each model (Figure 17) already explained a lot of the variance.

Table 15. Subgroup excluding patients with stem cell transplantation: Association between CSPN[1] occurrence and the dose (continuous) of substances or substance groups for treatment of an FPN in childhood (n = 875, 240 match groups). [2] The OR[1] for selected doses against nonexposure are presented (see Figure 34-Figure 37 for association across full dose range). Only substance (groups) were assessed which were significant at the 10% significance level in univariable analysis. [3]

Substance (group)	Number of patients having received the substance	Selected doses	univariable models: OR (90% CI)[1]	multivariable model without covariates[4]: OR (90% CI)	multivariable with covariates[4]: OR (90% CI)
cyclophos-phamide	611	0 mg/m²	reference	reference	reference
		1000 mg/m²	0.89 (0.83-0.95)	0.91 (0.85-0.98)	0.91 (0.85-0.98)
		3000 mg/m²	0.69 (0.57-0.85)	0.76 (0.61-0.94)	0.76 (0.61-0.95)
		6000 mg/m²	0.48 (0.32-0.73)	0.57 (0.37-0.88)	0.58 (0.38-0.90)
antimetabolites excluding methotrexate	456	yes vs. no[5]	0.64 (0.49-0.85)	0.61 (0.44-0.85)	0.61 (0.42-0.87)
antimetabolites excluding cytarabine	497	yes vs. no[5]	0.66 (0.50-0.86)	-[6]	-[6]
epipodo-phyllotoxins	222	0 mg/m²	reference	-[6]	-[6]
		165 mg/m²	0.44 (0.25-0.77)		
		330 mg/m²	0.63 (0.43-0.93)		
		1000 mg/m²	1.13 (0.80-1.59)		
		3000 mg/m²	2.01 (1.12-3.61)		
		6300 mg/m²	2.97 (1.33-6.62)		
methotrexate	486	yes vs. no[5]	0.67 (0.51 0.88)	-[6]	-[6]
antimetabolites	527	yes vs. no[5]	0.68 (0.52-0.89)	-[6]	-[6]

antibiotics	125	0 mg/m²	reference	reference	reference
		6 mg/m²	0.51 (0.29-0.89)	0.37 (0.20-0.68)	0.39 (0.21-0.71)
		9 mg/m²	0.70 (0.46-1.06)	0.49 (0.31-0.79)	0.52 (0.32-0.84)
		15 mg/m²	1.32 (0.81-2.15)	0.87 (0.50-1.51)	0.95 (0.53-1.69)
		21 mg/m²	2.50 (1.05-5.95)	1.54 (0.61-3.91)	1.72 (0.65-4.56)

[1]CSPN = carcinoma or malignant melanoma according to ICCC-3 group XI as subsequent primary neoplasm after childhood cancer, ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005), FPN = first primary neoplasm OR = odds ratio, 90% CI = 90% confidence interval;

[2]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months; only patients in complete match groups, i.e. case and at least one control

[3]only substance (groups) are reported which were significant at an alpha-level of 0.1 in univariable explorative logistic regression analyses with fractional polynomials with spike at zero (out of the nine substance groups alkylating agents, anthracyclines, antibiotics, antimetabolites, enzymes (Asparaginase), epipodophyllotoxins, platinum derivates, vinca alkaloids, corticosteroids, the five single substances cyclophosphamide, cytarabine, doxorubicin, methotrexate, vincristine, and their complementary substance groups alkylating agents without cyclophosphamide, anthracycline excluding doxorubicin, antimetabolites excluding cytarabine, antimetabolites excluding methotrexate, antimetabolites excluding cytarabine and methotrexate, vinca alkaloids excluding vincristine), the variable “other” was binary and not subject to the FP procedure; it was not significant at an alpha-level of 0.1 in univariable logistic regression;; see Appendix I.18.4, Table 36, for model details

[4]relapse, radiotherapy

[5] the best model selected in univariable explorative analysis was a spike model, i.e., exposure vs. nonexposure

[6]epipodophyllotoxins and methotrexate were not selected because upon entry into the model their p-value was >0.1 and the AIC increased, respectively; antimetabolites excluding cytarabine and antimetabolites were not entered into the model to avoid multicollinearity and partial redundancy which would occur because antimetabolites excluding methotrexate were already selected into the model

4.2.2.3 Covariates

Three covariates (radiotherapy, relapse during latency period, stem cell transplantation) statistically significantly increased the odds of CSPN occurrence in univariable analysis (Table 16). Therefore, they were all entered into the forward selection process in the final model building process. The effect of the covariates hardly differed between univariable and multivariable models and among main, sensitivity, and subgroup analyses. The only prominent difference was that the effect of SCT was cut in half in the multivariable model of the main and sensitivity analysis compared to the univariable model. As a further sensitivity analysis, having had a relapse was omitted from the multivariable main analysis; as a result, the effect of SCT decreased only slightly ((main analysis: OR: 3.65, 90% CI: 2.17-6.12), data not shown). The risk increased by about 100% for irradiation near the CSPN site and by about 50% for irradiation not near the CSPN site. Having had a relapse or a SCT more than doubled the CSPN risk; in the subgroup without relapse patients, the risk by SCT even increased by about 350%. The type of FPN was not significantly associated with CSPN risk (Table 16).

Table 16. Association between CSPN occurrence and covariates.[1]

	Main analysis		Sensitivity analysis: Including influential point		Subgroup: no relapse patients		Subgroup: no stem cell transplantation patients	
n	1010		1011[2]		748[3]		875[3]	
match groups[4]	272		272		212		240	
covariate	**univariable: OR (90% CI)[5]**	**multivariable: OR (95% CI)**	**univariable: OR (90% CI)**	**multivariable: OR (95% CI)**	**univariable: OR (90% CI)**	**multivariable: OR (95% CI)**	**univariable: OR (90% CI)**	**multivariable: OR (95% CI)**
radiotherapy								
none	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
not near SPN site	1.42 (1.03-1.97)	1.420 (1.01-2.00)	1.42 (1.03-1.97)	1.43 (1.01-2.01)	1.73 (1.18-2.53)	1.711 (1.16-2.53)	1.28 (0.91-1.79)	1.185 (0.82-1.72)
near SPN site	2.27 (1.62-3.18)	2.022 (1.40-2.91)	2.27 (1.62-3.18)	2.02 (1.40-2.92)	2.35 (1.58-3.50)	2.487 (1.64-3.78)	1.91 (1.32-2.76)	2.006 (1.35-2.97)
relapse (yes vs. no)	2.66 (1.92-3.69)	2.207 (1.51-3.22)	2.66 (1.92-3.69)	2.24 (1.53-3.28)	-	-	2.31 (1.57-3.41)	2.514 (1.67-3.78)
stem cell transplantation (yes vs. no)	4.10 (2.53-6.63)	2.276 (1.29-4.01)	4.10 (2.53-6.63)	2.27 (1.28-4.00)	5.54 (2.25-13.63)	4.543 (1.79-11.56)	-	-
ICCC-3 group FPN[1]								
I leukemias	1 (ref.)	-[6]	1 (ref.)	-[6]	1 (ref.)	-[6]	1 (ref.)	-[6]
II lymphomas	1.69 (1.24-2.30)		1.70 (1.24-2.31)		1.92 (1.34-2.74)		1.78 (1.28-2.47)	
III CNS tumors[5]	2.02 (0.82-4.96)		2.03 (0.83-4.97)		2.94 (1.05-8.23)		2.32 (0.86-6.28)	
IV neuroblastoma[5]	0.63 (0.16-2.60)		0.63 (0.15-2.59)		0.80 (0.20-3.26)		0.62 (0.15-2.54)	
V retinoblastoma	1.21 (0.35-4.23)		1.20 (0.34-4.21)		1.08 (0.26-4.58)		1.12 (0.32-3.97)	
VI renal tumors	0.99 (0.52-1.89)		0.94 (0.49-1.79)		1.12 (0.51-2.44)		1.14 (0.58-2.24)	
VII hepatic tumors	3.10 (0.30-32.16)		3.10(0.30-2.13)		3.04 (0.29-31.57)		3.06(0.30-31.67)	
VIII bone tumors[5]	0.64 (0.33-1.26)		0.66 (0.34-1.29)		0.65 (0.28-1.52)		0.69 (0.35-1.36)	
IX soft tissue[5]	1.37 (0.76-2.47)		1.37 (0.76-2.47)		1.31 (0.67-2.58)		1.42 (0.78-2.59)	
X germ cell[5]	1.20 (0.63-2.31)		1.24 (0.65-2.38)		1.11 (0.52-2.39)		1.40 (0.72-2.75)	

other	0.67 (0.46-0.97)			
p-value (X^2-test, α-level 0.1)	0.1672	0.1663	0.1298	0.1470

[1]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005), see Appendix I.18, Table 30 for model details

[2]due to risk set sampling, this corresponded to data from 939 individuals: 17 cases also served as control(s), 40 controls were controls for several cases

[3]for number of cases and controls by covariate, see Table 10 and Appendix I.17.1, Table 24

[4]only patients in complete match groups, i.e. case and at least one control

[5]OR = odds ratio, 90% CI = 90% confidence interval, ICCC-3 groups: III central nervous system (CNS) tumors, IV neuroblastoma and other peripheral nervous cell tumors, VIII malignant bone tumors, IX soft tissue and other extraosseous sarcomas, X germ cell tumors, trophoblastic tumors and neoplasms of gonads

[6]FPN diagnosis was not entered because it was not significant in univariable analysis, and it increased the AIC compared to the null model

5 Discussion

5.1 Scoping review

5.1.1 Summary of evidence and discussion of results

In the scoping review, I identified 14 primary studies which addressed the relationship between the exposure to different doses of chemotherapeutic substances and the risk for having a carcinoma or skin cancer as a SPN in patients who had a first malignancy in childhood, adolescence, or early adulthood.

5.1.1.1 SPN diagnosis specific discussion of results

Concerning **thyroid cancer** risk, the prior treatment with chemotherapeutic substances seems to play a minor role. One study reported a slightly significantly elevated RR for treatment with the lowest dose category of epipodophyllotoxins (RR of 5.00 (1.04-23.99), dose 1-1000 mg/m²) (Neglia et al., 2001). In patients having received no or relatively low radiation doses, treatment with alkylating agents statistically significantly increased the thyroid cancer risk (Veiga et al., 2012a).

While there may be truly no or hardly any dose-response-relationship between the substances investigated and thyroid SPN risk, there are some factors which may have masked an association: In the three studies based on the North American CCSS, an effect might have been attenuated because the CSPN was self-reported (compare Chapter 4.1.4.1). The case-control study by Tucker et al. (1991) matched on FPN histology. This may have resulted in overmatching (Chapter 2.6.2), and an underestimation of dose-response associations, as Kaatsch et al. (2009b) have pointed out. Lastly, the number of cases in the studies by Tucker et al. (1991) and Neglia et al. (2001) were relatively low with 23 and 39 patients respectively; thus, the power of the studies might have been too low to detect a weak association.

Seven studies investigated secondary **breast cancer** risk. For alkylating agents, the evidence is inconclusive with results indicating an increased risk, a decreased risk, or no risk change (in three North American CCSS studies) with increasing dose. For anthracyclines, there is evidence from several studies for a significantly increased BC risk with increasing doses; other chemotherapeutic groups were rarely investigated. The results by Guibout et al. (2005) were little meaningful for a comparison to the other studies because they did not report effect estimates. Moreover, they classified

chemotherapeutic substances in a different way, using moles/m² instead of mg/m² as a unit, and only included a small number of patients with breast cancer.

The studies investigating **colorectal cancer**, **basal cell carcinoma**, or **salivary gland cancer** found little evidence for dose-response relationships with any chemotherapeutic substance group in multivariable analyses (Allodji et al., 2019, Watt et al., 2012a, Boukheris et al., 2013). Only the risk for gastrointestinal cancer was significantly higher with high procarbazine doses compared to nonexposure (Henderson et al., 2012a). Some analyses on chemotherapeutics as dichotomous variables resulted in significant associations between the SPN and Carmustine (an alkylating agent) (Inskip et al., 2009), ifosfamide (Teepen et al., 2017), anthracyclines (Ehrhardt et al., 2019, Henderson et al., 2016, Allodji et al., 2019), alkylating agents in general (Henderson et al., 2016), platinum derivates (Henderson et al., 2012a), or MOPP, respectively (Allodji et al., 2019). This shows that it is worthwhile investigating associations between chemotherapy and carcinomas other than thyroid or breast cancer, which are the focus of most studies on subsequent carcinomas.

5.1.1.2 Role of radiotherapy

There was a risk increase with chemotherapeutic dose in some subgroup analyses of patients having received little or no radiation, which was not seen in the analysis of the entire cohort: Thyroid cancer risk was increased at a high AAS in patients with no or little thyroid irradiation and lower in high radiation dose categories (Veiga et al., 2012a). Breast cancer risk was increased in women with anthracycline doses ≥250 mg/m² and <10 Gy radiation (Ehrhardt et al., 2019). In a study without any chest irradiation, breast cancer risk increased with increasing alkylating agent dose (Henderson et al., 2016). This suggests that the dose-response relationship between some chemotherapeutic substances and CSPN risk might be modified by radiotherapy or other (measured or unmeasured) factors, i.e., some substances may become relevant as risk factors only in patients with no or little irradiation. In an analysis stratified by radiation dose categories, Veiga et al. (2012a) suggested that alkylating agents had a small or no effect on CSPN risk if radiation doses were high. They explain this by the “cell killing effect observed for high radiation doses”.

Similarly, in her clinical practice recommendations, Derman (2018) pointed out that alkylating agents “may have a protective effect against radiation-induced breast cancer”, but since “survivors still have excess breast cancer risk”, surveillance

guidelines of the Children's Oncology Group from 2013 (updated version: (Children`s Oncology Group, 2018)) should not be changed.

However, there is also a counter-example: Breast cancer risk was significantly increased in the presence of ifosfamide, an alkylating agent, but in a subgroup not treated with chest irradiation, there was no effect (Teepen et al., 2017).

5.1.1.3 Genetic predispositions

Five studies included patients who had had a subsequent neoplasm between the FPN and the SPN in question (Inskip et al., 2009, Sigurdson et al., 2005, Veiga et al., 2012a, Allodji et al., 2019, Teepen et al., 2017). Considering that there might be a genetic predisposition to multiple primary cancers (Chapters 2.2.3 and 4.1.4.4), excluding patients with an intermittent neoplasm may be favorable in order to avoid introducing even more unmeasured confounding. If these patients are not excluded, adding the therapy of the intermittent neoplasm to the cumulative dose used for the analysis, like Inskip et al. (2009) did, is advisable. This helps to avoid an overestimation of the therapy effect, which may occur if the doses between CSPN patients and non-CSPN patients are truly more different than what is recorded in the data.

In Ehrhardt et al. (2019), the results on breast cancer risk (by anthracyclines, alkylating agents) did not differ between groups including and excluding women with pathogenic mutations, except for a slight difference in alkylating agents: the HR stayed the same (0.4); however, the protective effect was not significant in the subgroup excluding genetically predisposed women due to a wider confidence interval. This is possibly due to the somewhat decreased power in the subgroup (40 instead of 45 BC patients), making it less likely to detect a difference small in magnitude.

Two studies on breast cancer SPNs conducted subgroup analyses with patients with Li-Fraumeni-syndrome-associated FPN diagnoses (Chapter 2.2.3). Teepen et al. (2017) reported a significantly increased risk with higher doxorubicin doses in survivors with LFS-associated FPN diagnoses but not in survivors excluding LFS-associated FPNs (Chapter 4.1.4.4). They suggested a "gene-anthracycline interaction in the development of breast cancer". Henderson et al. (2016) reported significant dose-response relationships between the substance groups analyzed (alkylating agents, anthracyclines) and breast cancer risk in both the whole cohort and leukemia/sarcoma survivors only. They did not perform analyses excluding leukemia/sarcoma survivors

but reported that including FPN diagnosis as a predictor in their SIR analyses "did not meaningfully change the results."

5.1.2 Strengths and limitations of the studies and articles evaluated

A critical appraisal of the individual sources of evidence is not required according to the PRISMA extension for scoping reviews (Tricco et al., 2018); nevertheless I list strengths and limitations of the studies as the authors described them in their articles and additional strengths and limitations of the studies and the articles according to my evaluation in Appendix I.14. This helped in the interpretation of the results.

Generally, strengths included:

1) The cohort studies included between 1467 and 14,135 patients, which are reasonable sample sizes considering the rarity of childhood cancer. The cohorts were well-defined and had long follow-up times. Some studies had relatively high numbers of CSPNs of up to 199.
2) No active participation was required in three studies, which eliminated self-selection (Guibout et al., 2005, Tucker et al., 1991, Teepen et al., 2017), and four did not rely on self-report of SPNs, two of them cohort studies (Guibout et al., 2005, Tucker et al., 1991, Teepen et al., 2017, Allodji et al., 2019), two of them case-control studies (Guibout et al., 2005, Tucker et al., 1991, Teepen et al., 2017, Allodji et al., 2019), which eliminated potential differential misclassification of the outcome.
3) The treatment information was thoroughly collected, and where applicable radiotherapy, an important confounder, was included in all the analyses.
4) Most studies considered common risk factors for SPNs except genetic predisposition in their analyses.

There are general limitations regarding the cohort, the methods, or the reporting of results:

1) The number of patients with the SPN in question was very low in some studies (n = 16 in Guibout et al. (2005)), which may make it difficult to detect risk differences.
2) The nine studies based on CCSS-US/Canada required active consent for medical record abstraction and SPNs were self-reported. This means that an underreporting is possible if a substance is a risk factor and some patients with

CPSN were thus misclassified as patients without a CSPN; thus, the results might be biased and the true effect of the dose on CSPN risk attenuated.

3) Most studies assumed a latency period of at least five years. In a few instances, this might be too short to capture solid SPNs, especially if they were induced by chemotherapy and not radiotherapy (Blettner and Scholz-Kreisel, 2018, Turcotte et al., 2018, Scholz-Kreisel et al., 2018a). In the case-control study of this thesis, nine CSPN cases had latency periods of less than five years (Table 8).
4) The AAS was cohort-specific and the doses corresponding to the scores were not reported. Therefore, the SPN risk in the studies can only be compared with respect to a tendency from low to high doses but not with respect to specific dose ranges. For most other substance groups and single substances, the dose category boundaries were reported; however, apart from four (Henderson et al., 2016, Teepen et al., 2017, Ehrhardt et al., 2019, Allodji et al., 2019), the boundaries differed among studies, which limits comparability as well. Except for one study which used tertiles (Inskip et al., 2009), the rationale behind choosing the reported category boundaries was not described.
5) The use of dose categories instead of continuous measures for both chemo- and radiotherapy resulted in a loss of information and power and residual confounding was possible.
6) Not all articles explicitly reported their method of summarizing chemotherapy doses within substance groups. In several cases, I had reason to assume that the score method was used (Tucker et al., 1987b). Some articles on the CCSS-US/Canada refer to a design paper for their methods; however, the method is not described in this paper (Robison et al., 2002).
7) Third, only three studies considered genetic predisposition to cancer directly or indirectly, even though this may play a big role in the development of a SPN. With the progress in genetic analyses, future studies will more easily be able to include this factor in their analyses.

5.1.3 Strengths and limitations of scoping review

A strength of this scoping review was that the method was laid out beforehand in a review protocol (Appendix II) which followed the PRISMA extension of Scoping Reviews (Tricco et al., 2018). Thus, a good methodological and reporting quality

should be ensured. The studies included were thoroughly charted (Appendices 0 to 0). Since these charts are so extensive, the evidence was summarized in several ways to ensure giving a good overview: besides a description of the results, summarizing tables and diagrams were presented in Chapter 4.1.4.3.

This scoping review has some limitations. First, I was the only reviewer. Therefore, the selection of articles based on title/abstract screening and full text assessment was subject to the risk of bias. Articles relevant to the research question may not have been selected despite careful screening. In order to reduce the risk of missing relevant articles, I added a forward and backward search of recent relevant reviews (since 2011) which I had found in the database search but which were excluded because they were no original research articles.

Deviations from the review protocol with the rationale are described in Chapter 3.1. In my opinion, the deviations either improved the quality of the review or were necessary to perform the review at all.

I could have avoided some problems with the reporting quality in some articles if I had restricted my literature search to articles published in the previous 10-15 years, when reporting guidelines have become available. For instance, the STROBE statement for the reporting of observational studies in epidemiology was published in 2007 (von Elm et al., 2007). It seemed to me that the reporting quality of earlier articles were not as good as the one of more recent ones; for instance, Tucker et al. 1991 and Guibout et al. 2005 did not report all effect estimates with confidence intervals or p-values or did not report effect estimates at all.

I had found one recent article (Ehrhardt et al., 2019) during general research and not through my search strategy. This may have several reasons. The article was published shortly before my final search with PubMed and after my searches with Embase and Scopus, which is why I focus on why the PubMed search missed the article. I identified two problems: First, the search concept #3 “Second Neoplasms” (Appendix II) was not indexed for this article in PubMed although it dealth with “subsequent breast cancer” (Ehrhardt et al., 2019). In Embase or Scopus, I used proximity operators to search words near one another, so my search term “subsequent cancer” would have found the term “subsequent breast cancer”. However, the artile by Ehrhadrt et al (2019) was published after I had finished my search in Embase and Scopus, to which I had access

for a limited period of time. Second, the article did not contain the Medical Subject Heading (MeSH) term "Dose-Response Relationship, Drug" from concept #4 (Appendix II) although it dealt with this concept. This could be due to human error since MeSH terms are entered by human indexers to describe the content of an article. Furthermore, it takes several weeks to several months between the entry of an article into PubMed and its indexing with MeSH terms (Irwin and Rackham, 2017). Although I also searched for key words related to dose-response relationships, I restricted them to the title and abstract. Without this restriction and the addition of th search term ‘breast cancer’, my search strategy would have found the article by Ehrhardt et al. (2019) at the expense of having more than six times as many results for the PubMed search (1,872 instead of 298, Appendix I.19).

I criticize the indexing of the article by Ehrhardt et al. (2019) in PubMed; in my opinion, the MeSH terms "Neoplasms, Second Primary” and "Dose-Response Relationship, Drug" should be added. I assume that priority was given to the many other different aspects of SPNs in CCS which the article deals wih (compare MeSH terms in Appendix I.19). To avoid this type of shortcoming, I had supplemented my search strategy with a back- and forward search of relevant review articles. Moreover, I had chosen to include all types of SPNs in my search strategy instead of limiting it to CSPNs because I had seen a potential to miss articles which deal with CSPNs in addition to other SPNs. This is why I think that I nevertheless found nearly all relevant articles published on the topic up to the date of inclusion. For future systematic literature searches, I will consider broadening the search of concepts which are similarly difficult to grasp as “Dose-Response Relationship” and, if possible, perform the search of in different literature databases at the same point in time.

5.1.4 Conclusions

Overall, there is limited and inconclusive evidence for dose-response relationships between chemotherapeutic substances and carcinomas as SPNs. Patients treated with high doses of alkylating agents or anthracyclines, especially doxorubicin, might be at higher risk for breast cancer. Those treated with high doses of procarbazine might be at higher risk for gastrointestinal cancer compared to patients not receiving these substances. Malignant melanomas had not been investigated in any of the evaluated studies. Radiotherapy seems to be a more relevant factor for therapy-related second

carcinomas and malignant melanomas than chemotherapy (Berrington De Gonzalez et al., 2013).

The sparse evidence for a dose-response-relationship and the heterogeneity in the dose-categories considered means that it is not appropriate or possible to perform a systematic review or a meta-analysis. The scoping review revealed gaps in knowledge but also made it clear that chemotherapy may be a relevant risk factor and the dosage should not be neglected. The relevance may be greater for the group of patients receiving little or no radiotherapy.

5.2 Case-control study

5.2.1 Summary and discussion of results

The results are reported in the light of statistical significance with confidence intervals and p-values, but the analyses were explorative and not confirmatory. The significance level was an aid for decision-making in the model building process. The analyses were not adjusted for multiple testing.

5.2.1.1 Main analysis

In the main analysis, four out of 20 chemotherapeutic groups or substances were statistically significantly associated with a CSPN occurrence in univariable analysis at an α-level of 0.10. Three of these were selected into the multivariable model during the model building process. The effect estimates hardly differed between the models.

An increasing cyclophosphamide dose decreased the CSPN risk. The most common alkylating agent was cyclophosphamide (85.0%), but the group of alkylating agents in general was not significantly associated with CSPN risk, neither when cyclophosphamide was included nor when it was excluded from the alkylating agents group.

On average, the risk for a CSPN did not significantly differ between patients having received antibiotics and those who did not, but the risk might vary depending on dose: the dose-response analysis showed that low antibiotic doses were protective and high doses increased the risk for CSPNs. Patients with and without antibiotic treatment differed, and those with low cumulative doses differed from those with no treatment or high antibiotic doses. First, in the group with low antibiotic doses, proportionally fewer patients had had radiotherapy treatment compared to patients without antibiotic treatment or with higher doses. Radiotherapy is known to increase the SPN risk;

therefore, the patients with low antibiotic doses and less radiotherapy may have a lower CSPN risk overall. I deem this interpretation valid although the model was adjusted for radiotherapy: since radiotherapy was only considered as variable category, residual confounding is expected. Second, 91.1% of patients without antibiotic treatment had a hematological FPN while 98.5% of patients with antibiotic treatment had a solid FPN, so differences may be attributed to differences in underlying SPN risk (Chapter 2.2.3). Although FPN itself was not a risk factor for CSPNs, I speculate that it might modify the CSPN risk posed by antibiotics. I did not investigate this hypothesis due to power concerns.

Methotrexate and other antimetabolites might have a protective effect with regard to CSPN risk. The application of methotrexate was protective in the univariable models of the case-control study. The direction of the effect did not change in the multivariable models, however, methotrexate was not statistically significant anymore and thus omitted from the final model. Methotrexate and cyclophosphamide seem to explain the same variation in CSPN risk to some extent, so the effects by these substances may be convoluted.

Methotrexate is applied in the maintenance therapies of some TOS to maintain the disease-free status. For instance, maintenance therapy in the COALL-07-03 protocol (Janka-Schaub, 2003) consists of applying a cumulative dose of 2080 mg/m² methotrexate over two years. This might also explain the slight protective effect regarding SPN risk.

Low doses of epipodophyllotoxins up to about 600 mg/m² seemed to decrease the CSPN risk (Figure 20), but the results were not significant. Doses above seemed to increase the risk; those above 3000 mg/m² significantly increased the risk. Doses of 3000 mg/m² or above are often used in conditioning as a preparation for a SCT. However, none of the twelve concerned patients had a known SCT. Eleven of these patients had, however, received radiotherapy, only one had not. Radiotherapy might have confounded the relationship somewhat. High doses of epipodophyllotoxins might generally be associated with a more intense therapy.

5.2.1.2 Covariates

There were hardly any differences in the results of the case-control study between the univariable models, the multivariable models without covariate, and the multivariable

models with covariates. The association between chemotherapeutic substances and the CSPN risk seems rather independent from other factors.

As expected, the CSPN risk was increased in patients having received radiotherapy. The risk doubled when radiotherapy had been administered near the anatomical site of the SPN. A lower but still significant risk increase was observed when sites not close to the SPN site had been irradiated. The latter was not expected because previous studies showed that the effect of radiotherapy on SPN risk is usually confined to the site of radiation (Scholz-Kreisel et al., 2018b, Hennewig et al., 2014). My partitioning of irradiation area into ‘near SPN site’ and ‘not near SPN site’ may have been too crude. Moreover, treatment in earlier calendar year involved bigger irradiation fields and more scatter irradiation. Many leukemia patients were irradiated craniospinally in the early years of this data set and the scattered irradiation may be an explanation for thyroid carcinomas and skin cancers. The SCAR study of the joint study STATT-SCAR will investigate irradiated organ doses, which will shed light on the question how much influence the proximity of irradiation to the SPN site has on SPN risk.

Being a relapse or stem cell transplantation patient significantly increased the CSPN risk by a magnitude of two in almost all multivariable models. Different aspects of being a relapse or SCT patient may lead to the risk increase: High-dose chemo- and radiotherapy treatment, which were not included in the doses used for the analysis (compare Chapter 2.5.3), as well as genetic predispositions or other unknown factors may play a role (Chapter 2.2.3).

The fourfold risk increase by SCT in the univariable analysis was cut in half to a twofold risk in the multivariable models including chemotherapy substances and other covariates (Table 11). In the subgroup analysis without relapse patients, the decrease was much smaller. A lot of the variation in CSPN risk, which was explained by having had a SCT, was already explained by having had a relapse, which became apparent when having had a relapse was omitted from the final model (Chapter 4.2.2). After all, two thirds of SCT patients had also had a relapse (Table 10). Taking into account the effect of all variables in the final model, having had a SCT and having had a relapse each doubled the CSPN risk.

5.2.1.3 Subgroup and sensitivity analyses

The two subgroup analyses excluded patients with known relapses and known stem cell transplantation, respectively, and the sensitivity analysis included a control with a high antibiotic dose value, which strongly influenced the dose-response relationship. Patients in the main analysis received higher chemotherapy doses than reported. This is because relapse and stem cell transplantation patients were included, but the treatment those patients usually receive was not acquired. Thus, the reported substance doses in the main analysis were likely underestimated. Patients with a CSPN had relapses and SCTs more frequently than controls (Table 10), leading to a differential underestimation. On the other hand, the doses may be approximately correct in the subgroup analyses. Thus, even if the same dose was reported in the main and subgroup analyses, the true dose may be different in reality between main and subgroup analyses.

This may be a partial explanation why – different from the main analysis – antibiotics and epipodophyllotoxins were not selected into the model in the sensitivity analysis excluding relapse patients: The *reported* doses possibly did not influence the risk. Moreover, the lower sample size implies a lower statistical power to detect an effect. The application of cyclophosphamide was protective in both the main analysis and the analysis excluding relapse patients. However, different from the main analysis, the protective effect did not increase with increasing dose in the subgroup analysis. The reduced power in the smaller dataset may not have been sufficient to show such a dose-response relationship.

In the subgroup analysis excluding stem cell transplantation, the CSPN risk increase at 1000 mg/m² epipodophyllotoxin and 15 mg/m² antibiotic was not significant in contrast to the main analysis. The reason might be that the power in the reduced dataset was not big enough to detect a statistically significant effect.

Similar to the main analysis, methotrexate and other antimetabolites, no matter if methotrexate or cytarabine was excluded or not, were all protective in univariate analysis in both subgroup analyses. They also seemed protective in the forward selection process of the multivariable model building, but only one was statistically significant and stayed in the final multivariable model (‘antimetabolites excluding methotrexate’ stayed in the model of the subgroup analysis excluding patients with

SCT). Antimetabolites and cyclophosphamide seem to explain the same variation in CSPN risk to some extent, so the effects by these substances may be convoluted.

A striking difference between the sensitivity analysis including the data of all patients and the main analysis excluding the data of one patient was seen in the dose-response relationship between antibiotics and CSPN risk. The risk increase in the sensitivity analysis was due to one influential point, the largest antibiotic dose. All other results were almost identical, which was expected.

5.2.2 Discussion of methods

5.2.2.1 Study design

Information on the outcome CSPN was easily accessible for this study. If therapy exposure information had also been readily available for the base population at the GCCR, a cohort study would have been the ideal approach (Kaatsch et al., 2009b). However, retrospectively acquiring therapy exposure information is costly and time-consuming and was thus not feasible for 54,420 patients. Therefore, carrying out a nested case-control study, in which only therapy information for the cases and up to four controls was collected, was more efficient.

One to four controls were matched to one case; the matching of at least two controls had been the aim. In the choice of the number of matched controls, two aspects had been considered: First, limited time, personnel, and funding resources constrained the number of controls. Second, the higher the number of controls and thus the entire sample, the less random error occurs in the analyses and the higher the power of the study. The reduction of the random error and the power do not, however, increase linearly with the number of controls; the gain in power becomes smaller with an increasing number of controls. Therefore, matching to three to four controls is commonly recommended (Kreienbrock et al., 2012). This was achieved in 59% of match groups of the case-control study (Table 7); only ten percent of match groups included only one control.

Matching was used to control for potential confounding factors. FPN diagnosis was not a matching factor to avoid overmatching (Chapter 2.6.2). Risk set sampling (Chapter 2.6.2) inherently involved matching on time of survival; this allowed adequately dealing with competing risks (SPN occurrence and death) (Kaatsch et al., 2009b). Risk set

sampling is deemed the most attractive type of sampling because it includes person-time in the analysis rather than person count data.

I had chosen to investigate the therapy-related risk for a specific SPN group instead of a particular FPN group. Both approaches, called SPN and FPN approach hereafter, are valid and come with advantages and disadvantages. From a clinical point of view, the SPN approach has the advantage that based on the risk assessment, physicians can select screening tools specific to this type of SPN, if available. As Maeda (2008) put it:

> It is important to recognize that it may not be best to categorize surviving patients by primary diagnosis. Instead, strategies for surveillance of survivors should be based on the treatment each patient received.

To make best use of this approach, confirmatory analyses on specific, common CSPNs, like thyroid, breast, or skin cancer, should be carried out in future studies. The results of this case-controls study and the literature review generated hypotheses to be investigated. On the other hand, the risk for a SPN may differ among FPN types (Chapter 2.2.3). This may favor the FPN approach, which compares the risk between patients with the same baseline risk based on FPN. For the patients in this case-control study, however, the baseline risk may have been similar because first, the majority of patients had leukemia or lymphomas as FPN, and second, FPN type was not significantly associated with CSPN risk (Chapter 4.2.2). Therefore, the SPN approach seems sensible. The assumption of a similar baseline risk may not be generalized to all CCS with regard to CSPN because the patients included in the analyses were subject to selection and might differ from other CCS cohorts (Chapter 5.2.3).

From a clinical point of view, the FPN approach has the advantage that physicians can focus on a defined group of patients for their risk assessment of a specific therapeutic regimen. However, this approach may have a methodological disadvantage, pointed out by Kaatsch et al. (2009b). The baseline risk for SPNs may differ both between FPN types and between risk groups within one particular FPN type. As the therapies used to treat specific FPN types and risk groups tend to be similar, “the dose range is thus often small so that therapy-related changes in risk cannot be determined.”

5.2.2.2 Statistical analyses

In contrast to most other studies, this study treated chemotherapeutic doses as continuous variables for characterizing the dose-response-relationship between substance dose and CSPN risk instead of categorizing them and testing for a trend. Thus, information loss and residual confounding were minimized. The fractional polynomial approach allowed fitting flexible shapes of dose response curves, which was useful for describing the associations with the substances epipodophyllotoxins and antibiotics in this thesis. Since a proportion of patients had zero exposure, the fractional polynomial approach was extended to allow a spike-variable (yes/no) to be included in the function that describes the dose-response-relationship. This proved useful and revealed, for instance, that patients with exposure to antibiotics in the low-dose range had a lower CSPN risk than nonexposed patients. This approach adjusts for confounding by factors, by which zero-exposed patients differ from exposed patients without having to know these factors in detail.

The alpha level was set to 0.1 instead of the most common 0.05 due to the explorative nature of the analyses. Thus I allowed for the generation of more hypothesis at the expense that a higher percentage of the statistically significant associations were possibly false, compared to a lower alpha level.

The number of exposure and covariate variables was high, whereas the sample size was not high; therefore, to avoid problems with statistical power, a two-step process was used to arrive at a multivariable model. First, the functional form of each continuous variable was determined in univariable analysis; next, only the variables significant in the univariable analysis were entered into a forward selection process. This process selected a parsimonious model. Data problems, which may have occurred in a backward elimination process due to a too complex model or high correlation of variables, were avoided with the forward selection process.

The subgroup analyses had smaller sample sizes than the main analysis. With smaller sample sizes, simpler models are more likely chosen during the model building process. This may explain why the multivariable analysis on the subset excluding relapse patients contained only one substance group, for which, moreover, a binary variable was selected as best functional form.

5.2.2.3 Summing substances and using equivalence ratios

An effort was made to find a balance between analyzing all single chemotherapeutic substances separately and analyzing only groups of substances: all groups were evaluated, and in addition, single substances which at least 500 patients had received and the complementary substances within that substance group were included.

Not all single substances were analyzed because for some substances the number of treated patients would have been very low, resulting in too little power for the analysis.

Nevertheless, the effect of frequently given single substances was also investigated because, although chemotherapeutic substances may be in the same substance group, they do not necessarily have the same carcinogenic potency. Equivalence ratios were applied to take this fact into account, but it is not clear if the substances can be truly equated. Nevertheless, I deem this approach more appropriate than alternative ones. Though defining a score such as the AAS is a valid approach in my opinion, it categorizes the exposure and requires more degrees of freedom. In this project, however, the doses were sought to be treated as continuous variables. I do not consider summing the substance doses in mg/m² without any conversion appropriate because it is common practice in childhood oncology treatment to substitute substances using a conversion factor due to different potencies of effect (Children`s Oncology Group, 2018).

5.2.3 Bias

The FPN distributions differed between the patient data included here and patient data from match groups with CSPNs from the entire STATT-SCAR population (Chapter 4.2.1.4). There may be a selection bias (Chapter 2.6.4.2), if the type of FPN modifies the dose-response relationship between chemotherapy dose and CSPN risk. Differences in FPN distributions were firstly due to the fact that the acquisition of therapy data was diagnosis-specific, and the data of the majority of brain tumor patients was missing by the end of data inclusion for this thesis. Second, the data for almost all leukemia and lymphoma patients was ITT data, whereas for other tumor entities, a portion of data was of a different type which was not included in the analyses of this thesis (Chapter 3.2.2). Moreover, the FPN distribution in this case-control study does not reflect the distribution in the GCCR registry population because survival and SPN occurrence are associated with FPN type (Chapters 2.2.3 and 4.2.1.4). Therefore, it is

unclear whether conclusions can be drawn for childhood cancer patients of the types of malignancies underrepresented in the data, especially patients with solid FPNs.

Only 7.2% of data analyzed was from patients treated for a FPN between 2000 and 2014; in the group whose data could not be analyzed, 35.9% of patients were diagnosed in 2000 or later. Therefore, the results of these analyses might not be generalizable to treatment in more recent years (Chapter 4.2.1.3).

Only ITT data was available; the true treatment (AT) was not known. Patients may have received different substances or different doses than recorded. To test whether the misclassification is differential or non-differential, one would need to find out whether the differences between the ITT data and the AT data are different or the same for cases and controls. This issue could not be addressed in this thesis as there was no AT data available yet. From my conversations with employees from different TOS groups, I assume that the true dose in patients from some TOS was on average lower than the ITT dose, especially in the 1980ies, which may have two consequences. If the effect was stronger with higher substance doses, it is possible that an effect of the substances at the doses reported was not detected. If the true dose was higher in cases than in controls, the misclassification would be non-differential, and the dose-effect might be overestimated.

Only data for the treatment of the FPN was available. To fully investigate associations between chemotherapy and CSPN risk, one ideally includes all therapy a patient received between diagnosis of the FPN until before onset of the SPN in the case or for the corresponding time span in the matched control. This includes data on therapies which is systematically missing for the present analyses, namely data of relapse therapy, and chemotherapy related to stem cell transplantation. Thus, the true exposure to chemotherapy may be underestimated; patients who had a relapse or a SCT received more therapy (higher substance doses and more substances) than is reported by the ITT data for this thesis. Since proportionally more cases than controls had a relapse or a SCT (Chapter 4.2.1.5), there will be a differential misclassification bias, i.e., these patients really received higher doses than reported, but the CSPN is associated with reported lower doses. Thus, the effect may be overestimated. I included a binary variable for relapse treatment and SCT to address this bias in a crude way, which leaves, however, room for residual confounding. Therefore, I additionally

performed subgroup analyses on groups excluding relapse patients or excluding SCT patients.

5.2.4 Strengths

The case-control study design with four controls is a good compromise between efficiency with respect to time, personnel, and costs, and statistical power. Moreover, matching eliminated the effect of some potential confounders (Chapter 5.2.2.1). The statistical methods allowed to model dose-response relationships with a great variety of possible forms and was not restricted to a categorical or linear (i.e. untransformed) modeling. Nevertheless, a parsimonious multivariable model was preferred. Modeling the continuous dose also helped to avoid residual confounding (Chapter 5.2.2.2). Summarizing substances into groups allowed to analyze the effect of all applied substances, including rare ones, instead of restricting the analysis to common substances with enough power (Chapter 5.2.2.3).

Furthermore, the data is based on a well-defined, population-based, nationwide cohort of childhood cancer patients who have been registered with a high completeness of about 95% (Steliarova-Foucher et al., 2006). Data from 35 years of registration was included, which is a good basis for the study of SPNs because the number of subsequent neoplasms increases as the population gets older.

Since SPNs are registered at the GCCR with a high completeness, I assume that there is hardly any information bias (Chapter 2.6.4.1) for the outcome CSPN.

The case-control study included a relatively large number of cases, including quite recent ones. This was enabled by several factors: the number of patients registered at the GCCR, the inclusion of FPNs and CSPNs occurring as recently as 2014, and a short minimum latency time of six months. Thus, nine patients with a latency between one and four years were included whom similar studies would have excluded. These CSPNs may or may not be therapy-induced. If they were not therapy-induced, genetics most likely played a role in their development because these tumors usually do not occur at the reported ages between six and 16 years (data not shown).

In addition to therapy information of the FPN, information on which patient had had a SCT could be retrieved through a linkage to the pediatric registry on stem cell transplantation and the ALL-REZ study center for 2/3 or more of the patients.

The subgroup analyses addressed some of the possible information biases of the exposure reported in Chapter 5.2.3.

5.2.5 Limitations

A criticism of the MFP approach with continuous dose data is that it assumes a precision which may not be there, given all the uncertainties in the dose measurements. In this context, I would like to emphasize that the nature of my analyses was explorative, aiming at developing hypotheses that need testing in future studies.

Applying equivalence ratios to convert doses of chemotherapeutic substances within one substance group (Chapter 5.2.2.3) is based on the assumption that the toxicities, on which the ratios are based, correlate with the potency of causing cancer. Although this assumption is frequently made in studies on SPNs, it might be too strong. To address this limitation, frequent single substances were analyzed in addition to substance groups.

Information on genetic predisposition is not systematically collected at the GCCR and could not be taken into account. If some of the CSPNs were primarily induced by genetic predispositions, the effect of substances as risk factors may have been overestimated. It is also possible that patients' genetic patterns modify the dose-response-relationships observed: due to genetic variations in enzymes metabolizing chemotherapeutic substances, the substances may have different effects, e.g. they may act more toxic or they may be inefficient (Mutschler, 2012). Epidemiological studies with large numbers of patients, whose genetic profile are well characterized, might shed light on such pharmacogenetic modifications.

Factors possibly influencing the effect of chemotherapeutic substances, such as interaction between substances, timing of administration, type of administration (intravenous, intrathecal etc.) (Gadner et al., 2006). In addition, the timing of administration and the type of administration (except for two substances with explicit intrathecal administration) were not available. Administration of most chemotherapeutics in the acute treatment phase (before maintenance) is intravenously. The mode of application of alkylating agents (oral versus intravenous) did not play a role in a study on gastrointestinal SPNs in CCS (Henderson et al., 2012a). The timing of administration, however, might play a role in SPN development: Le Deley et al. (2003) point out that excess leukemia risk among CCS with high

cumulative epipodophyllotoxin doses differed between patients who received the treatment once or twice a week compared to every other week. It is also questionable if the sample size would have been sufficient for such an analysis. Interactions between substances may, for example increase the toxicity or reduce the efficacy of a substance during the treatment, which might influence the carcinogenic potency as well. Though it is possible that the dose-response relationship differs between, e.g., males and females, effect modifiers have rarely been investigated. A study looking at factors potentially modifying the effect of radiotherapy on thyroid cancer in CCS did not find statistically significant modifications (Ronckers et al., 2006). The investigation of effect modification was beyond the scope of this thesis.

Stratifications of the analyses by FPN and CSPN were not carried out due to relatively small sample sizes. Lifestyle factors influencing cancer risk, such as smoking, nutrition, sunlight exposure, and the level of physical activity were not available and could not be included in the analysis. Those are typical risk factors for cancer in the general population. I assume that these factors play a minor role in the development of CSPNs for the group analyzed because the risk increases in the general population in part due to these factors are usually seen at a much later age: The median age at cancer diagnosis for the general population was 69-70 years in 2016 (Krebs in Deutschland 2015/2016. 12. Ausgabe, 2019), whereas the median age at CSPN for patients included in this case-control study was 26 years.Joint discussion of results from case-control study and scoping review

5.3 Joint discussion of results from case-control study and scoping review

The results of the case-control study are integrated into the results of the scoping review. This integrated view may suggest directions for future research and suggests that dose-response-relationships between chemotherapy dose and CSPN risk might want to be considered in future survivor care. Due to the explorative nature of my analyses and the heterogeneity in study design, outcome, and results of the studies reviewed, the results cannot provide recommendations for specific action.

5.3.1 Comparability of results from case-control study and scoping review

I regard the patient groups from the case-control study and those from the scoping review comparable with respect to time after FPN. The studies included in the literature were comprised of patients who had survived for at least two years, with the majority

including five-year-survivors. In contrast, the case-control study of this thesis included patients who had survived for at least six months. If the case-control study had excluded CSPNs occurring in the first five years after FPN diagnosis, data of only nine patients (3.3%) would not have been analyzed (Table 8). In contrast, for hematological SPNs, which occur sooner, comparisons would not have been possible.

The latency periods are roughly comparable. The studies from the reviews had median latencies between 12.6 and 30.0 years (Appendix I.10); the case-control study had a median latency of 18 years (Table 8). This goes along with similar time ranges of around 35 years which the studies covered: Most studies from the review included FPNs from patients as early as 1970, some even earlier, which is ten years earlier than what the case-control study covered (starting in 1980). Most studies from the review included SPNs occurring until the early 2000s; the case-control study stopped inclusion in 2014.

The case-control study covered a more recent FPN treatment era than the studies evaluated in the review: The case-control study covered the calendar years 1980 to 2014 whereas most studies from the review covered the 1970s to 2000s. Moreover, the CCSS-US/Canada, which makes up the majority of studies, only included FPNs diagnosed up to 1986; in the case-control study, median year of FPN diagnosis was 1988 (Chapter 4.2.1.3). Treatment has become less aggressive over the years in an effort to reduce side effects and late effects such as SPNs ((Rossig et al., 2013) and personal communication with physicians and documentalists from therapy optimization study groups).

I presented ORs for specific doses in the case-control study (e.g. 6000 mg/m²), whereas the estimates in the review were for entire dose ranges (e.g. 6000-17,999 mg/m²). Thus, only a tendency in the increase or decrease of CSPN risk could be compared. The dose ranges investigated were similar: In the studies from the review, epipodophyllotoxin dose categories of 1-1000, 1001-4000, and 4001 mg/m² or higher were investigated (Appendix I.16); in the case-control study, the range of the cumulative epipodophyllotoxin dose was 165-6300 mg/m². The dose range for cyclophosphamide was similar as well: one study investigated cumulative, intravenously administered cyclophosphamide up to 39,999 mg/m² (Watt et al., 2012a); the dose range in the case-control study was 75-23,900 mg/m². Dose categories for

alkylating agents in the review fall in the same range with >0-5999, 6000-17,999, and 18,000 mg/m² or more (Appendix I.16).

The level of confidence in the results of the studies included in the review (5%-significance level) is higher than that used for reporting the results of the case-control study (10% significance level, explorative analyses). This also means, that associations would have been reported for the case-control study, albeit with less confidence, which the studies from the review would not have detected, given all other parameters being equal. On the other hand, the number of patients with a CSPN was higher in the case-control study than in the studies from the review, which indicates a higher precision of the estimates and a greater power.

The FPN distribution differed. The case-control study included primarily hematological FPNs, whereas the studies included in the review potentially covered a variety of FPN entities (Chapter 4.1.4.1). This may have two consequences. First, the CSPN patterns may differ because the type of SPN may be linked to FPN type (Chapter 2.2.3). Second, patients in the case-control study received more chemotherapy treatment because FPNs with less chemotherapy treatment (such as CNS tumors) were underrepresented. In my opinion, rough comparisons between the results of the articles reviewed and the results of the case-control study can be made nevertheless. In the case-control study, there was no association between FPN and the risk for an SPN, leaving the focus on the FPN treatment.

The proportion of patients having received chemotherapy was higher in the case-control study (97.6%) than in the studies included in the review (Appendix I.12). First, this may be due to differences in treatment protocols between countries. Second, the FPN distribution most likely plays a role, see above. Third, this might reflect the shift towards more chemotherapeutic treatment while reducing radiotherapy in more recent years (Kenney et al., 2004, Olsen et al., 2009, Teepen et al., 2017). This does not hamper comparability in my opinion since there was always a number of patients in the case-control study who had not received the chemotherapeutic group in question.

5.3.2 Evidence by substance (groups)

5.3.2.1 Cyclophosphamide and other alkylating agents

Overall, there seems to be a protective effect of cyclophosphamides with regard to the development of CSPNs. In the case-control study, an increasing cyclophosphamide

dose decreased the CSPN risk. This is in line with the case-control study by Watt et al. (2012a). They found that the OR for basal cell carcinomas decreased with increasing dose categories up to <20,000 mg/m², albeit the associations were statistically not significant. Beyond <20,000 mg/m², the OR increased again, though not significantly, possibly due to the small number of cases and controls of 13. In the case-control study of this thesis, only one patient had received doses above 20,000 mg/m² which is why these high dose ranges cannot be compared. Just as in my analysis, Inskip et al. (2009) reported no significant relationship between cyclophosphamide as a binary variable and a CSPN (breast cancer in Inskip et al. (2009)).

The Children's Oncology Group follow-up guidelines list cyclophosphamides as potential risk factor for bladder malignancies (Children`s Oncology Group, 2018). However, I do not deem this association relevant for the current analysis as only one patient had a bladder carcinoma in the case-control study.

The association between alkylating agents as a group and CSPN risk is unclear. There was no significant association in the case-control study. In the review, both decreasing (Boukheris et al., 2013, Neglia et al., 2001, Teepen et al., 2017, Watt et al., 2012a, Ehrhardt et al., 2019) and increasing (Veiga et al., 2012a, Henderson et al., 2016) risks with increasing doses were observed, even if not all were significant. The direction of the effect seemed to be modified by radiotherapy (Chapter 5.1.1.2), with a risk increase in patients having received no or little irradiation. This observation is supported by a recent study on the dose-response relationship between cyclophosphamide and any SPN in CCS with chemo- but without radiotherapy treatment: The risk was significantly elevated at doses >10,000 mg/m² (Turcotte et al., 2019).

Alkylating agents might indirectly have a protective effect on subsequent breast cancer. Female CCS exposed to chemotherapy are at risk of premature menopause (Overbeek et al., 2017). The resulting reduction in the exposure to ovarian hormones may decrease breast SPN risk (Turcotte et al., 2018). However, in the data from the case-control study, there was no evidence that more cases with breast SPN than their matched controls had a treatment with cyclophosphamide or methotrexate, substances both acting protective on CSPN risk overall (Chapter 4.2.1.6). A separate analysis on breast cancer had not been performed due to small numbers of cases.

Further studies are needed to evaluate the effect of cyclophosphamide and alkylating agents on CSPN risk.

5.3.2.2 Antibiotics

None of the studies from the scoping review investigated the dose-response-relationship between antibiotics and CSPN risk. Five studies, however, analyzed risk differences in patients having received an antibiotic compared to patients not having received one (Appendix I.13). None of them found significant risk differences between the groups, neither for bleomycin (Inskip et al., 2009, Veiga et al., 2012a), nor for actinomycin D (Inskip et al., 2009, Tucker et al., 1991) or plant alkaloids, which is a group that includes both antibiotics and anthracyclines (Ehrhardt et al., 2019, Henderson et al., 2012a). Likewise, there was no significant association between antibiotic treatment versus no treatment (binary variable) and CSPN risk in the case control study. The association became significant upon the investigation of the dose-response relationship: antibiotics were protective or a risk factor depending on the dose. These opposite effects may have canceled each other out when only treatment versus non-treatment is taken into account. It is desirable that further studies investigate the hypothesis that there may be a dose-response relationship even though no association shows for antibiotics as binary variable.

5.3.2.3 Methotrexate and antimetabolites

Two studies from the review analyzed antimetabolites as dichotomous variables; one found that they were protective (Ehrhardt et al., 2019), one did not find significant differences (Henderson et al., 2012a) (Appendix I.13). This is similar to the results of the case-control study, where methotrexate and 'antimetabolites without methotrexate' were statistically significant as binary variables and showed protective effects in univariable analysis only. The dose-response relationship of antimetabolites as a group was not investigated by the studies included in the review.

5.3.2.4 Epipodophyllotoxins

The association between epipodophyllotoxin dose and CSPN risk is unclear; the existing evidence for a risk-increasing effect should not be overinterpreted. The case-control-study indicated a risk decrease with doses below 600 mg/m² (albeit non-significant) and a risk increase with higher doses. One study from the review found a significant risk increase at doses between 1 and 1000 mg/m² (but not at higher doses) despite a small sample size (Appendix I.16) (Neglia et al., 2001), whereas another one

did not find a significant dose-response relationship in univariate analysis (Allodji et al., 2019). The rather crude dose category 1-1000 mg/m² does not allow to see if there is a risk change within the dose range similar to what was seen in the case-control study. The authors do not report how many patients received what dose exactly within this category, nor a mean or median. So, it remains speculative whether any changes in effect within the category were hidden by misclassification.

Four studies included in the review investigated whether the application of epipodophyllotoxins (yes/no) was associated with CSPN risk, but none found a significant association (Ehrhardt et al., 2019, Henderson et al., 2012a, Allodji et al., 2019, Sigurdson et al., 2005). This is in line with the case-control study, which also found no association for the dichotomized variable epipodophyllotoxin. Like with antibiotics, the risk-decreasing and -increasing effects seen in the dose-response relationship may have canceled each other out when only treatment versus non-treatment is taken into account.

5.3.2.5 Other substances

There was a significant dose-response-relationship in three out of ten studies analyzing anthracyclines as a whole or doxorubicin as a single anthracycline substance (Appendix I.16) (Teepen et al., 2017, Ehrhardt et al., 2019, Henderson et al., 2016). Although it should have been easier to detect an association in the case-control study than in the studies from the reviews (due to a different significance-level and higher CSPN number), the case-control study did not find significant dose-response relationships for anthracyclines or doxorubicin. A recent CCSS on patients having received only chemotherapy found a breast cancer risk increase with increasing anthracycline doses (Turcotte et al., 2019). The association became significant at doses beyond 300 mg/m².

Similarly, two out of three studies included in the review found associations with procarbazine, an alkylating agent (Appendix I.16), but there was no dose-response-relationship in the case-control study. Neither the study from the review nor the case-control study detected a dose-response-relationship between platinum compounds and CSPN risk (Appendix I.16); moreover, the case-control study additionally did not find associations for asparaginase (an enzyme) or vinca alkaloids.

5.3.3 Evidence for other types of SPNs

Although the dose-response-relationship between alkylating agents and CSPN occurrence was unclear, and cyclophosphamide seemed protective in the present analyses, there is evidence for an increased risk of other solid SPNs and hematological SPNs after the treatment with cyclophosphamide and other alkylating agents (Turcotte et al., 2018, Turcotte et al., 2019, Felix, 2010).

Anthracyclines were found to be a risk factor for other solid SPNs after childhood cancer (Turcotte et al., 2018, Henderson et al., 2012b), which is in line with the results from the review. However, in a CCS group with chemotherapy treatment only, anthracyclines were no risk factor for SPNs at any dose level (Turcotte et al., 2019).

Epipodophyllotoxin treatment is a risk factor for secondary hematological malignancies (Jenkins, 2013). However, there was no association between epipodophyllotoxin dose and any SPN in patients with chemotherapy treatment only (Turcotte et al., 2019).

In the same study, having received high doses of platinum compounds was found to increase SPN risk (Turcotte et al., 2019). This is in contrast to both the results from the case-control study of this thesis and the results of a study from the review (Allodji et al., 2019), which did not find significant dose-response relationships.

Methotrexate, which seemed rather protective in the case-control study of this thesis, was a risk factor for CNS tumors in CCS when applied intrathecally (Taylor et al., 2010). These opposing effects of some substances or groups illustrate the importance of analyses stratified by SPN type.

5.4 Conclusions and outlook

There are some pieces of evidence for an increased CSPN risk after treatment for a neoplasm in childhood with certain cumulative doses of anthracyclines, epipodophyllotoxins, antibiotics, or the alkylating agent procarbazine. However, due to overall inconclusive results, recommendations for action cannot be deduced. In addition, there is some evidence for a risk reduction by cyclophosphamide and methotrexate.

There are indications from the scoping review that chemotherapeutic substances may be a risk factor especially - or only - in patient groups having received no or little irradiation. It would be desirable if a study investigated the dose-response relationship between chemotherapeutic substances and CSPN risk stratified by patients having

received chemotherapy only and other patients (patients with radiotherapy only, with radiotherapy and chemotherapy, with neither chemo- nor radiotherapy). This kind of stratification or a subgroup analysis with patients receiving only chemo- but no radiotherapy had not been planned for the case-control study because an adjustment for radiotherapy was included. The sample size of 76 matchgroups for such a subanalysis might be big enough to detect an effect for common chemotherapeutic groups in future analyses.

With the decreasing use of radiotherapy in childhood cancer treatment, results of dose-response investigations of chemotherapy and CSPN risk become more relevant. First, they might be taken into account when protocols of therapy optimization studies are adapted to minimize the risk of late sequelae while keeping the treatment outcome at a high level. Second, the results may be relevant for the revision of follow-up guidelines. Current guidelines base the majority of their CSPN screening recommendations on the treatment with radiation, which is a well-defined risk factor for several SPNs. Guidelines give CCS a certain amount of assurance and empowerment over their health care. If future studies confirm the results of this thesis, it is worth considering to include screening recommendations based on chemotherapy treatment in future guidelines. Patients treated with chemotherapy but not radiotherapy may especially benefit from these.

This thesis also showed that it is worthwhile to include cumulative doses in CSPN risk assessment instead of merely considering if a patient has received a chemotherapeutic substance or not: A substance might be protective or a risk factor for a CSPN depending on its dose, the association might only become significant with higher substance doses, and the magnitude of the association may change with increasing doses; further research is needed in order to investigate the nature of these associations. A better knowledge of the matter might help to make treatment decisions and screening recommendations.

6 Summary

In Germany, 8.3% of CCS were diagnosed with a SPN within 35 years after diagnosis. One third of them were CSPNs. The therapy of the FPN is a risk factor for a SPN. There is much evidence for the effect of radiotherapy, but chemotherapy was also found to increase SPN risk. However, the evidence for a CSPN risk increase is scarce, especially for a dose-dependent risk association. This thesis investigated the dose-response-relationship between chemotherapeutic treatment for cancer in children and adolescents and the risk for a carcinoma or malignant melanoma as subsequent primary neoplasm.

Two approaches were used. First, a systematic literature search in the manner of a scoping review was performed using the search results from three different literature databases. Inclusion of articles stopped in July 2019. The results of 14 original research articles were used to describe the dose-response-relationship between different chemotherapeutic groups or substances and the risk for several carcinomas (thyroid cancer, breast cancer, salivary gland carcinomas, colorectal cancer, basal cell carcinoma, or gastrointestinal cancer).

Second, a case-control study was conducted with 272 patients with a CSPN and one to four matched controls with a first neoplasm during childhood. This is a subgroup analysis of the case-control study STATT (Second Tumour After Tumour Therapy) carried out by the German Childhood Cancer Registry on all patients with a subsequent primary neoplasm and matched controls registered between 1980 and 2014 (n = 1244). Only patients with intention-to-treat therapy data were included in the analyses of this thesis. Logistic regression analysis with the principle of fractional polynomials with a spike at zero was used to exploratively model the dose-response relationship between different chemotherapeutic groups or substances and the CSPN risk. Substances were pooled into pharmacological groups, their doses were converted using equivalence ratios into the dose of a reference drug of the group, and all doses within a group were summed.

There is evidence for both a risk-increasing and a protective effect of certain chemotherapeutic groups or substances on CSPN occurrence.

The low number of studies with this topic published over a period of 29 years shows the importance of adding to the knowledge base. There was some evidence from the

scoping review that anthracyclines and specifically doxorubicin might increase CSPN risk. Procarbazine, an alkylating agent, might be a risk factor, but the results for alkylating agents in general were inconsistent. Cyclophosphamide might decrease the risk, at least up to a relatively high dose. In some studies, the risk by chemotherapeutic substances became only or especially visible in patient groups with little or no radiotherapy treatment.

The case-control study found a risk decrease with increasing cyclophosphamide dose. Methotrexate and other antimetabolites might have a protective effect as well. CSPN risk increased with increasing epipodophyllotoxin and antibiotic dose whereas low doses seemed protective. There were no associations with other common substance groups such as anthracyclines or platinum compounds.

Taken together, cyclophosphamide might be protective, but the association with alkylating agents in general is unclear. Methotrexate and other antimetabolites might have a protective effect with regard to CSPN risk. The association between epipodophyllotoxin dose and CSPN risk is unclear even though there were first indications for a risk-increasing effect. Anthracyclines seem to increase the risk in a dose-dependent manner. Antibiotics showed a significant association with CSPN risk only in the explorative case-control study, which is why the level of evidence is very low. All in all, there were significant associations for few groups or substances.

Nevertheless, it is worthwhile investigating the dose-response relationship between chemotherapy treatment of an FPN and the CSPN risk in CCS, at least for some substances. However, recommendations for actions are hard to draw from the current evidence. This thesis pointed out directions for future research on this topic; patients might prospectively benefit from this research both during FPN treatment and for CSPN screening.

Zusammenfassung

In Deutschland wurden 8,3% der Langzeitüberlebenden nach Krebs im Kindesalter innerhalb von 35 Jahren nach Diagnose mit einem Folgetumor diagnostiziert. Ein Drittel davon hatten Karzinome und maligne Melanome. Die Therapie des Ersttumors ist ein Risikofaktor für Folgetumore. Es gibt viele Hinweise auf einen Zusammenhang mit Radiotherapie, aber es wurde festgestellt, dass auch die Chemotherapie das Folgetumorrisiko erhöhen kann. Jedoch gibt es wenige Belege für eine Erhöhung des Risikos für Karzinome und maligne Melanome, besonders für Dosis-Wirkungs-Beziehungen. Diese Arbeit untersuchte die Dosis-Wirkungsbeziehung zwischen der Chemotherapiebehandlung bei Krebs im Kindes- und Jugendalter und dem Risiko für ein Karzinom oder malignes Melanom als Folgetumor (CSPN).

Zwei Ansätze wurden dafür verfolgt. Erstens wurde eine systematische Literatursuche in Form eines Scoping Reviews durchgeführt, wobei die Suchergebnisse von drei verschiedenen Literaturdatenbanken verwendet wurden. Eingeschlossen wurden Artikel bis Juli 2019. Die Ergebnisse von 14 Forschungsartikeln wurden verwendet, um die Dosis-Wirkungs-Beziehung zwischen verschiedenen chemotherapeutischen Gruppen oder Substanzen und dem Risiko für verschiedene Karzinome zu beschreiben (Schilddrüsenkrebs, Brustkrebs, Speicheldrüsenkrebs, Basalzellkarzinome, Dickdarmkrebs, gastrointestinale Krebserkrankungen).

Zweitens wurde eine Fall-Kontroll-Studie mit 272 Patienten mit CSPN und ein bis vier gematchten Kontrollen mit einem Ersttumor im Kindesalter durchgeführt. Dies ist eine Untergruppen-Analyse der Fall-Kontroll-Studie STATT (Second Tumour After Tumour Therapie), die vom Deutschen Kinderkrebsregister ausgeführt wird mit allen Patienten mit einem Folgetumor sowie gematchten Kontrollen, die zwischen 1980 und 2014 (n = 1244) registriert wurden. Nur Patienten mit intention-to-treat Therapiedaten wurden in die Analyse dieser Dissertation eingeschlossen. Logistische Regressionsanalysen, auf die das Fractional-polynomial-Prinzip mit “Spike at zero” angewendet wurden, modellierten explorativ die Dosis-Wirkungs-Beziehung zwischen verschiedenen chemotherapeutischen Gruppen oder Substanzen und dem CSPN Risiko. Substanzen wurden in pharmakologische Gruppen gepoolt, ihre Dosen wurden mittels eines Äquivalenz-Quotienten in die Dosis einer Referenz-Substanz oder -Gruppe umgerechnet, und alle Dosen innerhalb einer Gruppe wurden aufaddiert.

Es gibt sowohl Hinweise auf einen risikoreduzierenden als auch einen protektiven Effekt bestimmter chemotherapeutischen Gruppen bzw. Substanzen hinsichtlich des CSPN Auftretens.

Die niedrige Anzahl an Studien, die in den letzten 29 Jahren zu diesem Thema publiziert wurden, zeigt die Wichtigkeit, den Wissensstand zu erweitern. Aus dem Scoping Review gab es einige Hinweise dafür, dass Anthrazykline und speziell Doxorubicin das CSPN-Risiko erhöhen könnte. Das Alkylans Procarbazin könnte ein Risikofaktor sein, aber für Alkylanzien als Gruppe waren die Ergebnisse widersprüchlich. Cyclophosphamide könnten das Risiko senken, zumindest bis zu einer relative hohen Substanzdosis. In einigen Studien wurde das Risiko durch Chemotherapeutika nur oder besonders sichtbar bei Patientengruppen, die keine oder wenig Bestrahlung erhalten hatten.

Die Fall-Kontroll-Studie zeigte eine Risikoreduktion mit steigender Cyclophosphamid-Dosis. Methotrexat und andere Antimetabolite könnten ebenfalls einen protektiven Effekt haben. Das CSPN-Risiko stieg mit steigenden Epidpodophyllotoxin- und Antibiotika-Dosen, wohingegen niedrige Dosen protektiv erschienen. Es gab keine Assoziationen mit anderen typischen Substanzgruppen wie Anthrazyklinen und Platinum-Derivaten.

In der Zusammenschau scheint Cyclophosphamid protektiv zu sein, aber die Assoziation mit Alkylanzien ist unklar. Methotrexat und andere Antimetabolite könnten einen protektiven Effekt hinsichtlich des CSPN-Risikos haben. Die Assoziation zwischen der Epipodophylltoxin-Dosis und dem CSPN-Risiko ist unklar, auch wenn es erste Anzeichen für einen risiko-erhöhenden Effekt gibt. Anthrazykline scheinen das Risiko dosisabhängig zu erhöhen. Antibiotika zeigten nur in der explorativen Analyse der Fall-Kontroll-Studie eine signifikante Assoziation mit dem CSPN-Risiko, weshalb das Evidenzlevel sehr gering ist. Insgesamt gab es mit wenigen Chemotherapeutika signifikante Assoziationen.

Nichtsdestotrotz ist es lohnenswert, die Dosis-Wirkungsbeziehung zwischen der chemotherapeutischen Behandlung eines Ersttumors und dem CSPN-Risiko bei Langzeitüberlebenden nach Krebs im Kindesalter zu untersuchen, zumindest für einige Chemotherapeutika. Von der vorliegenden Evidenz können jedoch kaum Handlungsempfehlungen abgeleitet werden. Diese Arbeit hat Felder für zukünftige

Untersuchungen zu diesem Thema aufgezeigt; Patienten könnten zukünftig sowohl hinsichtlich der Behandlung des Ersttumors als auch eines CSPN-Screenings von dieser Forschung profitieren.

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APPENDIX I

1 Background: Large childhood cancer studies and cumulative incidence of subsequent primary neoplasms

Table 17. Characteristics of large childhood cancer studies and subsequent primary neoplasms.

Cohort/study	Population	Country	n	Age at diagnosis	Study period (diagnosis of FPN[1], SPN[1] follow-up)	Cumulative incidence	Time period for SPN evaluation	Reference
GCCR[1]	6-month survivors, FPN and SPN according to ICCC-3	Germany	47,650	0-14	1980-2014	8.3%	up to 35 years after FPN diagnosis	Scholz-Kreisel et al. (2018a)
CCSS[1]-US/Canada	5-year-survivors, FPN: leukemia, CNS tumor, HL, NHL, renal tumor, neuroblastoma, soft-tissue sarcoma, bone cancer, SPN: SMNs, nonmelanoma skin cancer, meningioma, SPN: malignancies with a /3 behavior morphology code following the US States Surveillance, Epidemiology, and End Results Program.	United States/Canada	14,358	0-20	treatment between 1970-1986, SPN follow-up through Jan 1, 2006	9.3%	up to 30 years after FPN diagnosis	Meadows et al. (2009)
BCCSS[1]	5-year-survivors, FPN not specified, SPNs grouped according to ICD, including all tumors of the bladder irrespective of behavior	Great Britain	17,981	0-14	1940-1991, SPN follow-up until 2006	13.8% (95% CI[1], 12.3%-15.5%),	attained age of 60 years	Reulen et al. (2011), (Hawkins et al., 2008).
DCOG LATER[1]	5-year-survivors, FPN: all malignancies according to ICCC-3 plus multifocal Langerhans cell histiocytosis, selected nonmalignant ependymomas, astrocytomas, SPN: excluded MDS[1], basal cell carcinoma of the skin	The Netherlands	6,165	0-17	1963-2001, SPN follow-up until Jan 1, 2013	3.9% (95% CI, 3.4% to 4.6%)	up to 25 years after FPN diagnosis	Teepen et al. (2017)

Nordic countries	no restriction reported, FPN: according to (Birch and Marsden, 1987), SPN: carcinoma, sarcoma, leukemia, lymphoma, multiple myeloma, papillomas of the lower urinary tract, benign CNS[1] tumors, intracranial meninges, nonmelanoma skin cancers,	Denmark, Finland, Iceland, Norway, Sweden	47,697	0-19	1943-2005 (varied among countries, max. period 61 years)	see [21] SIR[1] of 3.3 (95% CI: 3.1-3.5)	before age 50 years	Olsen et al. (2009)
British-French study	3-year-survivors, FPN: all types except leukemia, and except retinoblastoma (in British centers), SPN: solid	8 centers in the United Kingdom and France	4,400	0-16	diagnosis before 1986, mean year of first cancer treatment was 1974, follow-up through Jan 1, 1992 in French centers and Jan 1, 1991 in British centers	4.9%, (95% CI: 3.7–5.8%) and 7.7% (95% CI: 5.0–8.2%)	up to 25 and 30 years after FPN diagnosis, respectively	de Vathaire et al. (1999)
Japanese study	2-months survivors, FPN: hematological malignancies including MDS, retinoblastoma, neuroblastoma, hepatoblastoma, nephroblastoma, germ cell tumors, brain tumors, bone/soft tissue sarcoma, others (Langerhans cell histiocytosis, adult-type carcinoma, and others), SPN: not specified	Japan	10,069	0-15	1980-2009, follow-up through March 31, 2010	1.3%	up to 20 years after FPN diagnosis	Ishida et al. (2018)

[1]GCCR = German Childhood Cancer Registry, CCSS = Childhood Cancer Survivor Study, BCCSS = British CCSS, DCOG LATER = Dutch cohort Childhood Cancer Oncology Group–Long-Term Effects After Childhood Cancer, FPN = first primary neoplasm, SPN = subsequent primary neoplasm, 95% CI = 95% confidence interval, SIR = standardized incidence ratio, MDS = myelodysplastic syndrome

[2]Cumulative incidence of SPN for subcohorts with FPN diagnosis in:
1943-1959 (prechemotherapy era): 8.6% for SPN before age 50, 18% for SPN before age 60
1960-1974 (first generation chemotherapy era): 12.2% before age 50,
1975-2005 (combination chemotherapy era): 13.3% before age 50

2 Background: Example of a therapy strategy

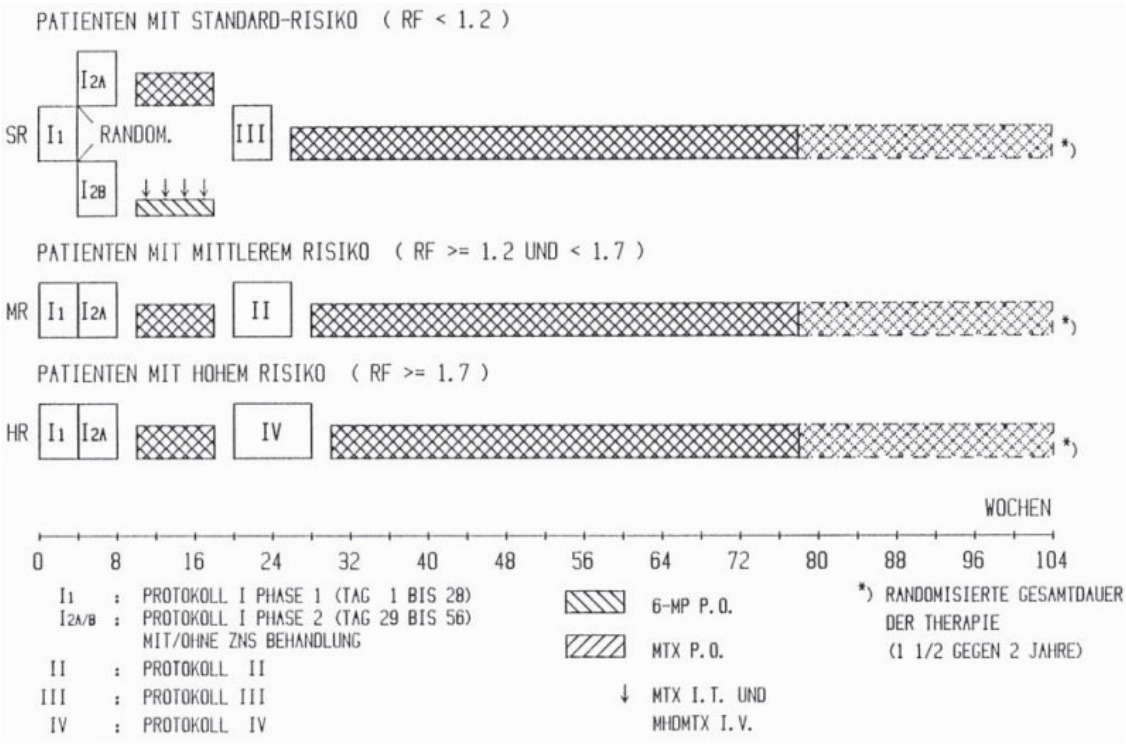


Figure 21. Therapy strategy according to the protocol ALL-BFM 81 (Müller, 2016). Rhiem H. Multizentrische Therapiestudie BFM 81 zur Behandlung der akuten lymphoblastischen Leukämie im Kindes- und Jugendalter. Therapieprotokoll, 1981 (Müller, 2016).

3 Background: Epidemiological study designs

Table 18. Measures of description and of effect in a cohort study according to Ressing et al. (2010), Kreienbrock et al. (2012), and Zwiener et al. (2011).

Effect measure	Definition	Description
incidence rate **mortality rate**	number of persons with outcome during study period / person-years at risk of study population $\frac{C}{pyar} * 100{,}000$	per 100,000 person-years, equals cumulative incidence if all persons are followed up for the entire study period
cumulative incidence (CI)	number of incident cases during study period x 100,000/ number of persons at risk in cohort $\frac{C}{P} * 100{,}000$	per 100,000 persons, equals incidence rate if all persons are followed up for the entire study period
absolute excess risk (AER)	(number observed events – number expected events) / number of person-years follow-up, expressed per 10,000 person-years $\frac{Cobserved - Cexpected}{pyar} * 10{,}000$	definition used in study included in scoping review (Henderson et al., 2016)
standardized incidence ratio (SIR) **standardized mortality ratio (SMR)**	number of observed cases / number of expected cases $\frac{Cobserved}{Cexpected}$	compares incidence or mortality to another cohort, usually the general population; in the studies included in the scoping review, incidence was compared to the general population; SIRs are usually standardized by sex and age group
relative risk (RR), risk ratio	(number of exposed with outcome/ number of exposed) / (number of nonexposed with outcome/ number of nonexposed) $\frac{EC/E}{UC/U}$	estimated from 2x2 contingency table or with the use of the binomial distribution
risk difference (RD)	(number of exposed with outcome/ number of exposed) - (number of nonexposed with outcome/ number of nonexposed) $\frac{EC}{E} - \frac{UC}{U}$	
(incidence) rate ratio (IRR)	incidence rate in exposed / incidence rate in unexposed $\frac{\frac{EC}{pyar\ study\ population} * 100{,}000}{\frac{UC}{pyar\ study\ population} * 100{,}000}$	sometimes called relative risk (Rothman and Greenland), can be estimated using the Poisson distribution
hazard ratio (HR)	$\frac{hazard\ rate\ in\ group\ 1, e.g. exposed}{hazard\ rate\ in\ group\ 2, e.g. unexposed}$	results from Cox proportional hazard regression with time to event as outcome; assumption

	hazard is the risk to have the outcome/event at the point in time t, this risk may change over time	that risk differs between groups by a certain factor

C = cases/number of persons with outcome in study period, e.g. a disease or death
H = number of persons without outcome in study period
P = number of persons at risk of getting the outcome
E = exposed population
U = unexposed population
pyar = person-years at risk

Table 19. Case control-study designs. Table adapted from Rodrigues and Kirkwood (1990).

Sampling design (synonyms)	Cases	Controls sampled	Definition	Effect measure
risk set sampling (incidence) density sampling, concurrent design)	sampled during study period when case is diagnosed	"selected concurrently from those still at risk when a new case is diagnosed" (Rodrigues and Kirkwood, 1990), may become cases later on	incidence rate in exposed group / incidence rate in unexposed group $\frac{C_E}{pyar_E}$ $\frac{C_U}{pyar_U}$	incidence density ratio, relative rate, incidence rate ratio
case-cohort sampling (inclusive design, case-base design, or hybrid retrospective design)	sampled at end of study period	people at risk at the start of the study, case may also be selected as a control and vice versa	incidence risk for exposed / incidence risk for unexposed $\frac{C_E}{P_E}$ $\frac{C_U}{P_U}$ incidence risk = (number of cases/population initially at risk)/(usually expressed per 1000 people)	cumulative incidence ratio/relative risk
cumulative incidence sampling (survivor sampling, traditional/exclusive design, or cumulative design)	sampled at end of study period	people without the disease at the end of the study	odds of disease in exposed group / odds of disease in unexposed group $\frac{C_E}{(P_E-C_E)}$ $\frac{C_U}{(P_U-C_U)}$ odds of disease = total number of cases (C) / number of people still at risk at the end of the study (P-C)	odds ratio (OR) – if the disease is rare, the OR may approximate the risk ratio (rare disease assumption)

Abbreviations:
C = number of cases
P = number of persons at risk
$_E$ = exposed population
$_U$ = unexposed population
pyar = person-years at risk (sum of lengths of time each person stayed at risk during the period of observation = average number at risk during the period*length of observation period;

4 Case-control study: List of relevant TOS protocols and study arms

TOS protocol	Study arm
ALCL 99	Gruppe mit niedrigem Risiko (MTX 1g/m²)
ALL BFM 2000	ALL-2000, HR, R1: Dexa, R3: Protokoll III, Schädelbestrahlun
ALL BFM 2000	ALL-2000, HR, R1: Pred, R3: HR-Blöcke, Schädelbestrahlung
ALL BFM 2000	ALL-2000, HR, R1: Pred, R3: Protokoll III, Schädelbestrahlun
ALL BFM 2000	ALL-2000, MR, R1 Pred, R2 Protokoll III, Schädelbestrahlung
ALL BFM 2000	ALL-2000, MR, R1: Dexa, R2: Protokoll II, ohne Schädelbestr
ALL BFM 2000	ALL-2000, MR, R1: Dexa, R2: Protokoll III, ohne Schädelbest
ALL BFM 2000	ALL-2000, MR, R1: Dexa, R2: Protokoll III, Schädelbestrahlun
ALL BFM 2000	ALL-2000, MR, R1: Pred, R2: Protokoll II, ohne Schädelbestra
ALL BFM 2000	ALL-2000, MR, R1: Pred, R2: Protokoll III, ohne Schädelsbest
ALL BFM 2000	ALL-2000, SR, R1: Dexa, R2: Protokoll II, ohne Schädelbestra
ALL BFM 2000	ALL-2000, SR, R1: Dexa, R2: Protokoll III, ohne Schädelbestr
ALL BFM 2000	ALL-2000, SR, R1: Pred, R2: Protokoll II, ohne Schädelbestra
ALL BFM 2000	ALL-2000, SR, R1: Pred, R2: Protokoll III, ohne Schädelbestr
ALL BFM 79	ALL-79, SR, Arm A1, ZNS neg
ALL BFM 79	ALL-79, SR, Arm A2, ZNS neg
ALL BFM 81	ALL-81, HR, DX 24 Monate
ALL BFM 81	ALL-81, MR, DX 18 Monate
ALL BFM 81	ALL-81, MR, DX 24 Monate
ALL BFM 81	ALL-81, SR, Zweig A, DX 18 Monate
ALL BFM 81	ALL-81, SR, Zweig A, DX 24 Monate
ALL BFM 81	ALL-81, SR, Zweig B, DX 18 Monate
ALL BFM 81	ALL-81, SR, Zweig B, DX 24 Monate
ALL BFM 83	ALL-83, HR, ZNS neg, DX 24 Monate
ALL BFM 83	ALL-83, MR, ZNS neg, DX 18 Monate
ALL BFM 83	ALL-83, MR, ZNS neg.DX 24 Monate
ALL BFM 83	ALL-83, MR, ZNS pos, DX 24 Monate
ALL BFM 83	ALL-83, SR-H/1, ZNS neg, DX 18 Monate
ALL BFM 83	ALL-83, SR-H/1, ZNS neg, DX 24 Monate
ALL BFM 83	ALL-83, SR-H/2, ZNS neg, DX 18 Monate
ALL BFM 83	ALL-83, SR-H/2, ZNS neg, DX 24 Monate
ALL BFM 83	ALL-83, SR-L/1, DX 18 Monate
ALL BFM 83	ALL-83, SR-L/1, DX 24 Monate
ALL BFM 83	ALL-83, SR-L/2, DX 18 Monate
ALL BFM 83	ALL-83, SR-L/2, DX 24 Monate
ALL BFM 86	ALL-86, EG, 18 Monate
ALL BFM 86	ALL-86, EG, 24 Monate
ALL BFM 86	ALL-86, RG, RF < 1,2 , 24 Monate
ALL BFM 86	ALL-86, RG, RF < 1,2, 18 Monate
ALL BFM 86	ALL-86, RG, RF > 1,2, 24 Monate
ALL BFM 86	ALL-86, RG, RF<1,2, 24 Monate inkl. Prot. S
ALL BFM 86	ALL-86, RG, RF>1,2, 18 Monate, inkl. Prot. S
ALL BFM 86	ALL-86, RG, RF>1,2, 24 Monate inkl. Prot. S

ALL BFM 86	ALL-86, SRG, Diagnose ab 01.04.88
ALL BFM 86	ALL-86, SRG, Diagnose bis 31.3.88
ALL BFM 86 PILOT	ALL-86, EG, 18 Monate
ALL BFM 86 PILOT	ALL-86, RG, RF < 1,2, 18 Monate
ALL BFM 90	ALL-90, HRG-1, ZNS-neg
ALL BFM 90	ALL-90, HRG-1, ZNS-neg, SZT vom MSD
ALL BFM 90	ALL-90, MRG-1, ZNS-neg
ALL BFM 90	ALL-90, MRG-2, ZNS-neg
ALL BFM 90	ALL-90, SRG
ALL BFM 95	ALL-95, HR, ZNS neg
ALL BFM 95	ALL-95, HR, ZNS-neg, mit SZT vom MFD, Alter >= 2 Jahre
ALL BFM 95	ALL-95, MR, T-ALL, ZNS neg, MR-1, MR-A
ALL BFM 95	ALL-95, MR, T-ALL, ZNS neg, MR-1, MR-B
ALL BFM 95	ALL-95, MR, T-ALL, ZNS neg, MR-2, MR-A
ALL BFM 95	ALL-95, MR, T-ALL, ZNS neg, MR-2, MR-B
ALL BFM 95	ALL-95, MR, ZNS pos, MR-1, MR-B
ALL BFM 95	ALL-95, MR, non T, ZNS neg, MR-1, MR-A
ALL BFM 95	ALL-95, MR, non T, ZNS neg, MR-1, MR-B
ALL BFM 95	ALL-95, MR, non T, ZNS neg, MR-2, MR-B
ALL BFM 95	ALL-95, MR, non-T, ZNS neg, MR-2, MR-A
ALL BFM 95	ALL-95, SR, ZNS-neg, weiblich
AML BFM 2004	AML-BFM 2004 HR, AIE, ZNS neg, AI/CDA, 12 Gy
AML BFM 2004	AML-BFM 2004 SR, AdxE, ZNS neg, Rx 18 Gy
AML BFM 78	AML-78, alle Studienteilnehmer
AML BFM 83	AML-83, ZNS-neg
AML BFM 87	AML-87, alle Gruppen ohne SZT, ZNS pos
AML BFM 87	AML-87, ohne SZT, ZNS neg
AML BFM 87	AML-87, ohne SZT, ZNS neg, 18 Gy
AML BFM 93	AML-93, ADE, HR 2, ZNS neg
AML BFM 93	AML-93, AIE, HR 1, ZNS neg
AML BFM 93	AML-93, AIE, HR 2, ZNS neg, SZT
AML BFM 93	AML-93, SR, ADE
AML BFM 93	AML-93, SR, AIE
AML BFM 93 JENA	AML-93, SR, ADE
AML BFM 98	AML-98, Arm A, mit GCSF, 12 Gy
AML BFM 98	AML-98, Arm B, mit GCSF, 18 Gy
AML BFM 98	AML-98, Arm B, ohne GCSF, 12 Gy
AML BFM 98 JENA	AML-98, Arm A, mit GCSF, SZT
AML BFM 98 JENA	AML-98, Arm B, ohne GCSF, 12 Gy
B-NHL BFM 04	B-NHL BFM 04, R1
B-NHL BFM RX	B-NHL BFM 04, R3
CESS 81	CESS 81, Arm A, Bestrahlung 60 Gy
CESS 81	CESS 81, Arm A, inkomplette OP, Bestrahlung 36 Gy
CESS 81	CESS 81, Arm A, komplette Resektion
CESS 81	CESS 81, Arm B, Bestrahlung 40 Gy
CESS 86	CESS 86, Zentraler Tumor oder Extremitätentumor > 100 ml, ke
CESS 86	CESS 86, Zentraler Tumor oder Extremitätentumor > 100 ml, ma

CESS 86	CESS 86, Zentraler Tumor oder Extremitätentumor > 100 ml, ra
CESS 86 ASKIN	CESS 86, Zentraler Tumor oder Extremitätentumor > 100 ml, ke
CESS 86 PILOT	CESS 86, Zentraler Tumor oder Extremitätentumor > 100 ml, ke
CESS 91	EICESS-92, HR, Arm EVAIA, Bestrahlung, keine OP, Metastasen
CESS 91	EICESS-92, HR, Arm EVAIA, OP-CR, Metastasen
CESS 91	EICESS-92, HR, Arm VAIA, Bestrahlung, OP-PR/OP inkomplett
COALL 03	COALL 07-03 LR-Intensiviert/HR-Standard, ADR in der Vorphase
COALL 03	COALL 07-03 LR-Intensiviert/HR-Standard, DNR 30 in der Vorph
COALL 03	COALL 07-03 LR-Intensiviert/HR-Standard, DNR 40 in der Vorph
COALL 03	COALL 07-03 LR-Standard, ADR in der Vorphase
COALL 03	COALL 07-03 LR-Standard, DNR 40 in der Vorphase
COALL 03	COALL 07-03 LR-reduziert, DNR 30 in der Vorphase
COALL 03	COALL 07-03 LR-reduziert, DNR 40 in der Vorphase
COALL 09	COALL 08-09, HR-Intensiviert,T-ALL, 1. Rando Clofarabin, 2.
COALL 09	COALL 08-09, HR-Intensiviert,proB-ALL, 1. Rando Clofarabin,
COALL 80	COALL-80, Nicht-Risikopatienten, Erhaltung mit MTX
COALL 80	COALL-80, Nicht-Risikopatienten, Erhaltung mit VCR
COALL 80	COALL-80, Risikopatienten, Erhaltung mit MTX
COALL 82	COALL-82, High-risk
COALL 82	COALL-82, High-risk, ZNS-Pos, DX mit MTX
COALL 82	COALL-82, Low-risk, mit ZNS-Bestrahlung
COALL 82	COALL-82, Low-risk, ohne ZNS-Bestrahlung
COALL 85	COALL-85, HR-Gruppe, Zweig: Schneller Wechsel, <50.000 /nl
COALL 85	COALL-85, HR-Gruppe, Zweig: konventionell, <50.000 Zellen
COALL 85	COALL-85, HR-Gruppe, Zweig: konventionell, >50.000/nl
COALL 85	COALL-85, HR-Gruppe, Zweig: schneller Wechsel, > 50.000/nl
COALL 85	COALL-85, LR-Gruppe, mit ZNS-Bestrahlung
COALL 89	COALL-89, HR, ZNS neg, langsamer Wechsel, >2 Jahre
COALL 89	COALL-89, HR, ZNS neg, schneller Wechsel, >2 Jahre
COALL 89	COALL-89, LR, <10.000 Leukos, ZNS neg
COALL 89	COALL-89, LR, >10.000 Leukos, ZNS neg, > 2 Jahre
COALL 92	COALL-92, HR, ZNS neg, DNR 1h, Alter >2J, Dauertx. 6-TG
COALL 92	COALL-92, HR, ZNS neg, DNR 24h, Alter >2J, Dauertx. 6-MP
COALL 92	COALL-92, LR, DNR 1h, Dauertx. Mit 6-TG
COALL 92	COALL-92, LR, DNR 24h, Dauerthx 6-TG
COALL 92	COALL-92, LR, DNR 24h, Dauerthx. 6-MP
COALL 97	COALL 97, HR, High-Risk Reduziert, ZNS-negativ
COALL 97	COALL 97, HR, High-Risk Standard, ZNS negativ
COALL 97	COALL 97, LR, Low-Risk Intensiviert, ZNS-negativ
COALL 97	COALL 97, LR, Low-Risk Reduziert, ZNS negativ
COALL 97	COALL 97, LR, Low-Risk Standard, ZNS-negativ
COSS 80	COSS 80, Gruppe A, mit Interferon
COSS 80	COSS 80, Gruppe A, ohne Interferon
COSS 80	COSS 80, Gruppe B, mit Interferon
COSS 86	COSS 86, High Risk Gruppe, stratifiziert in Platin i.a präop
COSS 86	COSS 86, High Risk Gruppe, stratifiziert in Platin i.v. präo
COSS 86	COSS 86, Low Risk Gruppe

COSS 86C	COSS 86c, Zweig Cisplatin 5 Std. Infusion
COSS 86C	COSS 86c, Zweig Cisplatin 72 Std. Infusion
COSS 91	COSS 91, Zweig Cisplatin 5 Std-Infusion
COSS 96	COSS 96, SR2
CWS 81	CWS 81, Stadium I
CWS 81	CWS 81, Stadium IIA, mit Bestrahlung
CWS 81	CWS 81, Stadium IIB und III, anhaltende Response
CWS 81	CWS 81, Stadium IIB und III, keine Response nach VACA (1), R
CWS 86	CWS 86, Stadium I-II, Tumor in Extremität, Bestrahlung
CWS 86	CWS 86, Stadium I-II, ohne Bestrahlung
CWS 86	CWS 86, Stadium III, PR<2/3, Bestrahlung
CWS 86	CWS 86, Stadium III, PR>2/3, in 16. Wo Stadium Ipc
CWS 86	CWS 86, Stadium III, PR>2/3, in 16. Woche Stadium Iiipc oder
CWS 86	CWS 86, Stadium III-IV, CR nach 1. VAIA II
CWS 91	CWS 91, Arm A, mit Bestrahlung bei ungünstiger Histologie od
CWS 91	CWS 91, Arm B, Stadium I und II oder Stadium III mit Low ris
CWS 91	CWS 91, Arm B, Stadium I-III, Bestrahlung mit 32 Gy
CWS 91	CWS 91, Arm C, Stadium III, high risk, mit Second look OP, B
CWS 91 PILOT	CWS 91, Arm C, Stadium III, high risk, mit Second look OP, B
CWS 96	CWS 96, High Risk, ARM CEVAIE, Bestrahlung 44,8 Gy
CWS 96	CWS 96, High risk, Arm VAIA, Bestrahlung 44,8 Gy
CWS 96 PILOT	CWS 96, Low risk, Stadium I: pT1
EICESS 92	EICESS-92, HR, Arm EVAIA, Bestrahlung, OP, Metastasen
EICESS 92	EICESS-92, HR, Arm EVAIA, OP, Bestrahlung 45 Gy
EICESS 92	EICESS-92, HR, Arm EVAIA, OP-CR
EICESS 92	EICESS-92, SR, Arm VACA, OP, späte Radiotherapie
GCT 96	GCT 96, alle anderen Histologien, mit Metastasen
HB 89	HB-89, Stadium I, Primäre OP, Chemotherapie
HB 89	HB-89, Stadium III-IV, Tumorbiopsie, Response nach Chemother
HD 2002 PILOT	HD-95, TG 1, Stadium I-IIA, Jungen, inkompl. Remission, Herd
HD 78	HD 78, Stadien IIB, III, IV, R1, 4 COPP, Splenektomie
HD 78	HD 78, Stadien IIB-III, IV, R2, 4 Blöcke COPP, Splenektomie
HD 78	HD 78, Stadium I und IIA, R1, Splenektomie
HD 78	HD 78, Stadium I und IIA, R2, Splenektomie
HD 82	HD-82, Stadium I-IIA, mit Splenektomie, Herdbestrahlung
HD 82	HD-82, Stadium I-IIA, ohne Splenektomie, Herdbestrahlung
HD 82	HD-82, Stadium IIB-IIIA, mit Splenektomie, Remission, Herdbe
HD 82	HD-82, Stadium IIB-IIIA, ohne Splenektomie, Remission, Herdb
HD 82	HD-82, Stadium IIB-IIIA, ohne Splenektomie, inkompl. Remissi
HD 82	HD-82, Stadium IIIB-IV, mit Splenektomie, Remission, Herdbes
HD 82	HD-82, Stadium IIIB-IV, mit Splenektomie, inkompl. Remission
HD 82	HD-82, Stadium IIIB-IV, ohne Splenektomie, Remission, Herdbe
HD 85	HD-85, Diagnose nach 01.12.86, Stadium I-IIA, ohne Splenekto
HD 85	HD-85, Diagnose nach 01.12.86, Stadium IIB-IIIA, mit Splenek
HD 85	HD-85, Diagnose vor 01.12.86, Stadium I-IIA, ohne Splenekto
HD 85	HD-85, Diagnose vor 01.12.86, Stadium I-IIA, mit Splenektomi
HD 85	HD-85, Diagnose vor 01.12.86, Stadium IIB-IIIA, mit Splenekt

HD 85	HD-85, Diagnose vor 01.12.86, Stadium IIB-IIIA, ohne Splenek
HD 85	HD-85, Diagnose vor 01.12.86, Stadium IIB-IV, ohne Splenekto
HD 85	HD-85, Diagnose vor 01.12.86, Stadium IIIB-IV, mit Splenekto
HD 85	HD-85, Diagnose vor 01.12.86, Stadium IIIB-IV, ohne Splenekt
HD 87	HD-87, Stadium I-IIA, ohne Splenektomie, Remission, Herdbest
HD 87	HD-87, Stadium I-IIA, ohne Splenektomie, inkompl. Remission,
HD 87	HD-87, Stadium IIB-IIIA, ohne Splenektomie, Remission, Herdb
HD 87	HD-87, Stadium IIB-IIIA, ohne Splenektomie, inkompl. Remissi
HD 87	HD-87, Stadium IIIB-IV, mit Splenektomie, Remission, Herdbes
HD 87	HD-87, Stadium IIIB-IV, mit Splenektomie, inkompl. Remission
HD 87	HD-87, Stadium IIIB-IV, ohne Splenektomie, inkompl. Remissio
HD 90	HD-90, Stadium I-IIA, Jungen, Remission, Herdbestrahlung
HD 90	HD-90, Stadium I-IIA, Mädchen, Remission, Herdbestrahlung
HD 90	HD-90, Stadium I-IIA, Mädchen, inkompl. Remission, Herdbest
HD 90	HD-90, Stadium IIB-IIIA, Jungen, Remission, Herdbestrahlung
HD 90	HD-90, Stadium IIB-IIIA, Jungen, inkompl. Remission, Herdbes
HD 90	HD-90, Stadium IIB-IIIA, Mädchen, Remission, Herdbestrahlung
HD 90	HD-90, Stadium IIB-IIIA, Mädchen, inkompl. Remission, Herdbe
HD 90	HD-90, Stadium IIIB-IV, Jungen, Remission, Herdbestrahlung
HD 90	HD-90, Stadium IIIB-IV, Jungen, inkompl. Remission, Herdbest
HD 90	HD-90, Stadium IIIB-IV, Mädchen, Remission, Herdbesrahlung
HD 90	HD-90, Stadium IIIB-IV, Mädchen, inkompl. Remission, Herdbes
HD 95	HD-95, TG 1, Stadium I-IIA, Mädchen, Remission
HD 95	HD-95, TG 1, Stadium I-IIA, Mädchen, inkompl. Remission, Her
HD 95	HD-95, TG 2, Stadium IIB-IIIA, II E, II EA, Jungen, inkompl.
HD 95	HD-95, TG 2, Stadium IIB-IIIA, II E, II EA, Mädchen, Remissi
HD 95	HD-95, TG 2, Stadium IIB-IIIA, II E, II EA, Mädchen, inkompl
HD 95	HD-95, TG 3, Stadium IIIB-IV, II EB, III E, Mädchen und Jung
HD 95	HD-95, TG 3, Stadium IIIB-IV,II EB, III E, Jungen, inkompl.
HD INTERVALL	HD95 Intervall, TG 1, Jungen, CR
HD INTERVALL	HD95 Intervall, TG 2, Jungen
HD INTERVALL	HD95 Intervall, TG 3, Jungen
HIT-CHEM 91	HIT-91, Erhaltungstherapie 1 Jahr
HIT-CHEM 91	HIT-91, Sandwichtherapie, bei Therapieende CR
HIT-CHEM 91	HIT-91, Sandwichtherapie, SD, PD oder Rezidiv nach 1 Zyklus-
HIT-CHEM-O	HIT-91, Erhaltungstherapie 1 Jahr
HIT-ENDO	HIT-Endo, Totalresektion, keine Bestrahlung
HIT-LGG	HIT-LGG96, 1. OP, inkomplette Resektion aber symptomfrei, Be
HIT-LGG	HIT-LGG96, 1. OP, inkomplette Resektion, Symptome oder Progr
HIT-LGG	HIT-LGG96, 1. OP, komplette Resektion R1
MAHO 98	MAHO 98, Stadium IA, YST und TD, unilaterale Orchiektomie, B
MAKEI 83	MAKEI 86, intrakranielles Germinom, Liquor pos
MAKEI 83	Makei 83, Serminom/Dysgerminom, nur OP
MAKEI 83	Makei 83, Serminom/Dysgerminom, OP, Chemotherapie
MAKEI 83	Makei 83, TD imm, Grad 2
MAKEI 86	MAKEI 86, Germinom Stadium Iai
MAKEI 86	MAKEI 86, Germinom, Stadium Iaii-III

MAKEI 86	MAKEI 86, Immatures Teratom Grad 2, Ovar
MAKEI 86	MAKEI 86, Karzinom Ovar Grad 1
MAKEI 89	Makei 89, Dysgerminom, Ovar Stadium III-IV, EGT Stadium I-IV
MAKEI 89	Makei 89, Dysgerminom, Ovar Stadium Ia
MAKEI 89	Makei 89, Matures Teratom intra- und extragonadal
MAKEI 89	Makei 89, intrakraniales Immatures Teratom, Grad 2-3, inkomp
MAKEI 89	Makei 89, intrakraniales Immatures Teratom, Grad 2-3, komple
MAKEI 89	Makei 89, intrakranielles Germinom
MAKEI 89	Makei 89, intrakranielles Karzinom
MAKEI 89	Makei 89, mNSKZT, Ovar Stadium II und EGT Stadium I
MAKEI 89	Makei 89, mNSKZT, Ovar Stadium III-IV, EGT Stadium II-IV
MAKEI 89	Makei 89, mNSKZT, Ovar, Stadium I
MAKEI 96	Makei 96, Strategie A, Ovar Ia und Ib, EGT T1a N0, M0
MAKEI 96	Makei 96, Strategie C, Ovar IIIa, IIIb, IV, EGT T2 Nx/1 M0/1
NB 82	NB-82, Stadium II, jedes Alter, OP, Chemotherapie reduziert
NB 82	NB-82, Stadium IV, >= 12 Monate
NB 85	NB-85, Stadium I und II, ohne LK-Befall
NB 85	NB-85, Stadium II mit LK-Befall
NB 85	NB-85, Stadium III
NB 85	NB-85, Stadium III, Nichtresizierbarkeit/ Resttumor nach Sec
NB 85	NB-85, Stadium IV-S, Leberbestrahlung, CPM oral, OP
NB 90	NB-90, Stadium 4, CR, VGPR, PR, lok. Bestrahlung Knochen un
NHL BFM 81	NHL-81, Arm NHL-B1
NHL BFM 81	NHL-81, Arm NHL-B2
NHL BFM 81	NHL-81, Arm NHL-NB1
NHL BFM 81	NHL-81, Arm NHL-NB2
NHL BFM 83	NHL-83, Arm NHL-B-H, ZNS neg
NHL BFM 83	NHL-83, Arm NHL-B-L
NHL BFM 83	NHL-83, Arm NHL-NB-H, ZNS neg
NHL BFM 86	NHL-86, B-NHL, Stadien IINR und III
NHL BFM 86	NHL-86, B-NHL, Stadium I und II-R
NHL BFM 86	NHL-86, B-NHL, Stadium IV und B-ALL
NHL BFM 86	NHL-86, B-NHL, Stadium IV, mit Radiotherapie
NHL BFM 86	NHL-86, NB-NHL, Experimentelle Gruppe, Diagnose vor dem 01.1
NHL BFM 86	NHL-86, NB-NHL, Risikogruppe 01, Diagnose nach dem 01.10.88
NHL BFM 90	NHL-90, B-NHL/B-ALL, R1
NHL BFM 90	NHL-90, B-NHL/B-ALL, R2, Remission
NHL BFM 90	NHL-90, B-NHL/B-ALL, R3, ZNS neg, Remission
NHL BFM 90	NHL-90, LCAL, K2
NHL BFM 90	NHL-90, LCAL, K3, ZNS neg
NHL BFM 90	NHL-90, Non-B-NHL, RG, ZNS neg
NHL BFM 90	NHL-90, Non-B-NHL, SRG
NHL BFM 95	NHL-95, Therapiegruppe I, MR
NHL BFM 95	NHL-95, Therapiegruppe II, R1-Arm, Arm A24
NHL BFM 95	NHL-95, Therapiegruppe II, R1-Arm, Arm A4
NHL BFM 95	NHL-95, Therapiegruppe II, R2-Arm, Arm A24
NHL BFM 95	NHL-95, Therapiegruppe II, R2-Arm, Arm A4

NHL BFM 95	NHL-95, Therapiegruppe II, R3-Arm, Arm AA24
NHL BFM 95	NHL-95, Therapiegruppe II, R4-Arm, ZNS neg, Arm AA24
NHL BFM 95	NHL-95, Therapiegruppe II, R4-Arm, ZNS neg, Arm AA4
NHL BFM 95	NHL-95, Therapiegruppe III, K2
NHL BFM 95	NHL-95, Therapiegruppe III, K3
NHL BFM 95V	NHL-90, B-NHL/B-ALL, R2, Remission
NHL BFM 95V	NHL-90, B-NHL/B-ALL, R3, ZNS neg, Remission
RB	RB, Lokalmaßnahmen
RB	RB, Enukleation, adjuvante Chemotherapie < 15 kg
RB	RB, Enukleation, adjuvante Chemotherapie ab 15 kg
SIOP9/GPO	SIOP9, Stadium I, 4 Wochen präoperative Therapie
SIOP9/GPO	SIOP9, Ungünstige Histologie, Stadien I-III, 4 Wochen präope
SIOP93-01/GPOH	SIOP93, initial Stadium I-III, mittlere Malignität, post OP
SIOP93-01/GPOH	SIOP93, initial Stadium IV, CR der Metastasen, mittlere Mali
SIOP93-01/GPOH	SIOP93, initial Stadium IV, pulmonale Metastasen ohne CR, mi
WTS 80	WTS 80, Stadium II, >2 Jahre
WTS 80	WTS 80, Stadium III und IV, Alter > 2 Jahre, keine Metastase
WTS 80	WTS 80, Stadium IV, Alter > 2 Jahre, Lungenmetastasen
WTS 82	WTS 82, Chemotherapie A, jede Histologie, ohne Radiotherapie
WTS 82	WTS 82, Chemotherapie B, pT2N0M0, Alter < 2 Jahre, keine Ra
WTS 82	WTS 82, Chemotherapie C, Alter >2 Jahre, kein anaplastisch-s
WTS 82	WTS 82, Chemotherapie C, pT2N0M0, Alter > 2 Jahre, keine Ra

5 Case-control study: Dose values for which odds ratios are presented

Table 20. Dose values for which odds ratios are presented in the case-control study of this thesis.[1]

Substance (group)	Dose (mg/m²)	N	Example of study arm	ICCC-3[1] diagnosis of patients in example study arm	N in example study arm
cyclophosphamide (n = 727)	1000	76	AML-83, ZNS-neg	I(b)	25
	3000	237	ALL-90, MRG-2, ZNS-neg	I(a)	18
	6000	5	ALL-83, HR, ZNS neg, DX 24 Monate	I(a)	3
antibiotics (n = 135)	6	24	CESS 86, Zentraler Tumor oder Extremitätentumor > 100 ml, ma	VIII(3)	6
	9	18	CWS 86, Stadium I-II, ohne Bestrahlung	IX(1)	12
	15	10	CWS 86, Stadium III, PR>2/3, in 16. Wo Stadium Ipc	IX(1)	6
epipodophyllotoxins (n = 286)	165	24	several COALL studies	I(a)	21
	330	50	several COALL studies	I(a)	44
	1000	25	several Hodgkin lymphoma studies	II(a)	18
	6300	6	EICESS-92 studies	VIII(3)	6

[1]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005)

6 Case-control study: Distribution of substance doses (histograms)

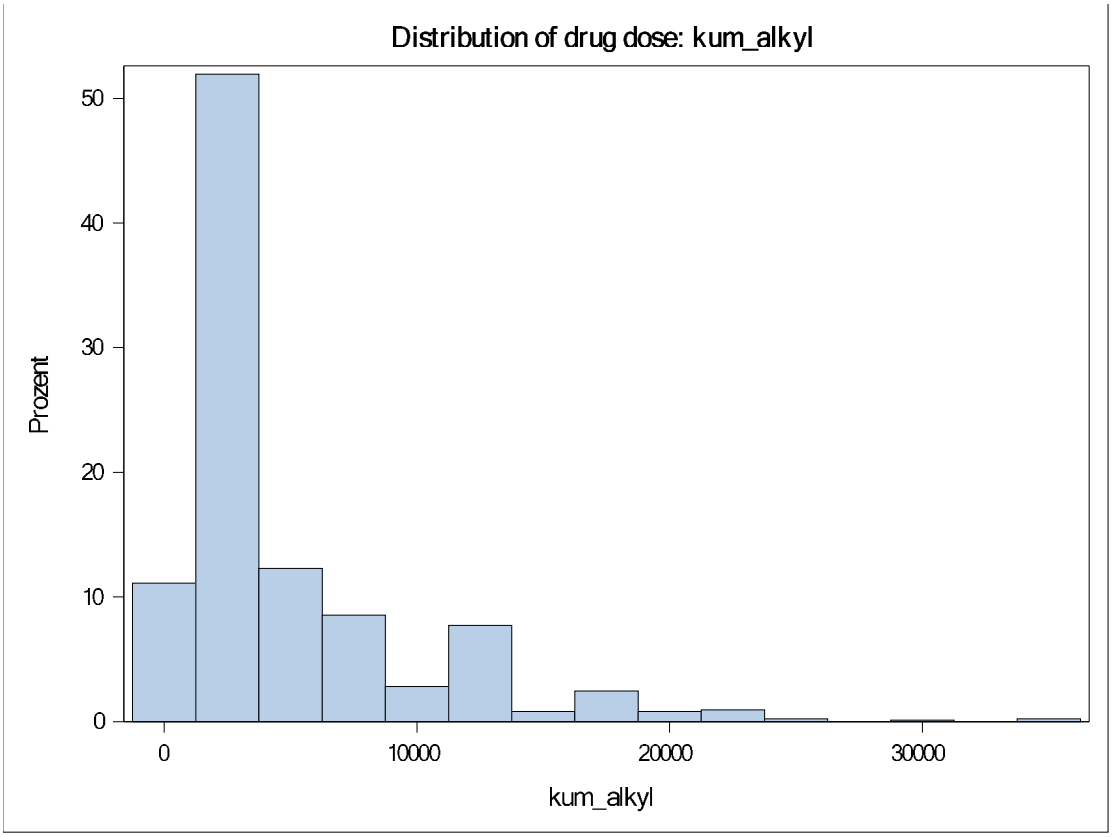
Distribution of doses of different chemotherapeutic groups.

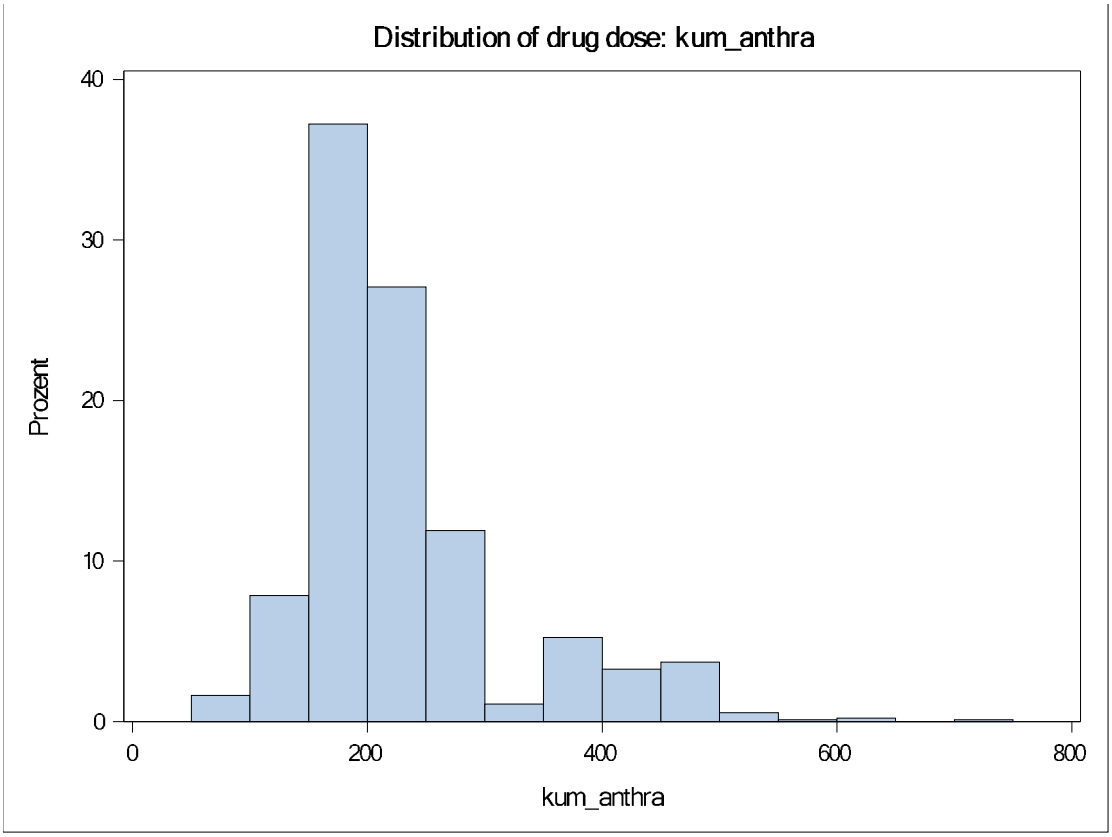
y-axis: percent

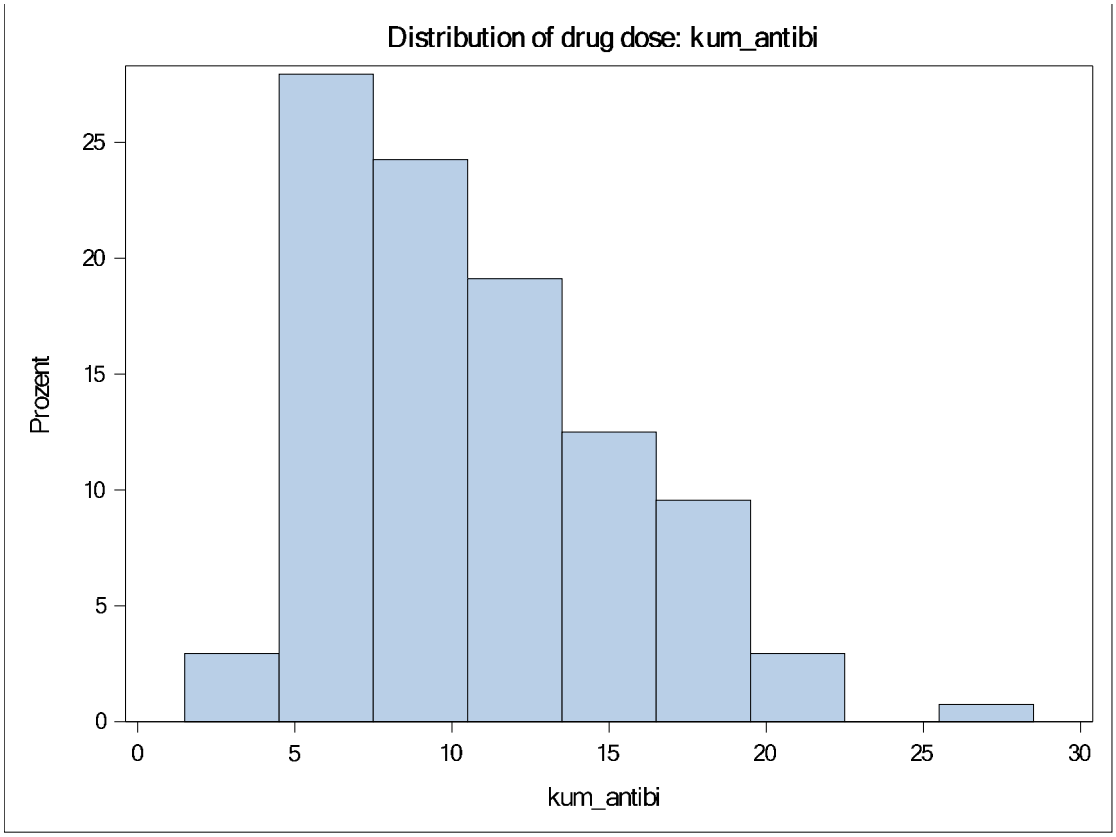
x-axis: dose in mg/m² except enzymes (U/m²)

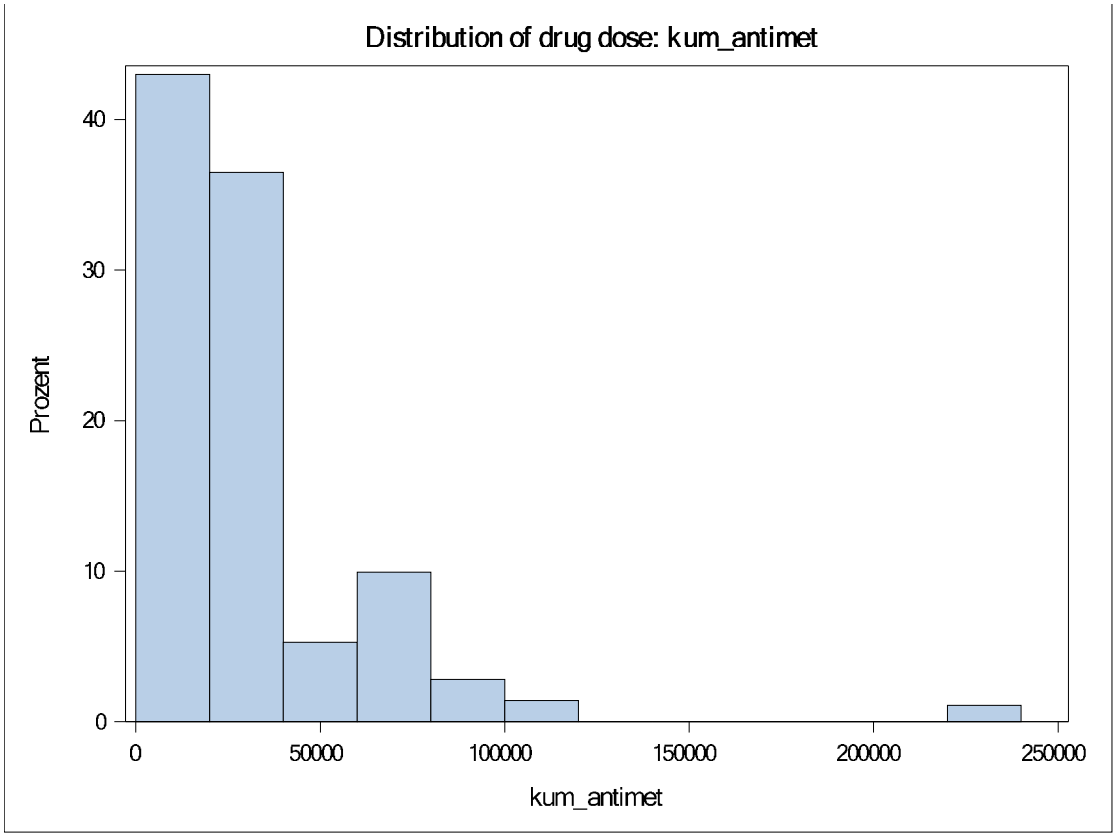
Abbreviations of drug groups (the prefix “kum” means cumulative dose of all drugs in this group):

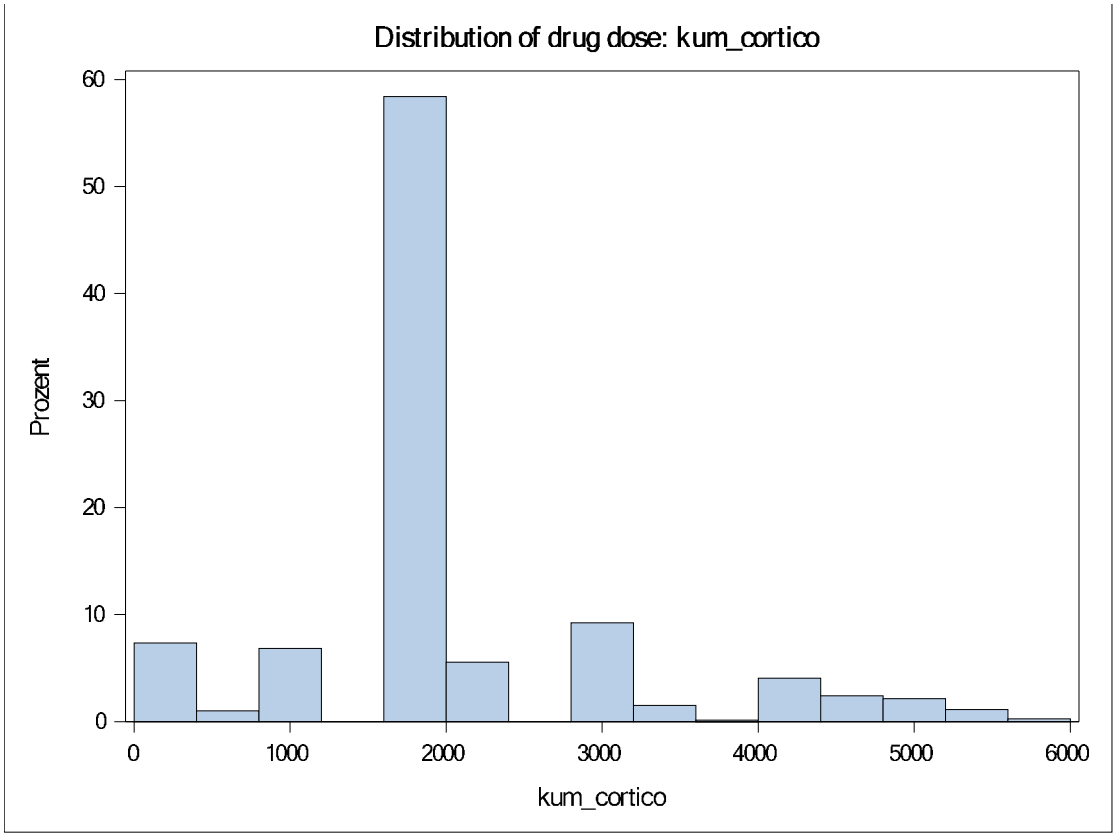
Abbreviation	Drug group
kum_alkyl	alkylating agents
kum_anthra	anthracyclines
kum_antibi	antibiotics
kum_antimet	antimetabolites
kum_cortico	corticosteroids
kum_	enzymes (Asparaginase)
kum_epipodo	epidpodophylltoxins
kum_plat	platinum derivates
kum_vinca	vinca alkaloids

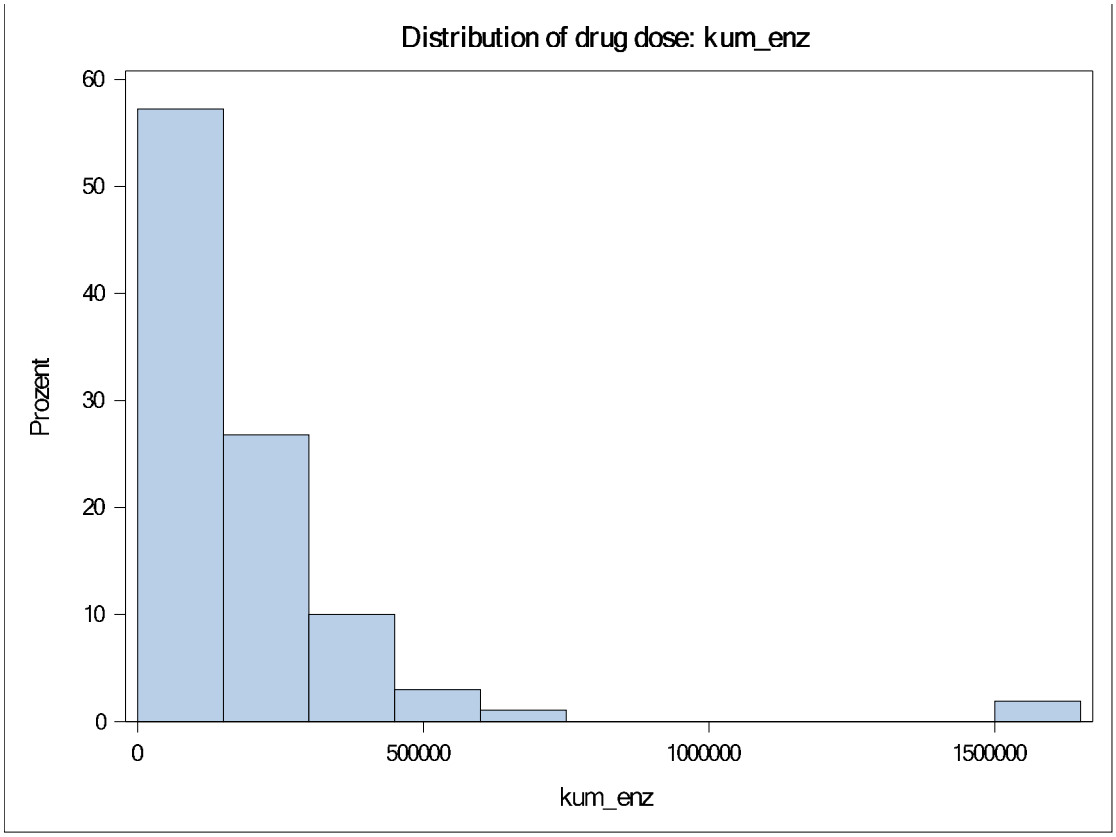

Distribution of drug dose: kum_alkyl
Prozent
50
40
30
20
10
0
0
10000
20000
30000
kum_alkyl

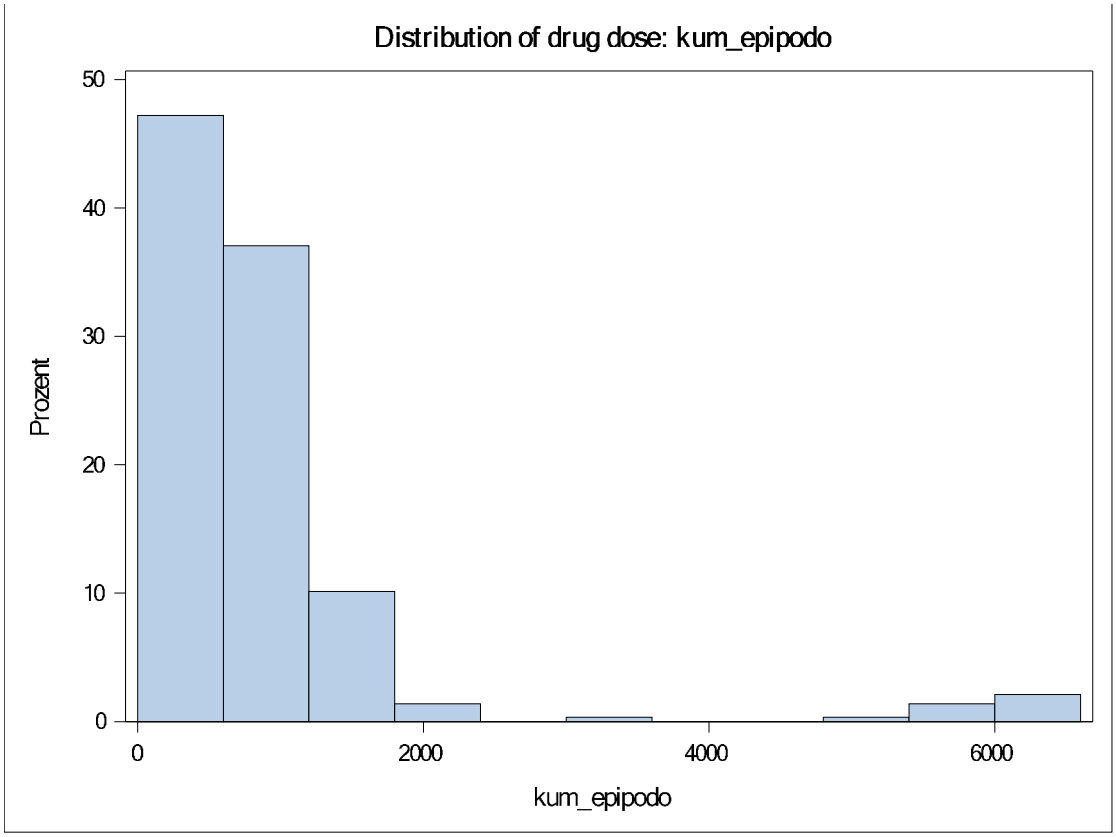

Distribution of drug dose: kum_anthra
Prozent
40
30
20
10
0
0
200
400
600
800
kum_anthra

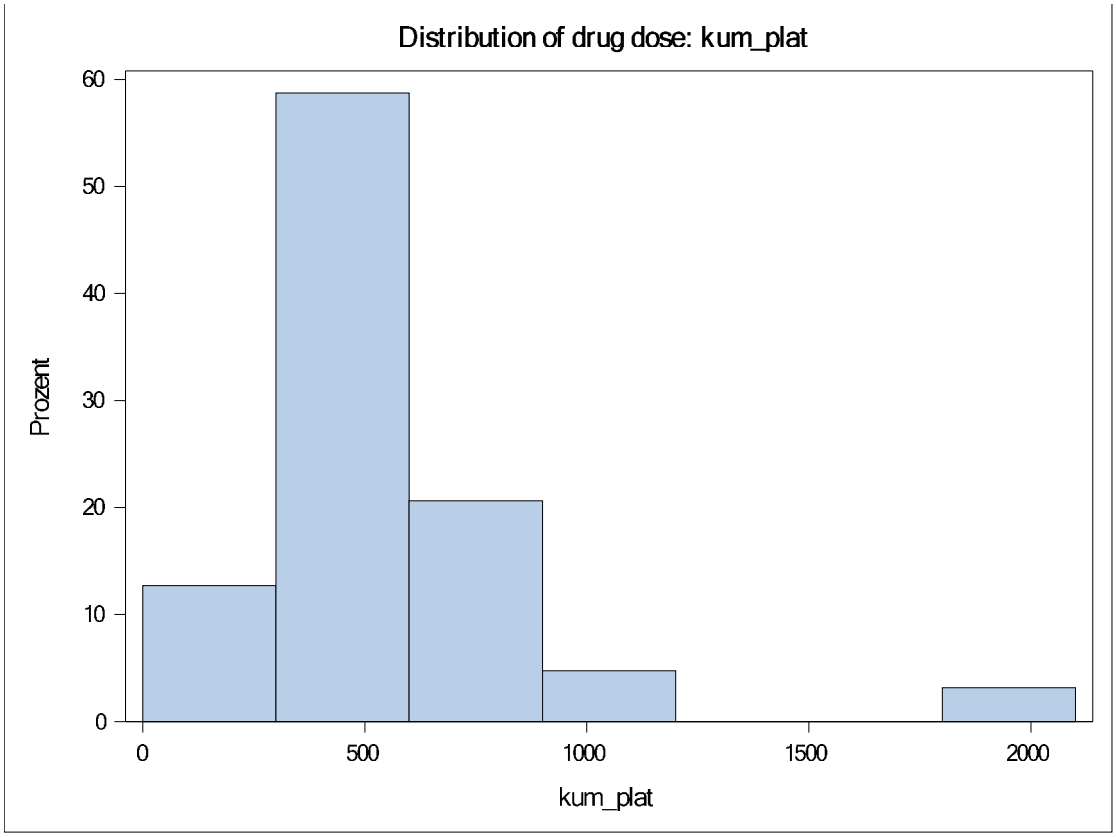

Distribution of drug dose: kum_antibi
Prozent
0
5
10
15
20
25
0
5
10
15
20
25
30
kum_antibi

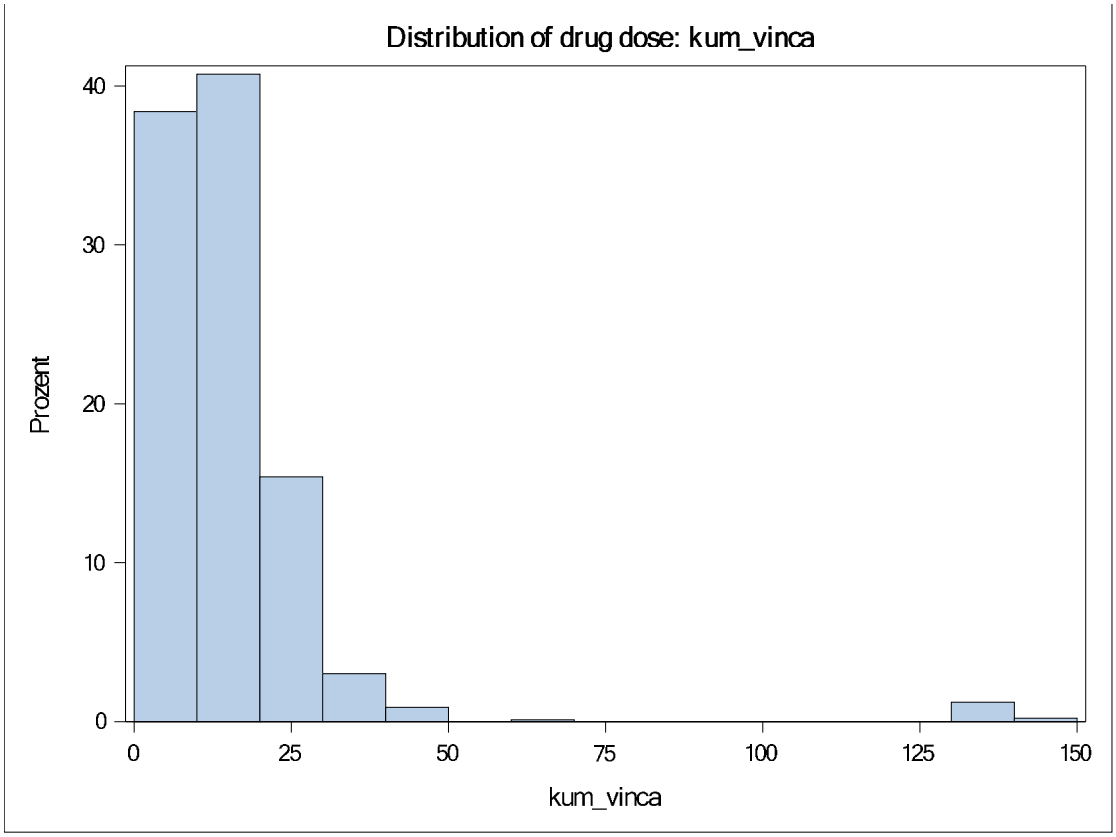

Distribution of drug dose: kum_antimet
Prozent
0
10
20
30
40
0
50000
100000
150000
200000
250000
kum_antimet


Distribution of drug dose: kum_cortico
Prozent
60
50
40
30
20
10
0
0
1000
2000
3000
4000
5000
6000
kum_cortico


Distribution of drug dose: kum_enz
Prozent
60
50
40
30
20
10
0
0
500000
1000000
1500000
kum_enz


Distribution of drug dose: kum_epipodo
Prozent
50
40
30
20
10
0
0
2000
4000
6000
kum_epipodo


Distribution of drug dose: kum_plat
Prozent
60
50
40
30
20
10
0
0
500
1000
1500
2000
kum_plat


Distribution of drug dose: kum_vinca
Prozent
40
30
20
10
0
0
25
50
75
100
125
150
kum_vinca

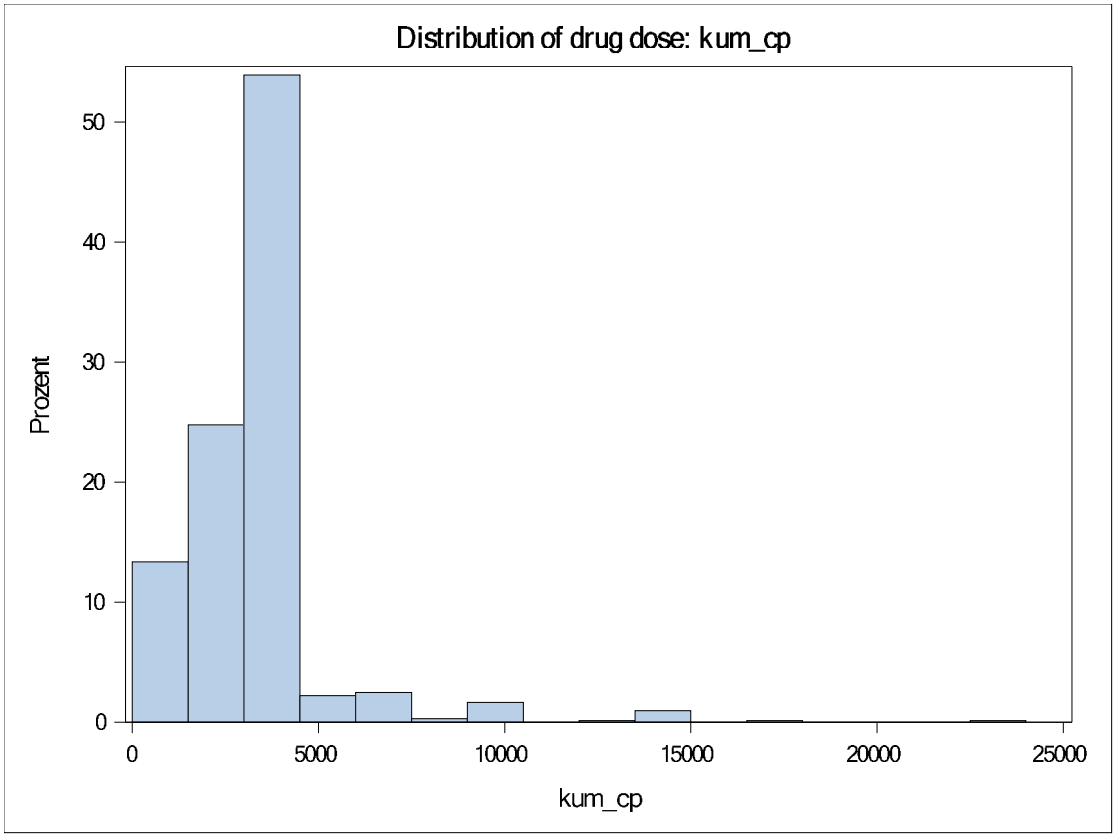
Distribution of doses of different chemotherapeutic agents.

y-axis: percent

x-axis: dose in mg/m^2 except asparaginase (U/m^2)

Abbreviations of drug names (the prefix “viv_kum” means cumulative dose of this drug):

Abbreviation	Drug
bus	Busulfan
cp	Cyclophosphamide
dtic	Dacarbazine
ifo	Ifosfamide
ccnu	Lomustine
mel	Melphalan
pro	Procarbazine[1]
dnr	Daunorubicin
daux	Daunoxome
adr	Doxorubicin
epi	Epirubicin
ida	Idarubicin
mito	Mitoxantrone
act	Actinomycin D (Dactinomycin)
ble	Bleomycin
clad	Cladribine
arac	Cytarabine (Cytosine Arabinoside)
fu	Fluorouracil
merc	Mercaptopurine
mtx	Methotrexate
thio	Thioguanine
asp	Asparaginase (L-Asparaginase)
asp	Coli Asparaginase[3]
asp	PEG-L-Asparaginase
vp16	Etoposide (VP-16)
vm26	Teniposid
amsa	Amsacrine
dex	Dexamethasone
fa	Folinic Acid
g	G-CSF
inter	Interferon ALPHA
oth	Other
pred	Prednisone
car	Carboplatin
ddp	Cisplatin
vin	Vinblastine
vcr	Vincristine
vds	Vindesine


Distribution of drug dose: kum_cp
Prozent
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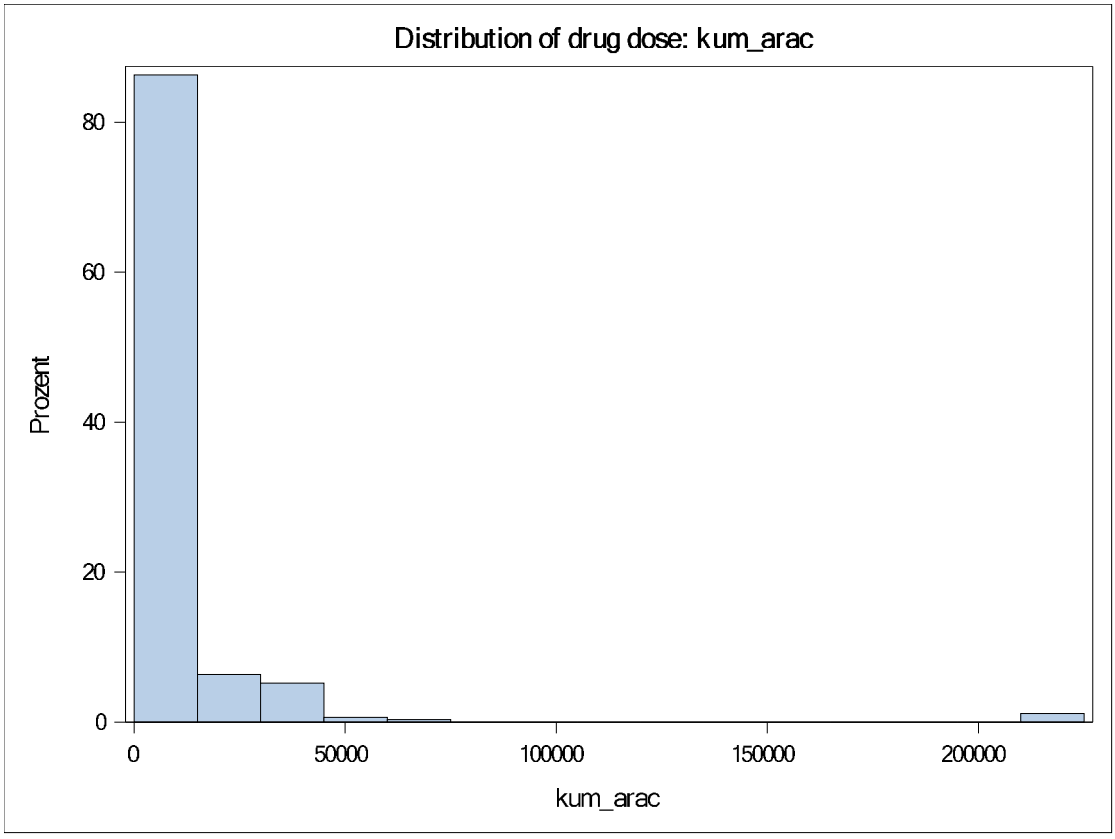
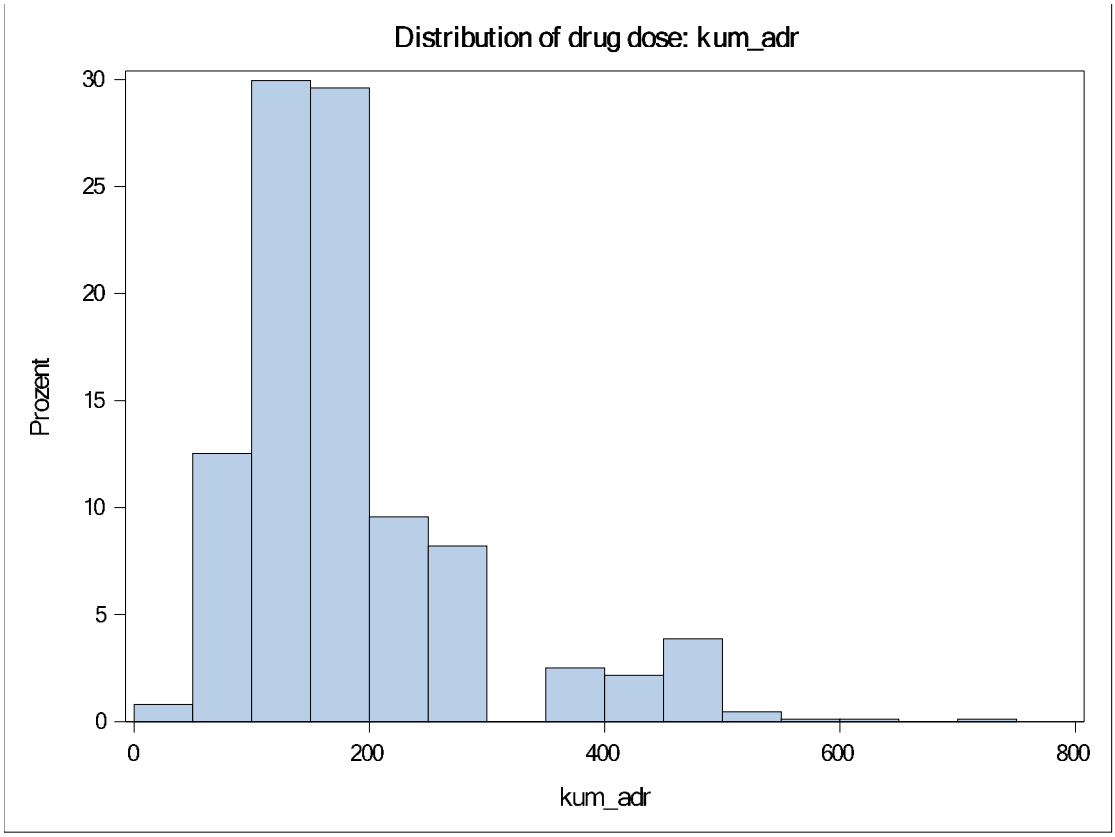
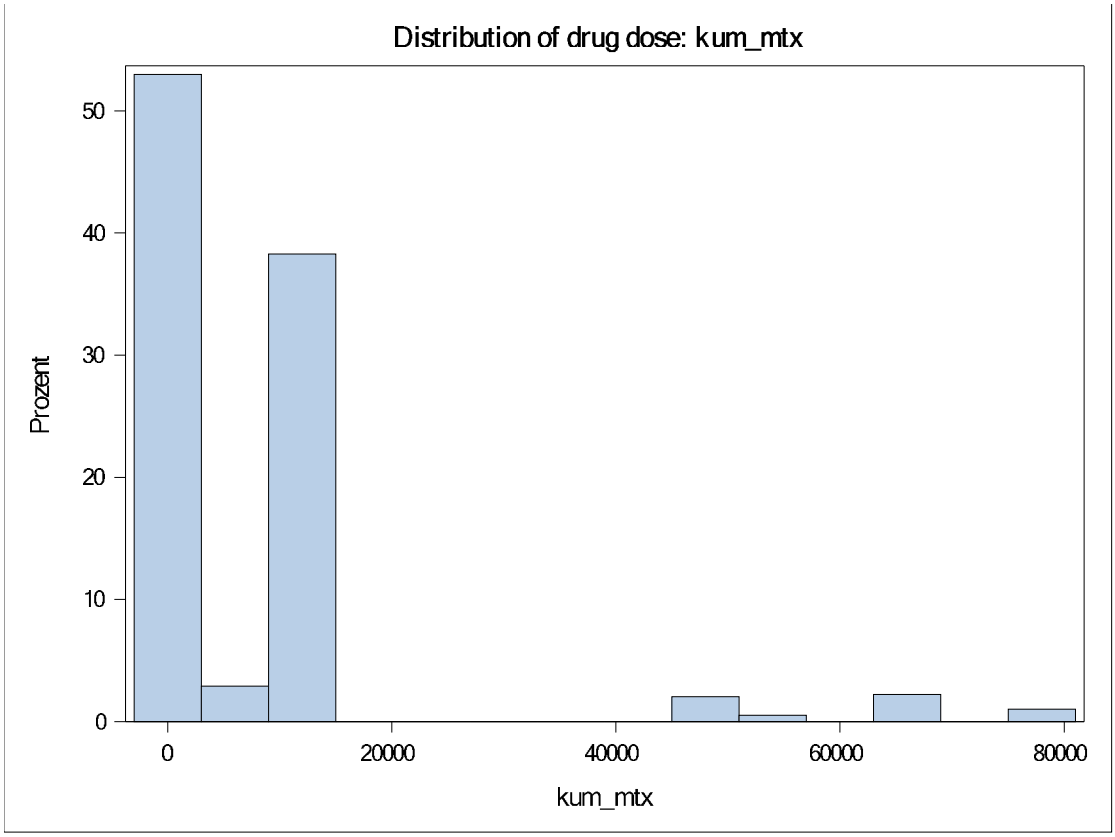
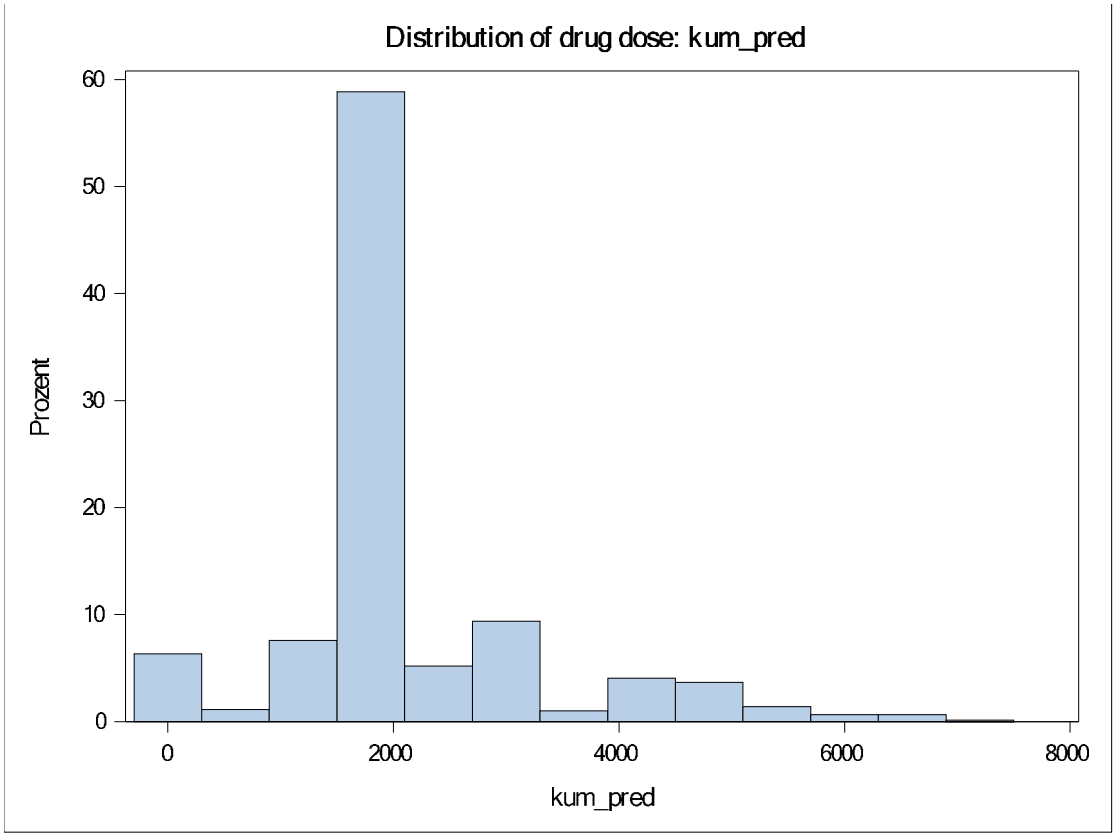
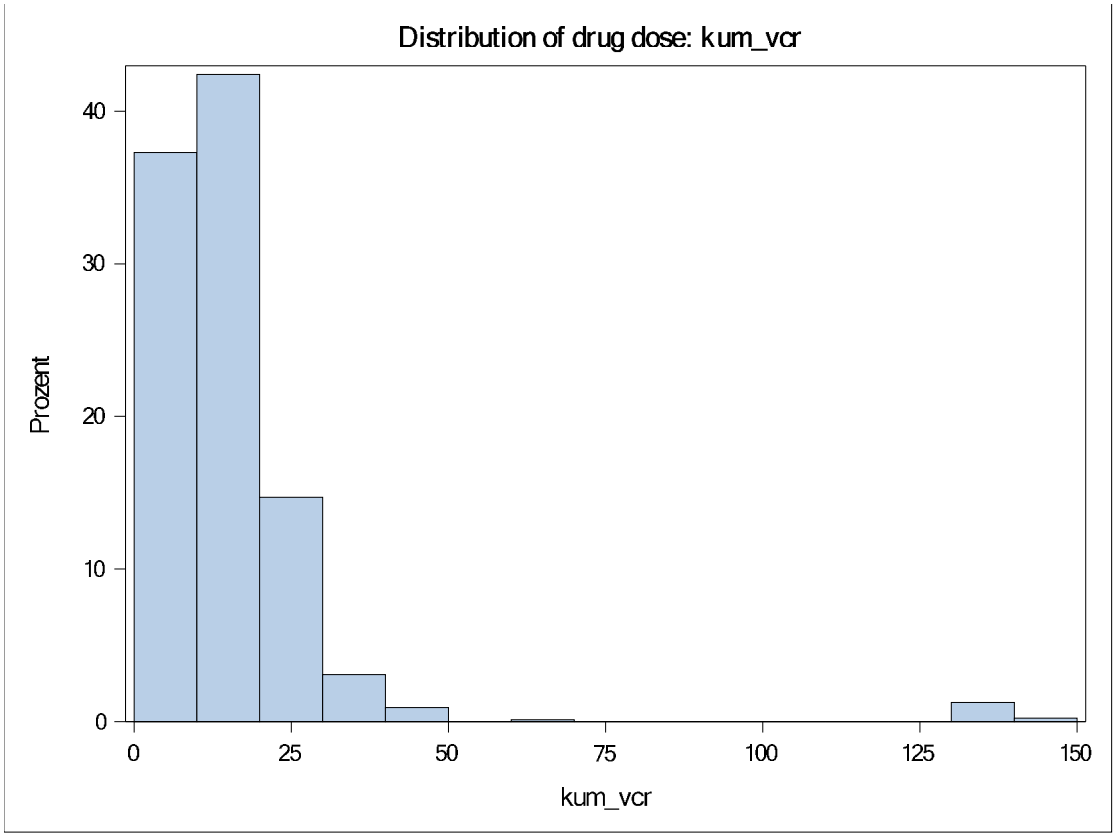
10
20
30
40
50
0
5000
10000
15000
20000
25000
kum_cp

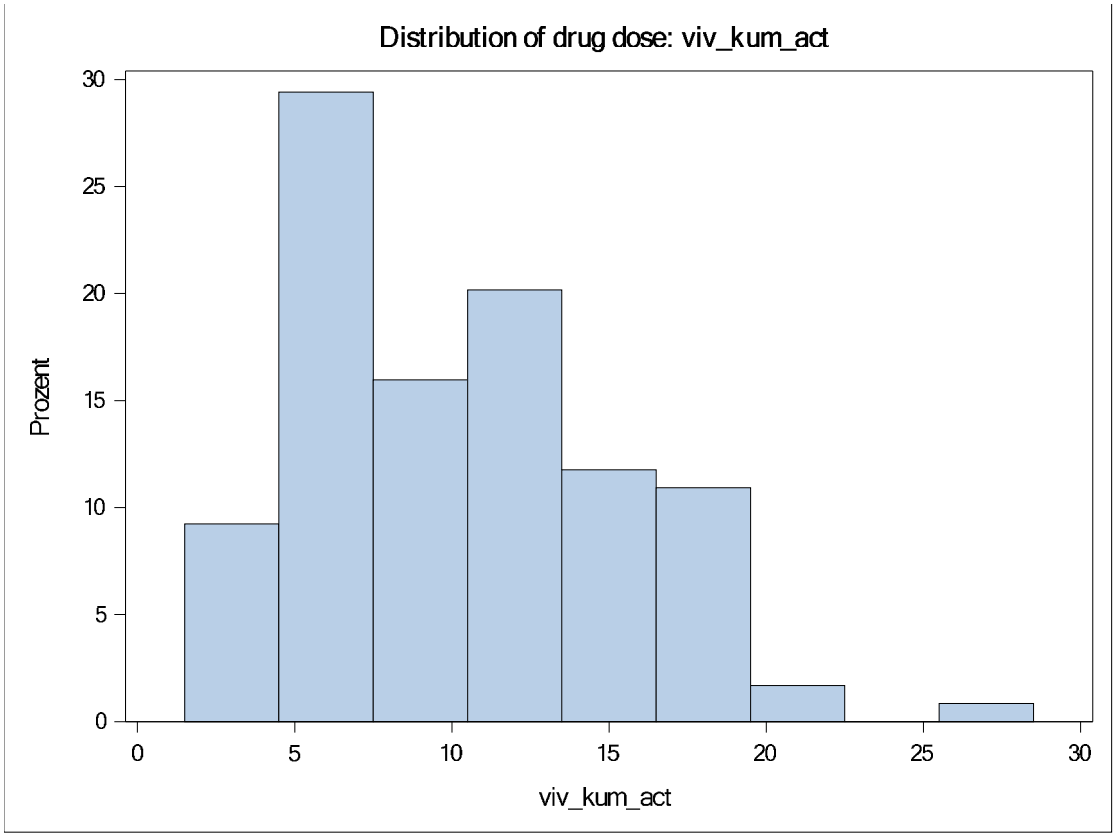

Distribution of drug dose: kum_arac
Prozent
0
20
40
60
80
0
50000
100000
150000
200000
kum_arac

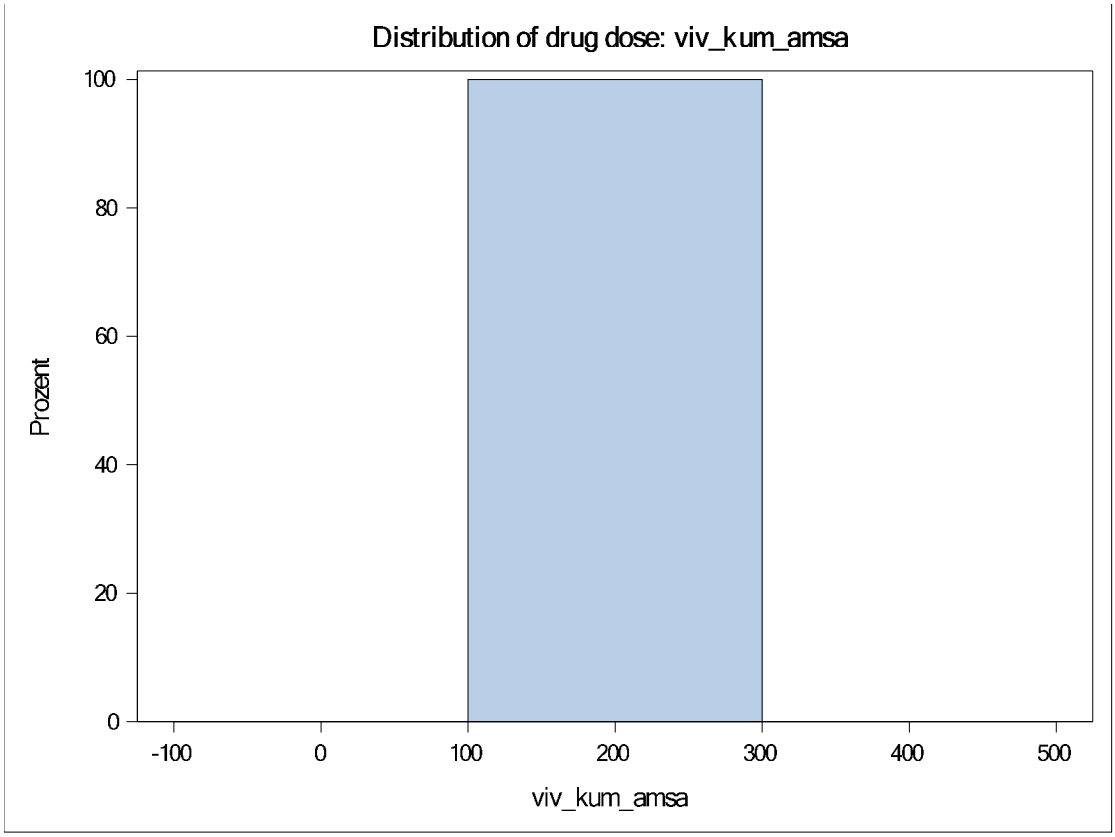

Distribution of drug dose: kum_adr
Prozent
30
25
20
15
10
5
0
0
200
400
600
800
kum_adr

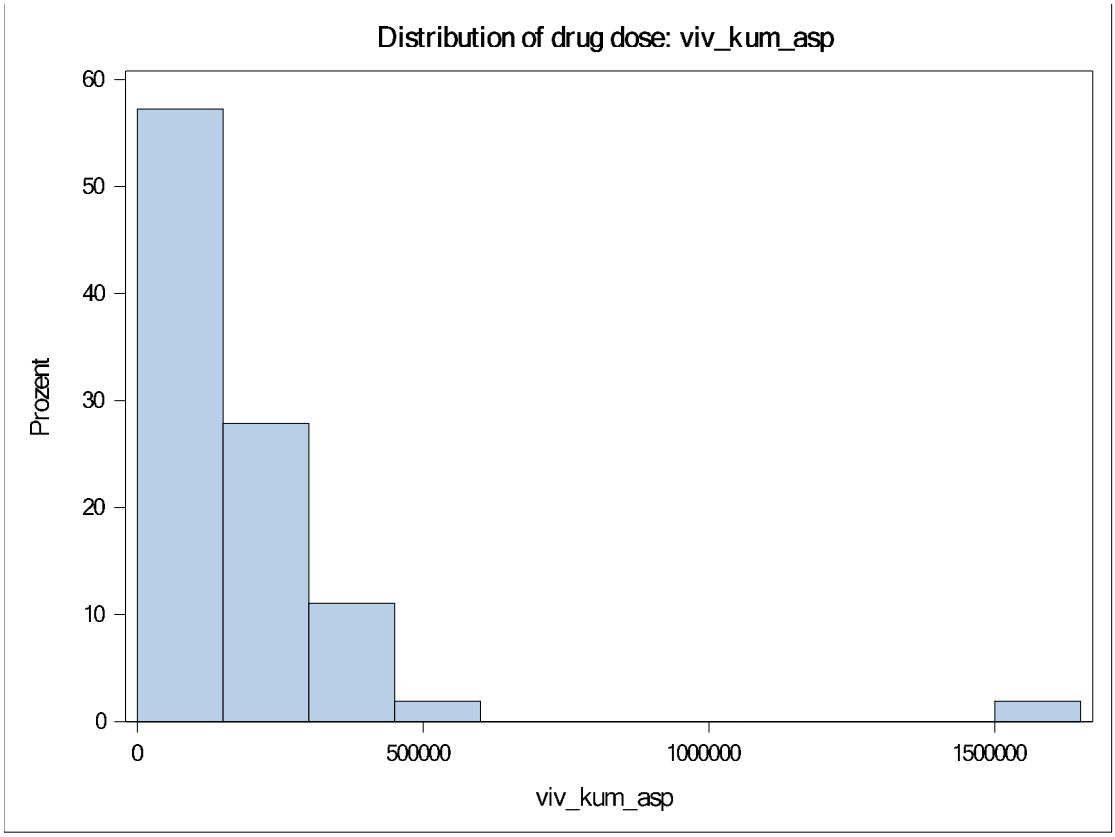

Distribution of drug dose: kum_mtx
Prozent
50
40
30
20
10
0
0
20000
40000
60000
80000
kum_mtx

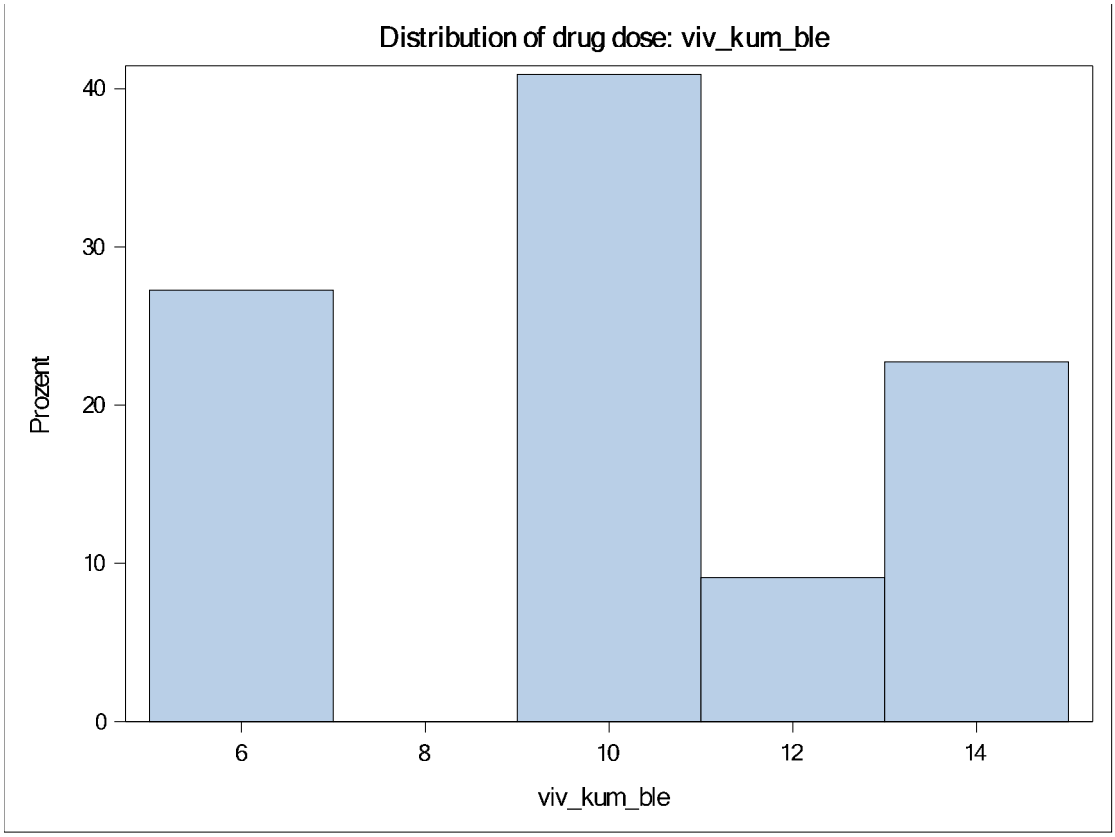

Distribution of drug dose: kum_pred
Prozent
60
50
40
30
20
10
0
0
2000
4000
6000
8000
kum_pred

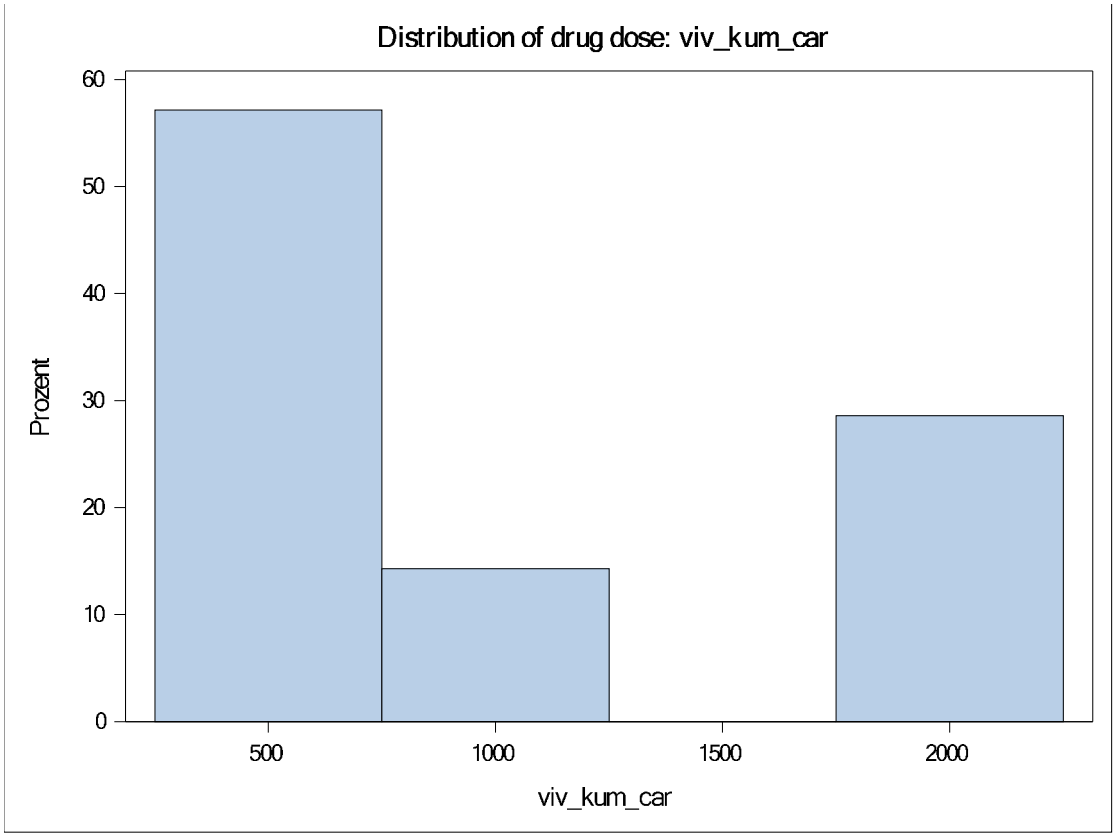

Distribution of drug dose: kum_vcr
Prozent
40
30
20
10
0
0
25
50
75
100
125
150
kum_vcr

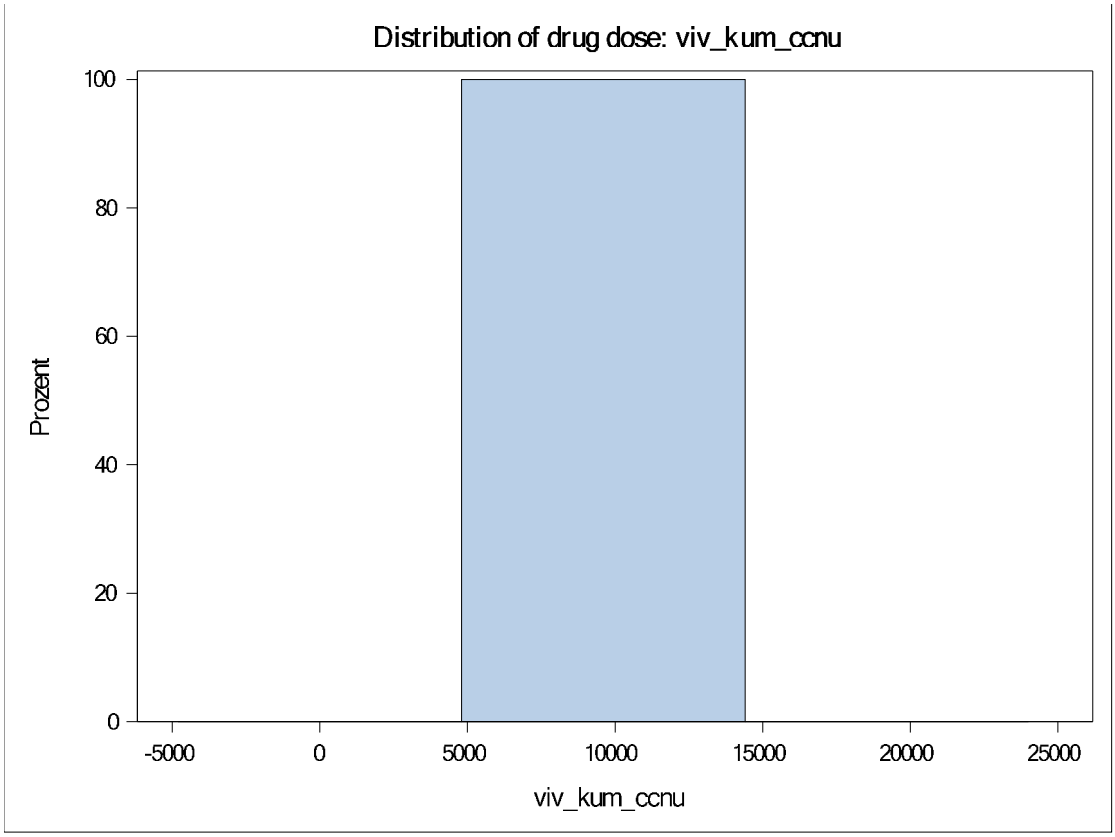

Distribution of drug dose: viv_kum_act
Prozent
30
25
20
15
10
5
0
0
5
10
15
20
25
30
viv_kum_act

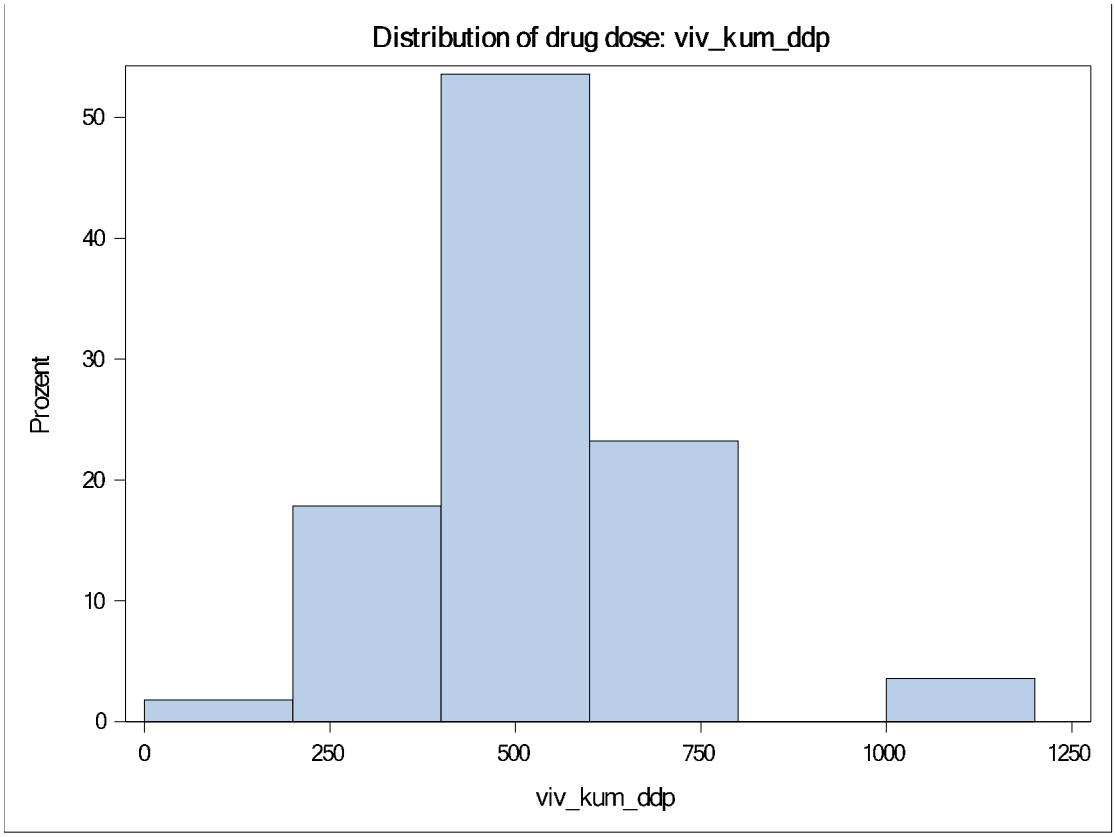

Distribution of drug dose: viv_kum_amsa
Prozent
100
80
60
40
20
0
-100
0
100
200
300
400
500
viv_kum_amsa

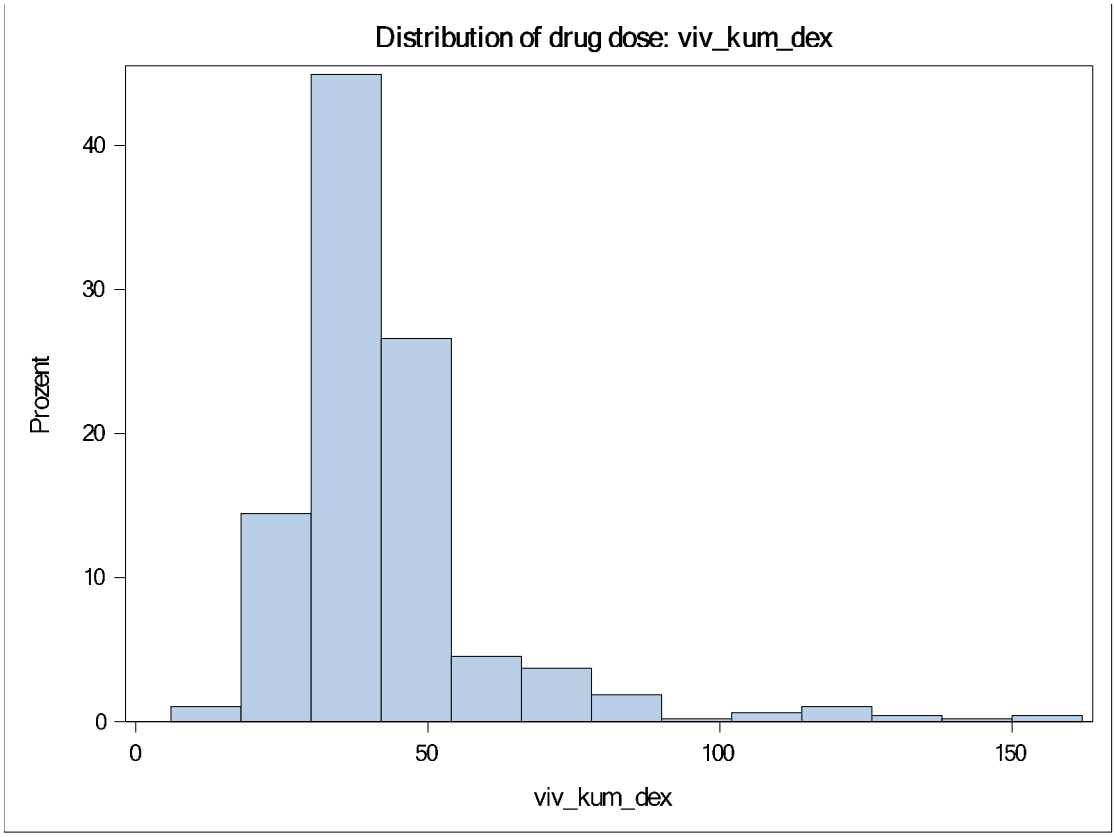

Distribution of drug dose: viv_kum_asp
Prozent
60
50
40
30
20
10
0
0
500000
1000000
1500000
viv_kum_asp

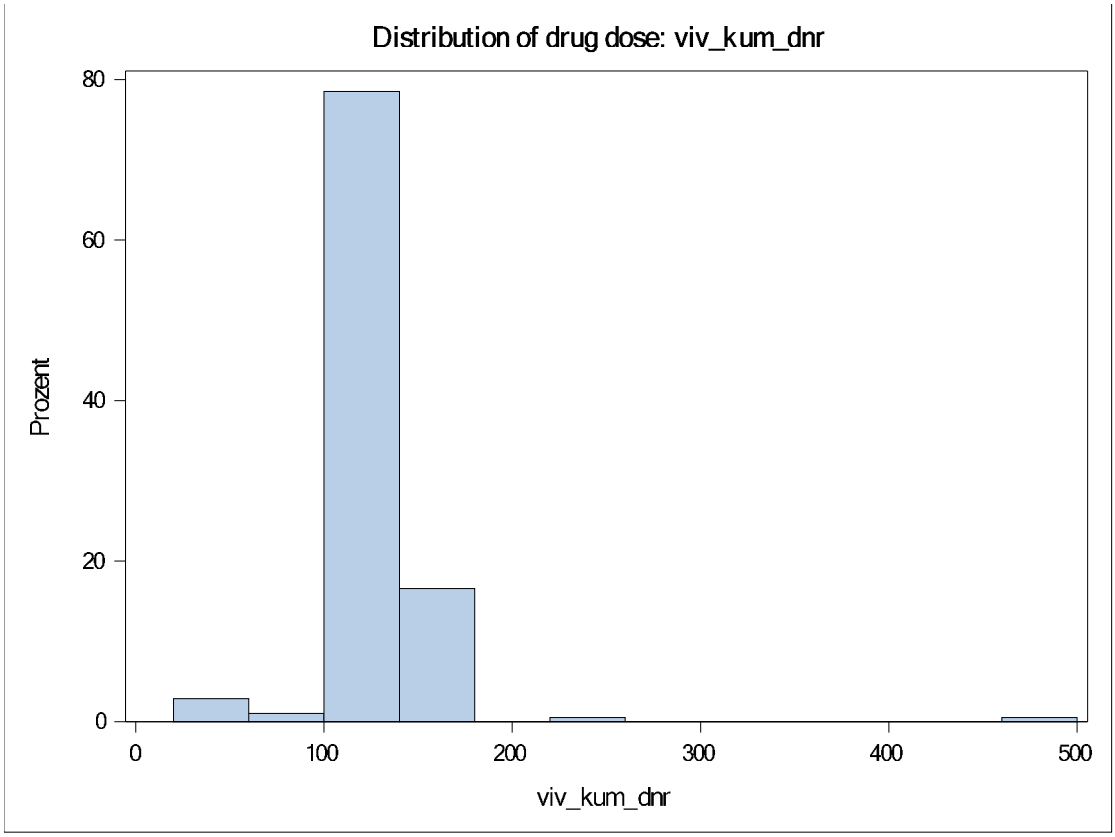

Distribution of drug dose: viv_kum_ble
Prozent
40
30
20
10
0
6
8
10
12
14
viv_kum_ble

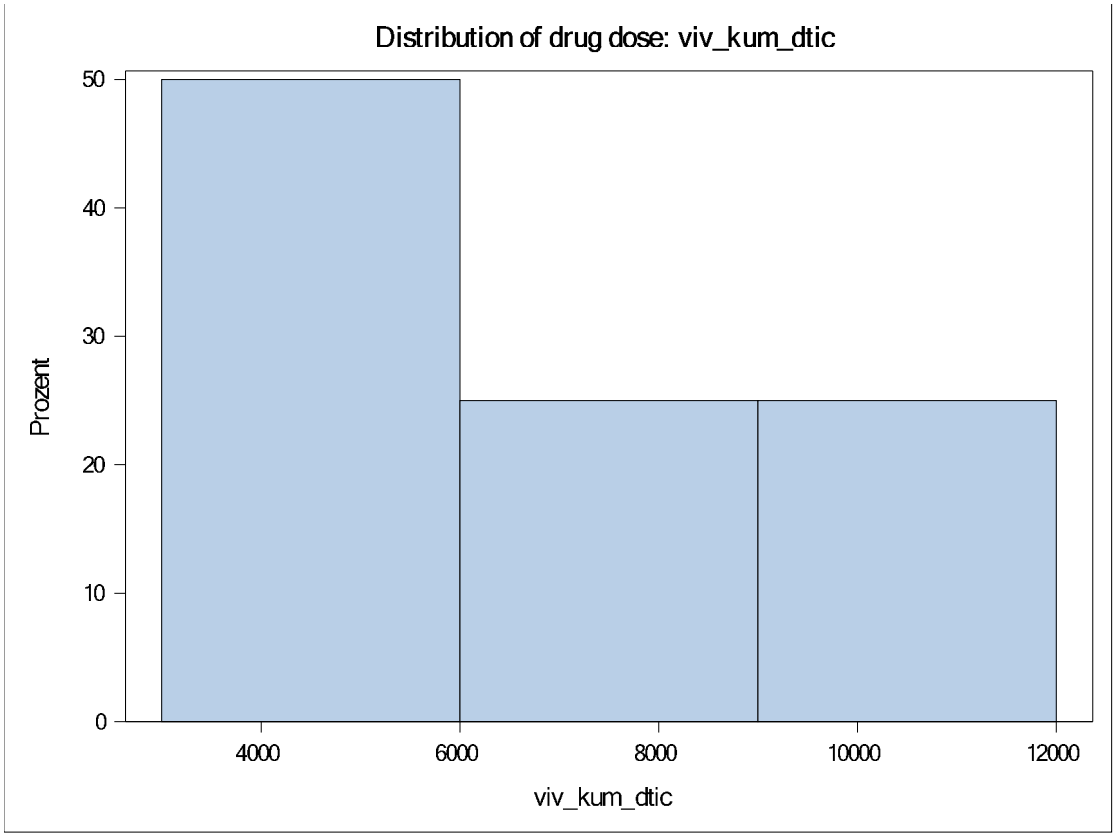

Distribution of drug dose: viv_kum_car
Prozent
60
50
40
30
20
10
0
500
1000
1500
2000
viv_kum_car

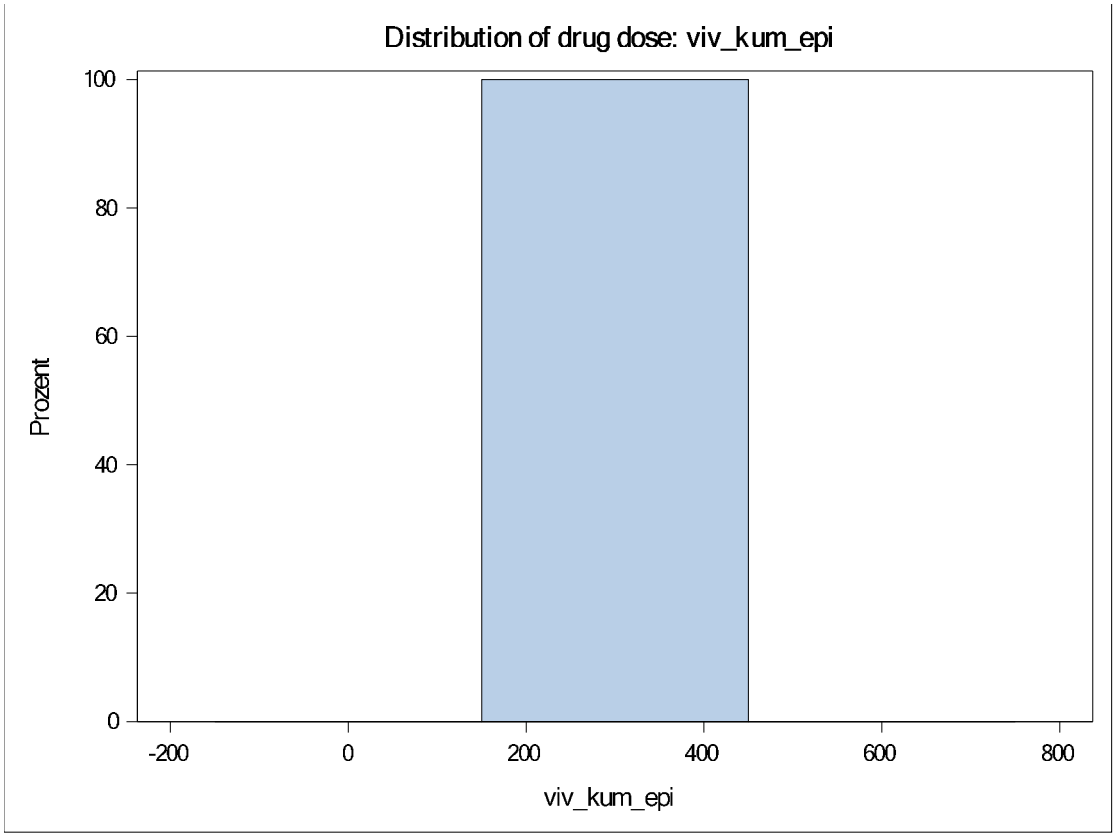

Distribution of drug dose: viv_kum_ccnu
Prozent
100
80
60
40
20
0
-5000
0
5000
10000
15000
20000
25000
viv_kum_ccnu

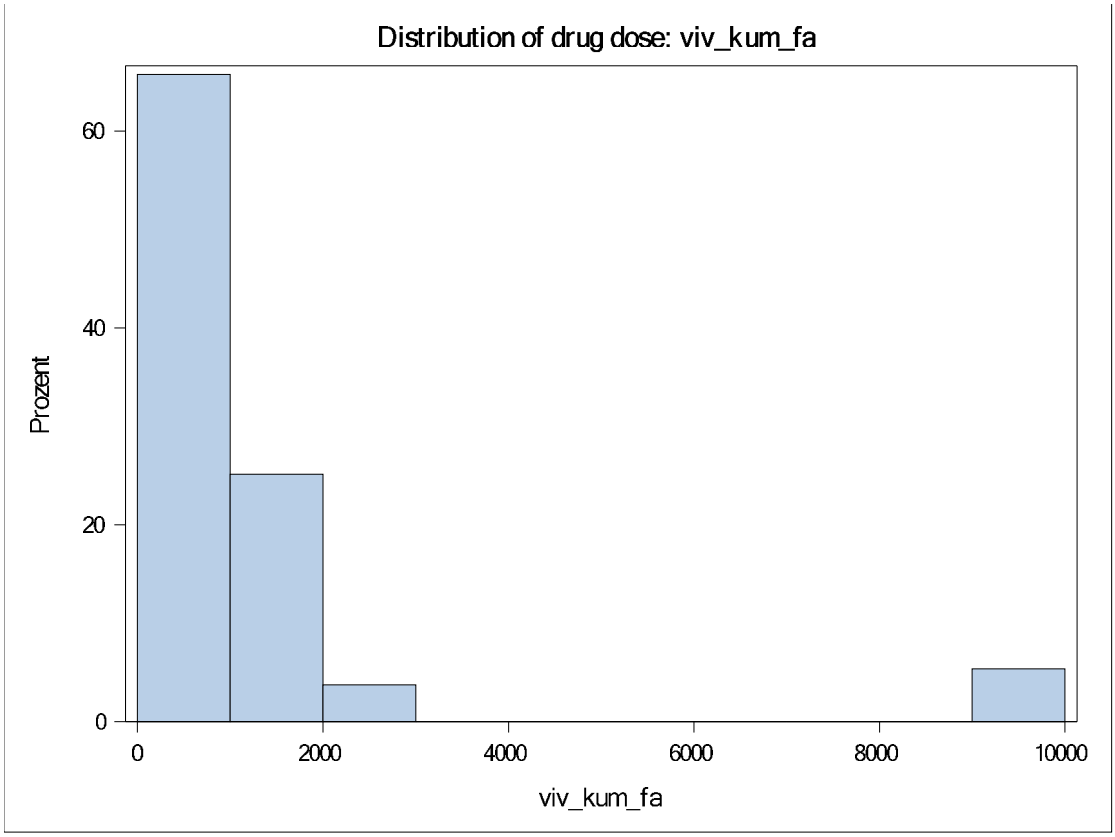

Distribution of drug dose: viv_kum_ddp
Prozent
0
10
20
30
40
50
0
250
500
750
1000
1250
viv_kum_ddp

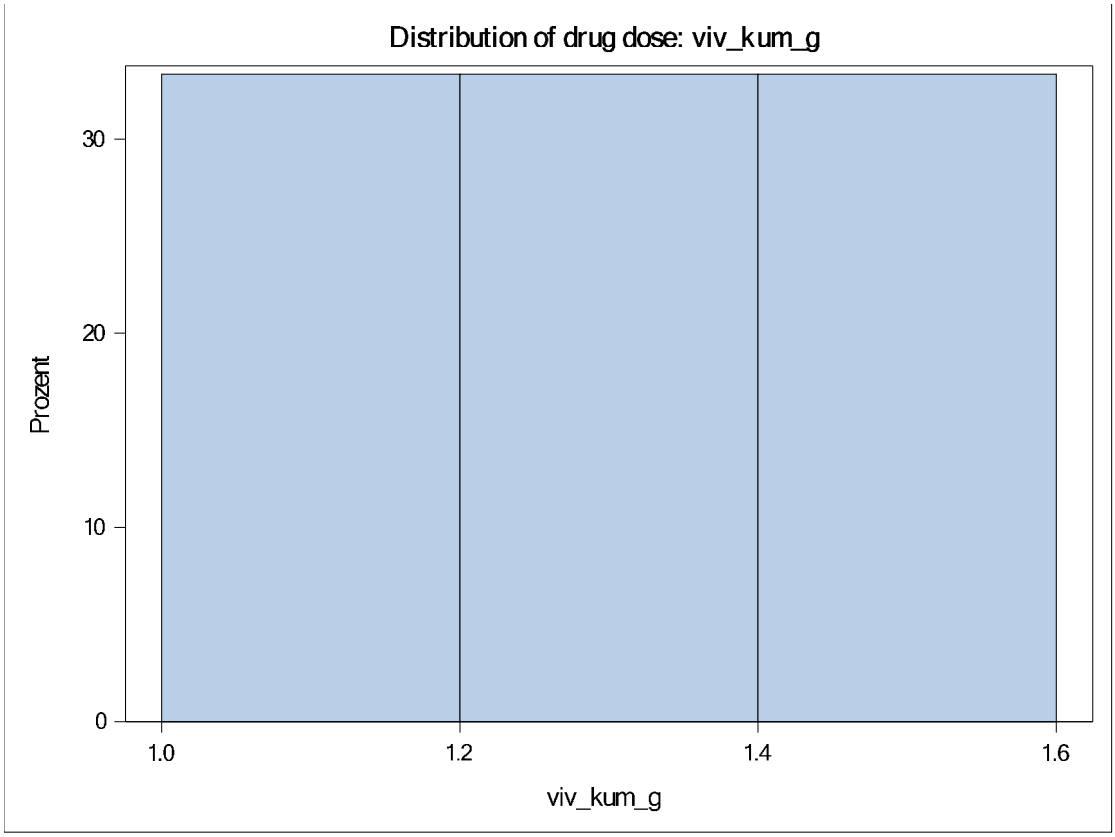

Distribution of drug dose: viv_kum_dex
Prozent
0
10
20
30
40
0
50
100
150
viv_kum_dex

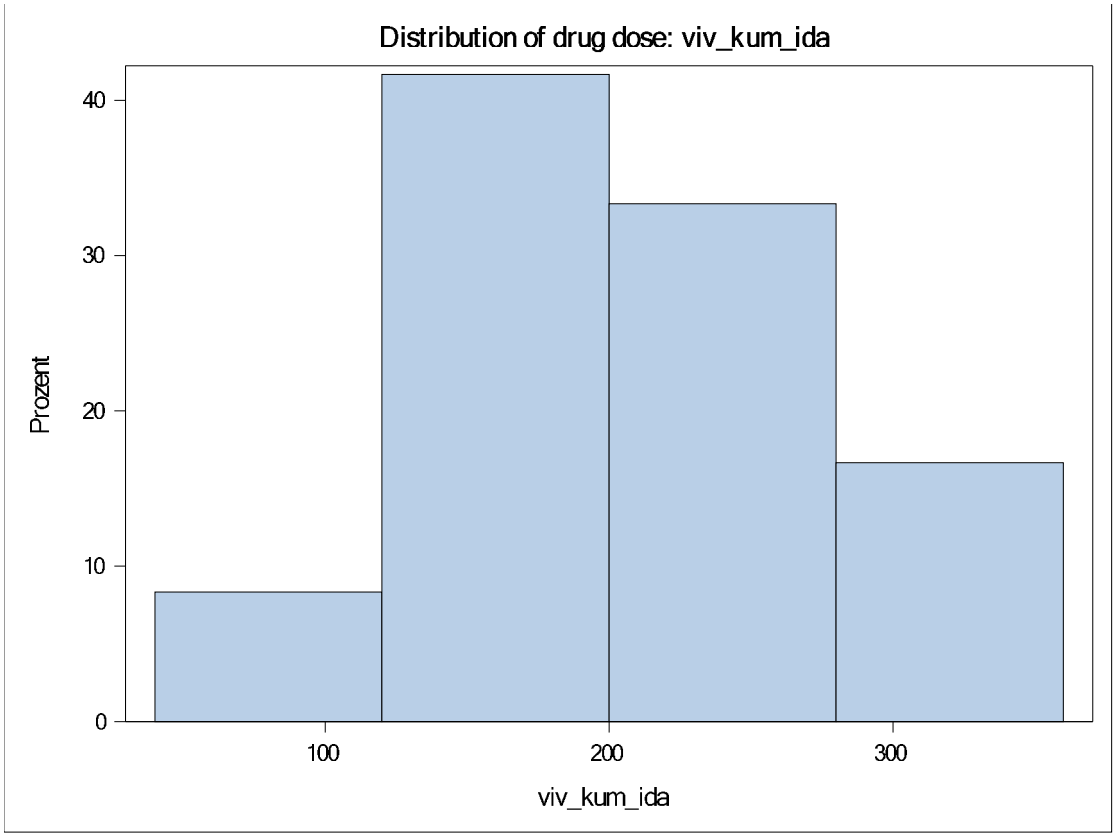

Distribution of drug dose: viv_kum_dnr
Prozent
80
60
40
20
0
0
100
200
300
400
500
viv_kum_dnr

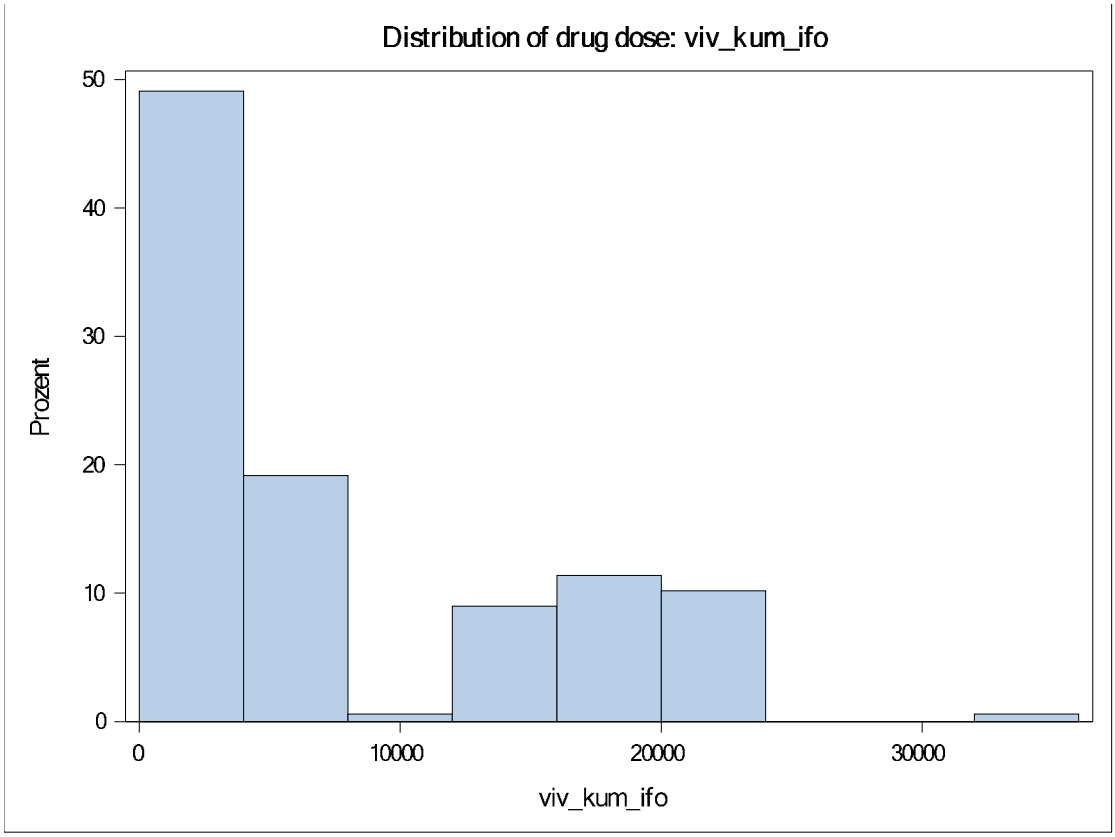

Distribution of drug dose: viv_kum_dtic
Prozent
50
40
30
20
10
0
4000
6000
8000
10000
12000
viv_kum_dtic

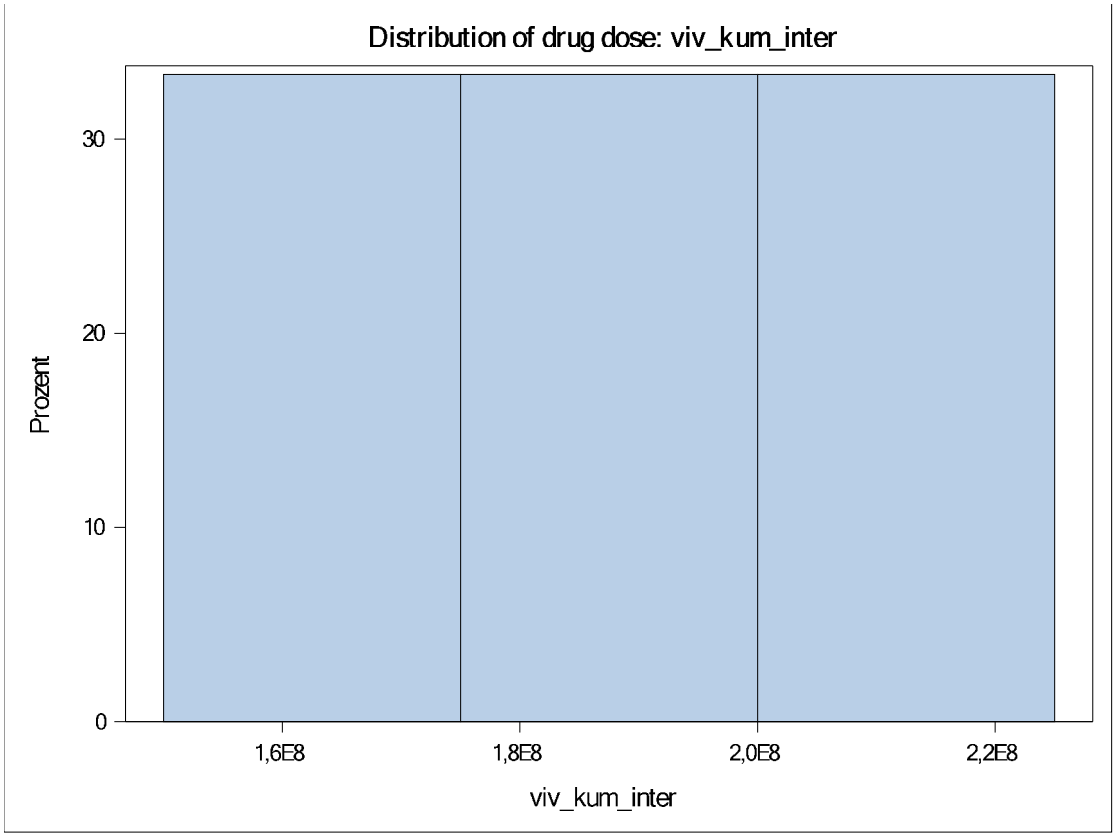

Distribution of drug dose: viv_kum_epi
Prozent
100
80
60
40
20
0
-200
0
200
400
600
800
viv_kum_epi

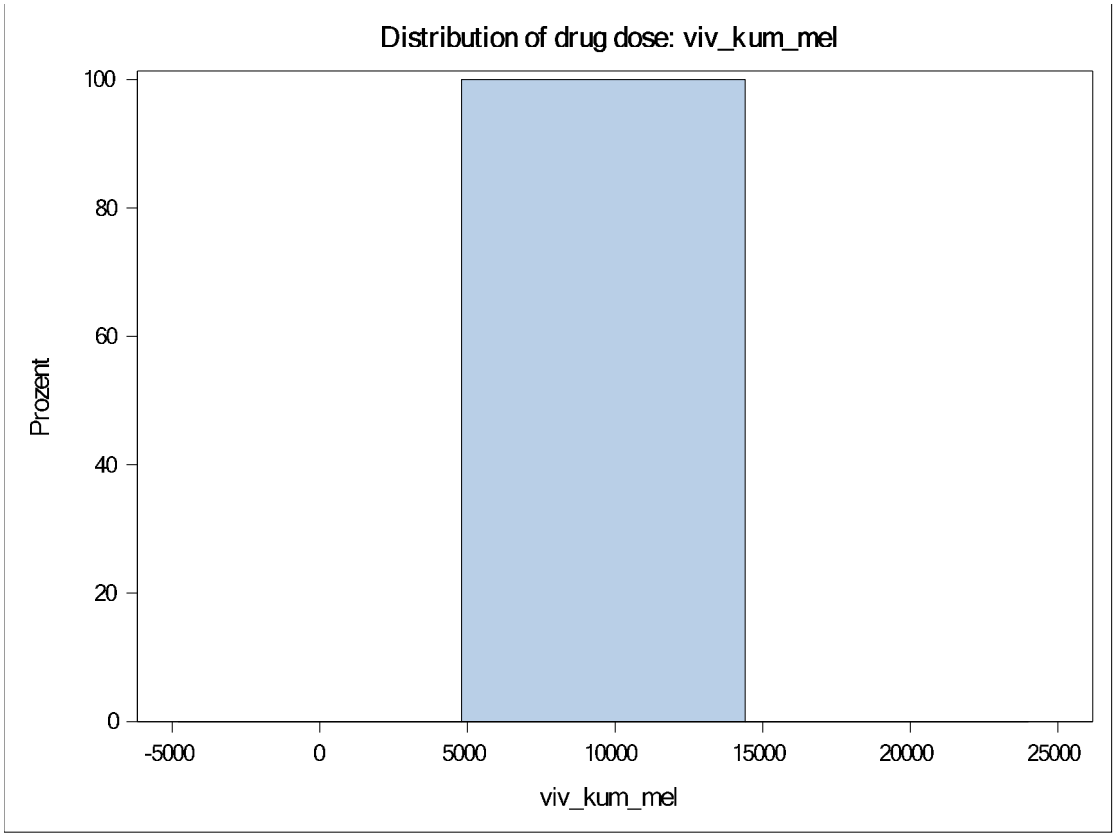

Distribution of drug dose: viv_kum_fa
Prozent
60
40
20
0
0
2000
4000
6000
8000
10000
viv_kum_fa

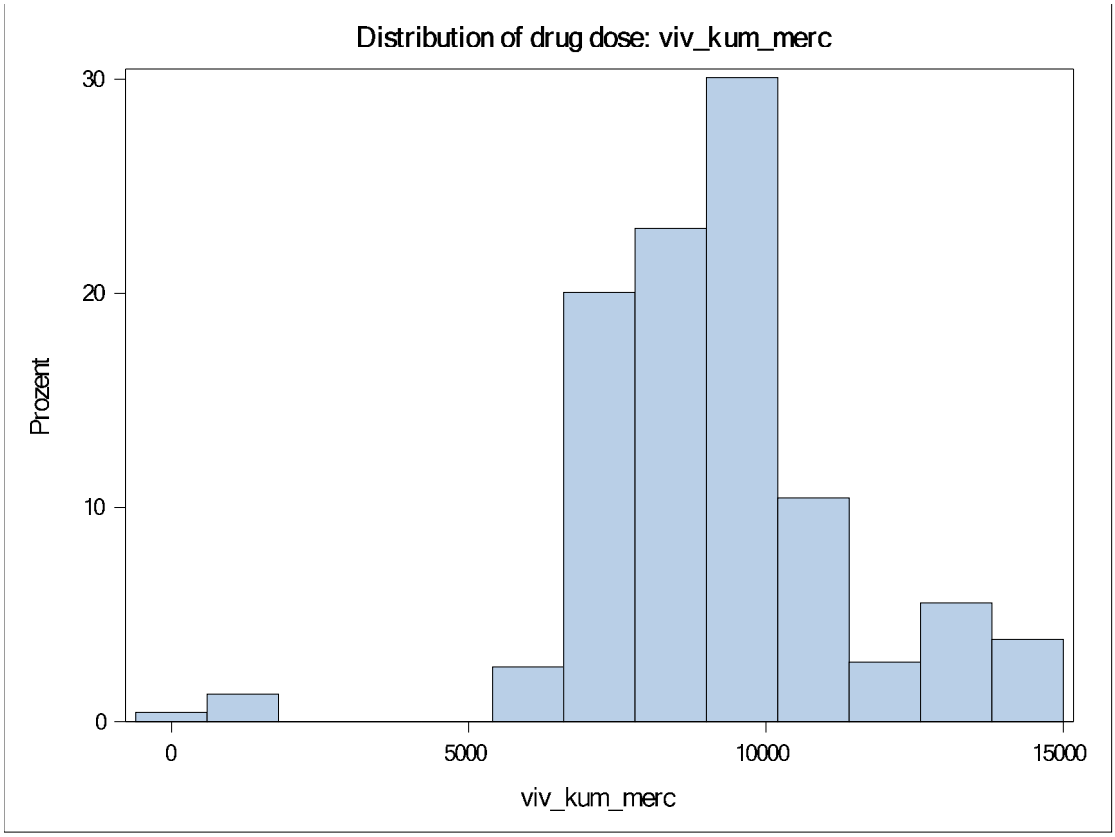

Distribution of drug dose: viv_kum_g
Prozent
0
10
20
30
1.0
1.2
1.4
1.6
viv_kum_g

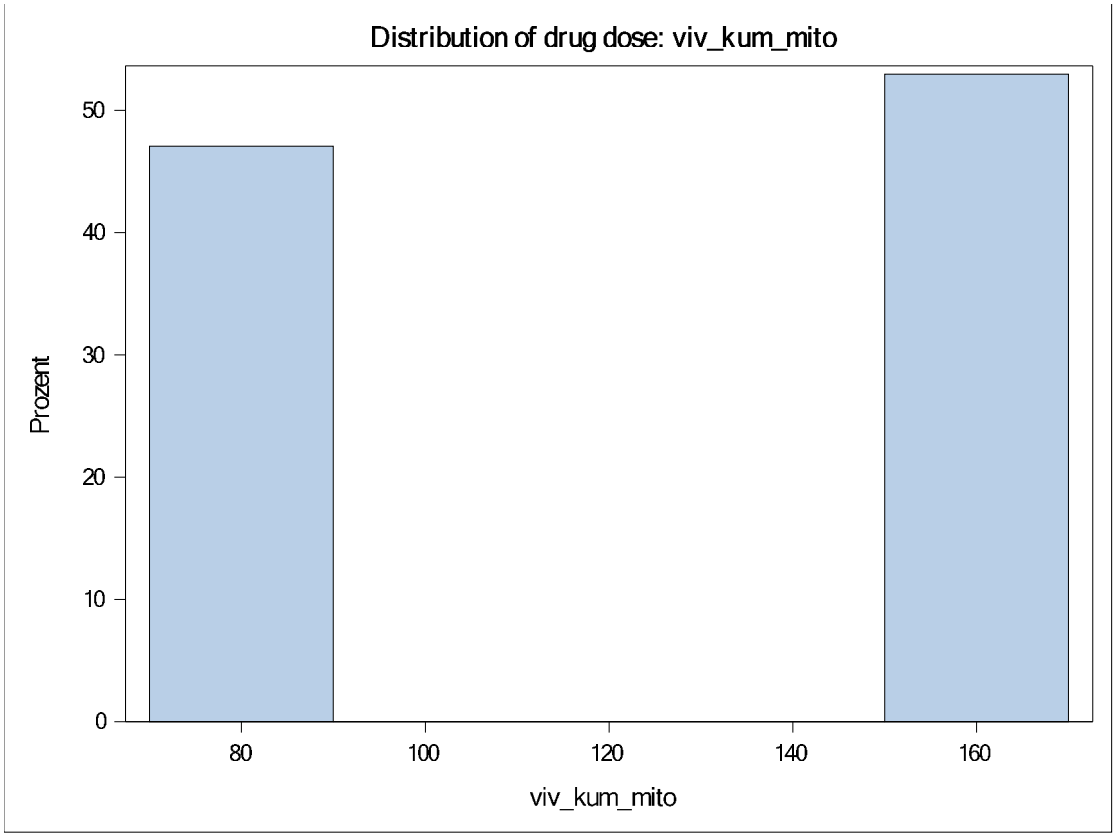

Distribution of drug dose: viv_kum_ida
Prozent
0
10
20
30
40
100
200
300
viv_kum_ida

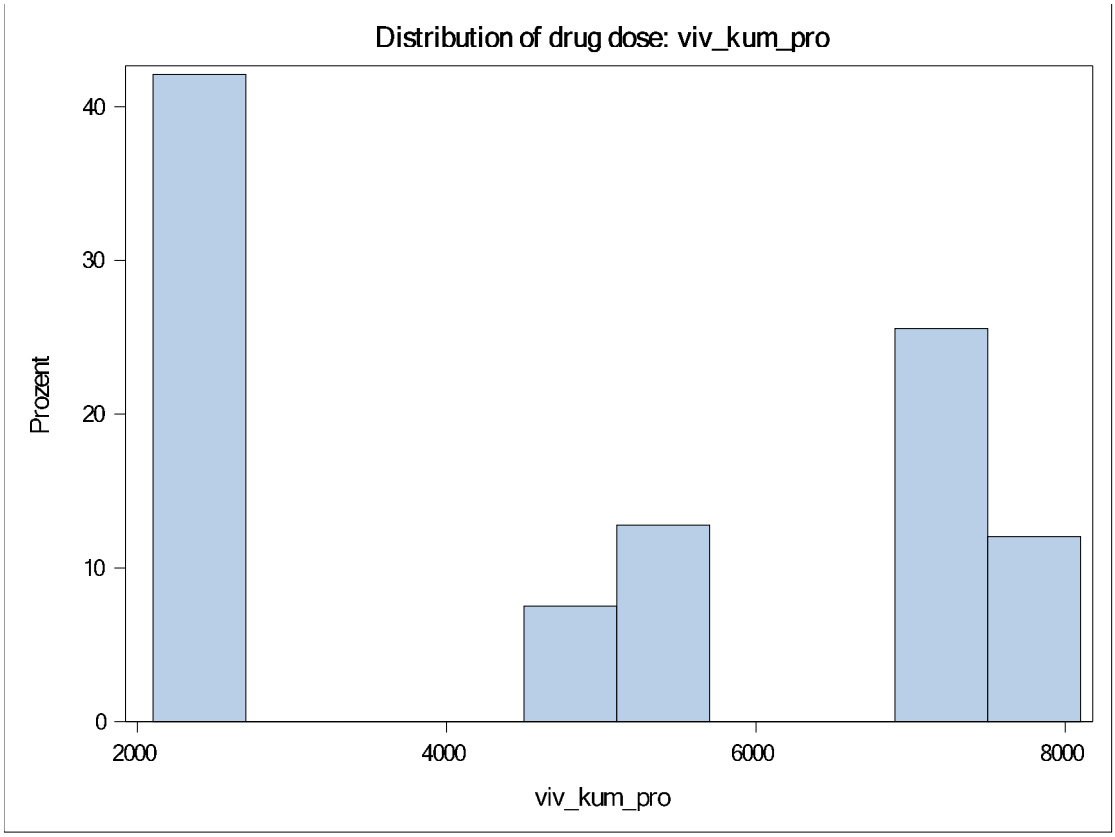

Distribution of drug dose: viv_kum_ifo
Prozent
50
40
30
20
10
0
0
10000
20000
30000
viv_kum_ifo

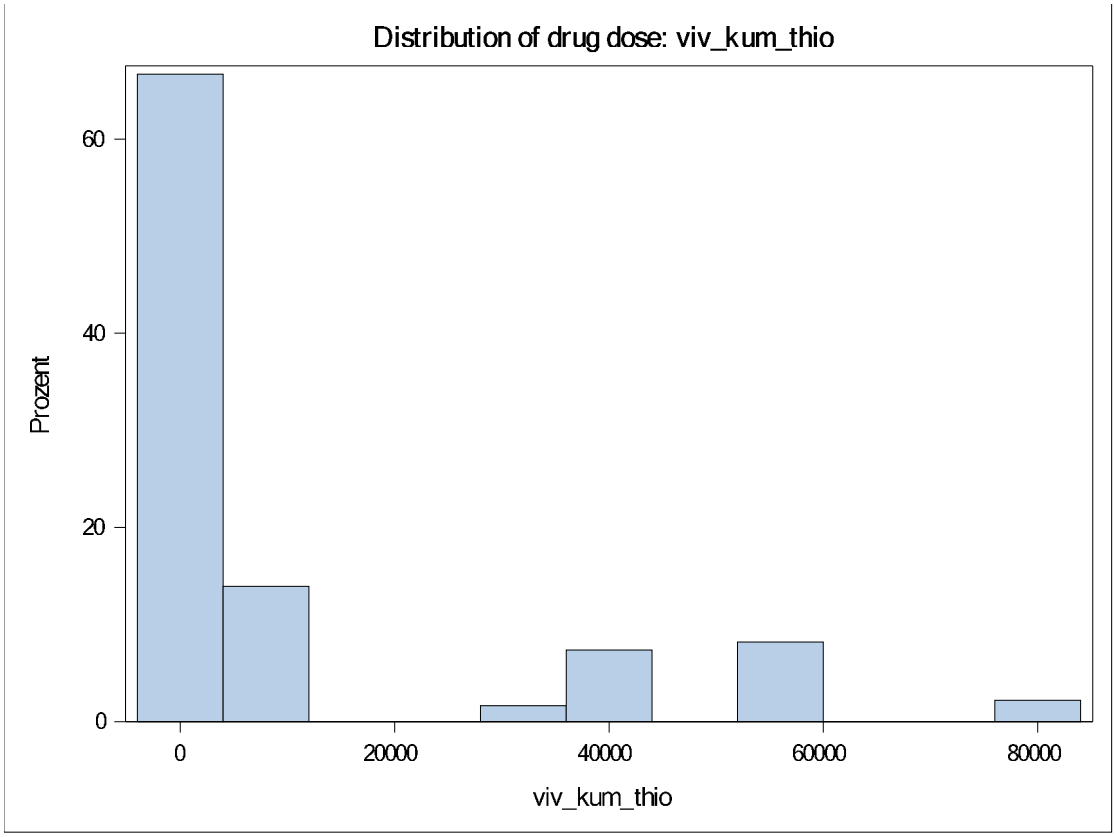

Distribution of drug dose: viv_kum_inter
Prozent
30
20
10
0
1,6E8
1,8E8
2,0E8
2,2E8
viv_kum_inter

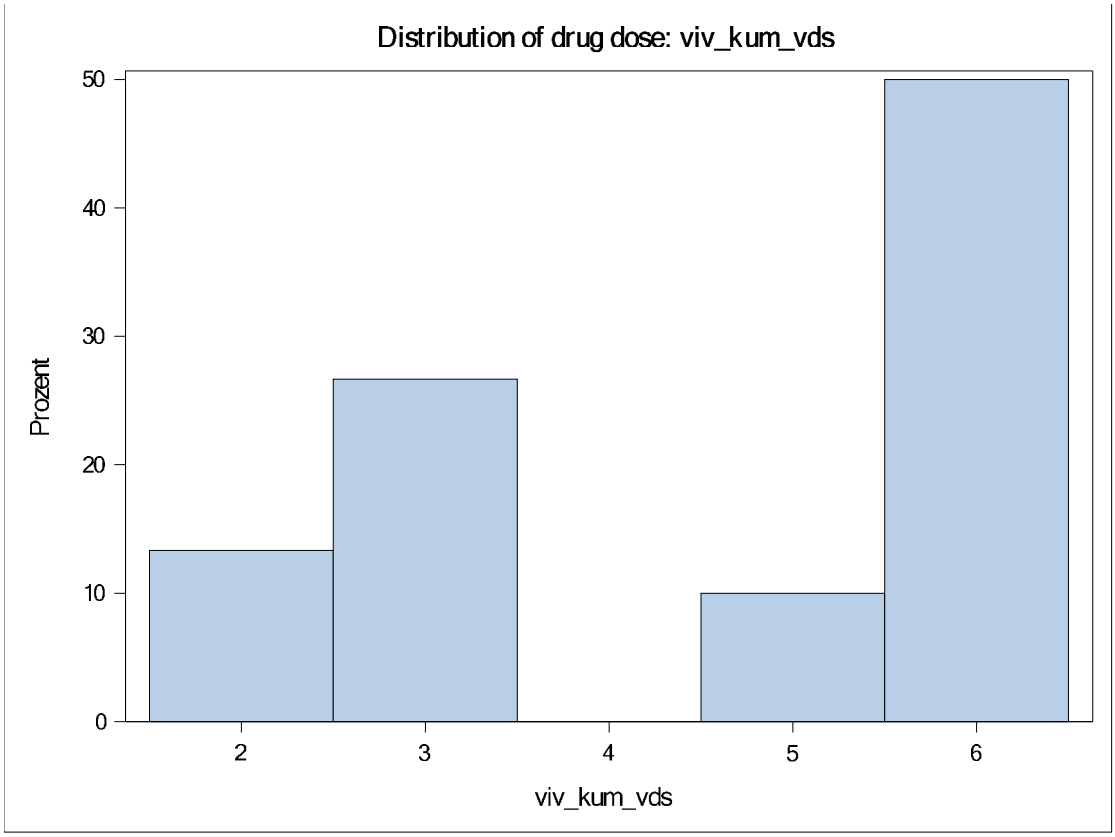

Distribution of drug dose: viv_kum_mel
Prozent
100
80
60
40
20
0
-5000
0
5000
10000
15000
20000
25000
viv_kum_mel

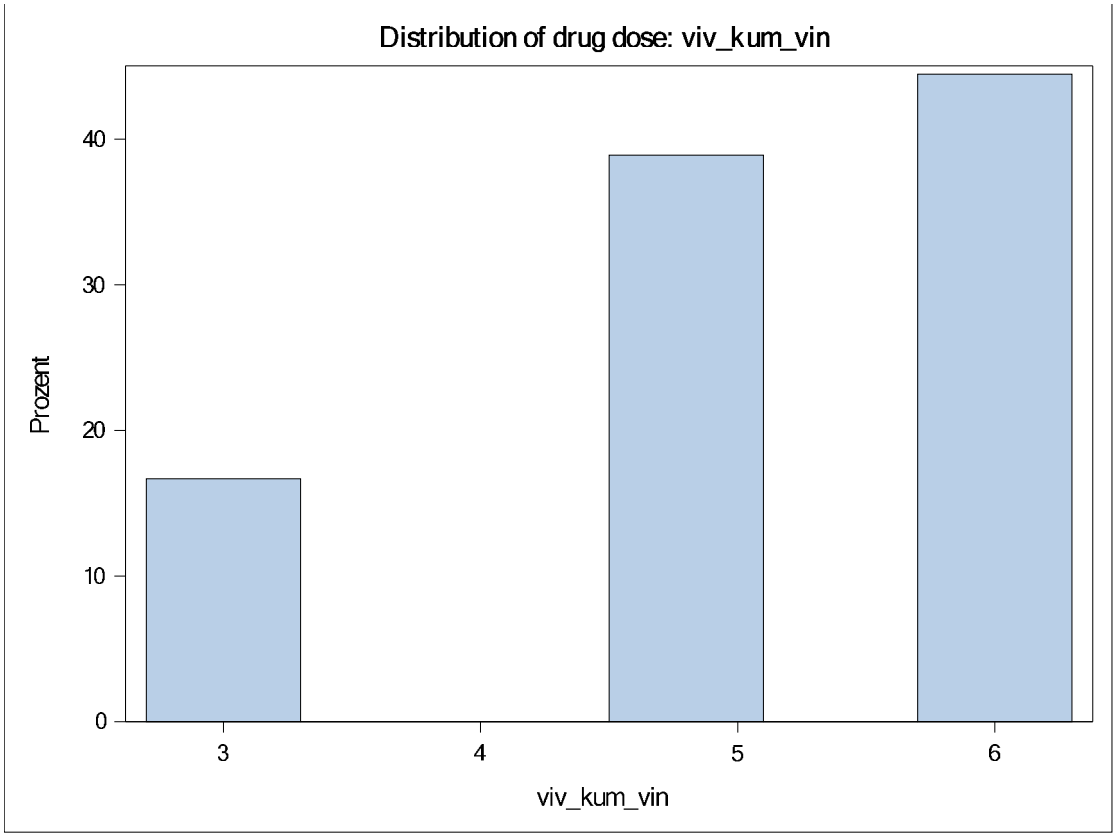

Distribution of drug dose: viv_kum_merc
Prozent
30
20
10
0
0
5000
10000
15000
viv_kum_merc

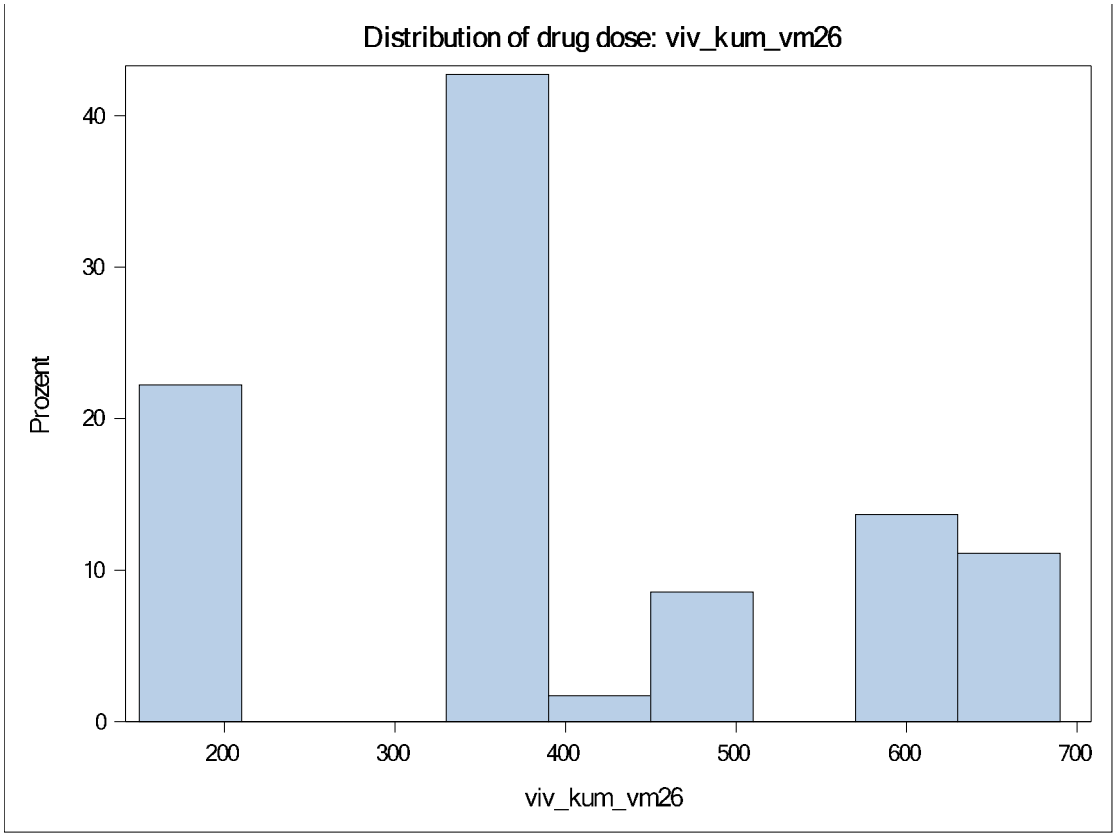

Distribution of drug dose: viv_kum_mito
Prozent
0
10
20
30
40
50
80
100
120
140
160
viv_kum_mito

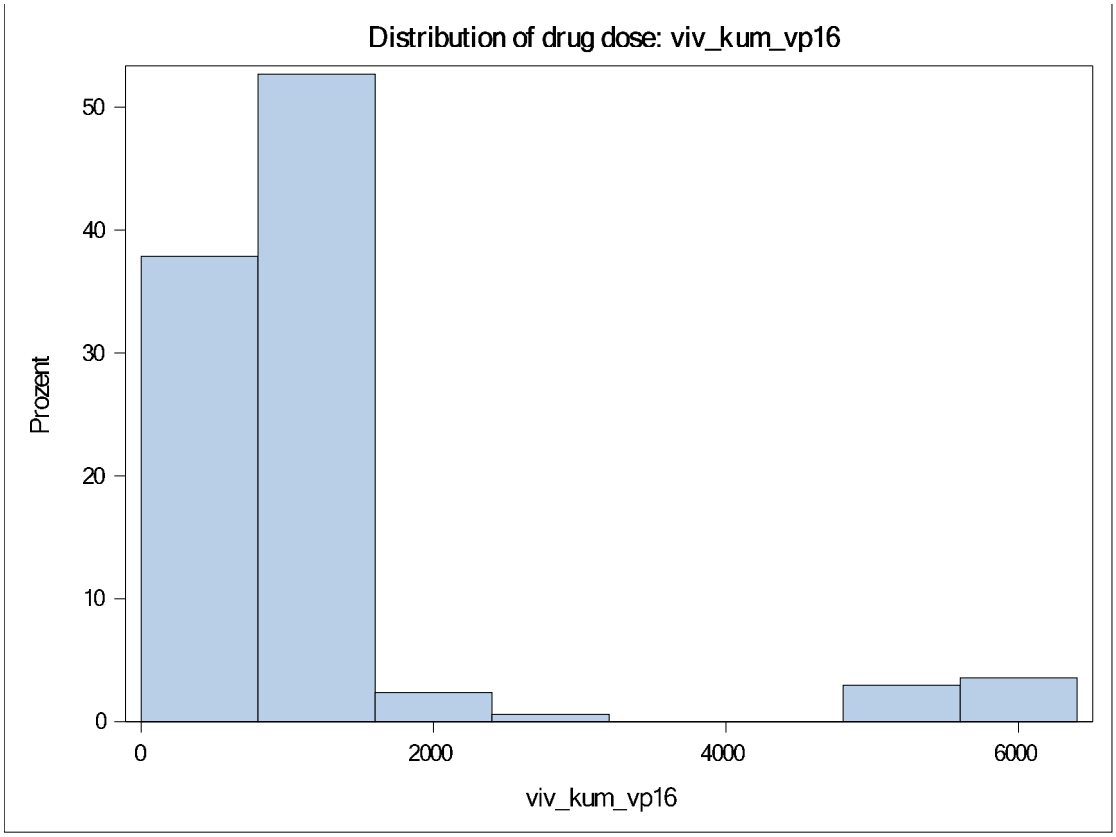

Distribution of drug dose: viv_kum_pro
Prozent
0
10
20
30
40
2000
4000
6000
8000
viv_kum_pro


Distribution of drug dose: viv_kum_thio
Prozent
60
40
20
0
0
20000
40000
60000
80000
viv_kum_thio


Distribution of drug dose: viv_kum_vds
Prozent
50
40
30
20
10
0
2
3
4
5
6
viv_kum_vds


Distribution of drug dose: viv_kum_vin
Prozent
0
10
20
30
40
3
4
5
6
viv_kum_vin


Distribution of drug dose: viv_kum_vm26
Prozent
0
10
20
30
40
200
300
400
500
600
700
viv_kum_vm26


Distribution of drug dose: viv_kum_vp16
Prozent
50
40
30
20
10
0
0
2000
4000
6000
viv_kum_vp16

7 Case-control study: Decisions on handling extreme dose values

If patients were the only patients in a study arm, I assumed that the extreme dose value was part of the treatment in this arm. For some protocols, I could verify this assumption. COALL (Co-operative Study Group for Childhood Acute Lymphoblastic Leukemia) protocols were protocols which generally seemed to use higher chemotherapy doses than other protocols. High dose values in COALL study arms were therefore not regarded as unusual. In summary, I assumed that the cumulative doses extracted from the GPOH database were correct and did not exclude any values.

Table 21 Decisions extreme dose values.[1]

Sub-stance	Description of extreme dose value[2]	Basis for decision: if patients were the only patient in a study arm, I assumed that the extreme dose value was part of the treatment in this arm	Decision
Ifos-famide	highest value 35,136 mg/m² (n = 1) much higher than second highest value of 21,960 mg/m²	patient with high value is the only patient in therapy group: CWS 86, Stadium III, PR<2/3, Bestrahlung therapy group includes several cycles of VAIA II, which each includes 18,000 mg/m² ifosfamide high dose is possible	leave in
Cyclo-phos-phamide	lowest value is 75mg/m² (n = 1), which is much lower than the rest of the dose range	patient with low value is the only patient in therapy group: NB-85, Stadium IV-S, Leberbestrahlung, CPM oral, OP S stands for Säugling (infant), and I assume that this is the reason for the low dose	leave in
Vin-cristine	highest values of >134 mg/m² (n = 13) much higher than next highest value of 60	all patients with high values treated according to protocol COALL 97 high dose is part of the protocol	leave in
Cy-tarabine	highest value of 217,320 (n = 7) much higher than second highest value of 66,285	all patients treated in therapy group COALL-85, HR-Gruppe, Zweig: konventionell, >50.000/nl	leave in
Aspara-ginase	highest value of 1,620,000 (n = 9) is much higher than second highest value of 540,000	all patients treated according to protocol COALL 07-03	leave in
Dauno-rubicin	highest value of 480 (479.9999981) (n = 2) is much higher than	patients with high values are the only patients in high risk groups in protocol COALL 08-09	leave in

	second highest value of 225		
Mer-capto-purine	lowest values below 871 (n = 8) are much lower than next values starting with 5647	patients are only patients each from groups: ALL-90, HRG-1, ZNS-neg, SZT vom MSD, COALL 08-09, HR-Intensiviert,proB-ALL, 1. Rando Clofarabin, COALL-92, HR, ZNS neg, DNR 1h, Alter >2J, Dauertx. 6-TG, COALL-92, LR, DNR 1h, Dauertx. Mit 6-TG, COALL-92, LR, DNR 24h, Dauerthx 6-TG, patients in the treatment arms SRG and MRG had much higher doses of Mercaptopurine than those in the HRG arm	leave in
meto-threxate	majority of values below 14912, data gap to next highest value of 45,369	patients with high values are the only patients treated according to COSS protocols (80,86, 86S, 91, 96), and two patients with high values were treated according to the two high risk ALL-2000 groups ALL-2000, HR, R1: Dexa, R3: Protokoll III, Schädelbestrahlun, ALL-2000, HR, R1: Pred, R3: Protokoll III, Schädelbestrahlun	leave in
anti-metabo-lites	highest values of 238,323 – 238,384 (n = 7) much higher than second highest value of 109,540	patients treated according to study arm COALL-85, HR-Gruppe, Zweig: konventionell, >50.000/nl	leave in
enzymes	highest values of 1,625,000-1,630,000 (n = 9) much higher than second highest value of 720,000	patients treated according to COALL 07-03 protocol	leave in
platinum deri-vates	80 (n = 1), 200 (n = 2), 1080 (n = 2), 2062.5 (n = 2)	only 5 patients from 4 study arms: 1: NB-85, Stadium III, Nichtresizierbarkeit/ Resttumor nach Sec 2. NB-85, Stadium III, GCT 96, alle anderen Histologien, mit Metastasen 3. COSS 96, SR2, 4. CWS 86, Stadium III, PR<2/3, Bestrahlung, HIT-LGG96, 1. OP, inkomplette Resektion, Symptome oder Progr,	leave in
vinca alkaloids	highest values of 135-144 (n = 13) much higher than second highest value of 60	patients treated according to COALL 97 protocol	leave in

[1]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI

(CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005)

[2]values are converted according to the statistical analysis plan, Appendix III, Chapter 2.2.1.2

8 Case-control study: Documentation of explorative analysis

During the process of selecting the best univariable FP model, some models with the variables anthracyclines, antimetabolites, cyclophosphamide, doxorubicin, methotrexate, or enzymes produced an error and the model fit was questionable (both main analysis and subgroup analysis with patients with SCT excluded). This is probably due to the data structure of the variables. Increasing the maximum number of iterations from the default of 25 (https://documentation.sas.com/?docsetId=statug&docsetTarget=statug_logistic_syntax22.htm%3Flocale&docsetVersion=14.2&locale=de, Accessed 10 Dec 2019) to 500 did not help the models to converge. A simple data transformation reduced the number of models with errors to two in the main analysis and none in the subgroup analysis. The final model was selected from the estimable ones.

Table 22. Transformations of substance (group) doses for logistic regression analysis to eliminate errors in the analysis process.

Analysis	Substance	transformation of dose
Main	anthracycline	multiplication by 10
	antimetabolites	division by 10 → unit cg/m²
	methotrexate	division by 10 → unit cg/m²
Subgroup: without SCT	doxorubicin	multiplication by 10
	methotrexate	division by 10 → unit cg/m²
	cyclophosphamide	division by 10 → unit cg/m²

The best univariable FP model for epipodophyllotoxins (FP1+z-model with power -0.5) did not yield valid results due to numeric problems. Therefore, the second best FP1+z model was chosen (with power 0, i.e. log(x)) for building the multivariable model.

The best univariable FP model for antibiotics was a FP2+z-model with powers 3 and 3 in the main analysis. A visual inspection of the functional form revealed that the decrease in the log odds was due to the influence of one high dose value of antibiotics (Appendix I.18.2): one control had received a cumulative dose of 27.3 mg/m². The next highest dose was 22.04 mg/m², which a patient treated in the same study arm had received. Although this dose is clinically sound, statistically, it was an influential point, i.e. a datapoint which greatly affects the slope of the regression line. Therefore, the data of the patient with this datapoint was removed in the main analysis and the subgroup analyses. The main analysis including the influential point was carried out as additional sensitivity analysis.

9 Scoping review: Backward and forward literature search of reviews

Number of papers included in abstract scan after backward and forward search of recent reviews which were identified by the electronic database search but excluded.

Review	Type of search	Date	Results: Number of papers included in abstract scan
Turcotte et al. (2018)	Backward	14 July 2019	14
	Forward	14 July 2019	0 (cited by 2 PMC[1] articles)
Gibson and Robison (2015)	Backward	14 July 2019	7
	Forward	14 July 2019	0 (cited by 1 PMC articles)
Choi et al. (2014)	Backward	14 July 2019	9
	Forward	14 July 2019	2 (cited by 11 PMC articles)
Pirani et al. (2011)	Backward	14 July 2019	10
	Forward	14 July 2019	0 (cited by 9 PMC articles)
Blettner and Scholz-Kreisel (2018)	Backward	14 July 2019	4
	Forward	14 July 2019	Not listed in Pubmed – forward search not possible
Jenkins (2013)	Backward	14 July 2019	0
	Forward	14 July 2019	0 (cited by 10 PMC articles)
Varan and Kebudi (2011)	Backward	15 July 2019	11
	Forward	14 July 2019	1 (Demoor-Goldschmidt et al. 2018) (cited by 2 PMC articles)
Demoor-Goldschmidt and de Vathaire (2018)	Backward	15 July 2019	11
	Forward	14 July 2019	Not cited by any article

[1]PMC = PubMed Central

10 Scoping review: Descriptive table

Description of studies included in full text evaluation of scoping review. Studies investigate the dose-response relationship between chemotherapeutic substances and a carcinoma or skin cancer as second primary neoplasm after childhood cancer.

Author	Setting, Sample	Sex	Calendar years FPN/SPN diagnosis	Median age at FPN/SPN in years (range)	Median latency in years (range)	FPN n; entities: inclusion criteria if any; coding[1]	SPN n; order, if reported; start of risk period, if reported; entities included; coding[1]
Retrospective cohort studies							
Boukheris et al. (2013): Risk of salivary gland cancer after childhood cancer: a report from the Childhood Cancer Survivor Study	CCSS-US/Canada; 5-year-survivors	SPN patients: 43.5% females (n = 10) cohort: 46.3% females (n = 6,550)	FPN: 1970-1986; SPN: through 2004	FPN: mean age: 8.3 (-<21); SPN: mean age: 24.6	12.6	14,135; leukemia, CNS tumor, HL, NHL, renal tumor, neuroblastoma, soft-tissue sarcoma, bone cancer; no codes provided	23, 20 for dose-response analysis due to missing radiation dose; risk period for cancer started 5 years after diagnosis; **salivary gland carcinomas**: 14 mucoepidermoid carcinoma, 3 adenocarcinoma, 3 acinar cell carcinoma, 3 miscellaneous other types; 22 occurred in parotid glad, 1 in submandibular gland; no codes provided
Ehrhardt et al. (2019): Subsequent Breast Cancer in Female Childhood Cancer Survivors in the St Jude Lifetime Cohort Study (SJLIFE	St. Jude Lifetime Cohort Study (SJLIFE); female 10-year survivors, min. 18 years old; 976 (66.5%) of eligible patients were also participants in CCSS-US/Canada	100% females	FPN: starting at least 1971, more likely in the 1960s; SPN: n/a, at least through Jan 1, 2001	FPN: 6.9 (0-22.7) SPN: 38.6 (range 24.5-53.0)	median time since FPN diagnosis for BC patients: 25.2 (12.7-44.6)	1467; not restricted; no codes provided	56 women (68 breast cancers), only 45 women for dose-response relationship due to missing alkylating agent dose; **breast cancer**: 38 invasive ductal carcinomas, 2 infiltrating lobular carcinomas, 1 mucinous carcinoma, 1 combined secretory carcinoma and ductal carcinoma in situ, 26 in situ carcinomas (22 ductal, 2 lobular, 2 combined ductal and lobular); synchronous, ipsilateral carcinomas counted as one, contralateral

Author	Setting, Sample	Sex	Calendar years FPN/SPN diagnosis	Median age at FPN/SPN in years (range)	Median latency in years (range)	FPN n; entities: inclusion criteria if any; coding[1]	SPN n; order, if reported; start of risk period, if reported; entities included; coding[1]
							cancers as 2 cancers; no codes provided
Guibout et al. (2005): Malignant breast tumors after radiotherapy for a first cancer during childhood	8 childhood cancer treatment centers in France and the United Kingdom; female 3-year survivors	100% females	FPN: 1946-1986; SPN: French centers: through Jan 1, 1993; UK centers: through Jan 1, 1991	FPN: 5, mean 6; SPN: 31.5 (12-63)	n/a	1814; all types except leukemia, and except retinoblastoma (in UK centers); classified according to ICD-O-2, but codes not provided	16; risk period for cancer started 3 years after diagnosis; **breast cancer**: 12 invasive ductal carcinoma, 3 malginant phyllodes tumors, 1 tumor of unknown type; carcinoma in situ excluded; ICD-O-2 codes not provided
Henderson et al. (2016): Breast Cancer Risk in Childhood Cancer Survivors Without a History of Chest Radiotherapy: A Report From the Childhood Cancer Survivor Study	CCSS-US/Canada; female 5-year survivors without a history of chest radiotherapy within 5 years of FPN diagnosis	100% females	FPN: 1970-1986; SPN: n/a	FPN: BC SPN patients: 14 (3-20) controls w/o BC SPN: 5 (0-20); SPN: 38 (22-47)	24 (10-34)	3768; leukemia, CNS tumor, HL, NHL, renal tumor, neuroblastoma, soft-tissue sarcoma, bone cancer; leukemia and sarcoma: 85% no codes provided	47, 44 with chemotherapy information; only patients without recurrence or other SPN before BC diagnosis; risk period for cancer started 5 years after diagnosis; **breast cancer**: 41 invasive BC, 6 ductal carcinoma in situ; no codes provided

Author	Setting, Sample	Sex	Calendar years FPN/SPN diagnosis	Median age at FPN/SPN in years (range)	Median latency in years (range)	FPN n; entities: inclusion criteria if any; coding[1]	SPN n; order, if reported; start of risk period, if reported; entities included; coding[1]
Henderson et al. (2012a): **Secondary gastrointestinal cancer in childhood cancer survivors: a cohort study**	CCSS-US/Canada; 5-year-survivors	gastorintestinal (GI) SPN patients: 42.2% females (n=19) patients w/o GI SPN: 46.3% females (n=6617)	FPN: 1970-1986; SPN: through Nov 2008	FPN: GI SPN patients: 13.9 (1.7-19.9); SPN: 33.5 (range: 9.7-44.8)	median follow-up: 22.8 (5.5-30.2)	12,592 (14,337 for analyses not involving treatment data); leukemia, CNS tumor, HL, NHL, renal tumor, neuroblastoma, soft-tissue sarcoma, bone cancer; no codes provided	45, 44 with chemotherapy information; risk period for cancer started 5 years after diagnosis; **gastrointestinal cancers**: 25 adenocarcinomas (56%), 4 neuroendocrine tumors (9%), 2 leiomyosarcomas (4%), 2 hepatocellular carcinomas (4%), 1 linea plastica (2%), 1 Klatskin's tumor (2%), 1 islet cell carcinoma (2%), 1 hemangiosarcoma (2%), 1 gastrinoma (2%), 1 goblet cell carcinoma (2%), 1 endometrial stromal cell sarcoma (2%), 3 carcinomas NOS (7%), 2 neoplasms NOS (4%); neoplasms according to the SEER classification of tumors of the oral cavity and pharynx, excluding the salivary glands or digestive system; no codes provided
Kenney et al. (2004): Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study	CCSS-US/Canada; female 5-year survivors	100% females	FPN: 1970-1986; SPN: through 2002	FPN: BC SPN patients: 16 (5-20) patients w/o BC SPN: 6 (0-20); SPN: 35 (20-49)	19 (6-29)	6068; leukemia, CNS tumor, HL, NHL, renal tumor, neuroblastoma, soft-tissue sarcoma, bone cancer; no codes provided	95 women (111 BC); only first subsequent BC; risk period for cancer started 5 years after diagnosis; **breast cancer**: 77 invasive ductal carcinomas (85.6%), 4 lobular carcinomas (4.4%), 3 mixed ductal or lobular carcinomas (3.3), 2 poorly differentiated carcinomas (2.2%), 2 malignant phylloides

Author	Setting, Sample	Sex	Calendar years FPN/SPN diagnosis	Median age at FPN/SPN in years (range)	Median latency in years (range)	FPN n; entities: inclusion criteria if any; coding[1]	SPN n; order, if reported; start of risk period, if reported; entities included; coding[1]
							tumors (2.2%), 1 breast angiosarcoma (1.1%), 1 malignant fibrosarcoma (1.1%)
Neglia et al. (2001): Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study	CCSS-US/Canada; 5-year survivors	patients with any SPN: 61.4% females (n = 183) patients w/o any SPN: 46.1% (n = 6121)	FPN: 1970-1986; SPN: through Jan 1, 2000	FPN: patients with any SPN: 11; patients w/o any SPN: 6; SPN: mean: 23.3	BC: 15.7; thyroid cancer: 13.3	13,581; leukemia, CNS tumor, HL, NHL, renal tumor, neuroblastoma, soft-tissue sarcoma, bone cancer; no codes provided	**BC**: n = 55 (+ 5 neoplasms subsequent to second BC), 53 with CT information (for AAS only 49); **thyroid cancer**: n = 40 (+ 3 neoplasms subsequent to second thyroid cancer), 39 with CT information (for AAS only 36); subsequent neoplasms not included in risk analysis; **breast cancer, thyroid cancer**; risk period for cancer started 5 years after diagnosis; ICD-O coded and grouped according to ICCC, but not reported
Teepen et al. (2017): Long-term risk of subsequent malignant neoplasms after treatment of childhood cancer in the DCOG LATER study cohort: Role of chemotherapy	DCOG LATER cohort study; 5-year survivors, only data of analyses on BC risk reported in this table	data analyzed for breast cancer (BC) risk: 100% females (1 man with BC was excluded)	FPN: 1963-2001; SPN: through Jan 1, 2013	n/a	n/a	2869 (entire cohort, not reported in this table: 6165 (103,949 person-years)); all malignancies according to ICCC-3 plus multifocal Langerhans cell histiocytosis and selected nonmalignant ependymomas and astrocytomas	49 (31 without chest radiotherapy or TBI); preceding SPNs of other entities possible, probably only 1st BC included; risk period for cancer started 5 years after diagnosis; **breast cancer**, including 5 ductal carcinomas in situ; ICD-10 code: C50 (excluding ductal carcinoma in situ)

Author	Setting, Sample	Sex	Calendar years FPN/SPN diagnosis	Median age at FPN/SPN in years (range)	Median latency in years (range)	FPN n; entities: inclusion criteria if any; coding[1]	SPN n; order, if reported; start of risk period, if reported; entities included; coding[1]
Veiga et al. (2012a): Chemotherapy and thyroid cancer risk: a report from the childhood cancer survivor study	CCSS-US/Canada; 5-year survivors	cohort: 47.2% females (n = 5926)	FPN: 1970-1986; SPN: 1975-2005	FPN: mean: 8 (0-21); SPN: mean: 28 (12-47)	n/a	12,547 (449 patients with unknown radiation dose excluded from analysis); leukemia, CNS tumor, HL, NHL, renal tumor, neuroblastoma, soft-tissue sarcoma, bone cancer; no codes provided	119, 8 of which were the 3rd malignancy in patient, 111 patients for dose-response analysis in anthracyclines and bleomycin, 106 for dose-response analysis with AAS; risk period for cancer started 5 years after diagnosis; **thyroid cancer**: 96 papillary and mixed papillary thyroid cancers, 14 follicular thyroid cancers, 3 others, 6 with unknown histology; no codes provided
Nested case-control studies							
Allodji et al. (2019): Risk of subsequent colorectal cancers after a solid tumor in childhood: Effects of radiation therapy and chemotherapy	French Childhood Cancer Survivor Study (FCCSS); solid tumor 5-year-survivors	cases: 41.7% females (n = 15) controls: 40.7% females (n = 57)	FPN: 1947 - 1994; SPN: through 2000	FPN: cases: 6.0 (0.02-14.4); controls: 6.5 (0.04-15.0); SPN: 38.0 (8.0-59.0)	30.0 (5.0-49.4)	176; solid tumors; no codes provided	36; risk period for cancer started 5 years after diagnosis; **colorectal cancer**: 33 adenocarcinomas of colon and rectum, 3 neuroendocrine tumors; for 10 it was the 3rd primary neoplasm, for 1 it was the 4th primary neoplasm; ICD-O grouping applied but not reported

Author	Setting, Sample	Sex	Calendar years FPN/SPN diagnosis	Median age at FPN/SPN in years (range)	Median latency in years (range)	FPN n; entities: inclusion criteria if any; coding[1]	SPN n; order, if reported; start of risk period, if reported; entities included; coding[1]
Inskip et al. (2009): Radiation dose and breast cancer risk in the childhood cancer survivor study	CCSS-US/Canada; female 5-year survivors	100% females	FPN: 1970-1986; SPN: 1983-2001	FPN: 16 (<5-20); SPN: 35.9 (20.9-49.6)	19.4 (6.7-29.6)	584, 491 with CT information; leukemia, CNS tumor, HL, NHL, renal tumor, neuroblastoma, soft-tissue sarcoma, bone cancer; no codes provided	120, 94-103 with CT information for dose-response analysis; restricted to first BC if more than one BC, in synchronous BC, invasive BC given priority; invasive (80%) or in situ (20%) primary **breast cancer**, in 7 women, BC followed another type of SPN; no codes provided
Sigurdson et al. (2005): Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study	CCSS-US/Canada; 5-year-survivors; n = 329 with complete treatment information	cases: 71% females (n = 51 of 72) controls: 71% females (n = 203 of 287)	FPN: 1970-1986; SPN: 1976-2001	FPN: n/a; SPN: n/a	15.9	329 with complete treatment information (359 total); leukemia, CNS tumor, HL, NHL, renal tumor, neuroblastoma, soft-tissue sarcoma, bone cancer; no codes provided	68 with complete treatment information (72 reported); also included if there was a different SPN earlier (n = 5); risk period for cancer started 5 years after diagnosis; **thyroid cancer**: 56 (78%) papillary, 11 (15%) follicular, 5 (7%) of other or unspecified histology; no codes provided
Tucker et al. (1991): Therapeutic Radiation at a Young Age Is Linked to Secondary Thyroid Cancer	US Late Effects Study Group; 2-year survivors	cases: 60.9% females (n = 14) base cohort: 45.2% females (n = 4149)	FPN: base cohort: 1936-1979; SPN: n/a	FPN: mean for cohort of 9170 survivors: 7 (0-18); SPN: n/a	mean latency between dactinomycin treatment and thyroid SPN: 13.8 (6.7-20.6)	112; any type of childhood cancer; no codes provided	23, thyroid cancer was SPN in all cases; risk period for cancer started 2 years after diagnosis; **thyroid cancer**: 11 mixed papillary and follicular adenocarcinoma, 8 papillary, 3 follicular, 1 papillary squamous carcinoma; no codes provided

Author	Setting, Sample	Sex	Calendar years FPN/SPN diagnosis	Median age at FPN/SPN in years (range)	Median latency in years (range)	FPN n; entities: inclusion criteria if any; coding[1]	SPN n; order, if reported; start of risk period, if reported; entities included; coding[1]
Watt et al. (2012a): Radiation-related risk of basal cell carcinoma: a report from the Childhood Cancer Survivor Study	CCSS-US/Canada; 5-year-survivors	cases: 46.7% females (n = 93) controls: 52.3% females (n = 312)	FPN: 1970-1986; SPN: through 2001	FPN: n/a (0-20); SPN: 31 (11-46)	18.2 (5.2-29.6)	796; leukemia, CNS tumor, HL, NHL, renal tumor, neuroblastoma, soft-tissue sarcoma, bone cancer; no codes provided	199; risk period for cancer started 5 years after diagnosis; **basal cell carcinoma**; first BCC used if multiple ones occurred; no codes provided

[1] Any type of classification system of diagnostic codes for classifying diseases, e.g. ICCC, ICD-O, ICD

Abbreviations:
BC = breast cancer
BCC = basal cell carcinoma
CCSS = childhood cancer survivor study
CNS = central nervous system
CRC = colorectal cancer
FCCSS = French Childhood Cancer Survivor Study
FPN = first primary neoplasm
GI = gastrointestinal
HL = Hodgkin lymphoma
ICCC = international classification of childhood cancer, (Kramarova and Stiller, 1996), (Steliarova-Foucher et al., 2005)
ICD = international classification of diseases
ICD-O = international
n/a = not available
NHL = non-Hodgkin lymphoma
NOS = not otherwise specified
SGC = salivary gland carcinomas
SPN = second primary neoplasm
TBI = total body irradiation

11 Scoping review: Case-control characteristics

Characteristics of case-control studies included in full text evaluation of scoping review. Studies investigate the dose-response relationship between chemotherapeutic substances and a carcinoma or skin cancer as second primary neoplasm after childhood cancer.

Author	Cases n Controls n	Base cohort n	Matching	Matching by FPN dignosis
Allodji et al. (2019); **FCCSS; colorectal**	36 140	7032	1 : 2-4 sex, age at FPN diagnosis, duration of follow-up, date of diagnosis; controls without subsequent colorectal cancer; presumably risk set sampling	no due to risk of overmatching
Inskip et al. (2009); **CCSS-US/Canada; BC**	120, 106 with CT information 464, 385 with CT information	6647	1:4 age at FPN diagnosis, duration of survival (follow up ±2 years), for analysis of cases and controls with same FPN diagnosis: FPN diagnosis; presumably risk set sampling	only for subgroup analysis, but results of this analysis were only reported for radiotherapy
Sigurdson et al. (2005); **CCSS-US/Canada; Thyroid cancer**	68 with complete treatment information 261 with complete treatment information	14,054	1:4 sex, age at FPN diagnosis (±2 years), follow-up interval; presumably risk set sampling, though not explicitly mentioned	only for subgroup analysis, but results of this analysis were only reported for radiotherapy
Tucker et al. (1991); **US Late Effects Study Group; Thyroid cancer**	23 89	9170	1:min.2 sex, age at FPN diagnosis (±2 years), duration of follow-up, race, histology of FPN, min. 1 control matched on year of FPN diagnosis (±2 years), min. 1 control was not matched on year of diagnosis; presumably risk set sampling	yes, on histology
Watt et al. (2012a); **CCSS-US/Canada; BCC**	199 597, BCC subsequent to first BCC not included	12,858	1:3 age at FPN diagnosis (±5 years), duration of follow-up presumably risk set sampling	no
Abbreviations: BC = breast cancer BCC = basal cell carcinoma CCSS = childhood cancer survivor study			CRC = colorectal cancer FPN = first primary neoplasm GI = gastrointestinal SGC = salivary gland carcinomas SPN = second primary neoplasm	

12 Scoping review: Therapy exposure description

Description of therapy exposure of studies included in full text evaluation of scoping review. Studies investigate the dose-response relationship between chemotherapeutic substances and a carcinoma or skin cancer as second primary neoplasm after childhood cancer.

Author; **Setting;** **SPN type**	**Chemotherapy exposure: groups or substances collected or analyzed**	**Units of chemotherapy dose;** **Method for pooling chemotherapeutic doses in groups**	**CT-dose exposure;** ***CT exposure, non-dose; non-exposure as reference unless otherwise specified***	**% with any chemotherapy**	**Radiation exposure: doses measured continuously in Gray unless otherwise specified; doses usually reported as categorial or dichotomous variables**
Cohort studies					
Boukheris et al. (2013); **CCSS-US/Canada;** **Salivary gland carcinomas**	doses of 22 agents; 2 groups: alkylating agents, anthracyclines	mg/m²; AAS; 5 anthracycline dose categories (method of pooling not reported)	AAS: 0, 1, 2, 3, unknown; anthracyclines (mg/m², (mean)): no, 0.12–174 (109.7), 175–290 (227.9), 291–390 (339.1), 391–8370 (498.8), unknown; *categorical: treatment modalitiy: RT and CT (ref.), CT only, RT only, no RT or CT;* *dichotomous: alkylating agents, anthracyclines*	cohort: 70.4% (n = 9956) cases: 69.6% (n = 16)	dose to the salivary glands estimated; continuous dose for analysis, categorized doses reported
Ehrhardt et al. (2019); **SJLIFE;** **BC**	5 groups: alkylating agents, anthracyclines, antimetabolites, plant alkaloids, epipodophyllotoxins; substances: carboplatin, cisplatin, doxorubicin	mg/m²; anthracyclines: dose equivalency ratios; alkylators: CED	CED (mg/m²): 0 (ref.), >0-5,999, ≥6,000; anthracyclines (mg/m²): 0 (ref.), 1-249, ≥250; doxorubicin (mg/m²): 0 (ref.), 1-249, ≥250; *dichotomous: single substances, single groups*	for separate groups, see **	chest and pelvic radiation doses; reported as dichotomized and categorized variables
Guibout et al. (2005); **France and the United Kingdom;** **BC**	5 groups: electrophilic agents, spindle inhibitors, nucleotide synthesis inhibitors, topoisomerase II inhibitors, other compounds; MOPP regimen (mechlorethamine,	moles/m2; dose of each cytotoxic substance converted into moles/m^2; assumingly, doses were summed within substance category	median dose in moles/m2 (range): electrophilic agents: 17.1 (3.2 × 10^−2-668.6); spindle inhibitors: 1.6 × 10^−2 (7.0 × 10^−4-0.8); topoisomerase II inhibitors: 0.19 (2.9 × 10^−4-18.9);	64.3% (n = 1167)	main focus; dose to each breast estimated; dichotomized, categorized, and continuous radiation for analysis

Author; **Setting;** **SPN type**	**Chemotherapy exposure: groups or substances collected or analyzed**	**Units of chemotherapy dose;** **Method for pooling chemotherapeutic doses in groups**	**CT-dose exposure;** ***CT exposure, non-dose; non-exposure as reference unless otherwise specified***	**% with any chemotherapy**	**Radiation exposure: doses measured continuously in Gray unless otherwise specified; doses usually reported as categorial or dichotomous variables**
	vincristine, procarbazine, prednisone)		NSI: 13.7 (3.9 × 10^−2-1,452.9); other categories: 3.0 (0.1-13.9); median for single substances reported as well; *dichotomous: any chemotherapy, single groups*		
Henderson et al. (2016); **CCSS-US/Canada;** **BC**	6 groups: anthracyclines, alkylating agents, platinum compounds, antimetabolites, plant alkaloids, epipodophyllotoxins	mg/m²; CED; method of pooling for anthracyclines not described in references provided; assumingly score method*	CED (mg/m²): 0 (ref. for relative SIR), 1-5,999, 6,000-17,999, ≥18,000; anthracycline dose (mg/m²): 0 (ref. for relative SIR), 1-249, ≥250; *dichotomous: alkylating agents, anthracyclines*	n/a	no chest radiation within 5 years of FPN diagnosis but scatter radiation examined, chest radiation: mantle, mediastinal, hemithorax, whole-lung irradiation, spinal including posterior thoracic/paravertebral, abdominal, or total body irradiation
Henderson et al. (2012a); **CCSS-US/Canada;** **Gastrointestinal cancer**	42 chemotherapy substances of which 22 with doses; 4 groups: alkylating agents, anthracyclines, platinum compound, plant alkaloids; substance: procarbazine	mg/m²; method of pooling anthracyclines and alkylating agents not described in reference cited (Robison et al. 2002), assumingly score method*	procarbazine dose (mg/m²): 0 (ref.), >0-4200, >4200-7036, >7036; method of categorization not described; *dichotomous: platinum compounds, anthracyclines, plant alkaloids*	patients with GI SPN: 84.1% (n = 37); patients without GI SPN: 80.6 (n = 10,084)	proximity of the SPN to the primary tumor radiation field: in the beam, near the beam (0-10 cm from radiation field edge), out of beam; doses to SPN site not estimated; dichotomous abdominal radiation for analysis
(Kenney et al., 2004); **CCSS-US/Canada;** **BC**	49 substances, of which 26 with doses (Robison et al. 2002); group: alkylating agents	mg/m²; AAS	AAS: 0 (ref.), 1-2, 3-4, ≥5; -	alkylating agents: patients with BC: 49.5% (n = 47); patients w/o BC: 49.2% (n = 2939)	main focus; chest and pelvic doses; dichotomized for analysis
Neglia et al. (2001); **CCSS-US/Canada;** **BC+thyroid cancer**	doses of 28 substances: 4 groups: alkylating agents, anthracyclines, epipodophyllotoxins, platinum compounds	mg/m²; AAS; anthracycline exposure: daunorubicin + doxorubicin	AAS: 0 (ref.), 1-2, 3-4, ≥5; anthracycline (mg/m²): 0 (ref.), 1-100, 101-300, ≥301; epipodophyllotoxins (mg/m²): 0 (ref.), 1-1000, 1001-4000, ≥4001;	patients w/o any SPN: alkylating agents (n = 13,283): 52.8% (n = 5880), anthracycline: 41.0% (n = 4566), epipodophyllotoxins:	for BC SPN: breast radiation (dichotomous); for thyroid SPN: thyroid radiation (dichotomous)

Author; **Setting;** **SPN type**	**Chemotherapy exposure: groups or substances collected or analyzed**	**Units of chemotherapy dose;** **Method for pooling chemotherapeutic doses in groups**	**CT-dose exposure;** ***CT exposure, non-dose; non-exposure as reference unless otherwise specified***	**% with any chemotherapy**	**Radiation exposure: doses measured continuously in Gray unless otherwise specified; doses usually reported as categorial or dichotomous variables**
		+ (idarubicin*3); epipodophyllotoxin exposure: etoposide + teniposide; platinum compounds: cisplatin + (carboplatin/4)	platinum compounds (mg/m²): 0, 1-400, 401-750, ≥751; -	9.4% (n = 1044), platinum agents: 6.0% (n = 668); ***	
Teepen et al. (2017); **DCOG LATER BC**	6 groups: alkylating agents, anthracyclines, epipodophyllotoxins, vinca alkaloids, platinum agents, antimetabolites; substances for BC risk : ifosfamide, mechlorethamine, procarbazine, cyclophosphamide, doxorubicin, daunorubicin, etoposide, cytarabine, methotrexate, thioguanine, mercaptopurine	mg/m²; CED; way of pooling anthracyclines not described; doxorubicin equivalence ratio cited (Feijen et al., 2015), but assumingly not applied	chemotherapy of initial treatment and recurrences; dose tertiles for agents with at least 10 exposed cases: CED (mg/m²): no (ref.), <6,000, 6,000-17,999, ≥18,000; doxorubicin (mg/m²): no (ref.), ≤270, 271-443, >443; anthracyclines (mg/m²): no (ref.), 1-249, ≥250; *dichotomous: ifosfamide*	n/a; for entire cohort including males: 81.0% (n = 4994)	prescribed doses; dichotomized for analysis: chest radiotherapy TBI; categorized for analysis if at least 10 exposed cases for outcome of interest occurred (not reported)
Veiga et al. (2012a); **CCSS-US/Canada;** **Thyroid cancer**	42 substances, of which 22 with doses; 4 groups: alkylating agents, anthracycines, epipodophyllotoxins, platinum-based compounds; substance: bleomycin	mg/m²; AAS; anthracycline exposure: daunorubicin + doxorubicin + (idarubicin*3)	AAS: 0 (ref.), 1-2, 3; anthracyclines (mg/m²): 0 (ref.), <340, ≥340; bleomycin (mg/m²): 0 (ref.), <100, ≥100; *categorical: no RT but CT (ref.), RT only, concomitant CT and RT, sequential CT and RT, RT then CT CT then RT;* *dichotomous: CT, alkylating agents, anthracyclines, bleomycin, epipodophyllotxins, platinum compounds;* *dichotomous for patients with <20*	93% (n = 11,624)	thyroid gland dose exposure within 10 years of FPN diagnosis; categorized (overall analysis) and continuous dose (for groups ≤20 Gy and > 20 Gy) for analysis; interaction dose (continuous) x chemotherapy (yes/no) tested

Author; Setting; SPN type	Chemotherapy exposure: groups or substances collected or analyzed	Units of chemotherapy dose; Method for pooling chemotherapeutic doses in groups	CT-dose exposure; *CT exposure, non-dose; non-exposure as reference unless otherwise specified*	% with any chemotherapy	Radiation exposure: doses measured continuously in Gray unless otherwise specified; doses usually reported as categorial or dichotomous variables
			Gy radiation: procarabzine, cyclophosphamide, mechorethamine, daunorubicin, doxorubicin, dactinomycin, cytosine arabinoside, methotrexate; *categorical substance combinations: no anthracyclines/alykalting agents/bleomycin (ref.), anthracyclines, bleomycin, alkylating agents, alkylating agents+bleomycin, anthracyclines+bleomycin, anthracyclines+alkylating agents, anthracyclines+alkylating agents+bleomycin*		
Nested case-control studies					
Allodji et al. (2019); **FCCSS;** **colorectal**	6 groups: alkylating agents, epipodophyllotoxins, anthracyclines, vinca alkaloids,mainly vincristine, platinum compounds, antimetabolites; MOPP regimen (mechlorethamine, vincristine (Oncovin), procarbazine, with or without prednisone)	g/m^2; sum of cumulative dose of different chemotherapy substances within specific groups/regimen (based on the assumption that all substances share an equal carcinogenic potency)	univariable analyses only: categorical AND continuous approach for all groups (total cumulative dose in g/m2); categorical approach: any alkylating agent except procarbazine (g/m2, (mean)): no (ref.), 0-5.9 (1.96), ≥ 6.0 (13.65) procarbazine (g/m^2, (mean)): no (ref.), 0-4.19 (2.43), ≥ 4.20 (8.36) anthracyclines (g/m^2, (mean)): no (ref.), 0-0.29 (0.21), ≥ 0.30 (0.50) vincristine (g/m^2, (mean)): no (ref.), 0-0.01 (0.01), ≥ 0.02 (0.11) MOPP (g/m^2, (mean)): no (ref.), 0–5.29 (2.84), ≥5.30 (9.11) vincristine not in MOPP (g/m^2,	cases: 97.2% (n = 35); controls: 71.4% (n = 100)	average SPN site dose estimated; dichotomized, categorized, and continuous dose for analysis

Author; Setting; SPN type	Chemotherapy exposure: groups or substances collected or analyzed	Units of chemotherapy dose; Method for pooling chemotherapeutic doses in groups	CT-dose exposure; *CT exposure, non-dose; non-exposure as reference unless otherwise specified*	% with any chemotherapy	Radiation exposure: doses measured continuously in Gray unless otherwise specified; doses usually reported as categorial or dichotomous variables
			(mean)): no (ref.), 0-0.01 (0.01), ≥ 0.02 (0.11) antimetabolites (g/m^2, (mean)): no (ref.), 0-1.85 (0.60), ≥ 1.86 (52.98); <u>continuous approach:</u> any alkylating agent except procarbazine: 1 (1-1.1), p = 0.22; platinum compounds: 0.8 (0-1.4), p = 0.58; anthracyclines: 4.3 (0.8-27.5), p = 0.11; epipodophyllotoxins: 1.3 (0.6-2.6), p = 0.54; vincristine: 1.2 (0.1-3.7), p = 0.85; antimetabolites: 1 (1-1), p = 0.98 <u>multivariable analysis</u>: anthracyclines (g/m^2, (mean)): no (ref.), 0–0.29 (0.21), ≥0.30 (0.50); MOPP (g/m^2, (mean)): no (ref.), 0–5.29 (2.84), ≥5.30 (9.11); *dichotomous: single substances, single groups*		
Inskip et al. (2009); **CCSS-US/Canada;** **BC**	doses of 28 substances; 2 groups: alkylating agents, anthracyclines; substances: mechlorethamine, procarabzine, BCNU, CCNU, cyclophosphamide, dacarbazine, dactinomycin, bleomycin, daunorubicin, doxorubicin	mg/m²; AAS	AAS: 0 (ref.), 1, 2, 3 tertiles: mechlorethamine (mg/m²): 0 (ref.), >0-44, >44-63.7, ≥63.7; procarabzine (mg/m²): 0 (ref.), >0-4178.6, >4178.6-<7000, ≥7000; doxorubicin (mg/m²): 0 (ref.), >0-198.8, >198.8-<350.8, ≥350.8;	cases: 62.3% (n = 66); controls: 67.3% (n = 259)	main focus; breast doses estimated for radiation up to 5 years before BC diagnosis; continuous dose for analysis

Author; **Setting;** **SPN type**	**Chemotherapy exposure: groups or substances collected or analyzed**	**Units of chemotherapy dose;** **Method for pooling chemotherapeutic doses in groups**	**CT-dose exposure;** ***CT exposure, non-dose; non-exposure as reference unless otherwise specified***	**% with any chemotherapy**	**Radiation exposure: doses measured continuously in Gray unless otherwise specified; doses usually reported as categorial or dichotomous variables**
			dichotomous: any chemotherapy, single substances		
Sigurdson et al. (2005); **CCSS-US/Canada;** **Thyroid cancer**	49 substances, of which 22 with cumulative doses; 3 groups: alkylating agents, anthracyclines, epipodophyllotoxins	mg/m²; not reported, assumingly score method*	dose-response assessed for any substance associated with a significant increased risk for dichotomized substance (p<0.05); *dichotomous: any chemotherapy, alkylating agents, anthracyclines, epipodophyllotoxins; each substance separately if at least 5 cases and 5 controls underwent that treatment*	cases: 91% (n = 62), controls: 76% (n = 197)	main focus; total dose of radiation between FPN diagnosis until 5 years before thyroid cancer diagnosis; doses to left and right lobes of thyroid gland and to pituitary gland; probably continuous dose for analysis
Tucker et al. (1991); **US Late Effects Study Group;** **Thyroid cancer**	3 groups: alkylating agents, vinca alkaloids, other antimetabolites; substance: dactinomycin	mg/m²; scores method* for substances and groups	not reported; *dichotomous: single substances, single groups*	n/a	main focus; dose to thyroid gland estimated; categorized and coninuous dose for analysis
Watt et al. (2012a); **CCSS-US/Canada;** **BCC**	2 groups: alkylating agents, anthracyclines; substances: procarabzine, cycophosphamide IV and oral	mg/m²; AAS; anthracyclines: score method*	cyclophosphamide oral (mg/m²): 0 (ref.), 1-3999, ≥4000, unknown; procarbazine (mg/m²): 0 (ref.), 1-3999, ≥4000, unknown; cyclophosphamide IV (mg/m²): 0 (ref.), 1-3999, 4000-9999, 10,000-19,999, 20,000-39,999, unknown; AAS: 0 (ref.), 1, 2, 3, unknown; anthracycline score: 0 (ref.), 1, 2, 3, unknown; *categorical: treatment modalitiy: no CT or RT (ref.), RT only, CT only, RT and CT, unknown;* *categorical for alkylating agents, anthracyclines, prednisone: no (ref.), yes, unknown*	cases: 68.3% (n = 136); controls: 68.3% (n = 408)	main focus; dose to BCC site estimated; presumably continuous dose for analysis, not clear if categorized dose for analysis; categorized doses reported

Author; Setting; SPN type	Chemotherapy exposure: groups or substances collected or analyzed	Units of chemotherapy dose; Method for pooling chemotherapeutic doses in groups	CT-dose exposure; *CT exposure, non-dose; non-exposure as reference unless otherwise specified*	% with any chemotherapy	Radiation exposure: doses measured continuously in Gray unless otherwise specified; doses usually reported as categorial or dichotomous variables
*score method: assigning numbers to tertiles of cumulatve dose of all subjects receiving substance (0: no substance, 1: lowest tertile, 2, 3: highest tertile); for substance groups: summing tertiles for all substances in group ** Sirgudson et al. 2005: % with any chemotherapy: patients w/o any SPN: alkylating agents (n = 13,283): 52.8% (n = 5880), anthracycline: 41.0% (n = 4566), epipodophyllotoxins: 9.4% (n = 1044), platinum agents: 6.0% (n = 668); *** Neglia et al. 2001: % with any chemotherapy: patients with results reported in this table: patients with BC: alkylating agents: 46.9% (n = 23 out of 49), anthracycline: 26.4% (n = 14 out of 53), epipodophyllotoxins: 0% (n = 0 out of 53), platinum agents: 0% (n = 0 out of 53); patients with thyroid cancer: alkylating agents: 58.3% (n = 21 out of 36), anthracycline: 33.3% (n = 13 out of 39), epipodophyllotoxins: 0.8% (n = 3 out of 39), platinum agents: 0% (n = 0 out of 39); patients with any SPN: alkylating agents: 47.3% (n = 95 out of 203), anthracycline: 36.5% (n = 96 out of 263), epipodophyllotoxins: 6.7% (n = 18 out of 270), platinum agents: 3.0% (n = 8 out of 269)			**Abbreviations:** AAS = alkylating agent score according to (Tucker et al., 1987b), unless otherwise specified, see score method BC = breast cancer BCC = basal cell carcinoma CCSS = childhood cancer survivor study CED = cyclophosphamide equivalent dose (Green et al., 2014) CRC = colorectal cancer CT = chemotherapy GI = gastrointestinal NSI = Nucleotide synthesis inhibitors (here: only methotrexate) n/a = not available ref. = reference category RT = radiotherapy SGC = salivary gland carcinomas TBI = total body irradiation		

13 Scoping review: Analyses and results

Analyses and results of studies included in full text evaluation of scoping review. Studies investigate the dose-response relationship between chemotherapeutic substances and a carcinoma or skin cancer as second primary neoplasm after childhood cancer.

Author; **Setting;** **SPN type**	**Statistical models for CT-dose analysis;** ***Adjustments/further covariates***	**Statistical models for dichotomous CT, if different from CT-dose analyses;** ***Adjustments/further covariates if different from CT-dose analyses***	**Outcome CT-dose;** ***Outcome of subgroup or subgroup analyses in italic***	**Outcome CT, dichotomous;** ***Outcome of subgroup or subgroup analyses in italic***
Retrospective cohort studies				
Boukheris et al. (2013); **CCSS-US/Canada;** **Salivary gland carcinomas**	RR with 95% CI using PR, two-sided p-values for linear trend and 95% CI based on likelihood ratio statistic; *attained age as continuous variable; indirect adjustment for sex, race, attained age, attained calendar period;* *radiation dose (as untransformed variable)*		RR: AAS: **4.1 (1.4-13.7)**, 2.0 (0.4-8.1), 1.1 (0.2-5.3), 1.6 (0.2-7.5), linear trend n.s. (p >0.5); anthracyclines: 1.8 (0.3-6.7), 1.8 (0.3-6.8), 0.9 (0.05-4.8), 2.0 (0.3-7.7), 3.1 (0.5-11.6), trend n.s (p = 0.42)	RR: treatment modality: 1.0 (0.0-1.0), 0.3 (0.053-1.3), 1.1. (0.3-3.2); alkylating agents yes/no (reference): 2.5 (0.9-7.9); anthracyclines: 1.6 (0.6-4.2)
Ehrhardt et al. (2019); **SJLIFE;** **BC**	CI with 95% CI stratified by anthracycline exposure, compared using Gray's test for equality of CI functions; HR using Cox model, several subgroup analyses: model with doxorubicin instead of anthracyclines, women with <10 Gy chest radiation, women without pathogenic mutations, excluding women with in situ BC; *model includes age at diagnosis,*	Fisher's exact text	CI highest in women with ≥250 mg/m² anthracyclines, lowest in women without anthracyclines **(p <0.001)**; HR: CED: 1.0 (0.4-2.6), **0.4 (0.2-0.9)**; anthracyclines: **2.6 (1.1-6.2), 13.4 (5.5-32.5)**; *model with doxorubicin instead of anthracyclines*: CED: 0.8 (0.3-1.9), 0.4 (0.2-1.0), doxorubicin: **7.3 (2.9-18.5), 17.5 (6.7-45.7)**; *women with <10 Gy chest radiation*:	Comparing patients with versus without breast cancer with respect to relative frequency of application: CED: **p = 0.001** (more frequent in patients with BC); anthracyclines: **p = 0.036** (more frequent in patients with BC); carboplatin: p = 0.186; cisplatin: p = 0.858; antimetabolites: **p = 0.006** (more frequent in patients without BC); plant alkaloids: p = 0.522; epipodophyllotoxins: p = 0.066

Author; **Setting;** **SPN type**	**Statistical models for CT-dose analysis;** ***Adjustments/further covariates***	**Statistical models for dichotomous CT, if different from CT-dose analyses;** ***Adjustments/further covariates if different from CT-dose analyses***	**Outcome CT-dose;** ***Outcome of subgroup or subgroup analyses in italic***	**Outcome CT, dichotomous;** ***Outcome of subgroup or subgroup analyses in italic***
	mutation, chest and pelvic radiation, alkylating agents, anthracyclines		CED: 0.7 (0.1-5.2), 0.4 (0.1-2.4), anthracyclines: 1.1 (0.1-11.8), **11.1 (1.8-66.3)**; *women without pathogenic mutations*: CED: 1.5 (0.6-4.1), 0.4 (0.2-1.1), anthracyclines: 2.5 (1.0-6.1), **15.1 (6.1-37.6)**; *model with doxorubicin instead of anthracyclines:* CED: 0.8 (0.3-1.9), 0.4 (0.2-1.0), doxorubicin: **6.3 (2.3-17.1), 22.2 (8.3-59.6),** *women with ≥ 10 Gy and pathogenic mutation:* alkylating agents: 0.7 (0.1-6.3), 0.5 (0.1-3.5), doxorubicin: 8.2 (0.8-81.1), 18.2 (2.4-136.1) *excluding women with in situ BC*: CED: 2.0 (0.6-6.5), 0.5 (0.1-1.5), anthracyclines: 1.9 (0.6-6.3), **24.1 (7.9-73.2)**	
Guibout et al. (2005); **France and the United Kingdom;** **BC**	RR with 95% CI assuming number of BC follows Poission distribution, unclear how chemotherapy was included in model; *adjustements unclear*	RR and SIR with 95% CI assuming number of BC follows Poission distribution, SIR compared to general population; *radiation dose to breast, FPN type (Wilms' tumor, neuroblastoma, Hodgkin lymphoma, NHL, soft tissue sarcoma, bone sarcoma, brain tumor, gonadal tumor, thyroid carcinoma, retinoblastoma, other);* *in a further model, adjustment*	"There was no evidence for a role of the number of moles per square meter for any of the drug categories or of the total number of moles per square meter administered."	RR (95% CI): Chemotherapy: 2.7 (95% CI 0.9-7.6), p = 0.07; electrophilic agents: 1.4 (0.3-4.0); spindle inhibitors: 1.9 (0.4-7.4); topoisomerase II inhibitors: 2.3 (0.5-8.4); NSI: 4.7 (0.7-20.1); MOPP: 5.4 (0.6-45.7); *RR additionally adjusted to other substance categories and age at FPN*: NSI: 4.6 (0.6-19.9); p = 0.06; SIR (95% CI) in unexposed vs. exposed: chemotherapy:

Author; **Setting;** **SPN type**	**Statistical models for CT-dose analysis;** ***Adjustments/further covariates***	**Statistical models for dichotomous CT, if different from CT-dose analyses;** ***Adjustments/further covariates if different from CT-dose analyses***	**Outcome CT-dose;** ***Outcome of subgroup or subgroup analyses in italic***	**Outcome CT, dichotomous;** ***Outcome of subgroup or subgroup analyses in italic***
		additionally to other substance categories, age at FPN		10.2 (4.6-18.9) vs. 50.2 (23.0-93.5); electrophilic agents: 14.9 (8.2-24.9) vs. 40.0 (9.8-102.6); spindle inhibitors: 13.5 (7.2-22.6) vs. 69.8 (21.7-162.2); topoisomerase II inhibitors: 14.9 (8.2-24.5) vs. 41.4 (10.3-107.3); NSI: 15.5 (8.7-25.0) vs. 48.4 (8.0-149.3); MOPP: 14.9 (8.4-24.2) vs. 201.1 (33.5-621.1)
Henderson et al. (2016); **CCSS-US/Canada;** **BC**	univariable: SIR (O/Ex) with 95% CI compared to general population (with same age and calendar-year distribution), AER with 95% CI ((O-Ex)/person-years follow-up per 10,000 person years); multivariable: relative SIRs with 95% CI using PR with age as the time scale; test for trend; separate analyses for only leukemia and sarcoma survivors; *cumulative anthracycline dose, CED, age at FPN; adjustment variables: race/ethnicity (white, non-Hispanic, other), attained age, FPN diagnosis (sarcoma/leukemia vs other); additional adjustment for FPN diagnosis*	univariable: relative SIR with 95% CI; separate analyses for leukemia and sarcoma survivors	results of univariable analyses see footnote** multivariable: relative SIR: CED: 0.6 (0.2-2.0), 1.6 (0.7-3.5), **3.0 (1.2-7.7), p = 0.044**; anthracycline: 2.6 (0.8-8.7), **3.8 (1.7-8.3), p = 0.004**; *leukemia/sarcoma survivors:* CED: 0.7 (0.2-2.3), 1.9 (0.8-4.5), **3.4 (1.2-9.7), p = 0.045**; anthracyclines: **4.3 (1.1-16.6), 5.1 (1.9-13.7), p = 0.005;** "alkylators and anthracyclines were associated with breast cancer development in a dose-dependent fashion (test for trend, P values both **<.01)**"; relative SIRs: inclusion of FPN diagnosis (sarcoma/leukemia vs other) was not significant and did not meaningfully change the results	SIR for treatment with anthracyclines and alkylating agents: **8.6 (5.7-12.8)**; *for sarcoma and leukemia survivors*: **9.8 (6.5-14.7)**;

Author; **Setting;** **SPN type**	**Statistical models for CT-dose analysis;** ***Adjustments/further covariates***	**Statistical models for dichotomous CT, if different from CT-dose analyses;** ***Adjustments/further covariates if different from CT-dose analyses***	**Outcome CT-dose;** ***Outcome of subgroup or subgroup analyses in italic***	**Outcome CT, dichotomous;** ***Outcome of subgroup or subgroup analyses in italic***
Henderson et al. (2012a); **CCSS-US/Canada;** **Gastrointestinal cancer**	final multivariable model: HR with 95% CI using Cox regression with age as time scale; *abdominal radiation, procarbazine dose, platinum, anthracyclines, plant alkaloids*	HR with 95% CI using Cox regression; initial multivariable model: using significant univariable factors (p<0.10) and variables hypothesized a priori to have an impact; final multivariable model: excluding covariates not significantly affecting time to GI SPN development; three subgroup analyses including patients with missing treatment data (assuming that all missing participants received 1) all treatments, 2) no teratment, 3) treatment pattern most common for their primary cancer); *initial multivariable model:* *sex, race (white vs. non-white), Hodgkin lymphoma, Wilms tumor, bone cancer, treatment era 1970-74, treatment era 1975-79, neck RT, chest RT, abdomen RT, spine RT, pelvis RT, alkylating agents, platinum drugs, antimetabolites, anthracyclines, plant alkaloids, epipodophyllotoxins*	multivariable HR: procarbazine dose: 1.02 (0.22-4.80), 2.08 (0.64-6.78), **3.15 (1.06-9.38)**; "we did not find that procarbazine without abdominal radiation was associated with increased risk of" GI SPN (unclear, which model this refers to)	initial multivariable model: alkylating agents: **5.05 (1.86-13.71), p<0.02**; platinum drugs: **4.60 (1.21-17.48), p = 0.03**; antimetabolites: 0.51 (0.18-1.42), p = 0.20; anthracyclines: 0.58 (0.24-1.41), p = 0.23; plant alkaloids: 0.45 (0.18-1.13), p = 0.09; epipodophyllotoxins: 0.00 (0.00), p = 0.98; final multivariable model: platinum: **7.57 (2.25-25.51), p<0.01**; anthracyclines: 0.66 (0.27-1.63), p = 0.37; plant alkaloids: 0.84 (0.37-1.92), p = 0.68 subgroup analyses: risk estimates consitent with final model, data not shown
Kenney et al. (2004);	relative rate with 95% CI using PR (incidence rate ratio, i.e. RR,	-	AAS: 0.8 (0.4-1.6), 0.8 (0.4-1.4), 1.11 (0.6-2.0), p >0.2	-

Author; **Setting;** **SPN type**	**Statistical models for CT-dose analysis;** ***Adjustments/further covariates***	**Statistical models for dichotomous CT, if different from CT-dose analyses;** ***Adjustments/further covariates if different from CT-dose analyses***	**Outcome CT-dose;** ***Outcome of subgroup or subgroup analyses in italic***	**Outcome CT, dichotomous;** ***Outcome of subgroup or subgroup analyses in italic***
CCSS-US/Canada; **BC**	reported); p-values reported presumably for test for trend *chest radiation (dichotomous)*			
Neglia et al. (2001); **CCSS-US/Canada;** **BC+thyroid cancer**	RR with 95% CI using PR for SIRs, p for trend; *radiation exposure to tumor sites (dichotomous); sex, age at FPN diagnosis, treatment era, FPN diagnosis, splenectomy, AAS, anthracyclines, epipodophyllotoxins, platinum compounds*		BC: AAS: 0.97 (0.38-2.48), 1.03 (0.41-2.63), 1.05 (0.47-2.34), p >0.5; anthracyclines: 2.59 (0.32-20.79), 1.78 (0.76-4.19), 1.97 (0.58-6.68), p = 0.15; epipodophyllotoxins and platinum compounds: n/a; thyroid cancer: AAS: 1.23 (0.50-3.06), 0.94 (0.33-2.62), 0.72 (0.26-2.00), p >0.5; anthracyclines: 0, 1.55 (0.66-3.64), 0.77 (0.16-3.69), p >0.5; epipodophyllotoxins: **5.00 (1.04-23.99**), 0, 3.42 (0.42-27.85), p= 0.29; platinum compounds: n/a	
Teepen et al. (2017); **DCOG LATER** **BC**	HR with 95% CI using Cox regression with attained age as time scale; <u>initial multivariable model</u>: all variables with p <0.1 in univariable model except for chemotherapy substances with <5 exposed cases for outcome of interest; <u>final multivariable models</u>: all variables from initial model with p<0.05 or variables considerably changing the effect of other		<u>final multivariable models:</u> model 1: doxorubicin: 1.1 (0.4-2.9), **2.6 (1.1-6.5), 5.8 (2.7-12.5)**, trend: **p<0 .001**; model 2: CED: 2.0 (0.9-4.8), 1.7 (0.7-3.9), 1.0 (0.2-4.5), trend: p = 0.99; anthracyclines: 1.3 (0.5-3.2), **3.1 (1.4-6.5)**, trend: **p = 0.004**; *model without radiotherapy*: doxorubicin: 1.3 (0.3-6.1), **5.6 (1.9-16.2), 9.9 (4.2-23.8)**, trend: **p=0.002**;	<u>final multivariable models:</u> model 1: ifosfamide: **3.4 (1.3-8.8)**; *model without radiation*: ifosfamide: 2.3 (0.6-8.0); *model with LFS-associated FPN diagnoses*: ifosfamide: 2.8 (0.9-8.8); *model with FPN diagnoses not associated with LFS*: ifosfamide: **5.1 (1.1-24.3)**, p for difference in trend: 0.64

Author; Setting; SPN type	Statistical models for CT-dose analysis; *Adjustments/further covariates*	Statistical models for dichotomous CT, if different from CT-dose analyses; *Adjustments/further covariates if different from CT-dose analyses*	Outcome CT-dose; *Outcome of subgroup or subgroup analyses in italic*	Outcome CT, dichotomous; *Outcome of subgroup or subgroup analyses in italic*
	variables in the model; tests for trend; additional analysis restricted to 2451 female patients without chest radiotherapy or TBI; additionally stratified by Li-Fraumeni syndrome-associated childhood cancers (leukemia, CNS tumor, sarcoma except Ewing vs. other childhood cancers), p for difference in trend to LFS-associated model; *covariates final multivariable models: chest radiotherapy, total body irradiation*		*model with LFS-associated FPN:* doxorubicin: 0.6 (0.1-3.2), **9.1 (2.5-32.8), 14.8 (5.1-43.2)**, trend: p<0.001; *model with FPN diagnoses not associated with LFS:* doxorubicin: 1.9 (0.6-6.2), 1.1 (0.2-4.9), 2.4 (0.7-8.4), trend: p =0.94; p for difference in trend: **0.008**	
Veiga et al. (2012a); **CCSS-US/Canada;** **Thyroid cancer**	RR with 95% CI using PR, overall analysis (n = 115 cases) and additionally stratified by thyroid radiation exposure (0 Gy n = 12 cases), ≤20 Gy (n = 61 cases), >20 Gy (n = 54 cases)), test for heterogeneity; updated analysis in Inskip et al. (2016): RR for group with radiation dose 0-5 Gy; *sex, natural logarithm of attained age, type of FPN (HL, leukemia, others);* *overall analyses additionally*	additionally for patients with any CT and any class of CT: effect modification included as interaction term: radiation dose (continuous) x CT (dichotomous)	overall: AAS: 1.5 (1.0-2.3), 1.5 (0.8-2.6), p = 0.14; anthracyclines: 1.3 (0.8-2.1), 1.4 (0.7-2.5), p = 0.36; bleomycin: 0.7 (0.2-1.9), 1.0 (0.2-4.2), p = 0.56; *no thyroid radiation*: AAS: 1.8 (0.3-10.0), **9.4 (1.4-56.8)**, p = 0.08; anthracyclines: 4.5 (0.9-22.9), 4.3 (1.0-21.4), p = 0.05; bleomycin: 4.5 (0.6-20.7), 3.3 (0.5-15.2), p = 0.17; *thyroid dose >0-5 Gy (results from Inskip et al. (2016)):*	type of treatment: 3.0 (0.9-9.7), **4.7 (1.5-15.0), 5.4 (1.6-18.4), 8.0 (2.2-28.5), 5.2 (1.3-21.3)**; dichotomous for overall cohort: CT: 1.6 (1.0-2.7), p = 0.06; alkylating agent: 1.4 (1.0-2.1), p = 0.07; anthracyclines: 1.4 (0.9-2.1), p = 0.10; bleomycin: 1.1 (0.6-2.0), p = 0.98; joint effects of RT with CT: risk decreased with increasing radiation dose category for any chemotherapy (p = 0.21), alkylating agents (**p = 0.03**), anthracyclines (p = 0.09), bleomycin (p = 0.30), suggesting that the cell-killing effect observed for high radiation

Author; **Setting;** **SPN type**	**Statistical models for CT-dose analysis;** ***Adjustments/further covariates***	**Statistical models for dichotomous CT, if different from CT-dose analyses;** ***Adjustments/further covariates if different from CT-dose analyses***	**Outcome CT-dose;** ***Outcome of subgroup or subgroup analyses in italic***	**Outcome CT, dichotomous;** ***Outcome of subgroup or subgroup analyses in italic***
	adjusted for radiation dose categories; *subgroups with >0-5 Gy, ≤20 Gy or >20 Gy additionally thyroid radiation dose (continuous)*		AAS: 2.5, 5.5, **p = 0.02**; *thyroid dose ≤20 Gy*: AAS: **2.3 (1.3-4.5), 2.8 (1.1-6.7), p = 0.009**; anthracyclines: 1.9 (1.0-3.4), 1.7 (0.8-3.3), p = 0.07; bleomycin: 1.5 (0.4-5.3), 2.2 (0.5-9.3), p = 0.69; *thyroid dose >20 Gy*: AAS: 1.0 (0.5-2.1), 1.0 (0.5-2.1), p = 0.99; anthracyclines: 0.9 (0.4-2.1), 0.8 (0.2-3.4), p = 0.97; bleomycin: 0.2 (0.03-1.9), -, p = 0.09	doses decreased the chemotherapy effect; results of other subgroup analyses not reported in this table
Nested case-control studies				
Allodji et al. (2019); **FCCSS; colorectal**	OR using conditional logistic regression and Firth method; p for trend; subgroup analysis with patients with <30 Gy radiation; *radiation, chemotherapy group: anthracyclines adjusted for RT dose category, MOPP dose category; MOPP adjusted for RT dose category, anthracycline dose category;* *additional analysis with adjustment for FPN*	p-value for heterogeneity; *radiation, chemotherapy group (unless otherwise specified): anthracyclines adjusted for RT dose category, MOPP dose category; MOPP adjusted for RT dose category, anthracycline dose category;*	univariable analyses: any alkylating agent treatment except procarbazine: **2.8 (1.1-7.2)**, 1.0 (0.6-5.7), p = 0.16; procarbazine: 2.4 (0.5-9.3), **4.5 (1.3-16.9)**, p-value **0.01,** continuous: **1.3 (1.1-1.5)**, p = **0.01;** anthracyclines: 3.3 (1-11.7), 3.0 (0.9-10.5), p = 0.06, continuous: 4.3 (0.8-27.5), p = 0.11; vincristine: 2.9 (0.8-12.4), **5.0 (1.6-21.1)**, **p = 0.01**, continuous: 1.2 (0.1-3.7), p = 0.85; MOPP: 3.1 (0.8-11.3), **4.8 (1.2-21.4)**, **p = 0.01**, continuous: .12 (0.1-3.7), p = 0.85; vincristine not in MOPP: 0.7 (0.2-2.2.), 1.4 (0.6-3.7), p = 0.42, continuous: 1.1 (0.1-3.5), p = 0.9; antimetabolites: 0.9 (0.2-3.5), **4 (1.1-15.0)**, p = 0.07, continuous: 1 (1-1), p = 0.09; platinum compounds, continuous: 0.8 (<0.1-	univariable analyses: any chemotherapy: **10.7 (2.6-99.5)**, p = **0.01**; alkylating agents: **2.4 (1.1-5.9)**, p = **0.05**; procarbazine: **3.4 (1.3-9)**, p = **0.01**; platinum compounds: 0.8 (0.1-3.2), p = 0.77; anthracyclines: **3.2 (1.2-9.3)**, p = **0.03**; epipodophyllotoxins: 0.7 (0.1-3.4), p = 0.71; vincristine: **3.9 (1.3-15.3)**, p = **0.03**; MOPP: **3.8 (1.4-10.5)**, p = **0.01**; vincristine not in MOPP: 1.1 (0.4-2.7), p = 0.85; OR for further chemotherapy substances not reported in this table; *subgroup with <30 Gy radiation:* anthracyclines: 1.8 (0.55-5.8), p = 0.34; MOPP: **3.6 (1.2-1.8)**, p = **0.03**; multivariate analyses:

Author; **Setting;** **SPN type**	**Statistical models for CT-dose analysis;** ***Adjustments/further covariates***	**Statistical models for dichotomous CT, if different from CT-dose analyses;** ***Adjustments/further covariates if different from CT-dose analyses***	**Outcome CT-dose;** ***Outcome of subgroup or subgroup analyses in italic***	**Outcome CT, dichotomous;** ***Outcome of subgroup or subgroup analyses in italic***
			1.4), p = 0.58; epipodophyllotoxins, continuous: 1.3 (0.6-2.6), p = 0.54 <u>multivariate analyses:</u> anthracyclines: 3.3 (0.9-13.8), 3.2 (0.8-15.1), p = 0.06, *additionally adjusted for FPN type*: 2.4 (0.6-9.6), 1.8 (0.4-9.4), p = 0.39; MOPP: 2.2 (0.5-10.3), 2.4 (0.5-11.8), p = 0.16, *additionally adjusted for FPN type*: 2 (0.3-13.1), 1.6 (0.3-10), p = 0.47; *for subgroup RT <30 Gy:* anthracyclines: 2.3 (0.5-10.4), 2.3 (0.5-11.4), p = 0.17; MOPP: 2.2 (0.5-10.2), 2.6 (0.5-13.1), p = 0.25	any CT (adjusted for any RT): **10.1 (2.4-93.8)**, p = **0.01**; anthracyclines: 3.3 (1.1-11.7), p = 0.05; anthracyclines (adjusted for any RT, MOPP): **4.3 (1.4-15)**, p = **0.02**; MOPP: 2.3 (0.7-7.7), p = 0.18; MOPP (adjusted for any RT, anthracyclines): **3.7 (1.2-12)**, p = **0.03**; *subgroup with <30 Gy radiation:* any CT (adjusted for RT dose category): **7.1 (1.6-68.9)**, p = **0.04**; anthracyclines: 2.3 (0.63-8.6), p = 0.18; MOPP: 2.4 (0.71-8.1), p = 0.16
Inskip et al. (2009); **CCSS-US/Canada;** **BC**	OR with 95% CI using conditional logistic regression with 95% CI; *radiation dose to breast and ovary, type of FPN (Hodgkin's lymphoma, sarcoma, other), analyses for mechlorethamine and procarbazine dose categories also adjusted for cumulative dose of doxorubicin*	*radiation dose to breast and ovary, type of FPN (Hodgkin's lymphoma, sarcoma, other), analyses for mechlorethamine and procarbazine yes/no also adjusted for doxorubicin yes/no*	AAS: 0.67 (0.30-1.51), 1.40 (0.58-3.39), 1.15 (0.55-2.41); mechlorethamine: 0.71 (0.20-2.53), 0.41 (0.09-1.75), 0.61 (0.10-3.59); procarbazine: 0.69 (0.26-1.86), 0.69 (0.23-2.02), 0.92 (0.28-3.09); doxorubicin: 2.09 (0.71-6.14), 1.93 (0.64-5.87), 1.28 (0.44-3.73)	any: 0.9 (0.53-1.54); alkylating agent: 0.93 (0.56-1.55); mechlorethamine: 0.81 (0.37-1.76); procarbazine: 0.70 (0.37-1.35); BCNU: **3.71 (1.12-12.30)**; CCNU: 1.73 (0.55-5.44); cyclophosphamide: 1.37 (0.79-2.38); dacarbazine:3.49 (0.96-12.68); dactinomycin: 2.40 (0.96-5.96); bleomycin: 1.82 (0.99-3.48); anthracycline: 1.86 (0.99-3.48); daunorubicin: 0.84 (0.17-4.22); doxorubicin: 1.87 (0.98-3.55)
Sigurdson et al. (2005);	OR with 95% CI (interpreted as RR) using conditional logistic regression; *adjustments unclear*	*radiation dose, FPN*	"No significant trend in the dose-response was noted for alkylating agents or anthracyclines (data not shown)."	chemotherapy: 1.1 (0.5-2.6); alkylating agents: 1.3 (0.6-2.5); anthracyclines: 1.8 (0.9-4.0); epipodophyllotoxins: 1.4 (0.3-6.3);

Author; **Setting;** **SPN type**	**Statistical models for CT-dose analysis;** ***Adjustments/further covariates***	**Statistical models for dichotomous CT, if different from CT-dose analyses;** ***Adjustments/further covariates if different from CT-dose analyses***	**Outcome CT-dose;** ***Outcome of subgroup or subgroup analyses in italic***	**Outcome CT, dichotomous;** ***Outcome of subgroup or subgroup analyses in italic***
CCSS-US/Canada; **Thyroid cancer**				chemotherapy did not modify risk from radiotherapy
Tucker et al. (1991); **US Late Effects Study Group;** **Thyroid cancer**	OR with 95% CI (interpreted as RR) using conditional logistic regression; test for trend with midpoint of each dose category; in addition linear and linear exponential models using continuous dose data; *adjustments unclear*	*dichotomous variables alkylating agents and dactinomycin adjusted for radiation*	"There was also no indication of increasing risk with higher doses of alkylating agents (RR 1.0). No excess risk was associated with Vinca alkaloid treatment (RR 1.0) even in the higher dose categories (RR 0.5)."	alkylating agents: RR 1.2 (95% CI 0.4-3.8); vinca alkaloids: RR 1.0, n.s.; dactinomycin: RR 1.7 (95% CI 0.3-11.6)
Watt et al. (2012a); **CCSS-US/Canada;** **BCC**	OR with 95% CI using conditional logistic regression, p-values for trend; univariable models for each covariate, covariates entered in multivariable models if significant at 0.05 level or OR was altered by 10% or more; *sex, race (non-Hispanic white vs other), Hodgkin lymphoma (yes/no); one model additionally adjusted for radiation dose*		cyclophosphamide oral: 1.3 (0.3-5.0), 0.7 (0.2-2.2), -, p = 0.69; model additionally adjusted for radiation dose: procarbazine: 1.6 (0.5-4.5), 0.9 (0.4-1.8), -, p = 0.76; cyclophosphamide IV: 0.9 (0.5-1.8), 0.5 (0.2-1.3), 0.5 (0.2-1.4), 1.7 (0.2-12.5), -, p = 0.23; AAS: 1.0 (0.5-2.0), 1.5 (0.8-3.1), 0.7 (0.3-1.3), -, p = 0.62; anthracycline score: 2.3 (1.0-5.3), 1.3 (0.6-2.8), 0.9 (0.4-2.4), -; p = 0.63	treatment modality: **4.3 (1.4-13.3)**, 0.7 (0.2-2.7), **4.1 (1.4-11.6)**, -; model additionally adjusted for radiation dose: alkylating agent: 1.1 (0.7-1.8), -; anthracycline: 1.3 (0.8-2.1), -; prednisone: 1.2 (0.7-1.8), -
*score method: assigning numbers to tertiles of cumulative dose of all subjects receiving substance (0: no substance, 1: lowest tertile, 2, 3: highest tertile); for substance groups: summing tertiles for all substances in group **** Henderson et al. 2016: Outcome CT-dose:** <u>univariable:</u> SIR: CED: 2.6 (1.6-4.2), 2.8 (1.1-7.5), 7.9 (4.8-12.9), 9.4 (4.5-19.7); anthracycline: 2.0 (1.2-3.3), 4.0 (1.5-10.7), 8.3 (5.7-12.2);			**Abbreviations:** 95% CI = 95% confidence interval - = not applicable AAS = alkylating agent score according to (Tucker et al., 1987b), unless otherwise specified, see score method AER = absolute excess risk BC = breast cancer BCC = basal cell carcinoma SIR = standardized incidence ratio	

Author; **Setting;** **SPN type**	**Statistical models for CT-dose analysis;** ***Adjustments/further covariates***	**Statistical models for dichotomous CT, if different from CT-dose analyses;** ***Adjustments/further covariates if different from CT-dose analyses***	**Outcome CT-dose;** ***Outcome of subgroup or subgroup analyses in italic***	**Outcome CT, dichotomous;** ***Outcome of subgroup or subgroup analyses in italic***
AER: CED: 2.5 (0.6-4.5), 2.3 (-1.2-5.7), 11.2 (4.9-17.4), 17.7 (3.1-32.3); anthracycline: 1.5 (-0.1-3.1), 3.1 (-0.9-7.1), 15.2 (8.6-21.9); "exposures to alkylator and anthracycline chemotherapy were associated with breast cancer development in a dose-dependent fashion (P values both <.01)"; *leukemia/sarcoma survivors:* SIR: CED: 2.8 (1.5-4.8), 3.3 (1.2-8.7), 10.0 (6.1-16.7), 10.3 (4.6-22.9); anthracycline: 1.8 (0.9-3.6), 5.0 (1.8-13.1), 9.5 (6.4-14.0); AER: CED: 3.4 (0.4-6.4), 2.9 (-1.2-7.0), 16.1 (7.0-25.1), 20.9 (2.3-39.5); anthracycline: 1.5 (-0.8-3.7), 4.5 (-0.1-9.9), 19.2 (10.8-27.5);			CCSS = childhood cancer survivor study CED = cyclophosphamide equivalent dose (Green et al., 2014) CI = cumulative incidence Cox model = Cox proportional hazards regression CRC = colorectal cancer Abbreviations: CT = chemotherapy Ex = number of SPN cases expected GI = gastrointestinal HR = hazard ratio LFS = Li Fraumeni syndrome n/a = not available NSI = Nucleotide synthesis inhibitors (here: only methotrexate) n.s. = not significant (used if only significance was reported but no p-value or 95% CI) O = number of SPN cases observed PR = Poisson regression RR = relative risk RT = radiotherapy SGC = salivary gland carcinomas TBI = total body irradiation	

14 Scoping review: Strengths and limitations

Strengths and limitations of studies included in full text evaluation of scoping review. Studies investigate the dose-response relationship between chemotherapeutic substances and a carcinoma or skin cancer as second primary neoplasm after childhood cancer.

Title	Strengths mentioned in article	Limitations mentioned in article	Further strengths	Further limitations
Cohort studies				
CCSS-US/Canada in general			+ standardized data collection, including cumulative doses of many CT substances + large, clearly defined cohort	- participation of survivors required --> selection bias possible - self-reporting of SPNs means that underreporting is possible
Boukheris et al. (2013); **CCSS-US/Canada; Salivariy glad carcinomas**	+ large, well defined and characterized cohort + nearly complete treatment information, detailed radiation dosimetry, information about other possible risk factors available + non-participants did not differ significantly from participant with respect to known risk factors	- small number of subsequent SGC did not allow more detailed analyses - self-reported, thus number of SGC may be underreported - 30% of potentially eligible survivors did not participate (they refused or could not be traced)	+ see CCSS-US/Canada in general	- see CCSS-US/Canada in general - boundaries of dose categories for AAS not reported - method of pooling doses of each substance into anthracycline group not reported
Ehrhardt et al. (2019); **SJLIFE; BC**	+ cohort clinically assessed and prospectively followed up + chest dosimetry systematically estimated (as opposed to prescribed field dose)	- small number of subsequent BC cases - dosimetry estimations limited to chest rather than breast -in situ carcinomas included, but did not change results in subgroup analyses - 65% participation rate may bias results, but subgroup analyses did not change results - underestimation of BC incidence possible	+ genetic risk/breast cancer predisposition gene mutation taken into account	- unclear if radiation dose was categorized for analysis or only for reporting results - participation of survivors required --> selection bias possible
Guibout et al. (2005); **France and the United Kingdom; BC**	+ low rate of loss-to-follow-up (12%) + wide range of RT doses available	- relatively small cohort size, limited number of patients treated with RT (n = 1258) - selection bias possible because no patients with leukemia as FPN included - overestimation of BC incidence possible	+ no reliance on active participation for case ascertainment	- pooling of doses within each substance category not described, presumably sum of doses - adjustments or inclusion of other covariates in dose-response analyses is

Title	Strengths mentioned in article	Limitations mentioned in article	Further strengths	Further limitations
		because of heightened medical surveillance of survivors compared to general population and because women lost to follow-up received less CT than those included		unclear - results on dose analyses reported verbally without estimates - women lost to follow-up (n=210) received less chemotherapy than those included --> potential source of bias
Henderson et al. (2016); **CCSS-US/Canada; BC**	+ largest study on BC risk in childhood cancer survivors without chest RT for FPN	- small number of patients with BC resulted in too little power for more detailed analyses - sparse family history data did not allow to explore familial cancer risk - scatter radiotherapy dose of therapeutic radiation not calculated (only yes/no); - exposure to diagnostic radiation not quantified	+ see CCSS-US/Canada in general + cohort without chest radiation eliminates effect of this covariate	- see CCSS-US/Canada in general - method of pooling anthracyclines not described in references cited - risk for breast cancer started 5 years after diagnosis - incidence for CCSS-cohort may be overestimated due to heightened medical surveillance → SIR may be overestimated
Henderson et al. (2012a)**;** **CCSS-US/Canada; Gastrointestinal cancer**	+ largest study on GI SPN in childhood cancer survivors	- small number of GI SPN does not allow more detailed analyses - SPN and family history self-reported, which may lead to underreporting and inaccuracies - risks of early GI SPNs could not be identified because only SPNs occurring 5 years after the FPN were included	+ see CCSS-US/Canada in general	- see CCSS-US/Canada in general - method of pooling anthracyclines and alkylating agents not described in reference cited - unclear if models prior to final multivariable model also included doses of chemotherapeutic substances
Kenney et al. (2004); **CCSS-US/Canada; BC**	+ largest series of secondary BC to that date + non-treatment related variables included	- risk estimates might be biased because health status of nonparticipants unknown - disease burden probably underestimated because patients had not attained age at greatest risk yet	+ see CCSS-US/Canada in general	- see CCSS-US/Canada in general - only adjustment for chest radiation even though family history and other variables were available
Neglia et al. (2001); **CCSS-US/Canada; BC+thyroid cancer**	+ large retrospective cohort with common childhood cancers + SIR regression model adjusted for fact that older patients are at higher BC risk in general population	- exclusion of patients with SPN within 5 years of FPN diagnosis or patients with SPN who died before 5 years of FPN diagnosis limit comparability to other studies - exclusion of patients with retinoblastoma who are well known to be at increased SPN risk - SPNs self-reported --> overall risk of SPNs from time of FPN diagnosis underestimated - RT included as dichotomous variable	+ see CCSS-US/Canada in general	- see CCSS-US/Canada in general - error in reporting: p for trend reported for chemotherapy substances which none of the patients had received - boundaries of dose categories for AAS not reported

Title	Strengths mentioned in article	Limitations mentioned in article	Further strengths	Further limitations
Teepen et al. (2017); **DCOG LATER;** **BC**	+ large cohort size + detailed individual treatment information + SPN follow-up through record linkage and medical information	- low number of SPNs - correlations between patient and treatment factors hampered ability to disentangle effects - many tested variables and various post hoc tests might have led to chance findings .	+ stratification by patients with Li-Fraumeni syndrome associated childhood cancers as a surrogate for genetic susceptibility + no reliance on self-report of SPNs	- unclear, if treatment of SPNs preceding BC contributed to cumulative dose; I suppose not; details on “treatment of primary tumor and all recurrences were collected” - way of pooling anthracyclines not described
Veiga et al. (2012a); **CCSS-US/Canada;** **Thyroid cancer**	+ large cohort size, substantial number of thyroid cancer cases + pathologic confirmation of reported cancers + CT and RT information on all cohort members, individual radiation dosimetry	- strong correlation between FPN type and type of treatment can make it difficult to distinguish between the two effects of the two variables; most relevant for procarbazine, which is predominantly used to treat HL and CNS cancers - SPNs self-reported - uncertainty in radiation doses - possibility of targeted clinical surveillance for HL patients	+ see CCSS-US/Canada in general	- see CCSS-US/Canada in general - results of analyses including HL patients or CNS patients mentioned in discussion but not reported in results - boundaries of dose categories for AAS not reported
Nested case-control studies				
Allodji et al. (2019); **FCCSS;** **colorectal**	+ long follow-up period (average 30 years) + availability of detailed treatment data + validation of CRC with medical records and by contacting patients and referring physician	- small number of CRC cases strongly limits interpretation of risk factors - bias possible through choice of radiation dose cutoff points - radiation dose distribution estimated at site of CRC, but no whole organ dose-volume - limited generalizability due to changes in patient treatment overtime - limited information on genetics and lifestyle factors, which may influence CRC risk - many models without adjustment for multiple testing may lead to chance significant findings	+ chemotherapy dose included as continuous predictor + no sole reliance on self-report of SPNs	- assumption of equal carcinogenic potency of substances in one substance group contradicts current body of evidence; validity of summing doses within groups is questionable - unclear if therapy of SPNs between FPN and CSPN was included - unclear if neuroendocrine tumors were carcinomas because dignity was not reported
Inskip et al. (2009); **CCSS-US/Canada;** **BC**	+ large number of BC cases + detailed radiation dosimetry	- imprecise anatomic location of BC and tumor progenitor cell at time of irradiation, incomplete stage information - description of radiation dose-response curve compromised due to few patients with low and intermediate radiation doses	+ see CCSS-US/Canada in general	- see CCSS-US/Canada in general - results of modification of association between RT dose and BC risk by CT not reported - boundaries of dose categories for AAS not reported

Title	Strengths mentioned in article	Limitations mentioned in article	Further strengths	Further limitations
		- limited ability to evaluate variation in radiation subgroup before and after menarche due to strong correlations among FPN type, age at FPN, radiation dose		
Sigurdson et al. (2005); **CCSS-US/Canada; Thyroid cancer**	+ detailed treatment information for the first cancer and specific organ radiation doses + thyroid cancers pathologically confirmed + modifying factors from questionnaire data considered	- small number of patients - possibly not all relevant risk factors for thyroid cancer included - wide 95% CI around radiation dose-response curves		- see CCSS-US/Canada in general - reporting of sample size confusing - results of dose-response analysis with CT not shown - results of matching on FPN type not reported for CT, only for radiotherapy - boundaries of dose categories for alkylating agents and anthracyclines not reported - method of pooling doses of each substance into each substance groups not reported
Tucker et al. (1991); **US Late Effects Study Group; Thyroid cancer**	+ no case-control differences in family history of cancer at time of diagnosis of FPN	- CT data too limited to support strong conclusions - exclusion of study subjects with imputed radiation doses increased risks for each RT dose level - using only controls matched on calendar year increased RR associated with RT dose compared to controls not match on calendar year - effects of age at FPN and radiation dose could not be separated	+ 2-year-survivors instead of 5-year survivors + no reliance on active participation for case ascertainment	- boundaries of dose categories for AAS and anthracyclines not reported - some estimates lack 95% CI - results of subgroup analyses not reported as they relate to CT
Watt et al. (2012a); **CCSS-US/Canada; BCC**		- large proportion of data self-reported, number of BCC may be underreported, unconfirmed, or BCC location may be incorrect - effect of CT in survivors with low RT doses (<1 Gy) or no RT not examined due to small numbers	+ see CCSS-US/Canada in general	- see CCSS-US/Canada in general - multivariable model includes variables IV cyclophosphamide dose and AAS; - boundaries of dose categories for AAS and anthracyclines not reported - unclear if multivariable models were additionally adjusted for other covariates reported in Table 2 of article; since AAS includes cyclophosphamide, multicollinearity may occur which may influence the validity of the estimates

Abbreviations:
AAS = alkylating agent score according to (Tucker et al., 1987b),
BC = breast cancer
BCC = basal cell carcinoma
CCSS = childhood cancer survivor study
CNS = central nervous system
CRC = colorectal cancer
CT = chemotherapy
FCCSS = French Childhood Cancer Survivor Study
FPN = first primary neoplasm
GI = gastrointestinal
HL = Hodgkin lymphoma
RT = radiotherapy
SGC = salivary gland carcinomas
SIR = standardized incidence ratio
SPN = second primary neoplasm

15 Scoping review: Illustration of results

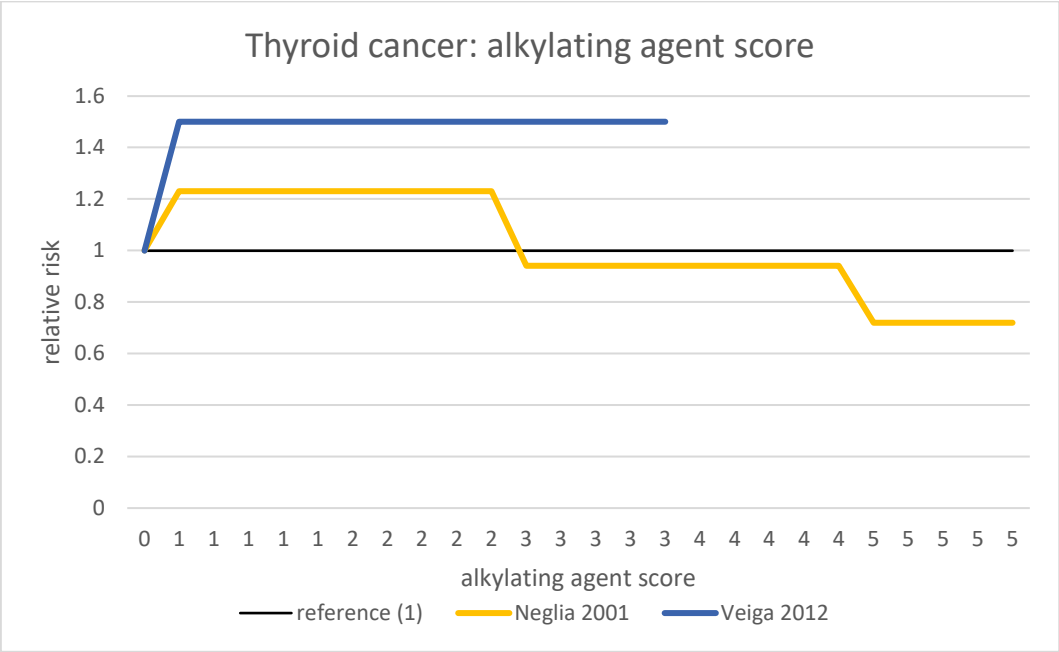


Figure 22. Thyroid cancer risk after childhood cancer treatment by alkylating agent score (cohort-specific score by Tucker, Meadows, et al. (1987)). None of the relative risks were significant at the 5%-level. Results of articles from a scoping review on the dose-response relationship between chemotherapy and subsequent cancers according to ICCC-3 XI with original research studies published by July 2019. ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005).

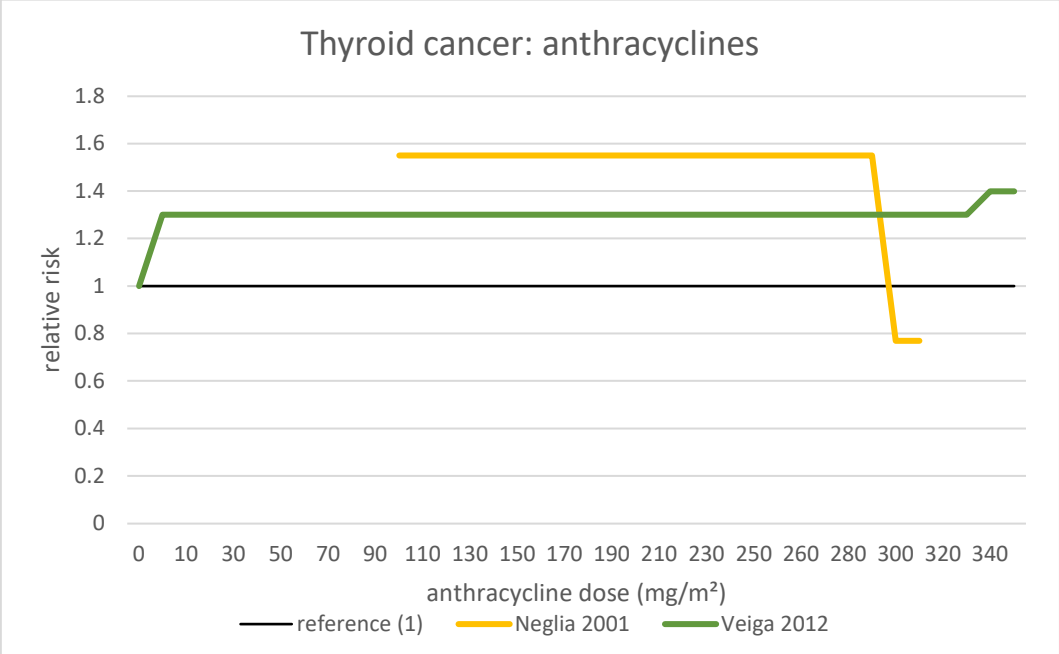


Figure 23. Thyroid cancer risk after childhood cancer treatment by cumulative anthracycline dose. None of the relative risks were significant at the 5%-level. Results of articles from a scoping review on the dose-response relationship between chemotherapy and subsequent cancers according to ICCC-3 XI with original research studies published by July 2019. ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005).

16 Scoping review: Main study results by substance (group)

Summary of main results by substance (group) and SPN type and points important for interpretation of the results: anthracyclines, doxorubicin, alkylating agents, cyclophosphamide, procarbazine, epipodophyllotoxins, platinum compounds.

Anthracyclines (mg/m², unless otherwise specified)						
Author Setting	**Cumulative dose categories or test**	**Measure**	**Outcome**	**Confidence interval**	**Notes**	**Adjustment of multivariable model; matching in case-controls studies; potential SPN risk factors not considered**
Thyroid SPN						
Neglia et al. 2001; CCSS-US/Canada	0	RR	1 (ref.)		cohort study; SPN n = 39 with chemotherapy information (for AAS only 36); self-reporting of SPN → underreporting possible; neoplasms following second primary neoplasm not included in risk analysis; risk period for cancer started 5 years after diagnosis;	adjusted for radiation exposure to tumor sites (dichotomous); sex, age at FPN diagnosis, treatment era, FPN diagnosis, splenectomy, AAS, anthracyclines, epipodophyllotoxins, platinum compounds; not considered: genetics
	1-100		-			
	101-300		1.55	0.66-3.64		
	≥301;		0.77	0.16-3.69		
	p for trend		p>0.5			
Veiga et al. 2012; CCSS-US/Canada	0	RR	1 (ref.)		cohort study; SPN n = 119 (for 8, thyroid cancer was the 3rd malignancy), 111 patients for dose-response analysis in anthracyclines; self-reporting of SPN → underreporting possible; risk period for cancer started 5 years after diagnosis;	adjusted for sex, natural logarithm of attained age, type of FPN (HL, leukemia, others); overall analyses additionally adjusted for radiation dose categories; subgroups with >0-5 Gy, ≤20 Gy or >20 Gy additionally thyroid radiation dose (continuous); not considered: age at diagnosis, genetics
	<340		1.3	0.8-2.1		
	≥340		1.4	0.7-2.5		
	test for heterogeneity		p = 0.36			
Sirgudson et al. 2005; CCSS-US/Canada	OR: "No significant trend in the dose-response was noted for alkylating agents or anthracyclines (data not shown)."				case-control study; SPN n = 68, for 5, thyroid cancer was the third malignancy → therapy of neoplasm preceding thyroid cancer probably included in cumulative dose; self-reporting of SPN → underreporting possible; risk period for cancer started 5 years after diagnosis;	adjustments unclear; matched for sex, age at FPN diagnosis (±2 years), follow-up interval; unclear if considered: radiation, genetics; FPN considered in subgroup analysis

					for alkylating agents and anthracyclines: boundaries of dose categories not reported	
Breast SPN						
Teepen et al. 2017; DCOG LATER	0	HR	1 (ref.)		cohort study; SPN n = 49; preceding SPNs of other entities possible, probably only 1st BC included but → unclear, if treatment of preceding tumor included in cumulative doses; risk period for cancer started 5 years after diagnosis; chance findings possible due to various post hoc tests; anthracyclines: way of pooling not described	final model adjusted for chest radiotherapy, total body irradiation; probably considered: attained age; unclear if considered: sex, age at diagnosis, period of diagnosis; FPN and indirectly genetics considered through subgroup analysis with Li-Fraumeni-associated FPNs (non-Ewing sarcoma, CNS tumors, leukemia)
	1-249		1.3	0.5-3.2		
	≥250		**3.1**	**1.4-6.5**		
	test for trend		**p = 0.004**			
Ehrhardt et al. 2019; SJLIFE	0	HR	1 (ref.)		cohort study; SPN n = 45 for dose-response analysis; participation of survivors required → selection bias possible	adjusted for age at diagnosis, mutation, chest and pelvic radiation, alkylators, anthracyclines; no considered: attained age, FPN
	1-249		**2.6**	**1.1-6.2**		
	≥250		**13.4**	**5.5-32.5**		
Henderson et al. 2016; CCSS-US/Canada	0	relative SIR	1 (ref.)		cohort study; SPN n = 44 for dose-response analysis; patients without chest radiation for FPN; self-reporting of SPN → underreporting possible; only patients without recurrence or other SPN before BC diagnosis; risk for breast cancer started 5 years after diagnosis; incidence for CCSS-cohort may be overestimated due to heightened medical surveillance → SIR may be overestimated	adjusted for cumulative anthracycline dose, CED, age at FPN; adjustment variables: race/ethnicity (white, non-Hispanic, other), attained age, FPN diagnosis (sarcoma/leukemia vs other); additional adjustment for FPN diagnosis; FPN and indirectly genetics considered through subgroup analysis with Li-Fraumeni-associated FPNs (sarcoma, leukemia)
	1-249		2.6	0.8-8.7		
	≥250		**3.8**	**1.7-8.3**		
	p for trend		**p = 0.004**			
Neglia et al. 2001; CCSS-US/Canada	0	RR	1 (ref.)		cohort study; SPN n = 53 for dose-response analysis (for AAS only 49); self-reporting of SPN → underreporting possible; neoplasms following second primary neoplasm not included in risk analysis; risk period for cancer started 5 years after diagnosis;	adjusted for radiation exposure to tumor sites (dichotomous); sex, age at FPN diagnosis, treatment era, FPN diagnosis, splenectomy, AAS, anthracyclines, epipodophyllotoxins, platinum compounds; not considered: genetics
	1-100		2.59	0.32-20.79		
	101-300		1.78	0.76-4.19		
	≥301;		1.97	0.58-6.68		
	p for trend		p = 0.15			
Other CSPNs						

Boukheris et al. 2013; CCSS-US/Canada; salivary gland carcinomas	0 (ref.) 0.12–174 175–290 291–390 391–8370 unknown test for linear trend	RR	1 (ref.) 1.8 1.8 0.9 2.0 3.1 p = 0.42	 0.3-6.7 0.3-6.8 0.05-4.8 0.3-7.7 0.5-11.6	cohort study; SPN n = 20 for dose-response analysis due to missing RT dose; self-reporting of SPN → underreporting possible; anthracycline: method of pooling doses not reported; risk period for cancer started 5 years after diagnosis;	adjusted for attained age as continuous variable; indirect adjustment for sex, race, attained age, attained calendar period; radiation dose (as linear variable); not considered: age at diagnosis, genetics, FPN
Allodji et al. 2019 French CCSS; colorectal cancer	0 0–290 ≥ 300 test for heterogeneity	OR	1 (ref.) 3.3 3.2 p = 0.06	 0.9-13.8 0.8-15.1	case-control study; SPN n = 36; FPN solid tumors; risk period for cancer started 5 years after diagnosis; for 10 patients, colorectal cancer was the 3rd malignancy but → unclear, if treatment of preceding tumor included in cumulative doses; many models without adjustment for multiple testing may lead to chance significant findings	adjusted for radiation, chemotherapy group: anthracyclines adjusted for RT dose category, MOPP dose category; MOPP adjusted for RT dose category, anthracycline dose category; additional analysis with adjustment for FPN; matched for sex, age at FPN diagnosis, duration of follow-up, date of diagnosis; not considered: genetics; FPN considered in subgroup analysis (no change in significance)
Watt et al. 2012a; CCSS-US/Canada; basal cell carcinoma	Score: 0 1 2 3 unknown test for trend	OR	1 (ref.) 2.3 1.3 0.9 - p = 0.63	 1.0-5.3 0.6-2.8 0.4-2.4	case-control study; SPN n = 199, first basal cell carcinoma only; risk period for cancer started 5 years after diagnosis; for AAS and anthracyclines: boundaries of dose categories not reported;	adjusted for radiation dose, sex, race (non-Hispanic white vs other), Hodgkin lymphoma (yes/no); unclear if there were additional adjustments, AAS and cyclophosphamide (an alkylating agent) possibly in same model, which may influence validity of estimates; matched for age at FPN diagnosis (±5 years), duration of follow-up; not considered: genetics

Abbreviations:
AAS = alkylating agent score
BC = breast cancer
CCSS = childhood cancer survivor study
CED = cyclophosphamide equivalent dose
CNS = central nervous system
CSPN = carcinoma or malignant melanoma according to ICCC-3 XI as subsequent primary neoplasm after childhood cancer

FPN = first primary neoplasm
HL = Hodgkin lymphoma
HR = hazard ratio
MOPP = mechlorethamine, vincristine, procarbazine with or without prednisone
OR = odds ratio
RR = relative risk
RT = radiotherapy
SPN = second primary neoplasm

Doxorubicin (mg/m²), unless otherwise specified)						
Author Setting	**Cumulative dose categories or test**	**Measure**	**Outcome**	**Confidence interval**	**Notes**	**Adjustment of multivariable model; matching in case-controls studies; potential SPN risk factors not considered**
Breast SPN						
Inskip et al. 2009; CCSS-US/Canada	0	OR	1 (ref.)		case-control study;	adjusted for radiation dose to breast and ovary, type of FPN (Hodgkin's lymphoma, sarcoma, other), analyses for mechlorethamine and procarbazine dose categories also adjusted for cumulative dose of doxorubicin;
	>0-198.8		2.09	0.71-6.14	SPN for dose-response analysis: n = 94 for AAS, n = 103 for mechlorethamine, n = 101 for procarbazine, n = 100 for doxorubicin;	
	>198.8-<350.8		1.93	0.64-5.87		
	≥350.8		1.28	0.44-3.73		
					for 7 out of 120 women, BC was the third neoplasm → therapy for neoplasm preceding BC probably included in cumulative dose;	matched for age at FPN diagnosis, duration of survival (follow up ±2 years), for analysis of cases and controls with same FPN diagnosis: FPN diagnosis;
						not considered: genetics
Teepen et al. 2017; DCOG LATER	0	HR	1 (ref.)		cohort study;	final model adjusted for chest radiotherapy, total body irradiation;
	≤270		1.1	0.4-2.9	SPN n = 49;	
	271-443		**2.6**	**1.1-6.5**	preceding SPNs of other entities possible, probably only 1st BC included but → unclear, if treatment of preceding tumor included in cumulative doses;	probably considered: attained age; unclear if considered: sex, age at diagnosis, period of diagnosis;
	>443		**5.8**	**2.7-12.5**		
	test for trend		**p<0.001**			
					risk period for cancer started 5 years after diagnosis;	FPN and indirectly genetics considered through subgroup analysis with Li-Fraumeni-associated FPNs (non-Ewing sarcoma, CNS tumors, leukemia);
					chance findings possible due to various post hoc tests;	there was no change in significance in the models without radiotherapy and with LFS-associated FPNs; the model with FPN diagnoses not associated with Li-Fraumeni Syndrome was not significant
Ehrhardt et al. 2019; SJLIFE	0	HR	1 (ref.)		cohort study;	adjusted for age at diagnosis, mutation, chest and pelvic radiation, alkylators;
	1-249		**7.3**	**2.9-18.5**	SPN n = 45 for dose-response analysis;	
	≥250		**17.5**	**6.7-45.7**		
					participation of survivors required → selection bias possible	no considered: attained age, FPN

Abbreviations:
BC = breast cancer
CCSS = childhood cancer survivor study
CNS = central nervous system
FPN = first primary neoplasm
HR = hazard ratio
OR = odds ratio
SPN = second primary neoplasm

Alkylating agents (mg/m²) or alkylating agent score (AAS) or cyclophosphamide equivalent dose (CED, mg/m²)						
Author Setting	**Cumulative dose categories or test**	**Measure**	**Outcome**	**Confidence interval**	**Notes**	**Adjustment of multivariable model; matching in case-controls studies; potential SPN risk factors not considered**
Thyroid SPN						
Neglia et al. 2001; CCSS-US/Canada	AAS: 0	RR	1 (ref.)		cohort study; SPN n = 39 with chemotherapy information (for AAS only 36); self-reporting of SPN → underreporting possible; neoplasms following second primary neoplasm not included in risk analysis; risk period for cancer started 5 years after diagnosis; for AAS: boundaries of dose categories not reported	adjusted for radiation exposure to tumor sites (dichotomous); sex, age at FPN diagnosis, treatment era, FPN diagnosis, splenectomy, AAS, anthracyclines, epipodophyllotoxins, platinum compounds; not considered: genetics
	1-2		1.23	0.50-3.0		
	3-4		0.94	0.33-2.62		
	≥5		0.72	0.26-2.00		
	test for trend		p >0.5			
Veiga et al. 2012; CCSS-US/Canada	AAS: 0	RR	1 (ref.)		cohort study; SPN n = 119 (for 8, thyroid cancer was the 3rd malignancy), 106 for dose-response analysis with AAS; self-reporting of SPN → underreporting possible; risk period for cancer started 5 years after diagnosis; for procarbazine: predominantly used for HL and CNS cancer treatment → strong correlation between FPN type and treatment; for AAS: boundaries of dose categories not reported	adjusted for sex, natural logarithm of attained age, type of FPN (HL, leukemia, others); overall analyses additionally adjusted for radiation dose categories; subgroups with >0-5 Gy, ≤20 Gy or >20 Gy additionally thyroid radiation dose (continuous); not considered: age at diagnosis, genetics
	1-2		1.5	1.0-2.3		
	3		1.5	0.8-2.6		
	test for heterogeneity		p = 0.14			
Sirgudson et al. 2005; CCSS-US/Canada	OR: "No significant trend in the dose-response was noted for alkylating agents or anthracyclines (data not shown)."				case-control study SPN n = 68, for 5, thyroid cancer was the third malignancy → therapy of neoplasm preceding thyroid cancer probably included in cumulative dose; self-reporting of SPN → underreporting possible; risk period for cancer started 5 years after diagnosis; for alkylating agents and anthracyclines: boundaries of dose categories not reported	adjustments unclear; matched for sex, age at FPN diagnosis (±2 years), follow-up interval; unclear if considered: radiation, genetics; FPN considered in subgroup analysis
Tucker et al. 1991;	OR: "There was also no indication of increasing risk with higher doses of alkylating agents (RR 1.0).				case-control study SPN n = 23, thyroid cancer was second	adjustments unclear;

US Late Effects Study Group					primary neoplasm in all cases; risk period for cancer started 2 years after diagnosis; for AAS and anthracyclines: boundaries of dose categories not reported	matched for sex, age at FPN diagnosis (±2 years), duration of follow-up, race, histology of FPN; unclear if considered: radiation, genetics
Breast SPN						
Inskip et al. 2009; CCSS-US/Canada	AAS: 0	OR	1 (ref.)		case-control study; SPN for dose-response analysis: n = 94 for AAS; for 7 out of 120 women, BC was the third neoplasm → therapy for neoplasm preceding BC probably included in cumulative dose; for AAS: category boundaries not reported	adjusted for radiation dose to breast and ovary, type of FPN (Hodgkin's lymphoma, sarcoma, other), analyses for mechlorethamine and procarbazine dose categories also adjusted for cumulative dose of doxorubicin; matched for age at FPN diagnosis, duration of survival (follow up ±2 years), for analysis of cases and controls with same FPN diagnosis: FPN diagnosis; not considered: genetics
	1		0.67	0.30-1.51		
	2		1.40	0.58-3.39		
	3		1.15	0.55-2.41		
Kenney et al 2004; CCSS-US/Canada	AAS: 0	RR	1 (ref.)		cohort study; SPN n = 95; self-reporting of SPN → underreporting possible; risk period for cancer started 5 years after diagnosis; only first primary BC considered; disease burden probably underestimated because patients had not attained age at greatest risk yet; p-values reported presumably for test for trend	adjusted for chest radiation (dichotomous); no potential risk factor considered except radiation
	1-2		0.8	0.4-1.6		
	3-4		0.8	0.4-1.4		
	≥5		1.11	0.6-2.0		
			p >0.2			
Neglia et al. 2001; CCSS-US/Canada	AAS: 0	RR	1 (ref.)		cohort study; SPN n = 53 for dose-response analysis (for AAS only 49); self-reporting of SPN → underreporting possible;	adjusted for radiation exposure to tumor sites (dichotomous); sex, age at FPN diagnosis, treatment era, FPN diagnosis, splenectomy, anthracyclines, epipodophyllotoxins, platinum compounds;
	1-2		0.97	0.38-2.48		
	3-4		1.03	0.41-2.63		
	≥5		1.05	0.47-2.34		
	test for trend		p >0.5			

					neoplasms following second primary neoplasm not included in risk analysis; risk period for cancer started 5 years after diagnosis; for AAS: boundaries of dose categories not reported	not considered: genetics
Ehrhardt et al. 2019; SJLIFE	alkylating agents: 0	HR	1 (ref.)		cohort study; SPN n = 45 for dose-response analysis; participation of survivors required → selection bias possible	adjusted for age at diagnosis, mutation, chest and pelvic radiation, anthracyclines; no considered: attained age, FPN
	>0-5,999,		1.0	(0.4-2.6)		
	≥6,000		**0.4**	**(0.2-0.4)**		
Teepen et al. 2017; DCOG-LATER	CED: 0	HR	1 (ref.)		cohort study; SPN n = 49; preceding SPNs of other entities possible, probably only 1st BC included but → unclear, if treatment of preceding tumor included in cumulative doses; risk period for cancer started 5 years after diagnosis; chance findings possible due to various post hoc tests;	final model adjusted for chest radiotherapy, total body irradiation; probably considered: attained age; unclear if considered: sex, age at diagnosis, period of diagnosis; FPN and indirectly genetics considered through subgroup analysis with Li-Fraumeni-associated FPNs (non-Ewing sarcoma, CNS tumors, leukemia)
	<6,000		2.0	0.9-4.8		
	6,000-17,999		1.7	0.7-3.9		
	≥18,000		1.0	0.2-4.5		
	test for trend		p = 0.99			
Henderson et al. 2016; CCSS-US/Canada	CED: 0 (ref. for relative SIR)	SIRs	1 (ref.)		cohort study; SPN n = 44 for dose-response analysis; patients without chest radiation for FPN; self-reporting of SPN → underreporting possible; only patients without recurrence or other SPN before BC diagnosis; risk for breast cancer started 5 years after diagnosis; incidence for CCSS-cohort may be overestimated due to heightened medical surveillance → SIR may be overestimated	adjusted for cumulative anthracycline dose, CED, age at FPN; adjustment variables: race/ethnicity (white, non-Hispanic, other), attained age, FPN diagnosis (sarcoma/leukemia vs other); additional adjustment for FPN diagnosis; FPN and indirectly genetics considered through subgroup analysis with Li-Fraumeni-associated FPNs (sarcoma, leukemia)
	1-5,999		0.6	0.2-2.0		
	6,000-17,999		1.6	0.7-3.5		
	≥18,000		**3.0**	**1.2-7.7**		
	test for trend		p = 0.044			
Other CSPNs						
Allodji et al. 2019; French CCSS; colorectal cancer	alkylating agents except procarbazine: 0	OR	1 (ref.)		case-control study; SPN n = 36; FPN solid tumors; risk period for cancer started 5 years after diagnosis; for 10 patients, colorectal cancer was the 3rd malignancy but → unclear, if treatment of	model reported is univariable matched for sex, age at FPN diagnosis, duration of follow-up, date of diagnosis; not considered: radiotherapy, genetics; FPN considered in subgroup analysis
	0-5900		**2.8**	**1.1-7.2**		
	≥ 6000		1.0	0.6-5.7		
	test for heterogeneity		p = 0.16			

					preceding tumor included in cumulative doses; many models without adjustment for multiple testing may lead to chance significant findings;	
Boukheris et al. 2013; CCSS-US/Canada; salivary gland carcinomas	AAS: 0	RR	1 (ref.)		cohort study; SPN n = 20 for dose-response analysis due to missing RT dose; self-reporting of SPN → underreporting possible; for AAS: category boundaries not reported anthracycline: method of pooling doses not reported; risk period for cancer started 5 years after diagnosis;	adjusted for attained age as continuous variable; indirect adjustment for sex, race, attained age, attained calendar period; radiation dose (as linear variable); not considered: age at diagnosis, genetics, FPN
	1		**4.1**	**1.4-13.7**		
	2		2.0	0.4-8.1		
	3		1.1	0.2-5.3		
	unkown		1.6	0.2-7.5		
	linear trend n.s.		p >0.5			
Watt et al. 2012; CCSS-US/Canada; basal cell carcinoma	AAS: 0	OR	1 (ref.)		case-control study; SPN n = 199, first basal cell carcinoma only; risk period for cancer started 5 years after diagnosis; for AAS and anthracyclines: boundaries of dose categories not reported;	adjusted for radiation dose, sex, race (non-Hispanic white vs other), Hodgkin lymphoma (yes/no); unclear if there were additional adjustments, AAS and cyclophosphamide (an alkylating agent) possibly in same model, which may influence validity of estimates; matched for age at FPN diagnosis (±5 years), duration of follow-up; not considered: genetics
	1		1.0	0.5-2.0		
	2		1.5	0.8-3.1		
	3		0.7	0.3-1.3		
	unkown		-	-		
	test for trend		p = 0.62			

Abbreviations:
AAS = alkylating agent score
BC = breast cancer
CCSS = childhood cancer survivor study
CED = cyclophosphamide equivalent dose
CNS = central nervous system
CSPN = carcinoma or malignant melanoma according to ICCC-3 XI as subsequent primary neoplasm after childhood cancer
FPN = first primary neoplasm
HL = Hodgkin lymphoma
HR = hazard ratio
MOPP = mechlorethamine, vincristine, procarbazine with or without prednisone
OR = odds ratio
RR = relative risk
RT = radiotherapy
SIR = standardized incidence ratio
SPN = second primary neoplasm

Cyclophosphamide (mg/m²)						
Author Setting	**Cumulative dose categories or test**	**Measure**	**Outcome**	**Confidence interval**	**Notes**	**Adjustment of multivariable model; matching in case-controls studies; potential SPN risk factors not considered**
Other CSPNs						
Watt et al. 2012; CCSS-US/Canada; basal cell carcinoma	Cyclophosphamide IV: 0	OR	1 (ref.)		case-control study; SPN n = 199, first basal cell carcinoma only; risk period for cancer started 5 years after diagnosis	adjusted for radiation dose, sex, race (non-Hispanic white vs other), Hodgkin lymphoma (yes/no); unclear if there were additional adjustments, AAS and cyclophosphamide (an alkylating agent) possibly in same model, which may influence validity of estimates; matched for age at FPN diagnosis (±5 years), duration of follow-up; not considered: genetics
	1-3999		0.9	0.5-1.8		
	4000-9999		0.5	0.2-1.3		
	10,000-19,999		0.5	0.2-1.4		
	20,000-39,999		1.7	0.2-12.5		
	unknown		-	-		
	test for trend		p = 0.23			
	Cyclophosphamide oral: 0	OR	1 (ref.)			
	1-3999		1.3	0.3-5.0		
	≥4000		0.7	0.2-2.2		
	unknown		-	-		
	test for trend		p = 0.69			

Abbreviations:
AAS = alkylating agent score
CCSS = childhood cancer survivor study
CSPN = carcinoma or malignant melanoma according to ICCC-3 XI as subsequent primary neoplasm after childhood cancer
FPN = first primary neoplasm
OR = odds ratio
SPN = second primary neoplasm

Procarbazine (mg/m²)						
Author Setting	**Cumulative dose categories or test**	**Measure**	**Outcome**	**Confidence interval**	**Notes**	**Adjustment of multivariable model; matching in case-controls studies; potential SPN risk factors not considered**
Other CSPNs						
Henderson et al. 2012; CCSS-US/Canada; gastrointestinal cancer	0	HR	1 (ref.)		cohort study; SPN n = 44 with chemotherapy information; self-reporting of SPN → underreporting possible; risk period for cancer started 5 years after diagnosis; "we did not find that procarbazine without abdominal radiation was associated with increased risk of" GI SPN (unclear, which model this refers to)	adjusted for abdominal radiation, procarbazine dose, platinum, anthracyclines, plant alkaloids; not considered: genetics, sex, age at diagnosis, year of diagnosis, FPN
	>0-4200		1.02	0.22-4.80		
	>4200-7036		2.08	0.64-6.78		
	>7036		**3.15**	**1.06-9.38**		
Allodji et al. 2019 French CCSS; colorectal cancer	0	OR	1 (ref.)		case-control study; SPN n = 36; FPN solid tumors; risk period for cancer started 5 years after diagnosis; for 10 patients, colorectal cancer was the 3rd malignancy but → unclear, if treatment of preceding tumor included in cumulative doses; many models without adjustment for multiple testing may lead to chance significant findings; univariable analysis with any alkylating agent except procarbazine	model reported is univariable; matched for sex, age at FPN diagnosis, duration of follow-up, date of diagnosis; not considered: radiotherapy, genetics; FPN considered in subgroup analysis
	0-4199		2.4	0.5-9.3		
	≥ 4200		**4.5**	**1.3-16.9**		
	test for heterogeneity		p = 0.01			
	dose continuous		**1.3**	**1.1-1.5**		
Watt et al. 2012a; CCSS-US/Canada; basal cell carcinoma	0	OR	1 (ref.)		case-control study; SPN n = 199, first basal cell carcinoma only; risk period for cancer started 5 years after diagnosis	adjusted for radiation dose, sex, race (non-Hispanic white vs other), Hodgkin lymphoma (yes/no); unclear if there were additional adjustments, AAS and cyclophosphamide (an alkylating agent) possibly in same model, which may influence validity of estimates;
	1-3999		1.6	0.5-4.5		
	≥4000		0.9	0.4-1.8		
	unknown		-	-		
	test for trend		p = 0.76			

		matched for age at FPN diagnosis (±5 years), duration of follow-up; not considered: genetics

Abbreviations:
BC = breast cancer
CCSS = childhood cancer survivor study
CSPN = carcinoma or malignant melanoma according to ICCC-3 XI as subsequent primary neoplasm after childhood cancer
FPN = first primary neoplasm
GI = gastrointestinal
HR = hazard ratio
MOPP = mechlorethamine, vincristine, procarbazine with or without prednisone
OR = odds ratio
SPN = second primary neoplasm

Epipodophyllotoxins (mg/m², unless otherwise specified)						
Author Setting	**Cumulative dose categories or test**	**Measure**	**Outcome**	**Confidence interval**	**Notes**	**Adjustment of multivariable model; matching in case-controls studies; potential SPN risk factors not considered**
Thyroid SPN						
Neglia et al. 2001; CCSS-US/Canada	0	RR	1 (ref.)		cohort study; SPN n = 3 with epipodophyllotoxin treatment; self-reporting of SPN → underreporting possible; neoplasms following second primary neoplasm not included in risk analysis; risk period for cancer started 5 years after diagnosis	adjusted for radiation exposure to tumor sites (dichotomous); sex, age at FPN diagnosis, treatment era, FPN diagnosis, splenectomy, AAS, anthracyclines, epipodophyllotoxins, platinum compounds; not considered: genetics
	1-1000		**5.00**	**1.04-23.99**		
	1001-4000		0			
	≥4001		3.42	0.42-27.85		
	test for trend		p= 0.29			
Breast SPN						
Neglia et al. 2001; CCSS-US/Canada	Epipodophyllotoxins: 0	RR	-		cohort study; SPN n = 0 with epipodophyllotoxin treatment; self-reporting of SPN → underreporting possible; neoplasms following second primary neoplasm not included in risk analysis; risk period for cancer started 5 years after diagnosis	adjusted for radiation exposure to tumor sites (dichotomous); sex, age at FPN diagnosis, treatment era, FPN diagnosis, splenectomy, AAS, anthracyclines, epipodophyllotoxins, platinum compounds; not considered: genetics
	1-1000		-[1]			
	1001-4000		-[1]			
	≥4001		-[1]			
	test for trend		-[1]			
Other CSPNs						

Allodji et al. 2019; French CCSS; colorectal cancer	dose continuous	OR	1.3	0.6-2.6	case-control study; SPN n = 36; FPN solid tumors; risk period for cancer started 5 years after diagnosis; for 10 patients, colorectal cancer was the 3rd malignancy but → unclear, if treatment of preceding tumor included in cumulative doses; many models without adjustment for multiple testing may lead to chance significant findings;	model reported is univariable; matched for sex, age at FPN diagnosis, duration of follow-up, date of diagnosis; not considered: radiotherapy, genetics; FPN considered in subgroup analysis

[1]none of the patients received that dose

Abbreviations:

AAS = alkylating agent score
CCSS = childhood cancer survivor study
CSPN = carcinoma or malignant melanoma according to ICCC-3 XI as subsequent primary neoplasm after childhood cancer
FPN = first primary neoplasm
OR = odds ratio
RR = relative risk
SPN = second primary neoplasm

Platinum compounds (mg/m², unless otherwise specified)						
Author Setting	**Cumulative dose categories or test**	**Measure**	**Outcome**	**Confidence interval**	**Notes**	**Adjustment of multivariable model; matching in case-controls studies; potential SPN risk factors not considered**
Thyroid SPN						
Neglia et al. 2001; CCSS-US/Canada	platinum compounds: 0	RR	1 (ref.)		cohort study; SPN n = 39 with chemotherapy information (for AAS only 36); self-reporting of SPN → underreporting possible; neoplasms following second primary neoplasm not included in risk analysis; risk period for cancer started 5 years after diagnosis	adjusted for radiation exposure to tumor sites (dichotomous); sex, age at FPN diagnosis, treatment era, FPN diagnosis, splenectomy, AAS, anthracyclines, epipodophyllotoxins, platinum compounds; not considered: genetics
	1-400		-[1]	-		
	401-750		-[1]	-		
	≥751		-[1]	-		
Breast SPN						
Neglia et al. 2001; CCSS-US/Canada	platinum compounds: 0	RR	1 (ref.)		cohort study; SPN n = 53 for dose-response analysis (for AAS only 49); self-reporting of SPN → underreporting possible; neoplasms following second primary neoplasm not included in risk analysis; risk period for cancer started 5 years after diagnosis	adjusted for radiation exposure to tumor sites (dichotomous); sex, age at FPN diagnosis, treatment era, FPN diagnosis, splenectomy, AAS, anthracyclines, epipodophyllotoxins, platinum compounds; not considered: genetics
	1-400		-[1]	-		
	401-750		-[1]	-		
	≥751		-[1]	-		
Other CSPNs						
Allodji et al. 2019; French CCSS; colorectal cancer	dose continuous	OR	0.8	<0.1-1.4	case-control study; SPN n = 36; FPN solid tumors; risk period for cancer started 5 years after diagnosis; for 10 patients, colorectal cancer was the 3rd malignancy but → unclear, if treatment of preceding tumor included in cumulative doses; many models without adjustment for multiple testing may lead to chance significant findings;	model reported is univariable; matched for sex, age at FPN diagnosis, duration of follow-up, date of diagnosis; not considered: radiotherapy, genetics; FPN considered in subgroup analysis

[1]none of the patients received that dose

Abbreviations:

AAS = alkylating agent score

CCSS = childhood cancer survivor study
CED = cyclophosphamide equivalent dose
CSPN = carcinoma or malignant melanoma according to ICCC-3 XI as subsequent primary neoplasm after childhood cancer
FPN = first primary neoplasm
OR = odds ratio
RR = relative risk
SPN = second primary neoplasm

17 Case-control study: Details of descriptive analysis

17.1 Cases and controls analyzed

Table 23. Matching criteria of cases and matched controls.[1]

Matching criteria	Cases N=272	Controls N=739	Difference for matched pairs: deviation of cases from control value
Male sex (%)	101 (37.1%)	279 (37.8%)	none
age at diagnosis of FPN[1] in years, median (range)	8 (0-14)	8 (0-14)	- 1 day (-234 - +222 days)
Year of birth, median (range)	1980 (1966-2003)	1980 (1966-2003)	+3 days (-214 - +213 days)

[1]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

Table 24. Diagnoses of FPNs in cases and controls according to ICCC-3.[1]

Characteristic	ICCC-3[1] group	Cases N (%)[2]	Controls N (%)[2]	Total N (%)[2]
HEMATOLOGICAL MALIGNANCIES	I-II	217 (79.78)	581 (78.62)	798 (78.93)
I Leukemias	I(a)-I(e)	122 (44.85)	379 (51.29)	501 (49.55)
ALL[3]	I(a)	104 (38.24)	328 (44.38)	432 (42.73)
AML[3]	I(b)	15 (5.51)	49 (6.63)	64 (6.33)
MDS[3]	I(d)	1 (0.37)	1 (0.14)	2 (0.20)
II Lymphomas	II(a)-II(c)	95 (34.93)	202 (27.33)	297 (29.38)
Hodgkin lymphomas	II(a)	67 (24.63)	119 (16.10)	186 (18.40)
Non-Hodgkin lymphomas	II(b)	25 (9.19)	61 (8.25)	86 (8.51)
SOLID TUMORS	III-XII	55 (20.22)	158 (21.38)	213 (21.07)
III Brain tumors	III(a)-III(e)	6 (2.21)	12 (1.62)	18 (1.78)
Astrocytomas	III(b)	0 (0.00)	5 (0.68)	5 (0.49)
Meningiomas	III(e)5	-	-	-
IV Neuroblastoma and other peripheral nervous cell tumors	IV(a)-IV(b)	2 (0.74)	8 (1.08)	10 (0.99)
V Retinoblastoma	V	4 (1.47)	7 (0.95)	1 (0.10)
VI Renal tumors	VI(a)-VI(c)	10 (3.68)	28 (3.79)	38 (3.76)
VII Hepatic tumors	VII(a)-VII(c)	1 (0.37)	1 (0.14)	2 (0.20)
VIII Malignant bone tumors	VIII(a)-VIII(e)	8 (2.94)	44 (5.95)	52 (5.14)
Osteosarcoma	VIII(a)	5 (1.84)	17 (2.30)	22 (2.18)
Ewingsarcoma	VIII(c)	3 (1.10)	27 (3.65)	30 (2.97)
IX Soft tissue and other extraosseous sarcomas	IX(a)-IX(e)	13 (4.78)	29 (3.92)	42 (4.15)
X Germ cell tumors, trophoblastic tumors and neoplasms of gonads	X(a)-X(e)	11 (4.04)	29 (3.92)	40 (3.96)
XI Other malignant epithelial neoplasms and malignant melanomas	XI(a)-XI(f)	-	-	-
XII Other and unspecified malignant neoplasms	XII(a)-XII(b)	-	-	-
Total		272	739	1011

[1]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years;

study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

[2] The percentages sum up to 100% in each of the two levels of diagnosis: hematological malignancies and solid tumors, ICCC-3 groups I-XII; the ICCC-3 subgroups do not add up to 100% because not all subgroups were reported

[3] ALL = lymphoid leukemia, AML = acute myeloid leukemia, MDS = myelodysplastic syndrome and other myeloproliferative diseases

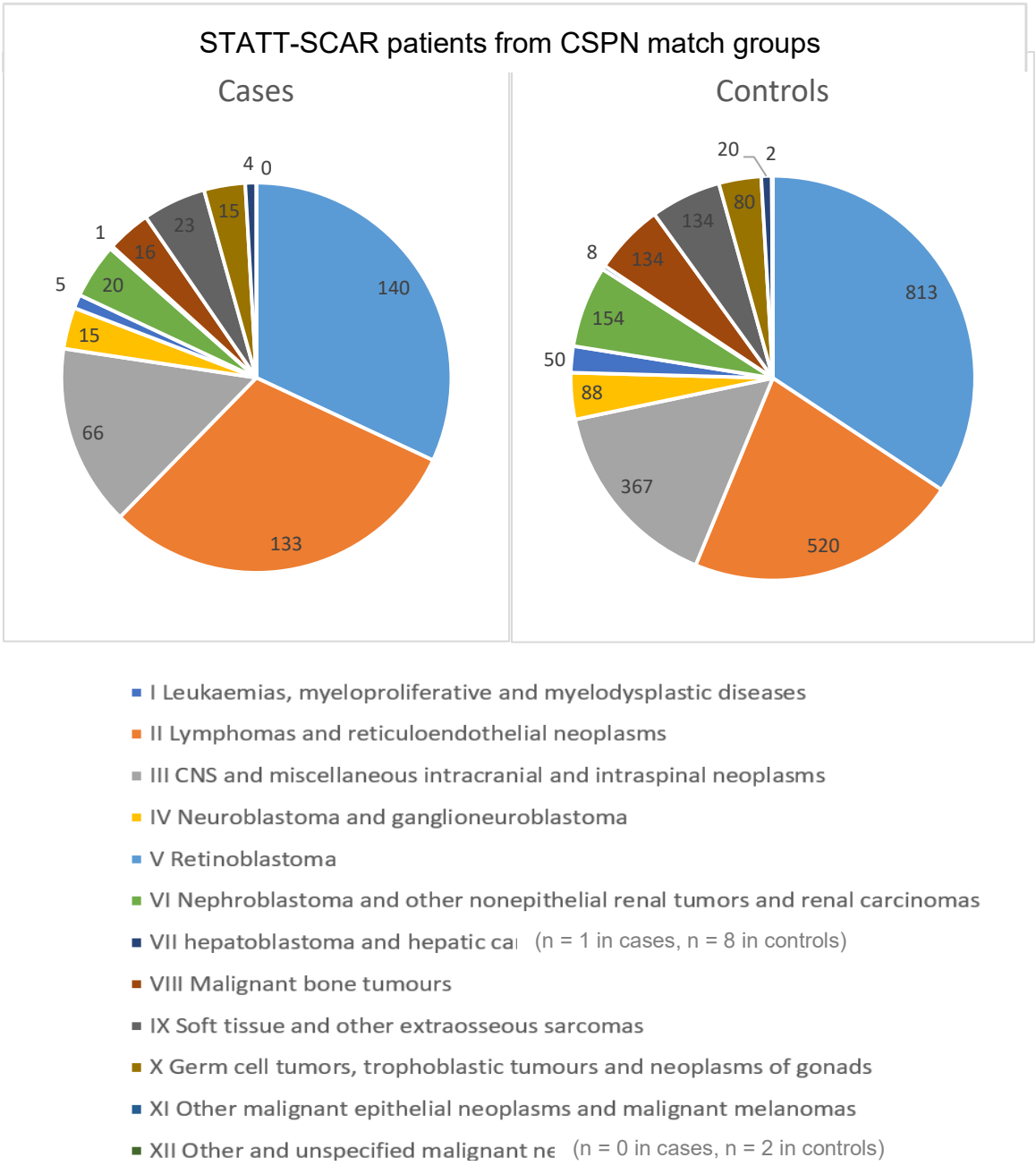


Figure 24. First primary neoplasm (FPN) diagnoses by ICCC-3 in cases (n = 438) and controls (n = 2908) of all cases with a CSPN diagnosis and their matched controls in the STATT-SCAR study. CSPN = subsequent primary neoplasm (SPN) diagnoses of ICCC-3 group XI. Subgroup of patients of the case-control study STATT-SCAR by the German Childhood Cancer Registry: FPN diagnoses: ICCC-3 groups I-XII; age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

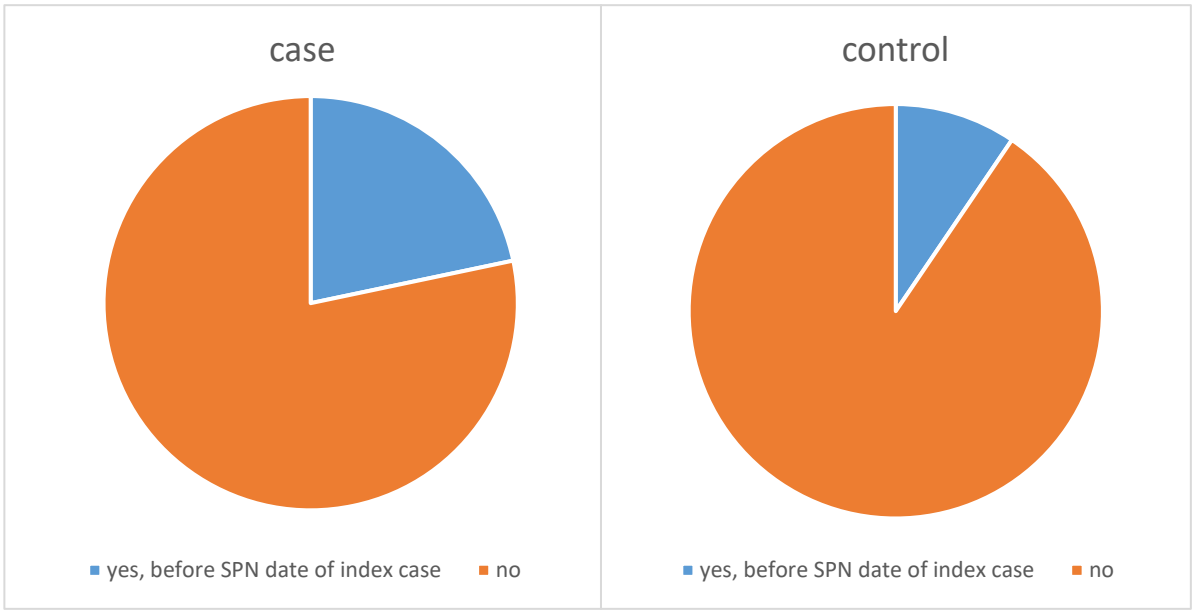


Figure 25. Relapse status of cases and controls. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

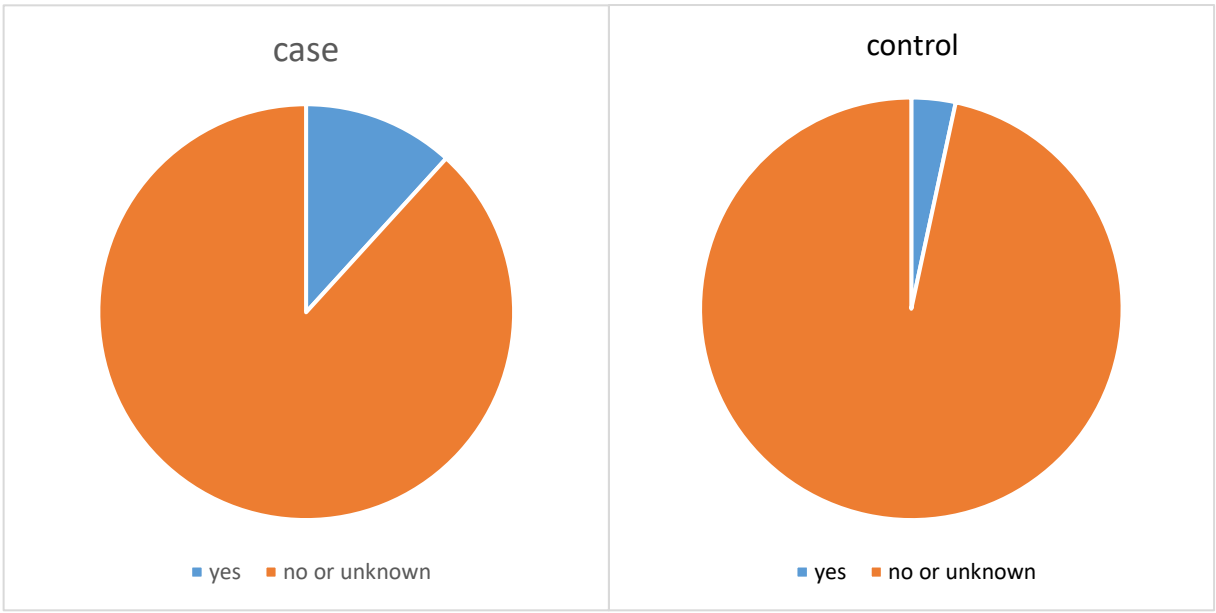
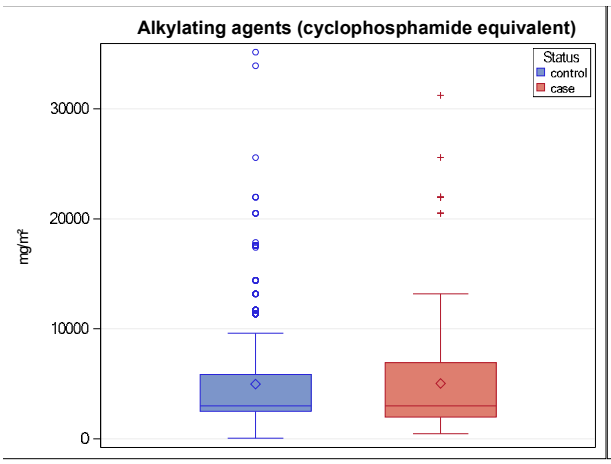


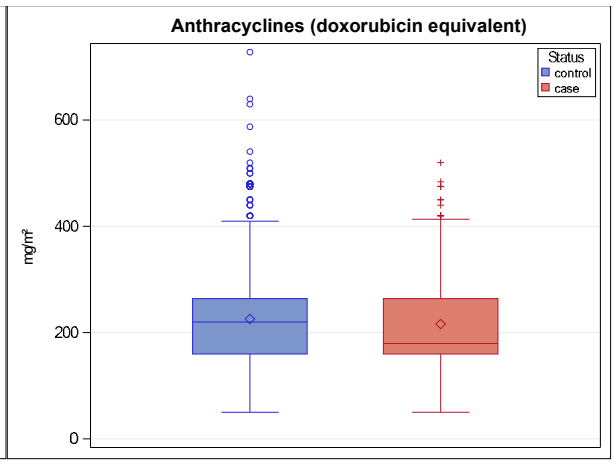
Figure 26. Stem cell transplantation status of cases and controls. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

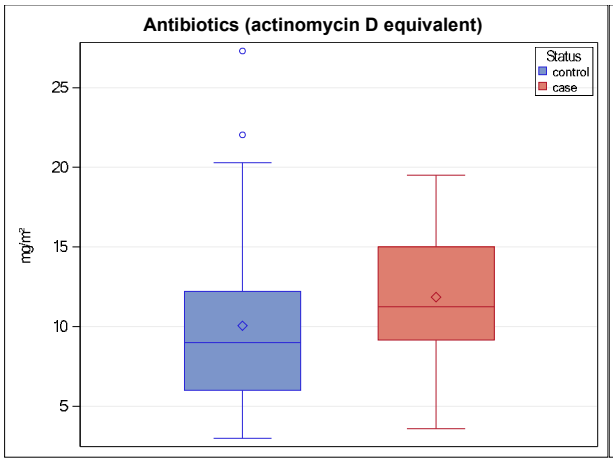
Table 25. Chemo- and radiotherapy exposure of cases and controls. Chemotherapy includes exposure to other substances (Dexamethasone, Folinic Acid, G-CSF, Interferon ALPHA, Other, Prednisone).[1]

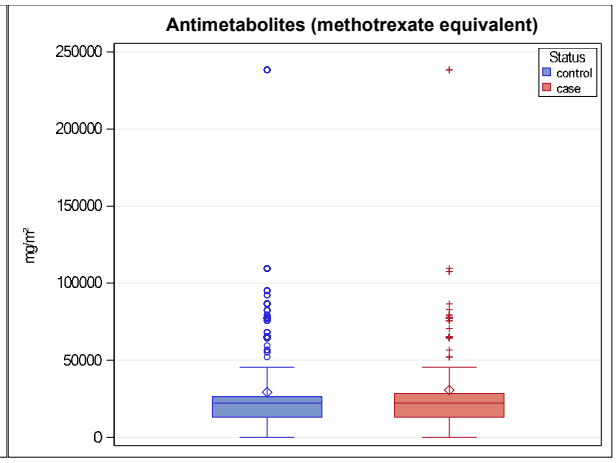
Characteristic	Cases N %	Controls N %	Total N %
Treatment modalities			
Chemotherapy, radiotherapy	191 (70.22)	442 (59.81)	633 (62.61)
Chemotherapy, no radiotherapy	76 (27.94)	278 (37.62)	354 (35.01)
No chemotherapy, radiotherapy	2 (0.74)	3 (0.41)	5 (0.49)
No chemo- or radiotherapy	3 (1.10)	16 (2.17)	19 (1.88)
Number of substances a patient received			
Mean, median	7.4, 8	7.7, 9	
0	7 (2.57)	25 (3.38)	32 (3.17)
1-3	29 (10.66)	77 (10.42)	106 (10.48)
4-8	116 (42.65)	266 (35.99)	382 (37.78)
9-15	120 (44.12)	371 (50.20)	491 (48.57)
Radiotherapy exposure			
0: no radiotherapy	79 (29.04)	294 (39.78)	373 (36.89)
1: imprecise radiation site; or for cases, radiotherapy not near the site of the SPN; or for controls, radiotherapy not near the site of the SPN in the index case of the match group	94 (34.56)	243 (32.88)	337 (33.33)
2: for cases, radiotherapy at or near the site of the SPN; for controls, radiotherapy at or near the site of the SPN in the index case of the match group	99 (36.40)	202 (27.33)	301 (29.77

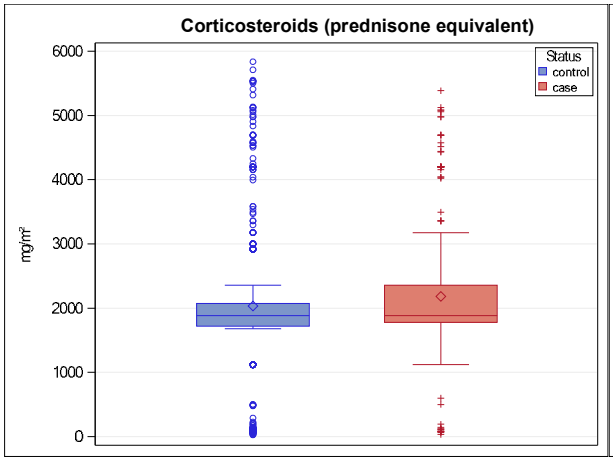
[1]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

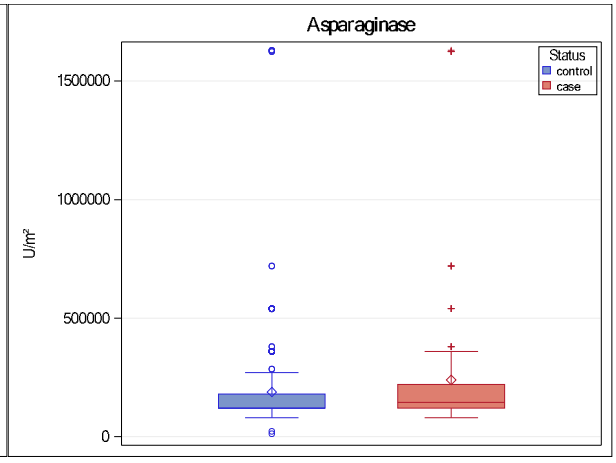












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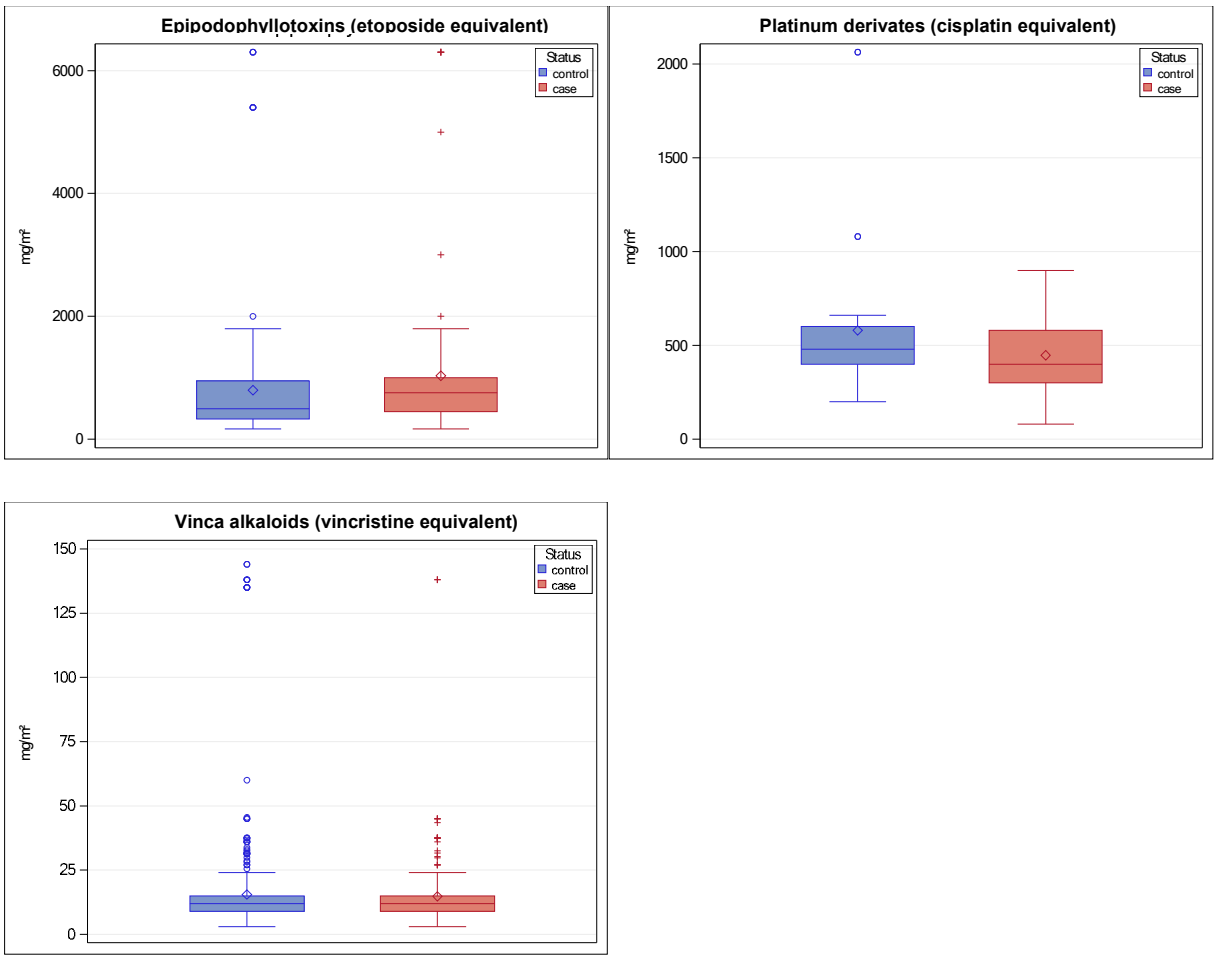

Figure 27. Dose ranges of substance groups by cases (blue) and controls (red) for patients having received the drug. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

Table 26. Doses of chemotherapeutic groups, of chemotherapeutic substances, and of radiotherapeutic treatment in cases and controls having received the treatment out of 1011 patients. Groups shaded grey, reference substances in bold.[1]

Cases

Treatment	N	Mean (mg/m²)²	Minimum (mg/m²)²	Lower Quartile (mg/m²)²	Upper Quartile (mg/m²)²	Maximum (mg/m²)²
Alkylating agents	229	5045.1	488.0	2000.0	6928.0	31220.0
Busulfan	0	.	.	.	.	.
Cyclophosphamide	181	2869.9	900.0	2000.0	3600.0	9600.0
Dacarbazine	1	8000.0	8000.0	8000.0	8000.0	8000.0
Ifosfamide	49	7643.7	488.0	1952.0	12444.0	21960.0
Lomustine	3	9600.0	9600.0	9600.0	9600.0	9600.0
Melphalan	1	9600.0	9600.0	9600.0	9600.0	9600.0
Procarbazine	47	4573.1	2399.6	2571.0	7370.2	7713.0
Anthracyclines (antibiotics)	245	216.3	50.0	160.0	264.0	519.9
Daunorubicin	100	114.1	50.0	100.0	121.7	180.0
Daunoxome	0	.	.	.	.	.
Doxorubicin	232	171.1	30.0	120.0	180.0	519.9
Epirubicin	1	300.0	300.0	300.0	300.0	300.0
Idarubicin	4	215.0	180.0	180.0	250.0	250.0
Mitoxantrone	5	144.0	80.0	160.0	160.0	160.0
Antibiotics	32	11.9	3.6	9.2	15.0	19.5
Actinomycin D (Dactinomycin)	27	12.1	3.6	9.0	15.0	19.5

Bleomycin	5	10.4	6.2	9.3	12.4	14.5
Antimetabolite	163	30612.8	75.6	12968.7	28487.0	238354.1
Cladribine	0	.	.	.	.	.
Cytarabine	153	10463.5	600.0	1800.0	7648.5	217320.0
Fluorouracil	0	.	.	.	.	.
Mercaptopurine	119	8981.8	155.5	7076.8	10270.1	14551.6
Methotrexate	146	8111.2	23.6	1486.2	10185.3	79396.2
Thioguanine	93	12214.0	1017.9	1710.0	5700.0	81754.2
Corticosteorids	214	2184.0	34.5	1777.5	2360.0	5385.5
Prednisone	214	2224.5	19.5	1740.0	2360.0	6825.5
Dexamethasone	113	44.3	15.0	34.5	46.5	148.4
Enzymes	120	239275.0	80000.0	120000.0	220000.0	1630000.0
Asparaginase	120	228466.7	80000.0	120000.0	220000.0	1620000.0
Epipodophyllotoxines	82	1032.8	165.0	450.0	1000.0	6300.0
Etoposide (VP-16)	59	1293.8	200.0	600.0	1350.0	6300.0
Teniposid	23	363.3	165.0	165.0	495.0	660.0
Platinum derivates	24	447.0	80.0	300.0	580.0	900.0
Carboplatin	4	487.3	300.0	337.1	637.5	900.0
Cisplatin	20	439.0	80.0	290.0	580.0	680.0
Vinca alkaloids	244	14.8	3.0	9.0	15.0	138.0
Vinblastine	3	4.5	3.0	3.0	6.0	6.0
Vincristine	241	14.6	5.6	9.0	15.0	138.0
Vindesine	13	4.3	1.5	3.0	6.0	6.0
Other						

Amsacrine	0	.	.	.	.	.
Folinic Acid	44	1252.2	90.0	210.0	540.0	9540.0
G-CSF	1	1.4	1.4	1.4	1.4	1.4
Interferon ALPHA	0	.	.	.	.	.
Other[3]	0	.	.	.	.	.
Radiotherapy						
Irradiation of the tumor site	85	28.7	14.0	23.4	30.0	60.0
CNS irradiation	109	21.4	0.0	12.0	24.0	54.4
Spinal cord irradiation	2	27.0	24.0	24.0	30.0	30.0
Total body irradiation	1	12.0	12.0	12.0	12.0	12.0

Controls

Treatment	**N**	**Mean (mg/m²)²**	**Minimum (mg/m²)²**	**Lower Quartile (mg/m²)²**	**Upper Quartile (mg/m²)²**	**Maximum (mg/m²)²**
Alkylating agents	626	4989.6	75.0	2500.0	5856.0	35136.0
Busulfan	0	.	.	.	.	.
Cyclophosphamide	546	3142.8	75.0	2000.0	3600.0	23900.0
Dacarbazine	3	6000.0	4000.0	4000.0	10000.0	10000.0
Ifosfamide	118	7821.9	780.8	1952.0	13176.0	35136.0
Lomustine	3	9600.0	9600.0	9600.0	9600.0	9600.0
Melphalan	0	.	.	.	.	.
Procarbazine	86	5090.2	2399.6	2571.0	7370.2	7713.0

Anthracyclines (antibiotics)	671	226.0	50.0	160.0	264.0	728.0
Daunorubicin	286	115.2	50.0	100.0	120.0	480.0
Daunoxome	1	167.2	167.2	167.2	167.2	167.2
Doxorubicin	646	178.6	30.0	120.0	220.0	728.0
Epirubicin	0	.	.	.	.	.
Idarubicin	8	218.8	70.0	180.0	285.0	320.0
Mitoxantrone	12	113.3	80.0	80.0	160.0	160.0
Antibiotics	104	10.1	3.0	6.0	12.2	27.3
Actinomycin D (Dactinomycin)	92	9.4	1.5	6.0	11.6	27.3
Bleomycin	17	9.8	6.2	6.6	12.4	14.5
Antimetabolite	481	29216.5	75.6	12978.0	26398.7	238326.8
Cladribine	1	9014.7	9014.7	9014.7	9014.7	9014.7
Cytarabine	461	8482.5	600.0	1800.0	2600.0	217320.0
Fluorouracil	0	.	.	.	.	.
Mercaptopurine	350	9229.3	761.8	8084.2	9906.3	14551.6
Methotrexate	439	8519.0	23.6	1532.1	10203.4	79396.2
Thioguanine	273	11621.3	1425.0	1710.0	5700.0	81754.2
Corticosteorids	577	2034.7	29.1	1722.0	2071.5	5837.4
Prednisone	576	2055.9	6.1	1680.0	2085.0	7245.5
Dexamethasone	372	43.4	10.5	34.5	46.5	157.4
Enzymes	350	188549.1	12500.0	120000.0	180000.0	1630000.0
Asparaginase	350	180412.0	12500.0	120000.0	180000.0	1620000.0

Epipodophyllotoxines	204	798.0	165.0	330.0	950.0	6300.0
Etoposide (VP-16)	110	1148.7	200.0	450.0	1300.0	6300.0
Teniposid	94	387.7	165.0	330.0	600.0	660.0
Platinum derivates	39	579.6	200.0	400.0	600.0	2062.5
Carboplatin	3	1475.0	300.0	300.0	2062.5	2062.5
Cisplatin	36	505.0	200.0	400.0	600.0	1080.0
Vinca alkaloids	652	15.5	3.0	9.0	15.0	144.0
Vinblastine	15	5.0	3.0	4.5	6.0	6.0
Vincristine	636	15.6	3.0	9.0	15.0	144.0
Vindesine	17	4.6	1.5	3.0	6.0	6.0
Other	doses not combined					
Amsacrine	2	200.0	200.0	200.0	200.0	200.0
Folinic Acid	143	1069.7	48.0	240.0	1440.0	9540.0
G-CSF	2	1.3	1.0	1.0	1.5	1.5
Interferon ALPHA	3	184919254.0	158587611.0	158587611.0	209978018.0	209978018.0
Other[3]	2	200.0	200.0	200.0	200.0	200.0
Radiotherapy	doses not combined					
Irradiation of the tumor site	171	30.4	2.0	24.0	36.0	60.8
CNS irradiation	279	18.7	0.0	12.0	18.0	54.4
Spinal cord irradiation	1	36.0	36.0	36.0	36.0	36.0
Total body irradiation	0	.	.	.	.	.

[1]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)
[2]enzymes and Asparaginase have the unit U/m², radiotherapy treatments have the unit Gray
[3]substance “other” was not specified in dataset

17.2 Cases and controls not analyzed

Table 27. Baseline characteristics of cases and controls in the analysis and of those not in the analysis. [1]

Characteristic		Cases and controls in analysis N (%)	Cases and controls not in analysis N (%)	Total N (%)
Sex	**male**	380 (37.59)	123 (36.50)	503 (37.31)
	female in match group without breast SPN[1]	464 (45.90)	170 (50.45)	634 (47.03)
	female in match group with breast SPN	167 (16.52)	44 (13.06)	211 (15.65)
Age at FPN[1] **diagnosis**	**< 1 year**	13 (1.29)	15 (4.45)	28 (2.08)
	1-4 years	209 (20.67)	113 (33.53)	322 (23.89)
	5-9 years	353 (34.92)	93 (27.60)	446 (33.09)
	10-14 years	436 (43.13)	116 (34.42)	552 (40.95)
Period of FPN diagnosis	**1980-1989**	610 (60.34)	108 (32.05)	718 (53.26)
	1990-1999	328 (32.44)	108 (32.05)	436 (32.34)
	2000-2009	68 (6.73)	117 (34.72)	185 (13.72)
	2010-2014	5 (0.49)	4 (1.19)	9 (0.67)
Period of SPN[2] **diagnosis**	**1980-1989**	1 (0.10)	0 (0.00)	1 (<0.01)
	1990-1999	28 (2.77)	3 (0.89)	31 (2.30)
	2000-2009	139 (13.75)	37 (10.98)	176 (13.06)
	2010-2014	104 (10.29)	18 (5.34)	122 (9.05)
Latency (time be-tween FPN and SPN)[2]	**6 months to <1 year**	0	0	987 (73.22)
	1-4 years	9 (3.31)	8 (13.79)	17 (1.26)
	5-9 years	32 (11.76)	18 (31.03)	50 (3.71)
	10-19 years	128 (47.06)	21 (36.21)	156 (11.57)
	20-29 years	99 (36.40)	9 (15.52)	127 (9.42)

	≥ 30 years	4 (1.47)	2 (3.45)	11 (0.82)
Total		1011	337	1348

Characteristic in years	**Cases and controls in analysis**	**Cases and controls not in analysis**
Median age at FPN diagnosis	8	7
Median year of FPN diagnosis	1988[3]	1997[3]
Median age at SPN[2] diagnosis	26	18
Median year of SPN[2] diagnosis	2008	2008
Median latency time	18	11

[1]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

[2]only cases

[3]mean year was 1989 in patients included in the analysis and 1995 in patients not included

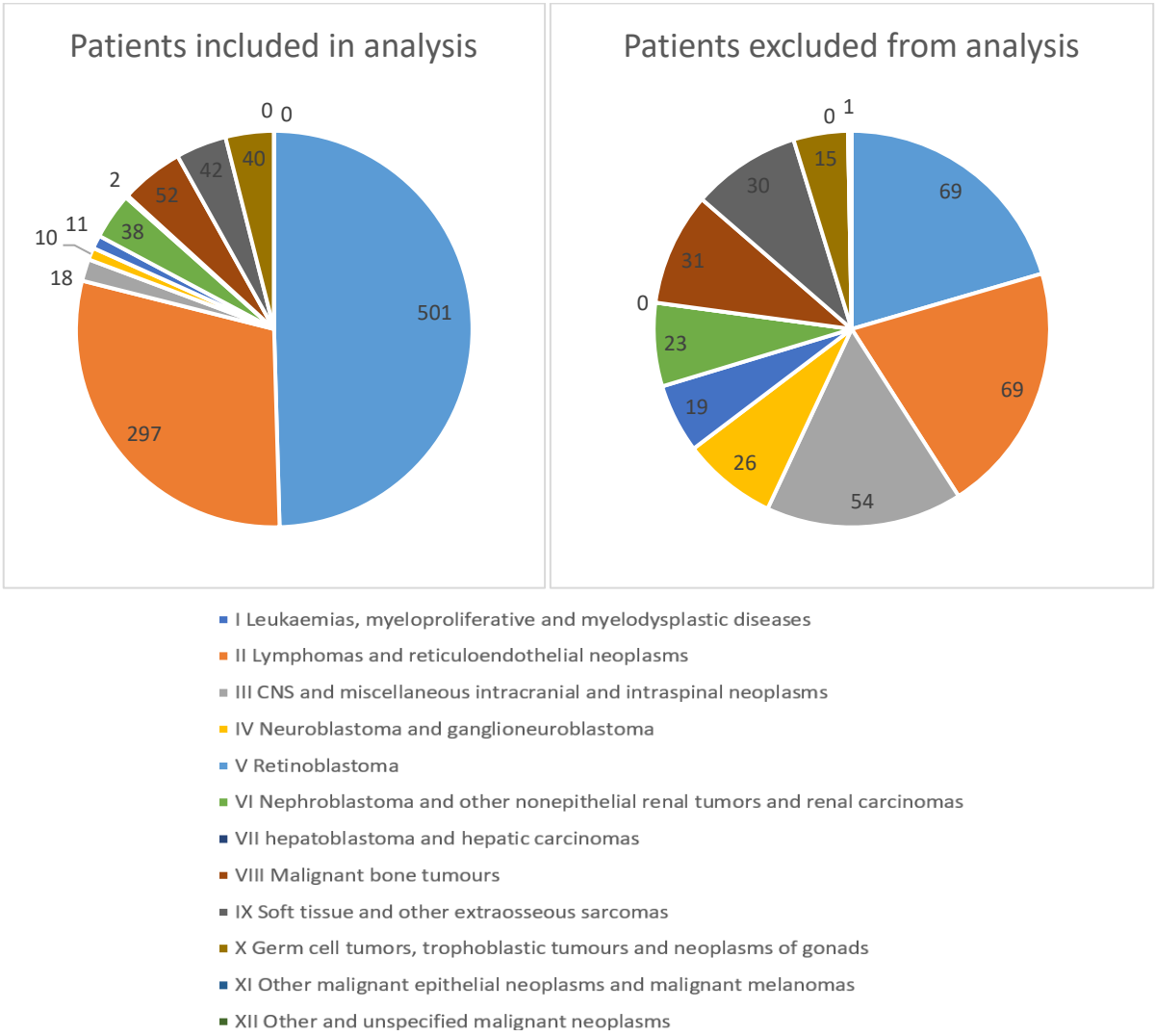

Figure 28. Number of patients included in and excluded from the analysis by diagnostic group of first primary neoplasms according to ICCC-3. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

Table 28. Diagnoses of first primary neoplasms in cases and controls in the analysis and of those not in the analysis.[1]

FPN[2] diagnosis		ICCC-3[2] group	Cases and controls in analysis N (%)[3]	Cases and controls not in analysis N (%)[3]	Total N
HEMATOLOGICAL MALIGNANCIES		I-II	798 (78.93)	138 (40.95)	936 (69.43)
I	**Leukaemias**	I(a)-I(e)	501 (49.55)	69 (20.47)	570 (42.28)
	ALL	I(a)	432 (42.73)	59 (17.51)	491 (36.42)
	AML	I(b)	64 (6.33)	10 (2.97)	74 (5.49)
	MDS	I(d)	2 (0.20)	0 (0.00)	2 (0.15)
II	**Lymphomas**	II(a)-II(c)	297 (29.38)	69 (20.47)	366 (27.15)
	Hodgkin lymphomas	II(a)	186 (18.40)	47 (13.95)	233 (17.28)
	Non-Hodgkin lymphomas	II(b)	86 (8.51)	16 (4.75)	102 (7.57)
SOLID TUMORS		III-XII	213 (21.07)	199 (59.05)	412 (30.56)
III	**Brain tumors**	III(a)-III(e)	18 (1.78)	54 (16.02)	72 (5.34)
	Astrocytomas	III(b)	5 (0.49)	25 (7.42)	30 (2.23)
	Meningiomas	III(e)5	0 (0.00)	3 (0.89)	3 (0.22)
IV	**Neuroblastoma and other peripheral nervous cell tumors**	IV(a)-IV(b)	10 (0.99)	26 (7.72)	36 (2.67)
V	**Retinoblastoma**	V	11 (1.09)	19 (5.64)	30 (2.23)
VI	**Renal tumors**	VI(a)-VI(c)	38 (3.76)	23 (6.82)	61 (4.53)
VII	**Hepatic tumors**	VII(a)-VII(c)	2 (0.20)	0 (0.00)	2 (<0.01)
VIII	**Malignant bone tumors**	VIII(a)-VIII(e)	52 (5.14)	31 (9.20)	83 (6.16)
	Osteosarcoma	VIII(a)	22 (2.18)	24 (7.12)	46 (3.41)
	Ewingsarcoma	VIII(c)	30 (2.97)	7 (2.08)	37 (2.74)
IX	**Soft tissue and other extra-osseous sarcomas**	IX(a)-IX(e)	42 (4.15)	30 (8.90)	72 (5.34)
X	**Germ cell tumors, trophoblastic tumors and neoplasms of gonads**	X(a)-X(e)	40 (3.96)	15 (4.45)	55 (4.08)
XI	**Other malignant epithelial neoplasms and malignant melanomas**	XI(a)-XI(f)	-	-	-
XII	**Other and unspecified malignant neoplasms**	XII(a)-XII(b)	0 (0.00)	1 (0.30)	1 (<0.01)
Total			1011	337	1348

[1]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN)

diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

[2]FPN = first primary neoplasm, ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005), ALL = lymphoid leukemia, AML = acute myeloid leukemia, MDS = myelodysplastic syndrome and other myeloproliferative diseases

[3]The percentages sum up to 100% in each of the three levels of diagnosis: hematological malignancies and solid tumors, ICCC-3 1-XII, the ICCC-3 subgroups.

Table 29. Diagnoses of subsequent primary neoplasms of cases in the analysis and of those not in the analysis.[1]

SPN[2] diagnosis	ICCC-3[2] group	Cases in analysis N %	Cases not in analysis N %	Total
Adrenocortical carcinomas	XI(a)	0 (0)	0 (0)	0 (0)
Thyroid carcinomas	XI(b)	89 (32.72)	26 (49.06)	115 (35.28)
Nasopharyngeal carcinomas	XI(c)	2 (0.74)	1 (1.89)	3 (0.01)
Malignant melanomas	XI(d)	25 (9.19)	0 (0)	25 (7.67)
Skin carcinomas	XI(e)	72 (26.47)	3 (5.66)	75 (23.01)
Other and unspecified carcinomas	XI(f)			
Carcinomas of salivary glands	XI(f)1	8 (2.94)	2 (3.77)	10 (3.07)
Carcinomas of colon and rectum	XI(f)2	11 (4.04)	4 (7.55)	15 (4.60)
Carcinomas of appendix	XI(f)3	0 (0)	0 (0)	0 (0)
Carcinomas of lung	XI(f)4	0 (0)	0 (0)	0 (0)
Carcinomas of thymus	XI(f)5	0 (0)	0 (0)	0 (0)
Carcinomas of breast	XI(f)6	44 (16.18)	9 (16.98)	53 (16.26)
Carcinomas of cervix uteri	XI(f)7	4 (1.47)	0 (0	4 (1.23)
Carcinomas of bladder	XI(f)8	1 (0.37)	0 (0)	1 (0.31)
Carcinomas of eye	XI(f)9	0 (0)	0 (0)	0 (0)
Carcinomas of other specified areas	XI(f)10	16 (5.88)	8 (15.09)	24 (7.36)
Carcinomas of unspecified site	XI(f)11	0 (0)	1 (0.3)	1 (0.31)
Total		272	54	326

[1]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis (see below) and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; subsequent primary neoplasm (SPN) diagnoses: ICCC-3 group XI (CSPN); age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and SPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

18 Case-control study: Details of explorative analysis

Table 30. Association between CSPN[1] occurrence and covariates: model details for Table 16.[2]

	Main analysis		Including influential point		Subgroup: no relapse patients		Subgroup: no stem cell transplantation patients	
AIC[3] null model without variables	694.538		695.349		519.358		603.982	
covariate	**univariable: AIC[3]**	**multivariable[4]: AIC**	**univariable: AIC**	**multivariable[4]: AIC**	**univariable: AIC**	**multivariable[4]: AIC**	**univariable: AIC**	**multivariable[4]: AIC**
radiotherapy	681.510	646.807	682.321	644.441	508.767	497.473	599.388	575.629
relapse	672.660	659.741	673.471	657.165	-	-	593.769	580.532
stem cell transplantation	672.958	653.528	673.769	651.116	510.628	491.806	-	-
FPN diagnosis (ICCC-3 I-XII)	699.005	-[5]	699.834	-[5]	522.992	-[5]	607.965	-[5]

[1]CSPN = carcinoma or malignant melanoma according to ICCC-3 group XI as subsequent primary neoplasm after childhood cancer, ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005)

[2]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005)

[3]AIC = Akaike information criterion

[4]in multivariable analysis, the covariates were entered in the following order: the covariate with the smallest AIC in univariable analysis was entered first, the one with the second smallest next; therefore, the covariate with the smallest AIC in univariable analysis has the largest AIC (since first covariate in multivariable model)

[5]FPN diagnosis was not entered because it was not significant in univariable analysis, and it increased the AIC compared to the null model

18.1 Main analysis

Table 31. Association between CSPN[1] occurrence and the dose (continuous) of substances or substance groups for treatment of an FPN[1] in childhood (n = 1010, 272 match groups): model details for Table 11.[2]

	Model[3]	Power (p, q)[3]	univariable		multivariable without covariates	multivariable with covariates[4]
AIC[5]			**null model:** 694.538		680.335	646.807
Substance (group)			**AIC**	**p-value**	**p-value**	**p-value**
cyclophosphamide	FP1	1	687.048	0.0040	0.0059	0.0133
antibiotics	FP1+z	1	692.342	0.0600	0.0193	0.0563
methotrexate	z	-	692.015	0.0338	- [6]	- [6]
epipodophyllotoxins	FP1+z[7]	0	691.677	0.0335	0.0167	0.1566
other	[8]	[8]	693.359	0.0779	- [6]	

[1]CSPN = carcinoma or malignant melanoma according to ICCC-3 group XI as subsequent primary neoplasm after childhood cancer, ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005); FPN = first primary neoplasm according to ICCC-3

[2]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; FPN diagnoses: ICCC-3 groups I-XII; age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months

[3]This is the model selected by univariable logistic regression with the fractional polynomial (FP) with spike at zero procedure, see Statistical Analysis Plan, Appendix III. FP1 means a first degree function was selected with power p for the transformation; FP2 means a second-decree function was selected with powers p and q for the two transformations; z means a binary spike-at-zero variable was selected, power 0 means natural logarithm of the substance dose

[4]relapse (yes/no), stem cell transplantation (yes/no), radiotherapy (near site of CSPN, not near site of CSPN, none); FPN diagnosis was not entered because it was not significant in univariable analysis, and it increased the AIC compared to the null model

[5]AIC = Akaike information criterion

[6]Methotrexate and “other” were not selected because its p-value upon entry into the model were >0.1

[7]This is the second best FP1+z model since the best FP1+z model (power -0.5) did not yield valid results due to numeric problems.

[8]The variable “other” was binary and not subject to the MFP procedure. It was entered into the model during the forward selection process according to its AIC.

Table 32. Association between CSPN[1] occurrence and substances or substance groups for FPN[1] treatment (as binary variable), n = 1010. AIC[1] without predictor variables: 694.538.[2]

Substance (group)	Number of patients having received the substance (group)	Univariable analysis: OR[1] (90% CI)[1]	AIC
cyclophosphamide	727	**0.66 (0.51-0.86)**	689.973
antibiotics	135	0.79 (0.54-1.14)	695.341
methotrexate	585	**0.71 (0.55-0.93)**	692.015
epipodophyllotoxins	286	1.14 (0.87-1.49)	695.943

[1]CSPN = carcinoma or malignant melanoma according to ICCC-3 group XI as subsequent primary neoplasm after childhood cancer, ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005); FPN = first primary neoplasm; AIC = Akaike information criterion; OR = odds ratio; 90% CI = 90% confidence interval

[2]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; FPN diagnoses: ICCC-3 groups I-XII; age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and CSPN diagnosis: min. 6 months

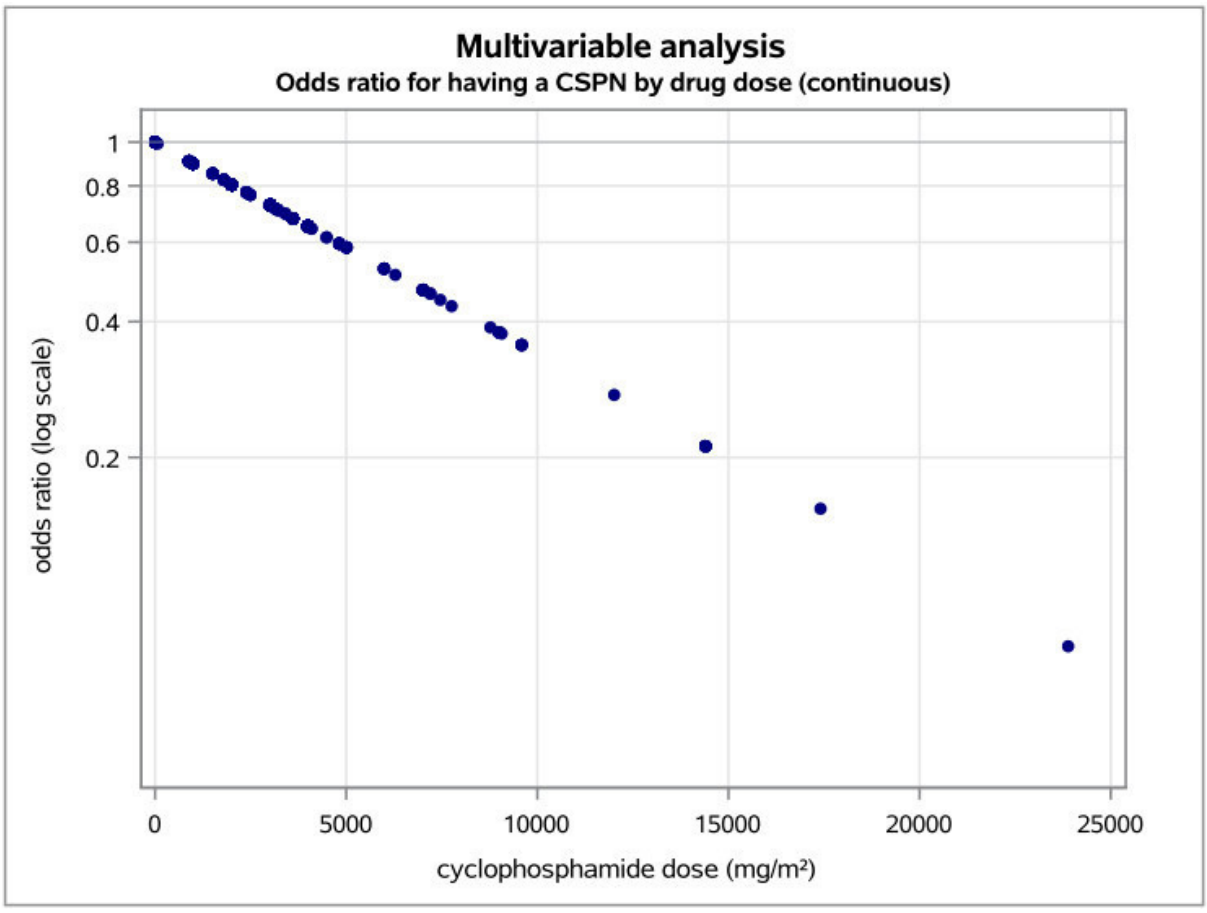

Figure 29. Multivariable analysis including covariates: Odds ratio for having a CSPN by cyclophosphamide dose. CSPN = carcinoma or malignant melanoma according to ICCC-3 XI as subsequent primary neoplasm after childhood cancer. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005)

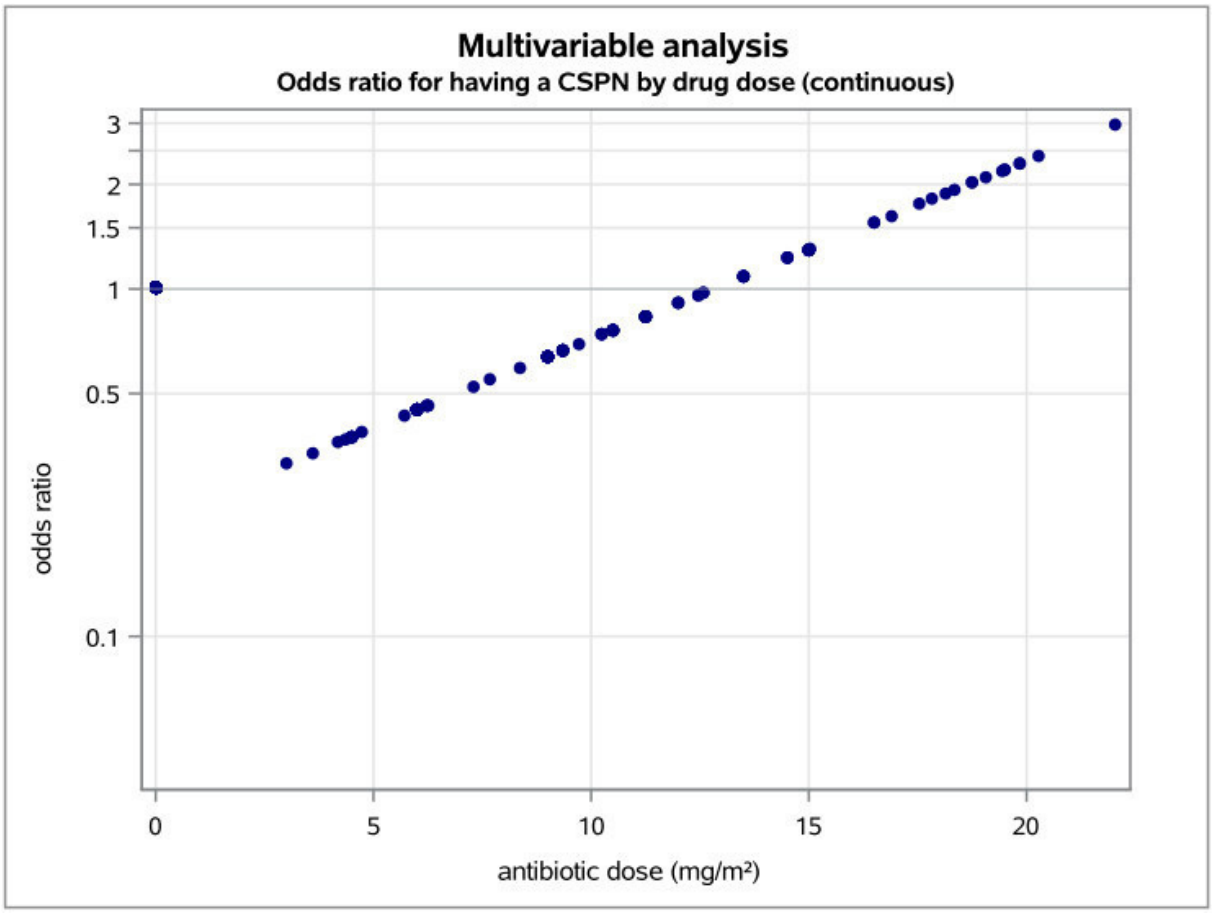

Figure 30. Multivariable analysis including covariates: Odds ratio for having a CSPN by antibiotics dose. CSPN = carcinoma or malignant melanoma according to ICCC-3 XI as subsequent primary neoplasm after childhood cancer. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005)

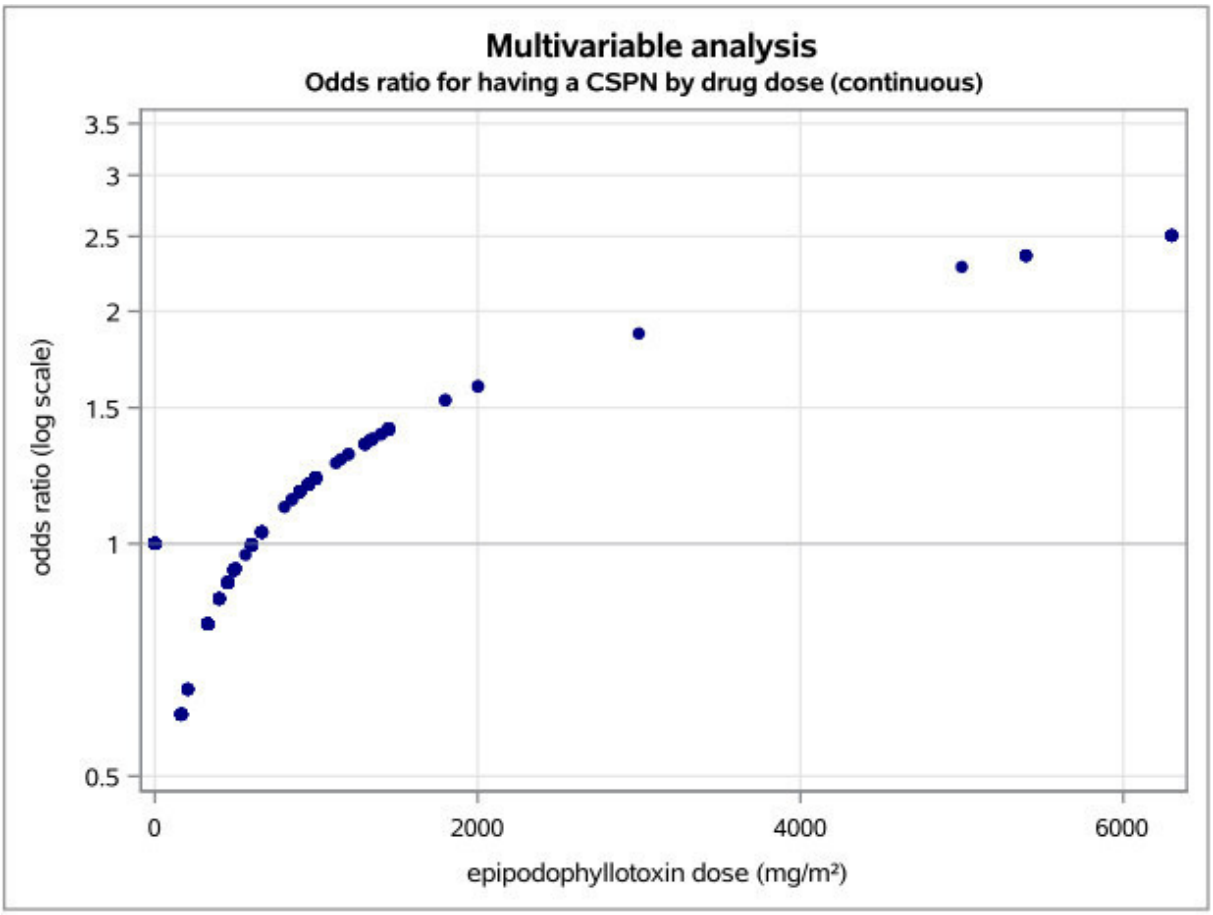

Figure 31. Multivariable analysis including covariates: Odds ratio for having a CSPN by epipodophyllotoxin dose. CSPN = carcinoma or malignant melanoma according to ICCC-3 XI as subsequent primary neoplasm after childhood cancer. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005).

For the graphical representation, an offset of +1 instead of +0.1 for the cumulative epipodophyllotoxin dose was used (compare SAP, Appendix III, Chapter 4.3) because of issues in data representation. The odds ratios reported in Table 12 were calculated with the usual +0.1 offset; they hardly differed compared to the odds ratios calculated with +1 offset.

18.2 Influential point included

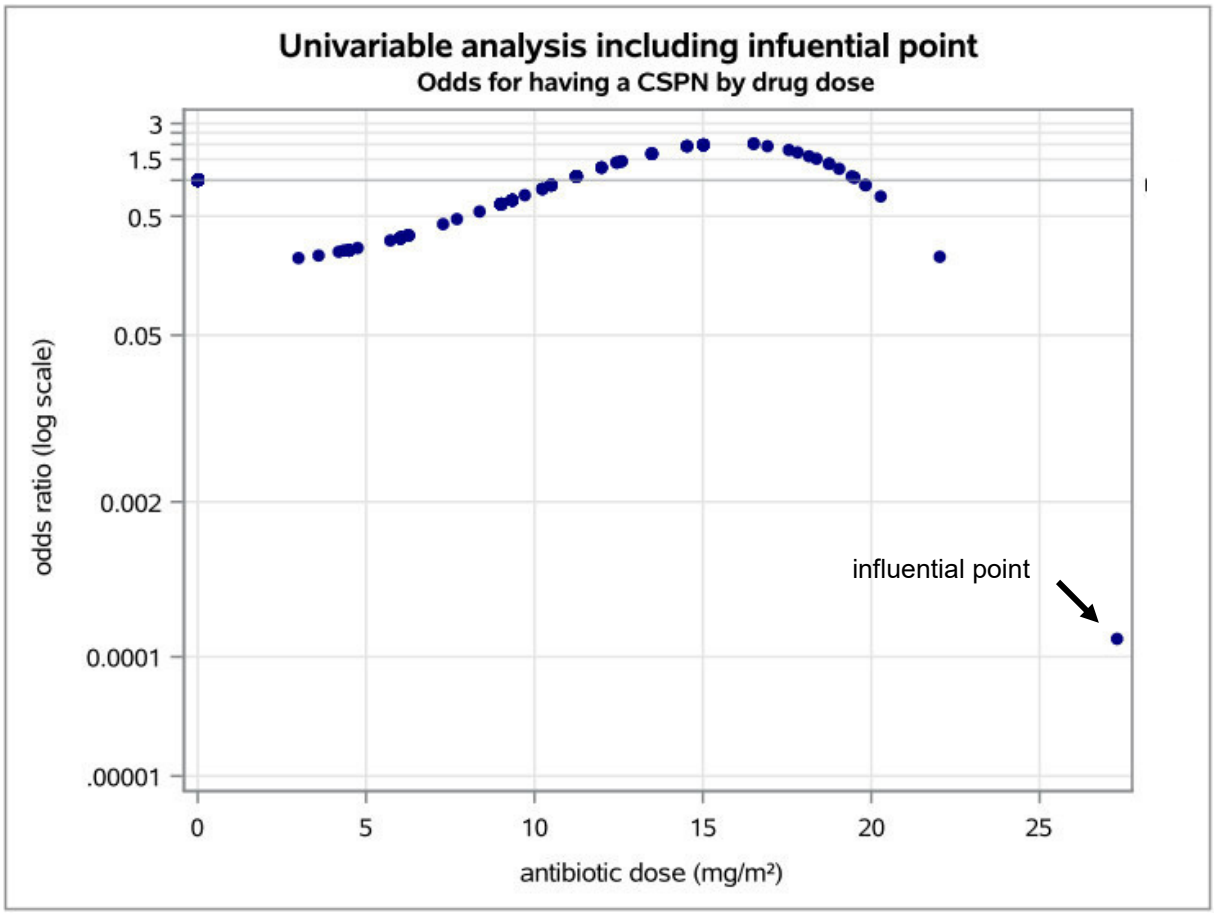

Figure 32. Univariable analysis including influential points: Odds ratio for having a CSPN by antibiotic dose. CSPN = carcinoma or malignant melanoma according to ICCC-3 XI as subsequent primary neoplasm after childhood cancer. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005)

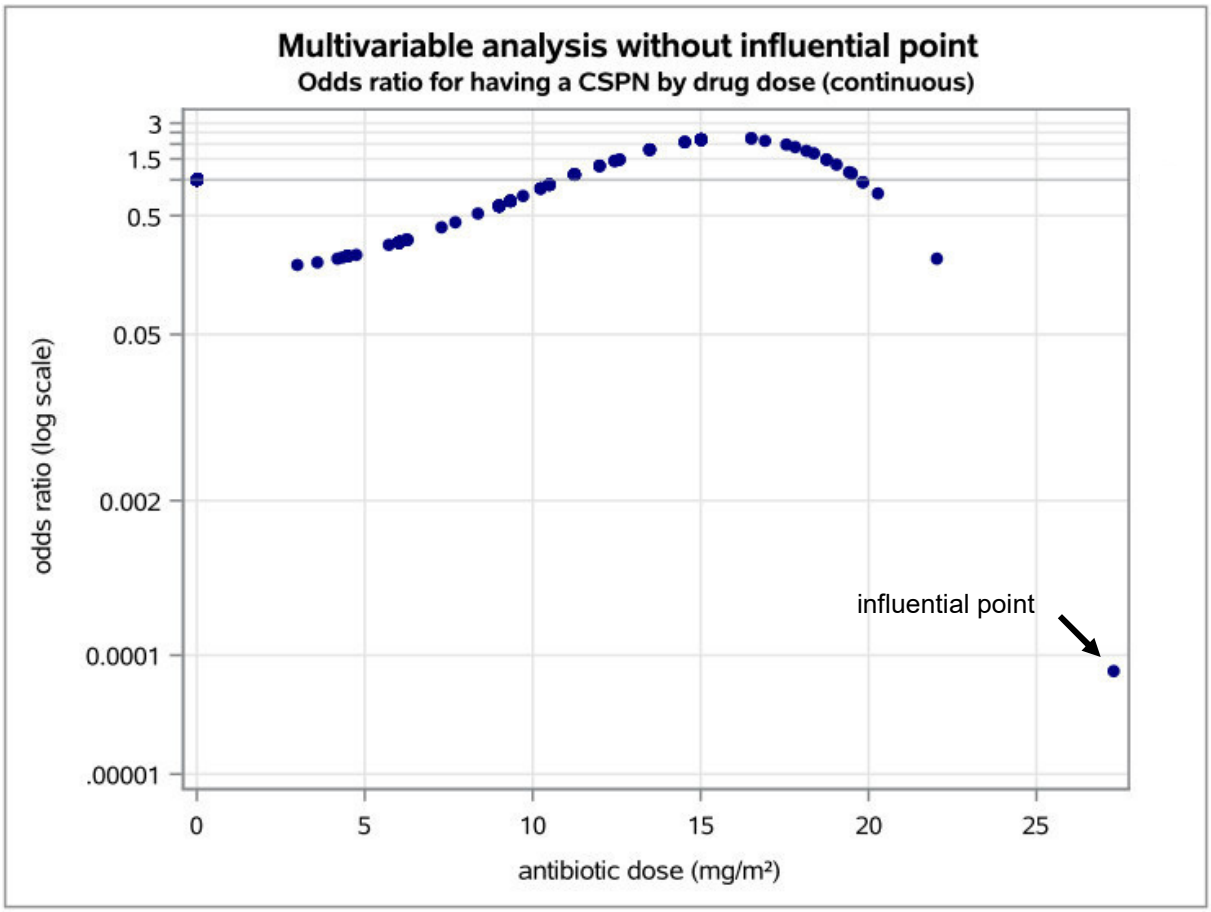

Figure 33. Multivariable analysis including covariates: Odds ratio for having a CSPN by antibiotic dose. CSPN = carcinoma or malignant melanoma according to ICCC-3 XI as subsequent primary neoplasm after childhood cancer. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005)

Table 33. Dataset including influential point: Association between CSPN[1] occurrence and the dose (continuous) of substances or substance groups for treatment of an FPN in childhood (n = 1011, 272 match groups).[2] The OR[1] for selected doses against nonexposure are presented (see Appendix I.5, see Figure 32 and Figure 33 for association across full dose range of antibiotics). Only substance (groups) were assessed which were significant at the 10% significance level in univariable analysis.[3]

Substance (group)[3]	Number of patients having received the substance	Selected doses	univariable models: OR (90% CI)[1]	multivariable model without covariates[4]: OR (90% CI)	multivariable with covariates[4]: OR (90% CI)
cyclophos-phamide	727	0 mg/m²	reference	reference	reference
		1000 mg/m²	0.89 (0.84-0.95)	0.89 (0.82-0.95)	0.90 (0.83-0.96)
		3000 mg/m²	0.71 (0.58-0.86)	0.69 (0.56-0.86)	0.72 (0.58-0.89)
		6000 mg/m²	0.50 (0.34-0.74)	0.48 (0.31 -0.73)	0.51 (0.33-0.80)
antibiotics	136	0 mg/m²	reference	reference	reference
		6 mg/m²	0.33 (0.17-0.65)	0.24 (0.11-0.60)	0.30 (0.14-0.63)
		9 mg/m²	0.63 (0.40-0.998	0.48 (0.29-0.79)	0.61 (0.37-1.01)
		15 mg/m²	1.99 (1.08-3.65)	1.70 (0.90-3.22)	2.17 (1.12-4.19)
		21 mg/m²	0.49 (0.09-1.79)	0.49 (0.07-2.71)	0.49 (0.08-3.19)
methotrexate	585	yes vs. no[5]	0.72 (0.55-0.93)	- 6	- 6
epipodo-phyllotoxins	286	0 mg/m²	reference	reference	reference
		165 mg/m²	0.64 (0.40-1.03)	0.67 (0.40-1.11)	0.63 (0.36-1.09)
		330 mg/m²	0.88 (0.63-1.22)	0.94 (0.66-1.32)	0.82 (0.56-1.20)
		1000 mg/m²	1.43 (1.05-1.96)	1.59 (1.15-2.21)	1.23 (0.87-1.75)
		3000 mg/m²	2.33 (1.35-4.02)	2.71 (1.52-4.81)	1.87 (1.02-3.43)
		6300 mg/m²	3.24 (1.54-6.80)	3.87 (1.76-8.50)	2.43 (1.05-5.66)

[1] CSPN = carcinoma or malignant melanoma according to ICCC-3 group XI as subsequent primary neoplasm after childhood cancer, ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005), FPN = first primary neoplasm, OR = odds ratio, 90% CI = 90% confidence interval;

[2]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months

[3]only substance (groups) are reported which were significant at an alpha-level of 0.1 in univariable explorative logistic regression analyses with fractional polynomials with spike at zero (out of the nine substance groups alkylating agents, anthracyclines, antibiotics, antimetabolites, enzymes (Asparaginase), epipodophyllotoxins, platinum derivates, vinca alkaloids, corticosteroids, the five single substances cyclophosphamide, cytarabine, doxorubicin, methotrexate, vincristine, and their complementary substance groups alkylating agents without cyclophosphamide, anthracycline excluding doxorubicin, antimetabolites excluding cytarabine, antimetabolites excluding methotrexate, antimetabolites excluding cytarabine and methotrexate, vinca alkaloids excluding vincristine); see Appendix I.18.2, Table 34, for model details

[4]relapse, stem cell transplantation, radiotherapy

[5] for methotrexate the best model selected in univariable explorative analysis was a spike model, i.e., methotrexate as binary variable

[6] methotrexate was not selected because upon entry into the model its p-value was >0.1 and the AIC increased

Table 34. Dataset including influential point: Association between CSPN[1] occurrence and the dose (continuous) of substances or substance groups for treatment of an FPN[1] in childhood (n = 1011, 272 match groups): model details for Table 33.[2]

	Model[3]	Power (p, q)[3]	univariable		multivariable without covariates	multivariable with covariates[4]
AIC[5]			**null model:** 695.349		678.065	644.441
Substance (group)			**AIC**	**p-value**	**p-value**	**p-value**
cyclophosphamide	FP1	1	687.859	0.0040	0.0049	0.0121
antibiotics	FP2+z	3,3	690.136	0.0352	0.0163	0.0312
methotrexate	z	-	692.934	0.0360	- [6]	- [6]
epipodophyllotoxins	FP1+z[7]	0	692.488	0.0324	0.0175	0.1945
other	[8]	[8]	694.298	0.0841	- [6]	- [6]

[1]CSPN = carcinoma or malignant melanoma according to ICCC-3 group XI as subsequent primary neoplasm after childhood cancer, ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005); FPN = first primary neoplasm according to ICCC-3

[2]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; FPN diagnoses: ICCC-3 groups I-XII; age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months

[3]This is the model selected by univariable logistic regression with the fractional polynomial (FP) with spike at zero procedure, see Statistical Analysis Plan, Appendix III. FP1 means a first degree function was selected with power p for the transformation; FP2 means a second-decree function was selected with powers p and q for the two transformations; z means a binary spike-at-zero variable was selected, power 0 means natural logarithm of the substance dose, if p = q, the second transformation in the model is changed, so that $H2(x) = \beta 1x^{p} + \beta 2x^{p}\log(x)$, see SAP (Appendix III)

[4]relapse (yes/no), stem cell transplantation (yes/no), radiotherapy (near site of CSPN, not near site of CSPN, none); FPN diagnosis was not entered because it was not significant in univariable analysis, and it increased the AIC compared to the null model

[5]AIC = Akaike information criterion

[6]Methotrexate and “other” were not selected because their p-values upon entry into the model was >0.1, respectively

[7]This is the second best FP1+z model since the best FP1+z model (power -0.5) did not yield valid results due to numeric problems.

[8]The variable “other” was binary and not subject to the MFP procedure. It was entered into the model during the forward selection process according to its AIC.

18.3 Subgroup analysis excluding patients with relapse during latency period of index case

Table 35. Subgroup excluding patients with relapse during latency period of index case: Association between CSPN[1] occurrence and the dose (continuous) of substances or substance groups for treatment of an FPN[1] in childhood (n = 748, 212 match groups): model details for Table 14.[2]

	Model[3]	Power (p, q)[3]	univariable		multivariable without covariates	multivariable with covariates[4]
AIC[5]			**null model:** 519.358		511.737	491.806
Substance (group)			**AIC**	**p-value**	**p-value**	**p-value**
cyclophosphamide	z	-	511.737	0.0019	0.0019	0.0002
antimetabolites	z	-	516.650	0.0302	- [7]	- [7]
methotrexate	z	-	516.991	0.0373	- [7]	- [7]

[1]CSPN = carcinoma or malignant melanoma according to ICCC-3 group XI as subsequent primary neoplasm after childhood cancer, ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al., 2005); FPN = first primary neoplasm according to ICCC-3

[2]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; FPN diagnoses: ICCC-3 groups I-XII; age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months

[3]This is the model selected by univariable logistic regression with the fractional polynomial (FP) with spike at zero procedure, see Statistical Analysis Plan, Appendix III. FP1 means a first degree function was selected with power p for the transformation; FP2 means a second-decree function was selected with powers p and q for the two transformations; z means a binary spike-at-zero variable was selected, power 0 means natural logarithm of the substance dose

[4]relapse (yes/no), stem cell transplantation (yes/no), radiotherapy (near site of CSPN, not near site of CSPN, none); FPN diagnosis was not entered because it was not significant in univariable analysis, and it increased the AIC compared to the null model

[5]AIC = Akaike information criterion

[6]Antimetabolites and methotrexate were not selected because the AIC increased upon entry into the model

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18.4 Subgroup analysis excluding patients with a stem cell transplantation

Table 36. Subgroup excluding patients with stem cell transplantation: Association between CSPN[1] occurrence and the dose (continuous) of substances or substance groups for treatment of an FPN[1] in childhood (n = 875, 240 match groups)[2]: model details for Table 15.

	Model[3]	Power (p, q)[3]	univariable		multivariable without covariates	multivariable with covariates[4]
AIC[5]			**null model:** 603.982		589.781	572.922
Substance (group)			**AIC**	**p-value**	**p-value**	**p-value**
cyclophosphamide	FP1	1	596.166	0.0035	0.0336	0.0433
antimetabolites excluding methotrexate	z	-	598.895	0.0082	0.0147	0.0234
antimetabolites excluding cytarabine	z	-	599.483	0.0111	- [6]	- [6]
epipodophyllotoxins	FP1+z	0[7]	600.502	0.0282	- [8]	- [8]
methotrexate	z	-	600.073	0.0155	- [8]	- [8]
antimetabolites	z	-	600.561	0.0201	- [6]	- [6]
antibiotics	FP1+z	1	602.437	0.0756	0.0244	0.0370

[1]CSPN = carcinoma or malignant melanoma according to ICCC-3 group XI as subsequent primary neoplasm after childhood cancer, FPN = first primary neoplasm

[2]Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; FPN diagnoses: ICCC-3 groups I-XII; age at FPN: 0-14 years; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months

[3]This is the model selected by univariable logistic regression with the fractional polynomial (FP) with spike at zero procedure, see Statistical Analysis Plan, Appendix III. FP1 means a first degree function was selected with power p for the transformation; FP2 means a second-decree function was selected with powers p and q for the two transformations; z means a binary spike-at-zero variable was selected,

[4]relapse (yes/no), stem cell transplantation (yes/no), radiotherapy (near site of CSPN, not near site of CSPN, none); FPN diagnosis was not entered because it was not significant in univariable analysis, and it increased the AIC compared to the null model

[5]AIC = Akaike information criterion

[6]Antimetabolites excluding cytarabine and antimetabolites as a whole were not included because of the overlap with antimetabolites excluding methotrexate, which were included first during the selection process

[7]power 0 means natural logarithm of the substance dose

[8]Epipodophyllotoxins and methotrexate were not selected because the AIC increased upon entry into the model

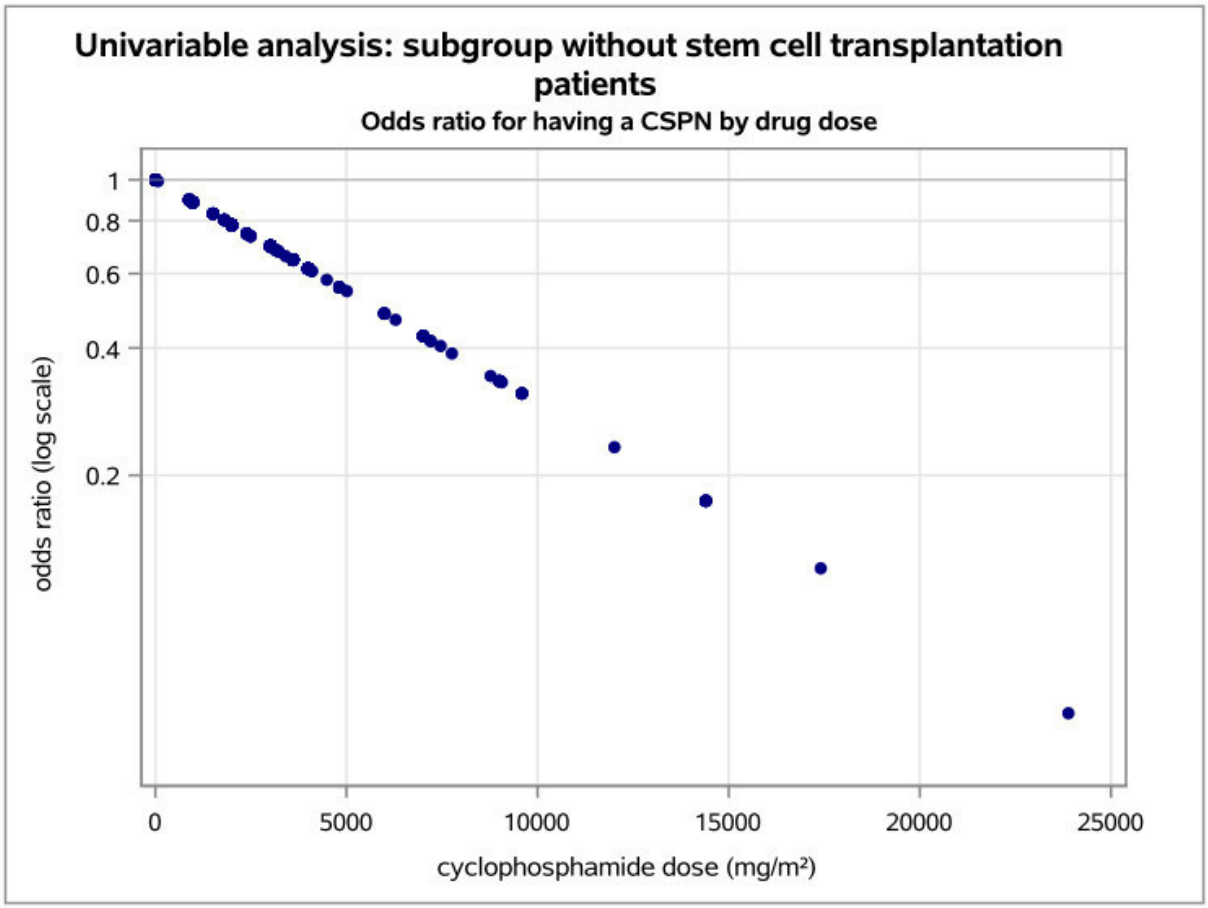

Figure 34. Subgroup excluding patients with stem cell transplantation: Univariable analysis: Odds ratio for having a CSPN by cyclophosphamide dose. CSPN = carcinoma or malignant melanoma according to ICCC-3 XI as subsequent primary neoplasm after childhood cancer. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005)

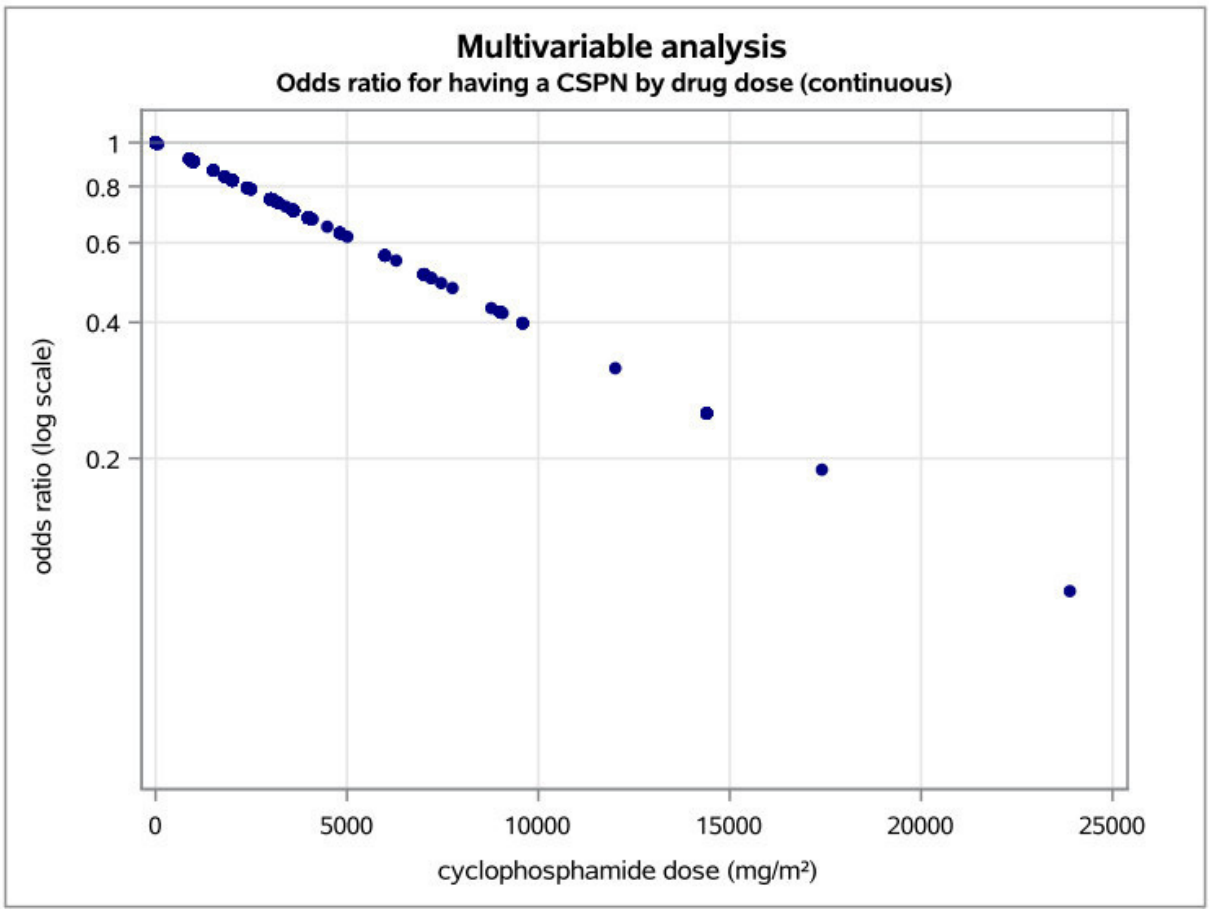

Figure 35. Subgroup excluding patients with stem cell transplantation: Multivariable analysis including covariates: Odds ratio for having a CSPN by cyclophosphamide dose. CSPN = carcinoma or malignant melanoma according to ICCC-3 XI as subsequent primary neoplasm after childhood cancer. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005)

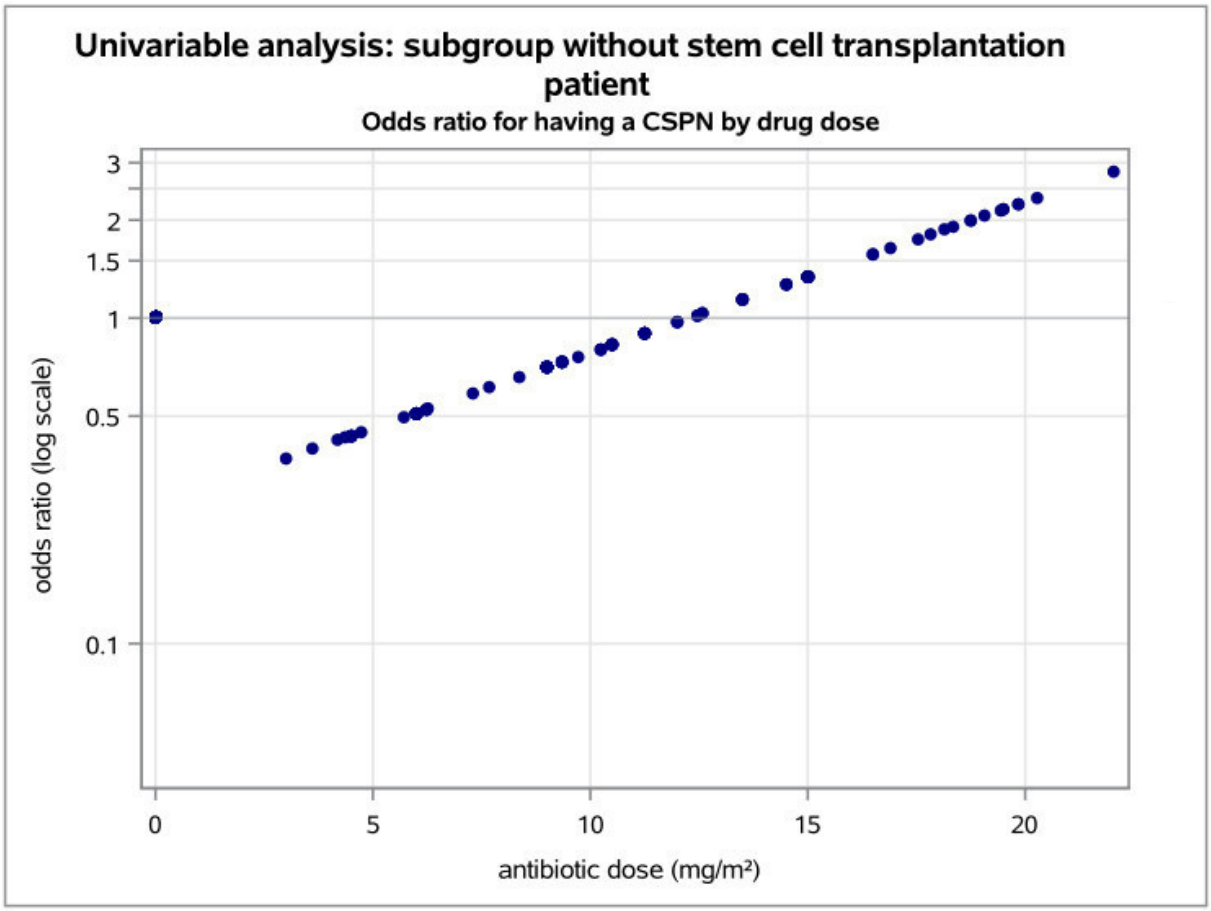

Figure 36. Subgroup excluding patients with stem cell transplantation: Univariable analysis: Odds ratio for having a CSPN by antibiotic dose. CSPN = carcinoma or malignant melanoma according to ICCC-3 XI as subsequent primary neoplasm after childhood cancer. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005)

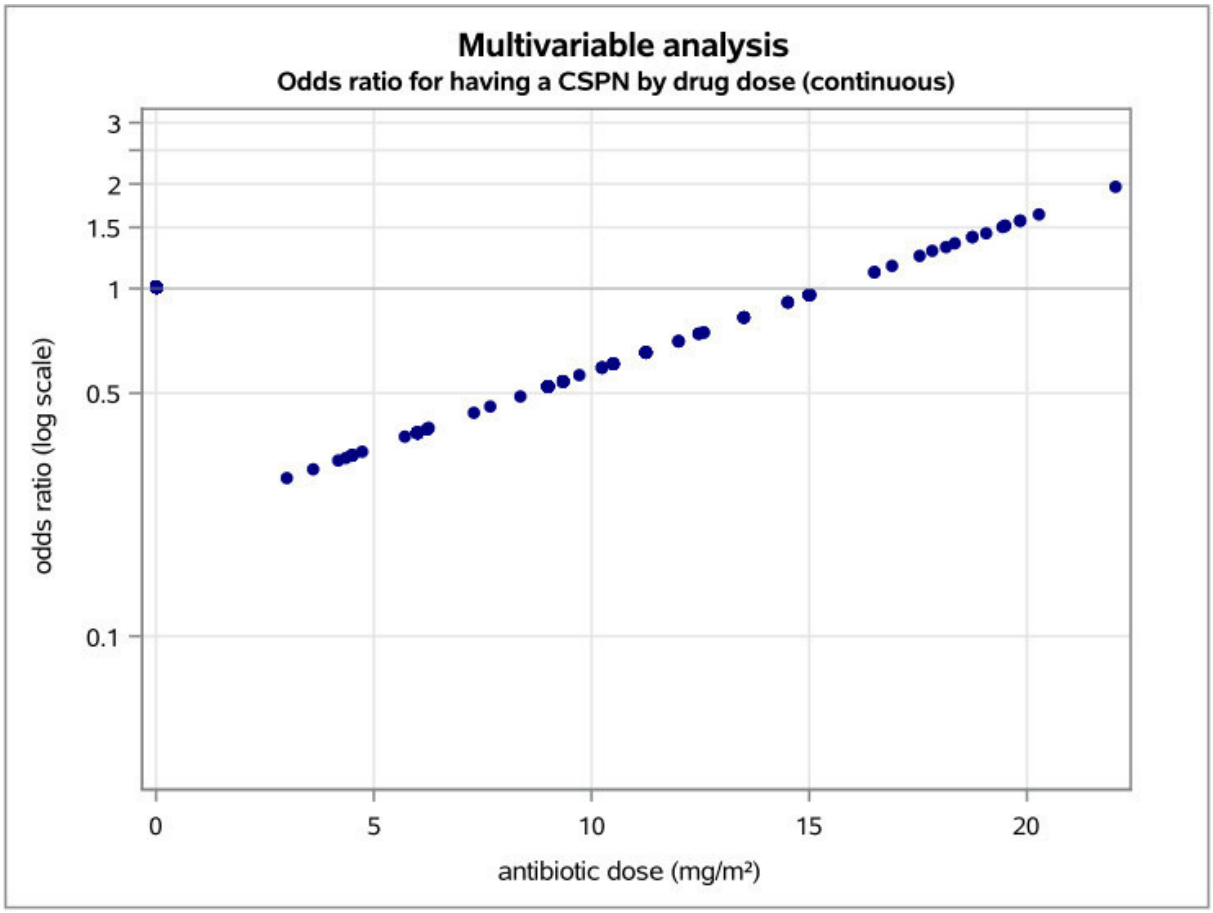

Figure 37. Subgroup excluding patients with stem cell transplantation: Multivariable analysis including covariates: Odds ratio for having a CSPN by antibiotic dose. CSPN = carcinoma or malignant melanoma according to ICCC-3 XI as subsequent primary neoplasm after childhood cancer. Subgroup of patients of the case-control study STATT by the German Childhood Cancer Registry: cases with CSPN diagnosis and their matched controls; first primary neoplasm (FPN) diagnoses: ICCC-3 groups I-XII; study period: 1980-2014; latency between FPN and CSPN diagnosis: minimum 6 months; ICCC-3 = International Classification of Childhood Cancer, 3rd edition, (Steliarova-Foucher et al. 2005)

19 Scoping Review: Modified search strategy in PubMed

This search strategy would have found the article by Ehrhardt et al. (2019), which was included from other sources in the article evaluation.

History and Search Details

Search	Actions	Details	Query	Results	Time
#5			Search: **(((#1) AND #2) AND (#3 OR breast neoplasm)) AND #4** Filters: **from 1000/1/1 - 2019/7/15** Sort by: **First Author**	1,872	12:40:19
#4			Search: **((((("Dose-Response Relationship, Drug"[Mesh]) OR ((((dose response) OR dose-response)) OR ((((dose* OR dosa* OR drugs OR dose-response OR dose response))) AND ((respons* OR effect* OR relation* OR dependen* OR curve*)))))))** Sort by: **Most Recent**	2,884,552	11:55:51
#3			Search: **(((((((("Neoplasms, Second Primary/analysis"[Mesh] OR "Neoplasms, Second Primary/drug therapy"[Mesh] OR "Neoplasms, Second Primary/epidemiology"[Mesh] OR "Neoplasms, Second Primary/etiology"[Mesh] OR "Neoplasms, Second Primary/therapy"[Mesh])))))) OR ((((((((((("second neoplasm" OR "second neoplasms")) OR ("second tumor" OR "second tumors")) AND ("subsequent tumor" OR "subsequent tumors")) OR ("subsequent neoplasm" OR "subsequent neoplasms")) OR ("secondary tumor" OR "secondary tumors")) OR ("secondary neoplasm" OR "secondary neoplasms")) OR ("second primary" OR "second primaries"))) OR ("second cancer" OR "second cancers")) OR ("subsequent cancer" OR "subsequent cancers")) OR ("secondary cancer" OR "secondary cancers")))))** Sort by: **Most Recent**	23,253	11:54:31

Search	Actions	Details	Query	Results	Time
#2			Search: **((((((("drug therapy"[Mesh]) OR (((anticancer*[Title/Abstract] OR antineoplas*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR carcino*[Title/Abstract])) AND therap*[Title/Abstract]))) OR (Antineoplastic Protocols[Title/Abstract] OR Antineoplastic Combined Chemotherapy Protocols[Title/Abstract] OR Chemoradiotherapy[Title/Abstract] OR Chemoradiotherapy, Adjuvant[Title/Abstract] OR Chemotherapy, Adjuvant[Title/Abstract] OR Consolidation Chemotherapy[Title/Abstract] OR Induction chemotherapy[Title/Abstract] OR Maintenance chemotherapy[Title/Abstract] OR Chemotherapy, Cancer, Regional Perfusion[Title/Abstract] OR Antineoplastic agents[Title/Abstract] OR chemotherap*[Title/Abstract] OR busulphan[Title/Abstract] OR busulfan*[Title/Abstract] OR Carmustine[Title/Abstract] OR BCNU[Title/Abstract] OR Chlorambucil[Title/Abstract] OR cyclophosphamide[Title/Abstract] OR cyclophosphane[Title/Abstract] OR cyclophosphan[Title/Abstract] OR endox*[Title/Abstract] OR cyclophospha*[Title/Abstract] OR Lomustine[Title/Abstract] OR CCNU[Title/Abstract] OR lomustine*[Title/Abstract] OR Mechlorethamine[Title/Abstract] OR mechlorethamine*[Title/Abstract] OR Chlormethine[Title/Abstract] OR Mustine[Title/Abstract] OR Chlorethazin[Title/Abstract] OR doxorubicin[Title/Abstract] OR doxorubic*[Title/Abstract] OR bleomycin[Title/Abstract] OR dactinomycin[Title/Abstract] OR gemcitabine[Title/Abstract] OR irinotecan[Title/Abstract] OR methotrexate[Title/Abstract] OR topotecan[Title/Abstract] OR tacrolimus[Title/Abstract] OR immunotherapy[Title/Abstract]))))** Sort by: **Most Recent**	2,173,719	11:52:56

Search	Actions	Details	Query	Results	Time
#1			Search: **((((((("Child"[Mesh]) OR "Adolescent"[Mesh])) OR (child* boy*[Title/Abstract] OR girl*[Title/Abstract] OR infan*[Title/Abstract] OR juvenile*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract] OR young*[Title/Abstract] OR adolescen*[Title/Abstract] OR teen*[Title/Abstract] OR youth*[Title/Abstract]))) AND (("Neoplasms"[Mesh]) OR (Neoplas*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR cancer*[Title/Abstract] OR malignan*[Title/Abstract] OR oncolog*[Title/Abstract] OR leukemia[Title/Abstract] OR leukemi*[Title/Abstract] OR leukaemi*[Title/Abstract] OR childhood ALL[Title/Abstract] OR AML[Title/Abstract] OR lymphoma[Title/Abstract] OR lymphom*[Title/Abstract] OR hodgkin[Title/Abstract] OR hodgkin*[Title/Abstract] OR T-cell[Title/Abstract] OR B-cell[Title/Abstract] OR non-hodgkin[Title/Abstract] OR sarcoma[Title/Abstract] OR sarcom*[Title/Abstract] OR sarcoma, Ewing's[Title/Abstract] OR Ewing*[Title/Abstract] OR osteosarcoma[Title/Abstract] OR osteosarcom*[Title/Abstract] OR wilms tumor[Title/Abstract] OR wilms*[Title/Abstract] OR nephroblastom*[Title/Abstract] OR neuroblastoma[Title/Abstract] OR neuroblastom*[Title/Abstract] OR rhabdomyosarcoma[Title/Abstract] OR rhabdomyosarcom*[Title/Abstract] OR teratoma[Title/Abstract] OR teratom*[Title/Abstract] OR hepatoma[Title/Abstract] OR hepatom*[Title/Abstract] OR hepatoblastoma[Title/Abstract] OR hepatoblastom*[Title/Abstract] OR PNET[Title/Abstract] OR medulloblastoma[Title/Abstract] OR medulloblastom*[Title/Abstract] OR PNET*[Title/Abstract] OR neuroectodermal tumors, primitive[Title/Abstract] OR**		

Search	Actions	Details	Query	Results	Time
			retinoblastoma[Title/Abstract] OR retinoblastom*[Title/Abstract] OR meningioma[Title/Abstract] OR meningiom*[Title/Abstract] OR glioma[Title/Abstract] OR gliom*[Title/Abstract] OR pediatric oncology[Title/Abstract] OR paediatric oncology[Title/Abstract] OR childhood cancer[Title/Abstract] OR childhood tumor[Title/Abstract] OR childhood tumors[Title/Abstract] OR brain tumor*[Title/Abstract] OR brain tumour*[Title/Abstract] OR brain neoplasms[Title/Abstract] OR central nervous system neoplasm[Title/Abstract] OR central nervous system neoplasms[Title/Abstract] OR central nervous system tumor*[Title/Abstract] OR central nervous system tumour*[Title/Abstract] OR brain cancer*[Title/Abstract] OR brain neoplasm*[Title/Abstract] OR intracranial neoplasm*[Title/Abstract] OR leukemia, lymphocytic, acute[Title/Abstract] OR leukemia, lymphocytic, acute*[Title/Abstract]))))) Sort by: **Most Recent**		

MeSH terms in PubMed for the article by Ehrhardt et al. (2019).

https://pubmed.ncbi.nlm.nih.gov/31075046/#mesh-terms (Accessed 3 October 2020)

- Adolescent
- Adult
- Anthracyclines / adverse effects*
- Breast Neoplasms / diagnosis*
- Breast Neoplasms / genetics*

- Breast Neoplasms / secondary*
- Cancer Survivors*
- Female
- Humans
- Magnetic Resonance Imaging
- Mammography
- Mass Screening / methods
- Mastectomy
- Middle Aged
- Multivariate Analysis
- Neoplasms / complications*
- Neoplasms / drug therapy*
- Proportional Hazards Models
- Prospective Studies
- Radiometry
- Retrospective Studies
- Risk Factors
- Sensitivity and Specificity
- Tumor Suppressor Protein p53 / genetics
- Whole Genome Sequencing

- Young Adult

APPENDIX II: Review protocol

1 Eligibility criteria

Inclusion criteria with rationale	Exclusion criteria with rationale
- original research in peer-reviewed journals (cohort study, case-control study, clinical trial, register study) → to ensure quality of research - occurrence of first neoplasm at age 0 to <15 years for at least 50% of the population with clear separation by age between <15 and ≥15 years → compare research question - exposure: dose of chemotherapy of first neoplasm and relapse, if applicable → compare research question - outcome: odds ratio, relative risk, or risk ratio for carcinoma or malignant melanoma as a SPN → compare research question - establishment of a dose-response relationship between exposure and outcome → compare research question - all publication years available - all languages available	- no original research (case studies, reviews or conference contributions) → relevant reviews and meta-analyses are searched to retrieve original research articles; case studies include too few subjects to be representative of childhood cancer patients in general, conference contributions are not peer-reviewed - studies with less than 10 cases of CSPN as outcome → too few cases do not allow conclusions for this group of patients - if multiple papers exist on data of the same cohort and all fulfill the inclusion criteria, the paper with the larger n of CSPN is chosen or – if there is no difference – the latest paper

2 Information sources

The following literature databases were searched on the dates indicated:

- Embase (https://embase.com), accessed 11 September 2018
- Scopus (https://www.scopus.com), accessed 20 February 2019

- PubMed (https://www.ncbi.nlm.nih.gov/pubmed), accessd 6 July 2019

PubMed had been searched multiple times in 2018 in order to test and refine the search strategy. The databases Embase and Scopus were available to the doctoral student only for limited periods of time.

3 Search

The four concepts “childhood cancer”, “second neoplasm”, “chemotherapy”, and “dose-response relationship” are included in the search strategies. The search strategy for the Embase search was discussed with librarian Beatrice Minder Wyssmann from the Social & Preventive Medicine Library, University Library of Bern, Switzerland.

3.1 Pubmed

In Pubmed, the search strategy consisted of combining a MeSH term with key words or a MeSH term with phrases from an index list. The four concepts were combined using the Boolean operator AND, see search history below. The search yielded 298 results.

Concept 1 **Childhood cancer**	SEARCH TERM ENTERED: (((((((("Child"[Mesh]) OR "Adolescent"[Mesh])) OR (child* boy*[Title/Abstract] OR girl*[Title/Abstract] OR infan*[Title/Abstract] OR juvenile*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract] OR young*[Title/Abstract] OR adolescen*[Title/Abstract] OR teen*[Title/Abstract] OR youth*[Title/Abstract]))) AND (("Neoplasms"[Mesh]) OR (Neoplas*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR cancer*[Title/Abstract] OR malignan*[Title/Abstract] OR oncolog*[Title/Abstract] OR leukemia[Title/Abstract] OR leukemi*[Title/Abstract] OR leukaemi*[Title/Abstract] OR childhood ALL[Title/Abstract] OR AML[Title/Abstract] OR lymphoma[Title/Abstract] OR lymphom*[Title/Abstract] OR hodgkin[Title/Abstract] OR hodgkin*[Title/Abstract] OR T-cell[Title/Abstract] OR B-cell[Title/Abstract] OR non-hodgkin[Title/Abstract] OR sarcoma[Title/Abstract] OR sarcom*[Title/Abstract] OR sarcoma, Ewing's[Title/Abstract] OR Ewing*[Title/Abstract] OR osteosarcoma[Title/Abstract] OR osteosarcom*[Title/Abstract] OR wilms tumor[Title/Abstract] OR wilms*[Title/Abstract] OR nephroblastom*[Title/Abstract] OR neuroblastoma[Title/Abstract] OR neuroblastom*[Title/Abstract] OR rhabdomyosarcoma[Title/Abstract] OR rhabdomyosarcom*[Title/Abstract] OR teratoma[Title/Abstract] OR teratom*[Title/Abstract] OR hepatoma[Title/Abstract] OR hepatom*[Title/Abstract] OR hepatoblastoma[Title/Abstract] OR hepatoblastom*[Title/Abstract] OR PNET[Title/Abstract] OR medulloblastoma[Title/Abstract] OR

	medulloblastom*[Title/Abstract] OR PNET*[Title/Abstract] OR neuroectodermal tumors, primitive[Title/Abstract] OR retinoblastoma[Title/Abstract] OR retinoblastom*[Title/Abstract] OR meningioma[Title/Abstract] OR meningiom*[Title/Abstract] OR glioma[Title/Abstract] OR gliom*[Title/Abstract] OR pediatric oncology[Title/Abstract] OR paediatric oncology[Title/Abstract] OR childhood cancer[Title/Abstract] OR childhood tumor[Title/Abstract] OR childhood tumors[Title/Abstract] OR brain tumor*[Title/Abstract] OR brain tumour*[Title/Abstract] OR brain neoplasms[Title/Abstract] OR central nervous system neoplasm[Title/Abstract] OR central nervous system neoplasms[Title/Abstract] OR central nervous system tumor*[Title/Abstract] OR central nervous system tumour*[Title/Abstract] OR brain cancer*[Title/Abstract] OR brain neoplasm*[Title/Abstract] OR intracranial neoplasm*[Title/Abstract] OR leukemia, lymphocytic, acute[Title/Abstract] OR leukemia, lymphocytic, acute*[Title/Abstract]))))) Search term consists of the two search terms CHILDHOOD AND CANCER combined with the Boolean operator AND: The search term CHILDHOOD: - MeSH: ("Child"[Mesh]) OR "Adolescent"[Mesh] - Keywords: (child* boy*[Title/Abstract] OR girl*[Title/Abstract] OR infan*[Title/Abstract] OR juvenile*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract] OR young*[Title/Abstract] OR adolescen*[Title/Abstract] OR teen*[Title/Abstract] OR youth*[Title/Abstract]) The search term CANCER consists of: - MeSH term: ("Neoplasms"[Mesh]) - Keywords: (Neoplas*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR cancer*[Title/Abstract] OR malignan*[Title/Abstract] OR oncolog*[Title/Abstract] OR leukemia[Title/Abstract] OR leukemi*[Title/Abstract] OR leukaemi*[Title/Abstract] OR childhood ALL[Title/Abstract] OR AML[Title/Abstract] OR lymphoma[Title/Abstract] OR lymphom*[Title/Abstract] OR hodgkin[Title/Abstract] OR hodgkin*[Title/Abstract] OR T-cell[Title/Abstract] OR B-cell[Title/Abstract] OR non-hodgkin[Title/Abstract] OR sarcoma[Title/Abstract] OR sarcom*[Title/Abstract] OR sarcoma, Ewing's[Title/Abstract] OR Ewing*[Title/Abstract] OR osteosarcoma[Title/Abstract] OR osteosarcom*[Title/Abstract] OR wilms tumor[Title/Abstract] OR wilms*[Title/Abstract] OR nephroblastom*[Title/Abstract]

	OR neuroblastoma[Title/Abstract] OR neuroblastom*[Title/Abstract] OR rhabdomyosarcoma[Title/Abstract] OR rhabdomyosarcom*[Title/Abstract] OR teratoma[Title/Abstract] OR teratom*[Title/Abstract] OR hepatoma[Title/Abstract] OR hepatom*[Title/Abstract] OR hepatoblastoma[Title/Abstract] OR hepatoblastom*[Title/Abstract] OR PNET[Title/Abstract] OR medulloblastoma[Title/Abstract] OR medulloblastom*[Title/Abstract] OR PNET*[Title/Abstract] OR neuroectodermal tumors, primitive[Title/Abstract] OR retinoblastoma[Title/Abstract] OR retinoblastom*[Title/Abstract] OR meningioma[Title/Abstract] OR meningiom*[Title/Abstract] OR glioma[Title/Abstract] OR gliom*[Title/Abstract] OR pediatric oncology[Title/Abstract] OR paediatric oncology[Title/Abstract] OR childhood cancer[Title/Abstract] OR childhood tumor[Title/Abstract] OR childhood tumors[Title/Abstract] OR brain tumor*[Title/Abstract] OR brain tumour*[Title/Abstract] OR brain neoplasms[Title/Abstract] OR central nervous system neoplasm[Title/Abstract] OR central nervous system neoplasms[Title/Abstract] OR central nervous system tumor*[Title/Abstract] OR central nervous system tumour*[Title/Abstract] OR brain cancer*[Title/Abstract] OR brain neoplasm*[Title/Abstract] OR intracranial neoplasm*[Title/Abstract] OR leukemia, lymphocytic, acute[Title/Abstract] OR leukemia, lymphocytic, acute*[Title/Abstract]))))
Concept 2 **Chemotherapy**	SEARCH TERM ENTERED: ((((((("drug therapy"[Mesh]) OR (((anticancer*[Title/Abstract] OR antineoplas*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR carcino*[Title/Abstract])) AND therap*[Title/Abstract]))) OR (Antineoplastic Protocols[Title/Abstract] OR Antineoplastic Combined Chemotherapy Protocols[Title/Abstract] OR Chemoradiotherapy[Title/Abstract] OR Chemoradiotherapy, Adjuvant[Title/Abstract] OR Chemotherapy, Adjuvant[Title/Abstract] OR Consolidation Chemotherapy[Title/Abstract] OR Induction chemotherapy[Title/Abstract] OR Maintenance chemotherapy[Title/Abstract] OR Chemotherapy, Cancer, Regional Perfusion[Title/Abstract] OR Antineoplastic agents[Title/Abstract] OR chemotherap*[Title/Abstract] OR busulphan[Title/Abstract] OR busulfan*[Title/Abstract] OR Carmustine[Title/Abstract] OR BCNU[Title/Abstract] OR Chlorambucil[Title/Abstract] OR cyclophosphamide[Title/Abstract] OR cyclophosphane[Title/Abstract] OR cyclophosphan[Title/Abstract] OR endox*[Title/Abstract] OR cyclophospha*[Title/Abstract] OR Lomustine[Title/Abstract] OR CCNU[Title/Abstract] OR lomustine*[Title/Abstract] OR Mechlorethamine[Title/Abstract] OR mechlorethamine*[Title/Abstract] OR Chlormethine[Title/Abstract] OR Mustine[Title/Abstract] OR

	Chlorethazin[Title/Abstract] OR doxorubicin[Title/Abstract] OR doxorubic*[Title/Abstract] OR bleomycin[Title/Abstract] OR dactinomycin[Title/Abstract] OR gemcitabine[Title/Abstract] OR irinotecan[Title/Abstract] OR methotrexate[Title/Abstract] OR topotecan[Title/Abstract] OR tacrolimus[Title/Abstract] OR immunotherapy[Title/Abstract]))))) SEARCH TERM CONSISTS OF - MeSH Term: "Drug Therapy"[Mesh] - Keywords: (((anticancer*[Title/Abstract] OR antineoplas*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR carcino*[Title/Abstract])) AND therap*[Title/Abstract]))) OR (Antineoplastic Protocols[Title/Abstract] OR Antineoplastic Combined Chemotherapy Protocols[Title/Abstract] OR Chemoradiotherapy[Title/Abstract] OR Chemoradiotherapy, Adjuvant[Title/Abstract] OR Chemotherapy, Adjuvant[Title/Abstract] OR Consolidation Chemotherapy[Title/Abstract] OR Induction chemotherapy[Title/Abstract] OR Maintenance chemotherapy[Title/Abstract] OR Chemotherapy, Cancer, Regional Perfusion[Title/Abstract] OR Antineoplastic agents[Title/Abstract] OR chemotherap*[Title/Abstract] OR busulphan[Title/Abstract] OR busulfan*[Title/Abstract] OR Carmustine[Title/Abstract] OR BCNU[Title/Abstract] OR Chlorambucil[Title/Abstract] OR cyclophosphamide[Title/Abstract] OR cyclophosphane[Title/Abstract] OR cytophosphan[Title/Abstract] OR endox*[Title/Abstract] OR cyclophospha*[Title/Abstract] OR Lomustine[Title/Abstract] OR CCNU[Title/Abstract] OR lomustine*[Title/Abstract] OR Mechlorethamine[Title/Abstract] OR mechlorethamine*[Title/Abstract] OR Chlormethine[Title/Abstract] OR Mustine[Title/Abstract] OR Chlorethazin[Title/Abstract] OR doxorubicin[Title/Abstract] OR doxorubic*[Title/Abstract] OR bleomycin[Title/Abstract] OR dactinomycin[Title/Abstract] OR gemcitabine[Title/Abstract] OR irinotecan[Title/Abstract] OR methotrexate[Title/Abstract] OR topotecan[Title/Abstract] OR tacrolimus[Title/Abstract] OR immunotherapy[Title/Abstract])
Concept 3 **Second Neoplasm**	SEARCH TERM ENTERED: (((((((("Neoplasms, Second Primary/analysis"[Mesh] OR "Neoplasms, Second Primary/drug therapy"[Mesh] OR "Neoplasms, Second Primary/epidemiology"[Mesh] OR "Neoplasms, Second Primary/etiology"[Mesh] OR "Neoplasms, Second Primary/therapy"[Mesh])))))) OR ((((((((((("second neoplasm" OR "second neoplasms")) OR ("second tumor" OR "second tumors")) AND ("subsequent tumor" OR "subsequent tumors")) OR ("subsequent neoplasm" OR "subsequent neoplasms")) OR ("secondary tumor" OR "secondary tumors")) OR ("secondary neoplasm" OR "secondary neoplasms")) OR ("second primary" OR "second primaries"))) OR ("second cancer" OR "second cancers")) OR ("subsequent cancer" OR

	"subsequent cancers")) OR ("secondary cancer" OR "secondary cancers"))))) SEARCH TERM CONSISTS OF - MeSH Terms: (((("Neoplasms, Second Primary/analysis"[Mesh] OR "Neoplasms, Second Primary/drug therapy"[Mesh] OR "Neoplasms, Second Primary/epidemiology"[Mesh] OR "Neoplasms, Second Primary/etiology"[Mesh] OR "Neoplasms, Second Primary/therapy"[Mesh]))) – Phrases from index list: ((((((((((("second neoplasm" OR "second neoplasms")) OR ("second tumor" OR "second tumors")) AND ("subsequent tumor" OR "subsequent tumors")) OR ("subsequent neoplasm" OR "subsequent neoplasms")) OR ("secondary tumor" OR "secondary tumors")) OR ("secondary neoplasm" OR "secondary neoplasms")) OR ("second primary" OR "second primaries"))) OR ("second cancer" OR "second cancers")) OR ("subsequent cancer" OR "subsequent cancers")) OR ("secondary cancer" OR "secondary cancers") –
Concept 4 **Dose response**	SEARCH TERM ENTERED: ((((("Dose-Response Relationship, Drug"[Mesh]) OR ((((dose response[Title/Abstract]) OR dose-response[Title/Abstract])) OR ((((dos*[Title/Abstract] OR drugs[Title/Abstract] OR dose-response[Title/Abstract] OR dose response[Title/Abstract]))) AND ((respons*[Title/Abstract] OR effect*[Title/Abstract] OR relation*[Title/Abstract] OR dependen*[Title/Abstract] OR curve*[Title/Abstract]))))))) SEARCH TERM CONSISTS OF - MeSH Term: "Dose-Response Relationship, Drug"[Mesh] - Key Words: (((dose response[Title/Abstract]) OR dose-response[Title/Abstract])) OR ((((dos*[Title/Abstract] OR drugs[Title/Abstract] OR dose-response[Title/Abstract] OR dose response[Title/Abstract]))) AND ((respons*[Title/Abstract] OR effect*[Title/Abstract] OR relation*[Title/Abstract] OR dependen*[Title/Abstract] OR curve*[Title/Abstract]))))

PubMed search history on 6 July 2019:

History

Download historyClear history

Recent queries

Search	Add to builder	Query	Items found	Time
#5	Add	Search **(((#1) AND #2) AND #3) AND #4**	298	12:10:42
#4	Add	Search **((((("Dose-Response Relationship, Drug"[Mesh]) OR ((((dose response[Title/Abstract]) OR dose-response[Title/Abstract])) OR ((((dos*[Title/Abstract] OR drugs[Title/Abstract] OR dose-response[Title/Abstract] OR dose response[Title/Abstract])))) AND ((respons*[Title/Abstract] OR effect*[Title/Abstract] OR relation*[Title/Abstract] OR dependen*[Title/Abstract] OR curve*[Title/Abstract])))))))**	1628576	12:10:24
#3	Add	Search **(((((((("Neoplasms, Second Primary/analysis"[Mesh] OR "Neoplasms, Second Primary/drug therapy"[Mesh] OR "Neoplasms, Second Primary/epidemiology"[Mesh] OR "Neoplasms, Second Primary/etiology"[Mesh] OR "Neoplasms, Second Primary/therapy"[Mesh])))))) OR ((((((((((("second neoplasm" OR "second neoplasms")) OR ("second tumor" OR "second tumors")) AND ("subsequent tumor" OR "subsequent tumors")) OR ("subsequent neoplasm" OR "subsequent neoplasms")) OR ("secondary tumor" OR "secondary tumors")) OR ("secondary neoplasm" OR "secondary neoplasms")) OR ("second primary" OR "second primaries"))) OR ("second cancer" OR "second cancers")) OR ("subsequent cancer" OR "subsequent cancers")) OR ("secondary cancer" OR "secondary cancers")))))**	21841	12:10:06
#2	Add	Search **((((((("drug therapy"[Mesh]) OR (((anticancer*[Title/Abstract] OR antineoplas*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR carcino*[Title/Abstract])) AND therap*[Title/Abstract]))) OR (Antineoplastic Protocols[Title/Abstract] OR Antineoplastic Combined Chemotherapy Protocols[Title/Abstract] OR Chemoradiotherapy[Title/Abstract] OR Chemoradiotherapy, Adjuvant[Title/Abstract] OR Chemotherapy, Adjuvant[Title/Abstract] OR Consolidation Chemotherapy[Title/Abstract] OR Induction chemotherapy[Title/Abstract] OR Maintenance chemotherapy[Title/Abstract] OR Chemotherapy, Cancer, Regional Perfusion[Title/Abstract] OR Antineoplastic agents[Title/Abstract] OR chemotherap*[Title/Abstract] OR busulphan[Title/Abstract] OR**	2019328	12:09:34

Recent queries

Search	Add to builder	Query	Items found	Time
		busulfan*[Title/Abstract] OR Carmustine[Title/Abstract] OR BCNU[Title/Abstract] OR Chlorambucil[Title/Abstract] OR cyclophosphamide[Title/Abstract] OR cyclophosphane[Title/Abstract] OR cyclophosphan[Title/Abstract] OR endox*[Title/Abstract] OR cyclophospha*[Title/Abstract] OR Lomustine[Title/Abstract] OR CCNU[Title/Abstract] OR lomustine*[Title/Abstract] OR Mechlorethamine[Title/Abstract] OR mechlorethamine*[Title/Abstract] OR Chlormethine[Title/Abstract] OR Mustine[Title/Abstract] OR Chlorethazin[Title/Abstract] OR doxorubicin[Title/Abstract] OR doxorubic*[Title/Abstract] OR bleomycin[Title/Abstract] OR dactinomycin[Title/Abstract] OR gemcitabine[Title/Abstract] OR irinotecan[Title/Abstract] OR methotrexate[Title/Abstract] OR topotecan[Title/Abstract] OR tacrolimus[Title/Abstract] OR immunotherapy[Title/Abstract])))		
#1	Add	Search **(((((((("Child"[Mesh]) OR "Adolescent"[Mesh])) OR (child* boy*[Title/Abstract] OR girl*[Title/Abstract] OR infan*[Title/Abstract] OR juvenile*[Title/Abstract] OR pediatr*[Title/Abstract] OR paediatr*[Title/Abstract] OR young*[Title/Abstract] OR adolescen*[Title/Abstract] OR teen*[Title/Abstract] OR youth*[Title/Abstract]))) AND (("Neoplasms"[Mesh]) OR (Neoplas*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR cancer*[Title/Abstract] OR malignan*[Title/Abstract] OR oncolog*[Title/Abstract] OR leukemia[Title/Abstract] OR leukemi*[Title/Abstract] OR leukaemi*[Title/Abstract] OR childhood ALL[Title/Abstract] OR AML[Title/Abstract] OR lymphoma[Title/Abstract] OR lymphom*[Title/Abstract] OR hodgkin[Title/Abstract] OR hodgkin*[Title/Abstract] OR T-cell[Title/Abstract] OR B-cell[Title/Abstract] OR non-hodgkin[Title/Abstract] OR sarcoma[Title/Abstract] OR sarcom*[Title/Abstract] OR sarcoma, Ewing's[Title/Abstract] OR Ewing*[Title/Abstract] OR osteosarcoma[Title/Abstract] OR osteosarcom*[Title/Abstract] OR wilms tumor[Title/Abstract] OR wilms*[Title/Abstract] OR nephroblastom*[Title/Abstract] OR neuroblastoma[Title/Abstract] OR neuroblastom*[Title/Abstract] OR rhabdomyosarcoma[Title/Abstract] OR rhabdomyosarcom*[Title/Abstract] OR teratoma[Title/Abstract] OR teratom*[Title/Abstract] OR hepatoma[Title/Abstract] OR hepatom*[Title/Abstract] OR hepatoblastoma[Title/Abstract] OR hepatoblastom*[Title/Abstract] OR PNET[Title/Abstract] OR medulloblastoma[Title/Abstract] OR medulloblastom*[Title/Abstract] OR PNET*[Title/Abstract] OR neuroectodermal tumors, primitive[Title/Abstract] OR retinoblastoma[Title/Abstract] OR retinoblastom*[Title/Abstract] OR meningioma[Title/Abstract] OR meningiom*[Title/Abstract] OR glioma[Title/Abstract] OR gliom*[Title/Abstract] OR pediatric oncology[Title/Abstract] OR paediatric oncology[Title/Abstract] OR childhood cancer[Title/Abstract] OR childhood tumor[Title/Abstract] OR childhood tumors[Title/Abstract] OR brain tumor*[Title/Abstract] OR brain**		

Recent queries

Search	Add to builder	Query	Items found	Time
		tumour*[Title/Abstract] OR brain neoplasms[Title/Abstract] OR central nervous system neoplasm[Title/Abstract] OR central nervous system neoplasms[Title/Abstract] OR central nervous system tumor*[Title/Abstract] OR central nervous system tumour*[Title/Abstract] OR brain cancer*[Title/Abstract] OR brain neoplasm*[Title/Abstract] OR intracranial neoplasm*[Title/Abstract] OR leukemia, lymphocytic, acute[Title/Abstract] OR leukemia, lymphocytic, acute*[Title/Abstract])))))		

3.2 Embase

The search strategy combined he four concepts with the operator AND into one single search string (AND printed in bold). The strategy made use of the proximity operator NEAR, which means that one word or phrase must be within n words of the other one. Here, a proximity of n = 3 words were chosen. The search yielded 331 results.

('childhood cancer'/exp OR (((paediatr* OR pediatr*) NEAR/3 (malignan* OR tumor* OR tumour* OR oncolog*)):ab,ti) OR 'childhood leukemia'/exp OR (((childhood OR juvenile) NEAR/3 (leukaemia OR leukemia)):ab,ti) OR (('child'/de OR 'boy' OR 'girl' OR 'infant'/exp OR 'hospitalized child' OR 'preschool child' OR 'school child' OR 'juvenile' OR youth OR 'adolescent'/de OR 'hospitalized adolescent' OR ((pediatr*:ab,ti OR paediatr*:ab,ti OR juvenil*:ab,ti) AND teen*:ab,ti) OR child*:ab,ti OR boy*:ab,ti OR girl*:ab,ti OR infan*:ab,ti OR youth*:ab,ti OR young*:ab,ti OR adolescen*:ab,ti) AND ('neoplasm'/exp OR 'malignant neoplasm'/exp OR 'oncology'/de OR leukemia OR leukemi* OR leukaemi* OR 'childhood all' OR aml OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR 't cell' OR 'b cell' OR 'non hodgkin' OR sarcoma OR sarcom* OR ewing* OR osteosarcoma OR osteosarcom* OR 'wilms tumor' OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR pnet OR medulloblastoma OR medulloblastom* OR pnet* OR 'neuroectodermal tumors, primitive' OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR 'brain tumor*' OR 'brain tumour*' OR 'brain neoplasms' OR 'central nervous system neoplasm' OR 'central nervous system neoplasms' OR 'central nervous system tumor*' OR 'central nervous system tumour*' OR 'brain cancer*' OR 'brain neoplasm*' OR 'intracranial neoplasm*' OR oncol*:ab,ti OR neoplas*:ab,ti OR tumour:ab,ti OR tumor:ab,ti OR malignan*:ab,ti OR cancer*:ab,ti)))
AND ('chemotherapy'/exp OR 'drug therapy'/de OR 'antineoplastic protocols' OR 'antineoplastic combined chemotherapy protocols' OR chemoradiotherapy OR 'consolidation chemotherapy' OR 'induction chemotherapy' OR 'maintenance chemotherapy' OR 'chemotherapy, cancer, regional perfusion' OR 'antineoplastic agents' OR chemotherap* OR busulphan OR busulfan* OR carmustine OR bcnu OR chlorambucil OR cyclophosphamide OR cyclophosphane OR cytophosphan OR endox* OR cyclophospha* OR lomustine OR ccnu OR lomustine* OR mechlorethamine OR mechlorethamine* OR chlormethine OR mustine OR chlorethazine OR doxorubicin OR doxorubic* OR bleomycin OR dactinomycin OR gemcitabine OR irinotecan OR methotrexate OR topotecan OR tacrolimus OR immunotherapy OR (((chemotherap* OR antiinfect* OR expos*) NEAR/3 (agent* OR drug* OR expos*)):ab,ti) OR (((anticancer* OR antineoplas* OR carcino* OR tumor* OR tumour*) NEAR/3 chemotherap*):ab,ti))
AND ('second cancer'/exp OR 'second primary' OR (((second* OR subsequent* OR previous* OR new*) NEAR/3 (neoplas* OR cancer* OR malignan* OR tumor* OR tumour*)):ab,ti))
AND ('dose response'/de OR 'dose response' OR (((dos* OR drug OR 'dose response') NEAR/3 (response* OR effect* OR relation* OR dependen* OR curve*)):ab,ti))

3.3 Scopus

The search strategy combined he four concepts with the operator AND into one single search string (AND printed in bold). The strategy made use of the proximity operator W, which means that one word or phrare must be within n words of the other one. Here, a proximity of n = 3 words was chosen. The search yielded 794 results.

TITLE-ABS(“childhood cancer“ OR (((paediatr* OR pediatr*) W/3 (malignan* OR tumor* OR tumour* OR oncolog*))) OR “childhood leukemia“ OR (((childhood OR juvenile) W/3 (leukaemia OR leukemia))) OR ((“child“ OR “boy“ OR “girl“ OR “infant“ OR “hospitalized

child“ OR “preschool child“ OR “school child“ OR “juvenile“ OR youth OR “adolescent“ OR “hospitalized adolescent“ OR ((pediatr* OR paediatr* OR juvenil*) AND teen*) OR child* OR boy* OR girl* OR infan* OR youth* OR young* OR adolescen*) AND (“neoplasm“ OR “malignant neoplasm“ OR “oncology“ OR leukemia OR leukemi* OR leukaemi* OR “childhood all“ OR aml OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR “t cell“ OR “b cell“ OR “non hodgkin“ OR sarcoma OR sarcom* OR ewing* OR osteosarcoma OR osteosarcom* OR “wilms tumor“ OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR pnet OR medulloblastoma OR medulloblastom* OR pnet* OR “neuroectodermal tumors, primitive“ OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR “brain tumor*“ OR “brain tumour*“ OR “brain neoplasms“ OR “central nervous system neoplasm“ OR “central nervous system neoplasms“ OR “central nervous system tumor*“ OR “central nervous system tumour*“ OR “brain cancer*“ OR “brain neoplasm*“ OR “intracranial neoplasm*“ OR oncol* OR neoplas* OR tumour OR tumor OR malignan* OR cancer*)))

AND TITLE-ABS(“chemotherapy“ OR “drug therapy“ OR “antineoplastic protocols“ OR “antineoplastic combined chemotherapy protocols“ OR chemoradiotherapy OR “consolidation chemotherapy“ OR “induction chemotherapy“ OR “maintenance chemotherapy“ OR “chemotherapy, cancer, regional perfusion“ OR “antineoplastic agents“ OR chemotherap* OR busulphan OR busulfan* OR carmustine OR bcnu OR chlorambucil OR cyclophosphamide OR cyclophosphane OR cytophosphan OR endox* OR cyclophospha* OR lomustine OR ccnu OR lomustine* OR mechlorethamine OR mechlorethamine* OR chlormethine OR mustine OR chlorethazine OR doxorubicin OR doxorubic* OR bleomycin OR dactinomycin OR gemcitabine OR irinotecan OR methotrexate OR topotecan OR tacrolimus OR immunotherapy OR (((chemotherap* OR antiinfect* OR expos*) W/3 (agent* OR drug* OR expos*))) OR (((anticancer* OR antineoplas* OR carcino* OR tumor* OR tumour*) W/3 chemotherap*)))

AND TITLE-ABS(“second cancer“ OR “second primary“ OR (((second* OR subsequent* OR previous* OR new*) W/3 (neoplas* OR cancer* OR malignan* OR tumor* OR tumour*)))) **AND** (“dose response“ OR “dose response“ OR (((dos* OR drug OR “dose response“) W/3 (response* OR effect* OR relation* OR dependen* OR curve*))))

4 Selection of sources of evidence

Using the reference management software EndNote X9, the search results of the three databases are deduplicated, titles/abstracts are evaluated and irrelevant papers are excluded based on the eligibility criteria. Though reviews were excluded, the reference lists of relevant reviews dating back until 2010 are searched backward. In addition, a forward search using PubMed was carried out and the title of PubMed Central articles which cite the reviews are screened. Articles form the backward and forward search with potentially relevant titles are selected for abstract screening and irrelevant articles are excluded based on the eligibility criteria.

Next, the full texts are evaluated for relevance to the study question and based on the eligibility criteria. The reasons for exclusion based on the eligibility criteria are recorded.

The results of the selection process are presented in a flowchart.

Since this is a doctoral thesis, only the doctoral student perfoms the selection process although ideally, a second reviewer would go through the process as well and disagreements on study selection and the following data extraction would be resolved by consensus and discussion.

Exclusion criteria for the full text evaluation:

Exclusion criterium	**Explanation**
age	irrelevant age group, see eligibility criteria
chemo	no chemotherapy or no chemotherapy doses as exposure variable; dose = at least some kind of score, quantiles or similar at least some kind of score, quantiles or similar that shows variation in chemotherapy, must have been analysed
SPN	irrelevant outcome (no CSPN) or too few cases of CSPN (<10)
no original research	case study, review article, meta-analysis editorial, conference contribution (poster, oral presentation), not in peer-reviewed journal…
dose-response	no dose-response relationship established between exposure and outcome
multiple	if multiple papers exist on data of the same cohort and all fulfill the inclusion criteria, the paper with the smaller n of CSPN is excluded or – if there is no difference in n – the earlier paper(s)

5 Data charting process

A data charting form is developed based on the evaluation of the full text of several papers which had been retrieved after an initial PubMed search in September 2018. It may be adapted upon evaluation of the first few full texts.

6 Data items

The following variables are recorded for each article to be read as full texts in an Excel spreadsheet. .

Variable	**Examples or explanation**
Author	
Year	
Title	
Journal	
Study design	e.g. case-control study, cohort study, clinical trial
Setting	Common childhood cancer survival cohorts: CCSS, DCOG LATER, …
Sample	Special characteristics, e.g., females without chest radiotherapy
Ages at FPN diagnosis	<= 18 y
Sex	53% males
Matching? (for case-control studies)	Type of matching, factors by which matched
Latency	Minimum time between FPN and SPN
Calendar years FPN diagnosis	1970-1986
Calendar years SPN diagnosis	through 2004
FPN: n entity if restricted	14,135 leukemia, CNS, HL, NHL, renal tumor, neuroblastoma, soft-tissue sarcoma, bone sarcoma
SPN n entity if restricted	23 salivary gland carcinomas
Chemotherapeutics or chemotherapeutic groups	epipodophyllotoxins, anthracyclines, alkylating agents, vinca alkaloids, antimetabolites, and antibiotics
Units of chemotherapy dose	mg/m^2, $mole/m^2$
Method for pooling/comparing chemotherapeutics	AAS (AAS = alkylating agents score , Tucker 1987) CED: 0, 1-5,999, 6,000-17,999, >= 18,000 (CED = cyclophosphamide equivalent dose, Green 2014)

Radiation exposure	- radio as y/n and in dose categories if at least 10 exposed cases for outcome of interest
Adjusting for	- radiation - race/ethnicity (white, non-Hispanic, and other) - attained age
Statistical Models	RR (relative risk) for salivary gland carcinomas (SGC) using Poisson regression, two-siced p-values and 95%CI based on likelihood ratio statistic,
Outcome	- RR of yes/no treatment with alkylating agents: 2.5 [0.9-7.9], anthracyclines: 1.6 [06-42] - RR of AAS: 0 (ref.), 1: 4.1 [1.4-13.7], 2: 2.0 [0.4-8.1], 3: 1.1 [0.2-5.3], unknown: 1.6 [0.2-7.5], trend n.s. (p >0.5) - RR of anthracyclines (mg/m2): none (ref.), 0.12-174: 1.8 [0.3-6.7], 175-290: 1.8 [0.3-6.8], 291-390: 0.9[0.05-4.8], 391-8370: 2.0 [0.3-7.7], unknown: 3.1 [0.5-11.6], trend n.s (p = 0.42)

7 Synthesis of results

The results are presented as a table and summarized as they relate to the research question.

STATISTICAL ANALYSIS PLAN (SAP)

Doctoral thesis Cornelia Becker

1 Contents

1. Research question and study design

1.1 Research question

In patients registered at the German Childhood Cancer Registry (GCCR) who had a first malignancy before the age of 15, is there a dose-response relationship between (a) exposure to different chemotherapeutic groups for the treatment of the first malignancy or relapse and (b) the risk for having a carcinoma according to ICCC-3 group XI as a SPN (CSPN)? The ICCC-3 is the International Classification of Childhood Cancer, 3rd edition (Steliarova-Foucher et al., 2005).

1.2 Study design

The study design is a nested case-control study. It is described in the main text of the doctoral thesis. In this dissertation, a subset of cases and controls are analyzed who were included in the STATT study (compare Chapter 4.1).

1.3 Therapy data

Therapy data inclusion stopped on October 31st, 2019.
Most childhood cancer patients are treated within therapy optimization studies (TOS) on the basis of a study protocol. These patients are called protocol patients in the STATT study and they are the only type of patients whose data is used for this dissertation.
The data from these patients is protocol data (intention-to-treat = ITT), which means this is the therapy which a protocol patient was supposed to receive according to the study arm of the TOS. The therapy comprises the cumulative dose of each substance in mg/m^2 or U/m^2 and of the radiotherapy in Gray. The substances include chemotherapeutics, corticosteroids, cytokines, and other substances (see Table 2 for a list of substances relevant to patient data included in this dissertation). Radiotherapy is specified by the site of therapy (Table 6). There is no information on any divergence from the protocol. Up to the inclusion date for the therapy data, there was no data on relapse treatment available.
The ITT data is retrieved from the therapy protocol database of the Society for Pediatric Oncology and Hematology (GPOH), the GPOH therapy protocol database. For each TOS in which a patient was treated, one set of therapy data may be retrieved.
For the analyses in this thesis, only ITT data is available. As treated data is not available, i.e., the true treatment which patients received is not known, and deviations from the protocol data cannot be estimated.

2 Data cleaning and preparation

2.1 Data cleaning

2.1.1 Exposure data

In the course of the STATT study, several errors in the units and cumulative doses stored in the GPOH therapy protocol database became apparent and I clarified these errors with the persons responsible for the database. Since a final update of the database was not available when I received my final dataset, I make the following corrections manually:

- In cases and controls treated according to therapy arm “NB-90, Stadium 4, CR, VGPR, PR, lok. Bestrahlung Knochen und Tumor, Dauertherapie”, 60 Gy instead of 900 Gy radiation for the variable TUM-RAD are used
- the unit “mg” should read “mg/m^2”
- Asparaginase is usually measured in units/m^2; units in mg/m^2 are a mistake in the dataset and are replaced by units/m^2

2.1.2 Outlier detection and handling

Outliers may indicate a great range in a variable or implausible values due to errors. The data is checked for outliers in order to identify errors in data measurement, data documentation, data acquisition, data entry etc.

Outliers in the continuous exposure are determined by visual inspection of dose histograms, which exclude patients with zero values for these variables. Multimodal distributions are expected since different therapy protocols use different dose ranges. Obvious deviations are looked at individually and decisions on how to handle these deviations are recorded.[1] This may include checking the original data and checking protocols for the expected magnitude of the dose. In addition, I visually inspect the dose-response-relationship of the final statistical model for potential influential points, which are looked at individually. They might be excluded from the model if they substantially modify the dose-response-relationship.

2.2 Data preparation

2.2.1 Exposure data

2.2.1.1 Conversion of units

The analyses are performed with the dose of chemotherapeutic agents in the unit mg/m^2. Asparaginase is the only substance which is evaluated in the unit U/m^2. In the dataset extracted from the GPOH therapy protocol database, some substances have units other than mg/m^2. Therefore, the conversions according to Table 1 are performed. Especially for infants, substances are usually applied on the basis of body weight (kg) instead of body surface area (m^2).

Cytarabine and Methotrexate have the unit mg/m^2 for intravenous application and mg age-adjusted (absolute dose) for intrathecal application. Even if the absolute dose in mg age-adjusted is converted into mg/m^2, the potency of a unit of the substance differs between

[1] All decisions are made without knowledge of the patient’s case-control-status.

application forms. Therefore, I first converted the intrathecal doses using data-driven equivalence ratios (*Table* 4) and then converted the units according to Table 1.

In addition, the following conversions are made:

- for units µg, the conversion factor of *0.001 to the international system of units is used.
- Actinomycin D was measured in µg/kg (n = 32) or mg/m2 (n = 93) in the dataset extracted from the GPOH database; for 5 patients, however, the unit µg/ED (ED = single dose) was reported; from my discussions on errors in the GPOH therapy protocol database, I assume that this is an error as well; therefore, I replaced µg/ED by µg/kg based on the rationale that the doses of the 5 patients fit well with the dose distribution of the patients receiving Actinomycin measured in µg/kg (but not with the dose distribution in mg/m^2)

Table 1. Conversion of units of substances to mg/m² and U/m².

unit	substances	conversion to mg/m2	rationale/reference for conversion
mg/kg	Dactinomycin, G-CSF, Methotrexate, Prednisone	$mg/m^2 = k * mg/kg$ $k = 9.09*W^{0.35}$, W = body weight in kg; the median body weight of the child according to age and sex is used	conversion formulae: (2005) median body weight: (Kromeyer-Hauschild et al., 2001)
mg age-adjusted	Cytarabine, Methotrexate	$mg/m2 = mg* 1/m^2$ if the body surface area (BSA) is not known, it is calculated with the formula **BSA = √ (height [cm] * weight [kg] / 3600);** the median body weight of the child according to age and sex is used	"mg age-adjusted" is the absolute dose, which is administered intrathecally (e.g., ALL BFM 95 Therapieprotokoll, p. 47, (Riehm), NHL-BFM 95 Therapieprotokoll, p. 80f, (Reiter, 1996)) ; therefore, the dose is related to body surface area median body weight and height: (Kromeyer-Hauschild et al., 2001) BSA formula: (Du Bois and Du Bois, 1989)
U/m^2	L-Asparaginase; Coli-Asparaginase; PEG-Asparaginase	not converted to mg/m^2;	The doses of L-Asparaginase and Coli-Asparaginase are taken as equivalent because L-Asparaginase is most likely purified Coli-Asparaginase (could not verified, but assumption by pharmacist "deleted in the electronic version for reasons of data protection"). According to www.kinderkrebsinfo.de[1], Coli-Asparaginase is L-Asparaginase produced by the bacterium Escherichia coli; PEG-Asparaginase is Conversion of PEG-Asparaginase to Coli-Asparaginase based on the COALL-07-03 protocol and used in practice (pharmacy University Medical Center Mainz).

BSA = body surface area
1 Dobke, J. PEG-Asparaginase. 9 May 2018. URL: https://www.kinderkrebsinfo.de/patienten/behandlung/behandlungsmethoden/pohkinderkrebsinfochemotherapie/zytostatika_glossar/peg_asparaginase/index_ger.html Date of access: 6 Jan 2020.

2.2.1.2 Grouping of chemotherapeutics and equivalence ratios

As there is a large number of chemotherapeutic agent and other medications (n = 36, all kinds of Asparaginase counted as on type), and some of them were given to small numbers of patients, they are classified by the known mechanisms of their effect as defined by the ATC index (Anatomisch-Therapeutisch-Chemische Klassifikation) (Fricke et al., 2019) and the Fachinformationen by the substance manufacturers (Table 3). Anthracyclines are antibiotics and are only defined as a separate group solely based on their structure. Nevertheless, I defined them as a separate group for this dissertation in order to make a comparison with the literature possible, where anthracyclines were routinely analyzed as a group. The group "other" is a heterogenous mixture of corticosteroids (which are routinely administered together with chemotherapeutics), folinic acid, cytokines, Amsacrine (a chemotherapeutic not fitting in any

group), and other medications. Corticosteroids and folinic acid make up the largest portion of this group.

I do not assume that the carcinogenic potency of substances within a substance group are equivalent, just as researchers in many other publications did not (Boukheris et al., 2013, Ehrhardt et al., 2019, Guibout et al., 2005, Teepen et al., 2017, Veiga et al., 2012, Neglia et al., 2001). Therefore, the doses of the chemotherapeutics are converted in relation to reference substances, if possible. The doses of chemotherapeutics with a reference substance are summed for each patient. This is based on the rational that several authors developed equivalence ratios/conversion factors for substances within the same substance category, i.e., the dose of a substance was converted to the dose of a reference substance within the same substance category so that the hematological toxicity of these two doses were equivalent. This method assumes that the carcinogenic potency of the substances is proportional to their hematological toxicity (Green et al., 2014, Le Deley et al., 2003, Guérin et al., 2007). In addition, the Children's Oncology Group reports formulas for converting several anthracyclines to an doxorubicin isotoxic equivalent (Children`s Oncology Group, 2018). Although the equivalence ratios of the different authors are not always exactly the same for each substance, the orders of magnitude are similar. The equivalence ratios chosen are listed in Table 3.
For substances with no external conversion factors available, data-driven internal equivalence ratios are developed (Table 4). For each patient, the following formula is applied:

$$\textbf{substance A dose}_{\textbf{analysis}} = \textbf{substance A dose}_{\textbf{ITT}} * (\textbf{reference substance dose}_{\textbf{mean}} / \textbf{substance A dose}_{\textbf{mean}})$$

substance A $dose_{analysis}$ = dose of substance A used for analysis
substance A $dose_{ITT}$ = ITT dose of substance A from GPOH therapy protocol database
reference dose $dose_{mean}$ = mean dose of a reference substance for all controls in the STATT-SCAR study (both without and with matching on FPN type), which did not become cases later on
substance A $dose_{mean}$ = mean dose of substance A for all controls in the STATT-SCAR study (both without and with matching on FPN type), which did not become cases later on

The doses of chemotherapeutics within a substance group are summed for each patient.

Table 2. Grouping of substances used for analysis of therapy data.

Substance group (ATC-Code)	Abbreviation for analysis	Substance name; reference substance printed in bold
alkylating agent (L01A)	bus	Busulfan
alkylating agent (L01A)	cp	**Cyclophosphamide**
alkylating agent (L01A)	dtic	Dacarbazine
alkylating agent (L01A)	ifo	Ifosfamide
alkylating agent (L01A)	ccnu	Lomustine
alkylating agent (L01A)	mel	Melphalan
alkylating agent	pro	Procarbazine[1]
anthracycline (antibiotic) (L01DB)	dnr	Daunorubicin
anthracycline (antibiotic) (L01DB)	daux	Daunoxome
anthracycline (antibiotic) (L01DB)	adr	**Doxorubicin**
anthracycline (antibiotic) (L01DB)	epi	Epirubicin
anthracycline (antibiotic) (L01DB)	ida	Idarubicin
anthracycline (antibiotic) (L01DB)	mito	Mitoxantrone
antibiotic except anthracycline (L01D)	act	**Actinomycin D (Dactinomycin)**
antibiotic except anthracycline (L01D)	ble	Bleomycin
antimetabolite (L01B)	clad	Cladribine
antimetabolite (L01B)	arac	Cytarabine (Cytosine Arabinoside
antimetabolite (L01B)	fu	Fluorouracil
antimetabolite (L01B)	merc	Mercaptopurine
antimetabolite (L01B)	mtx	**Methotrexate**
antimetabolite (L01B)	thio	Thioguanine
enzyme[2] (L01XX)	asp	Asparaginase (L-Asparaginase)
enzyme (L01XX)	asp	Coli Asparaginase[3]
enzyme (L01XX)	asp	PEG-L-Asparaginase
epipodophyllotoxine (L01CBB)	vp16	**Etoposide (VP-16)**
epipodophyllotoxine (L01CBB)	vm26	Teniposid
other	amsa	Amsacrine
other	fa	Folinic Acid
other	g	G-CSF
other	inter	Interferon ALPHA
other	oth	Other
platinum derivate (L01XA)	car	Carboplatin
platinum derivate (L01XA)	ddp	**Cisplatin**
vinca alkaloid (L01CA)	vin	Vinblastine
vinca alkaloid (L01CA)	vcr	**Vincristine**
vinca alkaloid (L01CA)	vds	Vindesine
corticosteroid	dex	Dexamethasone
corticosteroid	pred	**Prednisone**

1 According to the ATC index, Procarbazine is a Methylhydrazine (L01XB) and belongs to the group "other antineoplastic agents" (L01X); according to the Fachinformationen (2018), it is an alkylating agent

2 Called "other antineoplastic agents" in ATC index; belongs to group "other antineoplastic agents" (L01X)

3 Not listed in ATC index

Table 3. Conversion of substance doses using external equivalence ratios.

Group	Substance	Factor needed to convert to reference substance	Reference substance	Reference
enzyme	**L-Asparaginase**	**1**	**L-Asparaginase**	**reference substance**
enzyme	Coli-Asparaginase	18	L-Asparaginase	The doses of L-Asparaginase and Coli-Asparaginase are taken as equivalent because L-Asparaginase is most likely purified Coli-Asparaginase (not verified, but assumption by pharmacist "deleted in the electronic version for reasons of data protection").
enzyme	PEG-Asparaginase	1	L-Asparaginase	Conversion of PEG-Asparaginase to Coli-Asparaginase based on (ref. COALL-07-03) and used in practice (pharmacy University Medical Center Mainz).
alkylating agent	**Cyclophosphamide**	**1**	**Cyclophosphamide**	**reference substance**
alkylating agent	Busulfan	8.823	Cyclophosphamide	Green et al. 2014
alkylating agent	Dacarbazine	2	Cyclophosphamide	Le Deley et al. 2003
alkylating agent	Ifosfamide	0.244	Cyclophosphamide	Green et al. 2014
alkylating agent	Lomustine	16	Cyclophosphamide	Green et al. 2014
alkylating agent	Melphalan	40	Cyclophosphamide	Green et al. 2014
alkylating agent	Procarbazine	0.857	Cyclophosphamide	Green et al. 2014
anthracycline	**Doxorubicin**	**1**	**Doxorubicin**	**reference substance**
anthracycline	Daunorubicin	0.83333	Doxorubicin	Le Deley et al. 2003
anthracycline	Epirubicin	0.6666667	Doxorubicin	Le Deley et al. 2003
anthracycline	Idarubicin	5	Doxorubicin	**(Children`s Oncology Group, 2018)** (Blanco et al., 2012)
anthracycline	Mitoxantrone	4	Doxorubicin	Le Deley et al. 2003
corticosteroid	**Prednisone**	**1**	**Prednisone**	**reference substance**
corticosteroid	Dexamethasone	0.149925	Prednisone	(Inaba and Pui, 2010)
epipodophyllotoxine	**Etoposide**	**1**	**Etoposide**	**reference substance**
epipodophyllotoxine	Teniposid	1	Etoposide	Le Deley et al. 2003

platinum derivate	Carboplatin	0.25	Cisplatin	Le Deley et al. 2003
vinca alkaloid	**Vincristine**	**1**	**Vincristine**	**reference substance**
vinca alkaloid	Vinblastine	0.25	Vincristine	Guérin et al. 2007
vinca alkaloid	Vindesine	0.5	Vincristine	Guérin et al. 2007

Table 4. Conversion of substance doses using internal equivalence ratios with mean dose on which conversion is based.

Group	Substance	Mean dose mg/m^2	N	Factor needed for conversion	Reference substance
antimetabolite	**Cytarabine (mg/m^2)**	**9014.734572**	**3014**	**1**	**Cytarabine (mg/m^2)**
antimetabolite	Cytarabine (mg age-adjusted)	231.2152	604	38.9885032	Cytarabine (mg/m^2)
antimetabolite	Fluorouracil	15000	5	0.6009823	Cytarabine (mg/m^2)
antimetabolite	Mercaptopurine	28992.601786	2240	0.31093224	Cytarabine (mg/m^2)
antimetabolite	Methotrexate (mg/m^2)	19074.921707	2757	0.47259615	Cytarabine (mg/m^2)
antimetabolite	Methotrexate (mg age-adjusted)	160.500132	2530	56.1665243	Cytarabine (mg/m^2)
antimetabolite	Thioguanine	4428.295289	2059	2.03571216	Cytarabine (mg/m^2)
antimetabolite	Cladribine	12	28	751.227881	Cytarabine (mg/m^2)
anthracycline	**Doxorubicin**	**162.147286**	**3497**	**1**	**Doxorubicin (mg/m^2)**
anthracycline	Daunoxome	232.7272727	33	0.69672662	Doxorubicin (mg/m^2)
antibiotic	**Actinomycin D (Dactinomycin)**	**9.806629**	**466**	**1**	**Actinomycin D (mg/m^2)**
antibiotic	Bleomycin	141.8166667	60	0.06915005	Actinomycin D (mg/m^2)

[1]Conversion factor = reference substance dose mean /substance dose mean

2.2.1.3 Radiotherapy

Radiotherapy exposure is used as a confounder in the analyses. Radiotherapy information available is the ITT dose in Gray (Gy) according to the therapy protocol and the approximate region of radiotherapy: central nervous system (CNS), tumor site (TUM), spinal cord (SPIN), or total body irradiation (TBI). Radiotherapy seems to affect the site of radiation with respect to risk for SPNs, and there seems to be little effect by scatter radiation on adjacent body regions (Scholz-Kreisel et al., 2018, Hennewig et al., 2014). Calculation of the radiation dose which arrives at the site of the SPN requires therapy plan reconstruction and sophisticated dosimetry,

which is not the focus this thesis. Therefore, I take into account radiotherapy as an ordinal variable with three categories:

- 2: For cases, radiotherapy at or near the site of the SPN; for controls, radiotherapy at or near the site of the SPN in the index case of the match group
- 1: Imprecise radiation site or for cases, radiotherapy not near the site of the SPN; for controls, radiotherapy not near the site of the SPN in the index case of the match group
- 0: No radiotherapy

To determine whether radiation was given at or near the site of the SPN, I assign the sites of the SPNs, which is available as ICD-O-3 topology code, to body sites (Table 5. ICD-O-3 topology codes assigned to body sites.Table 5, **Fehler! Verweisquelle konnte nicht gefunden werden.**) as defined by Peter Scholz-Kreisel in his dissertation on SPNs after radiotherapy in childhood cancer survivors (Scholz-Kreisel, 2018). Moreover, for FPNs or SPNs of the limbs, the laterality (left or right) is considered. The radiation category used for the analysis is derived from the ITT dose using the rules I formulated in Table 6.

Figure 1. Body sites of ICD-O-3 topology codes.

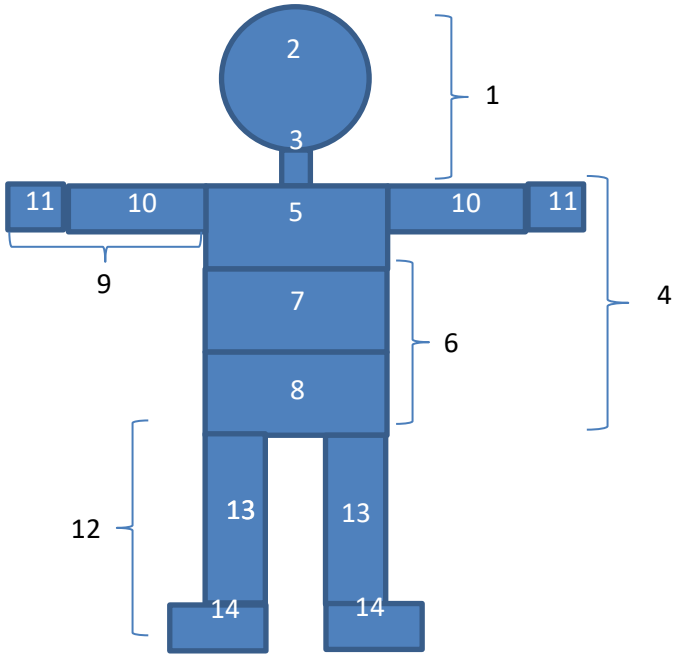

Table 5. ICD-O-3 topology codes assigned to body sites.

Code	ICDO-3 topology code				Body site
0	C408	C409	C424	C448	imprecise
	C449	C478	C479	C720	
	C447				
1	C443	C444	C470	C490	head
	C692	C696	C700	C709	
	C722	C723	C760	C770	
2	C441	C441	C694	C710	skull
	C711	C712	C713	C714	
	C715	C716	C717	C719	
	C751	C752	C753		
3	C019	C019	C021	C029	face/neck
	C031	C049	C051	C059	
	C079	C080	C099	C110	
	C111	C112	C119	C140	
	C159	C301	C310	C379	
	C442	C739			
4	C412	C412	C445	C496	trunk
5	C341	C341	C343	C380	thorax
	C383	C413	C473	C493	
	C502	C503	C504	C505	
	C508	C509	C761	C771	
6	C170	C182	C184	C186	abdomen
	C187	C189	C209	C474	
	C480	C481	C762	C772	
7	C169	C220	C250	C259	upper abdomen
	C268	C741	C749		
8	C172	C172	C179	C180	lower abdomen
	C414	C495	C510	C519	
	C529	C530	C539	C559	
	C569	C578	C629	C630	
	C649	C678	C679	C763	
9	C471	C491	C773		upper limb
10	C400	C446			arm
11	not applicable				hand
12	C472	C492			lower limb
13	C402	C402			leg
14	not applicable				foot
15	C421	C423	C768	C778	systemic

Table 6. Rules for deriving radiation doses for analysis from ITT doses.

Site/type of radiation according to protocol	Condition	Radiation category
no radiation		0
CNS	if SPN site = 1 (head) if SPN site = 2 (cranium) if SPN site = 3 (face/neck)	2
CNS	all other sites	1
TUM	if FPN site = SPN site	2
TUM	Head: • if FPN site = 1 and SPN site in (2 or 3) • if SPN site = 1 and FPN site in (2 or 3)	2
TUM	Limbs: • iF FPN site = 9 and SPN site in (10 or 11) and FPN laterality = SPN laterality • if SPN site = 9 and FPN site in (10 or 11) and FPN laterality = SPN laterality • iF FPN site = 12 and SPN site in (13 or 14) and FPN laterality = SPN laterality • if SPN site = 12 and FPN site in (13 or 14) and FPN laterality = SPN laterality	2
TUM	Trunk/thorax: • if FPN site = 6 and SPN site in (7 or 8) • if SPN site = 6 and FPN site in (7 or 8) • if FPN site = 4 and SPN site in (5 or 6 or 7 or 8) • if SPN site = 4 and FPN site in (5 or 6 or 7 or 8)	2
TUM	if none of the above conditions applies	1
TBI	any site	1
SPIN	any site	1

2.2.2 Other variables

2.2.2.1 Stem cell transplantation (SCT)

Information on treatment with a stem cell transplantation (SZT: yes/no or missing information) from the Pediatric Stem Cell Transplant Registry of Germany (PRST) and the clinical trials on relapses of acute lymphoblastic leukemias (ALL-REZ) of Germany are included. It is possible that the data linkage to the PRST was not able to link all patients from the STATT study. Therefore, no information on a stem cell transplantation might also mean that the patient could not be linked. If any the PRST or the ALL-REZ provided information on stem cell transplantation, the variable SZT is set to yes.

2.2.2.2 Relapse

Information of the first relapse is available at the GCCR. If the relapse occurred within the latency time of the case (between FPN and SPN diagnosis), a binary indicator for relapse is set to yes, otherwise to no.

2.2.3 Missing data

Missing therapy data is expected for patients who had a relapse and who had a stem cell transplantation. Therefore, a binary indicator for relapse and a binary variable for stem cell transplantation are included in multivariable analyses. Other than that, no missing data is expected.

3 Variables

3.1 Primary endpoint

Primary endpoint: case-control-status. Binary variable (case/control).

A case is defined as a person registered at the GCCR who has a SPN diagnosis according to the diagnostic group XI of the International Classification of Childhood Cancer, 3rd edition, ICCC-3 (Steliarova-Foucher et al., 2005) : Other malignant epithelial neoplasms and malignant melanomas. This group includes the following subgroups:

(a) Adrenocortical carcinomas
(b) Thyroid carcinomas
(c) Nasopharyngeal carcinomas
(d) Malignant melanomas
(e) Skin carcinomas
(f) Other unspecified carcinomas (carcinomas of salivary glands (1), colon and rectum (2), appendix (3), lung (4), thymus (5), breast (6), cervix uteri (7), bladder (8), eye (9), other specified sites (10), unspecified site (11))

A control is a patient from the GCCR who was free of a SPN at the point in time when the index case to whom they are matched had a their SPN.

3.2 Exposure

The exposure variable is data on chemotherapeutic treatment of the FPN (Appendix 5.1). Two variable types are relevant for the analysis:

- Chemotherapeutical substance classes, selected single chemotherapeutical agents (agents which 500 or more cases and controls received), and the complementary substances of the respective substance classes[2], see Appendix A. Binary variable (yes/no).
- Cumulative chemotherapeutic dose for substance classes, selected single substances, and the complementary substances of the respective substance classes[2]. Continuous variable (unit: mg/m^2 or U/m^2).

3.3 Covariates

Radiotherapy

- Radiation exposure as ordinal variable (at or near site of SPN in case of match group, any other radiation, no radiation)

Other therapy information

- SZT: Stem cell transplantation. Binary variable (yes/no or unknown).
- REZ_ja: Relapse of patient within latency period of index case, yes indicates that the patient may have been treated for his relapse. Binary variable (yes/no).

[2] For instance, the single substance cyclophosphamide would go with its complementary group 'alkylating agents excluding cyclophosphamide'. If a person received both cyclophosphamide and another alkylating agent, the binary variable for both variables would be "yes" and the dose for 'alkylating agents excluding cyclophosphamide' = alkylating agent dose – cyclophosphamide dose

3.4 Other variables

- Variables for description of data, such as demographic variables (age at diagnosis, sex) or diagnosis information (diagnosis, month and year of diagnosis), see Appendix 5.1.
- Organizational variables such as match group or diagnosis of case within a match group, see Appendix 5.2.

4 Statistical analysis

4.1 Datasets for analysis

Only cases and controls of the STATT-SCAR-study are included, which meet both of the following criteria:

a. case and control in a match group in which the case has a SPN diagnosis according to ICCC-3 XI
b. ITT therapy data of case and control available or ITT therapy data was expected in the STATT study

The analyses involving therapy data is carried out with a complete case dataset, i.e., a dataset that excludes cases and controls with no ITT data available.

4.2 Descriptive analysis

First, the availability of ITT data is described (available versus missing data). Since the main analysis is carried out with the complete dataset, further descriptive analyses are limited to cases and controls of the complete dataset if not otherwise specified. Characteristics of the study population are described separately for cases and controls.

4.2.1 Data sources and data availability

Table. Completeness of therapy data obtained for cases with ICCC-3 XI as SPN and their controls (Variable auswertbar = 1).

Patient	ITT data available	ITT data unavailable
Cases		
Controls		
Total		

Table. Overview of match groups in which case and controls have ITT data available: number of controls in a match group

Number of controls in a match group	Number of match groups
1	27 (9.9%)
2	86 (31.6%)
3	96 (35.3%)
4	63 (23.2%)
Total	272 (100%)

4.2.2 Cases and controls not analyzed

Cases and controls fulfilling the inclusion and exclusion criteria were not included into the analyses for two reasons:

a. they did not have ITT data available
b. they had ITT data available but they were a control in a match group in which the case had no ITT data available or they were a case in a match group, in which no ITT data was available for any of the controls

The baseline characteristics as well as the diagnoses for these cases and controls is compared to the characteristics of cases and controls included in the analyses.

Table. Baseline characteristics of cases and controls in the analysis and of those not in the analysis.

Characteristic	**Cases and controls in analysis N (%)**	**Cases and controls not in analysis N (%)**
Sex Male Female		
Age at diagnosis of FPN, years mean 0-4 5-9 10-14		
Period of Diagnosis of FPN Median year of diagnosis of FPN 1980-1989 1990-1999 2000-2009 2010-2014		
Vital status Alive Dead		
Period of diagnosis of SPN Median year of diagnosis of SPN 1980-1989 1990-1999 2000-2009 2010-2014		-
Latency (time between FPN and SPN), years mean <1 1-4 5-9 10-19 20-29 ≥30		-

Table. Diagnoses of FPNs in cases and controls in the analysis and of those not in the analysis.

Characteristic	**ICCC-3 group**	Cases and controls in analysis N (%)	Cases and controls not in analysis N (%)
Hematological malignancies	I-II		
I Leukaemias	I(a)-I(e)		
ALL	I(a)		
AML	I(b)		
MDS	I(d)		
II Lymphomas	II(a)-II(c)		
Hodgkin lymphomas	II(a)		
Non-Hodgkin lymphomas	II(b)		
Solid tumors	III-XII		
III Brain tumours	III(a)-III(e)		
Astrocytomas	III(b)		
Meningiomas	III(e)5		
IV Neuroblastoma and other peripheral nervous cell tumours	IV(a)-IV(b)		
V Retinoblastoma	V		
VI Renal tumours	VI(a)-VI(c)		
VII Hepatic tumours	VII(a)-VII(c)		
VIII Malignant bone tumours	VIII(a)-VIII(e)		
Osteosarcoma	VIII(a)		
Ewingsarcoma	VIII(c)		
IX Soft tissue and other extraosseous sarcomas	IX(a)-IX(e)		
X Germ cell tumours, trophoblastic tumours and neoplasms of gonads	X(a)-X(e)		
XI Other malignant epithelial neoplasms and malignant melanomas	XI(a)-XI(f)		
XII Other and unspecified malignant neoplasms	XII(a)-XII(b)		

Table. Diagnoses of SPNs of cases in the analysis and of those not in the analysis.

SPN diagnosis	**ICCC-3 group**	**Cases in analysis N**	**Cases not in analysis N**
Thyroid carcinomas	XI(b)		
Skin carcinomas	XI(e)0		
Carcinomas of salivary glands	XI(f)1		
Carcinomas of colon and rectum	XI(f)2		
Carcinomas of breast	XI(f)6		
Carcinomas of other specified areas	XI(f)10		
Malignant melanomas	XI(d)		
Other carcinomas			
Nasopharyngeal carcinomas	XI(c)11300		
Carcinomas of cervix uteri	XI(f) 7		
Carcinomas of bladder	XI(f) 8		
Adrenocortical carcinomas Carcinomas of appendix Carcinomas of lung Carcinomas of thymus Carcinomas of eye Carcinomas of unspecified site	nicht vorhanden: 11100 11603 11604 11605 11609 11611		

4.2.3 Baseline characteristics

Table. Baseline characteristics of cases and controls.

Characteristic	Cases N (%)	Controls N (%)
Sex Male Female		
Age at diagnosis of FPN, years mean 0-4 5-9 10-14		
Period of Diagnosis of FPN Median year of diagnosis of FPN 1980-1989 1990-1999 2000-2009 2010-2014		
Vital status Alive Dead		
Period of diagnosis of SPN Median year of diagnosis of SPN 1980-1989 1990-1999 2000-2009 2010-2014		-
Latency (time between FPN and SPN), years mean <1 1-4 5-9 10-19 20-29 ≥30		-

4.2.4 FPN and SPN diagnoses

Table. Diagnoses of FPNs in cases and controls according to ICCC-3.

Characteristic	**ICCC-3 group**	**FPN Cases N (%)**	**FPN Controls N (%)**
Hematological malignancies	I-II		
I Leukaemias	I(a)-I(e)		
ALL	I(a)		
AML	I(b)		
MDS	I(d)		
II Lymphomas	II(a)-II(c)		
Hodgkin lymphomas	II(a)		
Non-Hodgkin lymphomas	II(b)		
Solid tumors	III-XII		
III Brain tumours	III(a)-III(e)		
Astrocytomas	III(b)		
Meningiomas	III(e)5		
IV Neuroblastoma and other peripheral nervous cell tumours	IV(a)-IV(b)		
V Retinoblastoma	V		
VI Renal tumours	VI(a)-VI(c)		
VII Hepatic tumours	VII(a)-VII(c)		
VIII Malignant bone tumours	VIII(a)-VIII(e)		
Osteosarcoma	VIII(a)		
Ewingsarcoma	VIII(c)		
IX Soft tissue and other extraosseous sarcomas	IX(a)-IX(e)		
X Germ cell tumours, trophoblastic tumours and neoplasms of gonads	X(a)-X(e)		
XI Other malignant epithelial neoplasms and malignant melanomas	XI(a)-XI(f)		
XII Other and unspecified malignant neoplasms	XII(a)-XII(b)		

Table. Diagnoses of SPNs according to ICCC-3.

SPN diagnosis	**ICCC-3 group**	**N**	**%**
Thyroid carcinomas	XI(b)		
Skin carcinomas	XI(e)0		
Carcinomas of salivary glands	XI(f)1		
Carcinomas of colon and rectum	XI(f)2		
Carcinomas of breast	XI(f)6		
Carcinomas of other specified areas	XI(f)10		
Malignant melanomas	XI(d)		
Other carcinomas			
Nasopharyngeal carcinomas	XI(c)		
Carcinomas of cervix uteri	XI(f) 7		
Carcinomas of bladder	XI(f) 8		
Adrenocortical carcinomas Carcinomas of appendix Carcinomas of lung Carcinomas of thymus Carcinomas of eye Carcinomas of unspecified site	not available: 11100 11603 11604 11605 11609 11611		

4.2.5 Medical history/pre-existing conditions

Table. Medical history of patient and patient family.

Characteristic	**Cases N (%)**	**Controls N (%)**
relapse (REZ)		
yes		
no		
stem cell transplantation (SZT)		
yes		
no or unknown		

4.2.6 Exposure and covariate data

Table. Exposure and covariate information

Characteristic	Cases N (%)	Controls N (%)
Treatment of FPN Chemotherapy, radiotherapy No chemotherapy, radiotherapy Chemotherapy, no radiotherapy No chemo- or radiotherapy Missing values		
Number of chemotherapeutics a patient received mean 0 1-3 4-8 >9		
Radiotherapy exposure 0: no radiotherapy 1: imprecise radiation site; or for cases, radiotherapy not near the site of the SPN; or for controls, radiotherapy not near the site of the SPN in the index case of the match group 2: for cases, radiotherapy at or near the site of the SPN; for controls, radiotherapy at or near the site of the SPN in the index case of the match group		

Table. Doses of chemotherapeutic groups and of radiotherapy in cases and controls having received the treatment.

	Cases				Controls			
Group	**N**	**Mean dose [mg/m²] (IQR[1])**	**Minimum dose [mg/m²]**	**Maximum dose [mg/m²]**	**N**	**Mean dose [mg/m²] (IQR[1])**	**Minimum dose [mg/m²]**	**Maximum dose [mg/m²]**
alkylating agents	n	xy (x-y)	xy	xy				
anthracycline (antibiotic)								
antibiotic								

antimetabolite								
enzyme								
epipodophyllotoxine								
platinum derivate								
vinca alkaloid								
other		-	-	-		-	-	-
radiotherapy		Gy	Gy	Gy		Gy	Gy	Gy

IQR = interquartile range

Table. Doses of single chemotherapeutic agents in cases and controls having received the treatment

	Cases				Controls			
Agent listed in group	N	Mean dose [mg/m^2] (IQR[1])	Minimum dose [mg/m^2]	Maximum dose [mg/m^2]	N	Mean dose [mg/m^2] (IQR[1])	Minimum dose [mg/m^2]	Maximum dose [mg/m^2]
Alkylating agent								
Busulfan	n	xy (x-y)	xy	xy				
Cyclophosphamide								
Dacarbazine								
Ifosfamide								
Lomustine								
Melphalan								
Procarbazine								
Anthracycline (antibiotic)								
Daunorubicin								
Daunoxome								
Doxorubicin								
Epirubicin								
Idarubicin								
Mitoxantrone								
Antibiotic								
Actinomycin D (Dactinomycin)								
Bleomycin								

Antimetabolite								
Cladribine								
Cytarabine (Cytosine Arabinoside								
Fluorouracil								
Mercaptopurine								
Methotrexate								
Thioguanine								
Enzyme								
Asparaginase (L-Asparaginase)								
Coli Asparaginase								
PEG-L-Asparaginase								
Epipodophyllotoxine								
Etoposide (VP-16)								
Teniposid								
Platinum derivates								
Carboplatin								
Cisplatin								
Vinca alkaloids								
Vinblastine								
Vincristine								
Vindesine								
Other								
Amsacrine								
Dexamethasone								
Folinic Acid								
G-CSF								
Interferon ALPHA								
Other								
Prednisone								

IQR = interquartile range

4.3 Exploratory analyses, model selection

The dose-response relationship between therapy exposure and CSPN risk, i.e., being a case, is analyzed in an explorative manner. The association is modeled using conditional logistic regression. The dose-response relationship between exposure variable and outcome is determined based on the principle of fractional polynomials (FPs) with spike-at-zero (Lorenz et al., 2017, Royston and Sauerbrei, 2005, Royston et al., 2010). The exposure variables are the doses of each chemotherapeutic group or single agent; these variables have a spike at zero, i.e., a proportion of patients are not exposed and among the exposed patients, the variable is continuous (Lorenz et al., 2017).

The fractional polynomials approach allows to choose the best functional form for the relationship between a continuous predictor variable $x>0$ and an outcome variable (an odds ratio in the case of a logistic regression). For this, the predictor variable x is allowed to be transformed, rendering a first-degree fractional polynomial or FP1 function $\beta_1 x^p$. The power p for the transformation of x is chosen from a predefined set of 8 values with $p \in S = \{-2, -1, -0.5, 0, 0.5, 1, 2, 3\}$, where x^0 denotes log(x). A model with such a transformed predictor variable is called FP1 model and includes the constant term for linear regression models (Lorenz et al., 2017, Royston et al., 2010):

$H_1(x) = \beta_1 x^p$.

For linear regression models, the constant term β_0 (the intercept) is included. The FP1 model can be extended to the more flexible FP2 model

$H_2(x) = \beta_1 x^p + \beta_2 x^q$

with both p and $q \in S$. If $p = q$, the second transformation in the model is changed, so that

$H_2(x) = \beta_1 x^p + \beta_2 x^p \log(x)$ (Lorenz et al., 2017, Royston et al., 2010).

Eight different models are possible with an FP1 model, 36 with an FP2 model (Lorenz et al., 2017, Royston et al., 2010).

For the situation in which a proportion of patients had zero exposure, a binary spike-at-zero variable z can be introduced to the model, which takes the value 1 if $x = 0$ and 0 otherwise (Lorenz et al., 2017)):

$H_{2z}(x) = \beta_1 x^p + \beta_2 x^q + z$.

This model is called FP2+z model.

The procedure for choosing the best model for the data has two stages:

Stage 1:

a. The best FP2+z model for x is compared with the null model, i.e. a model without any predictor variables, at the chosen significance level α on 5 degrees of freedom (d.f.) to see if the predictor variable has any effect on the outcome variable at all. If there is no significant difference, the variable x has no effect at the α-level. If there is a significant difference, continue to b.
b. The best FP2+z model is tested against the default+z model at the chosen α-level on 3 df. The default model is often a linear model. If the test is not significant, the model chosen for stage 2 is the default+z model; if the test is significant, continue to c.
c. The best FP2+z model is tested against the best FP1+z model at the chosen α-level on 2 df. If the test is not significant, the model chosen for stage 2 is the FP1+z model; if the test is significant, the model chosen for stage 2 is the FP2+z model.

Stage 2:

d. The default component, the FP1 component, or the FP2 component from stage 1 is tested against the null model at the chosen α-level on 1 df, 2 df, or 4 df, respectively.
e. Z is tested against the null model at the chosen α-level on 1 df.
f. If both components from d. and e are significant, the final model contains both of them. If only one component from d. or e. is significant, the final model contains only that component.
   If none of the components from d. or e. is significant, the final model contains only the component with the smallest p-value.

The FP principle is used with a closed test procedure to make sure that the α-level is not being exceeded with each analysis (Royston, 2017, Lorenz et al., 2017, Royston et al., 2010).

For this thesis, the models are compared using the likelihood ratio test; I chose an untransformed model with spike at zero-variable as the default+z model. The alpha level is set to 0.10 due to the explorative character of the analyses.

The conditional logistic regression with FPs is carried out as univariable analysis for the cumulative dose of each of the 9 chemotherapeutic groups, for each single chemotherapeutic agents if at least 500 cases and controls had received it, and for each complementary group of the single substances (compare Chapter 3.2). This concerns the five single agents Cyclophosphamides, Cytarabine, Doxorubicin, Methotrexate, and Vincristine and the complementary groups 'alkylating agents without cyclophosphamide', 'anthracyclines without doxorubicin', 'antimetabolites without cytarabine', 'antimetabolites without methotrexate', 'antimetabolites without cytarabine or methotrexate', 'vinca alkaloids without vincristine'. An offset of 0.1 was added to the cumulative dose to avoid division by 0 for the transformed values and an error in the procedure. In addition, a univariable logistic regression is performed with each of the predictor variables radiotherapy (Chapter 2.2.1.3), relapse during latency period (Chapter 2.2.2.2), stem cell transplantation (Chapter 2.2.2.1).

To build the final multivariable model, a forward selection procedure is carried out:

a. For each substance (group) dose significant in FP logistic regression and each covariate, a regression model is calculated. If a substance had a functional form consisting of several elements (e.g. an FP2 model or an FP1+z model), a common p-value is reported. For the following step, if a single substance was selected by fp logistic regression and the substance group to which it belonged was selected as well, the variable is chosen with the smaller AIC (Akaike information criterion) estimator (ref. Akaike 1974).
b. The substance (groups) are entered into a multivariable model one by one as long as the AIC (Akaike information criterion) estimator becomes smaller, which indicates that the model is getting better (ref. Akaike 1974). If the substance (group) entered into the model has a p value >0.1 in the multivariable model upon entry, it is omitted from the model and the next substance (group) is entered.
c. The final model without covariates is the last model with a reduction in AIC or if no substance (groups) are left for entry into the model.
d. The covariates which were significant in univariable analysis (radiotherapy, relapse, stem cell transplantation) are entered to the model as long as the AIC estimator becomes smaller. If the covariate entered into the model has a p value >0.1 in the multivariable model upon entry, it is omitted from the model. The final multivariable model with covariates is the model which saw the last model improvement.

Odds ratios with a 90%-confidence interval (CI) are reported, and they are interpreted as risk ratios, as CSPNs are rare events (Rodrigues and Kirkwood, 1990). Dose-response relationships between selected chemotherapeutic groups and the risk for SPNs are illustrated with a line diagram.

Table. Results of fractional polynomial analysis.

Group	In/out of model*	Fractional polynomials	Univariable analysis OR (90% CI)	Multivariate analysis OR (90% CI)
alkylating agents				
anthracycline (antibiotic)				
antibiotic				
antimetabolite				
enzyme				
epipodophyllotoxine				
platinum derivate				
vinca alkaloid				
other				

* in multivariable analysis

4.4 Subgroup analyses

To test the robustness of the model selected in the explorative primary analysis, two subgroup analyses are carried out. The results are compared with respect to the models and the effect estimates.

a. Cases with a relapse in the latency time and controls with a relapse in the latency of their index case are excluded.
b. Patients with a stem cell transplantation or are excluded.

The reasons are that first, the treatment of the relapse and of the SCT is not known, introducing an error in the exposure. The patients with a relapse usually receive additional chemotherapy, and patients with SCT receive high doses of chemo- and radiotherapy during the transplantation process; not considering these doses may overestimate the CSPN risk by chemotherapy. Second, transplant patients do not only receive high doses of chemotherapy and radiation, some patients continue to take immunosuppressants indefinitely. As these can lead to an increased risk of cancer (Anisimov et al., 2010, Tallen and Yiallouros, 2004), this is a group with a special risk.

4.5 Software

The analyses are performed with the software SAS 9.4 and SAS University Edition 2.8 9.4 M6, Release: 3.8 (Basic Edition).

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5 Appendix

5.1 Appendix A: Base variables

Variable	Inhalt	Auspraegung_STATT	Bemerkungen
age	Alter bei Diagnose (Jahre)	0-14 Jahre	
agegroup			
alterintagen	Alter in Tagen bei Diagnose	Tage	
altj	Alter bei Diagnose der 1. Neoplasie in Jahren	berechnetes Alter in Jahren bei Diagnose	
altj_2	Alter bei Diagnose der 2. Neoplasie in Jahren	berechnetes Alter in Jahren bei Diagnose	
altm	Alter bei Diagnose in Monaten	berechnetes Alter in Monaten bei Diagnose	
carcinoma_diag	Diagnosen der Fälle nach ICCC-3 Gruppe XI	1 = 'Thyroid carcinomas ' 2 = 'Skin carcinomas ' 3 = 'Carcinomas of salivary gland 4 = 'Carcinomas of colon and rectum 5 = 'Carcinomas of breast ' 6 = 'Carcinomas of other specified areas 7 = 'Malignant melanomas ' 8 = 'Nasopharyngeal carcinomas 9 = 'Carcinomas of cervix uteri 10 = 'Carcinomas of bladder '	

Code_1	Körperregion des Auftretens des FPNs	0 = ungenau: Schlüssel , die sich nicht eindeutig zuordnen ließen 1 = Kopf: von der Linie des Unterkiefers bis zum Scheitel -> Aufgeteilt in „Schädel“ und „Gesicht/Hals“ 2 = Schädel: Hinterkopf, Bereich der Augen, oberhalb der Augen und Ohren 3 = Gesicht/Hals: Gesichtsschädel bis zu den Schultern 4 = Stamm: ungenau, Lokalisation etwa im Bereich von Thorax Abdomen bis zum Becken 5 = Thorax: Brustkorb, von den Schultern bis etwa zum Zwerchfell 6 = Abdomen: ungenau, Lokalisation unterhalb des Zwerchfells bis zum Beckenboden 7 = Oberes Abdomen: vom Zwerchfell bis zum Jejunum 8 = Unteres Abdomen: vom Ileum bis zum Beckenboden 9 = Obere Extremität: ungenau, Lokalisation Arme bis zur Schulter 10 = Arm: vom Schultergelenk bis zum Carpalgelenk 11 = Hand: vom Carpalgelenk bis zu den Fingerspitzen 12 = Untere Extremität: ungenau, Lokalisation Beine bis zur Hüfte 13 = Bein: vom Hüftgelenk bis zum Knöchel 14 = Fuß: vom Knöchel bis zu den Zehnspitzen 15 = Systemisch: Krankheiten, die den gesamten Körper betreffen	
Code_2	Körperregion des Auftretens des SPNs	s. Code_1	
Code_ICD_O3_1	Lokalisation des FPNs nach ICD-O3	3-stelliger Code und Bezeichnung	C.01 = C10
Code_ICD_O3_2	Lokalisation des SPNs nach ICD-O3	3-stelliger Code und Bezeichnung	C.01 = C10
dgdat	Diagnosedatum der 1. Neoplasie	01MMYYYY	Tag auf 01 gesetzt
dgdat_2	Diagnosedatum der 2. Neoplasie	01MMYYYY	Tag auf 01 gesetzt

dgtext	Diagnosetext	Klartext in Großbuchstaben	
diagnosis	Diagnose der FPN: Hauptgruppen nach ICCC-3, Übergruppe solide und systemische Neoplasien, häufige Untergruppen	1 = 'Hematological malignancies ' 2 = 'I Leukaemias ' 3 = 'ALL ' 4 = 'AML ' 5 = 'MDS ' 6 = 'II Lymphomas ' 7 = 'Hodgkin lymphomas ' 8 = 'Non-Hodgkin lymphomas ' 9 = 'Solid tumors ' 10 = 'III Brain tumours ' 11 = 'Astrocytomas ' 12 = 'Meningiomas ' 13 = 'IV Neuroblastoma and other peripheral nervous cell tumours ' 14 = 'V Retinoblastoma ' 15 = 'VI Renal tumours ' 16 = 'VII Hepatic tumours ' 17 = 'VIII Malignant bone tumours ' 18 = 'Osteosarcoma ' 19 = 'Ewingsarcoma ' 20 = 'IX Soft tissue and other extraosseous sarcomas ' 21 = 'X Germ cell tumours, trophoblastic tumours and neoplasms of gonads ' 22 = 'XI Other malignant epithelial neoplasms and malignant melanomas ' 23 = 'XII Other and unspecified malignant neoplasms ';	
erkrj	Jahr der Erkrankung der 1. Neoplasie	YYYY	8
erkrj_2	Jahr der Erkrankung der 2. Neoplasie	YYYY	

erkrj10	Jahrzehnt der Diagnose des FPN	1 = '1980-1989' 2 = '1990-1999' 3 = '2000-2009' 4 = '2010-2014'	
erkrj10_2	Jahrzehnt der Diagnose des SPN	s. erkrj10	
FAMBEL	familiäre Belastung	0 = keine Angabe 1 = nein 2 = ja	Erkrankungen im weitesten Sinne
gebdat	Geburtsdatum	01MMYYYY	
iccc3	IARC-Diagnoseklassifikation der 1. Neoplasie (ICCC-3: Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, Third Edition. Cancer 2005; 103(7):1457-67.)	ICCC 2005 (11-122) und DKKR-interner Code (991,992,994,995,996,997,999)	

ICCC3_10	Hauptdiagnosegruppe des FPN nach ICCC-3	1 = 'I Leukaemias, myeloproliferative and myelodysplastic diseases' 2 = 'II Lymphomas and reticuloendothelial neoplasms' 3 = 'III CNS and miscellaneous intracranial and intraspinal neoplasms' 4 = 'IV Neuroblastoma and ganglioneuroblastoma' 5 = 'V Retinoblastoma' 6 = 'VI Nephroblastoma and other nonepithelial renal tumors and renal carcinomas' 7 = 'VII hepatoblastoma and hepatic carcinomas' 8 = 'VIII Malignant bone tumours' 9 = 'IX Soft tissue and other extraosseous sarcomas' 10 ='X Germ cell tumors, trphoblastic tumours and neoplasms of gonads' 11 ='XI Adrenocortical, thyroid, nasopharyngeal carcinomas and malginant melanomas' 12 ='XII Other specified malignant tumors' ;
iccc3_2	IARC-Diagnoseklassifikation der 2. Neoplasie	ICCC 2005 (11-122) und DKKR-interner Code (991,992,994,995,996,997,999)
ICCC3_2_10	Hauptdiagnosegruppe des SPN nach ICCC-3	s. ICCC3_10
iccc3ext	IARC-Diagnoseklassifikation extended der 1. Neoplasie	1101 bis 12106
iccc3ext_2	IARC-Diagnoseklassifikation extended der 2. Neoplasie	1101 bis 12106
icd10	Diagnoseklassification	ICD10 (1993)
icdo3	histologische Tumorklassifikation des 1. Tumors	ICDO-3 morphologischer Code (2000)

icdo3_2	histologische Tumorklassifikation des 2. Tumors	ICDO-3 morphologischer Code (2000)	
latenz	Latenzzeit zwischen Diagnose des 1. und 2. Tumors	in Tagen	
lokal2	Tumorlokalisation der 1. Neoplasie	ICDO-3 Topographie DKKR-intern modifiziert	
lokal2_2	Tumorlokalisation der 2. Neoplasie	ICDO-3 Topographie DKKR-intern modifiziert	
lokal2_fall	Kennzeichnung aller Patienten, die auch Kontrolle sind mit der Tumorlokalisation ihres zugehörigen StudienFalls	ICDO-3 Topographie DKKR-intern modifiziert	
PREDISP	mögliche (genetische) Prädisposition für Krebs	0 = nein oder unbekannt 1 = ja	1 wenn eine der drei Variablen VORERKR, SYNDROME, FAMBEL ein ja haben
rez_latenz	Zeit zwischen FPN Diagnose und 1. Rezidiv, rez_latenz = rezdat-dgdat	in Tagen	hat Fehler, da Daten auf 1. Tag des Monats gesett wurden
rezdat	Datum des 1. Rezidivs	01MMYYYY	
sex	Geschlecht	0 = unbekannt 1 = männlich 2 = weiblich 9 = anonymisiert (vor 1995)	
SYNDROME	Syndrome ja/nein	0 = keine Angabe 1 = nein 2 = ja	

TOPO1	Seitenlokalisation des FPN	0 = keine Angabe 1 = rechts 2 = links 3 = beidseitig 4 = Systemerkrankung 5 = Mittellinie 9 = unbekannt	
TOPO2	Seitenlokalisation des SPN	s. TOPO2	
tot	Indikator für Sterbedatum	1 = nein (Vorbelegung) 2 = ja	
VORERKR	Vorerkrankung ja/nein	0 = keine Angabe 1 = nein 2 = ja	z.B. hereditäre Grunderkrankung, Organtransplantation

5.2 Appendix B: Organizational variables

Variable	Inhalt	Auspraegung_STATT	Bemerkungen
auswertbar	Fall o. Kontrolle auswertbar, d.h. es sind Daten für Fall und min. 1 Kontrolle da	1 = auswertbar	
case	Fall oder Kontrolle, Variable für logistische Regression	0 = Kontrolle 1 = Fall	
DISSID	Identitätsnummer für Fälle und Kontrollen	1 bis 1348	
fallnummer	**Matchingruppe (Fall und seine Kontrollen**)		
iccc3_fall	Kennzeichnung aller Patienten, die auch Kontrolle sind mit der IARC Diagnose ihres zugehörigen StudienFalls (bei Fällen iccc3 = iccc3_fall)	ICCC 2005 (11-122) und DKKR-interner Code (991,992,994,995,996,997,999)	
iccc3ext_fall	Kennzeichnung aller Patienten, die auch Kontrolle sind mit der Diagnose ihres zugehörigen StudienFalls (bei Fällen iccc3ext = iccc3ext_fall)		
icdo3_fall	Kennzeichnung aller Patienten, die auch Kontrolle sind mit der icdo3-Klassifikation ihres zugehörigen StudienFalls (bei Fällen icdo3 = icdo3_fall)		
ITT_daten_da	ITT-Daten sind vorhanden	. = nein 1 = ja	

latenz_fall	Latenzzeit zwischen Diagnose des 1. und 2. Tumors bei dem Fall innerhalb der Matchgruppe	in Tagen	
prioritaet	Priorität für die Therapiedatenerhebung	0 = Fall 1 = Kontrolle ohne Matching nach Erstdiagnose (2 pro Fall) 2 = Ersatzkontrolle ohne Matching nach Erstdiagnose (2 pro Fall) 3 = Kontrolle mit Matching nach Erstdiagnose (2 pro Fall) 4 = Ersatzkontrolle mit Matching nach Erstdiagnose (2 pro Fall)	
rez_ja	Indikator, ob Rezidivdatum innerhalb der Latenzzeit bei dem Fall innerhalb der Matchgruppe liegt	. = kein Rezidiv 0 = nein, Rezidivdatum außerhalb Latenzzeit 1 = ja	
zweitid	identisch mit Fallnummer		Variable umbenannt für fractional polynomial Analyse
scarid	ID in STATT-Studie		

5.3 Appendix C: Therapy variables

Variable	Inhalt	Auspraegung_STATT	Bemerkungen
cagent	Behandlung (Chemotherapeutikum oder anderes Medikament, Art der Bestrahlung)	Actinomycin D (Dactinomycin) Amsacrine (Acridinyl, Anisidid Asparaginase (L-asparaginase, Bleomycin Carboplatin (CBDCA, JM8, NSC 2 Cisplatin, (Cis-platinum, cis- Cladribine (CdA, 2-CdA, 2-chlo Coli Asparaginase Cyclophosphamide (Cyclo, CPA, Cytarabine (Cytosine Arabinosi Dacarbazine (DIC, Imidazole ca Daunorubicin (daunomycin, DNR, Daunoxome Dexamethasone Doxorubicin (Adriamycin, Hydro Epirubicin (4'-epi-doxorubicin Etoposide (VP-16) Folinic Acid (LV, calcium leuc G-CSF Idarubicin Ifosfamide Interferon ALPHA Lomustine Melphalan Mercaptopurine Methotrexate Mitoxantrone Other PEG-L-Asparaginase Prednisone Procarbazine SPIN-RAD TBI TUM-RAD	

		Teniposid Thioguanine Vinblastine Vincristine Vindesine ZNS-RAD
Chemo	Behandlung mit Chemotherapie oder anderen Medikamenten	0 = nein 1 = ja
Chemo_keine_Radio	Behandlung mit Chemotherapie oder andren Medikamenten aber ohne Radiotherapie	0 = nein 1 = ja
Chemo_und_Radio	Behandlung mit Chemo- und Radiotherapie und anderen Medikamenten	0 = nein 1 = ja
cunit_alkyl	Einheit Alykalanzien	mg/m^2
cunit_anthra	Einheit Anthracycline	mg/m^2
cunit_antibi	Einheit Antibiotika	mg/m^2
cunit_antimet	Einheit Antimetabolite	mg/m^2
cunit_enz	Einheit Enzyme (Asparaginase)	U/m^2
cunit_epipodo	Einheit Epipodophyllotoxine	mg/m^2
cunit_plat	Einheit Platinumderivate	mg/m^2
cunit_radio	Einheit Radiotherapie	mg/m^2
cunit_vinca	Einheit Vincaalkaloide	mg/m^2
cunit_cortico	Einheit Cortocosteroide	mg/m^2
exist_alkyl	Behandlung mit Alkylanzien	0 = nein 1 = ja
exist_anthra	Behandlung mit Anthracyclinen	0 = nein 1 = ja
exist_antibi	Behandlung mit Antibiotika	0 = nein 1 = ja

exist_antimet	Behandlung mit Antimetaboliten	0 = nein 1 = ja
exist_enz	Behandlung mit Enzymen (Asparaginase)	0 = nein 1 = ja
exist_epipodo	Behandlung mit Epipodophyllotoxinen	0 = nein 1 = ja
exist_other	Behandlung mit sonstigen Medikamenten	0 = nein 1 = ja
exist_plat	Behandlung mit Platinderivaten	0 = nein 1 = ja
exist_Radio	Behandlung mit Radiotherapie	0 = nein 1 = ja
exist_vinca	Behandlung mit Vincaalkaloiden	0 = nein 1 = ja
exist_cortico	Behandlung mit Corticosteroiden	0 = nein 1 = ja
exist_adr	Behandlung mit Doxorubicin	0 = nein 1 = ja
exist_arac	Behandlung mit Cytarabin	0 = nein 1 = ja
exist_cp	Behandlung mit Cyclophosphamid	0 = nein 1 = ja
exist_mtx	Behandlung mit Methotrexate	0 = nein 1 = ja
exist_vcr	Behandlung mit Vincristin	0 = nein 1 = ja
exist_al_ocp	Behandlung mit Alkylanzien außer Cyclophosphamiden	0 = nein 1 = ja

exist_an_oadr	Behandlung mit Anthracyclinen außer Doxorubicin	0 = nein 1 = ja
exist_am_oac	Behandlung mit Antimetaboliten außer Cyarabine	0 = nein 1 = ja
exist_am_om	Behandlung mit Antimetaboliten außer Methotrexate	0 = nein 1 = ja
exist_am_oacm	Behandlung mit Antimetaboliten außer Cytarabine oder Methotrexate	0 = nein 1 = ja
exist_vi_ovcr	Behandlung mit Vincaalkaloiden außer Vincristine	0 = nein 1 = ja
hsctdat	Datum der Stammzelltransplantation	01MMYYYY
hscttyp	Typ der Stammzelltransplantation	. = keine Angabe 1 = autolog 2 = allogen
kum_adr	kumulative Dosis Doxorubicin	
kum_alkyl	kumulative Dosis Alykalanzien	
kum_anthra	kumulative Dosis Anthracycline	
kum_antibi	kumulative Dosis Antibiotika	
kum_antimet	kumulative Dosis Antimetabolite	
kum_arac	kumulative Dosis Cytarabine	
kum_asp	kumulative Dosis Asparaginase	
kum_cp	kumulative Dosis Cyclophosphamide	
kum_enz	kumulative Dosis Enzyme (Asparaginase)	
kum_epipodo	kumulative Dosis Epipodophyllotoxine	
kum_merc	kumulative Dosis Mercaptopurine	
kum_mtx	kumulative Dosis Methotrexat	
kum_plat	kumulative Dosis Platinumderivate	
kum_pred	kumulative Dosis Prednisone	
kum_vcr	kumulative Dosis Vincristin	

kum_vinca	kumulative Dosis Vincaalkaloide	
kum_cortico	kumulative Dosis Corticosteroide	
kum_al_ocp	kumulative Dosis Alkylanzien außer Cyclophosphamiden	
kum_an_oadr	kumulative Dosis Anthracyclinen außer Doxorubicin	
kum_am_oac	kumulative Dosis Antimetaboliten außer Cyarabine	
kum_am_om	kumulative Dosis Antimetaboliten außer Methotrexate	
kum_am_oacm	kumulative Dosis Antimetaboliten außer Cytarabine oder Methotrexate	
kum_vi_ovcr	kumulative Dosis Vincaalkaloiden außer Vincristine	
Other	Behandlung mit anderer Therapie als Chemo- oder Radiotherapie	0 = nein 1 = ja
pagent	Behandlung kodiert, s. cagent	3 = Actinomycin D (Dactinomycin) 4 = Amsacrine (Acridinyl, Anisidid definiert: 5 = Cytarabine (Cytosine Arabinosi mg/m2 definiert: 5555 = Cytarabine mg age-adjusted 6 = Asparaginase (L-asparaginase, 9 = Coli Asparaginase 11 = PEG-L-Asparaginase 14 = Bleomycin 16 = Carboplatin (CBDCA, JM8, NSC 2 17 = Lomustine 18 = Cladribine (CdA, 2-CdA, 2-chlo 20 = Cyclophosphamide (Cyclo, CPA, 22 = Cisplatin, (Cis-platinum, cis- 23 = Dexamethasone 24 = Daunorubicin (daunomycin, DNR, 25 = Doxorubicin (Adriamycin, Hydro 26 = Dacarbazine (DIC, Imidazole ca 27 = Epirubicin (4'-epi-doxorubicin 30 = G-CSF 33 = Idarubicin 34 = Interferon ALPHA 36 = Ifosfamide 37 = Folinic Acid (LV, calcium leuc

		39 = Melphalan 42 = Mitoxantrone 43 = Mercaptopurine definiert: 44 = Methotrexate mg/m2 definiert: 44444 = Methotrexate mg age-adjusted 45 = Prednisone 46 = Procarbazine 49 = Thioguanine 51 = Vinblastine 52 = Vincristine 53 = Vindesine 54 = Teniposid 55 = Etoposide (VP-16) 56 = Daunoxome 999 = Other SPIN-RAD = SPIN-RAD TBI = TBI TUM-RAD = TUM-RAD ZNS-RAD = ZNS-RAD
Radio_keine_Chemo	Behandlung mit Radiotherapie aber ohne Chemotherapie	0 = nein 1 = ja
studnam1	Name der 1. Therapiestudie	Großschreibung
studnam2	Name der 2. Therapiestudie	Großschreibung
studnam3	Name der 3. Therapiestudie	Großschreibung
studnam4	Name der 4. Therapiestudie	Großschreibung (kein Patient mit 4. Studie in STATT-Menge)
SZT	Stammzelltransplantation	0 = nein oder unbekannt 1 = ja
tosnr1	Zuordnung des studnam1 zur tosnr1, die einem Studienleiter zugeordnet ist	vgl. Liste Zuordnung der Studienleiter und Studien 1 = Herr Prof. Schrappe 2 = Herr Prof. Horstmann 3 = Herr Prof. Reinhardt 4 = Herr Prof. Suttorp

		5 = Herr Dr. von Stackelberg 6 = Frau Prof. Niemeyer 7 = Herr Prof. Körholz 8 = Herr Prof. Körholz 9 = Herr Prof. Körholz 10 = Herr Prof. Wößmann 11 = Herr Prof. Klein 12 = Herr Prof. Rutkowski 13 = Herr Prof. Müller 14 = Herr Prof. Kramm 15 = Frau Dr. Gnekow 16 = Herr PD Dr. Kordes 17 = Frau Prof. Fleischhack 18 = Herr Prof. Simon 19 = Frau Dr. Temming 20 = Herr Prof. Graf 21 = Herr Prof. von Schweinitz 22 = Frau Prof. Dirksen 23 = Herr Prof. Bielack 24 = Frau Prof. Koscielniak 25 = Frau Dr. Calaminus 26 = Herr Prof. Dr. Vorwerk 27 = Herr Prof. Kontny 28 = Herr Prof. Frühwald 29 = Frau Dr. Strahm 30 = Herr Prof. Schneider 31 = Kontakt Herr Dr. Zimmermann 32 = DKKR 33 = Herr Prof. Minkov 34 = Prof. Mittler (em.), evtl. Rutkowski, der HIT-CHEM-West hat (Cl.Br.) 99 = kein Ansprechpartner
tosnr2	Zuordnung des studnam2 zur tosnr2, die einem Studienleiter zugeordnet ist	s. tosnr1
tosnr3	Zuordnung des studnam3 zur tosnr3, die einem Studienleiter zugeordnet ist	s. tosnr1

viv_cagent_act	Behandlung mit Actinomycin	Name des Medikaments = ja . = nein
viv_cagent_adr	Behandlung mit Doxorubicin	Name des Medikaments = ja . = nein
viv_cagent_amsa	Behandlung mit Amsacrine	Name des Medikaments = ja . = nein
viv_cagent_arac	Behandlung mit Cytarabine	Name des Medikaments = ja . = nein
viv_cagent_asp	Behandlung mit Asparaginase	Name des Medikaments = ja . = nein
viv_cagent_biop	Behandlung mit Biopsie	Name des Medikaments = ja . = nein
viv_cagent_ble	Behandlung mit Bleomycin	Name des Medikaments = ja . = nein
viv_cagent_car	Behandlung mit Carboplatin	Name des Medikaments = ja . = nein
viv_cagent_ccnu	Behandlung mit Lomustine	Name des Medikaments = ja . = nein
viv_cagent_clad	Behandlung mit Cladrine	Name des Medikaments = ja . = nein
viv_cagent_cp	Behandlung mit Cyclophamide	Name des Medikaments = ja . = nein
viv_cagent_daux	Behandlung mit Dauxonome	Name des Medikaments = ja . = nein
viv_cagent_ddp	Behandlung mit Cisplatin	Name des Medikaments = ja . = nein
viv_cagent_dex	Behandlung mit Dexamethasone	Name des Medikaments = ja . = nein

viv_cagent_dnr	Behandlung mit Daunorubicin	Name des Medikaments = ja . = nein
viv_cagent_dtic	Behandlung mit Dacarbazine	Name des Medikaments = ja . = nein
viv_cagent_epi	Behandlung mit Epirubicin	Name des Medikaments = ja . = nein
viv_cagent_fa	Behandlung mit Folinsäure	Name des Medikaments = ja . = nein
viv_cagent_g	Behandlung mit G-CSF	Name des Medikaments = ja . = nein
viv_cagent_ida	Behandlung mit Idarubicin	Name des Medikaments = ja . = nein
viv_cagent_ifo	Behandlung mit Ifosfamide	Name des Medikaments = ja . = nein
viv_cagent_inter	Behandlung mit Interferon ALPHA	Name des Medikaments = ja . = nein
viv_cagent_mel	Behandlung mit Melphalan	Name des Medikaments = ja . = nein
viv_cagent_merc	Behandlung mit Mercaptopurine	Name des Medikaments = ja . = nein
viv_cagent_mito	Behandlung mit Mitoxantrone	Name des Medikaments = ja . = nein
viv_cagent_mtx	Behandlung mit Methotrexate	Name des Medikaments = ja . = nein
viv_cagent_oth	Behandlung mit anderem Medikament	Other = ja . = nein
viv_cagent_pred	Behandlung mit Prednisone	Name des Medikaments = ja . = nein

viv_cagent_pro	Behandlung mit Procarbazine	Name des Medikaments = ja . = nein
viv_cagent_spin	Bestrahlung des Spinalkanals	SPIN = ja . = nein
viv_cagent_tbi	Ganzkörperbestrahlung (total body irradiation)	TBI = ja . = nein
viv_cagent_thio	Behandlung mit Thioguanine	Name des Medikaments = ja . = nein
viv_cagent_tum	Tumorbestrahlung	TUM = ja . = nein
viv_cagent_vcr	Behandlung mit Vincristine	Name des Medikaments = ja . = nein
viv_cagent_vds	Behandlung mit Vindesine	Name des Medikaments = ja . = nein
viv_cagent_vin	Behandlung mit Vinblastine	Name des Medikaments = ja . = nein
viv_cagent_vm26	Behandlung mit Teniposid	Name des Medikaments = ja . = nein
viv_cagent_vp16	Behandlung mit Etoposide	Name des Medikaments = ja . = nein
viv_cagent_zns	Bestrahlung des Zentralnervensystems (ZNS)	ZNS = ja . = nein
viv_cunit_act	Einheit für Actinomycin	mg/m^2
viv_cunit_adr	Einheit für Doxorubicin	mg/m^2
viv_cunit_amsa	Einheit für Amsacrine	mg/m^2
viv_cunit_arac	Einheit für Cytarabine	mg/m^2
viv_cunit_asp	Einheit für Asparaginase	U/m^2
viv_cunit_ble	Einheit für Bleomycin	mg/m^2

viv_cunit_car	Einheit für Carboplatin	mg/m^2
viv_cunit_ccnu	Einheit für Lomustine	mg/m^2
viv_cunit_clad	Einheit für Cladrine	mg/m^2
viv_cunit_cp	Einheit für Cyclophamide	mg/m^2
viv_cunit_daux	Einheit für Dauxonome	mg/m^2
viv_cunit_ddp	Einheit für Cisplatin	mg/m^2
viv_cunit_dex	Einheit für Dexamethasone	mg/m^2
viv_cunit_dnr	Einheit für Daunorubicin	mg/m^2
viv_cunit_dtic	Einheit für Dacarbazine	mg/m^2
viv_cunit_epi	Einheit für Epirubicin	mg/m^2
viv_cunit_fa	Einheit für Folinsäure	mg/m^2
viv_cunit_g	Einheit für G-CSF	mg/m^2
viv_cunit_ida	Einheit für Idarubicin	mg/m^2
viv_cunit_ifo	Einheit für Ifosfamide	mg/m^2
viv_cunit_inter	Einheit für Interferon ALPHA	mg/m^2
viv_cunit_mel	Einheit für Melphalan	mg/m^2
viv_cunit_merc	Einheit für Mercaptopurine	mg/m^2
viv_cunit_mito	Einheit für Mitoxantrone	mg/m^2
viv_cunit_mtx	Einheit für Methotrexate	mg/m^2
viv_cunit_oth	Einheit für Other	mg/m^2
viv_cunit_pred	Einheit für Prednisone	mg/m^2
viv_cunit_pro	Einheit für Procarbazine	mg/m^2
viv_cunit_spin	Einheit für Bestrahlung des Spinalkanals in Gray	Gy
viv_cunit_tbi	Einheit für Ganzkörperbestrahlung in Gray	Gy
viv_cunit_thio	Einheit für Thioguanine	mg/m^2
viv_cunit_tum	Einheit für Bestrahlung des Tumors in Gray	Gy

viv_cunit_vcr	Einheit für Vincristine	mg/m²	
viv_cunit_vds	Einheit für Vindesine	mg/m²	
viv_cunit_vin	Einheit für Vinblastine	mg/m²	
viv_cunit_vm26	Einheit für Teniposid	mg/m²	
viv_cunit_vp16	Einheit für Etoposide	mg/m²	
viv_cunit_zns	Einheit für Bestrahlung des ZNS Gray	Gy	
viv_cunit2_act	Einheit für Actinomycin bei Patienten mit zwei Dosisangaben	mg/m²	vgl. kum_act
viv_cunit2_arac	Einheit für Cytarabine bei Patienten mit zwei Dosisangaben	mg/m²	vgl. kum_arac
viv_cunit2_asp	Einheit für Asparaginase bei Patienten mit zwei Dosisangaben	U/m²	vgl. kum_asp
viv_cunit2_cp	Einheit für Cyclophamide bei Patienten mit zwei Dosisangaben	mg/m²	vgl. kum_cp
viv_cunit2_mtx	Einheit für Methotrexate bei Patienten mit zwei Dosisangaben	mg/m²	vgl. kum_mtx
viv_cunit2_pred	Einheit für Prednisone bei Patienten mit zwei Dosisangaben	mg/m²	
viv_cunit3_arac	Einheit für Cytarabine bei Patienten mit drei Dosisangaben	mg/m²	vgl. kum_arac
viv_cunit3_mtx	Einheit für Methotrexate bei Patienten mit drei Dosisangaben	mg/m²	vgl. kum_mtx
viv_group	Therapiearm/-gruppe in Studienprotokoll		
viv_kum_act	kumulative Dosis für Actinomycin	mg/m²	
viv_kum_adr	kumulative Dosis für Doxorubicin	mg/m²	
viv_kum_amsa	kumulative Dosis für Amsacrine	mg/m²	
viv_kum_arac	kumulative Dosis für Cytarabine	mg/m²	
viv_kum_asp	kumulative Dosis für Asparaginase	mg/m²	
viv_kum_biop	kumulative Dosis für biopsy	mg/m²	
viv_kum_ble	kumulative Dosis für Bleomycin	mg/m²	

viv_kum_car	kumulative Dosis für Carboplatin	mg/m²
viv_kum_ccnu	kumulative Dosis für Lomustine	mg/m²
viv_kum_clad	kumulative Dosis für Cladrine	mg/m²
viv_kum_cp	kumulative Dosis für Cyclophamide	mg/m²
viv_kum_daux	kumulative Dosis für Dauxonome	mg/m²
viv_kum_ddp	kumulative Dosis für Cisplatin	mg/m²
viv_kum_dex	kumulative Dosis für Dexamethasone	mg/m²
viv_kum_dnr	kumulative Dosis für Daunorubicin	mg/m²
viv_kum_dtic	kumulative Dosis für Dacarbazine	mg/m²
viv_kum_epi	kumulative Dosis für Epirubicin	mg/m²
viv_kum_fa	kumulative Dosis für Folinsäure	mg/m²
viv_kum_g	kumulative Dosis für G-CSF	mg/m²
viv_kum_ida	kumulative Dosis für Idarubicin	mg/m²
viv_kum_ifo	kumulative Dosis für Ifosfamide	mg/m²
viv_kum_inter	kumulative Dosis für Interferon ALPHA	mg/m²
viv_kum_mel	kumulative Dosis für Melphalan	mg/m²
viv_kum_merc	kumulative Dosis für Mercaptopurine	mg/m²
viv_kum_mito	kumulative Dosis für Mitoxantrone	mg/m²
viv_kum_mtx	kumulative Dosis für Methotrexate	mg/m²
viv_kum_oth	kumulative Dosis für Other	mg/m²
viv_kum_pred	kumulative Dosis für Prednisone	mg/m²
viv_kum_pro	kumulative Dosis für Procarbazine	mg/m²
viv_kum_spin	kumulative Dosis für Bestrahlung Spinalkanal	Gy
viv_kum_tbi	kumulative Dosis für Ganzkörperbestrahlung	Gy
viv_kum_thio	kumulative Dosis für Thioguanine	mg/m²
viv_kum_tum	kumulative Dosis für Tumorbestrahlung	Gy

viv_kum_vcr	kumulative Dosis für Vincristine	mg/m²	
viv_kum_vds	kumulative Dosis für Vindesine	mg/m²	
viv_kum_vin	kumulative Dosis für Vinblastine	mg/m²	
viv_kum_vm26	kumulative Dosis für Teniposid	mg/m²	
viv_kum_vp16	kumulative Dosis für Etoposide	mg/m²	
viv_kum_zns	kumulative Dosis für ZNS-Bestrahlung	Gy	
viv_kum2_act	kumulative Dosis für Actinomycin bei Patienten mit zwei Dosisangaben	mg/m²	vgl. kum_act
viv_kum2_arac	kumulative Dosis für Cytarabine bei Patienten mit zwei Dosisangaben	mg/m²	vgl. kum_arac
viv_kum2_asp	kumulative Dosis für Asparaginase bei Patienten mit zwei Dosisangaben	mg/m²	vgl. kum_asp
viv_kum2_cp	kumulative Dosis für Cyclophamide bei Patienten mit zwei Dosisangaben	mg/m²	vgl. kum_cp
viv_kum2_mtx	kumulative Dosis für Methotrexate bei Patienten mit zwei Dosisangaben	mg/m²	vgl. kum_mtx
viv_kum2_pred	kumulative Dosis für Prednisone bei Patienten mit zwei Dosisangaben	mg/m²	
viv_kum3_arac	kumulative Dosis für Cytarabine bei Patienten mit drei Dosisangaben	mg/m²	vgl. kum_arac
viv_kum3_mtx	kumulative Dosis für Methotrexate bei Patienten mit drei Dosisangaben	mg/m²	vgl. kum_mtx
radio	Radiotherapie-Exposition	2 = for cases, radiotherapy at or near the site of the SPN; for controls, radiotherapy at or near the site of the SPN in the index case of the match group 1 = imprecise radiation site; or for cases, radiotherapy not near the site of the SPN; or for controls, radiotherapy not near the site of the SPN in the index	

	case of the match group 0 = no radiotherapy

Danksagung

Aus Datenschutzgründen in der elektronischen Version gelöscht.

Tabellarischer Lebenslauf

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