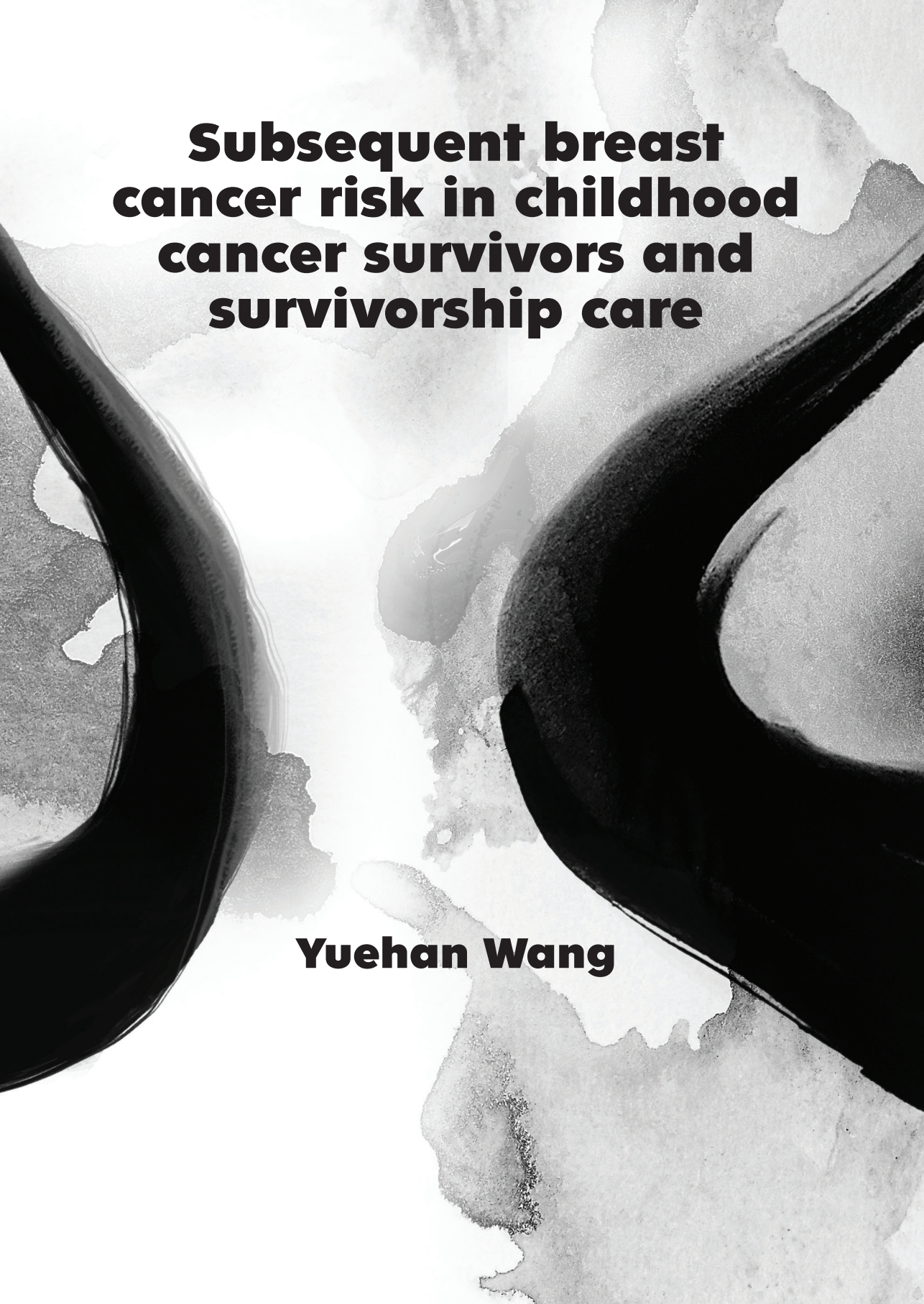
Subsequent breast cancer risk in childhood cancer survivors and survivorship care



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Where there's a will, there's a way

-- Ancient Chinese proverb

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CHAPTER 1

Introduction and thesis outline

Introduction

Childhood cancer includes malignancies diagnosed in children and/or adolescents, with defined age ranges from birth to an age of 15 to 21 years, depending on country (1-4). Cancer among children is much less common than among adults, and only represents approximately 1% of overall cancer diagnoses (5). Childhood cancer consists of many different types of cancer that can appear anywhere in the body. The most common types, which vary in different regions, are leukemia, lymphoma, and central nervous system and brain tumors (6). The diagnosis and treatment of a severe disease at such a young age intensely affects the lives of their parents, siblings, family, and the patients themselves in the long-term.

It is estimated that 400,000 children or adolescents develop cancer annually (6), of whom approximately 90% live in low-income and middle-income countries (7), where the cure rate of childhood cancer is still relatively low, between 10-50% (8). This low cure rate is caused by poverty, coexisting chronic health conditions (e.g., malnutrition and chronic infections), and lack of resources for appropriate cancer care and control. The difficulties in providing timely diagnoses for childhood cancer have also resulted indirectly in negative outcomes (9). Therefore, improving survival for children with cancer is a greater-priority in low- and middle-income countries than in high-income countries (10).

In contrast, childhood cancer survival rates have improved remarkably in resource-rich countries in recent decades due to improvements in treatment and supportive care. The five-year survival rate of childhood cancer has reached over 80% in regions with access to methods of early diagnosis, advanced treatment, and comprehensive care support (11, 12). Although childhood cancer survival rates have improved, bridging the gap to reach 100% survival and curing every child with cancer will always be the goal of pediatric oncology. Along with "beating" childhood cancer completely, improved treatments and outcomes/survival rates in resource-rich countries have also brought the factors that might affect the quality of life in the long-term into focus.

Late effects of childhood cancer

Generally, the treatments for childhood cancer include surgery, radiotherapy, and chemotherapy, depending on cancer type, cancer stage, diagnosis age, etc. Improved treatments have contributed drastically to better survival rates of childhood cancer. However, together with improved cure rates, some treatments can also cause other health conditions and/or damage healthy tissue in the body in the short- or long-term. The common short-term effects of the treatment that

may include, among others, pain, nausea, hair loss, loss of appetite, and tiredness, emerge during and soon after receiving treatments. The effects of the treatment that occur a relatively long time after the conclusion of cancer treatment are referred to as late effects, and may have a life-long impact on survivors not only physically but also mentally. The risks of these chronic health conditions, including subsequent tumors, cardiotoxicity, psychological effects, etc. vary in association with the cancer type and specific treatments administered, and other patient characteristics independent of the prior disease (13). The life expectancy and quality of life of long-term survivors can be compromised by long-term complications of treatments (14). About one fourth of late effects are severe or life-threatening conditions, which is approximately eight times more frequent than among their siblings who were not diagnosed with cancer (15). Also, late effects of treatment can cause a variety of diseases, signs, and symptoms (16, 17), which may drastically lower quality of life.

Nevertheless, the changes in childhood cancer therapy during the past decades (e.g., dose reduction of radiotherapy, adaptations to highly toxic chemotherapy regimens), as well as follow-up care for survivors of childhood and adolescent malignancies, have not only improved survival but also reduced treatment-related late effects (18). Survivors who were diagnosed and treated more recently are more likely to have a reduced late mortality, due to the strategy of reduced radiation doses and fields and changes in chemotherapy regimens (18-20). Accordingly, identifying the risk factors for adverse events after childhood cancer and gaining insight into factors potentially amenable to change the screening recommendations or the treatment protocol can improve survivors' quality of life.

Subsequent malignant neoplasms (SMNs)

The occurrence of SMNs following childhood cancer can be particularly devastating to the individual patient. With more patients surviving their childhood cancer and entering their 40s or even 50s and 60s, an increasing number of survivors are at risk of developing SMNs as the general population is also experiencing elevated risks of developing cancer (16). Studies mostly in North America and Europe have extensively investigated the risk of SMNs in childhood cancer survivors. Survivors have approximately 1.5- to 7-times increased risk of developing SMNs, depending on their primary cancer type and, accordingly, the treatments they have received, compared with the general population (21). The divergent risks of development of SMNs accross studies are caused by the heterogeneity of treatment exposure by cancer type, treatment era, as well as, attained age and follow-up, and country. SMNs are also one of the leading late effects causing death among survivors (19, 22). Therefore, evolving treatment regimens to improve the survival and

life expectancy without compromising the long-term quality of life, is of great significance. Additionally, the following aspects should also be addressed to achieve optimal quality of life for survivors: summarizing the currently available evidence to determine whether or not it is in favor of supporting active surveillance of asymptomatic individuals from the point of view of cost-effectiveness; establishing SMNs surveillance guidelines that use proper methods for careful evaluation of all relevant aspects of screenings and informed evidence-based recommendations to define the specific screening criteria for survivors and to determine the screening frequencies; screening survivors at the proper time with appropriate methods to allow both survivors and their healthcare providers to optimize care (23).

Subsequent breast cancer (SBC)

SBC represents one of the most common SMNs among survivors of pediatric cancer, after basal cell carcinoma (24), and is a commonly recognized late adverse event in female survivors (25). Breast cancer-specific mortality in survivors was about 1.3-times higher than in the general female population (hazard ratios (HR) 1.3, 95% confidence interval (CI) 0.9-2.0) (26). Although the risk of breast cancer increases in the general population with age, survivors still have a higher risk of developing breast cancer even after the age 40 (standardized incidence ratio (SIR) 5.5; 95% CI, 4.5-6.7) (27). It is of great importance for survivors and their healthcare providers to be aware that they are at a higher risk of developing SBC due to treatment they have received. Consequently, identifying risk factors for SBC development is warranted. Several studies have investigated the risk factors of SBC development (21), as alluded to in more detail below.

SBC risk factor: Radiation exposure

Treatment with chest-directed radiation is one of the most significant risk factors for breast cancer (28-30). Dose-response associations between chest radiotherapy dose and breast cancer risk were well examined in studies among women exposed to diagnostic or therapeutic radiation, or among atomic bomb survivors (28-31). Note that in most of the studies investigating the effect of radiation and radiation doses to the breast are based on absorbed radiation dose. For childhood cancer survivors, strong evidence indicated that women who had ≥10 Gray (Gy) chest radiotherapy are at a concerning increased risk of developing SBC (32). Chest radiation fields and volumes also affect the risk of developing SBC conjointly with chest radiation dose. The Dutch Hodgkin Late Effects cohort study (DHL) examined the effect of radiation volumes on SBC risk in Hodgkin lymphoma survivors, showing that small radiation volume appears to decrease the SBC risk after Hodgkin lymphoma (33). The Childhood Cancer Survivor Study

(CCSS) confirmed this finding, and further, demonstrated that women treated with lower dose radiotherapy to the whole volume of breast tissue had a greater risk of SBC than women treated with high dose radiotherapy exposures to only part of the breast tissue (whole lung irradiation, median delivered dose 14 Gy, range 2-20 Gy; with SIR 43.6, 95% CI 27.2-70.3 vs. mantle irradiation, median delivered dose 40 Gy, range 5-54 Gy; with SIR 24.2, 95% CI 20.7-28.3) (34). Furthermore, the timing of radiation exposure also affects the SBC risk in survivors. Radiation exposure around puberty is associated with increased SBC risk (35, 36), which was also confirmed by a study indicating that the strongest association between SBC and chest radiotherapy was observed near the time of menarche (37). The explanation behind this observation could presumably relate to the damage caused by radiotherapy, especially when cells have high division rates during breast development. Moreover, studies with an extended follow-up indicated that lower age at menopause reduced the risk of SBC in survivors (37-39). In addition, reduced SBC risk was observed in survivors with ≥5 Gy ovarian radiotherapy (28), which effectively stops ovarian function. Awareness of the risk of SBC associated with prior radiation treatments is important to both physicians and survivors. Recently, a breast cancer risk prediction model has been developed and validated to estimate the personalized risk of breast cancer for female childhood cancer survivors who treated with chest radiation incorporating treatment-related factors, family history, and reproductive factors (40).

SBC risk factor: Chemotherapy exposure

Moreover, recent work from various groups provides compelling evidence to suggest that certain chemotherapeutic regimens and/or agents may also increase the risk for SBC (4, 31, 41). A CCSS investigation showed that female survivors without any radiotherapy exposure to the chest had a 4-fold increase in breast cancer risk compared to the general population at a similar age (SIR 4.0, 95% CI 3.0-5.3) (41). In the Dutch Long-term Effects After Childhood Cancer Study (DCCSS LATER), increasing cumulative doxorubicin dose was associated with an increased risk of SBC, with HRs of 1.1 (95% CI 0.4-2.9), 2.6 (95% CI 1.1-6.5), and 5.8 (95% CI 2.7-12.5) for ≤270, 271-443, and >443 mg/m^2 doxorubicin, respectively (P_{trend}<0.001) (4). Both the CCSS study and the DCCSS LATER study suggested that there might be interaction between doxorubicin exposure and genetic predisposition, as the effects of doxorubicin were mainly present in childhood cancer types associated with Li-Fraumeni Syndrome (4, 41). However, a study from St. Jude Lifetime Cohort Study (SJLIFE) using whole genome sequencing demonstrated that an association between anthracyclines and SBC was still present in multivariable regression models excluding survivors with pathogenic or likely pathogenic mutations known to be associated with breast cancer in the general population (42). Furthermore,

a study within the CCSS population investigated the interaction between radiotherapy exposure to the chest and anthracycline treatment on SBC risk in survivors (31). The results indicated that the joint effects between chest radiotherapy exposure and anthracyclines were greater than the sum of the individual effects, consistent with an additive interaction (31). However, the effects of alkylating agents on SBC in childhood cancer survivors are not yet clear and may differ according to whether the survivors had chest radiotherapy (32). Alkylating agents seem to reduce risk of SBC in survivors treated with high-dose chest radiotherapy, because of ovarian damage. For survivors treated without chest radiotherapy, one study found a dose-dependent increased risk of SBC for alkylating agents (41), whereas several other studies did not find such effects (32).

SBC risk in male survivors

Most studies on SBC risk focus on female breast cancer; however, males are also at risk of breast cancer. Unlike female breast cancer, male breast cancer is much rarer, as it only accounts for approximately 0.5-1% of reported breast cancer cases in the general population (43). Compared to female breast cancer, male breast cancer tends to be diagnosed at a later stage, which may be due to the low levels of awareness of breast cancer among males. Due to the rarity of male breast cancer, information on subsequent male breast cancer after childhood cancer is limited. Only one study focused on subsequent male breast cancer in childhood cancer survivors particularly (44). In this study, four out of 3,893 male survivors developed breast cancer. All four survivors who developed male breast cancer had a history of radiation therapy.

Recommendations for breast cancer surveillance

Clinical practice guidelines for health providers have been developed to promote optimal health-related outcomes by screening survivors (45, 46). In 2010, the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) was established (https://www.ighg.org/) to harmonize the guidelines available worldwide according to a common methodology (23). In 2012, the IGHG formulated recommendations for breast cancer surveillance among high-risk groups based on the available literature (47), to which an update was recently published (32). In the latest version, strong recommendations have been formed by the IGHG for female survivors who were treated with ≥10 Gy chest radiation to perform mammography and breast exams at minimum annually up to age 60 years, based on substantial evidence (32). As part of the harmonization methodology (23), the expert group identified gaps in knowledge by specifying clinical questions for which empirical evidence was deemed insufficient to affect

or alter recommendations for clinical practice (32, 47). Despite the considerable size of childhood cancer survivor cohorts in various countries, they are considered too small to provide sufficient statistical power for these specific clinical questions. With regard to risk of SBC after anthracycline treatment, there was inconsistent evidence on dose thresholds for determining which survivors are at moderate or high risk. Furthermore, there was little information on the joint effects of anthracyclines and chest radiotherapy.

Pooled database

To address some of these questions, we established the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer to conduct individual patient data (IPD) analyses to initially address knowledge gaps regarding SBC in female survivors. Different from meta-analyses, IPD analysis involves the creation of a pooled cohort, comprising all eligible cohorts, with individual patient observations. Subsequently, the pooled cohort facilitates new analyses addressing current and future questions using the dataset available, rather than pooling published risk estimates only. Furthermore, all relevant covariates can be incorporated in a uniform manner across cohorts and differences between studies can be taken into account analytically.

Cohorts of female childhood cancer survivors meeting the following criteria were eligible to be included in the pooled study population: a primary cancer diagnosis at <21 years of age, survival ≥5 years from diagnosis, follow-up data on presence and type of subsequent neoplasms, as well as individual detailed accounts of radiotherapy and chemotherapy treatment available for the majority of cohort members. The data from seven cohorts that satisfied these criteria are included in our pooled study, three cohorts from North America and four from Europe. The cohorts from North America include the CCSS (2, 48), the SJLIFE (49, 50), and the US National Wilms' Tumor Study Group (NWTSG) (51, 52). The European cohorts consist of the DCCSS LATER (4, 53), the French Childhood Cancer Survivor Study (FCCSS) (54, 55), the Swiss Childhood Cancer Survivor Study (SCCSS) (3, 56), and the DHL (33, 57, 58). The included multi-institutional study groups represent long-standing and well-established research infrastructures to study health and well-being among childhood cancer survivors.

The consortium collaboration and structure can provide a robust source of information for identifying other knowledge gaps, including other subsequent malignancies. The established pipeline can be readily expanded to a larger cohort of childhood cancer survivors, including both female and male survivors.

Global pandemic period

In 2020, COVID-19 swept across the globe abruptly. The clinical presentation of COVID-19 ranges from asymptomatic to life-threatening infection requiring hospitalization and critical care (59). Emerging evidence in the general population indicates that individuals with comorbidities such as cardiopulmonary disease, diabetes and obesity, or those with advanced age have an increased risk of severe infection and death (60-63). Given that childhood cancer survivors are more vulnerable to chronic comorbidities than the general population, and often at a younger age, this raises concern that survivors may be at increased risk for severe COVID-19. There is very little known about the incidence of COVID-19 and its clinical course in childhood cancer survivors or whether preventive measures are warranted above and beyond those recommended for the general population. Therefore, we organized an international working group within the IGHG to establish a COVID-19 recommendation for childhood cancer survivors worldwide at the onset of the pandemic to be used as the international guide during this unexpected and unique period.

Outline of this thesis

The aims of this thesis are to: (1) establish an International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer and investigate the risk of and risk factors for female SBC within this consortium (**Chapters 2 & 3**); (2) examine the SBC risk in male survivors by conducting both a systematic review and data analyses (**Chapter 4**); (3) establish a statement to guide healthcare providers, long-term follow-up clinics, and childhood cancer survivors about how a history of cancer may affect the course of COVID-19 during the pandemic period (**Chapter 5**).

Chapter 2 addresses the methodology and characteristics of the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer. The consortium focuses on the following three initial objectives to: (1) explore the effects of prescribed radiation doses and radiation fields, as a proxy for exposed tissue volume, on the risk of SBC; (2) examine the role of anthracyclines and the contributions of individual anthracyclines drugs to the risk of SBC; (3) evaluate whether relative and absolute excess risks of SBC remain increased across the lifespan, especially after age 50.

In **Chapter 3**, I evaluate the dose-dependent effects of individual anthracycline agents on breast cancer development in survivors using the pooled data of our International Consortium. Furthermore, I analyze the interactions of individual

anthracycline agents with other clinical factors in developing SBC. These results may inform future breast cancer surveillance guidelines for healthcare providers and survivors.

In **Chapter 4**, I conduct both a systematic review and analysis in a large Pan-European cohort on male breast cancer risk in five-year childhood cancer survivors. In the systematic review, I summarize the existing evidence on subsequent male breast cancer in childhood cancer survivors. Furthermore, I do analyses in the PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup) cohort to investigate the risk of male breast cancer among five-year male survivors, and examine the clinical characteristics and survival of subsequent male breast cancer cases.

In **Chapter 5**, I organize an international working group within the IGHG to (1) summarize existing evidence and worldwide recommendations regarding relevant factors and conditions associated with risk for a severe course of COVID-19 and (2) develop a consensus statement to provide guidance for health care providers and childhood cancer survivors regarding COVID-19.

In **Chapter 6**, I interpret the findings and compare them with the results of other studies. The implications, strengths and limitations, and future perspectives are also discussed. The main findings and conclusion are summarized in **Chapter 6 & 7.**

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CHAPTER 2

Cohort Profile: Risk and risk factors for female breast cancer after treatment for childhood and adolescent cancer: an internationally pooled cohort

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Abstract

Purpose: The International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer was established in 2018 to address gaps in knowledge of risk and risk factors for breast cancer subsequent to childhood/adolescent cancer by pooling individual patient data from seven cohorts. Initially, the pooled cohort will focus on three clinically relevant questions regarding treatment-related subsequent breast cancer risk in female survivors, which are the risk related to low-dose radiotherapy exposure to the chest, specific chemotherapy agents, and attained age.

Participants: The consortium database includes pooled data on 21,892 female survivors from seven cohorts in North America and Europe with a primary cancer diagnosis at <21 years of age, and survival ≥5 years from diagnosis.

Findings to date: This is a newly established pooled study. The cohort profile summarized the data collected from each included cohort, including childhood cancer diagnosis information and treatment details (i.e., radiotherapy fields and cumulative doses, and chemotherapy agents and cumulative doses for each agent). Included cohorts' follow-up started 1951-1981 and ended 2013-2021, respectively, for a median follow-up duration of 24.3 (IQR 18.0-32.8) years since primary cancer diagnosis. The median age at primary cancer diagnosis was 5.4 (IQR 2.5-11.9) years. And the median attained age at last follow-up was 32.2 (IQR 24.0-40.4) years. In all, 4,240 (19.4%) survivors were treated with radiotherapy to the chest, and 9,308 (42.5%) with anthracyclines. At the end of the follow-up, 835 females developed a first subsequent breast cancer, including 635 invasive breast cancer only, 184 carcinomas in situ only (172 ductal carcinomas in situ and 12 lobular carcinomas in situ), and 16 with both an invasive and in situ diagnosis at the same moment. The cumulative incidences of subsequent breast cancer (both invasive and in situ) 25 and 35 years after primary cancer diagnosis were 2.2% and 6.2%, respectively.

Future plans: The consortium is intended to serve as a model and robust source of childhood/adolescent cancer survivor data for elucidating other knowledge gaps on subsequent breast cancer risk, and risk of other subsequent malignancies (including data on males) in the future.

Introduction

Although cancer remains a leading cause of death for children worldwide (1), the long-term survival of childhood, adolescent and young adult cancer patients has improved remarkably due to progress in treatment over the past decades in resource-rich countries (2, 3). However, childhood/adolescent cancer survivors experience impaired long-term health due to adverse effects of previous cancer treatments (4, 5). These chronic health conditions vary in association with the cancer type and specific treatments, and other patient characteristics that are independent of the prior disease (6).

Breast cancer represents one of the most common subsequent malignant neoplasms among survivors of childhood/adolescent cancer (7), which also causes increased mortality (8). Breast cancer is a long-recognized late adverse effect among women exposed to ionizing radiation at a young age, especially with chest-directed radiation (9). Moreover, recent work from various groups provides compelling evidence to suggest that certain chemotherapeutic agents may also increase the risk for subsequent breast cancer (10-12). However, individual studies have often been underpowered to fully explore potentially associated covariates. Therefore, pooling cohorts to expand knowledge of the risk and risk factors for subsequent breast cancer associated with prior treatments is of great importance to both physicians and survivors. For other types of subsequent malignancies such efforts are available (13-15) or are less likely to render a clear benefit owing to small numbers of cases even after pooling (16-19). These may be targeted in the future, though, when more person-years have accrued.

Clinical practice guidelines for providers have been developed to promote optimal health-related outcomes by screening survivors (20, 21). In 2010, the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) was established (https://www.ighg.org/) to harmonize the guidelines available worldwide, according to a common methodology (22). In 2012, the IGHG formulated recommendations for breast cancer surveillance among high-risk groups (23), to which an update was recently published (24). As part of the harmonization methodology (22), the expert group identified gaps in knowledge by specifying clinical questions for which empirical evidence was deemed insufficient to affect or alter recommendations for clinical practice (23, 24). For this reason, we established the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer funded by the Children Cancer Free Foundation (KiKa, Grant No. 325), to conduct individual patient data analyses. Initially, the consortium aimed to address three knowledge gaps regarding subsequent breast cancer identified in the IGHG breast cancer

guidelines (23, 24): (i) to explore the effects of prescribed radiation dose and radiation field, as a proxy for exposed tissue volume, on the risk of subsequent breast cancer; (ii) to examine the role of anthracyclines and the contributions of single anthracycline drugs regarding risk of subsequent breast cancer; (iii) to evaluate whether relative and absolute excess risks of subsequent breast cancer remain increased across lifespan, especially after age 50 years.

Knowledge gap #1: radiotherapy threshold associated with subsequent breast cancer

Substantial evidence demonstrates a linear dose-response relationship between radiotherapy dose exposure to the chest and the risk of subsequent breast cancer, based largely on doses of exposure ≥10 Gy (25, 26). However, less is known about the risk of subsequent breast cancer among female survivors exposed to lower doses of chest-directed or stray radiation in combination with radiation-exposed tissue volumes in the chest (23, 24, 27). This is especially relevant as contemporary cancer treatments utilize lower doses and smaller radiation volumes than cancer treatments from earlier years. Additionally, there is a paucity of radiation dose-volume data in long-term observational studies for childhood/adolescent cancer survivors for follow-up periods exceeding a decade. It is important to establish more precise subsequent breast cancer risk estimates for lower doses of radiotherapy exposure to the chest because women with very low dose ionizing radiation exposure in other circumstances (e.g., diagnostic radiation) have experienced an elevated risk of subsequent breast cancers (9). Furthermore, the Childhood Cancer Survivor Study (CCSS) evaluated parameters/characteristics of radiotherapy beyond cumulative radiation dose that may affect subsequent breast cancer risk. Specifically, women treated with lower dose radiotherapy to the whole volume of breast tissue (e.g., whole lung irradiation, median delivered dose, 14 Gy; range, 2-20 Gy) appeared to have excess risk of breast cancer; standardized incidence ratio (SIR), 43.6; 95% confidence interval (CI), 27.2-70.3). This exceeds the reported risk for females treated with high dose radiotherapy exposures to only part of the breast tissue (e.g., mantle irradiation, median delivered dose 40 Gy; range, 5-54 Gy; SIR, 24.2; 95% CI, 20.7-28.3) (27). Consequently, evaluation of the combined effects of radiation dose and radiation field, as an indicator of radiation-exposed tissue volume, in an adequately sized sample is essential to confirm and further specify this finding.

Knowledge gap #2: Association between anthracycline chemotherapy and subsequent breast cancer

The second gap in knowledge concerns the role of specific anthracycline derivatives and cumulative subsequent breast cancer risk among childhood/

adolescent cancer survivors, since anthracyclines have been shown to increase subsequent breast cancer risk (10, 11, 28). A CCSS investigation showed that female survivors without chest radiotherapy exposure had a 4-fold increase in breast cancer risk compared to the general population at a similar age (SIR 4.0; 95% CI, 3.0-5.3). Alkylating agents and anthracyclines were associated with a dose-dependent increase of breast cancer risk (*P* values from test for trend were both <0.01) (11). In the Dutch Long-term Effects After Childhood Cancer Study (DCCSS LATER), increasing cumulative doxorubicin dose was associated with increasing risk of subsequent breast cancer, with hazard ratios (HRs) of 1.1 (95% CI, 0.4-2.9), 2.6 (95% CI, 1.1-6.5), and 5.8 (95% CI, 2.7-12.5) for ≤270, 271-443, and >443 mg/m^2 doxorubicin dose, respectively (P_{trend}<.001) (10). In both, the CCSS and DCCSS LATER reports, the association between anthracyclines and subsequent breast cancer was stronger among survivors of tumor types known to be associated with Li-Fraumeni syndrome, that is, leukemia, central nervous system tumors, and non-Ewing sarcoma. It was postulated that interactions between anthracycline exposure and genes affecting cancer susceptibility in Li-Fraumeni and Li-Fraumeni-like syndromes may contribute to the mechanism underlying anthracycline-related breast cancer risk. A study from St. Jude Lifetime Cohort Study (SJLIFE) using whole genome sequencing demonstrated that an association between anthracyclines and subsequent breast cancer was still present in models excluding survivors with pathogenic or likely pathogenic mutations known to be associated with breast cancer in the general population (28). This highlights the need for large, pooled studies to better understand this association and to explore clues regarding the potential mechanisms. Others have leveraged the CCSS population to investigate the interaction between radiotherapy exposure to the chest and anthracycline treatment (i.e., additive interaction) on subsequent breast cancer risk in survivors (12). To date, it has not been possible to investigate the role of different anthracycline derivatives because most survivors who received anthracyclines were treated with doxorubicin, with small groups exposed to daunorubicin, epirubicine, idarubicin, and mitoxantrone.

Knowledge gap #3: Attained age and risk of subsequent breast cancer

The third gap in knowledge from the IGHG guideline that requires more investigation, concerns the subsequent breast cancer risk among post-menopausal women (e.g., ≥50 years (23) and ≥60 years (24)). Among atomic bomb survivors, breast cancer risk remains elevated up to the age of 70 (29). Also, in cohorts with young adult cancer survivors, who have typically already reached higher attained ages compared to childhood/adolescent cancer survivor cohorts, breast cancer risk remained elevated in female survivors aged ≥50 years (19). Increasing evidence

indicates that childhood/adolescent cancer survivors may remain at elevated risk of developing subsequent neoplasms compared to age-matched peers for as long as five decades after initial cancer treatment (30, 31). Others have reported that the effect of age on subsequent breast cancer risk may be substantially influenced by different cancer treatments (19, 27). However, the number of childhood/adolescent cancer survivors who have reached post-menopausal ages in the existing studies is too limited to demonstrate whether the risk of subsequent breast cancer remains elevated beyond post-menopausal ages.

Cohort description

Study population

Cohorts of female childhood/adolescent cancer survivors meeting the following criteria were eligible to be included in the pooled study population: a primary cancer diagnosis at <21 years of age, survival ≥5 years from diagnosis, follow-up data on presence and type of subsequent neoplasms, as well as individual detailed accounts of radiotherapy and chemotherapy treatment available for the majority of cohort members. The characteristics of seven cohorts that satisfied these criteria are shown in Supplemental Table 1: three cohorts from North America and four from Europe. The cohorts from North America include the CCSS (32, 33), the SJLIFE (34, 35), and the US National Wilms Tumor Study Group (NWTSG) (36, 37). The European cohorts consist of the DCCSS LATER (10), the French Childhood Cancer Survivor Study (FCCSS) (38, 39), the Swiss Childhood Cancer Survivor Study (SCCSS) (40, 41), and the Dutch Hodgkin Late Effects cohort (DHL) (42-44). The included multi-institutional study groups represent long-standing and well-established research infrastructures to study health and well-being among childhood/adolescent cancer survivors. A few specific aspects are mentioned below, as they impact the contribution of the respective study group to this effort. For the SCCSS, data collection on treatment details is ongoing; cohort-wide data is not available yet. Therefore, the SCCSS contributed data from a case-cohort study. The treatment details for survivors in a subcohort of their total cohort and all subsequent breast cancer cases were collected. Similarly, in the NWTSG some aspects of treatment have not been collected for all cohort members. As such, this cohort will be excluded for analyses of chemotherapy treatment dose effects.

Overlaps between the North American cohorts (CCSS / SJLIFE / NWTSG) and the Dutch cohorts (DCCSS LATER / DHL) were checked, and only unique patients were included. The data was prepared by analysts from the individual studies according to a jointly developed harmonized data protocol, and are stored at the Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands. The contributing

cohort-study teams obtained IRB and/or Ethics Committee approval or exemption in their respective contributing institute. See Supplemental Table 1 for an overview per data provider. The pooling effort is exempt from review in compliance with Dutch law and regulations for health research involving human beings. Data sharing agreements between the Princess Máxima Center for Pediatric Oncology and all data providers are in place.

Childhood/adolescent cancer diagnosis information and treatment exposures

For each individual cohort, details on childhood/adolescent cancer diagnosis and treatment were included in the pooled cohort (Table 1). For childhood/adolescent cancer diagnosis, the year and month were recorded as well as the ICD-O-3 morphology, behavior, and topography codes. Radiotherapy details included direct in-field exposure (yes/no and cumulative dose) to the following body regions: head/neck, chest, abdomen, pelvis, extremities, or total body irradiation. For chest radiotherapy, we also collected data on the specific field(s) that were treated. Each chest radiotherapy field was converted into one of the following field classifications based on the field description by the individual cohorts: whole lung, total body irradiation, mantle, mediastinum, axilla, spine, or other chest without axilla (left/right/unknown laterality). Details on delivered chemotherapy drugs and on cumulative doses were also recorded, except for NWTSG, for which only information on the drug name, but not on cumulative dose was available. In addition, for cohort members affected by one or multiple subsequent malignancies, diagnosis date and, if available, respective treatment information was collected. Since treatment for subsequent cancers (e.g., thyroid cancer, lung cancer, or a thoracic sarcoma) may affect the baseline risk of breast cancer thereafter, owing to further exposure to chest radiation, anthracyclines, or hormone therapy, such additional data allow for sensitivity analyses to evaluate the potential influence of these situations in clinical reality.

Table 1. Available items in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer database

Data information	Requested items for consortium database	Comments
Childhood cancer diagnosis characteristics	• Year and month of birth • Year and month of childhood cancer diagnosis • ICD-O-3 morphology code, behavior code, and topography code • Laterality (left/right/bilateral/not applicable/unknown)	° *SJLIFE:* no ICD-O-3 coding, but detailed description of tumor type in words ° *FCCSS:* no ICD-O-3 coding, but coded according to ICCC-3 ° *DHL:* no ICD-O-3 coding available *Consortium database*: childhood cancer type recoded into ICCC-3 groups
General treatment exposure	All: yes/no/unknown • Radiotherapy • Chemotherapy • Surgery	° *CCSS:* any treatment for the primary tumor up to five years following primary diagnosis ° *SJLIFE/NWTSG/DCCSS LATER/ FCCSS/ SCCSS/DHL:* all known treatments for primary tumors and/or recurrences
Radiotherapy body region exposure	All: yes/no/unknown and delivered dose to body compartment: • Head/neck • Chest • Abdomen • Pelvis • Extremities • Total body irradiation	° *CCSS/SJILFE:* body region dosimetry; maximum prescribed target dose to the specific body region; taken as the sum of dose from all overlapping fields in a region. At least 10% of body region in the field to be scored as direct exposure "yes", with the exception for the brain, where at least 50% of the brain segment had to be in the field. Exposure to head/neck was coded as exposure to either any of the brain segments, other head, or neck ° *NWTSG/DCCSS LATER/SCCSS/DHL:* in case of multiple radiotherapy treatments to a specific body region, the dose of the fields was summed if the fields were overlapping. If the fields were not overlapping, the dose to the field with the highest dose was assigned (highest dose to smallest field principle) ° *FCCSS:* exposure to body compartments was based on dosimetry information of organs at risk in that specific body compartment

Table 1. Available items in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer database (continued)

Data information	Requested items for consortium database	Comments
Chest fields	Data providers were requested to provide data on each field to the chest area as part of childhood cancer treatment according to the categories listed below, or to provide the coding of fields that they used in their own database. In case the data providers provided their own coding of fields (CCSS/SJLIFE/DCCSS LATER/DHL), these were then recoded by the Máxima team, in close collaboration with the data providers, into the categories listed below. • Total body irradiation • Whole lung • Mantle field • Mediastinal • Axilla (both/left/right/unknown) • Spine* • Chest without axilla (left/right/other/unknown) Also, the delivered dose of each field was recorded. *Comments:* ° The "Chest without axilla" category includes a mixed group of patients with treated radiotherapy fields that do not fit any of the other specific categories. Therefore, we have no information on the part of the breast that may or may not have been within the treatment beam. ° For analyses, if patients had multiple fields to the same region, the dose was summed, with two exceptions: 1. If a left axilla field and a right axilla field were irradiated, the maximum dose of the two respective fields was chosen. 2. If two or more fields were chest without axilla, we chose the maximum dose of the respective fields for that person, because it was unclear whether there was any overlap of radiation exposure from those respective fields.	
Chemotherapy	• Drug name • Cumulative dose	° *NWTSG:* cumulative dose not available
Follow-up information	• Year and month of last information on subsequent malignant neoplasms • Vital status (alive/deceased/unknown) • Year and month of last known vital status information • Invasive breast cancer diagnosis (yes/no/unknown) • In situ breast cancer diagnosis (yes/no/unknown) • Diagnosis of other subsequent malignancies (yes/no/unknown)	° *FCCSS:* information on subsequent malignancies other than breast cancers is only available for breast cancer cases
Invasive and in situ breast cancer	For each (in situ) breast cancer case: • ICD-O-3 morphology code • ICD-O-3 behavior code • ICD-O-3 topography code • Laterality (left/right/bilateral/unknown) • Year and month of diagnosis • Tumor receptor status: Estrogen, human epidermal growth factor receptor 2, and progesterone status (negative/positive/unknown)	° *DCCSS LATER:* no information on tumor receptor status

Table 1. Available items in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer database (continued)

Data information	Requested items for consortium database	Comments
Other subsequent malignant neoplasms	• ICD-O-3 morphology code, behavior code, and topography code • Year and month of diagnosis • Chest radiotherapy treatment for subsequent malignant neoplasm (yes/no/unknown) • Anthracycline treatment for subsequent malignant neoplasm (yes/no/unknown)	° *CCSS/DCCSS LATER/DHL:* information on chest radiotherapy and anthracycline treatment given for any other subsequent neoplasms is not available, but information on the other variables is. ° *FCCSS:* information on subsequent malignancies other than breast cancers is only available for breast cancer cases
Reproductive factors	• Age at menarche • Menopausal status (pre-menopausal/postmenopausal/unknown) and age at menopause • Parity and age first childbirth	° *SJLIFE:* menopausal status and age at menopause available for a few patients, but largely incomplete ° *NWTSG:* age at menarche, menopausal status, and age at menopause are not available ° *SCCSS:* data available for a subset of patients from questionnaires
Hormonal use	• Oral contraceptive use and duration of oral contraceptive use for contraception • Hormone replacement therapy and duration of hormone replacement therapy use	° *SJLIFE/NWTSG:* not available ° *SCCSS:* data available for a subset of patients from questionnaires
Other	• Family history of breast cancer in first-degree relatives and in second-degree relatives • Race • Treatment protocol name • Ovarian transplantation before pelvic field irradiation • Breast dosimetry performed, absorbed breast dose, ovarian dosimetry performed, absorbed ovarian dose	° *SCCSS:* not available ° *NWTSG/DHL:* only available for first-degree relatives ° *DCCSS LATER/FCCSS/SCCSS/DHL:* not available ° *DCCSS LATER/FCCSS/DHL:* not available ° *SJLIFE/NWTSG/DCCSS LATER/SCCSS/DHL:* not available ° *NWTSG/DCCSS LATER/SCCSS/DHL:* not available

CCSS = Childhood Cancer Survivor Study; SJLIFE = St. Jude Lifetime Cohort Study; NWTSG = US National Wilms Tumor Study group; DCCSS LATER = Dutch Long-term Effects After Childhood Cancer Study; FCCSS = French Childhood Cancer Survivor Study; SCCSS = Swiss Childhood Cancer Survivor Study; DHL = Dutch Hodgkin Late Effects cohort; ICD-O-3 = International Classification of Diseases for Oncology, Third Edition; ICCC = International Classification of Childhood Cancer, Third Edition

*Spine irradiation fields not involving a thoracic part of the spine were not considered chest radiotherapy.

Outcome ascertainment

The process of ascertainment of subsequent (invasive and in situ) breast cancer and other subsequent malignancies for each participating cohort is summarized in Table 2. For all subsequent malignancies, information of morphology, topography, diagnosis year and month was collected. For subsequent breast cancer, laterality, hormone receptor status (i.e., estrogen receptor, human epidermal growth factor receptor 2, and progesterone receptor) was additionally collected, when available.

Potential confounding and effect modifying variables

Information on age at menarche, menopausal status and age at menopause, pregnancies (age at first birth and number of children), oral contraceptives, and hormone replacement therapy (including duration of use) was collected from self-reported questionnaires and/or abstracted from medical records (Table 1). To date, this information is available for more than half of the cohort members, with varying completeness across variables. In addition, some other information was provided as optional variables if this data was available, for example: race/ethnicity, family history of breast cancer, treatment protocol name, ovarian transposition (oophorexy) before pelvic field irradiation, and cancer predisposition syndromes.

Depending on the specific research questions and the corresponding outcomes, we intend to apply multiple imputation methods to the relevant confounding and effect modifying variables, whenever necessary and feasible.

Patient and public involvement

Survivor representatives are invited and included in the process of guideline development for breast cancer surveillance among childhood cancer survivors in the IGHG, in which knowledge gaps and research priorities were identified and formulated. This work serves as a prelude to the initiation of this consortium. Survivors were represented in the grant development process and are involved throughout the project to provide survivors' research perspectives when needed and increase public awareness and understanding. When the studies are complete, survivors and their families through survivorship organizations (e.g., VOX in the Netherlands) will be involved in and also provide independent dissemination of research progress and findings to the survivor network and the public to motivate community engagement in and beyond the study.

Table 2. Subsequent breast cancer ascertainment/validation process for each participating study

	Subsequent breast cancer ascertainment			Subsequent breast cancer case validation
Participating studies	**Medical files**	**Record linkage**	**Other sources for SMN ascertainment**	
CCSS	None	National death index	Initial self- or proxy-reports	Medical records including pathology reports
SJLIFE	None	Cancer registry follow-up National Death Index	Prospective follow-up at St. Jude with breast imaging, self-report or next of kin reported	Medical records including pathology reports
NWTSG	Clinical records	None	Annual status reports	Medical records review
DCCSS LATER	Medical records	Population-based Netherlands Cancer Registry Nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA [Dutch Pathology Registry])	None	Pathology reports
FCCSS	Hospital clinical files Long term follow-up visits	National death certificate data National Public and Private Hospital and National Health Insurance Database	Self-completed questionnaire	Pathology reports
SCCSS	Medical records including pathology reports	Cantonal cancer registries Cause-of death statistics	Self-report	Medical records including pathology reports
DHL	Medical records Questionnaires sent to general practitioners	Population-based Netherlands Cancer Registry	None	Pathology reports

SMN = Subsequent malignant neoplasm; CCSS = Childhood Cancer Survivor Study; SJLIFE = St. Jude Lifetime Cohort Study; NWTSG = US National Wilms Tumor Study group; DCCSS LATER = Dutch Long-term Effects After Childhood Cancer Study; FCCSS = French Childhood Cancer Survivor Study; SCCSS = Swiss Childhood Cancer Survivor Study; DHL = Dutch Hodgkin Late Effects cohort

Findings to date

Currently, the consortium cohort includes 21,892 female five-year childhood/adolescent cancer survivors who accrued 444,023 person-years of follow-up attained from the date of five-year survival. The range of calendar years of childhood cancer diagnosis was from 1946 to 2012, and the latest follow-up ended in 2021. The median age at primary cancer diagnosis was 5.4 (IQR 2.5-11.9) years. The median duration from five-year survival to the end of follow-up was 19.3 (IQR 13.0-27.8) years; 18.9% (n=4,145) of females were followed for ≥30 years since five-year survival. The median attained age at last follow-up was 32.2 (IQR 24.0-40.4) years, and the consortium cohort included 1,592 (7.3%) survivors who reached age 50 years, and 211 (1.0%) survivors who reached age 60 years. In all, 4,240 (19.4%) childhood/adolescent cancer survivors were treated with radiotherapy to the chest, and 9,308 (42.5%) were treated with anthracyclines. At the end of the follow-up, 835 females developed a first subsequent breast cancer, including 635 invasive breast cancer only, 184 carcinomas in situ only (172 ductal carcinoma in situ and 12 lobular carcinomas in situ), and 16 with both an invasive and in situ diagnosis at the same moment. The cumulative incidences of subsequent breast cancer (both invasive and in situ) 25 and 35 years after primary cancer diagnosis were 2.2% and 6.2%, respectively. Table 3 describes the demographic and clinical characteristics of the pool of survivors eligible for our study. The consortium cohort includes relatively more renal tumor survivors (24.5% of all survivors) than the general childhood cancer survivor population, because of the inclusion of the NTWSG cohort, which exclusively includes renal tumor survivors. Table 4 and Table 5 present the specific information on radiotherapy treatment and anthracycline and alkylating agent chemotherapy treatment. For more detailed information on survivors included in our study, please see the Supplemental material Table 2.

The International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer represents a newly established pooled study. Several analyses on clinically relevant questions regarding subsequent breast cancer are currently ongoing. Individual study groups included in this consortium have published on subsequent breast cancer risks before. An overview of cohort-specific published findings relevant to the first tier of three clinical questions that led to the establishment of the consortium is summarized in Supplemental Table 3. In addition, selected other cohort-specific findings relating to subsequent breast cancer risk are highlighted.

Table 3. Demographic and clinical characteristics of female childhood/adolescent cancer survivors included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer by each participating study

	Participating study		
	CCSS (n=9,671)	**NWTS (n=3,989)**	**FCCSS (n=3,415)**
Primary childhood cancer type			
Leukemia	2,987 (30.9%)	-	-
Non-Hodgkin lymphoma	586 (6.1%)	-	235 (6.9%)
Hodgkin lymphoma	1,276 (13.2%)	-	189 (5.5%)
CNS tumor	1,841 (19.0%)	-	498 (14.6%)
Neuroblastoma	901 (9.3%)	-	505 (14.8%)
Retinoblastoma	-	-	293 (8.6%)
Renal tumor	389 (4.0%)	3,989 (100%)	558 (16.3%)
Hepatic tumor	-	-	32 (0.9%)
Bone tumor	884 (9.1%)	-	295 (8.6%)
Soft tissue tumor	763 (7.9%)	-	361 (10.6%)
Germ cell tumor	20 (0.2%)	-	249 (7.3%)
Other malignant epithelial neoplasms	-	-	187 (5.5%)
Other and unspecified	-	-	7 (0.2%)
Unclassified	24 (0.2%)	-	6 (0.2%)
Age at primary childhood cancer diagnosis (yr) category			
<5	3,666 (37.9%)	2,990 (75.0%)	1,671 (48.9%)
5-9	2,027 (21.0%)	869 (21.8%)	707 (20.7%)
10-14	2,204 (22.8%)	115 (2.9%)	744 (21.8%)
15-21	1,774 (18.3%)	15 (0.4%)	293 (8.6%)
Period of childhood cancer diagnosis category			
<1960	-	-	60 (1.8%)
1960-1969	-	3 (0.1%)	264 (7.7%)
1970-1979	2,639 (27.3%)	612 (15.3%)	693 (20.3%)
1980-1989	3,737 (38.6%)	1,440 (36.1%)	1,035 (30.3%)
1990-1999	3,295 (34.1%)	1,562 (39.2%)	1,233 (36.1%)
2000-2011	-	372 (9.3%)	130 (3.8%)
Duration of follow-up since 5-yr survival (yr)[†]			
Median [IQR]	20.2 [14.7, 28.0]	15.7 [7.8, 24.9]	23.2 [16.3, 31.8]

				Overall		
SJLIFE (n=2,236)	**LATER (n=2,237)**	**DHL (n=265)**	**SCCSS (n=79)**	**Total (n=21,892)**	**Non-SBC patients (n=21,057)**	**SBC patients* (n=835)**
802 (35.9%)	770 (34.4%)	-	15 (19.0%)	4,574 (20.9%)	4,492 (21.3%)	82 (9.8%)
115 (5.1%)	157 (7.0%)	-	4 (5.1%)	1,097 (5.0%)	1,060 (5.0%)	37 (4.4%)
227 (10.2%)	125 (5.6%)	265 (100%)	19 (24.1%)	2,101 (9.6%)	1,692 (8.0%)	409 (49.0%)
287 (12.8%)	312 (13.9%)	-	8 (10.1%)	2,946 (13.5%)	2,932 (13.9%)	14 (1.7%)
101 (4.5%)	145 (6.5%)	-	5 (6.3%)	1,657 (7.6%)	1,642 (7.8%)	15 (1.8%)
119 (5.3%)	14 (0.6%)	-	-	426 (1.9%)	424 (2.0%)	2 (0.2%)
170 (7.6%)	250 (11.2%)	-	5 (6.3%)	5,361 (24.5%)	5,270 (25.0%)	91 (10.9%)
10 (0.4%)	19 (0.8%)	-	-	61 (0.3%)	60 (0.3%)	1 (0.1%)
133 (5.9%)	141 (6.3%)	-	6 (7.6%)	1,459 (6.7%)	1,352 (6.4%)	107 (12.8%)
127 (5.7%)	151 (6.8%)	-	3 (3.8%)	1,405 (6.4%)	1,350 (6.4%)	55 (6.6%)
68 (3.0%)	101 (4.5%)	-	2 (2.5%)	440 (2.0%)	431 (2.0%)	9 (1.1%)
49 (2.2%)	50 (2.2%)	-	11 (13.9%)	297 (1.4%)	286 (1.4%)	11 (1.3%)
28 (1.3%)	2 (0.1%)	-	1 (1.3%)	38 (0.2%)	37 (0.2%)	1 (0.1%)
-	-	-	-	30 (0.1%)	29 (0.1%)	1 (0.1%)
973 (43.5%)	1,049 (46.9%)	-	17 (21.5%)	10,366 (47.4%)	10,282 (48.8%)	84 (10.1%)
468 (20.9%)	569 (25.4%)	7 (2.6%)	10 (12.7%)	4,657 (21.3%)	4,574 (21.7%)	83 (9.9%)
472 (21.1%)	471 (21.1%)	21 (7.9%)	18 (22.8%)	4,045 (18.5%)	3,759 (17.9%)	286 (34.3%)
323 (14.4%)	148 (6.6%)	237 (89.4%)	34 (43.0%)	2,824 (12.9%)	2,442 (11.6%)	382 (45.7%)
-	-	-	-	60 (0.3%)	51 (0.2%)	9 (1.1%)
42 (1.9%)	49 (2.2%)	29 (10.9%)	-	387 (1.8%)	352 (1.7%)	35 (4.2%)
274 (12.3%)	386 (17.3%)	81 (30.6%)	8 (10.1%)	4,693 (21.4%)	4,326 (20.5%)	367 (44.0%)
535 (23.9%)	711 (31.8%)	76 (28.7%)	27 (34.2%)	7,561 (34.5%)	7,254 (34.4%)	307 (36.8%)
633 (28.3%)	871 (38.9%)	76 (28.7%)	26 (32.9%)	7,696 (35.2%)	7,585 (36.0%)	111 (13.3%)
752 (33.6%)	220 (9.8%)	3 (1.1%)	18 (22.8%)	1,495 (6.8%)	1,489 (7.1%)	6 (0.7%)
18.0 [10.3, 27.5]	16.8 [10.8, 25.0]	17.6 [12.3, 25.7]	11.0 [6.7, 18.7]	19.3 [13.0, 27.8]	19.3 [12.9, 27.8]	20.6 [14.8, 26.2]

Table 3. Demographic and clinical characteristics of female childhood/adolescent cancer survivors included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer by each participating study (continued)

	Participating study		
	CCSS (n=9,671)	**NWTS (n=3,989)**	**FCCSS (n=3,415)**
Duration of follow-up since 5-yr survival (yr)[†] category			
<10	1,096 (11.3%)	1,308 (32.8%)	251 (7.4%)
10-19	3,672 (38.0%)	1,145 (28.7%)	1,130 (33.1%)
20-29	3,014 (31.2%)	1,007 (25.2%)	1,019 (29.8%)
≥30	1,889 (19.5%)	529 (13.3%)	1,015 (29.7%)
Attained age at last follow-up (yr)[†]			
Median [IQR]	34.4 [26.7, 42.0]	24.3 [16.7, 33.8]	35.8 [27.2, 44.0]
Attained age at last follow-up age (yr)[†] category			
<20	838 (8.7%)	1,484 (37.2%)	242 (7.1%)
20-29	2,552 (26.4%)	1,128 (28.3%)	862 (25.2%)
30-39	3,314 (34.3%)	921 (23.1%)	1,069 (31.3%)
≥40	2,967 (30.7%)	456 (11.4%)	1,242 (36.4%)
Any subsequent breast cancer (invasive or in situ)[¶]			
No	9,214 (95.3%)	3,943 (98.8%)	3,287 (96.3%)
Yes	457 (4.7%)	46 (1.2%)	128 (3.7%)
First subsequent breast cancer type			
Only invasive	336 (73.5%)	30 (65.2%)	110 (85.9%)
Only in situ	113 (24.7%)	12 (26.1%)	16 (12.5%)
Invasive and in situ diagnosed at the same moment	8 (1.8%)	4 (8.7%)	2 (1.6%)
Vital status at last point of contact			
Alive	8,174 (84.5%)	3,802 (95.3%)	2,759 (80.8%)
Deceased	1,497 (15.5%)	187 (4.7%)	656 (19.2%)

CCSS = Childhood Cancer Survivor Study; SJLIFE = St. Jude Lifetime Cohort Study; NWTSG = US National Wilms Tumor Study group; DCCSS LATER = Dutch Long-term Effects After Childhood Cancer Study; FCCSS = French Childhood Cancer Survivor Study; SCCSS = Swiss Childhood Cancer Survivor Study; DHL = Dutch Hodgkin Late Effects cohort; SBC = Subsequent breast cancer; CNS = Central nervous system; yr = year; IQR = Interquartile range; DCIS = Ductal carcinoma in situ; LCIS = Lobular carcinoma in situ

[*]Includes patients with invasive and/or in situ breast cancer.

[†]Follow-up time was calculated from five years after a primary cancer diagnosis to the date of subsequent breast cancer diagnosis, death, or the date of the last follow-up observation, whichever occurred first.

[¶]For more detailed information, please see the Supplemental material.

[§]Among survivors with an invasive first subsequent breast cancer, 103 developed a second subsequent breast

				Overall		
SJLIFE (n=2,236)	**LATER (n=2,237)**	**DHL (n=265)**	**SCCSS (n=79)**	**Total (n=21,892)**	**Non-SBC patients (n=21,057)**	**SBC patients* (n=835)**
543 (24.3%)	482 (21.5%)	40 (15.1%)	36 (45.6%)	3,756 (17.2%)	3,690 (17.5%)	66 (7.9%)
703 (31.4%)	859 (38.4%)	116 (43.8%)	24 (30.4%)	7,649 (34.9%)	7,326 (34.8%)	323 (38.7%)
570 (25.5%)	645 (28.8%)	69 (26.0%)	18 (22.8%)	6,342 (29.0%)	5,995 (28.5%)	347 (41.6%)
420 (18.8%)	251 (11.2%)	40 (15.1%)	1 (1.3%)	4,145 (18.9%)	4,046 (19.2%)	99 (11.9%)
31.8 [23.7, 39.9]	29.3 [22.1, 36.9]	40.9 [35.5, 48.8]	28.6 [24.3, 37.6]	32.2 [24.0, 40.4]	31.9 [23.7, 40.1]	39.3 [34.1, 44.5]
380 (17.0%)	395 (17.7%)	1 (0.4%)	14 (17.7%)	3,354 (15.3%)	3,350 (15.9%)	4 (0.5%)
614 (27.5%)	798 (35.7%)	26 (9.8%)	30 (38.0%)	6,010 (27.5%)	5,929 (28.2%)	81 (9.7%)
688 (30.8%)	666 (29.8%)	93 (35.1%)	18 (22.8%)	6,769 (30.9%)	6,413 (30.5%)	356 (42.6%)
554 (24.8%)	378 (16.9%)	145 (54.7%)	17 (21.5%)	5,759 (26.3%)	5,365 (25.5%)	394 (47.2%)
2,158 (96.5%)	2,196 (98.2%)	200 (75.5%)	59 (74.7%)	21,057 (96.2%)	21,057 (100%)	-
78 (3.5%)	41 (1.8%)	65 (24.5%)	20 (25.3%)	835 (3.8%)	-	835 (100%)
52 (66.7%)	36 (87.8%)	51 (78.5%)	20 (100%)	635 (76.1%)[§]	-	635 (76.1%)[§]
24 (30.8%)	5 (12.2%)	14 (21.5%)	-	184 (22.0%)[‖#]	-	184 (22.0%)[‖#]
2 (2.6%)	-	-	-	16 (1.9%)[**]	-	16 (1.9%)[**]
2,171 (97.1%)	1,928 (86.2%)	178 (67.2%)	68 (86.1%)	19,080 (87.2%)	18,489 (87.8%)	591 (70.8%)
65 (2.9%)	309 (13.8%)	87 (32.8%)	11 (13.9%)	2,812 (12.8%)	2,568 (12.2%)	244 (29.2%)

cancer (65 invasive, 34 DCIS, 4 LCIS), 4 developed a third subsequent breast cancer (all invasive), and 1 developed LCIS as a fourth subsequent breast cancer.

‖Among survivors with an in situ first subsequent breast cancer, 38 developed a second subsequent breast cancer (16 invasive, 17 DCIS, 5 LCIS), and 4 developed a third subsequent breast cancer (1 invasive, 2 DCIS, 1 LCIS).

#Includes 172 DCIS and 12 LCIS.

**Among survivors with both an invasive and in situ first subsequent breast cancer diagnosed at the same moment, 2 developed DCIS as a third subsequent breast cancer.

Table 4. Childhood cancer radiotherapy treatment characteristics of female childhood/adolescent cancer survivors included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer by each participating study

	Participating study			
	CCSS (n=9,671)	**NWTS (n=3,989)**	**FCCSS (n=3,415)**	**SJLIFE (n=2,236)**
Radiotherapy exposure to the chest				
No	6,607 (68.3%)	3,415 (85.6%)	2,728 (79.9%)	1,706 (76.3%)
Yes	2,098 (21.7%)	547 (13.7%)	482 (14.1%)	506 (22.6%)
Unknown	966 (10.0%)	27 (0.7%)	205 (6.0%)	24 (1.1%)
Chest radiation dose (Gy)				
Median [IQR]	30.0 [20.0, 39.0]	12.0 [12.0, 12.3]	27.5 [20.0, 40.0]	25.3 [15.0, 33.0]
Chest radiation dose (Gy) category				
No chest radiation	6,607(68.3%)	3,415 (85.6%)	2,728 (79.9%)	1,706 (76.3%)
<10	73 (0.8%)	4 (0.1%)	7 (0.2%)	5 (0.2%)
10-19	403 (4.2%)	509 (12.8%)	102 (3.0%)	133 (5.9%)
20-29	533 (5.5%)	19 (0.5%)	148 (4.3%)	210 (9.4%)
30-39	542 (5.6%)	12 (0.3%)	92 (2.7%)	85 (3.8%)
≥40	511 (5.3%)	3 (0.1%)	133 (3.9%)	41 (1.8%)
Unknown	1,002 (10.4%)	27 (0.7%)	205 (6.0%)	56 (2.5%)
Chest radiation field				
No chest radiation	6,607 (68.3%)	3,415 (85.6%)	2,728 (79.9%)	1,706 (76.3%)
Axilla	12 (0.1%)	-	-	5 (0.2%)
Mantle	723 (7.5%)	-	86 (2.5%)	191 (8.5%)
Mediastinal	227 (2.3%)	1 (0.0%)	134 (3.9%)	23 (1.0%)
Others	177 (1.8%)	19 (0.5%)	117 (3.4%)	33 (1.5%)
Spine	598 (6.2%)	-	98 (2.9%)	131 (5.9%)
Total body irradiation	223 (2.3%)	-	10 (0.3%)	67 (3.0%)
Whole lung	79 (0.8%)	527 (13.2%)	37 (1.1%)	44 (2.0%)
Unknown	1,025 (10.6%)	27 (0.7%)	205 (6.0%)	36 (1.6%)
Radiotherapy exposure to the Pelvis				
No	7,191 (74.4%)	1,922 (48.2%)	2,287 (67.0%)	1,873 (83.8%)
Yes	1,515 (15.7%)	-	923 (27.0%)	337 (15.1%)
Unknown	965 (10.0%)	2,067 (51.8%)	205 (6.0%)	26 (1.2%)
Pelvic radiation dose (Gy)				
Median [IQR]	26.0 [15.0, 36.0]	NA[†]	33.0 [22.0, 43.5]	23.4 [16.8, 36.0]

			Overall		
LATER (n=2,237)	**DHL (n=265)**	**SCCSS (n=79)**	**Total (n=21,892)**	**Non-SBC patients (n=21,057)**	**SBC patients* (n=835)**
1,892 (84.6%)	22 (8.3%)	49 (62.0%)	16,419 (75.0%)	16,145 (76.7%)	274 (32.8%)
341 (15.2%)	243 (91.7%)	23 (29.1%)	4,240 (19.4%)	3,735 (17.7%)	505 (60.5%)
4 (0.2%)	-	7 (8.9%)	1,233 (5.6%)	1,177 (5.6%)	56 (6.7%)
25.0 [13.8, 35.2]	38.0 [35.0, 40.0]	36.0 [19.8, 40.0]	25.0 [14.0, 36.0]	24.0 [13.8, 36.0]	36.0 [25.0, 40.9]
1,892 (84.6%)	22 (8.3%)	49 (62.0%)	16,419 (75.0%)	16,145 (76.7%)	274 (32.8%)
48 (2.1%)	-	-	137 (0.6%)	132 (0.6%)	5 (0.6%)
69 (3.1%)	2 (0.8%)	6 (7.6%)	1,224 (5.6%)	1,151 (5.5%)	73 (8.7%)
60 (2.7%)	11 (4.2%)	2 (2.5%)	983 (4.5%)	906 (4.3%)	77 (9.2%)
82 (3.7%)	90 (34.0%)	5 (6.3%)	908 (4.1%)	762 (3.6%)	146 (17.5%)
68 (3.0%)	85 (32.1%)	6 (7.6%)	847 (3.9%)	650 (3.1%)	197 (23.6%)
18 (0.8%)	55 (20.8%)	11 (13.9%)	1,374 (6.3%)	1,311 (6.2%)	63 (7.5%)
1,892(84.6%)	22 (8.3%)	49 (62.0%)	16,419 (75.0%)	16,145 (76.7%)	274 (32.8%)
15 (0.7%)	2 (0.8%)	-	34 (0.2%)	31 (0.1%)	3 (0.4%)
39 (1.7%)	192 (72.5%)	11 (13.9%)	1,242 (5.7%)	911 (4.3%)	331 (39.6%)
36 (1.6%)	45 (17.0%)	4 (5.1%)	470 (2.1%)	437 (2.1%)	33 (4.0%)
49 (2.2%)	-	1 (1.3%)	396 (1.8%)	344 (1.6%)	52 (6.2%)
109 (4.9%)	-	3 (3.8%)	939 (4.3%)	927 (4.4%)	12 (1.4%)
69 (3.1%)	-	2 (2.5%)	371 (1.7%)	348 (1.7%)	23 (2.8%)
22 (1.0%)	-	2 (2.5%)	711 (3.2%)	663 (3.1%)	48 (5.7%)
6 (0.8%)	4 (1.5%)	7 (8.9%)	1,310 (6.0%)	1,251(5.9%)	59 (7.1%)
2,129 (95.2%)	179 (67.5%)	68 (86.1%)	15,649 (71.5%)	15,133 (71.9%)	516 (61.8%)
105 (4.7%)	81 (30.6%)	3 (3.8%)	2,964 (13.5%)	2,740 (13.0%)	224 (26.8%)
3 (0.1%)	5 (1.9%)	8 (10.1%)	3,279 (15.0%)	3,184 (15.1%)	95 (11.4%)
12.0 [7.5, 38.5]	NA¶	11.0 [10.5, 11.5]	30.0 [19.0, 39.0]	28.0 [18.0, 38.0]	34.0 [24.0, 42.5]

Table 4. Childhood cancer radiotherapy treatment characteristics of female childhood/adolescent cancer survivors included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer by each participating study (continued)

	Participating study			
	CCSS (n=9,671)	**NWTS (n=3,989)**	**FCCSS (n=3,415)**	**SJLIFE (n=2,236)**
Pelvic radiation dose (Gy) category				
No pelvic radiation	7,191 (74.4%)	1,922 (48.2%)	2,287 (67.0%)	1,873 (83.8%)
<10	66 (0.7%)	-	25 (0.7%)	4 (0.2%)
10-19	369 (3.8%)	-	114 (3.3%)	89 (4.0%)
20-29	365 (3.8%)	-	232 (6.8%)	120 (5.4%)
30-39	398 (4.1%)	-	216 (6.3%)	66 (3.0%)
≥40	295 (3.1%)	-	336 (9.8%)	57 (2.5%)
Unknown	987 (10.2%)	2,067 (51.8%)	205 (6.0%)	27 (1.2%)

CCSS = Childhood Cancer Survivor Study; SJLIFE = St. Jude Lifetime Cohort Study; NWTSG = US National Wilms Tumor Study group; DCCSS LATER = Dutch Long-term Effects After Childhood Cancer Study; FCCSS = French Childhood Cancer Survivor Study; SCCSS = Swiss Childhood Cancer Survivor Study; DHL = Dutch Hodgkin Late Effects cohort; SBC = Subsequent breast cancer; CNS = Central nervous system; yr = year; IQR = Interquartile range; NA = Not applicable

Table 5. Childhood cancer anthracycline and alkylating agent chemotherapy treatment characteristics of female childhood/adolescent cancer survivors included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer by each participating study

	Participating study			
	CCSS (n=9,671)	**NWTS (n=3,989)**	**FCCSS (n=3,415)**	**SJLIFE (n=2,236)**
Anthracyclines[†]				
No	4,889 (50.6%)	2,237 (56.1%)	2,095 (61.3%)	955 (42.7%)
Yes	3,990 (41.3%)	1,738 (43.6%)	1,201 (35.2%)	1,263 (56.5%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)
Doxorubicin				
No	5,729 (59.2%)	2,237 (56.1%)	2,300 (67.4%)	1,377 (61.6%)
Yes	3,150 (32.6%)	1,738 (43.6%)	996 (29.2%)	841 (37.6%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)
Doxorubicin dose (mg/m²)				
Median [IQR]	224.7 [130.4, 358.3]	NA[¶]	235.7 [131.7, 346.8]	177.4 [135.1, 256.2]
Doxorubicin dose (mg/m²) category				
0	5,729 (59.2%)	2,237 (56.1%)	2,300 (67.4%)	1,377 (61.6%)
<100	502 (5.2%)	-	95 (2.8%)	121 (5.4%)
100-199	769 (8.0%)	-	347 (10.2%)	414 (18.5%)

			Overall		
LATER (n=2,237)	**DHL (n=265)**	**SCCSS (n=79)**	**Total (n=21,892)**	**Non-SBC patients (n=21,057)**	**SBC patients* (n=835)**
2,129 (95.2%)	179 (67.5%)	68 (86.1%)	15,649 (71.5%)	15,133 (71.9%)	516 (61.8%)
47 (2.1%)	-	-	142 (0.6%)	136 (0.6%)	6 (0.7%)
20 (0.9%)	-	2 (2.5%)	594 (2.7%)	570 (2.7%)	24 (2.9%)
2 (0.1%)	-	-	719 (3.3%)	681 (3.2%)	38 (4.6%)
6 (0.3%)	81 (30.6%)¶	-	767 (3.5%)	684 (3.2%)	83 (9.9%)
25 (1.1%)	-	-	713 (3.3%)	641 (3.0%)	72 (8.6%)
8 (0.4%)	5 (1.9%)	9 (11.4%)	3,308 (15.1%)	3,212 (15.3%)	96 (11.5%)

*Includes patients with invasive and/or in situ breast cancer.
†Pelvic radiation information was not available in the NWTSG.
¶Dose of pelvic radiation information was not available for the DHL. We assume the survivors in the DHL who had pelvic RT received 30 Gy RT exposure to the pelvis since Hodgkin lymphoma patients usually receive 30 Gy pelvic radiation.

			Overall		
LATER (n=2,237)	**DHL (n=265)**	**SCCSS (n=79)**	**Total (n=21,892)**	**Non-SBC patients (n=21,057)**	**SBC patients* (n=835)**
1,250 (55.9%)	155 (58.5%)	36 (45.6%)	11,617 (53.1%)	11,204 (53.2%)	413 (49.5%)
982 (43.9%)	98 (37.0%)	36 (45.6%)	9,308 (42.5%)	8,943 (42.5%)	365 (43.7%)
5 (0.2%)	12 (4.5%)	7 (8.9%)	967 (4.4%)	910 (4.3%)	57 (6.8%)
1,541 (68.9%)	181 (68.3%)	42 (53.2%)	13,407 (61.2%)	12,954 (61.5%)	453 (54.3%)
691 (30.9%)	84 (31.7%)	30 (38.0%)	7,530 (34.4%)	7,205 (34.2%)	325 (38.9%)
5 (0.2%)	-	7 (8.9%)	955 (4.4%)	898 (4.3%)	57 (6.8%)
150.0 [65.0, 300.0]	210.0 [140.0, 280.0]	200.0 [150.0, 300.0]	203.3 [120.0, 340.0]	200.0 [120.0, 337.3]	281.9 [179.7, 371.8]
1,541 (68.9%)	181 (68.3%)	42 (53.2%)	13,407 (61.2%)	12,954 (61.5%)	453 (54.3%)
188 (8.4%)	5 (1.9%)	1 (1.3%)	912 (4.2%)	896 (4.3%)	16 (1.9%)
232 (10.4%)	20 (7.5%)	13 (16.5%)	1,795 (8.2%)	1,725 (8.2%)	70 (8.4%)

Table 5. Childhood cancer anthracycline and alkylating agent chemotherapy treatment characteristics of female childhood/adolescent cancer survivors included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer by each participating study (continued)

	Participating study			
	CCSS (n=9,671)	**NWTS (n=3,989)**	**FCCSS (n=3,415)**	**SJLIFE (n=2,236)**
200-299	590 (6.1%)	-	207 (6.1%)	124 (5.5%)
300-399	568 (5.9%)	-	203 (5.9%)	146 (6.5%)
≥400	474 (4.9%)	-	137 (4.0%)	35 (1.6%)
Unknown	1,039 (10.7%)	1,752 (43.9%)	126 (3.7%)	19 (0.8%)
Daunorubicin				
No	7,660 (79.2%)	3,975 (99.6%)	3,239 (94.8%)	1,618 (72.4%)
Yes	1,219 (12.6%)	-	57 (1.7%)	600 (26.8%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)
Daunorubicin dose (mg/m²)				
Median [IQR]	151.0 [100.0, 319.4]	NA[¶]	255.7 [140.8, 419.7]	87.5 [50.0, 106.7]
Daunorubicin dose (mg/m²) category				
0	7,660 (79.2%)	3,975 (99.6%)	3,239 (94.8%)	1,618 (72.4%)
<100	263 (2.7%)	-	5 (0.1%)	339 (15.2%)
100-199	373 (3.9%)	-	17 (0.5%)	198 (8.9%)
≥200	494 (5.1%)	-	35 (1.0%)	62 (2.8%)
Unknown	881 (9.1%)	14 (0.4%)	119 (3.5%)	19 (0.8%)
Epirubicin				
No	8,877 (91.8%)	3,975 (99.6%)	3,116 (91.2%)	2,217 (99.2%)
Yes	2 (0.0%)	-	180 (5.3%)	1 (0.0%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)
Idarubicin				
No	8,814 (91.1%)	3,975 (99.6%)	3,296 (96.5%)	2,198 (98.3%)
Yes	65 (0.7%)	-	-	20 (0.9%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)
Alkylating agents				
No	4,003 (41.4%)	3,666 (91.9%)	1,597 (46.8%)	947 (42.4%)
Yes	4,876 (50.4%)	309 (7.7%)	1,699 (49.8%)	1,271 (56.8%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)
CED[§] dose (mg/m²)				
0	4,093 (42.3%)	3,666 (91.9%)	1,608 (47.1%)	956 (42.8%)
<6000	1,687 (17.4%)	-	606 (17.7%)	489 (21.9%)
6000-17999	1,876 (19.4%)	-	819 (24.0%)	631 (28.2%)
≥18000	561 (5.8%)	-	222 (6.5%)	139 (6.2%)
Unknown	1,454 (15.0%)	323 (8.1%)	160 (4.7%)	21 (0.9%)

CCSS = Childhood Cancer Survivor Study; SJLIFE = St. Jude Lifetime Cohort Study; NWTSG = US National Wilms Tumor Study group; DCCSS LATER = Dutch Long-term Effects After Childhood Cancer Study; FCCSS = French Childhood Cancer Survivor Study; SCCSS = Swiss Childhood Cancer Survivor Study; DHL = Dutch Hodgkin Late Effects cohort; SBC = Subsequent breast cancer; CNS = Central nervous system; yr = year; IQR = Interquartile range; NA = Not applicable; CED = Cyclophosphamide Equivalent Dose

[*]Includes patients with invasive and/or in situ breast cancer.

[†]Anthracyclines include doxorubicin, daunorubicin, epirubicin, and idarubicin.

			Overall		
LATER (n=2,237)	**DHL (n=265)**	**SCCSS (n=79)**	**Total (n=21,892)**	**Non-SBC patients (n=21,057)**	**SBC patients* (n=835)**
62 (2.8%)	38 (14.3%)	5 (6.3%)	1,026 (4.7%)	958 (4.5%)	68 (8.1%)
77 (3.4%)	11 (4.2%)	7 (8.9%)	1,012 (4.6%)	945 (4.5%)	67 (8.0%)
124 (5.5%)	6 (2.3%)	3 (3.8%)	779 (3.6%)	721 (3.4%)	58 (6.9%)
13 (0.6%)	4 (1.5%)	8 (10.1%)	2,961 (13.5%)	2,858 (13.6%)	103 (12.3%)
1,795 (80.2%)	253 (95.5%)	65 (82.3%)	18,605 (85.0%)	17,869 (84.9%)	736 (88.1%)
437 (19.5%)	-	7 (8.9%)	2,320 (10.6%)	2,278 (10.8%)	42 (5.0%)
5 (0.2%)	12 (4.5%)	7 (8.9%)	967 (4.4%)	910 (4.3%)	57 (6.8%)
120.0 [120.0, 175.0]	-	150.0 [120.0, 247.5]	120.0 [98.1, 234.1]	120.0 [98.0, 231.3]	175.0 [102.3, 362.9]
1,795 (80.2%)	253 (95.5%)	65 (82.3%)	18,605 (85.0%)	17,869 (84.9%)	736 (88.1%)
16 (0.7%)	-	-	623 (2.8%)	616 (2.9%)	7 (0.8%)
361 (16.1%)	-	4 (5.1%)	953 (4.4%)	937 (4.4%)	16 (1.9%)
51 (2.3%)	-	3 (3.8%)	645 (2.9%)	628 (3.0%)	17 (2.0%)
14 (0.6%)	12 (4.5%)	7 (8.9%)	1,066 (4.9%)	1,007 (4.8%)	59 (7.1%)
2,104 (94.1%)	251 (94.7%)	72 (91.1%)	20,612 (94.2%)	19,843 (94.2%)	769 (92.1%)
128 (5.7%)	14 (5.3%)	-	325 (1.5%)	316 (1.5%)	9 (1.1%)
5 (0.2%)	-	7 (8.9%)	955 (4.4%)	898 (4.3%)	57 (6.8%)
2,212 (98.9%)	253 (95.5%)	70 (88.6%)	20,818 (95.1%)	20,041 (95.2%)	777 (93.1%)
20 (0.9%)	-	2 (2.5%)	107 (0.5%)	106 (0.5%)	1 (0.1%)
5 (0.2%)	12 (4.5%)	7 (8.9%)	967 (4.4%)	910 (4.3%)	57 (6.8%)
1,152 (51.5%)	100 (37.7%)	33 (41.8%)	11,498 (52.5%)	11,167 (53.0%)	331 (39.6%)
1,080 (48.3%)	153 (57.7%)	39 (49.4%)	9,427 (43.1%)	8,980 (42.6%)	447 (53.5%)
5 (0.2%)	12 (4.5%)	7 (8.9%)	967 (4.4%)	910 (4.3%)	57 (6.8%)
1,160 (51.9%)	100 (37.7%)	34 (43.0%)	11,617 (53.1%)	11,272 (53.5%)	345 (41.3%)
265 (11.8%)	-	22 (27.8%)	3,069 (14.0%)	2,972 (14.1%)	97 (11.6%)
563 (25.2%)	-	10 (12.7%)	3,899 (17.8%)	3,706 (17.6%)	193 (23.1%)
192 (8.6%)	-	3 (3.8%)	1,117 (5.1%)	1,070 (5.1%)	47 (5.6%)
57 (2.5%)	165 (62.3%)	10 (12.7%)	2,190 (10.0%)	2,037 (9.7%)	153 (18.3%)

¶Chemotherapy dose information was not available in the NWTSG.
§Cyclophosphamide Equivalent Dose calculation: CED (mg/m^2) = 1.0 (cumulative cyclophosphamide dose (mg/m^2)) + 0.244 (cumulative ifosfamide dose (mg/m^2)) + 0.857 (cumulative procarbazine dose (mg/m^2)) + 14.286 (cumulative chlorambucil dose (mg/m^2)) + 15.0 (cumulative BCNU dose (mg/m^2)) + 16.0 (cumulative CCNU dose (mg/m^2)) + 40 (cumulative melphalan dose (mg/m^2)) + 50 (cumulative Thio-TEPA dose (mg/m^2)) + 100 (cumulative nitrogen mustard dose (mg/m^2)) + 8.823 (cumulative busulfan dose (mg/m^2)).

Strengths and Limitations

This study, to our knowledge, represents the largest cohort of childhood/adolescent cancer survivors with detailed information on treatment and subsequent breast cancer occurrences. Pooling individual patient observations from eligible cohorts worldwide will improve statistical power for the identification of risks of subsequent breast cancer associated with specific treatments, for which power was insufficient in the individual cohorts. Combining data will also increase the sample of childhood/adolescent cancer survivors who have attained 60 years of age, which will enable more precise estimation of the risk for subsequent breast cancers in this aging population. The differences between studies (e.g., primary cancer types, cancer treatment, reproductive factors) will also be considered analytically. Moreover, there may be more heterogeneity in treatment exposures in our study than in the single cohorts, given that childhood/adolescent cancer treatment protocols differ among the various countries contributing to this consortium (45). In childhood/adolescent cancer, specific treatment combinations tend to cluster by type of cancer (and, associated with that, treatment age), treatment era (and, thus, also attained age and follow-up), and country. The heterogeneity of treatment exposure, in particular regarding variation in treatment combinations across countries, creates a better possibility to disentangle single treatment exposures in the pooling effort, because better adjustments can be done for other treatments.

Of note, the participants in our study were recruited exclusively from North American and European cohorts, predominantly consisting of individuals of European ancestry. The homogeneity of our sample in this respect, may limit the generalizability of the results to other populations. Moreover, while initial full-consortium analyses focus on three a priori defined clinical research questions, the infrastructure of this individual pooled data project will facilitate analyses of additional effects of lifestyle, specific reproductive, and genetic factors, which are available for varying subgroups of the combined individual pooled data cohort, and which will be considered in future efforts. In addition, the consortium collaboration and structure can provide a robust source of information for identifying other knowledge gaps, including other subsequent malignancies. The established pipeline can be readily expanded to a larger cohort of childhood/adolescent cancer survivors, including both female and male survivors.

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Supplemental material

Supplemental Table 1. Key Characteristics of the original multi-institutional study cohorts included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer

	Participating collaborative groups		
	CCSS	**SJLIFE**	**NWTSG**
Main source publication	Leisenring et al. 2009 (32); Robison et al. 2009 (33)	Hudson et al. 2011 (34); Howell et al. 2021 (35)	Evans et al. 1991 (36); Lange et al. 2014 (37)
Study Methodology			
Setting	Multi-institutional cohort study	Single-center study*	Multi-institutional cohort study
Source for cohort identification	31 children's hospitals in the United States and Canada	Diagnosis of childhood malignancy treated at SJCRH	Clinical Trial databases of the NWTSG as basis for the Long Term Follow up Study
Treatment exposure assessment	- Data abstraction from medical records (ie, chemotherapy, radiation therapy, and surgery) - Region- and organ-based dosimetry from copies of all RT records for later dose reconstruction‡	- Data abstraction from medical records	NWTSG Clinical Trial Database
Follow-up methods	Self-reported/next of kin reported health surveys or followed by a telephonec call with validation of subsequent neoplasms. National Death Index for late mortality. Tracing protocol using multiple publicly available sources¶, including e.g. Social Security Administration and National Death Index	- Systematic clinical assessments supplemented by medical record validation of self-reported health events - Cancer Registry - For decedents: Next-of-Kin contact	- Bi-annual contact with family and health updates by treating center twice yearly
SMN outcome assessment	- Repeated questionnaire surveys; medical validation (including a pathology /oncology report review panel for subsequent malignancies, or the patient and/or parent response or death certificate and/ or other institutional records were reviewed) - Vital status and the cause of death were determined through the National Death Index (NDI)	- Comprehensive clinical evaluation on the SJCRH campus - Completion of health surveys by mail or phone interview for those survivors who decline to return to SJCRH or undergo a local evaluation - Systematic clinical assessments except limited to risk-based screening for breast and colon cancer surveillance since 2015	- At baseline (5 yr survival) abstraction of medical record for health outcomes - Follow-up via local physician (physical examination) and report to study center (physical examination forms) - Clinical records or annual status reports - Pathologic verification of subsequent malignant neoplasms
Source for population cancer rates	U.S. SEER Cancer Registries (National Cancer institute)	U.S. SEER Cancer Registries (National Cancer institute)	U.S. SEER Cancer Registries (National Cancer institute)

DCCSS LATER	FCCSS	SCCSS	DHL
Teepen et al. 2017 (10)	Demoor-Goldschmidt et al. 2020 (38); Gbetchedji et al. 2020 (39)	Michel et al. 2008 (40); Kuehni et al. 2012 (41)	Van Leeuwen et al. 2000 (42); De Bruin et al. 2009 (43); Van Eggermond et al. 2017 (44)
Multi-institutional cohort study	Multi-institutional cohort study	Nationwide population-based cohort study	Multi-institutional cohort study
7 pediatric oncology/ hematology centers, including 2 hematopoietic stem cell transplant centers	5- Pediatric Oncology-Departments of CLCC (Center for Struggle Against Cancer) in France	Swiss Childhood Cancer Registry	HL patients treated in 7 Dutch University Hospitals or Cancer Centers
- Medical record abstraction by trained data management staff - Digitization of RT paper-based records - Storage of X-ray reports	- Data abstraction from medical records (ie, chemotherapy, radiation therapy, and surgery) - Whole body and organ dosimetry from copies of RT records	Medical record abstraction	Medical record abstraction
- Medical record abstraction - Central Bureau for Genealogy (vital status, decedents) - Centralized municipal resident registry database (tracing) and vital status	- National death certificate data - National Public and Private Hospitals and National Health Insurance Database (SNDS) - Hospital clinical files - Long term follow-up visits - Self-completed questionnaires	- Medical record abstractions - Questionnaires surveys to patients or parents - Linkage to cantonal cancer registries - Linkage to national mortality statistics and birth statistics (Federal Statistical Office)	- Medical records - Netherlands Cancer Registry - Vital status through linkage with Municipal Personal Records Database
- Record linkage with national registries (cancer, pathology reports, hospital discharge diagnoses) - Clinical Visit including guideline-based surveillance - Self-administered questionnaire survey	- Algorithms for identification of the SMN from the ICD codes and the drugs codes in the SNDS - Specific item in self-questionnaires - Long term followup visits - Causes of deaths - Contact with pathologists, and getting copy of pathological records for all neoplasms	- Causes of death and death records from the Swiss mortality statistics in the Swiss Federal Statistical Office - Malignant neoplasms identified via linkage with Swiss cantonal cancer registries - Self-administered questionnaire survey	Up to 2004: - Medical records - By contacting general practitioners - By attending physicians in other hospitals Up to 2010: linkage with the nationalwide PALGA network and the Netherlands Cancer Registry
Netherlands Cancer Registry	FRANCIM (French Cancer Registry Network)	Swiss Childhood Cancer Registry and National Agency for Cancer Registration (www.nacr.ch)	Netherlands Cancer Registry

Supplemental Table 1. Key Characteristics of the original multi-institutional study cohorts included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer (continued)

	Participating collaborative groups		
	CCSS	**SJLIFE**	**NWTSG**
Inclusion Criteria			
Eligible survivors	Alive 5 yrs after diagnosis[§]	Alive 5 yrs after diagnosis at time of cohort entry	Alive 5 yrs post-surgery
Period of childhood cancer diagnosis	1970-1999	1962-2012	1969-2002
Age at childhood cancer diagnosis (yrs)	<21	<21[‖]	<20
Main Cohort Characteristics			
Source Cohort fulfilling eligibility criteria (n)	- For survivors diagnosed between 1970-1986: 20,687 (both male and female) - For survivors diagnosed between 1987-1999: 17,349 (both male and female)	8,192 (both male and female)	2,492 females
Base Cohort available for studies [**]	- For survivors diagnosed between 1970-1986: 14,361 - For survivors diagnosed between 1987-1999: 11,304	Contacted for recruitment: 7,471	2,492 females
Participation rates (including loss to follow-up)	- Follow-up 1, diagnosed 1970-86: 12,884 (participation 81%)[††] - Follow-up 2, diagnosed 1970-86: 11,859 (participation 78%) - Follow-up 3, diagnosed 1970-86:11,393 (participation 78%) - Follow-up 4, diagnosed 1970-86: 10,143 (participation 79%) - Follow-up 5, diagnosed 1970-1999: 18,041 (participation 63%) - Follow-up 6, diagnosed 1970-1999: 17,301 (participation 76%)	Survivors have completed a campus visit (n=5,223)/ Survivors contacted for recruitment (n=7,471) 69.9%	NA
Funding sources	National Cancer Institute: U24 CA55727, the Cancer Center Support (CORE) grant (CA21765, C. Roberts, Principal Investigator) and the American Lebanese Syrian Associated Charities (ALSAC)	National Cancer Institute at the National Institutes of Health Cancer Center Support grant [5P30CA021765-33] and the St. Jude Lifetime Cohort Study Grant [U01 CA195547], and the American Lebanese Syrian Associated Charities. Registered at Clinicaltrials.gov (#NCT00760656)	NIH grant 2 R01 CA054498

DCCSS LATER	FCCSS	SCCSS	DHL
Alive 5 yrs after diagnosis	Alive 5 yrs after diagnosis	Alive 5 yrs after diagnosis	Alive 5 yrs after receiving treatment
1963-2001	1946-2000	Since 1976	1965-1995
<18	<21	<21	<21[#]
6,165 (both male and female)	7,670 (both male and female)	By 31 December 2010: 5,553 (both male and female)	265 female pediatric HL survivors
6,015 (44% female)	7,670 (both male and female)	Questionnaire survey 2007-11: 2,738/5,553	265 female pediatric HL survivors
NA	1st self-questionnaire : 3,313/6,173 alive (53%) Linkage with SNDS : 5,679/6,173 alive (92%)	Questionnaire responded rate in adults and adolescents: 1,505/2,738 (for children aged 5-15 yr, mailing ongoing)	NA
Dutch Cancer Society KiKa Children Cancer Free ODAS Foundation European Union Dutch Childhood Oncology Group	Fondation Pfizer for childhood and Adolescent Health. Ligue Nationale Contre le Cancer (LNCC), Institut de Recherche en Santé Publique (IRES). Agence Nationale pour la Recherche (ANR). Fondation ARC pour la recherche sur le cancer, France Société Française pour les Cancer de l'Enfant (SFCE)	The SCCSS has been supported by the Swiss Cancer League and the Swiss Cancer Research foundation (KFS-02783-02-2011, KLS-3412-02-2014, KFS-4157-02-2017, KLS/KFS-4825-01-2019; KFS-4722-02-2019, KFS-5027-02-2020; KFS-5302-02-2021; KLS-5432-08-2021), Kinderkrebs Schweiz (www.kinderkrebs-schweiz.ch) and the parents association Kinderkrebshilfe Schweiz (www.kinderkrebshilfe.ch).	Dutch Cancer Society (NKI 2010-4720)

Supplemental Table 1. Key Characteristics of the original multi-institutional study cohorts included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer (continued)

	Participating collaborative groups		
	CCSS	**SJLIFE**	**NWTSG**
IRB and/or Ethics Committee approval	The St. Jude Children's Research Hospital Institutional Review Board provides oversight and approval for all CCSS activities	The St. Jude Children's Research Hospital Institutional Review Board provides oversight and approval for all SJLIFE activities	Institutional Review Board for the Fred Hutchinson Cancer Research Center provides oversight and approval for all NWTSG activities
Study website	https://ccss.stjude.org/	https://sjlife.stjude.org/	

CCSS = Childhood Cancer Survivor Study; SJLIFE = St. Jude Lifetime Cohort Study; NWTSG = US National Wilms Tumor Study group; DCCSS LATER = Dutch Long-term Effects After Childhood Cancer Study; FCCSS = French Childhood Cancer Survivor Study; SCCSS = Swiss Childhood Cancer Survivor Study; DHL = Dutch Hodgkin Late Effects cohort; Yr = Year; SJCRH = St Jude Childrens' Research Hospital, Memphis TN, USA; RT = Radiotherapy; NM = Not mentioned; NA = Not applicable

[*]Includes patients referred to St. Jude for treatment and follow-up care, largely from the USA; eligible survivors were recruited at their last annual follow-up visit to the After Completion of Therapy (ACT) Clinic upon reaching age 18 years or at high school graduation, whichever comes and from the SJCRH Cancer Registry.

[†]For details, see Stovall et al. 2006 (46) and Armstrong et al. 2009 (47).

[¶]Postal service address-correction requests, directory assistance, internet directories, reverse directories, contact of previous neighbors and/or relatives, voter registration records, post offices, Social Security Administration hand search, credit bureaus, property tax records, schools, social security death files, National Death Index.

[§]Craniopharyngioma and meningioma were excluded.

[||]The SJCRH generally restricts acceptance to children <25 years of diagnosis, but only survivors <21 years of diagnosis were included in our consortium.

[#]The DHL includes survivors who were <51 years at HL treatment. Only the information of the survivors who were diagnosed <21 years was provided to the consortium.

[**]Total/denominator as in column 'base cohort' unless otherwise specified.

[††]Participation among baseline participants still alive at initiation of Follow-up survey.

DCCSS LATER	FCCSS	SCCSS	DHL
The study protocol of the DCCSS LATER was declared exempt from the review of medical intervention research by the institutional review boards of all participating centers, in compliance with Dutch law and regulations for health research involving human beings	The FCCSS was approved by the French Data Protection Authority (CNIL) (Authorization n˚902287) and by the ethics committee of the INSERM. The FCCSSS also obtained a specific act in law from the French "Conseild'Etat", the highest court in France (Order 2014–96 of 2014 February 3), that approved the linkage with the SNDS (Système National des Données de Santé) data for all patients included in the FCCSS	The Swiss Childhood Cancer Registry and the Swiss Childhood Cancer Survivor Study have been approved by the cantonal ethics committee Bern (ethics approval KEK BE 166/2014); the data collection in Switzerland on second neoplasms within PanCareSurFup has been approved by the cantonal ethics committee Bern (ethics approval KEK BE 183/11)	The Netherlands Cancer Institute's Institutional Review Board approved participation in the current study
https://www.skionlaterstudie.nl/english/	www.fccss.fr		

Supplemental Table 2. Demographic, clinical, and childhood cancer treatment characteristics of female childhood/adolescent cancer survivors included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer by each participating study

	Participating study			
	CCSS (n=9,671)	**NWTS (n=3,989)**	**FCCSS (n=3,415)**	**SJLIFE (n=2,236)**
Primary childhood cancer type				
Leukemia	2,987 (30.9%)	-	-	802 (35.9%)
Non-Hodgkin lymphoma	586 (6.1%)	-	235 (6.9%)	115 (5.1%)
Hodgkin lymphoma	1,276 (13.2%)	-	189 (5.5%)	227 (10.2%)
CNS tumor	1,841 (19.0%)	-	498 (14.6%)	287 (12.8%)
Neuroblastoma	901 (9.3%)	-	505 (14.8%)	101 (4.5%)
Retinoblastoma	-	-	293 (8.6%)	119 (5.3%)
Renal tumor	389 (4.0%)	3989 (100%)	558 (16.3%)	170 (7.6%)
Hepatic tumor	-	-	32 (0.9%)	10 (0.4%)
Bone tumor	884 (9.1%)	-	295 (8.6%)	133 (5.9%)
Soft tissue tumor	763 (7.9%)	-	361 (10.6%)	127 (5.7%)
Germ cell tumor	20 (0.2%)	-	249 (7.3%)	68 (3.0%)
Other malignant epithelial neoplasms	-	-	187 (5.5%)	49 (2.2%)
Other and unspecified	-	-	7 (0.2%)	28 (1.3%)
Unclassified	24 (0.2%)	-	6 (0.2%)	-
Age at primary childhood cancer diagnosis (yr)				
Median [IQR]	7.5 [3.1, 13.7]	3.3 [1.8, 5.0]	5.2 [1.7, 11.4]	6.2 [2.7, 12.6]
Age at primary childhood cancer diagnosis (yr) category				
<5	3,666 (37.9%)	2,990 (75.0%)	1,671 (48.9%)	973 (43.5%)
5-9	2,027 (21.0%)	869 (21.8%)	707 (20.7%)	468 (20.9%)
10-14	2,204 (22.8%)	115 (2.9%)	744 (21.8%)	472 (21.1%)
15-21	1,774 (18.3%)	15 (0.4%)	293 (8.6%)	323 (14.4%)
Period of childhood cancer diagnosis, range				
Median [IQR]	1985 [1979, 1992]	1989 [1982, 1996]	1986 [1978, 1994]	1994 [1984, 2002]
Period of childhood cancer diagnosis category				
<1960	-	-	60 (1.8%)	-
1960-1969	-	3 (0.1%)	264 (7.7%)	42 (1.9%)
1970-1979	2,639 (27.3%)	612 (15.3%)	693 (20.3%)	274 (12.3%)
1980-1989	3,737 (38.6%)	1,440 (36.1%)	1,035 (30.3%)	535 (23.9%)
1990-1999	3,295 (34.1%)	1,562 (39.2%)	1,233 (36.1%)	633 (28.3%)
2000-2011	-	372 (9.3%)	130 (3.8%)	752 (33.6%)
Duration of follow-up since 5-yr survival (yr)[†]				
Median [IQR]	20.2 [14.7, 28.0]	15.7 [7.8, 24.9]	23.2 [16.3, 31.8]	18.0 [10.3, 27.5]
Duration of follow-up since 5-yr survival (yr)[†] category				
<10	1,096 (11.3%)	1,308 (32.8%)	251 (7.4%)	543 (24.3%)
10-19	3,672 (38.0%)	1,145 (28.7%)	1,130 (33.1%)	703 (31.4%)

			Overall		
LATER (n=2,237)	**DHL (n=265)**	**SCCSS (n=79)**	**Total (n=21,892)**	**Non-SBC patients (n=21,057)**	**SBC patients* (n=835)**
770 (34.4%)	-	15 (19.0%)	4,574 (20.9%)	4,492 (21.3%)	82 (9.8%)
157 (7.0%)	-	4 (5.1%)	1,097 (5.0%)	1,060 (5.0%)	37 (4.4%)
125 (5.6%)	265 (100%)	19 (24.1%)	2,101 (9.6%)	1,692 (8.0%)	409 (49.0%)
312 (13.9%)	-	8 (10.1%)	2,946 (13.5%)	2,932 (13.9%)	14 (1.7%)
145 (6.5%)	-	5 (6.3%)	1,657 (7.6%)	1,642 (7.8%)	15 (1.8%)
14 (0.6%)	-	-	426 (1.9%)	424 (2.0%)	2 (0.2%)
250 (11.2%)	-	5 (6.3%)	5,361 (24.5%)	5,270 (25.0%)	91 (10.9%)
19 (0.8%)	-	-	61 (0.3%)	60 (0.3%)	1 (0.1%)
141 (6.3%)	-	6 (7.6%)	1,459 (6.7%)	1,352 (6.4%)	107 (12.8%)
151 (6.8%)	-	3 (3.8%)	1,405 (6.4%)	1,350 (6.4%)	55 (6.6%)
101 (4.5%)	-	2 (2.5%)	440 (2.0%)	431 (2.0%)	9 (1.1%)
50 (2.2%)	-	11 (13.9%)	297 (1.4%)	286 (1.4%)	11 (1.3%)
2 (0.1%)	-	1 (1.3%)	38 (0.2%)	37 (0.2%)	1 (0.1%)
-	-	-	30 (0.1%)	29 (0.1%)	1 (0.1%)
5.4 [2.7, 10.7]	18.3 [16.6, 19.7]	14.2 [6.0, 17.3]	5.4 [2.5, 11.9]	5.2 [2.4, 11.3]	14.6 [11.6, 17.3]
1,049 (46.9%)	-	17 (21.5%)	10,366 (47.4%)	10,282 (48.8%)	84 (10.1%)
569 (25.4%)	7 (2.6%)	10 (12.7%)	4,657 (21.3%)	4,574 (21.7%)	83 (9.9%)
471 (21.1%)	21 (7.9%)	18 (22.8%)	4,045 (18.5%)	3,759 (17.9%)	286 (34.3%)
148 (6.6%)	237 (89.4%)	34 (43.0%)	2,824 (12.9%)	2,442 (11.6%)	382 (45.7%)
1989 [1981, 1996]	1982 [1974, 1991]	1990 [1984, 1999]	1987 [1980, 1995]	1987 [1980, 1995]	1980 [1974, 1986]
-	-	-	60 (0.3%)	51 (0.2%)	9 (1.1%)
49 (2.2%)	29 (10.9%)	-	387 (1.8%)	352 (1.7%)	35 (4.2%)
386 (17.3%)	81 (30.6%)	8 (10.1%)	4,693 (21.4%)	4,326 (20.5%)	367 (44.0%)
711 (31.8%)	76 (28.7%)	27 (34.2%)	7,561 (34.5%)	7,254 (34.4%)	307 (36.8%)
871 (38.9%)	76 (28.7%)	26 (32.9%)	7,696 (35.2%)	7,585 (36.0%)	111 (13.3%)
220 (9.8%)	3 (1.1%)	18 (22.8%)	1,495 (6.8%)	1,489 (7.1%)	6 (0.7%)
16.8 [10.8, 25.0]	17.6 [12.3, 25.7]	11.0 [6.7, 18.7]	19.3 [13.0, 27.8]	19.3 [12.9, 27.8]	20.6 [14.8, 26.2]
482 (21.5%)	40 (15.1%)	36 (45.6%)	3,756 (17.2%)	3,690 (17.5%)	66 (7.9%)
859 (38.4%)	116 (43.8%)	24 (30.4%)	7,649 (34.9%)	7,326 (34.8%)	323 (38.7%)

Supplemental Table 2. Demographic, clinical, and childhood cancer treatment characteristics of female childhood/adolescent cancer survivors included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer by each participating study (continued)

	Participating study			
	CCSS (n=9,671)	**NWTS (n=3,989)**	**FCCSS (n=3,415)**	**SJLIFE (n=2,236)**
20-29	3,014 (31.2%)	1,007 (25.2%)	1,019 (29.8%)	570 (25.5%)
≥30	1,889 (19.5%)	529 (13.3%)	1,015 (29.7%)	420 (18.8%)
Attained age at last follow-up (yr)[†]				
Median [IQR]	34.4 [26.7, 42.0]	24.3 [16.7, 33.8]	35.8 [27.2, 44.0]	31.8 [23.7, 39.9]
Attained age at last follow-up age (yr)[†] category				
<20	838 (8.7%)	1,484 (37.2%)	242 (7.1%)	380 (17.0%)
20-29	2,552 (26.4%)	1,128 (28.3%)	862 (25.2%)	614 (27.5%)
30-39	3,314 (34.3%)	921 (23.1%)	1,069 (31.3%)	688 (30.8%)
≥40	2,967 (30.7%)	456 (11.4%)	1,242 (36.4%)	554 (24.8%)
Subsequent invasive breast cancer diagnosis[¶]				
No	9,315 (96.3%)	3,955 (99.1%)	3,303 (96.7%)	2,181 (97.5%)
Yes	356 (3.7%)	34 (0.9%)	112 (3.3%)	55 (2.5%)
Subsequent in situ breast cancer diagnosis[¶]				
No	9,529 (98.5%)	3,971 (99.5%)	3,392 (99.3%)	2,206 (98.7%)
Yes	142 (1.5%)	18 (0.5%)	23 (0.7%)	30 (1.3%)
Any subsequent breast cancer (invasive or in situ)				
No	9,214 (95.3%)	3,943 (98.8%)	3,287 (96.3%)	2,158 (96.5%)
Yes	457 (4.7%)	46 (1.2%)	128 (3.7%)	78 (3.5%)
First subsequent breast cancer type				
Only invasive	336 (73.5%)	30 (65.2%)	110 (85.9%)	52 (66.7%)
Only in situ	113 (24.7%)	12 (26.1%)	16 (12.5%)	24 (30.8%)
Invasive and in situ diagnosed at the same moment	8 (1.8%)	4 (8.7%)	2 (1.6%)	2 (2.6%)
Vital status at last point of contact				
Alive	8,174 (84.5%)	3,802 (95.3%)	2,759 (80.8%)	2,171 (97.1%)
Deceased	1,497 (15.5%)	187 (4.7%)	656 (19.2%)	65 (2.9%)
Radiotherapy exposure to the chest				
No	6,607 (68.3%)	3,415 (85.6%)	2,728 (79.9%)	1,706 (76.3%)
Yes	2,098 (21.7%)	547 (13.7%)	482 (14.1%)	506 (22.6%)
Unknown	966 (10.0%)	27 (0.7%)	205 (6.0%)	24 (1.1%)
Chest radiation dose (Gy)				
Median [IQR]	30.0 [20.0, 39.0]	12.0 [12.0, 12.3]	27.5 [20.0, 40.0]	25.3 [15.0, 33.0]
Chest radiation dose (Gy) category				
No chest radiation	6,607 (68.3%)	3,415 (85.6%)	2,728 (79.9%)	1,706 (76.3%)
<10	73 (0.8%)	4 (0.1%)	7 (0.2%)	5 (0.2%)
10-19	403 (4.2%)	509 (12.8%)	102 (3.0%)	133 (5.9%)
20-29	533 (5.5%)	19 (0.5%)	148 (4.3%)	210 (9.4%)

			Overall		
LATER (n=2,237)	**DHL (n=265)**	**SCCSS (n=79)**	**Total (n=21,892)**	**Non-SBC patients (n=21,057)**	**SBC patients* (n=835)**
645 (28.8%)	69 (26.0%)	18 (22.8%)	6,342 (29.0%)	5,995 (28.5%)	347 (41.6%)
251 (11.2%)	40 (15.1%)	1 (1.3%)	4,145 (18.9%)	4,046 (19.2%)	99 (11.9%)
29.3 [22.1, 36.9]	40.9 [35.5, 48.8]	28.6 [24.3, 37.6]	32.2 [24.0, 40.4]	31.9 [23.7, 40.1]	39.3 [34.1, 44.5]
395 (17.7%)	1 (0.4%)	14 (17.7%)	3,354 (15.3%)	3,350 (15.9%)	4 (0.5%)
798 (35.7%)	26 (9.8%)	30 (38.0%)	6,010 (27.5%)	5,929 (28.2%)	81 (9.7%)
666 (29.8%)	93 (35.1%)	18 (22.8%)	6,769 (30.9%)	6,413 (30.5%)	356 (42.6%)
378 (16.9%)	145 (54.7%)	17 (21.5%)	5,759 (26.3%)	5,365 (25.5%)	394 (47.2%)
2,200 (98.3%)	211 (79.6%)	59 (74.7%)	21,224 (96.9%)	21,057 (100%)	167 (20.0%)
37 (1.7%)	54 (20.4%)	20 (25.3%)	668 (3.1%)	-	668 (80.0%)
2,232 (99.8%)	245 (92.5%)	79 (100%)	21,654 (98.9%)	21,057 (100%)	597 (71.5%)
5 (0.2%)	20 (7.5%)	-	238 (1.1%)	-	238 (28.5%)
2,196 (98.2%)	200 (75.5%)	59 (74.7%)	21,057 (96.2%)	21,057 (100%)	-
41 (1.8%)	65 (24.5%)	20 (25.3%)	835 (3.8%)	-	835 (100%)
36 (87.8%)	51 (78.5%)	20 (100%)	635 (76.1%)[§]	-	635 (76.1%)[§]
5 (12.2%)	14 (21.5%)	-	184 (22.0%)[‖#]	-	184 (22.0%)[‖#]
-	-	-	16 (1.9%)[**]	-	16 (1.9%)[**]
1,928 (86.2%)	178 (67.2%)	68 (86.1%)	19,080 (87.2%)	18,489 (87.8%)	591 (70.8%)
309 (13.8%)	87 (32.8%)	11 (13.9%)	2,812 (12.8%)	2,568 (12.2%)	244 (29.2%)
1,892 (84.6%)	22 (8.3%)	49 (62.0%)	16,419 (75.0%)	16,145 (76.7%)	274 (32.8%)
341 (15.2%)	243 (91.7%)	23 (29.1%)	4,240 (19.4%)	3,735 (17.7 %)	505 (60.5%)
4 (0.2%)	-	7 (8.9%)	1,233 (5.6%)	1,177 (5.6%)	56 (6.7%)
25.0 [13.8, 35.2]	38.0 [35.0, 40.0]	36.0 [19.8, 40.0]	25.0 [14.0, 36.0]	24.0 [13.8, 36.0]	36.0 [25.0, 40.9]
1,892 (84.6%)	22 (8.3%)	49 (62.0%)	16,419 (75.0%)	16,145 (76.7%)	274 (32.8%)
48 (2.1%)	-	-	137 (0.6%)	132 (0.6%)	5 (0.6%)
69 (3.1%)	2 (0.8%)	6 (7.6%)	1,224 (5.6%)	1,151 (5.5%)	73 (8.7%)
60 (2.7%)	11 (4.2%)	2 (2.5%)	983 (4.5%)	906 (4.3%)	77 (9.2%)

Supplemental Table 2. Demographic, clinical, and childhood cancer treatment characteristics of female childhood/adolescent cancer survivors included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer by each participating study (continued)

	Participating study			
	CCSS (n=9,671)	**NWTS (n=3,989)**	**FCCSS (n=3,415)**	**SJLIFE (n=2,236)**
30-39	542 (5.6%)	12 (0.3%)	92 (2.7%)	85 (3.8%)
≥40	511 (5.3%)	3 (0.1%)	133 (3.9%)	41 (1.8%)
Unknown	1,002 (10.4%)	27 (0.7%)	205 (6.0%)	56 (2.5%)
Chest radiation field				
No chest radiation	6,607 (68.3%)	3,415 (85.6%)	2,728 (79.9%)	1,706 (76.3%)
Axilla	12 (0.1%)	-	-	5 (0.2%)
Mantle	723 (7.5%)	-	86 (2.5%)	191 (8.5%)
Mediastinal	227 (2.3%)	1 (0.0%)	134 (3.9%)	23 (1.0%)
Others	177 (1.8%)	19 (0.5%)	117 (3.4%)	33 (1.5%)
Spine	598 (6.2%)	-	98 (2.9%)	131 (5.9%)
Total body irradiation	223 (2.3%)	-	10 (0.3%)	67 (3.0%)
Whole lung	79 (0.8%)	527 (13.2%)	37 (1.1%)	44 (2.0%)
Unknown	1,025 (10.6%)	27 (0.7%)	205 (6.0%)	36 (1.6%)
Radiotherapy exposure to the Pelvis				
No	7,191 (74.4%)	1,922 (48.2%)	2,287 (67.0%)	1,873 (83.8%)
Yes	1,515 (15.7%)	-	923 (27.0%)	337 (15.1%)
Unknown	965 (10.0%)	2,067 (51.8%)	205 (6.0%)	26 (1.2%)
Pelvic radiation dose (Gy)				
Median [IQR]	26.0 [15.0, 36.0]	NA[††]	33.0 [22.0, 43.5]	23.4 [16.8, 36.0]
Pelvic radiation dose (Gy) category				
No pelvic radiation	7,191 (74.4%)	1,922 (48.2%)	2,287 (67.0%)	1,873 (83.8%)
<10	66 (0.7%)	-	25 (0.7%)	4 (0.2%)
10-19	369 (3.8%)	-	114 (3.3%)	89 (4.0%)
20-29	365 (3.8%)	-	232 (6.8%)	120 (5.4%)
30-39	398 (4.1%)	-	216 (6.3%)	66 (3.0%)
≥40	295 (3.1%)	-	336 (9.8%)	57 (2.5%)
Unknown	987 (10.2%)	2,067 (51.8%)	205 (6.0%)	27 (1.2%)
Anthracyclines[§§]				
No	4,889 (50.6%)	2,237 (56.1%)	2,095 (61.3%)	955 (42.7%)
Yes	3,990 (41.3%)	1,738 (43.6%)	1,201 (35.2%)	1,263 (56.5%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)
Doxorubicin				
No	5,729 (59.2%)	2,237 (56.1%)	2,300 (67.4%)	1,377 (61.6%)
Yes	3,150 (32.6%)	1,738 (43.6%)	996 (29.2%)	841 (37.6%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)

			Overall		
LATER (n=2,237)	**DHL (n=265)**	**SCCSS (n=79)**	**Total (n=21,892)**	**Non-SBC patients (n=21,057)**	**SBC patients* (n=835)**
82 (3.7%)	90 (34.0%)	5 (6.3%)	908 (4.1%)	762 (3.6%)	146 (17.5%)
68 (3.0%)	85 (32.1%)	6 (7.6%)	847 (3.9%)	650 (3.1%)	197 (23.6%)
18 (0.8%)	55 (20.8%)	11 (13.9%)	1,374 (6.3%)	1,311 (6.2%)	63 (7.5%)
1,892 (84.6%)	22 (8.3%)	49 (62.0%)	16,419 (75.0%)	16,145 (76.7%)	274 (32.8%)
15 (0.7%)	2 (0.8%)	-	34 (0.2%)	31 (0.1%)	3 (0.4%)
39 (1.7%)	192 (72.5%)	11 (13.9%)	1,242 (5.7%)	911 (4.3%)	331 (39.6%)
36 (1.6%)	45 (17.0%)	4 (5.1%)	470 (2.1%)	437 (2.1%)	33 (4.0%)
49 (2.2%)	-	1 (1.3%)	396 (1.8%)	344 (1.6%)	52 (6.2%)
109 (4.9%)	-	3 (3.8%)	939 (4.3%)	927 (4.4%)	12 (1.4%)
69 (3.1%)	-	2 (2.5%)	371 (1.7%)	348 (1.7%)	23 (2.8%)
22 (1.0%)	-	2 (2.5%)	711 (3.2%)	663 (3.1%)	48 (5.7%)
6 (0.8%)	4 (1.5%)	7 (8.9%)	1,310 (6.0%)	1,251 (5.9%)	59 (7.1%)
2,129 (95.2%)	179 (67.5%)	68 (86.1%)	15,649 (71.5%)	15,133 (71.9%)	516 (61.8%)
105 (4.7%)	81 (30.6%)	3 (3.8%)	2,964 (13.5%)	2,740 (13.0%)	224 (26.8%)
3 (0.1%)	5 (1.9%)	8 (10.1%)	3,279 (15.0%)	3,184 (15.1%)	95 (11.4%)
12.0 [7.5, 38.5]	NA¶¶	11.0 [10.5, 11.5]	30.0 [19.0, 39.0]	28.0 [18.0, 38.0]	34.0 [24.0, 42.5]
2,129 (95.2%)	179 (67.5%)	68 (86.1%)	15,649 (71.5%)	15,133 (71.9%)	516 (61.8%)
47 (2.1%)	-	-	142 (0.6%)	136 (0.6%)	6 (0.7%)
20 (0.9%)	-	2 (2.5%)	594 (2.7%)	570 (2.7%)	24 (2.9%)
2 (0.1%)	-	-	719 (3.3%)	681 (3.2%)	38 (4.6%)
6 (0.3%)	81 (30.6%)¶¶	-	767 (3.5%)	684 (3.2%)	83 (9.9%)
25 (1.1%)	-	-	713 (3.3%)	641 (3.0%)	72 (8.6%)
8 (0.4%)	5 (1.9%)	9 (11.4%)	3,308 (15.1%)	3,212 (15.3%)	96 (11.5%)
1,250 (55.9%)	155 (58.5%)	36 (45.6%)	11,617 (53.1%)	11,204 (53.2%)	413 (49.5%)
982 (43.9%)	98 (37.0%)	36 (45.6%)	9,308 (42.5%)	8,943 (42.5%)	365 (43.7%)
5 (0.2%)	12 (4.5%)	7 (8.9%)	967 (4.4%)	910 (4.3%)	57 (6.8%)
1,541 (68.9%)	181 (68.3%)	42 (53.2%)	13,407 (61.2%)	12,954 (61.5%)	453 (54.3%)
691 (30.9%)	84 (31.7%)	30 (38.0%)	7,530 (34.4%)	7,205 (34.2%)	325 (38.9%)
5 (0.2%)	-	7 (8.9%)	955 (4.4%)	898 (4.3%)	57 (6.8%)

Supplemental Table 2. Demographic, clinical, and childhood cancer treatment characteristics of female childhood/adolescent cancer survivors included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer by each participating study (continued)

	Participating study			
	CCSS (n=9,671)	**NWTS (n=3,989)**	**FCCSS (n=3,415)**	**SJLIFE (n=2,236)**
Doxorubicin dose (mg/m²)				
Median [IQR]	224.7 [130.4, 358.3]	NA##	235.7 [131.7, 346.8]	177.4 [135.1, 256.2]
Doxorubicin dose (mg/m²) category				
0	5,729 (59.2%)	2,237 (56.1%)	2,300 (67.4%)	1,377 (61.6%)
<100	502 (5.2%)	-	95 (2.8%)	121 (5.4%)
100-199	769 (8.0%)	-	347 (10.2%)	414 (18.5%)
200-299	590 (6.1%)	-	207 (6.1%)	124 (5.5%)
300-399	568 (5.9%)	-	203 (5.9%)	146 (6.5%)
≥400	474 (4.9%)	-	137 (4.0%)	35 (1.6%)
Unknown	1,039 (10.7%)	1,752 (43.9%)	126 (3.7%)	19 (0.8%)
Daunorubicin				
No	7,660 (79.2%)	3,975 (99.6%)	3,239 (94.8%)	1,618 (72.4%)
Yes	1,219 (12.6%)	-	57 (1.7%)	600 (26.8%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)
Daunorubicin dose (mg/m²)				
Median [IQR]	151.0 [100.0, 319.4]	NA##	255.7 [140.8, 419.7]	87.5 [50.0, 106.7]
Daunorubicin dose (mg/m²) category				
0	7,660 (79.2%)	3,975 (99.6%)	3,239 (94.8%)	1,618 (72.4%)
<100	263 (2.7%)	-	5 (0.1%)	339 (15.2%)
100-199	373 (3.9%)	-	17 (0.5%)	198 (8.9%)
≥200	494 (5.1%)	-	35 (1.0%)	62 (2.8%)
Unknown	881 (9.1%)	14 (0.4%)	119 (3.5%)	19 (0.8%)
Epirubicin				
No	8,877 (91.8%)	3,975 (99.6%)	3,116 (91.2%)	2,217 (99.2%)
Yes	2 (0.0%)	-	180 (5.3%)	1 (0.0%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)
Idarubicin				
No	8,814 (91.1%)	3,975 (99.6%)	3,296 (96.5%)	2,198 (98.3%)
Yes	65 (0.7%)	-	-	20 (0.9%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)
Alkylating agents				
No	4,003 (41.4%)	3,666 (91.9%)	1,597 (46.8%)	947 (42.4%)
Yes	4,876 (50.4%)	309 (7.7%)	1,699 (49.8%)	1,271 (56.8%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)
CED*** dose (mg/m²)				

			Overall		
LATER (n=2,237)	**DHL (n=265)**	**SCCSS (n=79)**	**Total (n=21,892)**	**Non-SBC patients (n=21,057)**	**SBC patients* (n=835)**
150.0 [65.0, 300.0]	210.0 [140.0, 280.0]	200.0 [150.0, 300.0]	203.3 [120.0, 340.0]	200.0 [120.0, 337.3]	281.9 [179.7, 371.8]
1,541 (68.9%)	181 (68.3%)	42 (53.2%)	13,407 (61.2%)	12,954 (61.5%)	453 (54.3%)
188 (8.4%)	5 (1.9%)	1 (1.3%)	912 (4.2%)	896 (4.3%)	16 (1.9%)
232 (10.4%)	20 (7.5%)	13 (16.5%)	1,795 (8.2%)	1,725 (8.2%)	70 (8.4%)
62 (2.8%)	38 (14.3%)	5 (6.3%)	1,026 (4.7%)	958 (4.5%)	68 (8.1%)
77 (3.4%)	11 (4.2%)	7 (8.9%)	1012 (4.6%)	945 (4.5%)	67 (8.0%)
124 (5.5%)	6 (2.3%)	3 (3.8%)	779 (3.6%)	721 (3.4%)	58 (6.9%)
13 (0.6%)	4 (1.5%)	8 (10.1%)	2,961 (13.5%)	2,858 (13.6%)	103 (12.3%)
1,795 (80.2%)	253 (95.5%)	65 (82.3%)	18,605 (85.0%)	17,869 (84.9%)	736 (88.1%)
437 (19.5%)	-	7 (8.9%)	2,320 (10.6%)	2,278 (10.8%)	42 (5.0%)
5 (0.2%)	12 (4.5%)	7 (8.9%)	967 (4.4%)	910 (4.3%)	57 (6.8%)
120.0 [120.0, 175.0]	-	150.0 [120.0, 247.5]	120.0 [98.1, 234.1]	120.0 [98.0, 231.3]	175.0 [102.3, 362.9]
1,795 (80.2%)	253 (95.5%)	65 (82.3%)	18,605 (85.0%)	17,869 (84.9%)	736 (88.1%)
16 (0.7%)	-	-	623 (2.8%)	616 (2.9%)	7 (0.8%)
361 (16.1%)	-	4 (5.1%)	953 (4.4%)	937 (4.4%)	16 (1.9%)
51 (2.3%)	-	3 (3.8%)	645 (2.9%)	628 (3.0%)	17 (2.0%)
14 (0.6%)	12 (4.5%)	7 (8.9%)	1,066 (4.9%)	1,007 (4.8%)	59 (7.1%)
2,104 (94.1%)	251 (94.7%)	72 (91.1%)	20,612 (94.2%)	19,843 (94.2%)	769 (92.1%)
128 (5.7%)	14 (5.3%)	-	325 (1.5%)	316 (1.5%)	9 (1.1%)
5 (0.2%)	-	7 (8.9%)	955 (4.4%)	898 (4.3%)	57 (6.8%)
2,212 (98.9%)	253 (95.5%)	70 (88.6%)	20,818 (95.1%)	20,041 (95.2%)	777 (93.1%)
20 (0.9%)	-	2 (2.5%)	107 (0.5%)	106 (0.5%)	1 (0.1%)
5 (0.2%)	12 (4.5%)	7 (8.9%)	967 (4.4%)	910 (4.3%)	57 (6.8%)
1,152 (51.5%)	100 (37.7%)	33 (41.8%)	11,498 (52.5%)	11,167 (53.0%)	331 (39.6%)
1,080 (48.3%)	153 (57.7%)	39 (49.4%)	9,427 (43.1%)	8,980 (42.6%)	447 (53.5%)
5 (0.2%)	12 (4.5%)	7 (8.9%)	967 (4.4%)	910 (4.3%)	57 (6.8%)

Supplemental Table 2. Demographic, clinical, and childhood cancer treatment characteristics of female childhood/adolescent cancer survivors included in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer by each participating study (continued)

	Participating study			
	CCSS (n=9,671)	**NWTS (n=3,989)**	**FCCSS (n=3,415)**	**SJLIFE (n=2,236)**
0	4,093 (42.3%)	3,666 (91.9%)	1,608 (47.1%)	956 (42.8%)
<6000	1,687 (17.4%)	-	606 (17.7%)	489 (21.9%)
6000-17999	1,876 (19.4%)	-	819 (24.0%)	631 (28.2%)
≥18000	561 (5.8%)	-	222 (6.5%)	139 (6.2%)
Unknown	1,454 (15.0%)	323 (8.1%)	160 (4.7%)	21 (0.9%)
Epipodophyllotoxins				
No	7,567 (78.2%)	3,784 (94.9%)	2,531 (74.1%)	1,402 (62.7%)
Yes	1,312 (13.6%)	191 (4.8%)	765 (22.4%)	816 (36.5%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)
Vinca alkaloids				
No	3,351 (34.7%)	126 (3.2%)	1,367 (40.0%)	706 (31.6%)
Yes	5,528 (57.2%)	3,849 (96.5%)	1,929 (56.5%)	1,512 (67.6%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)
Platinum compounds				
No	7,817 (80.8%)	3,957 (99.2%)	2,473 (72.4%)	1,870 (83.6%)
Yes	1,062 (11.0%)	18 (0.5%)	823 (24.1%)	348 (15.6%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)
Antimetabolites				
No	5,012 (51.8%)	3,975 (99.6%)	2,816 (82.5%)	1,151 (51.5%)
Yes	3,867 (40.0%)	-	480 (14.1%)	1,067 (47.7%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)

CCSS = Childhood Cancer Survivor Study; SJLIFE = St. Jude Lifetime Cohort Study; NWTSG = US National Wilms Tumor Study group; DCCSS LATER = Dutch Long-term Effects After Childhood Cancer Study; FCCSS = French Childhood Cancer Survivor Study; SCCSS = Swiss Childhood Cancer Survivor Study; DHL = Dutch Hodgkin Late Effects cohort; SBC = Subsequent breast cancer; CNS = Central nervous system; yr = year; IQR = Interquartile range; NA = Not applicable; CED = Cyclophosphamide Equivalent Dose; DCIS = Ductal carcinoma in situ; LCIS = Lobular carcinoma in situ

*Includes patients with invasive and/or in situ breast cancer.

†Follow-up time was calculated from five years after a primary cancer diagnosis to the date of subsequent breast cancer diagnosis, death, or the date of the last follow-up observation, whichever occurred first.

¶71 patients developed both a subsequent invasive and in situ breast cancer.

§Among survivors with an invasive first subsequent breast cancer, 103 developed a second subsequent breast cancer (65 invasive, 34 DCIS, 4 LCIS), 4 developed a third subsequent breast cancer (all invasive), and 1 developed LCIS as a forth subsequent breast cancer.

||Among survivors with an in situ first subsequent breast cancer, 38 developed a second subsequent breast cancer (16 invasive, 17 DCIS, 5 LCIS), and 4 developed a third subsequent breast cancer (1 invasive, 2 DCIS, 1 LCIS).

#Includes 172 DCIS and 12 LCIS.

**Among survivors with both an invasive and in situ first subsequent breast cancer diagnosed at the same

			Overall		
LATER (n=2,237)	**DHL (n=265)**	**SCCSS (n=79)**	**Total (n=21,892)**	**Non-SBC patients (n=21,057)**	**SBC patients* (n=835)**
1,160 (51.9%)	100 (37.7%)	34 (43.0%)	11,617 (53.1%)	11,272 (53.5%)	345 (41.3%)
265 (11.8%)	-	22 (27.8%)	3,069 (14.0%)	2,972 (14.1%)	97 (11.6%)
563 (25.2%)	-	10 (12.7%)	3,899 (17.8%)	3,706 (17.6%)	193 (23.1%)
192 (8.6%)	-	3 (3.8%)	1,117 (5.1%)	1,070 (5.1%)	47 (5.6%)
57 (2.5%)	165 (62.3%)	10 (12.7%)	2,190 (10.0%)	2,037 (9.7%)	153 (18.3%)
1,796 (80.3%)	83 (31.3%)	55 (69.6%)	17,218 (78.6%)	16,555 (78.6%)	663 (79.4%)
436 (19.5%)	-	17 (21.5%)	3,537 (16.2%)	3,459 (16.4%)	78 (9.3%)
5 (0.2%)	182 (68.7%)	7 (8.9%)	1,137 (5.2%)	1,043 (5.0%)	94 (11.3%)
653 (29.2%)	83 (31.3%)	34 (43.0%)	6,320 (28.9%)	6,047 (28.7%)	273 (32.7%)
1,579 (70.6%)	-	38 (48.1%)	14,435 (65.9%)	13,967 (66.3%)	468 (56.0%)
5 (0.2%)	182 (68.7%)	7 (8.9%)	1,137 (5.2%)	1,043 (5.0%)	94 (11.3%)
1,911 (85.4%)	83 (31.3%)	65 (82.3%)	18,176 (83.0%)	17,485 (83.0%)	691 (82.8%)
321 (14.3%)	-	7 (8.9%)	2,579 (11.8%)	2,529 (12.0%)	50 (6.0%)
5 (0.2%)	182 (68.7%)	7 (8.9%)	1,137 (5.2%)	1,043 (5.0%)	94 (11.3%)
1,261 (56.4%)	83 (31.3%)	53 (67.1%)	14,351 (65.6%)	13,798 (65.5%)	553 (66.2%)
971 (43.4%)	-	19 (24.1%)	6,404 (29.3%)	6,216 (29.5%)	188 (22.5%)
5 (0.2%)	182 (68.7%)	7 (8.9%)	1,137 (5.2%)	1,043 (5.0%)	94 (11.3%)

moment, 2 developed DCIS as a third subsequent breast cancer.

[††]Pelvic radiation information was not available in the NWTSG.

[¶¶]Dose of pelvic radiation information was not available for the DHL. We assume the survivors in the DHL who had pelvic RT received 30 Gy RT exposure to the pelvis since Hodgkin lymphoma patients usually receive 30 Gy pelvic radiation.

[§§]Anthracyclines include doxorubicin, daunorubicin, epirubicin, and idarubicin.

[##]Chemotherapy dose information was not available in the NWTSG.

[***]Cyclophosphamide Equivalent Dose calculation: CED (mg/m^2) = 1.0 (cumulative cyclophosphamide dose (mg/m^2)) + 0.244 (cumulative ifosfamide dose (mg/m^2)) + 0.857 (cumulative procarbazine dose (mg/m^2)) + 14.286 (cumulative chlorambucil dose (mg/m^2)) + 15.0 (cumulative BCNU dose (mg/m^2)) + 16.0 (cumulative CCNU dose (mg/m^2)) + 40 (cumulative melphalan dose (mg/m^2)) + 50 (cumulative Thio-TEPA dose (mg/m^2)) + 100 (cumulative nitrogen mustard dose (mg/m^2)) + 8.823 (cumulative busulfan dose (mg/m^2)).

Supplemental Table 3. Published results from participating cohorts in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer

Study	Title	Study design	Number of female childhood/ adolescent cancer survivors	Follow-up duration
Research question 1: Chest radiotherapy-related subsequent breast cancer risk				
CCSS (Kenney et al. 2004) (48)	Breast Cancer after Childhood Cancer: A Report from the Childhood Cancer Survivor Study	Cohort	6,068 female 5-yr survivors Diagnosed 1970-1986	For subsequent breast cancer cases: median 19 (range 6-29) yr since primary cancer diagnosis; For non- subsequent breast cancer cases: median 18 (range 5-31) yr since primary cancer diagnosis
CCSS (Inskip et al. 2009) (25)	Radiation Dose and Breast Cancer Risk in the Childhood Cancer Survivor Study	Case-control	120 patients matched with 464 controls Female 5-yr survivors Treated 1970-1986	For subsequent breast cancer cases: Median 19.4 (range 6.7-29.6) yr since primary cancer diagnosis
CCSS (Moskowitz et al. 2014) (27)	Breast Cancer after Chest Radiation Therapy for Childhood Cancer	Cohort	1,230 female 5-yr survivors received chest irradiation within 5 years of their childhood cancer diagnosis Treated 1970-1986	Median 25.9 (range 8.4-40.6) yr
CCSS (Moskowitz et al. 2015) (49)	Breast Cancer following Spinal Irradiation for a Childhood Cancer: A Report from the Childhood Cancer Survivor Study	Cohort	363 female 5-yr survivors of a pediatric central nervous system tumor or leukemia treated with spinal irradiation Diagnosed 1970-1986	Median follow-up 27 (range 10-38) yr

Subsequent breast cancer	Subsequent breast cancer risk estimates	Findings
95 survivors developed 111 cases of breast cancer	Radiotherapy exposure to the chest, yes/no & SIR (95% CI): 24.7 (19.3-31.0)	Breast cancer risk was increased in survivors who had radiotherapy exposure to the chest
120 breast cancer cases	Radiation dose category, Gy & OR (95% CI) 0 Gy: ref. >0-0.13 Gy: 1.4 (0.5-4.4) 0.14-1.29 Gy: 1.9 (0.7-5.4) 1.30-11.39 Gy: 1.9 (0.7-5.0) 11.40-29.99 Gy: 7.1 (2.9-17) 30.00-60.00 Gy: 10.8 (3.8-31) *P trend* < 0.001 Analyses were adjusted for type of first cancer Excess OR per Gy: 0.36 for those who received ovarian doses <5 Gy; 0.06 for those who received higher doses	A dose-response relation between reconstructed radiation dose to the breast and subsequent breast cancer risk, which was reduced among women with dose to the ovaries of >5 Gy
203 women had a confirmed breast cancer diagnosis	Primary field of chest irradiation, dose in Gy & SIR (95% CI) Mantle (median, 40 Gy; range, 5-54): 24.2 (20.7-28.3) Mediastinal (median, 30 Gy; range, 3-54): 13.0 (8.4-20.2) Whole lung (median, 14 Gy; range, 2-20): 43.6 (27.1-70.1) Total body (median, 12 Gy; range, 4-16): 19.3 (7.3-51.5) Abdominal (median, 20 Gy; range, 4-40): 10.8 (2.7-43.2) Other one-sided anterior (median, 41 Gy; range, 10-61): 9.9 (3.2-30.6)	Delivered radiation dose/volume associated with subsequent breast cancer risk
3 women were diagnosed with breast cancer	Treated with spinal irradiation , yes/no & SIR (95% CI): 2.4 (0.8-7.5)	Spinal irradiation for treatment may not be associated with an increased breast cancer risk

Supplemental Table 3. Published results from participating cohorts in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer (continued)

Study	Title	Study design	Number of female childhood/ adolescent cancer survivors	Follow-up duration
CCSS (Moskowitz et al. 2017) (50)	Radiation-associated Breast Cancer and Gonadal Hormone Exposure: A Report from the Childhood Cancer Survivor Study	Cohort	1,108 female 5-yr survivors treated with chest radiotherapy, and survived to ages ≥20 years Diagnosed 1970-1986	Median follow-up 26 (range 5-38) yr
CCSS (Veiga et al. 2019) (12)	Association of Breast Cancer Risk after Childhood Cancer with Radiation Dose to the Breast and Anthracycline use: A Report from the Childhood Cancer Survivor Study	Case-control	271 cases matched with 1,044 controls Female 5-yr survivors Diagnosed 1970-1986	Range 5-40 yr since primary cancer diagnosis
SJLIFE (Ehrhardt et al. 2019) (28)	Subsequent Breast Cancer in Female Childhood Cancer Survivors in the St Jude Lifetime Cohort Study (SJLIFE)	Cohort	1,467 female 10-yr survivors	Median 22.7 (range 10.5-48.2) yr since primary cancer diagnosis
NWTSG (Lange et al. 2014) (37)	Breast Cancer in Female Wilms Tumor Survivors: A Report from the National Wilms Tumor Late Effects Study	Cohort	2,492 female 5-yr Wilms tumor survivors 1969-1995	NM

Subsequent breast cancer	Subsequent breast cancer risk estimates	Findings
195 women were diagnosed with breast cancer	Delivered chest radiation dose, dose in Gy & HR (95% CI) 1-19 Gy: ref. 20-29 Gy: 0.58 (0.31-1.11) 30-39 Gy: 0.68 (0.41-1.13) 40+ Gy: 0.80 (0.49-1.28) Univariable analysis Chest radiation ≤1 yr of menarche vs. >1 yr from menarche HR (95% CI): 1.80 (1.19-2.72) Analyses were adjusted for age at primary childhood cancer diagnosis, chest radiation field and delivered dose, and exposure to anthracyclines	Chest radiotherapy increases breast cancer risk especially when administered near menarche
271 breast cancer cases	Increasing radiation dose to the breast OR (95% CI) per 10 Gy, 3.9 (2.5-6.5) Analyses were adjusted for first cancer diagnosis, chemotherapy (yes/no), calendar year of breast cancer diagnosis, and family history of breast/ovarian cancer	Reconstructed breast radiation dose associated with subsequent breast cancer risk; the combined effect of anthracycline and radiotherapy was stronger than the individual effects of these two treatments on subsequent breast cancer risk
56 survivors developed 68 breast cancers	Chest radiation, Gy & HR (95% CI) None: ref. >0-<10 Gy: 0.7 (0.2-2.8) 10-<20 Gy: 2.4 (0.4-15.0) ≥20 Gy: 7.6 (2.9-20.4) Excluding survivors with pathogenic/likely pathogenic mutations: Chest radiation, Gy & HR (95% CI) None: ref. >0-<10 Gy: 1.2 (0.3-5.0) 10-<20 Gy: 8.0 (1.1-56.3) ≥20 Gy: 10.0 (3.3-30.5) Analyses were adjusted for age at diagnosis	Subsequent breast cancer risk was associated with 20 Gy or more of chest radiation
28 survivors developed 29 breast cancers	Cumulative risk (95% CI) of breast cancer at age 40: No RT: 0.3% (0.0-2.3) Chest RT: 14.8% (8.7-24.5) No chest dose: 2.3% (1.0-5.1) Chest dose 1-12 Gy: 14.4% (7.6-30.1) Chest dose >12 Gy: 14.2% (7.1-29.3) SIR (95% CI): No RT: 2.2 Chest RT: 27.6 (16.1-44.2) No chest dose: 4.6 Chest dose 1-12 Gy: 46.8 Chest dose >12 Gy: 18.9	Female Wilms tumor survivors treated with chest RT had high risk of breast cancer at early age

Supplemental Table 3. Published results from participating cohorts in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer (continued)

Study	Title	Study design	Number of female childhood/ adolescent cancer survivors	Follow-up duration
DCCSS LATER (Teepen et al. 2017) (10)	Long-Term Risk of Subsequent Malignant Neoplasms After Treatment of Childhood Cancer in the DCOG LATER Study Cohort: Role of Chemotherapy	Cohort	2,731 female 5-yr survivors Diagnosed 1963-2001	For the whole cohort (both males and females): Median 20.7 (range 5.0-49.8) yr since primary cancer diagnosis
DHL (van Leeuwen et al. 2003) (51)	Roles of Radiation Dose, Chemotherapy, and Hormonal Factors in Breast Cancer Following Hodgkin's Disease	Case-control	48 cases matched with 175 controls Female 5-yr HL survivors diagnosed before age 41 1965-1988	For the breast cancer cases: Median 18.7 yr since primary cancer diagnosis
DHL (Krul et al. 2017) (52)	Breast Cancer Risk After Radiation Therapy for Hodgkin Lymphoma: Influence of Gonadal Hormone Exposure	Case-control	174 cases matched with 466 controls Female 5-yr HL survivors treated before age 41 Treated 1965-2000	For the breast cancer cases: Median 21.9 (IQR 16.9-26.8) yr since primary cancer diagnosis
FCCSS (Guibout et al. 2005) (53)	Malignant Breast Tumors after Radiotherapy for a First Cancer during Childhood	Cohort*	1,814 female 3-yr survivors* Treated 1946-1986	Mean 16 (range 3-46) yr since primary cancer diagnosis

Subsequent breast cancer	Subsequent breast cancer risk estimates	Findings
45 breast cancer cases	HR (95% CI) Chest radiotherapy (yes vs. no): 2.5 (1.3-4.9) Total body irradiation (yes vs. no): 10.6 (3.7-30.2) Analyses were adjusted for alkylating agents, anthracyclines, and type of radiation	Chest radiotherapy and total body irradiation were risk factors for female breast cancer
48 breast cancer cases	Radiation dose to affected breast area (median), dose in Gy & RR (95% CI) 0.26-3.9 Gy (median 3.6): ref. 4-23.2 Gy (median 15.5): 1.11 (0.32-3.58) 24-38.2 Gy (median 30.2): 4.20 (0.99-17.8) 38.5-56 Gy (median 40.7): 5.16 (1.27-21.0) Analyses were adjusted for ovarian radiation dose and chemotherapy	Breast cancer risk increases with increasing reconstructed radiation dose up to at least 40 Gy; breast cancer risk following RT is strongly reduced in women who have experienced CT-induced premature menopause
174 breast cancer cases	Radiation dose to breast tumor location (median), dose in Gy & OR (95% CI) 0-2.9 Gy (median 1.2): ref. 3.0-7.9 Gy (median 4.9): 1.33 (0.64-2.77) 8.0-27.9 Gy (median 17.5): 2.21 (1.09-4.46) 28.0-35.9 Gy (median 33.9): 2.38 (1.17-4.83) 36.0-61.2 Gy (median 39.4): 4.70 (2.36-9.38) Analyses were adjusted for duration of post-radiation intact ovarian function	Breast cancer risk in female HL survivors increases linearly with radiation dose; no indications that endogenous and exogenous gonadal hormones affect the radiation dose-response relationship
16 patients developed breast cancers	Cumulative incidence: After a 30-yr follow-up cumulative incidence (95% CI): 2.8% (1.0-4.5) After a 40-yr follow-up (95% CI): 10.7% (1.4-19.9) Chest radiation dose, dose in Gy & RR (95% CI) Chest radiation yes vs. no: 1.3 (0.4-5.9) 0 Gy: ref. 0-<1 Gy: 1.3 (0.3-6.3) 1-<10 Gy: 1.5 (0.3-8.1) 10-<20 Gy: 3.7 (0.6-24.2) ≥20 Gy: 2.5 (0.1-22.1) *P trend* = 0.06 Excess relative risk per Gy to the breasts (95% CI): 0.13 (<0.0-0.75) Analyses were adjusted for castration, chemotherapy, and childhood cancer diagnosis	The high risk of breast cancer after HL may not only related to chemotherapy and a higher radiation dose to the breasts

Supplemental Table 3. Published results from participating cohorts in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer (continued)

Study	Title	Study design	Number of female childhood/ adolescent cancer survivors	Follow-up duration
Research question 2: Anthracycline-related subsequent breast cancer risk				
CCSS (Henderson et al. 2016) (11)	Breast Cancer Risk in Childhood Cancer Survivors Without a History of Chest Radiotherapy: A Report From the Childhood Cancer Survivor Study	Cohort	3,768 female 5-yr childhood cancer survivors without a history of chest radiotherapy Diagnosed 1970-1986	Median 25.5 (range 8.3-38.9) yr
CCSS (Turcotte et al. 2019) (54)	Chemotherapy and Risk of Subsequent Malignant Neoplasms in the Childhood Cancer Survivor Study Cohort	Cohort	10,440 female 5-yr survivors Diagnosed 1970-1999	Range 5-46.7 yr since primary cancer diagnosis

Subsequent breast cancer	Subsequent breast cancer risk estimates	Findings
47 women developed breast cancer	Anthracycline, dose in mg/m^2 & SIR (95% CI) 0 mg/m^2: 2.0 (1.2-3.3) 1-249 mg/m^2: 4.0 (1.5-0.7) ≥250 mg/m^2: 8.3 (5.7-12.2) Among childhood leukemia and sarcoma survivors Anthracycline, dose in mg/m^2 & SIR (95% CI) 0 mg/m^2: 1.8 (0.9-3.6) 1-249 mg/m^2: 5.0 (1.8-13.1) ≥250 mg/m^2: 9.5 (6.4-14.0) Anthracycline, dose in mg/m^2 & Relative SIR (95% CI) In childhood cancer survivors 0 mg/m^2: ref. 1-249 mg/m^2: 2.6 (0.8-8.7) ≥250 mg/m^2: 3.8 (1.7-8.3) *P trend* = 0.004 Among childhood leukemia and sarcoma survivors 0 mg/m^2: ref. 1-249 mg/m^2: 4.3 (1.1-16.6) ≥250 mg/m^2: 5.1 (1.9-13.7) *P trend* = 0.005	High-dose anthracycline chemotherapy increases the risk of subsequent breast cancer
51 breast cancer cases	Anthracyclines category, mg/m^2 & RR (95% CI) in survivors treated with only chemotherapy: per 100 mg/m^2: 1.3 (1.2-1.6) None: ref. 0-100 mg/m^2: 0.9 (0.1-9.1) 101-300 mg/m^2: 1.8 (0.6-6.0) 301-600 mg/m^2: 3.7 (1.3-10.8) >600 mg/m^2: 8.1 (1.2-56.0) *P trend* = 0.10 Analyses were adjusted for attained age, age at primary cancer diagnosis, 5-yr treatment era, history of splenectomy, cumulative dose levels of chemotherapy classes (alkylating agents, epi-podophyllotoxins, and platinum-based agents)	Dose-response relationship between anthracyclines and the risk of subsequent breast cancer

Supplemental Table 3. Published results from participating cohorts in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer (continued)

Study	Title	Study design	Number of female childhood/ adolescent cancer survivors	Follow-up duration
CCSS (Veiga et al. 2019) (12)	Association of Breast Cancer Risk after Childhood Cancer with Radiation Dose to the Breast and Anthracycline use: A Report from the Childhood Cancer Survivor Study	Case-control	271 cases matched with 1,044 controls Female 5-yr survivors Diagnosed 1970-1986	Range 5-40 yr since primary cancer diagnosis
SJLIFE (Ehrhardt et al. 2019) (28)	Subsequent Breast Cancer in Female Childhood Cancer Survivors in the St Jude Lifetime Cohort Study (SJLIFE)	Cohort	1,467 female 10-yr survivors	Median 22.7 (range 10.5-48.2) yr since primary cancer diagnosis

Subsequent breast cancer	Subsequent breast cancer risk estimates	Findings
271 breast cancer cases	Cumulative anthracycline dose OR (95% CI) per 100 mg/m^2: 1.23 (1.09-1.39) Anthracyclines dose OR (95% CI) per 100 mg/m^2 in survivors with LFS-associated cancers: 1.31 (1.1-1.5) Anthracyclines dose OR (95% CI) per 100 mg/m^2 in survivors with non LFS- associated cancers: 1.16 (1.0-1.4) Anthracycline, dose in mg/m^2 & OR (95% CI) None: ref. 1-223 mg/m^2: 2.3 (1.3-4.2) 224-343 mg/m^2: 2.4 (1.3-4.6) 344-455 mg/m^2: 1.5 (0.7-3.2) >455 mg/m^2: 3.8 (1.8-8.2) *P trend* < 0.01 Analyses were adjusted for type of first cancer, breast radiation dose, calendar year of follow-up, family history of breast/ ovarian cancer, and treatment with alkylating agents	Anthracycline dose associated with subsequent breast cancer risk; the combined effect of breast radiation and anthracycline was stronger than the individual effects of these two treatments on subsequent breast cancer risk
56 survivors developed 68 breast cancers	Anthracycline exposure, mg/m^2 & HR (95% CI): None: ref. 1-249 mg/m^2: 2.6 (1.1-6.2) ≥250 mg/m^2: 13.4 (5.5-32.5) Excluding pathogenic/ likely pathogenic mutations: Anthracycline exposure, mg/m^2 & HR (95% CI): None: ref. 1-249 mg/m^2: 2.5 (1.0-6.1) ≥250 mg/m^2: 15.1 (6.1-37.6) Excluding Survivors with ≥10 Gy of chest radiation and pathogenic/likely pathogenic mutations: Anthracycline exposure, mg/m^2 & HR (95% CI): None: ref. 1-249 mg/m^2: 2.1 (0.2-27.0) ≥250 mg/m^2: 16.9 (2.2-126.6)	Higher doses of anthracyclines are associated with increased risk of breast cancer independent of mutations in known cancer predisposition genes

Supplemental Table 3. Published results from participating cohorts in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer (continued)

Study	Title	Study design	Number of female childhood/ adolescent cancer survivors	Follow-up duration
DCCSS LATER (Teepen et al. 2017) (10)	Long-Term Risk of Subsequent Malignant Neoplasms After Treatment of Childhood Cancer in the DCOG LATER Study Cohort: Role of Chemotherapy	Cohort	2,731 female 5-yr survivors Diagnosed 1963-2001	For the whole cohort (both males and females): Median 20.7 (range 5.0-49.8) yr since primary cancer diagnosis
Research question 3: Attained age-related subsequent breast cancer risk				
CCSS (Kenney et al. 2004) (48)	Breast Cancer after Childhood Cancer: A Report from the Childhood Cancer Survivor Study	Cohort	6,068 female 5-yr survivors Diagnosed 1970-1986	For subsequent breast cancer cases: median 19 (range 6-29) yr since primary cancer diagnosis; For non- subsequent breast cancer cases: median 18 (range 5-31) yr since primary cancer diagnosis
CCSS (Turcotte et al. 2015) (30)	Risk of Subsequent Neoplasms During the Fifth and Sixth Decades of Life in the Childhood Cancer Survivor Study Cohort	Cohort	1,510 female 5-yr survivors completed at least one study questionnaire after age 40 yr Diagnosed 1970-1986	NM

Subsequent breast cancer	Subsequent breast cancer risk estimates	Findings
45 breast cancer cases	Doxorubicin dose, mg/m^2 & HR (95% CI) None: ref. ≤270 mg/m^2: 1.1 (0.4-2.9) 271-443 mg/m^2: 2.6 (1.1-6.5) >443 mg/m^2: 5.8 (2.7-12.5) *P trend* < 0.001 The LFS-associated survivors (leukemia, CNS tumors, and sarcoma, except for Ewing sarcoma): Doxorubicin dose, mg/m^2 & HR (95% CI) None: ref. ≤270 mg/m^2: 0.6 (0.1-3.2) 271-443 mg/m^2: 9.1 (2.5-32.8) >443 mg/m^2: 14.8 (5.1-43.2) *P trend* < 0.001 Non-LFS-associated CCSs: Doxorubicin dose, mg/m^2 & HR (95% CI) None: ref. ≤270 mg/m^2: 1.9 (0.6-6.2) 271-443 mg/m^2: 1.1 (0.2-4.9) >443 mg/m^2: 2.4 (0.7-8.4) *P trend* = 0.94 Analyses were adjusted for chest radiation, TBI, and chemotherapy groups	Doxorubicin was associated with a dose-dependent increased risk of female breast cancer, especially for survivors who had LFS-associated childhood cancer types (leukemia, CNS, and non-Ewing sarcoma)
95 survivors developed 111 cases of breast cancer	Subsequent breast cancer, cumulative incidence: At age 40 yr exposed to chest radiation in HL survivors: 12.9% (9.3-16.5)	Increased subsequent breast cancer risk in survivors at age 40 yr
103 breast cancer cases	In patients age 40 yr or older, subsequent breast cancer risk: SIR (95% CI): 5.5 (4.5-6.7); EAR 1.04	Childhood cancer survivors remain at increased risk for treatment related subsequent breast cancer even after age 40 yr

Supplemental Table 3. Published results from participating cohorts in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer (continued)

Study	Title	Study design	Number of female childhood/ adolescent cancer survivors	Follow-up duration
SJLIFE (Ehrhardt et al. 2019) (28)	Subsequent Breast Cancer in Female Childhood Cancer Survivors in the St Jude Lifetime Cohort Study (SJLIFE)	Cohort	1,467 female 10-yr survivors	Median 22.7 (range 10.5-48.2) yr since primary cancer diagnosis
DCCSS LATER (Teepen et al. 2017) (10)	Long-Term Risk of Subsequent Malignant Neoplasms After Treatment of Childhood Cancer in the DCOG LATER Study Cohort: Role of Chemotherapy	Cohort	2,731 female 5-yr survivors Diagnosed 1963-2001	For the whole cohort (both males and females): Median 20.7 (range 5.0-49.8) yr since primary cancer diagnosis
DHL (van Leeuwen et al. 2000) (42)	Long-Term Risk of Second Malignancy in Survivors of Hodgkin's Disease Treated During Adolescence or Young Adulthood	Cohort	544 female 1-yr survivors treated for HL before the age of 40 yr Treated 1966-1986	For the whole cohort (both males and females): Median 14.1 yr
DHL (Schaapveld et al. 2015) (19)	Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma	Cohort	1,698 female 5-yr HL survivors Treated 1965-2000	Range 5.0-47.2 yr

Subsequent breast cancer	Subsequent breast cancer risk estimates	Findings
56 survivors developed 68 breast cancers	Subsequent breast cancer, cumulative incidence: By age 35 yr unexposed to chest radiation: 1% By age 50 yr unexposed to chest radiation: 15% By age 35 yr ≥10 Gy chest radiation: 8% By age 50 yr ≥10 Gy chest radiation: 41% By age 35 yr unexposed to anthracyclines: 2% By age 50 yr unexposed to anthracyclines: 15% By age 35 yr ≥250 mg/m^2 anthracyclines: 7% By age 50 yr ≥250 mg/m^2 anthracyclines: 46%	Attained age associated with increased subsequent breast cancer risk
45 breast cancer cases	Attained age, yr & SIR (95% CI) and EAR <10 yr at childhood cancer diagnosis <20 yr: 10.5 (8.0-13.4); EAR: 13.5 20-29 yr: 4.6 (3.4-6.2); EAR: 14.6 30-39 yr: 4.3 (3.1-5.9); EAR: 32.1 ≥40 yr: 4.3 (2.3-7.2); EAR: 73.1 10-17 yr at childhood cancer diagnosis <30 yr: 5.8 (4.1-8.1); EAR: 16.9 30-39 yr: 5.6 (4.0-7.6); EAR: 43.4 40-49 yr: 3.2 (1.9-4.9); EAR: 51.4 ≥50 yr: 2.0 (0.8-4.2); EAR: 65.4	Chest radiotherapy and total body irradiation were risk factors for female breast cancer
27 breast cancer cases	Breast cancer risk, RR (95% CI) and EAR: 5.2 (3.4-7.6): EAR per 10 000 female patient-years: 29.4 Attained age, yr & RR (95% CI) <40 yr: 25.7 (11.1-50.6); 40-49 yr: 7.4 (4.1-12.1); ≥50 yr: 1.4 (0.4-3.6)	The increased risk of solid tumors in patients who were young (<20 yr of age) at the first treatment seems to decrease as these patients grow older
183 survivors with breast cancer	Attained age, yr & SIR (95% CI) and EAR 15-24 at HL <30 yr: 19.8 (5.4-50.6); EAR: 12.3 30-39 yr: 12.9 (8.8-18.3); EAR: 55.3 40-49 yr: 9.4 (6.6-12.9); EAR: 138 50-59 yr: 8.6 (5.1-13.4); EAR: 215 ≥60 yr: 7.4 (1.5-21.7); EAR: 218 SIR: *P trend* = 0.06; EAR: *P trend* < 0.001 25-34 at HL <40 yr: 3.7 (1.4-8.1); EAR: 15.2 40-49 yr: 5.2 (3.6-7.3); EAR: 69.3 50-59 yr: 4.0 (2.4-6.3); EAR: 82.5 60-69 yr: 2.7 (0.7-6.9); EAR: 57.5 SIR: *P trend* = 0.39; EAR: *P trend* < 0.001 35-50 at HL <50 yr: 1.4 (0.4-3.5); EAR: 6.4 50-59 yr: 1.8 (0.9-3.0); EAR: 20.1 60-69 yr: 1.7 (0.7-3.4); EAR: 21.1 70-79 yr: 2.9 (0.6-8.5); EAR: 67.8 SIR: *P trend* = 0.005; EAR: *P trend* = 0.012	Increased risk in survivors previously treated with (high dose) chest radiation with an attained age ≥60 yr

Supplemental Table 3. Published results from participating cohorts in the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer (continued)

Study	Title	Study design	Number of female childhood/ adolescent cancer survivors	Follow-up duration
Other papers on subsequent breast cancer				
Moskowitz et al. (2019) (8)	Mortality After Breast Cancer Among Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study	Case-control	274 cases matched with 1,095 controls with de novo breast cancer Female 5-yr survivors Diagnosed 1970-1986	For cases: Median 38 (range 20-58) yr
Moskowitz et al. (2021) (55)	Development and Validation of a Breast Cancer Risk Prediction Model for Childhood Cancer Survivors Treated With Chest Radiation: A Report From the Childhood Cancer Survivor Study and the Dutch Hodgkin Late Effects and LATER Cohorts	Cohort	Model development cohort: was based on 1,120 female 5-yr survivors treated with chest radiation (diagnosed 1970-1986); Model validation cohort: 1,027 female 5-yr survivors treated with chest radiation (diagnosed 1963-2001)	Among women alive at last contact: Model development cohort: Median 32.3 (range 9.7-45.7) yr; Model validation cohort: median 18.6 (range 6.3-46.0) yr

*Included both French and UK data

Yr = year; SIR = Standardized incidence ratio; CI = Confidence interval; OR = Odds ratio; HR = Hazard ratio; HL = Hodgkin lymphoma; IQR = Interquartile range; RR = Relative risk; LFS = Li-Fraumeni syndrome; TBI = Total body irradiation; CNS = Central nervous system; NM = Not mentioned; EAR = Excess absolute risk; RT = Radiotherapy; CT = Chemotherapy; CCSS = Childhood Cancer Survivor Study; SJLIFE = St. Jude Lifetime Cohort Study; NWTSG = US National Wilms Tumor Study group; DCCSS LATER = Dutch Long-term Effects After Childhood Cancer Study; FCCSS = French Childhood Cancer Survivor Study; DHL = Dutch Hodgkin Late Effects cohort

Subsequent breast cancer	Subsequent breast cancer risk estimates	Findings
274 breast cancer cases	HR (95% CI) Death after breast cancer (survivors vs. controls): 2.2 (1.7-3.0); after adjusting for breast cancer treatment with RT: 2.2 (1.7-3.1); after adjusting for breast cancer treatment with CT: 2.3 (1.8-3.2); both: 2.4 (1.7-3.2)	Mortality is significantly elevated among childhood cancer survivors
Model development cohort: 242 Model validation cohort: 105	Ten-year risk estimates: 2-23% for 30-year-old women; 5-34% for 40-year-old women	The model included current age, chest radiation field, whether chest radiation was delivered within 1 year of menarche, anthracycline exposure, age at menopause, and history of a first-degree relative with breast cancer

CHAPTER 3

Breast cancer risk after anthracyclines for childhood cancer: An international pooled analysis

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On behalf of The International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer

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Abstract

Anthracycline-based chemotherapy is associated with increased subsequent breast cancer (SBC) risk in female childhood cancer survivors, but the current evidence was deemed insufficient to support early breast cancer screening recommendations for survivors treated with anthracyclines. In this study, we pooled individual patient data from six well-established studies in Europe and North America and analyzed dose-dependent effects of individual anthracycline agents on developing SBC and interactions with chest radiotherapy. Among 17,903 survivors of childhood cancer (median age at diagnosis 6.7 years (interquartile range (IQR) 2.8-13.0)), 782 developed a first SBC with a median follow-up of 24.9 years (IQR 19.1-33.2) after the primary cancer diagnosis. A dose-dependent increased SBC risk was seen for doxorubicin (HR per 100 mg/m^2: 1.24, 95% CI: 1.18-1.31), and risk was more than two times higher for survivors treated with ≥200 mg/m^2 cumulative doxorubicin dose compared to the no doxorubicin treatment. For daunorubicin, a non-statistically significant increase was observed (HR per 100 mg/m^2: 1.10, 95% CI: 0.95-1.29). Epirubicin was also associated with increased SBC risk (yes vs. no, HR: 3.25, 95% CI: 1.59-6.63). For patients treated with or without chest irradiation, HRs per 100 mg/m^2 of doxorubicin were 1.11 (95% CI: 1.02-1.21) and 1.26 (95% CI: 1.17-1.36), respectively. Joint effects of doxorubicin and chest radiation were less than multiplicative ($HR_{multiplicative\ interaction}$: 0.86, 95% CI: 0.78-0.96, $P_{multiplicative\ interaction}$=0.006) and compatible with additivity ($P_{additive\ interaction}$=0.99). Our findings support that early initiation of breast cancer surveillance is reasonable for childhood cancer survivors who received ≥200 mg/m^2 cumulative doxorubicin dose. The results of our study should be implemented in SBC surveillance guidelines for survivors and will inform future treatment protocols for newly diagnosed childhood cancer patients.

Introduction

Over the past six decades, survival rates for childhood cancer have improved markedly in resource-rich countries due to improvements in treatment and supportive care. Unfortunately, the life expectancy and quality of life of long-term survivors are compromised by long-term complications of treatments such as subsequent neoplasms (1-4). Breast cancer is one of the most frequent subsequent malignant neoplasms among female survivors (5-7). Based on strong evidence regarding the effect of chest radiotherapy on subsequent breast cancer (SBC) risk, the International Guideline Harmonization Group (IGHG) recommends early initiation of annual breast cancer surveillance for female survivors who received ≥10 Gy chest radiotherapy (8). Over time, childhood cancer treatments have been modified to include decreased radiation doses and volumes and increased use of chemotherapy, especially anthracyclines (9). Although there are now studies showing that anthracycline exposure is associated with increased SBC risk (10-16), the evidence was deemed insufficient to alter the current SBC screening recommendations, because there was inconsistent evidence on dose thresholds for determining which survivors are at moderate or high risk and no data on possible differences in dose-effects with regard to SBC risk for the different individual anthracycline agents owing to the limited number of survivors treated with these specific modalities in individual cohort studies. Also, there is little information on the joint effects of anthracyclines and chest radiotherapy (15). To address the knowledge gaps, detailed treatment data from a large number of individuals is required. Therefore, we pooled individual patient data from six well-established childhood cancer survivor studies in Europe and North America with the aim of identifying the dose-dependent effects of specific anthracycline agents on developing SBC, as well as interactions with other clinical factors.

Methods

Study population

We pooled data from five cohort studies (Childhood Cancer Survivor Study (CCSS), St. Jude Lifetime Cohort Study (SJLIFE), Dutch Long-term Effects After Childhood Cancer Study (DCCSS LATER), French Childhood Cancer Survivor Study (FCCSS) and Dutch Hodgkin Late Effects cohort (DHL)), and one case-cohort study (Swiss Childhood Cancer Survivor Study (SCCSS)) in Europe and North America with available data on radiotherapy cumulative dose and fields and cumulative dose for chemotherapy. Details of the study design and methodology have been previously described (17). Briefly, eligibility criteria included a primary cancer diagnosis at <21 years of age, survival ≥5 year from primary cancer diagnosis, follow-up data on the presence and type of subsequent primary neoplasms (Figure 1).

Ascertainment of treatment information and SBC diagnosis

For each patient in the individual cohorts, diagnostic information of the childhood cancer and treatment details of the primary cancer and recurrences were ascertained by medical record abstraction (17). Cyclophosphamide equivalent dose (CED) was calculated and used as the cumulative exposure of alkylating agents (18). Radiotherapy fields involving the chest, collectively referred to as 'chest radiotherapy' included whole lung, total body irradiation (TBI), mantle, mediastinal, and other chest-exposing fields (e.g., axilla, spine). Pelvic radiotherapy included any field involving the pelvis, including TBI.

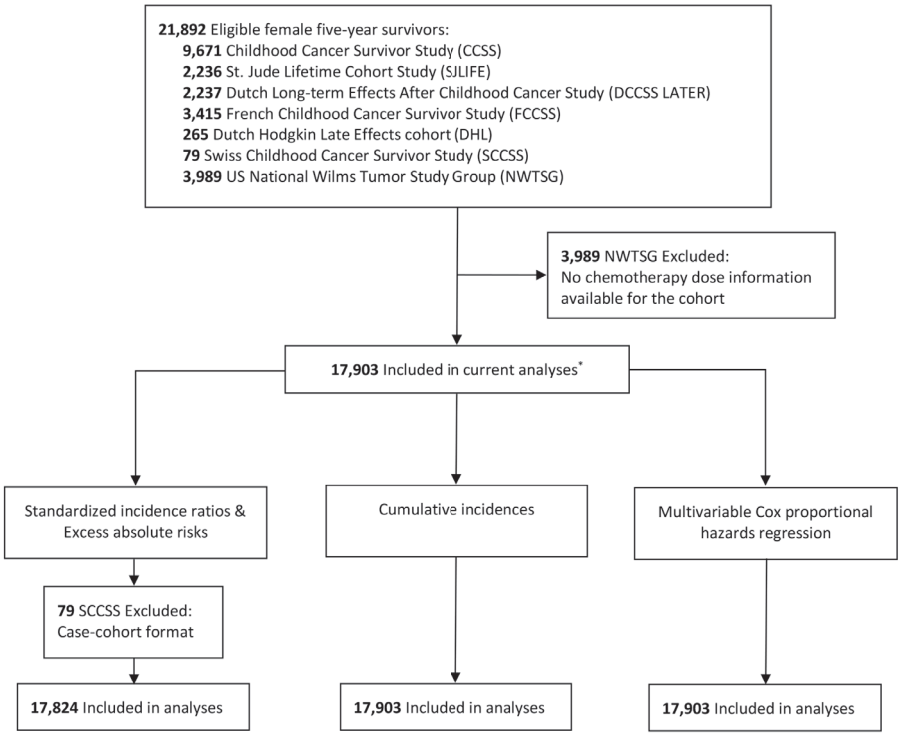
Methods for ascertainment and validation of SBC differed among the included cohorts. The study teams applied various combinations of cancer registry linkage, self-reported questionnaire survey data with medical record validation, and/or information extracted from pathology reports or medical records. Details regarding cohort-specific methodology for definitions of treatment exposures and subsequent tumor ascertainment were reported previously (17).

Statistical analysis

Childhood cancer survivors were considered at risk for developing SBC from five years after a primary cancer diagnosis until the date of the first SBC, death, or the date of the last follow-up observation, whichever occurred first.

The incidence of SBC in the pooled cohort was compared with the general female population using the International Agency for Research on Cancer accumulated worldwide cancer incidence rates (CI5) (https://ci5.iarc.fr/) (19), and the French cancer registry network Francim for the incidence rate of breast cancer in France (20-22). Standardized incidence ratios (SIRs) were calculated as the ratio of the observed number of SBC to the expected number of female breast cancers. Expected numbers were estimated by accumulating cohort-specific person-years at risk by country, age (5-year bands), and calendar year (1-year bands)-specific strata and multiplying by the corresponding female breast cancer incidence rates in the general population. Excess absolute risks (EARs) were calculated as the differences between observed and expected numbers of female breast cancer per 1,000 person-years at risk. Because population-based breast cancer incidence rates only include invasive tumors, we considered the first invasive breast cancer (IBC) as an event for these analyses. Cumulative incidences of SBC overall and by treatment subgroups were calculated, treating death as a competing risk.

Figure 1. Cohort composition diagram of eligible female five-year childhood cancer survivors in each analysis



*The number of included survivors in each analysis may vary due to missing values of analysis variables.

Multivariable Cox proportional hazards regression analyses, stratified by cohort, were used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) of SBC, either IBC or ductal carcinoma in situ (DCIS), according to treatment exposure categories with attained age as the time scale (23). Weights were applied to account for the case-cohort data from the SCCSS and for under-sampling of acute lymphoblastic leukemia cases in the CCSS data. The proportional hazards assumption was checked with scaled Schoenfeld residuals in Cox models; it was not violated. The base multivariable model included specific anthracycline agents, age at primary cancer diagnosis, the combination of the chest radiation field and its associated maximum dose, pelvic radiation dose ≥5 Gy, and alkylating agent CED exposure, all of which have been shown or suggested to be associated with breast cancer risk in previous studies (6, 10, 11, 24, 25). We modelled cumulative doxorubicin dose and daunorubicin dose (categories by steps of 100 mg/m^2 to ≥400 mg/m^2 for doxorubicin dose and to ≥200 mg/m^2 for daunorubicin dose due to statistical power reasons, respectively, and continuously per 100 mg/m^2

increase), and epirubicin (yes/no); this proved infeasible for idarubicin owing to limited numbers of females treated with this agent. We first categorized chest radiotherapy as the combination of each eligible radiation field (defined above) with the associated maximum chest radiotherapy dose below or above the median categorized as low-dose or high-dose, respectively; since results were comparable for fields with similar levels of potential radiation exposure to the breast, we categorized chest radiotherapy as follows: no chest radiotherapy, high-dose mantle, low-dose mantle, mediastinal, TBI, whole lung, and other. Because there is only evidence for associations between anthracyclines and alkylating agents on SBC risk, we applied the following selection procedure to evaluate other chemotherapeutic agents: we added binary indicators for epipodophyllotoxins, vinca alkaloids, platinum compounds, and antimetabolites to the base model; if addition of each variable changed any HRs of cumulative doxorubicin and/or daunorubicin dose by >10% compared to a model without the variable, it was included in the final models (Supplementary Table 1). Our final multivariable analyses did not include any of the additional classes of chemotherapeutic agents indicated above.

Interaction between cumulative doxorubicin/daunorubicin doses and chest radiotherapy and age at primary childhood cancer diagnosis on a multiplicative scale was evaluated by comparing models with and without the interaction term via likelihood ratio tests. Aalen's additive hazard models were applied to evaluate the interaction of cumulative doxorubicin/daunorubicin exposures and chest radiotherapy and age at primary childhood cancer diagnosis on an additive scale (26).

A series of sensitivity analyses were conducted by applying the same regression models to the data with: a) each cohort to evaluate between-cohort differences; b) outcome restricted to IBC to exclude DCIS, which does not always progress to IBC; c) censoring at the time of the first non-SBC subsequent malignant neoplasm diagnosis to rule out effects of treatments for those tumors; d) excluding 444 survivors treated for childhood cancer prior to 1970 to exclude a potentially influential group of women who reached comparatively high attained age yet showing deviating characteristics owing to improvements in clinical practice and survival trends since the 1970s; e) excluding survivors treated for Hodgkin lymphoma to exclude patients who generally received extensive radiotherapy fields to the chest; and g) excluding each cohort on a one-by-one basis to evaluate robustness of findings.

All analyses were conducted in R software (version 4.0.3). A P value of < 0.05 was considered statistically significant in 2-sided statistical tests.

Results

Among the eligible 17,903 five-year survivors, the median age at primary childhood cancer diagnosis was 6.7 years (interquartile range (IQR) 2.8-13.0), with leukemia (25.5%), CNS tumors (16.5%), and Hodgkin lymphoma (11.7%) as the most frequent childhood cancer types (Table 1), with some variations by cohort (Supplementary Table 2). Of all survivors, 5,714 (31.9%) received anthracyclines without chest radiotherapy, 1,962 (11.0%) received chest radiotherapy without anthracyclines, 1,634 (9.1%) received both anthracyclines and chest radiotherapy, 7,096 (39.6%) had neither treatment, and 1,497 (8.4%) had unknown treatment. The median follow-up time since primary cancer diagnosis was 24.9 years (IQR 19.1-33.2). In total, 782 survivors developed a first SBC at a median age of 39.7 years (IQR 34.3-44.9), including 616 IBC and 166 DCIS cases. The median attained age at the end of follow-up was 33.7 years (IQR 25.9-41.6) and 29.6% of survivors attained an age of 40 years or more.

Comparison with the general population

In Supplementary Table 3, breast cancer risk by doxorubicin and chest radiotherapy treatment is provided. Compared with the general female population, the risk of IBC was most elevated in survivors who received ≥200 mg/m^2 cumulative doxorubicin dose and chest radiotherapy (SIR 17.5, 95% CI 13.3-22.6; median attained age, 36.1 years), followed by the <200 mg/m^2 cumulative doxorubicin dose and chest radiotherapy group (SIR 13.9, 95% CI 9.7-19.2; median attained age, 33.8 years), then the chest radiotherapy-only group with no doxorubicin (SIR 10.7, 95% CI 9.4-12.1; median attained age, 38.4 years), the ≥200 mg/m^2 cumulative doxorubicin dose with no chest radiotherapy group (SIR 5.6, 95% CI 4.5-6.9; median attained age, 36.5 years), the <200 mg/m^2 cumulative doxorubicin dose with no chest radiotherapy group (SIR 3.2, 95% CI 1.9-5.1; median attained age, 28.9 years), and the group receiving neither of these treatments (SIR 1.7, 95% CI 1.4-2.1; median attained age, 32.8 years). The highest EAR was observed in the ≥200 mg/m^2 cumulative doxorubicin dose and chest radiotherapy group with 5.0 excess cases per 1,000 person-years.

Table 1. Demographic and treatment characteristics of 17,903 female five-year childhood cancer survivors (primary cancer diagnosis year 1946-2012) overall and by subsequent breast cancer status

	Total (n = 17,903)		Subsequent breast cancer[a] (n = 782)		No subsequent breast cancer (n = 17,121)	
	No.	(%)	No.	(%)	No.	(%)
Primary childhood cancer						
Leukemia	4,574	(25.5)	81	(10.4)	4,493	(26.2)
Non-Hodgkin lymphoma	1,097	(6.1)	37	(4.7)	1,060	(6.2)
Hodgkin lymphoma	2,101	(11.7)	405	(51.8)	1,696	(9.9)
CNS tumor	2,946	(16.5)	14	(1.8)	2,932	(17.1)
Neuroblastoma	1,657	(9.3)	15	(1.9)	1,642	(9.6)
Retinoblastoma	426	(2.4)	2	(0.3)	424	(2.5)
Renal tumor	1,372	(7.7)	45	(5.8)	1,327	(7.8)
Bone tumor	1,459	(8.1)	106	(13.6)	1,353	(7.9)
Soft tissue tumor	1,405	(7.8)	55	(7.0)	1,350	(7.9)
Germ cell tumor	440	(2.5)	9	(1.2)	431	(2.5)
Other malignant epithelial	297	(1.7)	11	(1.4)	286	(1.7)
Other[b]	129	(0.7)	2	(0.2)	127	(0.8)
Doxorubicin dose, mg/m²						
No doxorubicin	11,170	(62.4)	431	(55.1)	10,739	(62.7)
<100	912	(5.1)	16	(2.0)	896	(5.2)
100-199	1,795	(10.0)	69	(8.8)	1,726	(10.1)
200-299	1,026	(5.7)	67	(8.6)	959	(5.6)
300-399	1,012	(5.7)	64	(8.2)	948	(5.5)
≥400	779	(4.4)	58	(7.4)	721	(4.2)
Unknown[c]	1,209	(6.8)	77	(9.8)	1,132	(6.6)
Daunorubicin dose, mg/m²						
No daunorubicin	14,630	(81.7)	684	(87.5)	13,946	(81.5)
<100	623	(3.5)	7	(0.9)	616	(3.6)
100-199	953	(5.3)	16	(2.0)	937	(5.5)
≥200	645	(3.6)	17	(2.2)	628	(3.7)
Unknown[d]	1,052	(5.9)	58	(7.4)	994	(5.8)
Epirubicin						
No	16,637	(92.9)	717	(91.7)	15,920	(93.0)
Yes	325	(1.8)	9	(1.2)	316	(1.8)
Unknown	941	(5.3)	56	(7.2)	885	(5.2)
Idarubicin						
No	16,843	(94.1)	725	(92.7)	16,118	(94.1)
Yes	107	(0.6)	1	(0.1)	106	(0.6)
Unknown	953	(5.3)	56	(7.2)	897	(5.2)
CED[e]						

Table 1. Demographic and treatment characteristics of 17,903 female five-year childhood cancer survivors (primary cancer diagnosis year 1946-2012) overall and by subsequent breast cancer status (continued)

	Total (n = 17,903)		Subsequent breast cancer[a] (n = 782)		No subsequent breast cancer (n = 17,121)	
	No.	(%)	No.	(%)	No.	(%)
0	7,951	(44.4)	301	(38.5)	7,650	(44.7)
<6000	3,069	(17.1)	94	(12.0)	2,975	(17.4)
6000-17999	3,899	(21.8)	192	(24.6)	3,707	(21.7)
≥18000	1,117	(6.2)	47	(6.0)	1,070	(6.2)
Unknown	1,867	(10.4)	148	(18.9)	1,719	(10.0)
Epipodophyllotoxins						
No	13,434	(75.0)	611	(78.1)	12,823	(74.9)
Yes	3,346	(18.7)	78	(10.0)	3,268	(19.1)
Unknown	1,123	(6.3)	93	(11.9)	1,030	(6.0)
Vinca Alkaloids						
No	6,194	(34.6)	269	(34.4)	5,925	(34.6)
Yes	10,586	(59.1)	420	(53.7)	10,166	(59.4)
Unknown	1,123	(6.3)	93	(11.9)	1,030	(6.0)
Platinum Compounds						
No	14,219	(79.4)	642	(82.1)	13,577	(79.3)
Yes	2,561	(14.3)	47	(6.0)	2,514	(14.7)
Unknown	1,123	(6.3)	93	(11.9)	1,030	(6.0)
Antimetabolites						
No	10,376	(58.0)	504	(64.5)	9,872	(57.7)
Yes	6,404	(35.8)	185	(23.7)	6,219	(36.3)
Unknown	1,123	(6.3)	93	(11.9)	1,030	(6.0)
Chest radiotherapy fields and doses[f]						
No chest radiotherapy	13,004	(72.6)	250	(32.0)	12,754	(74.5)
High-dose mantle (≥36 Gy) median 40 Gy, IQR 39-44 Gy[g]	698	(3.9)	238	(30.4)	460	(2.7)
Low-dose mantle (<36 Gy) median 26 Gy, IQR 21-30 Gy[g]	524	(2.9)	93	(11.9)	431	(2.5)
Mediastinal median 26 Gy, IQR 21-36 Gy[g]	469	(2.6)	33	(4.2)	436	(2.5)
TBI median 12 Gy, IQR 11-13 Gy[g]	371	(2.1)	22	(2.8)	349	(2.0)
Whole lung median 16 Gy, IQR 12-23 Gy[g]	184	(1.0)	23	(2.9)	161	(0.9)
Other median 28 Gy, IQR 21-36 Gy[g]	1,316	(7.4)	63	(8.1)	1,253	(7.3)
Unknown	1,337	(7.5)	60	(7.7)	1,277	(7.5)
Pelvic radiotherapy dose[h]						

Table 1. Demographic and treatment characteristics of 17,903 female five-year childhood cancer survivors (primary cancer diagnosis year 1946-2012) overall and by subsequent breast cancer status (continued)

	Total (n = 17,903)		Subsequent breast cancer[a] (n = 782)		No subsequent breast cancer (n = 17,121)	
	No.	(%)	No.	(%)	No.	(%)
No pelvic radiotherapy	13,727	(76.7)	505	(64.6)	13,222	(77.2)
<10 Gy	142	(0.8)	6	(0.8)	136	(0.8)
10-19 Gy	594	(3.3)	24	(3.1)	570	(3.3)
20-29 Gy	719	(4.0)	38	(4.9)	681	(4.0)
30-39 Gy	767	(4.3)	82	(10.5)	685	(4.0)
≥40 Gy	713	(4.0)	72	(9.2)	641	(3.7)
Unknown	1,241	(6.9)	55	(7.0)	1,186	(6.9)
Age at diagnosis of primary cancer, yrs						
<5	7,376	(41.2)	66	(8.4)	7,310	(42.7)
5-9	3,788	(21.2)	65	(8.3)	3,723	(21.7)
10-14	3,930	(22.0)	273	(34.9)	3,657	(21.4)
15-21	2,809	(15.7)	378	(48.3)	2,431	(14.2)
Treatment subgroups[i]						
Anthracycline[j] & Chest radiotherapy	1,634	(9.1)	163	(20.8)	1,471	(8.6)
Anthracycline & No Chest radiotherapy	5,714	(31.9)	156	(19.9)	5,558	(32.5)
No Anthracycline & Chest radiotherapy	1,962	(11.0)	294	(37.6)	1,668	(9.7)
No Anthracycline & No Chest radiotherapy	7,096	(39.6)	83	(10.6)	7,013	(41.0)
Unknown	1,497	(8.4)	86	(11.0)	1,411	(8.2)
Period of primary cancer diagnosis						
<1960	60	(0.3)	9	(1.2)	51	(0.3)
1960-1969	384	(2.1)	34	(4.3)	350	(2.0)
1970-1979	4,081	(22.8)	343	(43.9)	3,738	(21.8)
1980-1989	6,121	(34.2)	283	(36.2)	5,838	(34.1)
1990-1999	6,134	(34.3)	107	(13.7)	6,027	(35.2)
2000-2012	1,123	(6.3)	6	(0.8)	1,117	(6.5)
Time since five-year of primary cancer diagnosis, yrs						
<10	2,448	(13.7)	64	(8.2)	2,384	(13.9)
10-19	6,504	(36.3)	310	(39.6)	6,194	(36.2)
20-29	5,332	(29.8)	315	(40.3)	5,017	(29.3)
≥30	3,619	(20.2)	93	(11.9)	3,526	(20.6)
Attained age, yrs						

Table 1. Demographic and treatment characteristics of 17,903 female five-year childhood cancer survivors (primary cancer diagnosis year 1946-2012) overall and by subsequent breast cancer status (continued)

	Total (n = 17,903)		Subsequent breast cancer[a] (n = 782)		No subsequent breast cancer (n = 17,121)	
	No.	(%)	No.	(%)	No.	(%)
<20	1,870	(10.4)	3	(0.4)	1,867	(10.9)
20-29	4,882	(27.3)	76	(9.7)	4,806	(28.1)
30-39	5,847	(32.7)	322	(41.2)	5,525	(32.3)
≥40	5,304	(29.6)	381	(48.7)	4,923	(28.8)
Vital status						
Alive at last contact	15,278	(85.3)	549	(70.2)	14,729	(86.0)
Deceased at last contact	2,625	(14.7)	233	(29.8)	2,392	(14.0)

CED = Cyclophosphamide Equivalent Dose; CNS = Central nervous system; IQR = Interquartile range; No. = number; TBI = Total Body Irradiation; yr = year

[a]Included both invasive and ductal carcinoma in situ breast cancer.

[b]Included the ICCC-3 classification groups "Hepatic Tumor" (0 case/61 survivors), "Other and Unspecified" (1 case/38 survivors), and "Unclassified" (1 case/30 survivors).

[c]The Unknown category under the variable "Doxorubicin dose" included both survivor groups with any doxorubicin (yes/no) unknown (56 cases/941 survivors) and with doxorubicin treatment but dose information unknown (21 cases/268 survivors).

[d]The Unknown category under the variable "Daunorubicin dose" included both survivor groups with any daunorubicin (yes/no) unknown (56 cases/953 survivors) and with daunorubicin treatment but dose information unknown (2 cases/99 survivors).

[e]Cyclophosphamide Equivalent Dose calculation: CED (mg/m^2) = 1.0 (cumulative cyclophosphamide dose (mg/m^2)) + 0.244 (cumulative ifosfamide dose (mg/m^2)) + 0.857 (cumulative procarbazine dose (mg/m^2)) + 14.286 (cumulative chlorambucil dose (mg/m^2)) + 15.0 (cumulative BCNU (carmustine) dose (mg/m^2)) + 16.0 (cumulative CCNU (lomustine) dose (mg/m^2)) + 40 (cumulative melphalan dose (mg/m^2)) + 50 (cumulative Thio-TEPA (thiotepa) dose (mg/m^2)) + 100 (cumulative nitrogen mustard dose (mg/m^2)) + 8.823 (cumulative busulfan dose (mg/m^2)).

[f]Included radiotherapy fields exposing (parts of) the chest. Radiation dose refered to the cumulative prescribed dose (including boost doses, if applicable), or slight variations, depending on definitions in the underlying cohorts (see Wang et al. 2022). Chest radiotherapy was categorized as the combination of chest radiation fields with the associated maximum chest radiotherapy dose below or above the median. The variable was classified as follows: high-dose mantle (median 40 Gy, IQR 39-44 Gy), low-dose mantle (median 26 Gy, IQR 21-30 Gy), mediastinal (median 26 Gy, IQR 21-36 Gy), TBI (median 12 Gy, IQR 11-13 Gy), whole lung (median 16 Gy, IQR 12-23 Gy), other (median 28 Gy, IQR 21-36 Gy), and unknown.

[g]Dose represents the maximum cumulative prescribed chest dose (including boost doses, if applicable) of survivors classified in this group. This could include doses to chest field other than this category.

[h]Included radiotherapy fields exposing (parts of) the pelvis (including TBI). Radiation dose refered to the cumulative prescribed dose (including boost doses, if applicable), or slight variations, depending on definitions in the underlying cohorts (see Wang et al. 2022). The Unknown category under the variable "Pelvic radiotherapy dose" included both survivor groups with any pelvic radiotherapy (yes/no) unknown (54 cases/1212 survivors) and with pelvic radiotherapy treatment but dose information unknown (1 cases/29 survivors).

[i]Treatment subgroup variable set to unknown if either of the treatment categories was unknown.

[j]Anthracyclines included doxorubicin, daunorubicin, epirubicin, and idarubicin.

Risk factors for SBC

In multivariable Cox regression analyses, cumulative doxorubicin dose was associated with an increased risk of SBC, with HRs of 1.76 (95% CI 0.88-3.51), 1.77 (95% CI 1.30-2.42), 2.50 (95% CI 1.85-3.40), 2.33 (95% CI 1.68-3.23), and 2.78 (95% CI 1.99-3.88) for <100, 100-199, 200-299, 300-399, and ≥400 mg/m^2 cumulative doxorubicin dose categories compared to the no doxorubicin treatment, respectively (Table 2 Model I; survivor characteristics by cumulative doxorubicin dose categories are shown in Supplementary Table 4). Compared to those not treated with daunorubicin, risks were close to unity for those with cumulative doses of daunorubicin <200 mg/m^2 (HR 0.98, 95% CI 0.46-2.09 and HR 0.98, 95% CI 0.55-1.75 for <100 and 100-199 mg/m^2, respectively), and the highest cumulative dose group, ≥200 mg/m^2, conferred a non-statistically significant 22% increased risk (HR 1.22, 95% CI 0.69-2.17). When the continuous cumulative doxorubicin and daunorubicin dose information was included in the model, the risk of developing SBC in survivors treated with doxorubicin increased 1.24-fold (95% CI 1.18-1.31) for every 100 mg/m^2 increase in cumulative doxorubicin dose after adjustments (Table 2 Model II). Cumulative daunorubicin dose was associated with a non-statistically significant increased risk of SBC (HR per 100 mg/m^2 1.10, 95% CI 0.95-1.29). Epirubicin treatment was associated with an increased SBC risk (yes vs. no, HR 3.25, 95% CI 1.59-6.63). Additionally, all chest radiotherapy field and dose categories were significantly associated with increased SBC risk, with highest HRs for those treated with high-dose mantle field (HR 8.99, 95% CI 7.00-11.53), followed by whole lung irradiation (HR 7.58, 95% CI 4.68-12.27), and TBI (HR 7.05, 95% CI 4.11-12.10) (Table 2 Model I). Survivors with a primary cancer diagnosis at ages 10-14 or 15-21 years had an elevated risk of SBC with HRs of 2.03 (95% CI 1.48-2.79) and 1.83 (95% CI 1.31- 2.55) compared with the survivors who were diagnosed at ages 0-4. We did not observe significant effects of pelvic radiotherapy or alkylating agents (CED) on SBC risk.

Table 2. Multivariable Cox proportional hazard regression analyses for subsequent breast cancer in female five-year childhood cancer survivors (primary cancer diagnosis year 1946-2012)

					Model I[a]		Model II[b]	
	Total (n)	**%**	**No. SBC (n)[c]**	**%**	**HR**	**95% CI**	**HR**	**95% CI**
Doxorubicin dose, mg/m²								
No doxorubicin	11,170	62.4	431	55.1	1.0	Ref.		
<100	912	5.1	16	2.0	1.76	0.88-3.51		
100-199	1,795	10.0	69	8.8	1.77	1.30-2.42		
200-299	1,026	5.7	67	8.6	2.50	1.85-3.40		..
300-399	1,012	5.7	64	8.2	2.33	1.68-3.23		
≥400	779	4.4	58	7.4	2.78	1.99-3.88		
Unknown	1,209	6.8	77	9.8	..	..		
Continuous variable: Doxorubicin dose (per 100 mg/m²)							1.24	1.18-1.31
Daunorubicin dose, mg/m²								
No daunorubicin	14,630	81.7	684	87.5	1.0	Ref.		
<100	623	3.5	7	0.9	0.98	0.46-2.09		
100-199	953	5.3	16	2.0	0.98	0.55-1.75		..
≥200	645	3.6	17	2.2	1.22	0.69-2.17		
Unknown	1,052	5.9	58	7.4	..	..		
Continuous variable: Daunorubicin dose (per 100 mg/m²)							1.10	0.95-1.29
Epirubicin								
No	16,637	92.9	717	91.7	1.0	Ref.	1.0	Ref.
Yes	325	1.8	9	1.2	3.40	1.66-6.98	3.25	1.59-6.63
Unknown	941	5.3	56	7.2	..	..	..	..
Chest radiotherapy field and dose								
No chest radiotherapy	13,004	72.6	250	32.0	1.0	Ref.	1.0	Ref.
High-dose mantle (≥36 Gy) median 40 Gy, IQR 39-44 Gy	698	3.9	238	30.4	8.99	7.00-11.53	9.12	7.09-11.75
Low-dose mantle (<36 Gy) median 26 Gy, IQR 21-30 Gy	524	2.9	93	11.9	4.72	3.48-6.41	5.23	3.86-7.09
Mediastinal median 26 Gy, IQR 21-36 Gy	469	2.6	33	4.2	1.65	1.02-2.67	1.71	1.06-2.78
TBI median 12 Gy, IQR 11-13 Gy	371	2.1	22	2.8	7.05	4.11-12.10	7.18	4.18-12.33

Table 2. Multivariable Cox proportional hazard regression analyses for subsequent breast cancer in female five-year childhood cancer survivors (primary cancer diagnosis year 1946-2012) (continued)

					Model I[a]		Model II[b]	
	Total (n)	**%**	**No. SBC (n)[c]**	**%**	**HR**	**95% CI**	**HR**	**95% CI**
Whole lung median 16 Gy, IQR 12-23 Gy	184	1.0	23	2.9	7.58	4.68-12.27	8.00	4.94-12.95
Other median 28 Gy, IQR 21-36 Gy	1,316	7.4	63	8.1	2.61	1.87-3.64	2.68	1.91-3.75
Unknown	1,337	7.5	60	7.7	..	..	..	..
Pelvic radiotherapy ≥5 Gy								
No	13,751	76.8	505	64.6	1.0	Ref.	1.0	Ref.
Yes	2,911	16.3	222	28.4	0.95	0.78-1.17	0.94	0.77-1.16
Unknown	1,241	6.9	55	7.0	..	..	..	..
Age at primary childhood cancer diagnosis, yr								
<5	7,376	41.2	66	8.4	1.0	Ref.	1.0	Ref.
5-9	3,788	21.2	65	8.3	1.13	0.76-1.69	1.12	0.75-1.67
10-14	3,930	22.0	273	34.9	2.03	1.48-2.79	2.04	1.49-2.81
15-21	2,809	15.7	378	48.3	1.83	1.31-2.55	1.84	1.32-2.57
CED[d], mg/m²								
None	7,951	44.4	301	38.5	1.0	Ref.	1.0	Ref.
<6000	3,069	17.1	94	12.0	0.87	0.67-1.14	0.95	0.73-1.25
6000-17999	3,899	21.8	192	24.6	1.02	0.82-1.27	1.07	0.86-1.32
≥18000	1,117	6.2	47	6.0	1.20	0.83-1.74	1.23	0.85-1.77
Unknown	1,867	10.4	148	18.9	..	..	..	..

CED = Cyclophosphamide Equivalent Dose; CI = Confidence interval; HR = Hazard ratio; IQR = Interquartile range; No. = number; SBC = Subsequent breast cancer; TBI = Total Body Irradiation; yr = year

[a]Model I included categorical variables of cumulative doxorubicin and daunorubicin dose by steps of 100 mg/m².

[b]Model II included continuous variables of cumulative doxorubicin and daunorubicin dose per 100 mg/m².

[c]One survivor had a SBC prior to five years after primary cancer.

[d]Cyclophosphamide Equivalent Dose calculation: CED (mg/m²) = 1.0 (cumulative cyclophosphamide dose (mg/m²)) + 0.244 (cumulative ifosfamide dose (mg/m²)) + 0.857 (cumulative procarbazine dose (mg/m²)) + 14.286 (cumulative chlorambucil dose (mg/m²)) + 15.0 (cumulative BCNU (carmustine) dose (mg/m²)) + 16.0 (cumulative CCNU (lomustine) dose (mg/m²)) + 40 (cumulative melphalan dose (mg/m²)) + 50 (cumulative Thio-TEPA (thiotepa) dose (mg/m²)) + 100 (cumulative nitrogen mustard dose (mg/m²)) + 8.823 (cumulative busulfan dose (mg/m²)).

Among survivors treated with or without chest radiation, HRs per 100 mg/m² of cumulative doxorubicin dose were 1.11 (95% CI 1.02-1.21) and 1.26 (95% CI 1.17-1.36), respectively (Table 3). Joint effects of continuous cumulative doxorubicin dose and chest radiation (yes vs. no) were sub-multiplicative ($HR_{multiplicative\ interaction}$ 0.86, 95% CI 0.78-0.96, $P_{multiplicative\ interaction}$=0.006) and compatible with additive effects

($P_{additive\ interaction}$=0.99) (Supplementary Table 5). The effect of cumulative doxorubicin dose on SBC risk was significantly less strong among those with high-dose mantle field ($HR_{multiplicative\ interaction}$ 0.84, 95% CI 0.71-0.98, $P_{multiplicative\ interaction}$=0.03) and mediastinal field irradiation ($HR_{multiplicative\ interaction}$ 0.65, 95% CI 0.45-0.96, $P_{multiplicative\ interaction}$=0.03), compared to those treated without chest radiotherapy. On an additive scale, the joint effects of cumulative doxorubicin dose and chest radiotherapy fields were equal to the sum of these two individual effects (all $P_{additive\ interaction}$>0.05). Joint effects of daunorubicin and chest radiation were on a multiplicative scale ($P_{multiplicative\ interaction}$=0.10) and significantly less than additive (no. additional cases per 10,000 person years: -9.67, $P_{additive\ interaction}$=0.002).

Age at childhood cancer diagnosis did not significantly modify the effects of cumulative doxorubicin and daunorubicin dose on SBC risk on a multiplicative scale ($P_{multiplicative\ interaction}$=0.09 and $P_{multiplicative\ interaction}$=0.30, respectively). However, on an additive scale, the joint effects of cumulative doxorubicin dose and age at childhood cancer diagnosis (5-9; 10- 14; 15-21 vs. 0-4 years) were all significantly greater than the sum of the individual effects (all $P_{additive\ interaction}$<0.05). Such an effect was not found for cumulative daunorubicin dose.

To rule out potential effects of other treatments that have been associated with SBC, such as chest radiotherapy and alkylating agents, we performed separate analyses in survivors who received neither chest radiotherapy nor alkylating agents; the effects of high cumulative doxorubicin dose on SBC risk remained statistically significant (300-399 mg/m² and ≥400 mg/m² categories: HR 2.67, 95% CI 1.08-6.59, and HR 3.58, 95% CI 1.66-7.71, respectively in Table 4).

Cumulative incidences

For survivors who did not receive chest radiotherapy, cumulative incidences at age 40 for no doxorubicin treatment group, <200, and ≥200 mg/m² cumulative doxorubicin dose groups were 0.8%, 1.9%, and 3.4%; for survivors who received chest radiotherapy, corresponding cumulative incidences at age 40 for the three cumulative dose groups were 7.9%, 10.1%, and 8.1% (Figure 2a), with some variation by chest radiation field (Figures 2b-2e). In Supplementary Table 6, multivariable Cox regression results for these cumulative doxorubicin dose categories are presented.

Table 3. Multivariable Cox proportional hazard regression analyses for subsequent breast cancer by chest radiotherapy status among female five-year childhood cancer survivors (primary cancer diagnosis year 1946-2012)

	Models without interaction			
	With chest radiotherapy[a]		Without chest radiotherapy[a]	
	HR	**95% CI**	**HR**	**95% CI**
Continuous variable: Doxorubicin dose (per 100 mg/m²)	1.11	1.02-1.21	1.26	1.17-1.36
Continuous variable: Daunorubicin dose (per 100 mg/m²)	0.95	0.74-1.21	1.12	0.93-1.36
Epirubicin				
No	1.0	Ref.	1.0	Ref.
Yes	2.28	1.00-5.21	2.13	0.49-9.17
Models with a multiplicative interaction				
	Interaction: Doxorubicin dose*Chest radiotherapy status (yes/no)		**Interaction: Daunorubicin dose*Chest radiotherapy status (yes/no)**	
	HR	**95% CI**	**HR**	**95% CI**
Continuous variable: Doxorubicin dose (per 100 mg/m²)	1.28	1.21-1.37	1.21	1.15-1.28
Continuous variable: Daunorubicin dose (per 100 mg/m²)	1.04	0.89-1.23	1.15	0.96-1.37
Epirubicin				
No	1.0	Ref.	1.0	Ref.
Yes	2.54	1.22-5.30	2.47	1.17-5.23
Interaction: Doxorubicin dose (per 100 mg/m²)*Chest radiotherapy status (yes/no)	0.86	0.78-0.96	..	..
Interaction: Daunorubicin dose (per 100 mg/m²)*Chest radiotherapy status (yes/no)	..	..	0.77	0.57-1.05

CI = Confidence interval; HR = Hazard ratio

[a]Models were further adjusted for pelvic radiotherapy ≥5 Gy (yes/no), age at primary childhood cancer diagnosis (categorical variable), and cyclophosphamide equivalent dose (categorical variable).

Sensitivity analyses

Sensitivity analyses including only IBC as an outcome, censoring at the time of first non-SBC subsequent malignant tumor, excluding females treated before 1970, excluding Hodgkin lymphoma patients (Supplementary Table 7), and excluding each cohort on a one-by-one basis (Supplementary Table 8) yielded similar results. The results of the models conducted in each cohort are shown in Supplementary Table 9.

Table 4. Multivariable Cox proportional hazard regression analyses for subsequent breast cancer in female five-year childhood cancer survivors whose treatment history did not include chest radiotherapy nor alkylating agent chemotherapy (primary cancer diagnosis year 1946-2012)[a]

	Total (n)	%	No. SBC (n)	%	HR[b]	95% CI
Doxorubicin dose, mg/m²						
No doxorubicin	5,880	90.5	61	71.8	1.0	Ref.
<300[c]	305	4.7	7	8.2	2.35	0.96-5.71
300-399	131	2.0	5	5.9	2.67	1.08-6.59
≥400	136	2.1	8	9.4	3.58	1.66-7.71
Unknown	47	0.7	4	4.7	..	..
Daunorubicin						
No	6,020	92.6	81	95.3	1.0	Ref.
Yes	479	7.4	4	4.7	1.43	0.48-4.24
Epirubicin						
No	6,362	97.9	84	98.8	1.0	Ref.
Yes	137	2.1	1	1.2	3.46	0.41-29.10

CI = Confidence interval; HR = Hazard ratio; No. = number; SBC = subsequent breast cancer

[a]In total, 6,499 female five-year survivors did not received chest radiotherapy nor alkylating agent chemotherapy, among whom 85 developed SBC during follow-up.

[b]Models were further adjusted for pelvic radiotherapy ≥5 Gy (yes/no) and age at primary childhood cancer diagnosis (categorical variable).

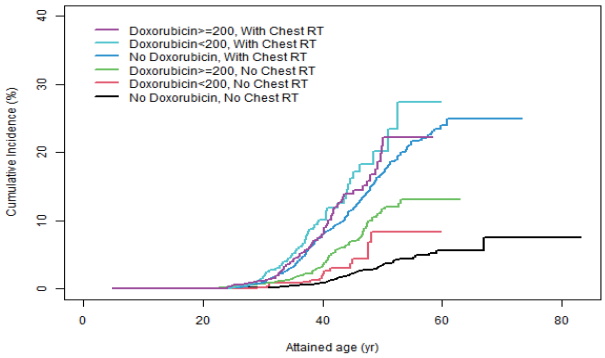
[c]The cumulative doxorubicin dose (mg/m²) categories <100 (0 case/46 survivors), 100-199 (1 case/129 survivors), and 200-299 (6 cases/130 survivors) were collapsed due to low numbers of SBC cases.

Discussion

Because this is the largest cohort analysis to evaluate the role of anthracyclines in the development of breast cancer after childhood cancer, we are able to estimate precise dose thresholds for doxorubicin and identify the effects of other types of anthracyclines on SBC risk. These pooled analyses demonstrate a relationship between increasing cumulative doxorubicin dose and SBC risk as well as an association between epirubicin exposure (yes vs. no) and an increased SBC risk. We observed that treatment with doxorubicin increases SBC risk both in survivors who received chest radiotherapy and in survivors treated without chest radiotherapy. Furthermore, the joint effects between doxorubicin and chest radiotherapy appear to be additive. In addition, our results suggest a possible association of daunorubicin and increased SBC risk, although the dose-response analyses did not achieve statistical significance.

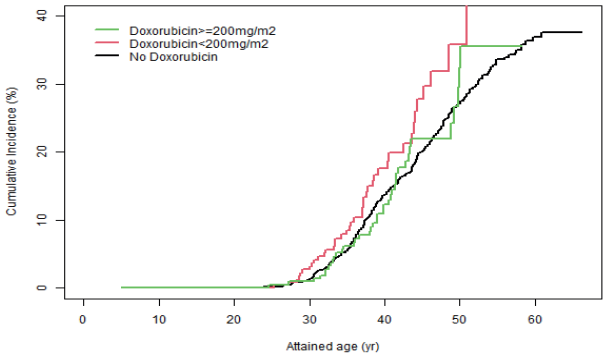
Figure 2. Cumulative incidence of subsequent breast cancer in female five-year childhood cancer survivors by cumulative doxorubicin dose, stratified by chest radiotherapy status (a) or chest radiotherapy field (b-e) (primary cancer diagnosis year 1946-2012)*

a. Chest RT (y/n)

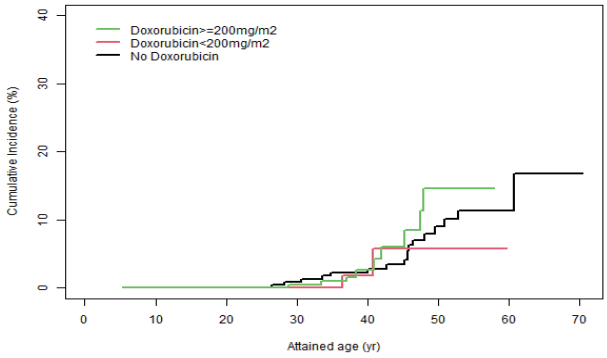


No. at risk at attained age:	5yr	20yr	40yr	60yr
No Doxorubicin, No Chest RT	111	6,835	2,410	127
Doxorubicin<200 mg/m², No Chest RT	16	1,472	252	0
Doxorubicin≥200 mg/m², No Chest RT	6	1,549	768	7
No Doxorubicin, With Chest RT	2	1,417	1,010	55
Doxorubicin<200 mg/m², With Chest RT	0	387	147	0
Doxorubicin≥200 mg/m², With Chest RT	0	336	190	0

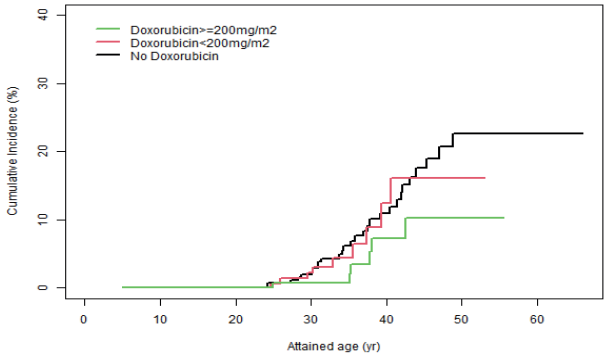
b. Mantle field RT



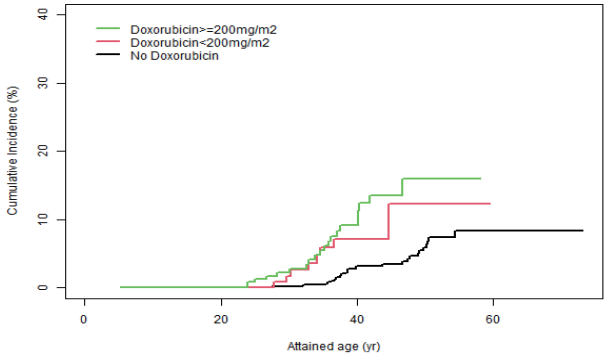
c. Mediastinal field RT



d. TBI/whole lung field RT



e. Other chest field RT



*The Swiss Childhood Cancer Survivor Study (SCCSS) was excluded from cumulative incidence analyses due to the case-cohort design. The cumulative incidence figures represent univariable comparisons. Multivariable Cox regression results for the cumulative doxorubicin dose categories presented in this figure are shown in Supplementary Table 6. No. = number; RT = radiotherapy; TBI = Total Body Irradiation; yr = year

Our results extend the findings of previous studies based on single cohorts, with relatively smaller sample sizes and case numbers, reporting that anthracycline exposure may increase the risk of SBC (10, 11, 13-16). In regard to our identification of differential risk between different anthracycline agents, potential differences in the mechanisms of developing subsequent neoplasms are unclear. Animal studies indicate that both doxorubicin and daunorubicin can induce mammary tumors (27, 28). The antineoplastic properties of doxorubicin and daunorubicin have both been assumed to result from DNA damage and chromatin damage (29), and based on limited studies, the anticancer efficacies are thought to be similar (30, 31). Evidence suggests that, in both mice models and human cells, chemically separating those activities by reducing the DNA damage effect, while retaining the chromatin damage, could detoxify the anthracycline variants, while maintaining anticancer efficacy (32). Possible factors that might underlie the differences in dose effects we observed between doxorubicin and daunorubicin are genetic factors, which were not examined in the current study, and the lower number of individuals and SBC cases exposed to daunorubicin, which might have limited the power to detect a significant dose-response relationship. For epirubicin (nine SBC cases exposed), we identified an association with SBC increased risk; and for idarubicin (one SBC case exposed), the number was too low. Future studies that elucidate mechanisms underlying carcinogenicity and anticancer efficacy among the various anthracycline agents are warranted.

Childhood cancer treatments often feature multi-modality regimens (33), which challenge elucidation of joint and independent effects of different treatments. Our study provides evidence of the joint effects of chest radiotherapy and individual anthracycline agents. Our findings indicate that the joint effects of doxorubicin and chest radiation are sub-multiplicative and compatible with additive effects, which implies that the combined effects of doxorubicin and chest radiation are not equal to the product of their individual effects, but to the sum of their individual effects. A previous CCSS case-control study showed that the joint effects of radiotherapy dose to the breast and anthracycline exposure (yes/no) were more than additive (15). However, they did not investigate the interaction between individual anthracycline agents and chest radiotherapy, and further comparison between the studies is difficult, because the CCSS study used a case-control design with estimated radiation dose to the breast cancer location.

We did not observe a statistically significant reduction of SBC risk among survivors with radiotherapy delivered to the pelvic region (≥5 Gy vs. no pelvic radiotherapy or <5 Gy, as an indicator of ovarian dose) in our entire cohort (Table 2), which aligns with a SJLIFE study (pelvic radiotherapy yes vs. no) that was also included in our

pooled cohort (14). However, when we restricted our analyses to survivors who received chest radiotherapy (Supplementary Table 10), we found a decreased SBC risk for pelvic radiotherapy, consistent with previous reports that showed reduced SBC risk associated with absorbed ovarian radiation dose ≥5 Gy in survivors treated with chest radiation, likely due to suppression of hormonal stimulation of breast tissue (10).

Some limitations should be taken into account when interpreting our study findings. For SIR/EAR and cumulative incidence analyses, one should be cautious with interpreting differences between categories, as there might be differences in the duration of follow-up and pelvic radiotherapy exposure between the categories. As we did not have complete data on treatments for subsequent malignant tumors prior to SBC (66 survivors had subsequent malignant tumors before SBC diagnosis), we were not able to explore the effects of those treatments on SBC risk. However, our sensitivity analyses censoring at the time of the first subsequent malignant tumor were consistent with the results in our main analyses. Our results of a 1.7-time increased risk of SBC compared to the general female population for survivors who received neither chest radiotherapy nor doxorubicin (Supplementary Table 3) suggest that other factors, such as genetic predisposition, may also play a role. As we had incomplete information on genetic cancer predispositions in our study, we were not able to evaluate genetic effects and possible gene-treatment interactions. The SJLIFE study, however, demonstrated that anthracycline effects are independent of cancer predisposition gene mutations (14). Future studies with germline genetic sequencing data may help to further elucidate the interplay of genetic modifiers and individual chemotherapeutic agent exposure on SBC risk.

According to the current IGHG breast cancer screening guideline, survivors with a relative risk more than two times higher than survivors not exposed to a specific treatment are considered to be at moderate or high risk for SBC. Recommendations for SBC screening in survivors are based on these risk levels (8). The current IGHG guideline was not able to formulate SBC screening recommendations for survivors treated with anthracyclines, because there was inconsistent evidence on dose thresholds for classifying survivors as moderate or high risk and no data on possible dose-effect differences in risks for the different individual anthracycline agents. In our study, we were able to calculate precise estimates for categories of cumulative doses of doxorubicin. We observed a more than two times higher risk of SBC for survivors treated with ≥200 mg/m^2 cumulative doxorubicin dose compared to the no doxorubicin treatment. Therefore, our findings support that early initiation of breast cancer surveillance is reasonable for childhood cancer survivors who have received ≥200 mg/m^2 cumulative doxorubicin dose. We

recommend updating the current IGHG surveillance recommendations on SBC risk in childhood cancer survivors. Our study provided insufficient information on the dose-response relation of epirubicin on SBC risk to advise on screening recommendations for this anthracycline agent.

In conclusion, doxorubicin is associated with a dose-dependent increase of SBC, both in women treated with and without chest radiotherapy. Epirubicin is also associated with an increased SBC risk. Our findings support that it is reasonable to initiate early breast cancer screening in female childhood cancer survivors who have received ≥200 mg/m^2 cumulative doxorubicin dose. The results of our study should be implemented in SBC surveillance guidelines for survivors and will inform future treatment protocols for newly diagnosed childhood cancer patients.

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Collaborators

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Supplemental material

Supplementary Table 1. Selection procedures for chemotherapeutic agents other than anthracyclines and alkylating agents in multivariable Cox proportional hazard regression analyses for subsequent breast cancer risk among female five-year childhood cancer survivors[a]

			Base model	
	No. SBC (n)[b]	**Total (n)**	**HR**	**95% CI**
Doxorubicin dose, mg/m²				
No doxorubicin	431 (55.1%)	11,170 (62.4%)	1.0	Ref.
<100	16 (2.0%)	912 (5.1%)	1.76	0.88-3.51
100-199	69 (8.8%)	1,795 (10.0%)	1.77	1.30-2.42
200-299	67 (8.6%)	1,026 (5.7%)	2.50	1.85-3.40
300-399	64 (8.2%)	1,012 (5.7%)	2.33	1.68-3.23
≥400	58 (7.4%)	779 (4.4%)	2.78	1.99-3.88
Unknown	77 (9.8%)	1,209 (6.8%)	-	-
Daunorubicin dose, mg/m²				
No daunorubicin	684 (87.5%)	14,630 (81.7%)	1.0	Ref.
<100	7 (0.9%)	623 (3.5%)	0.98	0.46-2.09
100-199	16 (2.0%)	953 (5.3%)	0.98	0.55-1.75
≥200	17 (2.2%)	645 (3.6%)	1.22	0.69-2.17
Unknown	58 (7.4%)	1,052 (5.9%)	-	-
Epipodophyllotoxins				
No	611 (78.1%)	13,434 (75.0%)		
Yes	78 (10.0%)	3,346 (18.7%)		
Unknown	93 (11.9%)	1,123 (6.3%)		
Vinca alkaloids				
No	269 (34.4%)	6,194 (34.6%)		
Yes	420 (53.7%)	10,586 (59.1%)		
Unknown	93 (11.9%)	1,123 (6.3%)		
Platinum compounds				
No	642 (82.1%)	14,219 (79.4%)		
Yes	47 (6.0%)	2,561 (14.3%)		
Unknown	93 (11.9%)	1,123 (6.3%)		
Antimetabolites				
No	504 (64.5%)	10,376 (58.0%)		
Yes	185 (23.7%)	6,404 (35.8%)		
Unknown	93 (11.9%)	1,123 (6.3%)		

CI = Confidence interval; HR = Hazard ratio; No. = number; SBC = Subsequent breast cancer;
[a]The base multivariable model included cumulative doxorubicin dose (categorical variable), cumulative daunorubicin dose (categorical variable), epirubicin (yes/no), age at primary cancer diagnosis (categorical variable), the combination of the chest radiation field and the associated maximum dose (categorical variable), pelvic radiation dose >5 Gy (yes/no), and alkylating agent cumulative exposure (cyclophosphamide equivalent dose, categorical variable). Because there is only evidence for associations between anthracyclines and

Base model + Epipodophyllotoxins		Base model + Vinca alkaloids		Base model + Platinum compounds		Base model + Antimetabolites	
HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
1.71	0.86-3.41	1.79	0.90-3.58	1.75	0.88-3.49	1.77	0.89-3.52
1.73	1.27-2.36	1.82	1.33-2.49	1.76	1.29-2.40	1.78	1.31-2.42
2.43	1.79-3.31	2.59	1.90-3.54	2.49	1.84-3.37	2.51	1.85-3.41
2.21	1.59-3.08	2.39	1.72-3.34	2.32	1.67-3.23	2.36	1.69-3.29
2.73	1.96-3.82	2.83	2.02-3.96	2.78	1.99-3.88	2.84	2.02-4.00
-	-	-	-	-	-	-	-
1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
0.91	0.42-1.95	1.01	0.47-2.18	0.98	0.46-2.09	1.02	0.47-2.22
0.93	0.53-1.64	1.01	0.57-1.81	0.98	0.55-1.75	1.03	0.56-1.88
1.14	0.64-2.03	1.24	0.69-2.20	1.22	0.68-2.16	1.28	0.71-2.32
-	-	-	-	-	-	-	-
1.0	Ref.						
1.33	0.98-1.80						
-	-						
		1.0	Ref.				
		0.86	0.68-1.09				
		-	-				
				1.0	Ref.		
				0.99	0.68-1.44		
				-	-		
						1.0	Ref.
						0.92	0.72-1.18
						-	-

alkylating agents on SBC risk, we applied the following selection procedure to evaluate other chemotherapeutic agents: we added binary indicators for epipodophyllotoxins, vinca alkaloids, platinum compounds, and antimetabolites to the base model; if addition of each variable changed any HRs of doxorubicin dose and/or daunorubicin dose by >10% compared to a model without the variable, it was included in the final models.

[b]One survivor had a SBC prior to five years after primary cancer.

Supplementary Table 2. Demographic and treatment characteristics of female five-year childhood cancer survivors by study

	CCSS (n = 9,671)	SJLIFE (n = 2,236)
Primary childhood cancer type		
Leukemia	2,987 (30.9%)	802 (35.9%)
Non-Hodgkin lymphoma	586 (6.1%)	115 (5.1%)
Hodgkin lymphoma	1,276 (13.2%)	227 (10.2%)
CNS tumor	1,841 (19.0%)	287 (12.8%)
Neuroblastoma	901 (9.3%)	101 (4.5%)
Retinoblastoma	-	119 (5.3%)
Renal tumor	389 (4.0%)	170 (7.6%)
Bone tumor	884 (9.1%)	133 (5.9%)
Soft tissue tumor	763 (7.9%)	127 (5.7%)
Germ cell tumor	20 (0.2%)	68 (3.0%)
Other malignant epithelial	-	49 (2.2%)
Other[a]	24 (0.2%)	38 (1.7%)
Age at primary childhood cancer diagnosis (yr)		
Median [IQR]	7.5 [3.1, 13.7]	6.2 [2.7, 12.6]
Age at primary childhood cancer diagnosis (yr) category		
<5	3,666 (37.9%)	973 (43.5%)
5-9	2,027 (21.0%)	468 (20.9%)
10-14	2,204 (22.8%)	472 (21.1%)
15-21	1,774 (18.3%)	323 (14.4%)
Period of childhood cancer diagnosis, range		
Median [IQR]	1985 [1979, 1992]	1994 [1984, 2002]
Period of childhood cancer diagnosis category		
<1960	-	-
1960-1969	-	42 (1.9%)
1970-1979	2,639 (27.3%)	274 (12.3%)
1980-1989	3,737 (38.6%)	535 (23.9%)
1990-1999	3,295 (34.1%)	633 (28.3%)
2000-2012	-	752 (33.6%)
Duration of follow-up since 5-yr survival and the end of follow-up[b] (yr)		
Median [IQR]	20.2 [14.7, 28.0]	18.0 [10.3, 27.5]

DCCSS LATER (n = 2,237)	FCCSS (n = 3,415)	DHL (n = 265)	SCCSS (n = 79)	Total (N = 17,903)
770 (34.4%)	-	-	15 (19.0%)	4,574 (25.5%)
157 (7.0%)	235 (6.9%)	-	4 (5.1%)	1,097 (6.1%)
125 (5.6%)	189 (5.5%)	265 (100%)	19 (24.1%)	2,101 (11.7%)
312 (13.9%)	498 (14.6%)	-	8 (10.1%)	2,946 (16.5%)
145 (6.5%)	505 (14.8%)	-	5 (6.3%)	1,657 (9.3%)
14 (0.6%)	293 (8.6%)	-	-	426 (2.4%)
250 (11.2%)	558 (16.3%)	-	5 (6.3%)	1,372 (7.7%)
141 (6.3%)	295 (8.6%)	-	6 (7.6%)	1,459 (8.1%)
151 (6.8%)	361 (10.6%)	-	3 (3.8%)	1,405 (7.8%)
101 (4.5%)	249 (7.3%)	-	2 (2.5%)	440 (2.5%)
50 (2.2%)	187 (5.5%)	-	11 (13.9%)	297 (1.7%)
21 (0.9%)	45 (1.3%)	-	1 (1.3%)	129 (0.7%)
5.4 [2.7, 10.7]	5.2 [1.7, 11.4]	18.3 [16.6, 19.7]	14.2 [6.0, 17.3]	6.7 [2.8, 13.0]
1,049 (46.9%)	1,671 (48.9%)	-	17 (21.5%)	7,376 (41.2%)
569 (25.4%)	707 (20.7%)	7 (2.6%)	10 (12.7%)	3,788 (21.2%)
471 (21.1%)	744 (21.8%)	21 (7.9%)	18 (22.8%)	3,930 (22.0%)
148 (6.6%)	293 (8.6%)	237 (89.4%)	34 (43.0%)	2,809 (15.7%)
1989 [1981, 1996]	1986 [1978, 1994]	1982 [1974, 1991]	1990 [1984, 1999]	1986 [1979, 1994]
-	60 (1.8%)	-	-	60 (0.3%)
49 (2.2%)	264 (7.7%)	29 (10.9%)	-	384 (2.1%)
386 (17.3%)	693 (20.3%)	81 (30.6%)	8 (10.1%)	4,081 (22.8%)
711 (31.8%)	1,035 (30.3%)	76 (28.7%)	27 (34.2%)	6,121 (34.2%)
871 (38.9%)	1,233 (36.1%)	76 (28.7%)	26 (32.9%)	6,134 (34.3%)
220 (9.8%)	130 (3.8%)	3 (1.1%)	18 (22.8%)	1,123 (6.3%)
16.8 [10.8, 25.0]	23.2 [16.3, 31.8]	17.6 [12.3, 25.7]	11.0 [6.7, 18.7]	19.9 [14.1, 28.2]

Supplementary Table 2. Demographic and treatment characteristics of female five-year childhood cancer survivors by study (continued)

	CCSS (n = 9,671)	SJLIFE (n = 2,236)
Duration of follow-up since 5-yr survival and the end of follow-up[b] (yr) category		
<10	1,096 (11.3%)	543 (24.3%)
10-19	3,672 (38.0%)	703 (31.4%)
20-29	3,012 (31.1%)	570 (25.5%)
≥30	1,891 (19.6%)	420 (18.8%)
Attained age at last follow-up[b] (yr)		
Median [IQR]	34.4 [26.7, 42.0]	31.8 [23.7, 39.9]
Attained age at last follow-up[b] age (yr) category		
<20	838 (8.7%)	380 (17.0%)
20-29	2,552 (26.4%)	614 (27.5%)
30-39	3,314 (34.3%)	688 (30.8%)
≥40	2,967 (30.7%)	554 (24.8%)
SBC[c]		
No	9,219 (95.3%)	2,159 (96.6%)
Yes	452 (4.7%)	77 (3.4%)
First SBC type		
Invasive	344 (3.6%)	54 (2.4%)
DCIS	108 (1.1%)	23 (1.0%)
Vital status		
Alive at last contact	8,174 (84.5%)	2,171 (97.1%)
Deceased at last contact	1,497 (15.5%)	65 (2.9%)
Radiotherapy exposure to the chest		
No	6,607 (68.3%)	1,706 (76.3%)
Yes	2,098 (21.7%)	506 (22.6%)
Unknown	966 (10.0%)	24 (1.1%)
Chest radiation dose (Gy)		
Median [IQR]	30.0 [20.0, 39.0]	25.3 [15.0, 33.0]
Chest radiation dose (Gy) category		
No chest radiation	6,607 (68.3%)	1,706 (76.3%)
<10	73 (0.8%)	5 (0.2%)
10-19	403 (4.2%)	133 (5.9%)
20-29	533 (5.5%)	210 (9.4%)
30-39	542 (5.6%)	85 (3.8%)
≥40	511 (5.3%)	41 (1.8%)

DCCSS LATER (n = 2,237)	FCCSS (n = 3,415)	DHL (n = 265)	SCCSS (n = 79)	Total (N = 17,903)
482 (21.5%)	251 (7.4%)	40 (15.1%)	36 (45.6%)	2,448 (13.7%)
859 (38.4%)	1,130 (33.1%)	116 (43.8%)	24 (30.4%)	6,504 (36.3%)
645 (28.8%)	1,018 (29.8%)	69 (26.0%)	18 (22.8%)	5,332 (29.8%)
251 (11.2%)	1,016 (29.8%)	40 (15.1%)	1 (1.3%)	3,619 (20.2%)
29.3 [22.1, 36.9]	35.8 [27.3, 44.0]	40.9 [35.5, 48.8]	28.6 [24.3, 37.6]	33.7 [25.9, 41.6]
395 (17.7%)	242 (7.1%)	1 (0.4%)	14 (17.7%)	1,870 (10.4%)
798 (35.7%)	862 (25.2%)	26 (9.8%)	30 (38.0%)	4,882 (27.3%)
666 (29.8%)	1,068 (31.3%)	93 (35.1%)	18 (22.8%)	5,847 (32.7%)
378 (16.9%)	1,243 (36.4%)	145 (54.7%)	17 (21.5%)	5,304 (29.6%)
2,196 (98.2%)	3,288 (96.3%)	200 (75.5%)	59 (74.7%)	17,121 (95.6%)
41 (1.8%)	127 (3.7%)	65 (24.5%)	20 (25.3%)	782 (4.4%)
36 (1.6%)	111 (3.3%)	51 (19.2%)	20 (25.3%)	616 (3.4%)
5 (0.2%)	16 (0.5%)	14 (5.3%)	-	166 (0.9%)
1,928 (86.2%)	2,759 (80.8%)	178 (67.2%)	68 (86.1%)	15,278 (85.3%)
309 (13.8%)	656 (19.2%)	87 (32.8%)	11 (13.9%)	2,625 (14.7%)
1,892 (84.6%)	2,728 (79.9%)	22 (8.3%)	49 (62.0%)	13,004 (72.6%)
341 (15.2%)	482 (14.1%)	243 (91.7%)	23 (29.1%)	3,693 (20.6%)
4 (0.2%)	205 (6.0%)	-	7 (8.9%)	1,206 (6.7%)
25.0 [13.8, 35.2]	27.5 [20.0, 40.0]	38.0 [35.0, 40.0]	36.0 [19.8, 40.0]	28.0 [20.0, 39.0]
1,892 (84.6%)	2,728 (79.9%)	22 (8.3%)	49 (62.0%)	13,004 (72.6%)
48 (2.1%)	7 (0.2%)	-	-	133 (0.7%)
69 (3.1%)	102 (3.0%)	2 (0.8%)	6 (7.6%)	715 (4.0%)
60 (2.7%)	148 (4.3%)	11 (4.2%)	2 (2.5%)	964 (5.4%)
82 (3.7%)	92 (2.7%)	90 (34.0%)	5 (6.3%)	896 (5.0%)
68 (3.0%)	133 (3.9%)	85 (32.1%)	6 (7.6%)	844 (4.7%)

Supplementary Table 2. Demographic and treatment characteristics of female five-year childhood cancer survivors by study (continued)

	CCSS (n = 9,671)	SJLIFE (n = 2,236)
Unknown	1,002 (10.4%)	56 (2.5%)
Chest radiation field		
No chest radiation	6,607 (68.3%)	1,706 (76.3%)
Axilla	12 (0.1%)	5 (0.2%)
Mantle	723 (7.5%)	191 (8.5%)
Mediastinal	227 (2.3%)	23 (1.0%)
Spine	598 (6.2%)	131 (5.9%)
Total body irradiation	223 (2.3%)	67 (3.0%)
Whole lung	79 (0.8%)	44 (2.0%)
Other	177 (1.8%)	33 (1.5%)
Unknown	1,025 (10.6%)	36 (1.6%)
Radiotherapy exposure to the pelvis		
No	7,191 (74.4%)	1,873 (83.8%)
Yes	1,515 (15.7%)	337 (15.1%)
Unknown	965 (10.0%)	26 (1.2%)
Pelvic radiation dose (Gy)		
Median [IQR]	26.0 [15.0, 36.0]	23.4 [16.8, 36.0]
Pelvic radiation dose (Gy) category		
No pelvic radiation	7,191 (74.4%)	1,873 (83.8%)
<10	66 (0.7%)	4 (0.2%)
10-19	369 (3.8%)	89 (4.0%)
20-29	365 (3.8%)	120 (5.4%)
30-39	398 (4.1%)	66 (3.0%)
≥40	295 (3.1%)	57 (2.5%)
Unknown	987 (10.2%)	27 (1.2%)
Anthracyclines[f]		
No	4,889 (50.6%)	955 (42.7%)
Yes	3,990 (41.3%)	1,263 (56.5%)
Unknown	792 (8.2%)	18 (0.8%)
Doxorubicin		
No	5,729 (59.2%)	1,377 (61.6%)
Yes	3,150 (32.6%)	841 (37.6%)
Unknown	792 (8.2%)	18 (0.8%)
Doxorubicin dose (mg/m²)		

DCCSS LATER (n = 2,237)	FCCSS (n = 3,415)	DHL (n = 265)	SCCSS (n = 79)	Total (N = 17,903)
18 (0.8%)	205 (6.0%)	55 (20.8%)	11 (13.9%)	1,347 (7.5%)
1,892 (84.6%)	2,728 (79.9%)	22 (8.3%)	49 (62.0%)	13,004 (72.6%)
15 (0.7%)	-	2 (0.8%)	-	34 (0.2%)
39 (1.7%)	86 (2.5%)	192 (72.5%)	11 (13.9%)	1,242 (6.9%)
36 (1.6%)	134 (3.9%)	45 (17.0%)	4 (5.1%)	469 (2.6%)
109 (4.9%)	98 (2.9%)	-	3 (3.8%)	939 (5.2%)
69 (3.1%)	10 (0.3%)	-	2 (2.5%)	371 (2.1%)
22 (1.0%)	37 (1.1%)	-	2 (2.5%)	184 (1.0%)
49 (2.2%)	117 (3.4%)	-	1 (1.3%)	377 (2.1%)
6 (0.3%)	205 (6.0%)	4 (1.5%)	7 (8.9%)	1,283 (7.2%)
2,129 (95.2%)	2,287 (67.0%)	179 (67.5%)	68 (86.1%)	13,727 (76.7%)
105 (4.7%)	923 (27.0%)	81 (30.6%)	3 (3.8%)	2,964 (16.6%)
3 (0.1%)	205 (6.0%)	5 (1.9%)	8 (10.1%)	1,212 (6.8%)
12.0 [7.5, 38.5]	33.0 [22.0, 43.5]	NA[d]	11.0 [10.5, 11.5]	30.0 [19.0, 39.0]
2,129 (95.2%)	2,287 (67.0%)	179 (67.5%)	68 (86.1%)	13,727 (76.7%)
47 (2.1%)	25 (0.7%)	-	-	142 (0.8%)
20 (0.9%)	114 (3.3%)	-	2 (2.5%)	594 (3.3%)
2 (0.1%)	232 (6.8%)	-	-	719 (4.0%)
6 (0.3%)	216 (6.3%)	81 (30.6%)[e]	-	767 (4.3%)
25 (1.1%)	336 (9.8%)	-	-	713 (4.0%)
8 (0.4%)	205 (6.0%)	5 (1.9%)	9 (11.4%)	1,241 (6.9%)
1,250 (55.9%)	2,095 (61.3%)	155 (58.5%)	36 (45.6%)	9,380 (52.4%)
982 (43.9%)	1,201 (35.2%)	98 (37.0%)	36 (45.6%)	7,570 (42.3%)
5 (0.2%)	119 (3.5%)	12 (4.5%)	7 (8.9%)	953 (5.3%)
1,541 (68.9%)	2,300 (67.4%)	181 (68.3%)	42 (53.2%)	11,170 (62.4%)
691 (30.9%)	996 (29.2%)	84 (31.7%)	30 (38.0%)	5,792 (32.4%)
5 (0.2%)	119 (3.5%)	-	7 (8.9%)	941 (5.3%)

Supplementary Table 2. Demographic and treatment characteristics of female five-year childhood cancer survivors by study (continued)

	CCSS (n = 9,671)	SJLIFE (n = 2,236)
Median [IQR]	224.7 [130.4, 358.3]	177.4 [135.1, 256.2]
Doxorubicin dose (mg/m²) category		
No doxorubicin	5,729 (59.2%)	1,377 (61.6%)
<100	502 (5.2%)	121 (5.4%)
100-199	769 (8.0%)	414 (18.5%)
200-299	590 (6.1%)	124 (5.5%)
300-399	568 (5.9%)	146 (6.5%)
≥400	474 (4.9%)	35 (1.6%)
Unknown	1,039 (10.7%)	19 (0.8%)
Daunorubicin		
No	7,660 (79.2%)	1,618 (72.4%)
Yes	1,219 (12.6%)	600 (26.8%)
Unknown	792 (8.2%)	18 (0.8%)
Daunorubicin (mg/m²)		
Median [IQR]	151.0 [100.0, 319.4]	87.5 [50.0, 106.7]
Daunorubicin dose (mg/m²) category		
No daunorubicin	7,660 (79.2%)	1,618 (72.4%)
<100	263 (2.7%)	339 (15.2%)
100-199	373 (3.9%)	198 (8.9%)
≥200	494 (5.1%)	62 (2.8%)
Unknown	881 (9.1%)	19 (0.8%)
Epirubicin		
No	8,877 (91.8%)	2,217 (99.2%)
Yes	2 (0.0%)	1 (0.0%)
Unknown	792 (8.2%)	18 (0.8%)
Idarubicin		
No	8,814 (91.1%)	2,198 (98.3%)
Yes	65 (0.7%)	20 (0.9%)
Unknown	792 (8.2%)	18 (0.8%)
Alkylating agents		
No	4,003 (41.4%)	947 (42.4%)
Yes	4,876 (50.4%)	1,271 (56.8%)
Unknown	792 (8.2%)	18 (0.8%)
CED[8] dose (mg/m²)		

DCCSS LATER (n = 2,237)	FCCSS (n = 3,415)	DHL (n = 265)	SCCSS (n = 79)	Total (N = 17,903)
150.0 [65.0, 300.0]	235.7 [131.7, 346.8]	210.0 [140.0, 280.0]	200.0 [150.0, 300.0]	203.3 [120.0, 340.0]
1,541 (68.9%)	2,300 (67.4%)	181 (68.3%)	42 (53.2%)	11,170 (62.4%)
188 (8.4%)	95 (2.8%)	5 (1.9%)	1 (1.3%)	912 (5.1%)
232 (10.4%)	347 (10.2%)	20 (7.5%)	13 (16.5%)	1,795 (10.0%)
62 (2.8%)	207 (6.1%)	38 (14.3%)	5 (6.3%)	1,026 (5.7%)
77 (3.4%)	203 (5.9%)	11 (4.2%)	7 (8.9%)	1,012 (5.7%)
124 (5.5%)	137 (4.0%)	6 (2.3%)	3 (3.8%)	779 (4.4%)
13 (0.6%)	126 (3.7%)	4 (1.5%)	8 (10.1%)	1,209 (6.8%)
1,795 (80.2%)	3,239 (94.8%)	253 (95.5%)	65 (82.3%)	14,630 (81.7%)
437 (19.5%)	57 (1.7%)	-	7 (8.9%)	2,320 (13.0%)
5 (0.2%)	119 (3.5%)	12 (4.5%)	7 (8.9%)	953 (5.3%)
120.0 [120.0, 175.0]	255.7 [140.8, 419.7]	-	150.0 [120.0, 247.5]	120.0 [98.1, 234.1]
1,795 (80.2%)	3,239 (94.8%)	253 (95.5%)	65 (82.3%)	14,630 (81.7%)
16 (0.7%)	5 (0.1%)	-	-	623 (3.5%)
361 (16.1%)	17 (0.5%)	-	4 (5.1%)	953 (5.3%)
51 (2.3%)	35 (1.0%)	-	3 (3.8%)	645 (3.6%)
14 (0.6%)	119 (3.5%)	12 (4.5%)	7 (8.9%)	1,052 (5.9%)
2,104 (94.1%)	3,116 (91.2%)	251 (94.7%)	72 (91.1%)	16,637 (92.9%)
128 (5.7%)	180 (5.3%)	14 (5.3%)	-	325 (1.8%)
5 (0.2%)	119 (3.5%)	-	7 (8.9%)	941 (5.3%)
2,212 (98.9%)	3,296 (96.5%)	253 (95.5%)	70 (88.6%)	16,843 (94.1%)
20 (0.9%)	-	-	2 (2.5%)	107 (0.6%)
5 (0.2%)	119 (3.5%)	12 (4.5%)	7 (8.9%)	953 (5.3%)
1,152 (51.5%)	1,597 (46.8%)	100 (37.7%)	33 (41.8%)	7,832 (43.7%)
1,080 (48.3%)	1,699 (49.8%)	153 (57.7%)	39 (49.4%)	9,118 (50.9%)
5 (0.2%)	119 (3.5%)	12 (4.5%)	7 (8.9%)	953 (5.3%)

Supplementary Table 2. Demographic and treatment characteristics of female five-year childhood cancer survivors by study (continued)

	CCSS (n = 9,671)	SJLIFE (n = 2,236)
0	4,093 (42.3%)	956 (42.8%)
<6000	1,687 (17.4%)	489 (21.9%)
6000-17999	1,876 (19.4%)	631 (28.2%)
≥18000	561 (5.8%)	139 (6.2%)
Unknown	1,454 (15.0%)	21 (0.9%)
Epipodophyllotoxins		
No	7,567 (78.2%)	1,402 (62.7%)
Yes	1,312 (13.6%)	816 (36.5%)
Unknown	792 (8.2%)	18 (0.8%)
Vinca alkaloids		
No	3,351 (34.7%)	706 (31.6%)
Yes	5,528 (57.2%)	1,512 (67.6%)
Unknown	792 (8.2%)	18 (0.8%)
Platinum compounds		
No	7,817 (80.8%)	1,870 (83.6%)
Yes	1,062 (11.0%)	348 (15.6%)
Unknown	792 (8.2%)	18 (0.8%)
Antimetabolites		
No	5,012 (51.8%)	1,151 (51.5%)
Yes	3,867 (40.0%)	1,067 (47.7%)
Unknown	792 (8.2%)	18 (0.8%)

CCSS = Childhood Cancer Survivor Study; CED = Cyclophosphamide Equivalent Dose; CNS = Central nervous system; DCCSS LATER = Dutch Long-term Effects After Childhood Cancer Study; DCIS = Ductal carcinoma in situ; DHL = Dutch Hodgkin Late Effects cohort; FCCSS = French Childhood Cancer Survivor Study; IQR = Interquartile range; NA = Not applicable; SBC = Subsequent breast cancer; SCCSS = Swiss Childhood Cancer Survivor Study; SJLIFE = St. Jude Lifetime Cohort Study; yr = year

[a]Includes the ICCC-3 classification groups "Hepatic Tumor", "Other and Unspecified", and "Unclassified".

[b]Follow-up time was calculated from five years after a primary cancer diagnosis to the date of subsequent breast cancer diagnosis, death, or the date of the last follow-up observation, whichever occurred first.

[c]Include both invasive and DCIS breast cancer.

[d]Precise pelvic radiation dose information was not available in the DHL.

[e]Dose of pelvic radiation information was not available for the DHL. We assume the survivors in the DHL who had pelvic radiotherapy received 30 Gy radiotherapy exposure to the pelvis since Hodgkin lymphoma patients usually receive 30 Gy pelvic radiation.

[f]Anthracyclines include doxorubicin, daunorubicin, epirubicin, and idarubicin.

[g]Cyclophosphamide Equivalent Dose calculation: CED (mg/m^2) = 1.0 (cumulative cyclophosphamide dose (mg/m^2)) + 0.244 (cumulative ifosfamide dose (mg/m^2)) + 0.857 (cumulative procarbazine dose (mg/m^2)) + 14.286 (cumulative chlorambucil dose (mg/m^2)) + 15.0 (cumulative BCNU (carmustine) dose (mg/m^2)) + 16.0 (cumulative CCNU (lomustine) dose (mg/m^2)) + 40 (cumulative melphalan dose (mg/m^2)) + 50 (cumulative Thio-TEPA (thiotepa) dose (mg/m^2)) + 100 (cumulative nitrogen mustard dose (mg/m^2)) + 8.823 (cumulative busulfan dose (mg/m^2)).

DCCSS LATER (n = 2,237)	FCCSS (n = 3,415)	DHL (n = 265)	SCCSS (n = 79)	Total (N = 17,903)
1,160 (51.9%)	1,608 (47.1%)	100 (37.7%)	34 (43.0%)	7,951 (44.4%)
265 (11.8%)	606 (17.7%)	-	22 (27.8%)	3,069 (17.1%)
563 (25.2%)	819 (24.0%)	-	10 (12.7%)	3,899 (21.8%)
192 (8.6%)	222 (6.5%)	-	3 (3.8%)	1,117 (6.2%)
57 (2.5%)	160 (4.7%)	165 (62.3%)	10 (12.7%)	1,867 (10.4%)
1,796 (80.3%)	2,531 (74.1%)	83 (31.3%)	55 (69.6%)	13,434 (75.0%)
436 (19.5%)	765 (22.4%)	-	17 (21.5%)	3,346 (18.7%)
5 (0.2%)	119 (3.5%)	182 (68.7%)	7 (8.9%)	1,123 (6.3%)
653 (29.2%)	1,367 (40.0%)	83 (31.3%)	34 (43.0%)	6,194 (34.6%)
1,579 (70.6%)	1,929 (56.5%)	-	38 (48.1%)	10,586 (59.1%)
5 (0.2%)	119 (3.5%)	182 (68.7%)	7 (8.9%)	1,123 (6.3%)
1,911 (85.4%)	2,473 (72.4%)	83 (31.3%)	65 (82.3%)	14,219 (79.4%)
321 (14.3%)	823 (24.1%)	-	7 (8.9%)	2,561 (14.3%)
5 (0.2%)	119 (3.5%)	182 (68.7%)	7 (8.9%)	1,123 (6.3%)
1,261 (56.4%)	2,816 (82.5%)	83 (31.3%)	53 (67.1%)	10,376 (58.0%)
971 (43.4%)	480 (14.1%)	-	19 (24.1%)	6,404 (35.8%)
5 (0.2%)	119 (3.5%)	182 (68.7%)	7 (8.9%)	1,123 (6.3%)

Supplementary Table 3. Standardized incidence ratios, excess absolute risks, and cumulative incidences by treatments

	No. of SBC cases		
Treatments: Cumulative doxorubicin dose & chest radiotherapy (yes/no)	**Observed**	**Expected**	**SIR**
Without chest radiotherapy			
No doxorubicin	91	53.0	1.7
Cumulative doxorubicin dose <200 mg/m^2	17	5.3	3.2
Cumulative doxorubicin dose ≥200 mg/m^2	84	15.0	5.6
With chest radiotherapy			
No doxorubicin	250	23.4	10.7
Cumulative doxorubicin dose <200 mg/m^2	36	2.6	13.9
Cumulative doxorubicin dose ≥200 mg/m^2	58	3.3	17.5

CI = Confidence interval; EAR = excess absolute risk; IQR = Interquartile range; No. = number; SBC = Subsequent breast cancer; SIR = Standardized incidence ratio; TBI = Total Body Irradiation; yr = year

Supplementary Table 4. Demographic and treatment characteristics of female five-year childhood cancer survivors by cumulative doxorubicin dose categories

	No doxorubicin (n = 11,170)	**<100 (n = 912)**	**100-199 (n = 1,795)**
Primary childhood cancer type			
Leukemia	2,974 (26.6%)	576 (63.2%)	404 (22.5%)
Non-Hodgkin lymphoma	445 (4.0%)	72 (7.9%)	245 (13.6%)
Hodgkin lymphoma	1,007 (9.0%)	63 (6.9%)	457 (25.5%)
CNS tumor	2,767 (24.8%)	1 (0.1%)	5 (0.3%)
Neuroblastoma	942 (8.4%)	104 (11.4%)	282 (15.7%)
Retinoblastoma	360 (3.2%)	9 (1.0%)	35 (1.9%)
Renal tumor	950 (8.5%)	28 (3.1%)	158 (8.8%)
Bone tumor	213 (1.9%)	23 (2.5%)	110 (6.1%)
Soft tissue tumor	814 (7.3%)	25 (2.7%)	74 (4.1%)
Germ cell tumor	376 (3.4%)	5 (0.5%)	9 (0.5%)
Other malignant epithelial	266 (2.4%)	-	6 (0.3%)
Other[b]	56 (0.5%)	6 (0.6%)	10 (0.6%)
Age at primary childhood cancer diagnosis (yr) category			
<5	5,076 (45.4%)	464 (50.9%)	700 (39.0%)
5-9	2,490 (22.3%)	188 (20.6%)	295 (16.4%)
10-14	2,139 (19.1%)	181 (19.8%)	452 (25.2%)
15-21	1,465 (13.1%)	79 (8.7%)	348 (19.4%)

95% CI	EAR/1,000 person-yr	Attained age (median, IQR)	Cumulative incidences at attained age 40
1.4-2.1	0.2	32.8 (25.1-41.2)	0.8%
1.9-5.1	0.3	28.9 (23.1-35.9)	1.9%
4.5-6.9	1.5	36.5 (29.1-43.5)	3.4%
9.4-12.1	4.5	38.4 (30.3-47.4)	7.9%
9.7-19.2	3.1	33.8 (27.2-39.1)	10.1%
13.3-22.6	5.0	36.1 (29.1-41.8)	8.1%

Cumulative doxorubicin dose (mg/m^2) category				
200-299 (n = 1,026)	300-399 (n = 1,012)	≥400 (n = 779)	Unknown[a] (n = 1,209)	Total (N = 17,903)
110 (10.7%)	116 (11.5%)	82 (10.5%)	312 (25.8%)	4,574 (25.5%)
91 (8.9%)	82 (8.1%)	73 (9.4%)	89 (7.4%)	1,097 (6.1%)
284 (27.7%)	104 (10.3%)	22 (2.8%)	164 (13.6%)	2,101 (11.7%)
4 (0.4%)	4 (0.4%)	2 (0.3%)	163 (13.5%)	2,946 (16.5%)
109 (10.6%)	55 (5.4%)	40 (5.1%)	125 (10.3%)	1,657 (9.3%)
3 (0.3%)	4 (0.4%)	-	15 (1.2%)	426 (2.4%)
98 (9.6%)	50 (4.9%)	22 (2.8%)	66 (5.5%)	1,372 (7.7%)
175 (17.1%)	417 (41.2%)	387 (49.7%)	134 (11.1%)	1,459 (8.1%)
111 (10.8%)	145 (14.3%)	136 (17.5%)	100 (8.3%)	1,405 (7.8%)
17 (1.7%)	14 (1.4%)	5 (0.6%)	14 (1.2%)	440 (2.5%)
5 (0.5%)	2 (0.2%)	-	18 (1.5%)	297 (1.7%)
19 (1.9%)	19 (1.9%)	10 (0.6%)	10 (0.8%)	129 (0.7%)
314 (30.6%)	224 (22.1%)	165 (21.2%)	433 (35.8%)	7,376 (41.2%)
157 (15.3%)	229 (22.6%)	179 (23.0%)	250 (20.7%)	3,788 (21.2%)
301 (29.3%)	326 (32.2%)	257 (33.0%)	274 (22.7%)	3,930 (22.0%)
254 (24.8%)	233 (23.0%)	178 (22.8%)	252 (20.8%)	2,809 (15.7%)

Supplementary Table 4. Demographic and treatment characteristics of female five-year childhood cancer survivors by cumulative doxorubicin dose categories (continued)

	No doxorubicin (n = 11,170)	<100 (n = 912)	100-199 (n = 1,795)
Childhood cancer diagnosis period			
<1980	3,254 (29.1%)	47 (5.2%)	141 (7.9%)
1980-1989	3,715 (33.3%)	264 (28.9%)	520 (29.0%)
≥1990	4,201 (37.6%)	601 (65.9%)	1,134 (63.2%)
Chest radiation fields and total doses combination			
No chest radiotherapy	8,541 (76.5%)	752 (82.5%)	1,215 (67.7%)
High-dose mantle (≥36 Gy)	537 (4.8%)	12 (1.3%)	44 (2.5%)
Low-dose mantle (<36 Gy)	190 (1.7%)	19 (2.1%)	171 (9.5%)
Mediastinal	226 (2.0%)	20 (2.2%)	105 (5.8%)
TBI	215 (1.9%)	41 (4.5%)	72 (4.0%)
Whole lung	68 (0.6%)	11 (1.2%)	38 (2.1%)
Other	970 (8.7%)	30 (3.3%)	71 (4.0%)
Unknown	423 (3.8%)	27 (3.0%)	79 (4.4%)
Treatment combinations[c]			
Anthracyclines[d] & Chest radiotherapy	288 (2.6%)	143 (15.7%)	530 (29.5%)
Anthracyclines & No chest radiotherapy	1,443 (12.9%)	752 (82.5%)	1,215 (67.7%)
No anthracyclines & Chest radiotherapy	1,962 (17.6%)	-	-
No anthracyclines & No chest radiotherapy	7,096 (63.5%)	-	-
Unknown	381 (3.4%)	17 (1.9%)	50 (2.8%)
Pelvic radiotherapy ≥5 Gy			
No	8,926 (79.9%)	781 (85.6%)	1,388 (77.3%)
Yes	1,863 (16.7%)	110 (12.1%)	351 (19.6%)
Unknown	381 (3.4%)	21 (2.3%)	56 (3.1%)

CNS = Central nervous system; IQR = Interquartile range; yr = year

[a]The Unknown category under the variable "Doxorubicin dose" includes both survivor groups with any doxorubicin (yes/no) unknown (941 survivors) and with doxorubicin treatment but dose information unknown (268 survivors).

[b]Includes the ICCC-3 classification groups "Hepatic Tumor" (61 survivors), "Other and Unspecified" (38 survivors), and "Unclassified" (30 survivors).

[c]Treatment subgroup variable set to unknown if either of the treatment categories was unknown.

[d]Anthracyclines include doxorubicin, daunorubicin, epirubicin, and idarubicin.

Cumulative doxorubicin dose (mg/m²) category				
200-299 (n = 1,026)	**300-399 (n = 1,012)**	**≥400 (n = 779)**	**Unknown[a] (n = 1,209)**	**Total (N = 17,903)**
148 (14.4%)	188 (18.6%)	306 (39.3%)	441 (36.5%)	4,525 (25.3%)
406 (39.6%)	448 (44.3%)	283 (36.3%)	485 (40.1%)	6,121 (34.2%)
472 (46.0%)	376 (37.2%)	190 (24.4%)	283 (23.4%)	7,257 (40.5%)
693 (67.5%)	775 (76.6%)	655 (84.1%)	373 (30.9%)	13,004 (72.6%)
40 (3.9%)	27 (2.7%)	13 (1.7%)	25 (2.1%)	698 (3.9%)
81 (7.9%)	39 (3.9%)	6 (0.8%)	18 (1.5%)	524 (2.9%)
54 (5.3%)	31 (3.1%)	11 (1.4%)	22 (1.8%)	469 (2.6%)
13 (1.3%)	11 (1.1%)	4 (0.5%)	15 (1.2%)	371 (2.1%)
23 (2.2%)	30 (3.0%)	10 (1.3%)	4 (0.3%)	184 (1.0%)
67 (6.5%)	62 (6.1%)	54 (6.9%)	62 (5.1%)	1,316 (7.4%)
55 (5.4%)	37 (3.7%)	26 (3.3%)	690 (57.1%)	1,337 (7.5%)
298 (29.0%)	208 (20.6%)	99 (12.7%)	68 (5.6%)	1,634 (9.1%)
693 (67.5%)	775 (76.6%)	655 (84.1%)	181 (15.0%)	5,714 (31.9%)
-	-	-	-	1,962 (11.0%)
-	-	-	-	7,096 (39.6%)
35 (3.4%)	29 (2.9%)	25 (3.2%)	960 (79.4%)	1,497 (8.4%)
803 (78.3%)	799 (79.0%)	652 (83.7%)	402 (33.3%)	13,751 (76.8%)
185 (18.0%)	180 (17.8%)	101 (13.0%)	121 (10.0%)	2,911 (16.3%)
38 (3.7%)	33 (3.3%)	26 (3.3%)	686 (56.7%)	1,241 (6.9%)

Supplementary Table 5. Joint effects of cumulative doxorubicin and daunorubicin doses and other relevant risk factors on subsequent breast cancer among female five-year childhood cancer survivors

Interaction: Chest radiotherapy (yes/no)*Anthracycline agent dose

	Cumulative doxorubicin dose per 100 mg/m²[a]			Cumulative daunorubicin dose per 100 mg/m²[b]		
Multiplicative interaction	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Chest radiotherapy status (yea/no)*Anthracycline agent dose	0.86	0.78 - 0.96	0.006	0.77	0.57 - 1.05	0.10
Additive interaction	**No. Additional Cases per 10,000 Person Years**	**95% CI**	**P value**	**No. Additional Cases per 10,000 Person Years**	**95% CI**	**P value**
Chest radiotherapy status(yea/no)*Anthracycline agent dose	0.04	-4.82 - 4.90	0.99	-9.67	-15.8 - -3.50	0.002

Interaction: Chest radiotherapy field and dose*Anthracycline agent dose

	Cumulative doxorubicin dose per 100 mg/m²[a]			Cumulative daunorubicin dose per 100 mg/m²[b,c]		
Multiplicative interaction	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
High-dose mantle (median 40 Gy, IQR 39-44 Gy)*Anthracycline agent dose	0.84	0.71 - 0.98	0.03	0.0003	0.0001 - 0.001	<0.001
Low-dose mantle (median 26 Gy, IQR 21-30 Gy)*Anthracycline agent dose	0.94	0.77 - 1.13	0.49	0.0007	0.0002 - 0.002	<0.001
Mediastinal (median 26 Gy, IQR 21-36 Gy)*Anthracycline agent dose	0.65	0.45 - 0.96	0.03	0.87	0.41 - 1.88	0.73
TBI (median 12 Gy, IQR 11-13 Gy)*Anthracycline agent dose	0.73	0.41 - 1.30	0.28	1.04	0.75 - 1.44	0.81
Whole lung (median 16 Gy, IQR 12-23 Gy)*Anthracycline agent dose	0.87	0.66 - 1.15	0.33	0.0003	0.00007 - 0.001	<0.001
Other (median 28 Gy, IQR 21-36 Gy)*Anthracycline agent dose	1.01	0.86 - 1.18	0.95	0.45	0.18 - 1.15	0.10
			$P_{Multiplicative\ interaction} = 0.07$			$P_{Multiplicative\ interaction} = 0.39$

Supplementary Table 5. Joint effects of cumulative doxorubicin and daunorubicin doses and other relevant risk factors on subsequent breast cancer among female five-year childhood cancer survivors (continued)

Additive interaction	**No. Additional Cases per 10,000 Person Years**	**95% CI**	**P value**	**No. Additional Cases per 10,000 Person Years**	**95% CI**	**P value**
High-dose mantle (median 40 Gy, IQR 39-44 Gy)*Anthracycline agent dose	-4.54	-25.5 - 16.4	0.66	-75.3	-88.8 - -61.8	<0.001
Low-dose mantle (median 26 Gy, IQR 21-30 Gy)*Anthracycline agent dose	7.99	-8.41 - 24.4	0.33	-20.6	-28.0 - -13.2	0.001
Mediastinal (median 26 Gy, IQR 21-36 Gy)*Anthracycline agent dose	-4.48	-12.2 - 3.28	0.26	-2.02	-17.0 - 12.9	0.80
TBI (median 12 Gy, IQR 11-13 Gy)*Anthracycline agent dose	-8.66	-27.3 - 9.98	0.35	4.96	-7.52 - 17.4	0.45
Whole lung (median 16 Gy, IQR 12-23 Gy)*Anthracycline agent dose	-7.48	-23.8 - 8.85	0.37	-20.5	-30.1 - -10.9	0.02
Other (median 28 Gy, IQR 21-36 Gy)*Anthracycline agent dose	5.41	-0.51 - 11.3	0.09	-7.51	-12.1 - -2.96	0.002

Interaction: Age at primary childhood cancer diagnosis*Anthracycline agent dose

	Cumulative doxorubicin dose per 100 mg/m²[d]			**Cumulative daunorubicin dose per 100 mg/m²[e]**		
Multiplicative interaction	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Diagnosis age 5-9 yr*Anthracycline agent dose	1.33	0.98 - 1.81	0.07	1.76	0.91 - 3.39	0.09
Diagnosis age 10-14 yr*Anthracycline agent dose	1.37	1.03 - 1.82	0.03	1.67	0.88 - 3.17	0.12
Diagnosis age 15-21 yr*Anthracycline agent dose	1.34	1.01 - 1.78	0.04	1.43	0.71 - 2.88	0.32
			$P_{Multiplicative\ interaction} = 0.09$			$P_{Multiplicative\ interaction} = 0.30$

Supplementary Table 5. Joint effects of cumulative doxorubicin and daunorubicin doses and other relevant risk factors on subsequent breast cancer among female five-year childhood cancer survivors (continued)

Additive interaction	**No. Additional Cases per 10,000 Person Years**	**95% CI**	**P value**	**No. Additional Cases per 10,000 Person Years**	**95% CI**	**P value**
Diagnosis age 5-9*Anthracycline agent dose	2.30	0.42 - 4.18	0.02	3.03	-0.81- 6.87	0.14
Diagnosis age 10-14*Anthracycline agent dose	6.53	3.55 - 9.51	<0.001	4.43	-1.78 - 10.6	0.16
Diagnosis age 15-21*Anthracycline agent dose	8.71	4.14 - 13.3	<0.001	-1.88	-10.2 - 6.45	0.66

CI = Confidence interval; HR = Hazard ratio; IQR = Interquartile range; No. = number; TBI = Total Body Irradiation

[a]Models were further adjusted for cumulative daunorubicin dose (continuous variable), epirubicin (yes/no), pelvic radiotherapy ≥5 Gy (yes/no), age at primary childhood cancer diagnosis category (categorical variable), and cyclophosphamide equivalent dose (categorical variable).

[b]Models were further adjusted for cumulative doxorubicin dose (continuous variable), epirubicin (yes/no), pelvic radiotherapy ≥5 Gy (yes/no), age at primary childhood cancer diagnosis category (categorical variable), and cyclophosphamide equivalent dose (categorical variable).

[c]The joint effects between cumulative daunorubicin dose and chest radiotherapy field and dose were not able to be evaluated due to limited numbers under chest radiotherapy field and dose*cumulative daunorubicin dose categories.

[d]Models were further adjusted for cumulative daunorubicin dose (continuous variable), epirubicin (yes/no), pelvic radiotherapy ≥5 Gy (yes/no), chest radiotherapy field and dose (categorical variable), and cyclophosphamide equivalent dose (categorical variable).

[e]Models were further adjusted for cumulative doxorubicin dose (continuous variable), epirubicin (yes/no), pelvic radiotherapy ≥5 Gy (yes/no), chest radiotherapy field and dose (categorical variable), and cyclophosphamide equivalent dose (categorical variable).

Supplementary Table 6. Multivariable Cox proportional hazard regression analyses for subsequent breast cancer in female five-year childhood cancer survivors with different chest radiotherapy fields irradiation[a]

	No chest radiotherapy		**Mantle field irradiation**		**Mediastinal field irradiation**		**TBI or whole lung field irradiation**		**Other chest fields irradiation**	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Doxorubicin dose, mg/m²										
No doxorubicin	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
<200	1.53	0.84-2.78	2.16	1.36-3.42	0.95	0.17-5.27	1.13	0.40-3.18	3.55	1.33-9.51
≥200	2.90	2.06-4.08	1.62	1.01-2.61	2.30	0.89-5.92	1.22	0.45-3.35	5.20	2.43-11.14

Supplementary Table 6. Multivariable Cox proportional hazard regression analyses for subsequent breast cancer in female five-year childhood cancer survivors with different chest radiotherapy fields irradiation[a] (continued)

	No chest radiotherapy		Mantle field irradiation		Mediastinal field irradiation		TBI or whole lung field irradiation		Other chest fields irradiation	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Continuous variable: Chest radiotherapy dose (Gy)			1.03	1.01-1.05	1.02	0.98-1.06	1.03	1.00-1.07	1.01	0.99-1.03
Pelvic radiotherapy ≥5 Gy										
No	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
Yes	1.79	1.24-2.58	0.90	0.69-1.18	0.41	0.14-1.23	0.53	0.24-1.18	0.91	0.48-1.75
Age at primary childhood cancer diagnosis, yr										
<5	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
5-9	1.27	0.75-2.14			1.58	0.23-10.76	1.82	0.51-6.46	0.69	0.27-1.77
10-14	2.17	1.44-3.29	3.86	1.42-10.54	1.29	0.26-6.47	2.19	0.64-7.48	0.99	0.46-2.13
15-21	1.80	1.15-2.79	3.45	1.26-9.42	0.91	0.18-4.74	1.77	0.43-7.35	1.80	0.70-4.66
CED[b], mg/m²										
None	1.0	Ref.	1.0	Ref.			1.0	Ref.	1.0	Ref.
<6000	0.92	0.58-1.44	0.59	0.37-0.93			1.20	0.53-2.71	1.17	0.48-2.86
6000-17999	1.28	0.88-1.87	0.76	0.54-1.05			1.30	0.54-3.17	0.48	0.20-1.12
≥18000	2.03	1.26-3.29	0.97	0.46-2.04			0.62	0.16-2.48	0.26	0.06-1.05
Alkylating agents										
No					1.0	Ref.				
Yes					0.75	0.26-2.17				

CED = Cyclophosphamide Equivalent Dose; CI = Confidence interval; HR = Hazard ratio; TBI = Total Body Irradiation; yr = year

[a]All models included cumulative doxorubicin dose (categorical variable), chest radiotherapy dose (continuous variable), pelvic radiotherapy ≥5 Gy (yes/no), age at primary childhood cancer diagnosis (categorical variable), and CED dose (categorical variable), except the model in survivors with no chest radiotherapy (no chest radiotherapy dose variable in the model), and the model in survivors with mediastinal field irradiation, which was adjusted for alkylating agents (yes/no), instead of CED dose, owing to a low number of cases in some of the CED categories.

[b]Cyclophosphamide Equivalent Dose calculation: CED (mg/m²) = 1.0 (cumulative cyclophosphamide dose (mg/m²)) + 0.244 (cumulative ifosfamide dose (mg/m²)) + 0.857 (cumulative procarbazine dose (mg/m²)) + 14.286 (cumulative chlorambucil dose (mg/m²)) + 15.0 (cumulative BCNU (carmustine) dose (mg/m²)) + 16.0 (cumulative CCNU (lomustine) dose (mg/m²)) + 40 (cumulative melphalan dose (mg/m²)) + 50 (cumulative Thio-TEPA (thiotepa) dose (mg/m²)) + 100 (cumulative nitrogen mustard dose (mg/m²)) + 8.823 (cumulative busulfan dose (mg/m²)).

Supplementary Table 7. Sensitivity analyses for risk of subsequent breast cancer on subgroups with different treatments or events

	Only invasive breast cancer as events[a]				Censoring at the time of the first non-SBC subsequent malignant neoplasm diagnosis[b]		
	No. SBC	Total	HR	95% CI	No. SBC	Total	HR
Doxorubicin dose, mg/m²							
No doxorubicin	347 (56.3%)	11,170 (62.4%)	1.0	Ref.	390 (54.5%)	11,150 (62.4%)	1.0
<100	12 (1.9%)	912 (5.1%)	1.64	0.74-3.64	16 (2.2%)	910 (5.1%)	1.90
100-199	46 (7.5%)	1,795 (10.0%)	1.43	0.99-2.08	63 (8.8%)	1,792 (10.0%)	1.63
200-299	54 (8.8%)	1,026 (5.7%)	2.49	1.77-3.49	64 (8.9%)	1,024 (5.7%)	2.48
300-399	47 (7.6%)	1,012 (5.7%)	1.95	1.34-2.84	60 (8.4%)	1,007 (5.6%)	2.36
≥400	48 (7.8%)	779 (4.4%)	2.54	1.76-3.66	52 (7.3%)	778 (4.4%)	2.70
Unknown	62 (10.1%)	1,209 (6.8%)	-	-	71 (9.9%)	1,208 (6.8%)	-
Daunorubicin dose, mg/m²							
No daunorubicin	530 (86.0%)	14,630 (81.7%)	1.0	Ref.	626 (87.4%)	14,602 (81.7%)	1.0
<100	7 (1.1%)	623 (3.5%)	1.22	0.56-2.63	6 (0.8%)	620 (3.5%)	0.95
100-199	12 (1.9%)	953 (5.3%)	0.82	0.41-1.64	15 (2.1%)	952 (5.3%)	0.92
≥200	14 (2.3%)	645 (3.6%)	1.26	0.68-2.33	16 (2.2%)	644 (3.6%)	1.35
Unknown	53 (8.6%)	1,052 (5.9%)	-	-	53 (7.4%)	1,051 (5.9%)	-
Epirubicin							
No	559 (90.7%)	16,637 (92.9%)	1.0	Ref.	657 (91.8%)	16,604 (92.9%)	1.0
Yes	6 (1.0%)	325 (1.8%)	2.67	1.10-6.44	8 (1.1%)	325 (1.8%)	4.00
Unknown	51 (8.3%)	941 (5.3%)	-	-	51 (7.1%)	940 (5.3%)	-
Chest radiotherapy field and dose							
No chest radiotherapy	208 (33.8%)	13,004 (72.6%)	1.0	Ref.	232 (32.4%)	12,984 (72.7%)	1.0
High-dose mantle (≥36 Gy)	179 (29.1%)	698 (3.9%)	7.65	5.78-10.12	218 (30.4%)	695 (3.9%)	8.27
Low-dose mantle (<36 Gy)	66 (10.7%)	524 (2.9%)	3.95	2.77-5.64	87 (12.2%)	523 (2.9%)	4.86
Mediastinal	28 (4.5%)	469 (2.6%)	1.50	0.87-2.58	29 (4.1%)	467 (2.6%)	1.72
TBI	15 (2.4%)	371 (2.1%)	5.51	2.94-10.33	12 (1.7%)	188 (1.1%)	10.18
Whole lung	18 (2.9%)	184 (1.0%)	6.66	3.88-11.42	19 (2.7%)	184 (1.0%)	6.18
Other	53 (8.6%)	1,316 (7.4%)	2.66	1.85-3.81	58 (8.1%)	1,312 (7.3%)	2.62
Unknown	49 (8.0%)	1,337 (7.5%)	-	-	61 (8.5%)	1,516 (8.5%)	-
Pelvic radiotherapy ≥5 Gy							
No	398 (64.6%)	13,751 (76.8%)	1.0	Ref.	468 (65.4%)	13,728 (76.8%)	1.0
Yes	172 (27.9%)	2,911 (16.3%)	0.99	0.78-1.24	198 (27.7%)	2,904 (16.3%)	0.99
Unknown	46 (7.5%)	1,241 (6.9%)	-	-	50 (7.0%)	1,237 (6.9%)	-

	Excluding 444 survivors treated for childhood cancer prior to 1970[c]				Excluding survivors treated for Hodgkin lymphoma[d]			
95% CI	No. SBC	Total	HR	95% CI	No. SBC	Total	HR	95% CI
Ref.	395 (53.5%)	10,752 (61.6%)	1.0	Ref.	163 (43.2%)	10,163 (64.3%)	1.0	Ref.
0.93-3.86	16 (2.2%)	912 (5.2%)	1.84	0.92-3.68	10 (2.7%)	849 (5.4%)	1.73	0.70-4.28
1.17-2.28	69 (9.3%)	1,792 (10.3%)	1.83	1.34-2.51	23 (6.1%)	1,338 (8.5%)	1.43	0.85-2.43
1.81-3.41	67 (9.1%)	1,025 (5.9%)	2.57	1.89-3.50	35 (9.3%)	742 (4.7%)	3.21	2.12-4.88
1.68-3.31	63 (8.5%)	1,011 (5.8%)	2.41	1.73-3.34	44 (11.7%)	908 (5.7%)	2.77	1.87-4.11
1.90-3.83	58 (7.8%)	778 (4.5%)	2.84	2.02-3.98	54 (14.3%)	757 (4.8%)	3.38	2.30-4.95
-	71 (9.6%)	1,189 (6.8%)	-	-	48 (12.7%)	1,045 (6.6%)	-	-
Ref.	648 (87.7%)	14,215 (81.4%)	1.0	Ref.	304 (80.6%)	12,667 (80.2%)	1.0	Ref.
0.42-2.18	6 (0.8%)	619 (3.5%)	0.88	0.39-2.00	7 (1.9%)	623 (3.9%)	1.02	0.47-2.20
0.49-1.72	16 (2.2%)	949 (5.4%)	1.05	0.58-1.87	16 (4.2%)	952 (6.0%)	1.03	0.56-1.88
0.75-2.44	17 (2.3%)	644 (3.7%)	1.26	0.71-2.24	17 (4.5%)	645 (4.1%)	1.35	0.74-2.46
-	52 (7.0%)	1,032 (5.9%)	-	-	33 (8.8%)	915 (5.8%)	-	-
Ref.	680 (92.0%)	16,210 (92.8%)	1.0	Ref.	339 (89.9%)	14,685 (92.9%)	1.0	Ref.
1.96-8.16	9 (1.2%)	325 (1.9%)	3.70	1.80-7.58	7 (1.9%)	300 (1.9%)	2.99	1.18-7.57
-	50 (6.8%)	924 (5.3%)	-	-	31 (8.2%)	817 (5.2%)	-	-
Ref.	233 (31.5%)	12,710 (72.8%)	1.0	Ref.	235 (62.3%)	12,666 (80.2%)	1.0	Ref.
6.41-10.66	232 (31.4%)	672 (3.8%)	9.42	7.31-12.16	3 (0.8%)	27 (0.2%)	3.05	0.91-10.21
3.55-6.65	91 (12.3%)	513 (2.9%)	4.74	3.47-6.47	1 (0.3%)	17 (0.1%)	1.52	0.22-10.40
1.07-2.79	27 (3.7%)	443 (2.5%)	1.42	0.84-2.39	13 (3.4%)	204 (1.3%)	1.35	0.62-2.94
4.94-20.99	22 (3.0%)	369 (2.1%)	7.45	4.32-12.85	21 (5.6%)	368 (2.3%)	7.07	3.82-13.09
3.61-10.58	23 (3.1%)	177 (1.0%)	8.51	5.23-13.85	18 (4.8%)	161 (1.0%)	7.54	4.25-13.35
1.85-3.72	51 (6.9%)	1,272 (7.3%)	2.42	1.68-3.47	55 (14.6%)	1,251 (7.9%)	2.44	1.65-3.61
-	60 (8.1%)	1,303 (7.5%)	-	-	31 (8.2%)	1,108 (7.0%)	-	-
Ref.	487 (65.9%)	13,528 (77.5%)	1.0	Ref.	262 (69.5%)	12,414 (78.6%)	1.0	Ref.
0.80-1.22	198 (26.8%)	2,720 (15.6%)	0.89	0.72-1.10	82 (21.8%)	2,298 (14.5%)	0.95	0.67-1.35
-	54 (7.3%)	1,211 (6.9%)	-	-	33 (8.8%)	1,090 (6.9%)	-	-

Supplementary Table 7. Sensitivity analyses for risk of subsequent breast cancer on subgroups with different treatments or events (continued)

	Only invasive breast cancer as events[a]				Censoring at the time of the first non-SBC subsequent malignant neoplasm diagnosis[b]		
	No. SBC	**Total**	**HR**	**95% CI**	**No. SBC**	**Total**	**HR**
Age at primary childhood cancer diagnosis, yr							
<5	55 (8.9%)	7,376 (41.2%)	1.0	Ref.	55 (7.7%)	7,363 (41.2%)	1.0
5-9	56 (9.1%)	3,788 (21.2%)	1.16	0.76-1.79	57 (8.0%)	3,781 (21.2%)	1.28
10-14	213 (34.6%)	3,930 (22.0%)	1.99	1.41-2.81	255 (35.6%)	3,920 (21.9%)	2.33
15-21	292 (47.4%)	2,809 (15.7%)	1.86	1.29-2.68	349 (48.7%)	2,805 (15.7%)	2.06
CED[e], mg/m²							
None	242 (39.3%)	7,951 (44.4%)	1.0	Ref.	276 (38.5%)	7,943 (44.5%)	1.0
<6000	75 (12.2%)	3,069 (17.1%)	0.95	0.71-1.28	85 (11.9%)	3,059 (17.1%)	0.84
6000-17999	149 (24.2%)	3,899 (21.8%)	1.09	0.86-1.40	179 (25.0%)	3,886 (21.7%)	1.03
≥18000	38 (6.2%)	1,117 (6.2%)	1.27	0.84-1.92	40 (5.6%)	1,115 (6.2%)	1.09
Unknown	112 (18.2%)	1,867 (10.4%)	-	-	136 (19.0%)	1,866 (10.4%)	-

CED = Cyclophosphamide Equivalent Dose; CI = Confidence interval; HR = Hazard ratio; No. = number; SBC = Subsequent breast cancer; TBI = Total body irradiation; yr = year

[a]Outcome restricted to invasive breast cancer to exclude ductal carcinoma in situ, which does not always progress to invasive breast cancer. In total, 616 survivors developed subsequent invasive breast cancer. One survivor had a SBC prior to five years after primary cancer.

[b]Censoring at the time of the first non-SBC subsequent malignant neoplasm diagnosis to rule out effects of treatments for those tumors. In total, 34 survivors who had a subsequent malignant neoplasm other than breast cancer within five years after primary cancer diagnosis were excluded. And 66 SBC cases were not included in the analysis because a subsequent malignant neoplasm other than breast cancer occurred before SBC.

[c]Excluding 444 survivors with 43 SBC cases treated for childhood cancer prior to 1970 to exclude a potentially influential group of women who reached comparatively high attained age yet showing deviating characteristics owing to improvements in clinical practice and survival trends since the 1970s.

[d]Excluding survivors treated for Hodgkin lymphoma to exclude patients who generally received extensive radiotherapy fields to the chest. In total, 2,101 survivors with 405 SBC cases were excluded.

[e]Cyclophosphamide Equivalent Dose calculation: CED (mg/m^2) = 1.0 (cumulative cyclophosphamide dose (mg/m^2)) + 0.244 (cumulative ifosfamide dose (mg/m^2)) + 0.857 (cumulative procarbazine dose (mg/m^2)) + 14.286 (cumulative chlorambucil dose (mg/m^2)) + 15.0 (cumulative BCNU (carmustine) dose (mg/m^2)) + 16.0 (cumulative CCNU (lomustine) dose (mg/m^2)) + 40 (cumulative melphalan dose (mg/m^2)) + 50 (cumulative Thio-TEPA (thiotepa) dose (mg/m^2)) + 100 (cumulative nitrogen mustard dose (mg/m^2)) + 8.823 (cumulative busulfan dose (mg/m^2)).

	Excluding 444 survivors treated for childhood cancer prior to 1970[c]				Excluding survivors treated for Hodgkin lymphoma[d]			
95% CI	No. SBC	Total	HR	95% CI	No. SBC	Total	HR	95% CI
Ref.	47 (6.4%)	7,149 (40.9%)	1.0	Ref.	66 (17.5%)	7,346 (46.5%)	1.0	Ref.
0.83-1.97	59 (8.0%)	3,704 (21.2%)	1.31	0.84-2.06	58 (15.4%)	3,601 (22.8%)	1.11	0.73-1.69
1.65-3.3	263 (35.6%)	3,837 (22.0%)	2.38	1.65-3.43	145 (38.5%)	3,203 (20.3%)	1.82	1.30-2.56
1.44-2.96	370 (50.1%)	2,769 (15.9%)	2.12	1.45-3.09	108 (28.6%)	1,652 (10.5%)	1.55	1.06-2.27
Ref.	272 (36.8%)	7,642 (43.8%)	1.0	Ref.	125 (33.2%)	7,310 (46.3%)	1.0	Ref.
0.63-1.12	91 (12.3%)	3,028 (17.3%)	0.89	0.68-1.17	61 (16.2%)	2,778 (17.6%)	1.01	0.70-1.46
0.82-1.30	190 (25.7%)	3,860 (22.1%)	1.06	0.85-1.32	96 (25.5%)	3,253 (20.6%)	1.13	0.80-1.59
0.73-1.63	44 (6.0%)	1,099 (6.3%)	1.19	0.81-1.75	37 (9.8%)	1,040 (6.6%)	1.29	0.80-2.06
-	142 (19.2%)	1,830 (10.5%)	-	-	58 (15.4%)	1,421 (9.0%)	-	-

Supplementary Table 8. Sensitivity analyses for risk of subsequent breast cancer by excluding each study on a one-by-one basis

	Without CCSS[a]				Without SJLIFE[b]				Without DCCSS	
	No. SBC	Total	HR	95%CI	No. SBC	Total	HR	95%CI	No. SBC	Total
Doxorubicin dose, mg/m²										
No doxorubicin	179 (54.2%)	5,441 (66.1%)	1.0	Ref.	395 (56.0%)	9,793 (62.5%)	1.0	Ref.	409 (55.2%)	9,629 (61.5%)
<100	6 (1.8%)	410 (5.0%)	1.18	0.47-2.97	15 (2.1%)	791 (5.0%)	2.10	1.01-4.35	14 (1.9%)	724 (4.6%)
100-199	42 (12.7%)	1,026 (12.5%)	2.34	1.49-3.67	54 (7.7%)	1,381 (8.8%)	1.72	1.20-2.47	66 (8.9%)	1,563 (10.0%)
200-299	27 (8.2%)	436 (5.3%)	2.35	1.39-3.99	61 (8.7%)	902 (5.8%)	2.74	1.99-3.78	66 (8.9%)	964 (6.2%)
300-399	28 (8.5%)	444 (5.4%)	3.03	1.8-5.11	52 (7.4%)	866 (5.5%)	2.02	1.40-2.92	60 (8.1%)	935 (6.0%)
≥400	23 (7.0%)	305 (3.7%)	4.09	2.35-7.14	51 (7.2%)	744 (4.7%)	2.42	1.68-3.48	49 (6.6%)	655 (4.2%)
Unknown	25 (7.6%)	170 (2.1%)	-	-	77 (10.9%)	1,190 (7.6%)	-	-	77 (10.4%)	1,196 (7.6%)
Daunorubicin dose, mg/m²										
No daunorubicin	284 (86.1%)	6,970 (84.7%)	1.0	Ref.	619 (87.8%)	13,012 (83.1%)	1.0	Ref.	648 (87.4%)	12,835 (81.9%)
<100	5 (1.5%)	360 (4.4%)	1.42	0.56-3.61	2 (0.3%)	284 (1.8%)	0.48	0.12-1.93	7 (0.9%)	607 (3.9%)
100-199	11 (3.3%)	580 (7.0%)	1.60	0.81-3.19	11 (1.6%)	755 (4.8%)	0.72	0.34-1.55	11 (1.5%)	592 (3.8%)
≥200	6 (1.8%)	151 (1.8%)	2.99	1.14-7.85	15 (2.1%)	583 (3.7%)	1.07	0.58-1.98	17 (2.3%)	594 (3.8%)
Unknown	24 (7.3%)	171 (2.1%)	-	-	58 (8.2%)	1,033 (6.6%)	-	-	58 (7.8%)	1,038 (6.6%)
Epirubicin										
No	297 (90.0%)	7,760 (94.3%)	1.0	Ref.	640 (90.8%)	14,420 (92.0%)	1.0	Ref.	677 (91.4%)	14,533 (92.8%)
Yes	9 (2.7%)	323 (3.9%)	3.64	1.72-7.72	9 (1.3%)	324 (2.1%)	3.35	1.63-6.89	8 (1.1%)	197 (1.3%)
Unknown	24 (7.3%)	149 (1.8%)	-	-	56 (7.9%)	923 (5.9%)	-	-	56 (7.6%)	936 (6.0%)
Chest radiotherapy field and dose										
No chest radiotherapy	96 (29.1%)	639,7 (77.7%)	1.0	Ref.	229 (32.5%)	11,298 (72.1%)	1.0	Ref.	226 (30.5%)	11,112 (70.9%)
High-dose mantle (≥36 Gy)	89 (27.0%)	237 (2.9%)	11.20	7.10-17.67	223 (31.6%)	652 (4.2%)	8.55	6.55-11.16	233 (31.4%)	669 (4.3%)
Low-dose mantle(<36 Gy)	43 (13.0%)	252 (3.1%)	5.83	3.63-9.37	69 (9.8%)	377 (2.4%)	4.29	3.02-6.11	90 (12.1%)	506 (3.2%)
Mediastinal	18 (5.5%)	242 (2.9%)	1.40	0.59-3.28	31 (4.4%)	446 (2.8%)	1.59	0.98-2.60	33 (4.5%)	433 (2.8%)

LATER[c]		Without FCCSS[d]				Without DHL[e]				Without SCCSS[f]			
HR	95%CI	No. SBC	Total	HR	95%CI	No. SBC	Total	HR	95%CI	No. SBC	Total	HR	95%CI
1.0	Ref.	370 (56.5%)	8,870 (61.2%)	1.0	Ref.	379 (52.9%)	10,989 (62.3%)	1.0	Ref.	423 (55.5%)	11,128 (62.4%)	1.0	Ref.
1.90	0.90-3.99	13 (2.0%)	817 (5.6%)	1.77	0.80-3.93	16 (2.2%)	907 (5.1%)	1.75	0.88-3.49	16 (2.1%)	911 (5.1%)	1.74	0.88-3.47
1.84	1.34-2.54	52 (7.9%)	1,448 (10.0%)	1.63	1.15-2.30	66 (9.2%)	1,775 (10.1%)	1.75	1.28-2.39	65 (8.5%)	1,782 (10.0%)	1.66	1.21-2.26
2.59	1.90-3.53	55 (8.4%)	819 (5.7%)	2.41	1.73-3.36	60 (8.4%)	988 (5.6%)	2.46	1.81-3.34	66 (8.7%)	1,021 (5.7%)	2.42	1.78-3.28
2.33	1.66-3.26	55 (8.4%)	809 (5.6%)	2.42	1.71-3.43	62 (8.6%)	1,001 (5.7%)	2.31	1.67-3.19	63 (8.3%)	1,005 (5.6%)	2.30	1.67-3.19
2.72	1.91-3.88	53 (8.1%)	642 (4.4%)	2.84	1.99-4.06	57 (7.9%)	773 (4.4%)	2.74	1.96-3.82	57 (7.5%)	776 (4.4%)	2.78	1.99-3.87
-	-	57 (8.7%)	1,083 (7.5%)	-	-	77 (10.7%)	1,205 (6.8%)	-	-	72 (9.4%)	1,201 (6.7%)	-	-
1.0	Ref.	581 (88.7%)	11,391 (78.6%)	1.0	Ref.	619 (86.3%)	14,377 (81.5%)	1.0	Ref.	669 (87.8%)	14,565 (81.7%)	1.0	Ref.
1.00	0.47-2.16	7 (1.1%)	618 (4.3%)	1.01	0.47-2.18	7 (1.0%)	623 (3.5%)	0.98	0.46-2.09	7 (0.9%)	623 (3.5%)	0.97	0.45-2.07
0.81	0.41-1.61	15 (2.3%)	936 (6.5%)	1.06	0.59-1.92	16 (2.2%)	953 (5.4%)	0.98	0.55-1.75	16 (2.1%)	949 (5.3%)	0.98	0.55-1.75
1.29	0.72-2.32	14 (2.1%)	610 (4.2%)	0.99	0.52-1.89	17 (2.4%)	645 (3.7%)	1.21	0.68-2.15	16 (2.1%)	642 (3.6%)	1.21	0.68-2.14
-	-	38 (5.8%)	933 (6.4%)	-	-	58 (8.1%)	1,040 (5.9%)	-	-	54 (7.1%)	1,045 (5.9%)	-	-
1.0	Ref.	616 (94.0%)	13,521 (93.3%)	1.0	Ref.	654 (91.2%)	16,386 (92.9%)	1.0	Ref.	701 (92.0%)	16,565 (92.9%)	1.0	Ref.
4.13	1.97-8.66	3 (0.5%)	145 (1.0%)	3.99	1.31-12.11	7 (1.0%)	311 (1.8%)	2.61	1.11-6.13	9 (1.2%)	325 (1.8%)	3.36	1.65-6.86
-	-	36 (5.5%)	822 (5.7%)	-	-	56 (7.8%)	941 (5.3%)	-	-	52 (6.8%)	934 (5.2%)	-	-
1.0	Ref.	205 (31.3%)	10,276 (70.9%)	1.0	Ref.	250 (34.9%)	12,982 (73.6%)	1.0	Ref.	244 (32.0%)	12,955 (72.7%)	1.0	Ref.
9.33	7.20-12.11	222 (33.9%)	651 (4.5%)	8.67	6.69-11.24	192 (26.8%)	591 (3.4%)	9.03	7.01-11.64	231 (30.3%)	690 (3.9%)	8.37	6.56-10.69
4.70	3.43-6.44	89 (13.6%)	485 (3.3%)	4.66	3.40-6.38	81 (11.3%)	477 (2.7%)	4.85	3.54-6.65	93 (12.2%)	523 (2.9%)	4.61	3.40-6.25
1.83	1.13-2.97	23 (3.5%)	335 (2.3%)	1.45	0.83-2.55	27 (3.8%)	424 (2.4%)	1.64	1.00-2.69	33 (4.3%)	465 (2.6%)	1.73	1.09-2.75

Supplementary Table 8. Sensitivity analyses for risk of subsequent breast cancer by excluding each study on a one-by-one basis (continued)

	Without CCSS[a]				Without SJLIFE[b]				Without DCCSS	
	No. SBC	Total	HR	95%CI	No. SBC	Total	HR	95%CI	No. SBC	Total
TBI	11 (3.3%)	148 (1.8%)	9.42	4.44-19.99	16 (2.3%)	304 (1.9%)	5.47	2.92-10.25	19 (2.6%)	302 (1.9%)
Whole lung	14 (4.2%)	105 (1.3%)	8.33	4.24-16.38	20 (2.8%)	140 (0.9%)	7.29	4.36-12.19	19 (2.6%)	162 (1.0%)
Other	39 (11.8%)	541 (6.6%)	4.58	2.97-7.07	59 (8.4%)	1,152 (7.4%)	2.54	1.79-3.60	62 (8.4%)	1,158 (7.4%)
Unknown	20 (6.1%)	310 (3.8%)	-	-	58 (8.2%)	1,298 (8.3%)	-	-	59 (8.0%)	1,324 (8.5%)
Pelvic radiotherapy ≥5 Gy										
No	192 (58.2%)	6,551 (79.6%)	1.0	Ref.	452 (64.1%)	1,1876 (75.8%)	1.0	Ref.	469 (63.3%)	11,620 (74.2%)
Yes	120 (36.4%)	1,427 (17.3%)	1.36	1.00-1.86	201 (28.5%)	2,577 (16.4%)	1.03	0.83-1.28	217 (29.3%)	2,813 (18.0%)
Unknown	18 (5.5%)	254 (3.1%)	-	-	52 (7.4%)	1,214 (7.7%)	-	-	55 (7.4%)	1,233 (7.9%)
Age at primary childhood cancer diagnosis, yr										
<5	46 (13.9%)	3,710 (45.1%)	1.0	Ref.	59 (8.4%)	6,403 (40.9%)	1.0	Ref.	58 (7.8%)	6,327 (40.4%)
5-9	33 (10.0%)	1,761 (21.4%)	0.90	0.54-1.52	59 (8.4%)	3,320 (21.2%)	1.14	0.75-1.74	58 (7.8%)	3,219 (20.5%)
10-14	117 (35.5%)	1,726 (21.0%)	1.87	1.23-2.83	240 (34.0%)	3,458 (22.1%)	1.92	1.37-2.69	257 (34.7%)	3,459 (22.1%)
15-21	134 (40.6%)	1,035 (12.6%)	1.51	0.93-2.45	347 (49.2%)	2,486 (15.9%)	1.81	1.27-2.58	368 (49.7%)	2,661 (17.0%)
CED[g], mg/m²										
None	120 (36.4%)	3,858 (46.9%)	1.0	Ref.	279 (39.6%)	6,995 (44.6%)	1.0	Ref.	285 (38.5%)	6,791 (43.3%)
<6000	48 (14.5%)	1,382 (16.8%)	1.03	0.68-1.57	76 (10.8%)	2,580 (16.5%)	0.87	0.65-1.17	91 (12.3%)	2,804 (17.9%)
6000-17999	80 (24.2%)	2,023 (24.6%)	0.85	0.57-1.26	159 (22.6%)	3,268 (20.9%)	1.10	0.87-1.39	180 (24.3%)	3,336 (21.3%)
≥18000	23 (7.0%)	556 (6.8%)	0.78	0.43-1.42	43 (6.1%)	978 (6.2%)	1.47	0.99-2.18	38 (5.1%)	925 (5.9%)
Unknown	59 (17.9%)	413 (5.0%)	-	-	148 (21.0%)	1,846 (11.8%)	-	-	147 (19.8%)	1,810 (11.6%)

CCSS = Childhood Cancer Survivor Study; CED = Cyclophosphamide Equivalent Dose; CI = Confidence interval; DCCSS LATER = Dutch Long-term Effects After Childhood Cancer Study; DHL = Dutch Hodgkin Late Effects cohort; FCCSS = French Childhood Cancer Survivor Study; HR = Hazard ratio; NA = Not applicable; No. = number; SBC = Subsequent breast cancer; SCCSS = Swiss Childhood Cancer Survivor Study; SJLIFE = St. Jude Lifetime Cohort Study; TBI = Total Body Irradiation; yr = year

[a]In total, 9,671 survivors with 452 SBC cases were excluded.

[b]In total, 2,236 survivors with 77 SBC cases were excluded.

[c]In total, 2,237 survivors with 41 SBC cases were excluded.

[d]In total, 3,415 survivors with 127 SBC cases were excluded.

LATER[c]		Without FCCSS[d]				Without DHL[e]				Without SCCSS[f]			
HR	95%CI	No. SBC	Total	HR	95%CI	No. SBC	Total	HR	95%CI	No. SBC	Total	HR	95%CI
7.31	4.08-13.10	21 (3.2%)	361 (2.5%)	7.55	4.30-13.26	22 (3.1%)	371 (2.1%)	7.38	4.30-12.69	21 (2.8%)	369 (2.1%)	6.93	4.04-11.86
6.83	4.02-11.60	18 (2.7%)	147 (1.0%)	8.42	4.86-14.59	23 (3.2%)	184 (1.0%)	7.74	4.77-12.56	21 (2.8%)	182 (1.0%)	7.04	4.32-11.46
2.95	2.09-4.16	30 (4.6%)	1,101 (7.6%)	1.42	0.88-2.29	63 (8.8%)	1,316 (7.5%)	2.67	1.91-3.73	62 (8.1%)	1,312 (7.4%)	2.51	1.80-3.51
-	-	47 (7.2%)	1,132 (7.8%)	-	-	59 (8.2%)	1,293 (7.3%)	-	-	57 (7.5%)	1,328 (7.5%)	-	-
1.0	Ref.	462 (70.5%)	11,453 (79.1%)	1.0	Ref.	462 (64.4%)	13,572 (76.9%)	1.0	Ref.	488 (64.0%)	13,683 (76.8%)	1.0	Ref.
0.94	0.76-1.15	151 (23.1%)	1,999 (13.8%)	0.83	0.65-1.06	200 (27.9%)	2,830 (16.0%)	0.90	0.73-1.11	221 (29.0%)	2,909 (16.3%)	0.97	0.79-1.19
-	-	42 (6.4%)	1,036 (7.2%)	-	-	55 (7.7%)	1,236 (7.0%)	-	-	53 (7.0%)	1,232 (6.9%)	-	-
1.0	Ref.	36 (5.5%)	5,705 (39.4%)	1.0	Ref.	66 (9.2%)	7,376 (41.8%)	1.0	Ref.	65 (8.5%)	7,359 (41.3%)	1.0	Ref.
1.25	0.81-1.92	46 (7.0%)	3,081 (21.3%)	1.20	0.72-2.02	65 (9.1%)	3,781 (21.4%)	1.13	0.76-1.69	64 (8.4%)	3,778 (21.2%)	1.13	0.76-1.69
2.25	1.60-3.17	220 (33.6%)	3,186 (22.0%)	2.22	1.46-3.36	265 (37.0%)	3,909 (22.2%)	2.01	1.46-2.76	266 (34.9%)	3,912 (21.9%)	2.03	1.47-2.79
1.97	1.38-2.81	353 (53.9%)	2,516 (17.4%)	1.89	1.24-2.88	321 (44.8%)	2,572 (14.6%)	1.86	1.33-2.59	367 (48.2%)	2,775 (15.6%)	1.91	1.37-2.66
1.0	Ref.	259 (39.5%)	6,343 (43.8%)	1.0	Ref.	266 (37.1%)	7,851 (44.5%)	1.0	Ref.	296 (38.8%)	7,917 (44.4%)	1.0	Ref.
0.86	0.66-1.13	71 (10.8%)	2,463 (17.0%)	0.84	0.62-1.14	94 (13.1%)	3,069 (17.4%)	0.87	0.67-1.14	90 (11.8%)	3,047 (17.1%)	0.85	0.65-1.11
1.00	0.80-1.26	160 (24.4%)	3,080 (21.3%)	1.06	0.84-1.34	192 (26.8%)	3,899 (22.1%)	1.03	0.82-1.28	189 (24.8%)	3,889 (21.8%)	1.01	0.81-1.26
1.18	0.79-1.75	38 (5.8%)	895 (6.2%)	1.26	0.84-1.89	47 (6.6%)	1,117 (6.3%)	1.21	0.84-1.76	46 (6.0%)	1,114 (6.3%)	1.16	0.80-1.68
-	-	127 (19.4%)	1,707 (11.8%)	-	-	118 (16.5%)	1,702 (9.6%)	-	-	141 (18.5%)	1,857 (10.4%)	-	-

[e]In total, 265 survivors with 65 SBC cases were excluded.
[f]In total, 79 survivors with 20 SBC cases were excluded.
[g]Cyclophosphamide Equivalent Dose calculation: CED (mg/m^2) = 1.0 (cumulative cyclophosphamide dose (mg/m^2)) + 0.244 (cumulative ifosfamide dose (mg/m^2)) + 0.857 (cumulative procarbazine dose (mg/m^2)) + 14.286 (cumulative chlorambucil dose (mg/m^2)) + 15.0 (cumulative BCNU (carmustine) dose (mg/m^2)) + 16.0 (cumulative CCNU (lomustine) dose (mg/m^2)) + 40 (cumulative melphalan dose (mg/m^2)) + 50 (cumulative Thio-TEPA (thiotepa) dose (mg/m^2)) + 100 (cumulative nitrogen mustard dose (mg/m^2)) + 8.823 (cumulative busulfan dose (mg/m^2)).

Supplementary Table 9. Multivariable Cox proportional hazard regression analyses for subsequent breast cancer in female five-year childhood cancer survivors in each study[a]

	CCSS[b]		SJLIFE[b]		DCCSS LATER[c]		FCCSS[d]		DHL[e]	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Doxorubicin dose, mg/m²										
No doxorubicin	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
<100	2.58	0.99-6.74	0.99	0.13-7.70	1.00	0.19-5.11	1.40	0.42-4.70	1.49	0.45-4.91
100-199	1.34	0.85-2.10	2.49	1.10-5.65	1.04	0.27-4.02	2.23	1.12-4.43		
200-299	2.60	1.80-3.75	1.42	0.54-3.74	0.97	0.13-7.55	2.79	1.39-5.59	1.74	0.76-3.96
300-399	1.96	1.30-2.97	4.82	2.16-10.75	3.51	1.02-12.10	1.60	0.68-3.74	1.50	0.35-6.34
≥400	2.22	1.46-3.39	6.73	2.54-17.83	5.49	1.97-15.25	2.42	0.90-6.49	1.84	0.24-14.00
Daunorubicin dose, mg/m²										
No daunorubicin	1.0	Ref.	1.0	Ref.						
<100	0.47	0.11-1.89	2.28	0.83-6.27						
100-199	0.47	0.16-1.40	3.00	1.05-8.60						
≥200	0.83	0.40-1.70	4.06	0.82-20.17						
Daunorubicin										
No					1.0	Ref.	1.0	Ref.		
Yes					1.53	0.49-4.79	1.92	0.57-6.38		
Epirubicin										
No					1.0	Ref.	1.0	Ref.		
Yes					1.80	0.24-13.79	3.18	1.12-9.05		
Chest radiotherapy field and dose										
No chest radiotherapy	1.0	Ref.	1.0	Ref.			1.0	Ref.		
High-dose mantle (≥36 Gy)	7.65	5.76-10.16	11.51	5.12-25.84			9.05	4.54-18.07		

Supplementary Table 9. Multivariable Cox proportional hazard regression analyses for subsequent breast cancer in female five-year childhood cancer survivors in each study[a] (continued)

	CCSS[b]		SJLIFE[b]		DCCSS LATER[c]		FCCSS[d]		DHL[e]	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Low-dose mantle (<36 Gy)	4.04	2.72-6.00	8.40	3.95-17.87			2.06	0.47-9.14		
Mediastinal	1.66	0.94-2.95	1.86	0.24-14.52			1.84	0.75-4.51		
TBI	6.75	3.25-14.02	12.43	3.76-41.08			5.41	0.67-43.44		
Whole lung	6.32	3.05-13.11	11.83	3.07-45.57			3.72	1.28-10.83		
Other	1.37	0.78-2.40	2.65	0.85-8.23			7.43	4.53-12.17		
Chest radiotherapy fields										
No chest radiotherapy					1.0	Ref.				
Mantle					8.11	2.99-21.95				
TBI & Whole lung					15.43	4.65-51.27				
Other fields					0.67	0.20-2.30				
Chest radiotherapy fields										
Non-mantle									1.0	Ref.
Mantle									2.80	1.18-6.63
Pelvic radiotherapy ≥5 Gy										
No	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
Yes	0.79	0.59-1.06	0.83	0.45-1.50	0.65	0.17-2.53	2.18	1.38-3.45	1.49	0.87-2.53
Age at primary childhood cancer diagnosis, yr										
<5	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
5-9	1.62	0.83-3.18	0.97	0.27-3.45	0.48	0.16-1.45	1.10	0.57-2.11		
10-14	2.61	1.49-4.57	3.30	1.19-9.16	0.93	0.36-2.41	1.86	1.06-3.28		
15-21	2.50	1.43-4.38	2.08	0.71-6.05	1.36	0.47-3.92	2.17	1.09-4.30	0.64	0.30-1.36

Supplementary Table 9. Multivariable Cox proportional hazard regression analyses for subsequent breast cancer in female five-year childhood cancer survivors in each study[a] (continued)

	CCSS[b]		SJLIFE[b]		DCCSS LATER[c]		FCCSS[d]		DHL[e]	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
CED[f], mg/m²										
None	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.		
<6000	0.78	0.55-1.11	0.96	0.45-2.08	0.73	0.18-2.99	1.04	0.57-1.90		
6000-17999	1.11	0.86-1.45	0.74	0.40-1.36	1.40	0.57-3.42	0.93	0.54-1.62		
≥18000	1.61	1.00-2.59	0.43	0.14-1.38	1.49	0.51-4.31	1.05	0.46-2.39		

CCSS = Childhood Cancer Survivor Study; CED = Cyclophosphamide Equivalent Dose; CI = Confidence interval; DCCSS LATER = Dutch Long-term Effects After Childhood Cancer Study; DHL = Dutch Hodgkin Late Effects cohort; FCCSS = French Childhood Cancer Survivor Study; HR = Hazard ratio; SBC = Subsequent breast cancer; SJLIFE = St. Jude Lifetime Cohort Study; TBI = Total Body Irradiation; yr = year

[a]The results of the multivariable Cox proportional hazard regression analyses in the Swiss Childhood Cancer Survivor Study (SCCSS) are not provided due to low numbers in the case-cohort data.

[b]The model included cumulative doxorubicin and daunorubicin dose (categorical variables), chest radiotherapy field and dose (categorical variable), pelvic radiotherapy ≥5 Gy (yes/no), age at primary childhood cancer diagnosis (categorical variable), and CED (categorical variable).

[c]The model included cumulative doxorubicin dose (categorical variable), daunorubicin (yes/no), epirubicin (yes/no), chest radiotherapy fields (categorical variable), pelvic radiotherapy ≥5 Gy (yes/no), age at primary childhood cancer diagnosis (categorical variable), and CED (categorical variable).

[d]The model included cumulative doxorubicin dose (categorical variable), daunorubicin (yes/no), epirubicin (yes/no), chest radiotherapy field and dose (categorical variable), pelvic radiotherapy ≥5 Gy (yes/no), age at primary childhood cancer diagnosis (categorical variable), and CED (categorical variable).

[e]The model included cumulative doxorubicin dose (categorical variable), chest radiotherapy fields (categorical variable), pelvic radiotherapy ≥5 Gy (yes/no), and age at primary childhood cancer diagnosis (categorical variable).

[f]Cyclophosphamide Equivalent Dose calculation: CED (mg/m^2) = 1.0 (cumulative cyclophosphamide dose (mg/m^2)) + 0.244 (cumulative ifosfamide dose (mg/m^2)) + 0.857 (cumulative procarbazine dose (mg/m^2)) + 14.286 (cumulative chlorambucil dose (mg/m^2)) + 15.0 (cumulative BCNU (carmustine) dose (mg/m^2)) + 16.0 (cumulative CCNU (lomustine) dose (mg/m^2)) + 40 (cumulative melphalan dose (mg/m^2)) + 50 (cumulative Thio-TEPA (thiotepa) dose (mg/m^2)) + 100 (cumulative nitrogen mustard dose (mg/m^2)) + 8.823 (cumulative busulfan dose (mg/m^2)).

Supplementary Table 10. Multivariable Cox proportional hazard regression analyses for subsequent breast cancer in female five-year childhood cancer survivors stratified by chest radiotherapy status (yes/no)

	Survivors with chest radiotherapy (478 cases/3,693 survivors)								Survivors without chest radiotherapy (250 cases/13,004 survivors)							
					Model I		Model II[a]						Model I		Model II[a]	
	Cohort Members	%	No. SBC	%	HR	95% CI	HR	95% CI	Cohort Members	%	No. SBC	%	HR	95% CI	HR	95% CI
Doxorubicin dose, mg/m²																
No doxorubicin	2,260	61.2	313	65.5	1.0	Ref.			8,541	65.7	101	40.4	1.0	Ref.		
<100	143	3.9	8	1.7	1.24	0.54-2.85			752	5.8	7	2.8	2.63	0.93-7.45		
100-199	530	14.4	54	11.3	1.88	1.33-2.65			1,215	9.3	12	4.8	1.25	0.63-2.49		
200-299	298	8.1	42	8.8	2.18	1.46-3.24		-	693	5.3	23	9.2	2.79	1.67-4.66		-
300-399	208	5.6	26	5.4	1.77	1.04-3.01			775	6.0	34	13.6	2.65	1.69-4.14		
≥400	99	2.7	7	1.5	0.43	0.09-2.01			655	5.0	49	19.6	3.65	2.41-5.53		
Unknown	155	4.2	28	5.9	-	-			373	2.9	24	9.6	-	-		
Continuous variable: Doxorubicin dose (per 100 mg/m²)							1.14	1.04-1.25							1.26	1.17-1.36
Daunorubicin dose, mg/m²																
No daunorubicin	3,247	87.9	441	92.3	1.0	Ref.			10,893	83.8	216	86.4	1.0	Ref.		
<100	65	1.8	2	0.4	1.06	0.26-4.42		-	548	4.2	5	2.0	0.99	0.39-2.52		
100-199	131	3.5	10	2.1	1.71	0.87-3.33			805	6.2	5	2.0	0.49	0.16-1.54		-
≥200	131	3.5	4	0.8	0.87	0.31-2.45			493	3.8	11	4.4	1.51	0.75-3.02		
Unknown	119	3.2	21	4.4	-	-			265	2.0	13	5.2	-	-		
Continuous variable: Daunorubicin dose (per 100 mg/m²)							1.04	0.82-1.33							1.12	0.93-1.36

Supplementary Table 10. Multivariable Cox proportional hazard regression analyses for subsequent breast cancer in female five-year childhood cancer survivors stratified by chest radiotherapy status (yes/no) (continued)

	Survivors with chest radiotherapy (478 cases/3,693 survivors)								Survivors without chest radiotherapy (250 cases/13,004 survivors)							
					Model I		Model II[a]						Model I		Model II[a]	
	Cohort Members	%	No. SBC	%	HR	95% CI	HR	95% CI	Cohort Members	%	No. SBC	%	HR	95% CI	HR	95% CI
Epirubicin																
No	3,567	96.6	452	94.6	1.0	Ref.	1.0	Ref.	12,533	96.4	236	94.4	1.0	Ref.	1.0	Ref.
Yes	39	1.1	5	1.0	3.76	1.81-7.82	3.36	1.61-7.01	279	2.1	3	1.2	2.18	0.51-9.38	2.13	0.49-9.17
Unknown	87	2.4	21	4.4	-	-	-	-	192	1.5	11	4.4	-	-	-	-
Chest radiotherapy field and dose																
High-dose mantle (≥36 Gy)	698	18.9	238	49.8	1.0	Ref.	1.0	Ref.								
Low-dose mantle (<36 Gy)	524	14.2	93	19.5	0.54	0.40-0.73	0.61	0.46-0.80								
Mediastinal	468	12.7	32	6.7	0.18	0.10-0.29	0.18	0.10-0.31								
TBI	369	10.0	21	4.4	0.93	0.56-1.54	1.02	0.60-1.71								
Whole lung	184	5.0	23	4.8	0.89	0.54-1.47	0.90	0.55-1.50								
Other	1312	35.5	63	13.2	0.31	0.22-0.44	0.31	0.22-0.44								
Unknown	138	3.7	8	1.7	-	-	-	-								
Pelvic radiotherapy ≥5 Gy																
No	1,882	51.0	296	61.9	1.0	Ref.	1.0	Ref.	11,869	91.3	209	83.6	1.0	Ref.	1.0	Ref.
Yes	1,783	48.3	181	37.9	0.75	0.60-0.94	0.76	0.60-0.95	1,127	8.7	41	16.4	1.82	1.25-2.64	1.88	1.29-2.72
Unknown	28	0.8	1	0.2	-	-	-	-	8	0.1	-	-	-	-	-	-

Supplementary Table 10. Multivariable Cox proportional hazard regression analyses for subsequent breast cancer in female five-year childhood cancer survivors stratified by chest radiotherapy status (yes/no) (continued)

	Survivors with chest radiotherapy (478 cases/3,693 survivors)								Survivors without chest radiotherapy (250 cases/13,004 survivors)							
					Model I		Model II[a]						Model I		Model II[a]	
	Cohort Members	%	No. SBC	%	HR	95% CI	HR	95% CI	Cohort Members	%	No. SBC	%	HR	95% CI	HR	95% CI
Age at primary childhood cancer diagnosis, yr																
<5	769	20.8	25	5.2	1.0	Ref.	1.0	Ref.	6,138	47.2	33	13.2	1.0	Ref.	1.0	Ref.
5-9	699	18.9	23	4.8	0.97	0.51-1.84	0.95	0.50-1.79	2,818	21.7	36	14.4	1.26	0.74-2.13	1.29	0.76-2.17
10-14	1,054	28.5	154	32.2	1.94	1.15-3.29	1.92	1.14-3.25	2,614	20.1	100	40.0	2.17	1.43-3.28	2.24	1.48-3.38
15-21	1,171	31.7	276	57.7	1.85	1.07-3.20	1.86	1.07-3.21	1,434	11.0	81	32.4	1.75	1.12-2.72	1.78	1.14-2.79
CED[b], mg/m²																
None	1,137	30.8	204	42.7	1.0	Ref.	1.0	Ref.	6,550	50.4	88	35.2	1.0	Ref.	1.0	Ref.
<6000	603	16.3	56	11.7	0.81	0.58-1.14	0.86	0.61-1.21	2,375	18.3	30	12.0	0.93	0.59-1.47	1.06	0.67-1.69
6000-17999	1,123	30.4	114	23.8	0.86	0.66-1.12	0.91	0.71-1.18	2,663	20.5	70	28.0	1.26	0.85-1.86	1.35	0.91-2.00
≥18000	309	8.4	17	3.6	0.68	0.38-1.21	0.66	0.37-1.16	776	6.0	30	12.0	1.92	1.18-3.14	2.15	1.33-3.47
Unknown	521	14.1	87	18.2	-	-	-	-	640	4.9	32	12.8	-	-	-	-

CED = Cyclophosphamide Equivalent Dose; CI = Confidence interval; HR = Hazard ratio; IQR = Interquartile range; No. = number; SBC = Subsequent breast cancer; TBI = Total Body Irradiation; yr = year

[a]Model II includes continuous variables of cumulative doxorubicin and daunorubicin dose per 100 mg/m².

[b]Cyclophosphamide Equivalent Dose calculation: CED (mg/m²) = 1.0 (cumulative cyclophosphamide dose (mg/m²)) + 0.244 (cumulative ifosfamide dose (mg/m²)) + 0.857 (cumulative procarbazine dose (mg/m²)) + 14.286 (cumulative chlorambucil dose (mg/m²)) + 15.0 (cumulative BCNU (carmustine) dose (mg/m²)) + 16.0 (cumulative CCNU (lomustine) dose (mg/m²)) + 40 (cumulative melphalan dose (mg/m²)) + 50 (cumulative Thio-TEPA (thiotepa) dose (mg/m²)) + 100 (cumulative nitrogen mustard dose (mg/m²)) + 8.823 (cumulative busulfan dose (mg/m²)).

CHAPTER 4

Male Breast Cancer After Childhood Cancer: Systematic Review and Analyses in the PanCareSurFup Cohort

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Abstract

Background

Breast cancer is a well-recognized late adverse effect in female childhood cancer survivors (CCSs), especially after chest radiotherapy; information on subsequent male breast cancer (SMBC) is limited. We summarized the existing evidence on SMBC after childhood cancer in a systematic review, and investigated the risk of SMBC among males in a Pan-European cohort.

Methods

We searched Medline/PubMed for cohort studies and case reports/series that assessed SMBC after childhood cancer (≤21 years). Furthermore, we analyzed data on SMBC in the PanCareSurFup cohort, reporting standardized incidence ratios (SIRs), absolute excess risks (AERs), and 5- and 10-year survival rates.

Results

The systematic review included 38 of 7,080 potentially eligible articles. Cohort-specific SMBC frequencies were 0-0.40% (31 studies). SMBC occurred after a follow-up ranging from 24.0-42.0 years. Nine case reports/series described 11 SMBC cases, occurring 11.0-42.5 years after primary childhood cancer. In the PanCareSurFup cohort (16 SMBC/37,738 males; 0.04%), we observed a 22.3-fold increased risk of SMBC relative to the general male population (95% CI 12.7-36.2; AER/100,000 person-years: 2.3, 95% CI 1.3-3.7). The five- and ten-year survival rates after SMBC diagnosis were 60.3% (95% CI 35.6%-85.0%) and 43.0% (95% CI 16.1%-69.9%), respectively. Clear evidence of risk factors did not emerge from these comprehensive efforts.

Conclusions

Compared to the general population, male CCSs have an elevated risk of developing subsequent breast cancer, although the absolute risk is low. Health care providers should be aware of this rare yet serious late effect; male CCSs with symptoms potentially related to SMBC warrant careful examination.

Introduction

Breast cancer is a well-recognized late adverse event in female childhood cancer survivors (CCSs), especially after treatment with chest-directed radiation. Overall risks of subsequent female breast cancer among CCSs have been shown to be elevated in the order of 5 to 10-fold compared to the general population (1, 2), though it varies by demographic, personal, and treatment-related risk factors. Moreover, radiation dose-dependent associations between received chest radiation and the risk of subsequent female breast cancer have been observed (3-6). Overall, male breast cancer is rare, as it only accounts for approximately 0.5 - 1% of reported breast cancer cases in the general population (7). Compared to female breast cancer, male breast cancer tends to be diagnosed at a later stage, which may be due to the low levels of consideration of breast cancer for males. Subsequently, the prognosis of breast cancer is poorer in men (8).

Due to the rarity of male breast cancer, information on subsequent male breast cancer (SMBC) after childhood cancer is limited. Anecdotally, SMBC cases have been brought to the attention of international collaborative groups with the intention of seeking guidance on surveillance for CCSs. While the International Late Effects of Childhood Cancer Guideline Harmonization Group recommends breast cancer surveillance for female childhood, adolescent and young adult cancer survivors treated with chest radiation (9, 10), the expert group did not develop recommendations for male survivors owing to lack of relevant evidence and an assumed low incidence. Accordingly, comprehensive cohort studies with robust sample sizes that thoroughly address the risk of SMBC among CCSs are warranted. Additionally, summarizing the current knowledge of SMBC risk after childhood cancer is necessary to inform male CCSs who are concerned about their breast cancer risk and their medical practitioners.

Therefore, we conducted both a systematic review to evaluate the existing evidence on SMBC in CCSs (part 1) and analyses in the PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup) (11-13), a large Pan-European cohort, to investigate the risk of subsequent breast cancer among five-year male CCSs, and examine the clinical characteristics and survival of SMBC cases (part 2).

Methods

Part 1. Systematic review

Search strategy and selection criteria

Inclusion criteria for the systematic review were defined as a study (including case-reports/series): (1) with at least 90% of the population diagnosed with any primary cancer at age ≤ 21 years (or with separate results for survivors aged ≤ 21 years at cancer diagnosis); (2) assessing SMBC as an outcome; (3) in any language; (4) with original data. In reports focusing on any subsequent malignant neoplasm (SMN), we only included the studies if the number of SMBC cases was mentioned explicitly, or if a zero-case result could reliably be deduced from case numbers on any SMN and SMN-subgroups. Studies focusing on synchronous cancer and case-reports/series with the time interval between primary cancer and SMBC within two years were excluded.

We conducted a search in the literature database PubMed on July 18, 2019 using a combination of controlled vocabulary and text words for "Second tumor," "Male," "Breast," "Radiotherapy," "Survivor," "Late effects," and "Follow-up Studies" (Appendix A). Additionally, references of included articles were checked for potentially relevant reports that were not identified in the literature search.

The titles and abstracts of all studies identified by the search were screened independently by two reviewers (first reviewer: YW; second reviewer: JCT / ECvD / CMR / WJvD). The full texts of the potentially eligible studies were then obtained, and two independent reviewers (first reviewer: YW; second reviewer: JCT / ECvD) checked whether the articles fully complied with the inclusion criteria. When multiple articles with (almost) full overlapping study populations were identified, the article with the most recent publication date, or with the longest follow-up time was included. When the amount of overlap was unclear, we included both studies reporting the possibility of overlap.

Data extraction

Data was extracted independently by two reviewers (first reviewer: YW; second reviewer: JCT / ECvD) using a standardized data extraction form. The following information was extracted: study characteristics (e.g., study design, number of participants fulfilling the review's inclusion criteria), patient characteristics (e.g., primary cancer type, age), treatment, outcome measures (including methods of subsequent cancer ascertainment and interval between primary and subsequent cancer), and follow-up time. For population studies, risk measures of the SMBC (e.g., standardized incidence ratio (SIR), absolute excess risk (AER), and cumulative

incidence) and treatment-related risk measures were collected from the studies if the data was available. For the case-reports, information on the MBC type, the family cancer history, and any information on genetic predisposition were also extracted, if reported.

Risk of bias assessment

The risk of bias in included studies was assessed by two reviewers (first reviewer: YW; second reviewer: JCT / ECvD) independently on potential for selection bias, attrition bias, detection bias, and confounding factors, as recommended by Cochrane Childhood Cancer (Appendix B).

Any discrepancies between the two reviewers in any of the above described sections were resolved by discussion until consensus was reached or, if this was not possible, via the consultation of a third reviewer (JCT / ECvD).

Part 2. PanCareSurFup Cohort

Study population and case definition

We analyzed data from the PanCareSurFup cohort, in which the occurrence of subsequent primary cancers has been collected and ascertained by 13 data providers from 12 countries. Details of the PanCareSurFup cohort have been previously described (11-13). Male breast cancer cases were defined as malignant tumors of the breast in males (ICD-O-3 behavior code 3 and topography code C50). Data on SMBC cases was collected, including primary childhood cancer diagnosis (age, month / year, and type) and treatment information (including chest radiotherapy field / dose, other radiation fields, and chemotherapeutic agents / dose, if available), SMBC diagnosis (age, month / year, ICD-O morphology, topography, and behavior codes) and treatment information, any subsequent primary malignancies other than breast cancer before the SMBC diagnosis and their treatment information, and patients' family history of cancer and vital status.

Statistical analysis

The time at risk of developing SMBC was calculated from five years after primary childhood cancer diagnosis to the date of death, or the date of the last follow-up observation, whichever occurred first.

Overall SIRs and AERs for SMBC were calculated. SIRs were calculated as the ratio of the observed numbers of SMBC to the expected numbers of male breast cancer. AERs were calculated as the differences between observed and expected numbers

of male breast cancer per 100,000 person-years at risk. Expected numbers were estimated by accumulating person-years at risk within country-, age- and calendar year-specific strata and multiplying by the corresponding male breast cancer incidence rates in the general population. Country-, age-, and calendar year-specific population incidence rates of MBC were obtained from the Cancer Incidence in Five Continents (CI5) (13, 14). Cumulative incidences of SMBC were calculated by treating death as a competing risk. Five- and ten-year survival rates after SMBC diagnosis were estimated using standard Kaplan-Meier methods. Stata version 16 (StataCorp, College Station, Texas, USA) was used for all analyses. In 2-sided statistical tests, a *P* value of < 0.05 was considered statistically significant.

Results

Part 1. Systematic Review

Our search generated 7,079 articles in total (Figure 1). After removal of the duplicates, the remaining 7,069 titles and abstracts were screened, yielding 512 articles for full-text screening, after which 37 studies were selected. We also identified one study through the references of the included articles (15), which resulted in a final total of 38 studies: 31 observational studies (15-45) and seven case reports (46-52). Two of the included observational studies provided SMBC descriptions, and accordingly were additionally considered as case reports/series (16, 19), resulting in a total number of nine SMBC case-reports/series with 11 SMBC cases.

Observational studies

The characteristics of the included studies are summarized below. For more detailed information, see Table 1. All of the aforementioned 31 observational studies utilized the cohort design. Most studies included either all cancer patients or five-year survivors; if reported, eligibility criteria varied between 2 months and 20 years. The total number of males varied dramatically, with a range of 14 to 26,168 male CCSs; five studies did not report the number of males. Most studies (n = 15, 48%) included CCSs with various types of primary cancer (15, 16, 18, 19, 21, 26, 28, 29, 31, 33, 34, 37, 42, 43, 45), but others included CCSs of one specific primary cancer type, of which Hodgkin lymphoma was the most common one (n = 9, 29%) (17, 22, 24, 27, 30, 38, 39, 41, 44). Treatment information for the primary cancer was specifically reported for male CCSs in only five studies (16%) (16, 27, 41, 44, 45). Only one study (3%) reported follow-up time of male CCSs, with a median follow-up time of 25 years (range, 5 - 67 years) since first diagnosis (16). Studies used different methods of SMBC ascertainment (e.g., self-report questionnaires, medical records, record linkage with cancer registry, hospital database, and/or death registry). Most studies examined the risks of all SMNs. Only one study

focused on SMBC risk in particular (16), and two other studies investigated subsequent breast cancer risk in both males and females (19, 20).

Due to missing data and clinical heterogeneity, pooling of data was not possible, and therefore we provide descriptive results. Among the 31 included observational studies, 12 SMBC cases were identified in six studies (16-21). The other 25 studies reported 0 SMBC cases. The frequency of SMBC ranged from 0 to 0.40%. Of note, there may be overlap among the SMBC cases referenced due to potential and partial overlap among studies. The interval between primary cancer diagnosis and SMBC was reported in three out of six (50%) studies with SMBC reported and ranged from 24 to 42 years.

Figure 1. Flow chart of study selection

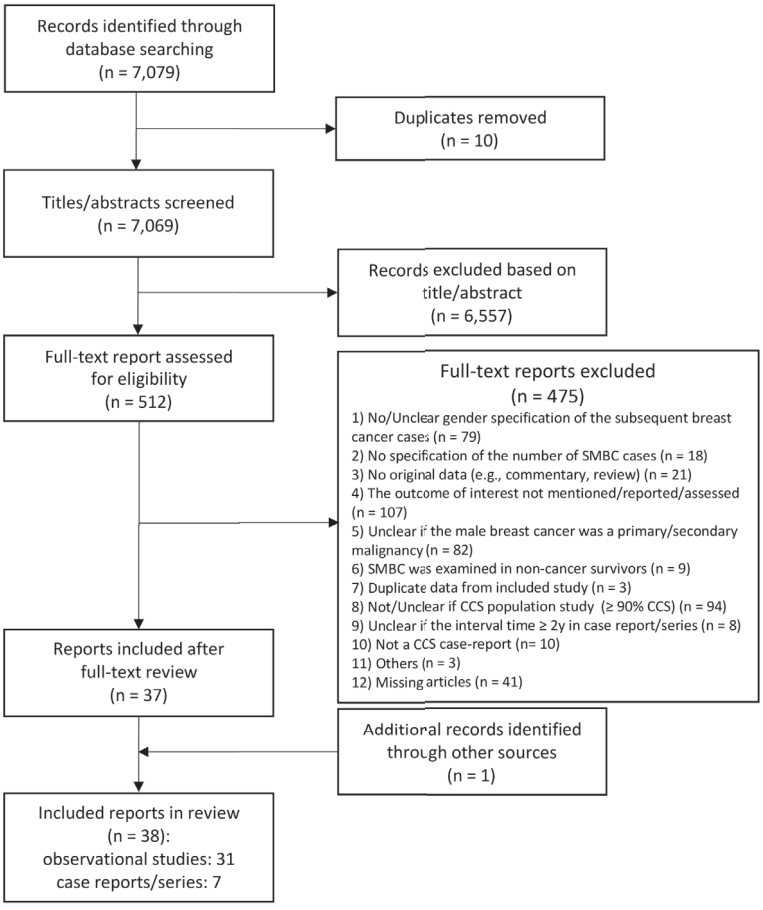

Table 1. Study characteristics of all 31 included observational studies [a]

Author (year)	Origin (cohort)	Inclusion period	Total No. of participants in study	Total males in study	Type of primary cancer	Methods of subsequent cancer ascertainment
Demoor-Goldschmidt (2018) (16)	NM	Treated before 2000	7,019 5-yr survivors	3,893	Any solid malignant tumor	- Medical records - Self-questionnaires - Record linkage with national hospital database and national health insurance database - Record linkage with national death registry
Holmqvist (2019) (17)	Late Effects Study Group cohort	Diagnosed between 1955 - 1986	1,136	At least 744 [d]	HL	Medical records + Pathology reports confirmation
Reulen (2011) (18)	British Childhood Cancer Survivor Study	Diagnosed between 1940 - 1991	17,981 5-yr survivors	9,887 [e]	Any diagnosis	Record linkage with population-based death and cancer registries + Diagnostic and pathology reports confirmation
Li (1983) (19)	NM	Diagnosed between 1931 - 1974	910 5-yr survivors	504	Any diagnosis	Medical records
Little (2014) (20)	NM	Diagnosed between 1914 - 1984	1,584 1-yr survivors	Min 829, max 846 [g]	Retinoblastoma	- Medical records - Telephone interviews - Search of the National Death Index + Confirmation by autopsy, pathology reports, hospital or physician records, death certificates, or questionnaires

Primary cancer RT and CT treatments [b]	Age at primary cancer diagnosis (yr) [b]	Follow-up time [b]	Follow-up starting point	No. of participants with SMBC (% in males)	Interval primary cancer - SMBC (yr)
In the male population: Neither CT nor RT: 391 (10%) CT but no RT: 1,215 (31%) RT but no CT: 564 (14%) RT and CT: 1,723 (44%) Chemotherapeutic drug: Alkylating agents: 2,192 (56%) Antimetabolites: 816 (21%) Vinca alkaloids: 2,313 (59%) Anthracyclines: 1,497 (38%) Epipodophyllotoxins: 682 (18%)	For the male population: Median 6 yr (range, 0 - 20 yr)	In the male population: Median 25 yr (range, 5 - 67 yr)	Since first diagnosis	4 (0.10%)	Median 27 yr (range, 24 - 42 yr) [c]
RT alone: 253 (22%) CT alone: 111 (10%) RT plus CT: 762 (67%)	Median 11 yr (range, 0 - 16 yr)	Median 26.6 yr	Starting point not mentioned	3 (0.40%)	Median 30 yr (range, 26 - 35 yr)
RT: 9147 (51%) CT: 6518 (36%) [e]	< 15 yr	Median 24.3 yr; mean: 25.6 yr; 25th - 75th percentile, 17.9 - 32.4 yr	Since first diagnosis	2 (0.02%)	NM
RT: 717 (79%) CT: 763 (84%)	0 - 17 yr	Median 13 yr (range, 5 - 49 yr)	Since first diagnosis	1 (0.20%)	30 yr [f]
NM	Mean 1.3 yr	Mean 26.9 yr	Since one year after first diagnosis	1 (0.12%)	NM

Table 1. Study characteristics of all 31 included observational studies [a] (continued)

Author (year)	Origin (cohort)	Inclusion period	Total No. of participants in study	Total males in study	Type of primary cancer	Methods of subsequent cancer ascertainment
Teepen (2017) (21)	Dutch Childhood Cancer Oncology Group Long-term Effects After Childhood Cancer cohort	Diagnosed between 1963 - 2001	6,165 5-yr survivors	3,434	Any diagnosis	- Record linkage with population-based cancer and pathology registries - Medical records + Pathology reports confirmation
Beaty III (1995) (22)	NM	Treated between 1962 - 1993	499	289	HL	- Medical records - Medical information from local physicians
Cohen (2005) (23)	SEER-9	Diagnosed and reported between 1973 - 2000	1,499 1-yr survivors	800	Various soft tissue sarcomas (rhabdomyosarcoma, fibromatous neoplasms, and other specified soft tissue sarcoma)	Cancer registry
Constine (2008) (24)	NM	Treated between 1960 - 1990	930	532	HL	Medical records
Dottorini (1996) (25)	NM	Treated between 1958 - 1995	85	22	Differentiated thyroid carcinoma	- Clinical examinations - Telephone contacts - Information from family/ referring physicians

Primary cancer RT and CT treatments [b]	Age at primary cancer diagnosis (yr) [b]	Follow-up time [b]	Follow-up starting point	No. of participants with SMBC (% in males)	Interval primary cancer - SMBC (yr)
CT, no RT: 2,970 (48%) RT, no CT: 481 (8%) RT and CT: 2,024 (33%) RT field: Head / cranium: 1,413 (23%) Spinal: 443 (7%) Thorax: 395 (6%) Abdomen / pelvis: 467 (8%) Neck: 240 (4%) Extremities: 133 (2%) Total body irradiation: 221 (4%) CT: Alkylating agents: 3,136 (51%) Anthracyclines: 2,788 (45%) Epipodophyllotoxins: 1,300 (21%) Vinca alkaloids: 4,431 (72%) Platinum agents: 804 (13.0%) Antimetabolites: 2,885 (47%)	< 18 yr	Median 20.7 yr (range, 5.0 - 49.8 yr)	Since first diagnosis	1 (0.03%)	NM
RT only: 123 (25%) Multiagent CT: 30 (6%) RT plus multiagent CT: 346 (69%) RT doses ranged from 20 - 42 Gy	Median 13.5 yr (range, 3.0 - 25.4 yr)	Median 9.0 yr (range, 0.1 - 27.4 yr)	Starting point not mentioned	0	NA
RT only: 102 (7%) CT only: 318 (21%) RT and CT: 555 (37%)	Median 10.3 yr (< 18 yr)	Median 7.1 yr	Since one year after first diagnosis	0	NA
RT alone: 401 (43%) CT alone: 82 (9%) Combined modality therapy: 447 (48%) RT fields: Mantle alone: 183 (20%) Mantle and para-aortic: 409 (44%) Total lymphoid: 185 (20%) Para-aortic and pelvic (inverted Y): 21 (2%) Other volumes: 50 (5%)	Mean 13.6 yr (range, 0.3 - 18.9 yr)	Mean 16.8 yr (range, 1 mon - 39.4 yr)	Starting point not mentioned	0	NA
External RT: 5 (6%) ^{131}I therapy: 59 (69%) Both modalities: 16 (19%)	Median 15 yr; mean (± SD) 14.7 (± 3.0) yr (range 5 - 18 yr)	Median 111 mo (range 1 - 324 mo)	Starting point not mentioned	0	NA

Table 1. Study characteristics of all 31 included observational studies [a] (continued)

Author (year)	Origin (cohort)	Inclusion period	Total No. of participants in study	Total males in study	Type of primary cancer	Methods of subsequent cancer ascertainment
Gold (2003) (26)	NM	Treated between 1954 - 1980	446 5-yr survivors	NM	Any diagnosis (bilateral retinoblastoma and neuro-fibromatosis were excluded)	- Medical records - Physicians - Patients - Parents The data obtained from patients or parents were verified by physicians
Green (2000) (27)	Long-Term Follow-Up Project at Roswell Park Cancer Institute	Treated between 1960 - 1989	182	100	HL	- Clinical follow-up - Mail contact with patient
Hisada (1998) (28)	Cancer Family Registry in the Division of Cancer Epidemiology and Genetics, National Cancer Institute	Diagnosed between 1968 - 1986	62 [h]	NM	All kinds of cancer featured in Li- Fraumeni syndrome	- Medical records - Pathology reports - Death certificates - Family members
Inskip (2007) (29)	SEER	Diagnosed between 1973 - 2002	25,965 2-mo survivors	14,043	Any diagnosis	Cancer registry
Kushner (1988) (30)	Memorial Sloan-Kettering Cancer Center tumor registry	Diagnosed between 1949 - 1983	254 1-yr survivors	156	HL	NM
MacArthur (2007) (31)	Population-based British Columbia Cancer Registry	Diagnosed between 1970 - 1995	2,322 5-yr survivors	1,217	Any diagnosis	Cancer registry

Primary cancer RT and CT treatments [b]	Age at primary cancer diagnosis (yr) [b]	Follow-up time [b]	Follow-up starting point	No. of participants with SMBC (% in males)	Interval primary cancer - SMBC (yr)
All patients received RT; CT and RT: 302 (68%)	Median 6.2 yr (range, 2 wk - 17 yr)	Median 19.5 yr (range, 4.8 - 40 yr)	Starting point not mentioned	0	NA
In the male population: CT only: 9 (9%) RT: 24 (24%) RT + CT: 67 (67%)	Mean (± SD) 15.30 (± 3.67) yr	Median 17.12 yr; mean (± SD) 17.28 (± 9.79) yr (range, 0.29 - 37.68 yr)	Starting point not mentioned	0	NA
Treatment information only available in 27 patients who had multiple primary cancers: RT: 9 CT: 3 Neither treatment: 15	Range 0 - 19 yr [h]	NM	NM	0	NA
Surgery: 12,957 (49.9%) RT: 9,633 (37.1%) CT: 16,981 (65.4%)	Median 8.2 yr (< 18 yr)	Median 6.3 yr; mean 8.9 yr (range, 2 mo - 30.0 yr)	Since first diagnosis	0	NA
RT alone or with single-agent CT: 145 (57%) Multi-agent CT: 109 (43%)	Median 11.4 yr (≤ 15 yr)	≥ 1 yr	Since first diagnosis	0	NA
NM	Mean (± SD) 10 (± 6.5) yr	Mean 11.2 yr [i]	Starting point not mentioned	0	NA

Table 1. Study characteristics of all 31 included observational studies [a] (continued)

Author (year)	Origin (cohort)	Inclusion period	Total No. of participants in study	Total males in study	Type of primary cancer	Methods of subsequent cancer ascertainment
Macklis (1991) (32)	National Wilms' Tumor Study	Evaluated between 1968 - 1988	51	22	Wilms' tumor	- Medical records - Questionnaires - Telephone contacts - Autopsy reports
Magnani (1996) (15)	Childhood Cancer Registry of Piedmont	Diagnosed between 1967 - 1989	2,328	NM	Any diagnosis	- Cancer registry - Medical records - Death certificates - Enquiry of general practitioners and adult oncology departments
Neglia (2001) (33)	Childhood Cancer Survivor Study	Diagnosed and treated 1970-1986	13,581 5-yr survivors	7,277	Various diagnoses (leukemia, HL, non-HL, neuroblastoma, soft-tissue sarcoma, bone cancer, or a malignant central nervous system tumor or kidney tumor)	- Self-report questionnaires + Verified by pathology reports
Olsen (2009) (34)	Five Nordic cancer registries	Reported between 1943 - 2005	47,697	26,168	Any diagnosis	Cancer registry
Ottaviani (2013) (35)	NM	Treated between 1972 - 2005 [k]	38 20-yr survivors	14	Osteosarcoma	- Questionnaires - Medical records - National and international databases

Primary cancer RT and CT treatments [b]	Age at primary cancer diagnosis (yr) [b]	Follow-up time [b]	Follow-up starting point	No. of participants with SMBC (% in males)	Interval primary cancer - SMBC (yr)
Whole abdominal RT: 19 (37%) Hemi-abdomen RT: 30 (59%) No abdominal RT: 2 (4%) Whole lung RT: 42 (82%) Patchwork local fields RT: 7 (14%) No RT due to their end-stage disease: 2 (4%) Additional boost RT to pulmonary lesions : 22 (43%) CT: intravenous vincristine and actinomycin-D, cyclophosphamide: 21 (41%) The regimen above with doxorubicin added: 30 (59%)	0 - 12 (mo): 5 13 - 24 (mo): 7 25 - 60 (mo): 22 > 60 (mo): 17 [j]	Median 83 mo	Starting point not mentioned	0	NA
NM	0 - 14 yr	Mean 6.6 yr [i]	Starting point not mentioned	0	NA
RT: 7,780 (68%) CT: Alkylating agents: 6,042 patients (53%) Anthracycline: 4,669 (41%) Epipodophyllotoxins: 1,062 (9%) Platinum agents: 677 (6%)	Median 6 yr; mean 7.8 yr (< 21yr)	Median 15.4 yr (range, 6.4 - 28.7 yr)	Since first diagnosis	0	NA
Some had CT but no further information provided	0 - 19 yr	Mean 10.0 yr [i]	Starting point not mentioned	0	NA
CT: 38 (100%); RT: 9 (24%)	Mean ± the SEM: 13.2 ± 0.7 yr (range, 3 - 19 yr)	Mean ± the SEM: 24.3 ± 0.7 yr (range, 20 - 39 yr)	Since first diagnosis	0	NA

Table 1. Study characteristics of all 31 included observational studies [a] (continued)

Author (year)	Origin (cohort)	Inclusion period	Total No. of participants in study	Total males in study	Type of primary cancer	Methods of subsequent cancer ascertainment
Paulino (2000) (36)	NM	Treated between 1968 - 1994	42 5-yr survivors	17	Wilms' tumor	- Clinical follow-up - Questionnaires to patients and physicians
Paulino (2005) (37)	NM	Treated between 1956 - 1998	429 4-yr survivors	NM	Any solid malignant tumor (except for neurofibromatosis and familial and hereditary retinoblastomas)	Medical records
Sankila (1996) (38)	Five Nordic cancer registries	Diagnosed and registered between 1943 - 1987	1,641	971	HL	Medical records
Schellong (2004) (39)	Hodgkin disease late effects project of the GPOH	Enrolled between 1978 - 1995	1,245	737	HL	- Submitted by centers - Mailing questionnaires Data were also annually compared with cancer registry
Strong (1987) (40)	NM	Diagnosed between 1944 - 1976	163 3-yr survivors	93	Soft tissue sarcoma	- Telephone interview - Death certificates - Medical records
Tarbell (1993) (41)	NM	Treated between 1969 - 1988	191	125	HL	NM

Primary cancer RT and CT treatments [b]	Age at primary cancer diagnosis (yr) [b]	Follow-up time [b]	Follow-up starting point	No. of participants with SMBC (% in males)	Interval primary cancer - SMBC (yr)
All received RT: 1,000 - 1,200 cGy: 12 (29%) 1,201 - 2,399 cGy: 11 (26%) 2,400 - 4,000 cGy: 19 (45%) Whole-lung RT (1,200 - 1,500 cGy, some received boosts of 1,000 cGy): 13 (31%) All received CT: the most common agents were actinomycin-D / vincristine / adriamycin:13 (31%) Actinomycin-D / vincristine:18 (43%)	Median 48 mo (range, 7 - 126 mo)	Median 181 mo (range, 60 - 306 mo)	Since first diagnosis	0	NA
All received RT, some had CT, but no further information provided	≤ 21 yr	Median 9.6 yr	Starting point not mentioned	0	NA
Some had RT, no specific treatment information mentioned	Median 16 yr (< 20 yr)	Mean 10.4 yr	Starting point not mentioned	0	NA
Some had RT, no further information provided All patients received CT	Median 12.6 yr (range, 2.0 - 17.9 yr)	Median 11.1 yr (range, 0 - 25.5 yr)	Since day 1 of therapy	0	NA
Some had RT, some had CT; no specific information mentioned	< 16 yr	Mean 13.55 yr (range, 3 - 31 yr)	Since first diagnosis	0	NA
In the male population: Total treatment: RT alone: 62 (50%) RT + CT: 56 (45%) CT alone: 7 (5%) CT therapy included mustine, vincristine, procarbazine, and prednisone Patients received a total dose of 36 - 40 Gy to mantle, para-aortic, and/or pelvic fields. Areas of initial disease involvement were boosted to 40 - 44 Gy	Median 13 yr (range, 3 - 16 yr)	Median 11yr (range, 3 - 21 yr)	Starting point not mentioned	0	NA

Table 1. Study characteristics of all 31 included observational studies [a] (continued)

Author (year)	Origin (cohort)	Inclusion period	Total No. of participants in study	Total males in study	Type of primary cancer	Methods of subsequent cancer ascertainment
Terracini (1987) (42)	Italian registry of offtherapy children	Diagnosed between 1960 - 1981	1,467	818	Various diagnoses (HL, non-HL, neuroblastoma, nephroblastoma, ALL and non lymphoblastic leukaemia)	Enquiry with institutions with histological confirmations
Tukenova (2010) (43) [l]	Multicentric French-UK cohort	Diagnosed between 1942 - 1986	4,230 5-yr survivors	NM	Any solid malignant tumor	Medical records
Wolden (1998) (44)	NM	Treated between 1960 - 1995	694 1-yr survivors	387	HL	Medical records
de Vathaire (1995) (45)	NM	Treated between 1942 - 1985	1,055 2-yr survivors	546	Any diagnosis	Medical records

[a] There are potential overlaps in study population and SMBC cases among the included studies, but the levels of overlap are unclear.
[b] The information of primary cancer treatments, age at primary cancer diagnosis, and follow-up time is for the overall cohort, including male and female population, unless otherwise specified.
[c] This time interval is calculated from the information of SMBC cases.
[d] Sex unknown in three patients.
[e] Information from the study design paper (64).
[f] The time interval is calculated by age at SMBC diagnosis minus age at primary cancer diagnosis.
[g] Based on the available information in the article.
[h] The study included patients who were diagnosed with cancer at all ages. 62 patients had childhood cancer as the primary cancer. Only the information of these 62 childhood cancer survivors are included in the table.
[i] The mean follow-up time is calculated from the person-year divided by the total population.
[j] Wilms' tumor happens rarely in adults, therefore we assume all patients who were diagnosed of Wilms' tumor > 60 month were pediatric patients.
[k] Information from the article reference (65).
[l] The study assessed mortality from second malignant neoplasms in 5-year survivors of solid childhood tumors.
[m] An integral dose of 1 J corresponds to a dose of 1 Gy in a 1-liter water volume.
SMBC = subsequent male breast cancer; RT = radiotherapy; CT = chemotherapy; HL = Hodgkin lymphoma; NM = not mentioned; NA = not applicable; yr = year; mo = month; SD = standard deviation; SEER = Surveillance, Epidemiology, and End Results; SEM = standard error of the mean; GPOH = Gesellschaft für Pädiatrische Onkologie und Hämatologie / Society for Paediatric Oncology and Haematology; ALL = acute lymphoblastic leukemia

Primary cancer RT and CT treatments [b]	Age at primary cancer diagnosis (yr) [b]	Follow-up time [b]	Follow-up starting point	No. of participants with SMBC (% in males)	Interval primary cancer - SMBC (yr)
11 patients with subsequent malignancies received both RT (2,400 - 9,600 rads) and CT	NM	NM	NM	0	NA
RT: Integral dose mean (min - max): 160.3 (0.1 - 1,247.9) J [m] CT categories included anthracyclines, alkylating agents, epipodophyllotoxins, antimetabolites, vinca alkaloids, and other drugs	< 17 yr	Median 28 yr (range, 5 - 63 yr)	Since first diagnosis	0	NA
In the male population: RT alone: 178 (46%) Combined modality therapy: 200 (52%) CT alone: 9 (2%)	Median 16 yr (< 21 yr)	Median 12.3 yr; mean 13.1 yr (range, 1.0 - 31.6 yr)	Since first diagnosis	0	NA
All had RT no CT	Year at radiation 6.9 yr (range, 0 - 16 yr)	Mean 19 yr (range, 2 - 48 yr)	Since first diagnosis	0	NA

Five studies with a total of 11 SMBC cases reported risk measures for SMBC in CCSs (Table 2). Significantly increased risk of SMBC in CCSs compared to the general male population were observed in two studies, with SIRs of 43.9 (95% confidence interval (CI) 10.9 - 113.7; with 3 cases) among survivors of Hodgkin lymphoma, and 12.8 (95% CI 3.2 - 51.3; with 2 cases) in a mixed CCS cohort; with AERs of 20 (95% CI not reported) per 100,000 person-years and 1.0 (95% CI -0.0 - 2.0) per 100,000 person-years, respectively (17, 18). Teepen et al. reported one case of SMBC in a mixed CCS cohort with a SIR of 30.4 (95% CI 0.8 - 169.5); no AER was reported (21). These represent cohorts for which substantial follow-up time was accrued, the median ranging from 20.7 to 26.6 years since first diagnosis. Li et al. examined the observed and expected MBC cases in a subgroup of 94 males who had received chest radiotherapy at ages five to 17 years and found that the SIR was 1,000 (with 1 case) (19). Two studies also reported the cumulative incidence of SMBC. The first study, including CCSs with any solid malignant tumor, found a 0.2% incidence 30 years after primary childhood cancer diagnosis, and a 0.7% incidence 50 years after primary childhood cancer diagnosis (16). The other study found a 0.2% incidence 30 years after primary Hodgkin lymphoma diagnosis, and a 1.1% incidence 40 years after primary Hodgkin lymphoma diagnosis (17). By age 40 years and 50

years, the cumulative incidences were 0.2% and 1.7%, respectively (17). None of the studies evaluated specific risk factors for the occurrence of SMBC.

The risk of bias for observational studies is shown in Appendix C. The risk of selection bias was low in 12 studies (39%). However, it was unclear in all other studies (n = 19, 61%). The risk of attrition bias was low in 20 studies (65%) and unclear in 11 (35%). Confounding bias was not applicable because no studies conducted specific analyses to examine risk factors for SMBC. The risk of detection bias was unclear in all studies.

Case reports/series

The characteristics of the included cases are summarized in Table 3. There were seven cases of SMBC from case-reports/series (46-52) and five cases described in two cohort studies (16, 19). Thompson et al. (52) described a patient who was also in the population study of Li et al. (19). Thus, we eventually included 11 SMBC cases in this section. The median age at primary cancer diagnosis was 8.0 years, with a range from 0.5 to 17.0 years. The most common primary childhood cancer diagnosis in these SMBC cases was acute lymphoblastic leukaemia (4 / 11 patients, 36%). The median interval between the primary childhood cancer and SMBC was 24.0 years, with a range from 11.0 to 42.5 years. One patient had Cowden syndrome and received chemotherapy for his non-Hodgkin lymphoma (48). The other ten SMBC patients were treated with both chemotherapy and chest radiotherapy for childhood cancer: in four cases, the estimated dose received by the breast was calculated and considered to be chest radiotherapy if there was any dose to the breast (16). SMBC was diagnosed at a median attained age of 34.0 years (range 23.0 - 43.0). All SMBC cases concerned invasive ductal carcinomas. Of the nine out of 11 cases with SMBC receptor information, all had an ER+ and PR+ tumor, three had a HER2- tumor out of five cases with HER2 status reported, and two had a HER2+ tumor. Five of the 11 patients (45%) indicated positive familial cancer histories; two of whom had family histories of breast cancer in female family members (47, 48), and one of whom had several paternal family members with malignancies diagnosed at early ages (48). As reported by the included studies, genetic predisposition was examined in two patients (18%) with positive familial cancer histories (Table 3). One patient was found to have a germline heterozygous missense variant (c.103A>G; p.Met35Val) in the PTEN gene (Cowden syndrome) (48), and the other patient did not have abnormalities of BRCA or p53 mutations (16).

Table 2. Overview of studies with risk measures for subsequent male breast cancer in survivors of childhood cancer compared to the general population

Author (year)	Total males in cohort/ study	Type of primary cancer	Follow-up time [a]	Follow-up starting point	No. of patients with SMBC (% in males)	SIR (95% CI)	AER (95% CI)	Cumulative incidence among males
Demoor-Goldschmidt (2018) (16)	3,893	Any solid malignant tumor	For the male population: Median 25 yr (range, 5 - 67 yr)	Since first diagnosis	4 (0.10%)	NM	NM	- 30 years after diagnosis: 0.2% (95% CI 0.01% - 0.4%) - 50 years after diagnosis: 0.7% (95% CI 0.2% - 2.8%)
Holmqvist (2019) (17)	At least 744 [b]	Hodgkin lymphoma	Median 26.6 yr	Starting point not mentioned	3 (0.40%)	43.9 (95% CI 10.9 - 113.7)	20 (95% CI not reported) per 100,000 person-years	- 30 years after diagnosis: 0.2% (95% CI 0% - 1.3%) - 40 years after diagnosis: 1.1% (95% CI 0.3% - 3.2%) - 40 years attained age: 0.2% (95% CI 0% - 1.2%) - 50 years attained age: 1.7% (95% CI 0.4% - 5.2%)
Reulen (2011) (18)	9,887	Any diagnosis	Median 24.3 yr; mean 25.6 yr; 25th - 75th percentile, 17.9 - 32.4 yr	Since first diagnosis	2 (0.02%)	12.8 (95% CI 3.2 - 51.3)	1.0 (95% CI -0.0 - 2.0) per 100,000 person-years	NM
Li (1983) (19)	504	Any diagnosis	Median 13 yr (range, 5 - 49 yr)	Since first diagnosis	1 (0.20%)	1,000 [c]	NM	NM
Teepen (2017) (21)	3,434	Any diagnosis	Median 20.7 yr (range, 5.0 - 49.8 yr)	Since first diagnosis	1 (0.03%)	30.4 (95% CI 0.8 - 169.5)	NM	NM

[a] The follow-up time is for the overall cohort, including male and female population, if without specific explanation.
[b] Sex unknown in three patients.
[c] The ratio for 94 males who had received chest radiotherapy between 5 and 17 years.
SMBC = subsequent male breast cancer; SIR = Standardized incidence ratio; AER = Absolute excess risk; CI = Confidence interval; NM = not mentioned; yr = year

Table 3. Study characteristics of all 9 included case reports/series (11 cases in total)

Author (year)	Type of primary cancer	Age at primary cancer diagnosis (yr)	Primary cancer treatment - chest RT information	Primary cancer treatment - CT information
Alazhri (2016) (46)	T-cell ALL	4.0	Treated with RT on paediatric POG 9398 protocol (no further RT info mentioned); TBI (included radiation to the chest wall)	For relapse: Paediatric POG 9110 protocol (no further info provided); for transplant: Cyclophosphamide (no further info provided)
Boussen (2000) (47)	HL	13.0	Mantle field (44 Gy) [a]	Vinblastine (10 mg/week for 13 months)
Demoor-Goldschmidt (2018) (16)	Neuro-blastoma	0.5	Estimated dose received by the breast mean 2.0 Gy; Max (D5% [b]) 2.3 Gy; Min (D95% [b]) 1.9 Gy	Cyclophosphamide (413 mg/m^2)
Demoor-Goldschmidt (2018) (16)	HL	7.5	Estimated dose received by the breast mean 16.4 Gy; Max (D5%) 23.6 Gy; Min (D95%) 11.2 Gy	Vinblastine (305 mg/m^2)
Demoor-Goldschmidt (2018) (16)	Malignant mesenchy-moma of the liver	14.0	Estimated dose received by the breast mean 28.2 Gy; Max (D5%) 38.1 Gy; Min (D95%) 26.6 Gy	Cyclophosphamide (1601 mg/m^2), Procarbazine (2775 mg/m^2), Vincristine (14 mg/m^2);
Demoor-Goldschmidt (2018) (16)	Medulloblas-toma	14.4	Estimated dose received by the breast mean 1.98 Gy; Max (D5%) 2.3 Gy; Min (D95%) 1.4 Gy	Cyclophosphamide (1800 mg/m^2), Procarbazine (450 mg/m^2), steroids, Vincristine (8 mg/m^2), Methotrexate (30 mg/m^2), Hydrea (1500 mg/m^2)
Hagelstrom (2016) (48)	B-cell lymphoblastic lymphoma	7.0	No RT	Treated as per the Children's Cancer Group study 503: cyclophosphamide, vincristine, prednisone, and both intravenous and intrathecal methotrexate

Age at SMBC diagnosis (yr)	Interval primary cancer - SMBC (yr)	Type of SMBC	SMBC receptor status	History of familial cancers	Genetic predisposition	Outcome	Others
23.0	19.0	Invasive ductal carcinoma, grade 2-3, T2N1M0	ER+, PR+, HER2+	No	Not performed	Alive (no further information provided)	Ki-67 level 20%; Patient received allo-HCT
24.0	11.0	Invasive ductal carcinoma, SBR III; 2 lymph nodes invasion with capsular rupture	NM	Yes: 3 breast cancer cases in female family members (second- and third- degree relatives)	NM	Alive in remission, 18 months after mastectomy	Diagnosed with thyroid carcinoma at the time of breast cancer diagnosis
43.0	42.5	Invasive ductal carcinoma, SBR I	ER+, PR+, HER2-	No	Not performed	NM	
34.0	26.5	Invasive ductal carcinoma, pT2N0	ER+, PR+	Yes: liver cancer grandfather	BRCA and p53 mutations negative	NM	
38.0	24.0	Invasive ductal carcinoma, SBRIII, pT2N1	ER+, PR+	No	Not performed	NM	
42.0	27.6	Invasive ductal carcinoma, SBRIII, pT2N2	ER+, PR+	Yes: father family: several leukemia, solid cancers	Not performed	NM	
31.0	24.0	Invasive ductal adenocarcinoma, stage I	ER+, PR+, HER2/ Neu-	Yes: familial cancer syndrome (several paternal family members presented with various types of malignancies at early ages, including breast cancer)	Germline heterozygous missense variant (c.103A>G; p.Met35Val) in the PTEN gene (Cowden Syndrome)	NM	Ki-67 level 12%

Table 3. Study characteristics of all 9 included case reports/series (11 cases in total) (continued)

Author (year)	Type of primary cancer	Age at primary cancer diagnosis (yr)	Primary cancer treatment - chest RT information	Primary cancer treatment - CT information
Latz (2004) (49)	ALL	16.0	TBI (12 Gy)	BMFT schedule: prednisone (100 mg per os, 28 days), vincristine (2 mg, 4 days), doxorubicin (40 mg, 4 days), crasnitin (10,000 E , 14 days), cyclophosphamide, cytarabine, and mercaptopurine. Later with methotrexate, prednisone, thioguanin, cytarabine, doxorubicin, vincristine, novantrone, etoposide and intrathecal injection of methotrexate, cytarabine and pred nisone
Li (1983) (19) / Thompson (1979) (52) [c]	Osteogenic sarcoma	8.0	Radiation left breast: 600 R (anterior), 400 R (posterior); Radiation right breast: 400 R (anterior), 400 R (posterior)	Nitrogen mustard (3x 3.2 mg), aminopterin
Lowe (2008) (50)	ALL	17.0	TBI (1320 cGy)	Vincristine, prednisone, doxorubicin, intrathecal chemotherapy, methotrexate, 6-mercaptopurine, daunorubicin, and etoposide
O'Flynn (2011) (51)	ALL	7.0	TBI (12 Gy with boosts to the brain and spine)	Yes but no further information provided

[a] The radiation fields are not completely clear, presumably mantle field.
[b] Doses received by the 5% and 95% of the breast.
[c] Li (1983) and Thompson (1979) presented the same case.
RT = radiotherapy; CT = chemotherapy; SMBC = subsequent male breast cancer; yr = year; ALL = acute lymphoblastic leukemia; HL = hodgkin lymphoma; SBR = Scarff-Bloom-Richardson; NM = not mentioned; TBI = total-body irradiation; allo-HCT = allogeneic hematopoietic cell transplantation; BMFT = Germany Ministry of Research and Technology; R = roentgen

Age at SMBC diagnosis (yr)	Interval primary cancer - SMBC (yr)	Type of SMBC	SMBC receptor status	History of familial cancers	Genetic predisposition	Outcome	Others
29.0	13.0	Invasive ductal carcinoma, final tumor stage was pT1c pN0 cM0 G1	ER+, PR+	No	NM	Died due to tumor progression after at least 19 months after SMBC RT	Patient received allo-HCT
38.0	30.0	Invasive ductal carcinoma, stage II, left breast	ER: not obtained; PR and HER2: NM	No	NM	Alive (no further information provided)	
34.0	17.0	Moderately differentiated invasive ductal carcinoma, stage IIB, T2N1	ER+, PR+, HER2+	Yes: brother with colon cancer	Not performed	Alive (no further information provided)	Patient received allo-HCT
27.0	20.0	Right breast: invasive ductal carcinoma, grade 2; Left breast: ductal carcinoma in situ	Right breast: ER +, PR +, HER2-	NM	NM	Alive (no further information provided)	Patient received allo-HCT

Part 2. PanCareSurFup Cohort

In the PanCareSurFup cohort, 37,738 male five-year survivors were eligible and included in our study with a median follow-up of 20.9 years (interquartile range (IQR) 11.7 - 31.7) since primary cancer diagnosis. The median age at primary cancer diagnosis was 7.2 years (IQR 3.2-13.0). The median attained age was 29.8 years (IQR 20.9 - 39.8). Of males with known radiotherapy status (19,431 / 37,738, 51%), 56% (n = 10,872) received radiotherapy as part of primary cancer treatment. The information on radiation field and chemotherapy agents was not available for the whole cohort.

Risk of SMBC

Sixteen SMBC cases were identified at a median attained age of 40.5 years (range 21.9 - 62.8), while 0.7 cases were expected during the entire follow-up period. The male breast cancer risk was 22.3-fold higher in male CCSs compared with the general population (SIR 22.3, 95% CI 12.7 - 36.2) corresponding to an excess of 2.3 cases per 100,000 person-years (AER 2.3, 95% CI 1.3 - 3.7) (Table 4). Elevated breast cancer SIRs were observed in most childhood cancer types, except for central nervous system tumors. The SIRs for SMBC were significantly increased in survivors of Wilms' tumor, neuroblastoma, leukemia, Hodgkin lymphoma, and soft tissue sarcoma. Wilms' tumor survivors were at greatest risk of developing SMBC (SIR 75.4, 95% CI 15.6 - 220.4), with corresponding AERs of 5.4 (95% CI 1.1 - 15.9) cases per 100,000 person-years (Table 4). The distribution of attained age, follow-up time since primary cancer diagnosis, and primary cancer treatment per childhood cancer type is described in Appendix D. The SIR decreased as attained age increased, but survivors remained at elevated risk of SMBC development even when attained age reached 50 years (SIR 9.2, 95% CI 1.9 - 26.8). In contrast, the AER increased with attained age, with the highest AER in those aged 50+ years (AER 10.8, 95% CI 2.0 - 33.5).

The cumulative incidences of SMBC were 0.02% (95% CI 0.01% - 0.04%), 0.04% (95% CI 0.02% - 0.08%), and 0.10% (95% CI 0.05% - 0.18%) by age 30, 40, and 50 years, respectively; and 0.02% (95% CI 0.01% - 0.05%), 0.06% (95% CI 0.03% - 0.10%), 0.12% (95% CI 0.06% - 0.24%), 0.24% (95% CI 0.10% - 0.50%) after 20, 30, 40, and 50 years of follow-up since primary childhood cancer diagnosis.

Table 4. General characteristics, and standardized incidence ratios and absolute excess risks of subsequent male breast cancer by childhood cancer diagnosis in the PanCareSurFup cohort

Characteristics	Male population	SMBC cases	SIR (95% CI)	AER (95% CI)
No. of CCSs	37,738	16	22.3 (12.7 - 36.2)	2.3 (1.3 - 3.7)
Age at childhood cancer				
0-4 yrs	14,470 (38.3%)	6	34.6 (12.7 - 75.2)	2.1 (0.7 - 4.6)
5-9 yrs	8,992 (23.8%)	5	32.5 (10.6 - 75.8)	3.0 (0.9 - 7.0)
10-14 yrs	8,244 (21.8%)	5	19.3 (6.3 - 45.0)	3.2 (1.0 - 7.6)
15-21 yrs	6,032 (16.0%)	0	0.0 (0.0 - 28.3)	0.0 (0.0 - 4.4)
Decade of childhood cancer diagnosis				
<1970	4,691 (12.4%)	5	11.8 (3.8 - 27.4)	2.9 (0.9 - 6.9)
1970-1979	7,280 (19.3%)	7	40.1 (16.1 - 82.6)	3.7 (1.5 - 7.6)
1980-1989	11,453 (30.3%)	2	20.8 (2.5 - 75.0)	0.9 (0.1 - 3.3)
1990-1999	10,567 (28.0%)	2	100.8 (12.2 - 364.1)	2.1 (0.2 - 7.5)
2000-2008	3,747 (9.9%)	0	0.0 (0.0 - 2435.2)	0.0 (0.0 - 27.6)
Type of primary cancer				
Leukemia	8,964 (23.8%)	3	48.3 (10.0 - 141.2)	2.2 (0.4 - 6.6)
Hodgkin lymphoma	3,603 (9.5%)	3	35.8 (7.4 - 104.6)	4.7 (0.9 - 13.9)
Non-Hodgkin lymphoma	2,309 (6.1%)	1	19.0 (0.5 - 106.1)	2.3 (0.0 - 13.1)
Central nervous system tumors	7,866 (20.8%)	0	0.0 (0.0 - 21.1)	0.0 (0.0 - 2.4)
Neuroblastoma	1,618 (4.3%)	1	50.4 (1.3 - 280.9)	3.2 (0.1 - 18.0)
Retinoblastoma	1,345 (3.6%)	1	23.6 (0.6 - 131.7)	2.7 (0.1 - 15.2)
Wilms' tumor	2,393 (6.3%)	3	75.4 (15.6 - 220.4)	5.4 (1.1 - 15.9)
Bone Sarcoma	1,730 (4.6%)	1	19.1 (0.5 - 106.3)	3.1 (0.1 - 17.9)
Soft tissue sarcoma	2,525 (6.7%)	2	28.7 (3.5 - 103.5)	3.8 (0.4 - 13.8)
Other	5,187 (13.7%)	1	9.4 (0.2 - 52.2)	1.0 (0.0 - 6.2)
Not in ICCC	198 (0.5%)	0	0.0 (0.0 - 281.0)	0.0 (0.0 - 57.3)

Table 4. General characteristics, and standardized incidence ratios and absolute excess risks of subsequent male breast cancer by childhood cancer diagnosis in the PanCareSurFup cohort (continued)

Characteristics	Male population	SMBC cases	SIR (95% CI)	AER (95% CI)
Follow-up duration since primary cancer diagnosis / Interval primary cancer diagnosis - SMBC				
5-9 yrs	7,506 (19.9%)	0	0.0 (0.0 - 514.5)	0.0 (0.0 - 2.2)
10-19 yrs	10,631 (28.2%)	3	65.2 (13.4 - 190.4)	1.2 (0.2 - 3.5)
20-29 yrs	8,777 (23.3%)	6	45.0 (16.5 - 97.9)	3.8 (1.4 - 8.4)
30-39 yrs	6,661 (17.7%)	2	9.7 (1.2 - 35.0)	2.5 (0.3 - 9.6)
40+ yrs	4,163 (11.0%)	5	15.4 (5.0 - 35.9)	15.6 (4.8 - 37.3)
Attained age (yrs)				
<30 yrs	19,171 (50.8%)	4	90.2 (24.6 - 231.0)	0.9 (0.2 - 2.3)
30-39 yrs	9,282 (24.6%)	4	30.1 (8.2 - 77.2)	2.8 (0.7 - 7.3)
40-49 yrs	5,877 (15.6%)	5	23.5 (7.6 - 54.8)	7.9 (2.5 - 18.8)
50+ yrs	3,408 (9.0%)	3	9.2 (1.9 - 26.8)	10.8 (2.0 - 33.5)

SIRs = Standardized incidence ratios; AERs = Absolute excess risks; CI = Confidence interval; PanCareSurFup = Pan-European PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies; SMBC = subsequent male breast cancer; CCSs = childhood cancer survivors; yrs = years; ICCC = International Classification of Childhood Cancer

Characteristics of SMBC cases

Information of SMBC characteristics of cases is provided in Table 5. Among the 16 PanCareSurFup SMBC cases, six were also included in the population studies identified in the systematic review part (16, 18, 21), and four were described in the included case-reports/series (16, 51).

The median age at primary cancer diagnosis was 6.4 years (range 0.5 - 14.9). All SMBC cases were invasive ductal carcinomas, except for one case that was reported as an unspecified malignant neoplasm. Of the 16 SMBC patients, 13 out of 15 patients with known chemotherapy information had chemotherapy. Of the 14 patients with available information on radiotherapy, six had chest radiotherapy. Five patients had both chemotherapy and chest radiotherapy. The three out of five who had SMBC histological grade information reported, were indicated as grade 3; the other two were grade 1 and 2, respectively. SMBC receptor status was available for eight cases (50%), and the PR status was only available in six (75%); six out of eight (75%) were ER-positive, three out of six (50%) were PR-positive. Two patients (13%) developed another SMN before MBC diagnosis: one had basal cell carcinoma with no chest radiotherapy and chemotherapy, the other received chemotherapy for acute lymphoblastic leukemia before SMBC. The intervals between basal cell carcinoma and ALL, and SMBC were seven and nine years, respectively. Only two patients had reported family histories of cancer (13%) (one had a retinoblastoma family history (unknown family member) and the other had a father and a sibling diagnosed with Hodgkin lymphoma and non-Hodgkin lymphoma, respectively). On the last follow-up, six out of the 16 patients were alive (38%), no further information was available on cause of death for the decedents. The 5- and 10-year survival rates after SMBC diagnosis were 60.3% (95% CI 35.6% - 85.0%) and 43.0% (95% CI 16.1% - 69.9%), respectively.

Table 5. Characteristics of subsequent male breast cancer cases in the PanCareSurFup cohort

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Age at primary cancer diagnosis	0-4 yrs	5-9 yrs	10-14 yrs	0-4 yrs	0-4 yrs	0-4 yrs	10-14 yrs	5-9 yrs
Year of primary cancer diagnosis	<1970	<1970	1970-79	<1970	1970-79	1970-79	1970-79	1990-2008
Type of primary cancer	HL	STS	Malignant teratoma	Retinoblas-toma	ALL	Nephro-blastoma	ALL	ALL
Chest field RT, yes/no	Yes	No	Yes	No	No	Yes	No	Yes
Chest radiation fields	Mediastinum, axillae	N/A	Chest right, chest left (posterior only)	N/A	N/A	Chest	N/A	TBI
Chest field radiation dose, Gy	20	N/A	30	N/A	N/A	15	N/A	N/I
Other radiation fields	Neck (R)	Thigh (L)	Para-aortic nodes anterior and posterior	Eye (L) Radon seeds	Testes, cranium	Abdominal field	No	No
Chemotherapy drug/dose, mg/m^2	Procarbazine 14302,1 mg/m^2, Vinblastine 190,5 mg/m^2, Mustine 34,2 mg/m^2, Cyclo-phosphamide 8992,4 mg/m^2, Prednisolone 9699,2 mg/m^2	No	Vinblastine, Bleomycin, Vepesid, Cisplatin (dose N/I)	No	Prednisolone, Vincristine, Cyclophospha-mide, Cytosine arabinoside, Asparaginase, Adriamyicin, Mercap-topurine, Methotrexate (dose N/I)	Vincristine, Actino-mycin D, Cyclophos-phamide (dose N/I)	Yes (infor-mation N/I)	N/I
HCT	No	No	No	No	Yes	No	Yes	Yes
Age at SMBC diagnosis, yr	50+ yrs	50+ yrs	40-49 yrs	50+ yrs	<30 yrs	<30 yrs	40-49 yrs	<30 yrs
Year of SMBC diagnosis	2010-2019	2010-2019	2000-2009	2010-2019	<2000	2000-2009	2000-2009	2010-2019
Interval primary cancer - SMBC, yr	40-49 yrs	50+ yrs	20-29 yrs	50+ yrs	10-19 yrs	20-29 yrs	30-39 yrs	10-19 yrs
Type of SMBC	Invasive ductal carcinoma	Invasive ductal carcinoma	Invasive ductal carcinoma	Invasive ductal carcinoma	Invasive ductal carcinoma	Invasive ductal carcinoma	Malignant neoplasm (no further infor-mation provided)	Invasive ductal carcinoma

Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15	Patient 16
5-9 yrs	0-4 yrs	10-14 yrs	10-14 yrs	0-4 yrs	5-9 yrs	10-14 yrs	5-9 yrs
1980-89	<1970	1990-2008	1980-89	<1970	1970-79	1970-79	1970-79
Non-HL	Nephroblas-toma	Bone sarcoma	HL	Neuroblas-toma and ganglioneu-roblastoma	HL	Rhabdomyosar-coma	Nephroblas-toma
N/I	N/I	No	No	No	Yes	Yes	No
N/I	N/I	N/A	N/A	N/A	N/I	N/I	N/A
N/I	N/I	N/A	N/A	N/A	N/I	N/I	N/A
N/I	N/I	No	Neck, spleen, paraaortal and billateral iliac regions	Abdominal field	Abdominal field	No	Abdominal field
Yes (infor-mation N/I)	Actinomycin, Vincristine (dose N/I)	Doxorubicin 330 mg/m^2, Methotrexate 40 gr/m^2, Cisplatin 480 mg/m^2	Procarbazine 4200 mg/m^2, Mustargen 36 mg/m^2, Adriamyicin 210 mg/m^2, Vinblastine 12 mg/m^2, Vincristine 12 mg/m^2, Bleomycin 60 mg/m^2, Prednisone (dose N/I)	Cyclophos-phamide 413 mg/m^2	Vinblastine 305 mg/m^2	Actinomycin D 3 mg/m^2, Vincris-tine 8 mg/m^2, Cyclophospha-mide 1601 mg/m^2, Procarba-zine 2775 mg/m^2, Doxorubicin 178 mg/m^2	Vincristine, Actinomycin D (dose N/I)
No	No	No	No	No	No	No	No
30-39 yrs	40-49 yrs	<30 yrs	30-39 yrs	40-49 yrs	30-39 yrs	30-39 yrs	40-49 yrs
2010-2019	2000-2009	2000-2009	2000-2009	2000-2009	<2000	<2000	2010-2019
20-29 yrs	40-49 yrs	10-19 yrs	20-29 yrs	40-49 yrs	20-29 yrs	20-29 yrs	30-39 yrs
Invasive ductal carcinoma	Invasive ductal carcinoma	Invasive ductal carcinoma	Invasive ductal carcinoma	Invasive ductal carcinoma	Invasive ductal carcinoma	Invasive ductal carcinoma	Invasive ductal carcinoma

Table 5. Characteristics of subsequent male breast cancer cases in the PanCareSurFup cohort (continued)

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
SMBC stage / grade	N/I	N/I	N/I	N/I	1/9 lymph nodes positive	T1c (17mm), N0, grade 3	N/I	N/I
SMBC receptor status [a]	N/I	N/I	N/I	N/I	ER+	ER+	N/I	N/I
SMBC laterality	N/I	N/I	N/I	Bilateral	Right	Left	N/I	N/I
SMBC location	Central	Overlapping lesion of breast	Nipple & areola/ central portion of breast	N/I	N/I	N/I	N/I	N/I
History of familial cancers	N/I	N/I	N/I	Retinoblastoma	N/I	N/I	Father (HL), sib (non-HL)	N/I
Patient status / Date of last known medical information	Alive, 12/2015	Alive, 12/2015	Deceased, 04/2009	Alive, 12/2015	Deceased, 09/2009	Alive, 12/2015	Deceased, 02/2010	Deceased, 04/2013

[a] The cut-off point of ER+ and PR+ is 60%.
SMBC = subsequent male breast cancer; PanCareSurFup = Pan-European PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies; HL = Hodgkin lymphomal; STS = soft tissue sarcoma; ALL = acute lymphocytic leukemia; RT = radiotherapy; HCT = hematopoietic cell transplantation; SMN = subsequent malignant neoplasm; ER = Estrogen receptor; PR = Progesterone receptor; HER2 = Human epidermal growth factor receptor 2; AR = Androgen receptor; TBI = total body irradiation; N/I = No information available; N/A = Not Applicable; R = right; L = left

Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15	Patient 16
N/I	N/I	T1c, N0, Stage I, grade 2	T3 (8 cm), N0, Stage III B, grade 3	Grade 1	N/I	T2 (25mm), grade 3	T4N+, 6x7 cm
N/I	N/I	ER 40%+, PR 90%+	ER-, HER2+, PR-	ER+, PR-	ER+, PR+	ER+, PR+	ER 100%+, PR 20-30%+, HER2+, AR 100%+
N/I	N/I	Left	Left	Left	Left	Right	Left
N/I	N/I	N/I	Central	N/I	N/I	N/I	N/I
N/I	N/I	N/I	No	N/I	N/I	N/I	Negative for breast cancer, prostate carcinoma and ovarian carcinoma
Deceased, 01/2015	Alive, 12/2015	Deceased, 05/2007	Alive, 12/2019	Deceased, 9/2009	Deceased, 4/2004	Deceased, 2/2007	Deceased, 8/2012

Discussion

This manuscript includes a systematic review on the risk of SMBC in CCSs and the largest study of SMBC in CCSs to date using data of the PanCareSurFup cohort. Although the absolute risk of SMBC is low, our pan-European cohort study showed that male CCSs were at a 22.3-fold increased risk of developing SMBC compared to the general male population, which was generally compatible with the results in the systematic review, and the risk remained elevated even beyond age 50 years. However, risk factors remained unclear.

The number of studies on SMBC in CCSs in our systematic review was limited, which may be due to the rarity of male breast cancer. Most of the included studies did not focus on the risk of SMBC specifically, but evaluated all SMNs in their cohort of CCSs. In all studies there was a risk of bias and due to missing data and clinical heterogeneity it was not possible to pool results. No multivariable risk factor analyses were performed, so risk factors remain largely unclear. Among the included cohort studies, the frequency of SMBC ranged from 0 to 0.40%, which aligns with the frequency of SMBC in our PanCareSurFup population (0.04%). Of note, there is a level of overlap between reports included in the systematic review. In addition, several cohorts captured in the review contribute to the PanCareSurFup cohort. The cumulative incidences of MBC in our PanCareSurFup cohort and the cumulative incidences reported in the included literature were similar. At 30 years after primary diagnosis cumulative incidence was 0.2% (95% CIs 0.01% - 0.4% and 0% - 1.3%, respectively) (16, 17) vs. 0.06% (95% CI 0.03% - 0.10%) in the PanCareSurFup cohort.

Our PanCareSurFup cohort data indicate that male CCSs have a 22.3-fold SMBC risk compared with the general male population which was compatible with the range of SIRs reported in the included cohort studies with SIR estimates in the systematic review. While the AERs are not drastically elevated, they do increase with attained age. The interval between the primary cancer diagnosis and SMBC ranged from 11.3 to 61.9 years in our PanCareSurFup cohort, which is broader than the interval ranges reported in the included cohort studies (ranging from 24.0 to 42.0 years) and case reports (ranging from 11.0 to 42.5 years). This is likely related to the combination of the wide inclusion period captured by the PanCareSurFup cohort, which in part extends back to childhood cancer diagnoses prior to 1960, and the long follow-up period. The median age of the SMBC cases in our study was 40.5 years (range 21.9 - 62.8). This is much younger than the peak occurrence age of MBC in the general population, which is 71 years (8). It is not clear yet how MBC risk will develop as the cohorts mature beyond age 60 years.

As already shown for female CCSs (1-4, 8), radiotherapy to fields in which breast tissue received more than 10 Gy radiation might also be an important risk factor for the development of SMBC. Analyses of data from male atomic bomb survivors showed evidence of a radiation dose-response for male breast cancer (53, 54). Demoor-Goldschmidt et al. reported that all four SMBC cases after childhood cancer in their cohort had received radiotherapy involving breast tissue and chemotherapy as the primary cancer treatment (16). In the reviewed case-reports/series (also including the four SMBC cases from Demoor-Goldschmidt et al.), we observed that all but one case had both chest- / breast-exposing radiotherapy and chemotherapy for the primary cancer treatment (n = 10, 91%). It should be kept in mind that the case reports/series are likely not a representative sample of all SMBC cases; it is not possible to draw conclusions on causality for potential risk factors from this type of evidence. Moreover, in the PanCareSurFup cohort, a history of chest radiotherapy was reported by only 38% of our MBC cases (6 / 16).

In recent years, chemotherapeutic agents used in childhood cancer protocols have been associated with subsequent female breast cancer risk, in particular anthracyclines and possibly alkylating agents (6, 21, 55). Of note, alkylating agents strongly reduce the excess risk of female breast cancer in the context of chest radiotherapy (56, 57). Mechanistically, this observation is related to alkylating agents' gonadotoxicity, which may lead to premature ovarian insufficiency and, accordingly, minimizes female hormone exposure. Yet, direct carcinogenic effects of alkylating agents on breast tissue have been demonstrated in experimental studies. While evidence from observational studies of female cancer survivors is dominated by the risk-reducing gonadotoxic effects of alkylating agents among women treated for Hodgkin Lymphoma with chest radiotherapy (58), direct toxic effects of alkylating agents among men who did not have chest radiotherapy cannot be excluded. In our PanCareSurFup cohort, prior treatment with anthracyclines and alkylating agents was only documented for two and six SMBC patients, respectively. Of note, drug-specific information was incomplete for three SMBC cases and no cohort-wide information on type of chemotherapy was available. In summary, the collective data on male cancer survivors provided here do not allow for further investigation of this question yet.

A family history of breast cancer is a significant risk factor for developing male breast cancer in the general population (59), indicating that genetic susceptibilities may be associated with male breast cancer risk. One included case report in our systematic review presents a SMBC case who had no radiotherapy history, but was diagnosed with Cowden syndrome (48), an associated germline PTEN mutation contributing to breast cancer development (60). However, the mutation

status of the PanCareSurFup-SMBC cases was not available and none of the SMBC cases in the PanCareSurFup cohort had a known familial history of breast cancer. Additionally, BRCA1 and especially BRCA2 mutations confer a significantly increased male breast cancer risk (61). To our knowledge, none of the SMBC cases included in the case reports/series or the PanCareSurFup cohort harboured BRCA mutations; it is unclear, though, how complete this information on family cancer history and genetic testing is for the SMBC cases reported here.

Our study set-up did not allow for further evaluation of clinical aspects of SMBC. Of note, general population-based comparisons of male to female breast cancer patients reveal later stage at diagnosis as well as poorer prognosis among males (62, 63). Further research should address potential diagnostic delay, treatment approaches, and survival patterns among men affected by SMBC compared to sporadic male breast cancer, to inform future clinical practice in survivorship care.

The strengths of our study include the largest ever cohort of five-year male CCSs with comprehensive and long follow-up and, therefore also with a comparatively large number of SMBC cases compared to other studies, in view of the low expected rate of male breast cancer. In addition, our systematic review used a very comprehensive search strategy, thereby limiting the possibility of having missed eligible studies. However, as SMBC is rare, few studies focused on SMBC risk in particular, which might have caused an underreporting of SMBC. We took a rigorous approach to limit bias by including reports from which the number of SMBC could be deduced without a doubt (also when it was 0). Furthermore, because studies that did explicitly report a SIR for SMBC were those with at least one case, the overview of the SIRs likely represents an overestimation of the true spectrum of SIRs.

Limitations of our PanCareSurFup analyses are that the information on radiation field and chemotherapy agents was limited to SMBC cases. Therefore, we were not able to clearly identify treatment-related risk factors for SMBC. Even though this is the largest effort on SMBC risk in male CCSs, the power of conducting comprehensive analyses was limited.

In summary, male CCSs in the PanCareSurFup cohort have a more than 20-fold elevated risk of developing subsequent breast cancer compared to the expected risk in the general population, which was generally compatible with the results of the systematic review. However, owing to the rarity of male breast cancer, the absolute risk is low. It is important that survivors and their caregivers are aware of signs and symptoms that might be related to male breast cancer. The

International Late Effects of Childhood Cancer Guideline Harmonization Group recommends regular surveillance for female survivors treated with ≥ 10 Gy chest radiation (10). Given the low absolute risk of SMBC and the incompleteness of the relevant evidence, regular breast cancer screening for males does not seem warranted at this time. However, awareness is relevant and CCSs with symptoms that might be related to SMBC should be carefully and comprehensively examined, considering the possibility of SMBC diagnosis, to avoid a delay in detection. More studies are warranted to investigate the SMBC risk, particularly pooling of data at an international scale is of great importance to obtain sufficient power to study the relevant risk factors for this rare diagnosis.

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Supplemental material

Appendix A. Search strategy in PubMed

Search date: July 18, 2019
Number of results: 7079
Search terms/literature search:
Second tumor AND Male AND Breast AND (Radiotherapy OR Survivor/Late effects OR Follow-up Studies)

Second tumor:
Neoplasms, Radiation-Induced OR Neoplasms, Radiation Induced OR Radiation-Induced Neoplasms OR Neoplasm, Radiation-Induced OR Radiation Induced Neoplasms OR Radiation-Induced Neoplasm OR Radiation-Induced Cancer OR Cancers, Radiation-Induced OR Radiation Induced Cancer OR Radiation-Induced Cancers OR Cancer, Radiation-Induced OR Cancer, Radiation Induced OR Neoplasms, Second Primary OR Neoplasm, Second Primary OR Second Primary Neoplasm OR Metachronous Second Primary Neoplasms OR Neoplasms, Metachronous OR Second Primary Neoplasms, Metachronous OR Second Malignancy OR Malignancies, Second OR Malignancy, Second OR Second Malignancies OR Second Neoplasm OR Neoplasm, Second OR Neoplasms, Second OR Second Neoplasms OR Second Primary Neoplasms OR Metachronous Neoplasms OR Metachronous Neoplasm OR Neoplasm, Metachronous OR Neoplasms, Metachronous Second Primary OR Neoplasms, Therapy-Associated OR Neoplasm, Therapy-Associated OR Neoplasms, Therapy Associated OR Therapy-Associated Neoplasm OR Neoplasms, Treatment-Associated OR Neoplasm, Treatment-Associated OR Neoplasms, Treatment Associated OR Treatment-Associated Neoplasm OR Neoplasms, Treatment-Related OR Neoplasm, Treatment-Related OR Neoplasms, Treatment Related OR Treatment-Related Neoplasm OR Therapy-Related Neoplasms OR Therapy Related Neoplasms OR Treatment-Associated Neoplasms OR Treatment Associated Neoplasms OR Treatment-Related Neoplasms OR Treatment Related Neoplasms OR Neoplasms, Therapy-Related OR Neoplasm, Therapy-Related OR Neoplasms, Therapy Related OR Therapy-Related Neoplasm OR Therapy-Associated Neoplasms OR Therapy Associated Neoplasms OR Therapy-Associated Cancer OR Cancer, Therapy-Associated OR Cancers, Therapy-Associated OR Therapy Associated Cancer OR Therapy-Associated Cancers OR Therapy-Related Cancer OR Cancer, Therapy-Related OR Cancers, Therapy-Related OR Therapy Related Cancer OR Therapy-Related Cancers OR Treatment-Related Cancer OR Cancer, Treatment-Related OR Cancers, Treatment-Related OR Treatment Related Cancer OR Treatment-Related Cancers OR Treatment-Associated Cancer OR Cancer, Treatment-Associated OR Cancers, Treatment-Associated OR Treatment Associated Cancer OR Treatment-Associated Cancers OR Cancer, Second Primary OR Cancers, Second Primary OR Second Primary Cancer OR Second Primary Cancers OR Second Cancer OR Cancer, Second OR Cancers, Second OR Second Cancers OR Neoplasms, Radiation-Induced/etiology OR Neoplasms, Radiation-Induced/epidemiology OR Neoplasms, Radiation effects OR Neoplasms, Second Primary/epidemiology[Mesh] OR Neoplasms, Second Primary/etiology[Mesh] OR Radiotherapy/adverse effects[Mesh] OR Radiotherapy/complications[Mesh] OR second primary malignancy OR second primary malignancies OR second malignant neoplasm OR second malignant neoplasms OR SMN OR second neoplasm OR second neoplasms OR secondary breast cancer OR subsequent malignant neoplasm OR subsequent malignant neoplasms OR subsequent neoplasm OR subsequent neoplasms OR second malignancy OR new malignancy OR new malignancies

Male:
male[tiab] OR males OR boy OR boys OR boyfriend OR boyhood

Breast:
breast

Radiotherapy:
radiometry OR radiometr* OR radiation dosage OR radiation dosage* OR radiation dose OR radiation doses OR radiation dosis OR radiation dosimetry OR radiation dosimetr* OR radiotherapy dosage OR radiotherapy[sh] OR irradiation dose OR radiotherapy dose OR dose calculation OR near beam dose OR in beam dose OR outside beam dose OR out of beam dose OR radiation/epidemiology OR Radiation monitoring OR Organs at risk OR radiation effects[sh] OR radiation injury OR radiation injuries OR radiation OR radiation* OR radiations OR Radiotherapy OR NCTP OR normal tissue complication probability OR DVH OR Dose Volume Histogram OR Radiotherapy Planning OR Conformal/adverse effects OR Dose Response Relationship, radiation OR Radiation Injuries/Prevention and Control OR Chemoradiotherapy/Adverse Effects OR radiation therapy OR irradiation OR irradiat* OR radiation syndrome OR radiation syndromes OR syndrome radiation OR radiation sickness OR radiation sicknesses OR sickness radiation

Survivors/late effects:
“late effect” OR “late effects” OR “late effect*” OR “late side effect” OR “late side effects” OR “late side effect*” OR “late adverse effect” OR “late adverse effects” OR “late adverse effect*” OR Survivor OR survivors OR Long-Term Survivors OR Long Term Survivors OR Long-Term Survivor OR Survivor, Long-Term OR Survivors, Long-Term OR survivo* OR surviving

Follow-up Studies:
Follow-up Studies

Appendix B. Risk of bias assessment criteria for observational studies

Selection bias: Was the study group representative?			
Yes/No/Unclear			
Yes if: The study group consists of more than 75% of the original cohort of male patients treated for childhood cancer	No if: The study group consists of less than 75% of the original cohort of male patients treated for childhood cancer	Unclear if: No or incomplete numbers were mentioned about the study group to enable full assessment according to these criteria	
Attrition bias: Was the follow-up adequate?			
Yes/No/Unclear			
Yes if: The outcome was assessed for more than 75% of the study group	No if: The outcome was assessed for less than 75% of the study group	Unclear if: No numbers were mentioned	
Confounding: Were the analyses adjusted for important confounding factors?			
Yes/No/Unclear/Not applicable (NA)			
Yes if: Important factors (i.e. age, co-treatment, follow-up) were taken adequately into account	No if: Important factors (i.e. age, co-treatment, follow-up) were not taken adequately into account	Unclear if: It is not mentioned if the analyses were adjusted for important factors	NA if: No risk estimation has been performed
Detection bias: Were the outcome assessors blinded for determinants related to the outcome?			
Yes/No/Unclear			
Yes if: The outcome assessors were blinded	No if: The outcome assessors were not blinded	Unclear if: It is not mentioned of the assessors were blinded	

Appendix C. Risk of bias in included observational studies

Author (year)	Selection bias: Was the study group representative?	Attrition bias: Was the follow-up adequate?	Confounding: Were the analyses adjusted for important confounding factors?	Detection bias: Were the outcome assessors blinded for determinants related to the outcome?
Demoor-Goldschmidt (2018)	Unclear	Unclear	NA	Unclear
Holmqvist (2018)	Unclear	Unclear	NA	Unclear
Reulen (2011)	Yes	Unclear	NA	Unclear
Li (1983)	Unclear	Unclear	NA	Unclear
Little (2014)	Yes	Yes	NA	Unclear
Teepen (2017)	Unclear	Yes	NA	Unclear
Beaty III (1995)	Yes	Yes	NA	Unclear
Cohen (2005)	Unclear	Unclear	NA	Unclear
Constine (2008)	Unclear	Unclear	NA	Unclear
Dottorini (1996)	Yes	Yes	NA	Unclear
Gold (2003)	Unclear	Unclear	NA	Unclear
Green (2000)	Yes	Yes	NA	Unclear
Hisada (1998)	Unclear	Unclear	NA	Unclear
Inskip (2007)	Unclear	Yes	NA	Unclear
Kushne (1988)	Unclear	Yes	NA	Unclear
MacArthur (2007)	Yes	Yes	NA	Unclear
Macklis (1991)	Unclear	Unclear	NA	Unclear
Magnani (1996)	Yes	Yes	NA	Unclear
Neglia (2001)	Unclear	Yes	NA	Unclear
Olsen (2009)	Yes	Yes	NA	Unclear
Ottaviani (2013)	Unclear	Unclear	NA	Unclear
Paulino (2000)	Yes	Yes	NA	Unclear
Paulino (2005)	Yes	Yes	NA	Unclear
Sankila (1996)	Unclear	Yes	NA	Unclear
Schellong (2004)	Yes	Yes	NA	Unclear
Strong (1987)	Unclear	Yes	NA	Unclear
Tarbell (1993)	Yes	Yes	NA	Unclear
Terracini (1987)	Unclear	Yes	NA	Unclear
Tukenova (2010)	Unclear	Yes	NA	Unclear
Wolden (1998)	Unclear	Yes	NA	Unclear
de Vathaire (1995)	Unclear	Unclear	NA	Unclear

NA = Not applicable

Appendix D. Characteristics of childhood cancer survivors in the PanCareSurFup study by type of primary cancer

Type of primary cancer	Attained age (yrs), median (range)	Follow-up time (yrs), median (range)	Primary cancer treatment (n, %)			
			CT only	RT only	RT + CT	Unknown
Leukemia	25.1 (16.8 - 34.0)	17.8 (10.5 - 27.8)	10 (0.1%)	4 (< 0.1%)	3,128 (34.9%)	5,822 (64.9%)
Hodgkin lymphoma	33.6 (25.2 - 43.2)	20.4 (11.0 - 31.5)	19 (0.5%)	435 (12.1%)	956 (26.5%)	2,193 (60.9%)
Non-Hodgkin lymphoma	31.9 (23.3 - 41.3)	22.0 (12.3 - 31.5)	39 (1.7%)	116 (5.0%)	477 (20.7%)	1,677 (72.6%)
Central nervous system tumors	29.6 (20.6 - 41.3)	20.3 (11.2 - 31.8)	1,268 (16.1%)	1,459 (18.5%)	767 (9.8%)	4,372 (55.6%)
Neuroblastoma	24.8 (15.2 - 34.8)	23.0 (12.9 - 33.2)	276 (17.1%)	100 (6.2%)	263 (16.3%)	979 (60.5%)
Retinoblastoma	32.8 (21.6 - 45.5)	31.3 (19.3 - 43.1)	246 (18.3%)	183 (13.6%)	103 (7.7%)	813 (60.4%)
Wilms' tumor	31.2 (21.0 - 40.6)	27.9 (17.6 - 37.2)	51 (2.1%)	111 (4.6%)	776 (32.4%)	1,455 (60.8%)
Bone Sarcoma	33.3 (24.1 - 44.1)	20.8 (11.2 - 31.6)	67 (3.9%)	129 (7.5%)	303 (17.5%)	1,231 (71.2%)
Soft tissue sarcoma	31.7 (22.2 - 42.8)	24.6 (13.3 - 34.6)	268 (10.6%)	142 (5.6%)	552 (21.9%)	1,563 (61.9%)
Other	31.4 (24.3 - 40.7)	18.9 (11.3 - 29.8)	453 (8.7%)	182 (3.5%)	238 (4.6%)	4,314 (83.2%)
Not in ICCC	45.4 (39.9 - 51.3)	37.9 (34.1 - 41.8)	75 (37.9%)	46 (23.2%)	54 (27.3%)	23 (11.6%)
Total	29.8 (20.9 - 39.8)	20.9 (11.7 - 31.6)	2,772 (7.3%)	2,907 (7.7%)	7,617 (20.2%)	24,442 (64.8%)

PanCareSurFup = Pan-European PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies; yrs = years; CT = chemotherapy; RT = radiotherapy; ICCC = International Classification of Childhood Cancer

CHAPTER 5

Guidance regarding COVID-19 for survivors of childhood, adolescent and young adult cancer: A statement from the International Late Effects of Childhood Cancer Guideline Harmonization Group

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Abstract

Childhood, adolescent, and young adult (CAYA) cancer survivors may be at risk for a severe course of COVID-19. Little is known about the clinical course of COVID-19 in CAYA cancer survivors, or if additional preventive measures are warranted. We established a working group within the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) to summarize existing evidence and worldwide recommendations regarding evidence about factors/conditions associated with risk for a severe course of COVID-19 in CAYA cancer survivors, and to develop a consensus statement to provide guidance for healthcare practitioners and CAYA cancer survivors regarding COVID-19.

Introduction

COVID-19 is an infectious disease caused by a coronavirus (SARS-CoV-2) that emerged in December 2019 in Wuhan, China (1). The coronavirus has spread rapidly across the globe, and on March 11, 2020, COVID-19 was declared a pandemic by the World Health Organization (WHO). The clinical presentation of COVID-19 ranges from asymptomatic to life-threatening infection requiring hospitalization and critical care (2). Emerging evidence in the general population indicates that individuals with comorbidities such as cardiopulmonary disease, diabetes and obesity, or those with advanced age have an increased risk of severe infection and death (3-6).

Long-term survival of childhood, adolescent and young adult (CAYA) cancer has improved remarkably due to advances in treatment strategies and supportive care over the past decades. Approximately 80% of children diagnosed with cancer achieve five-year survival, which has resulted in growing numbers of CAYA cancer survivors worldwide (7). Numerous studies have highlighted that CAYA cancer survivors have a higher risk of chronic health conditions such as subsequent cancers, diabetes mellitus, heart failure, and pulmonary disease (8-13), compared to the general population. There is further evidence to suggest that some survivors treated with intensive multi-modality approaches (e.g. chemotherapy plus radiation, hematopoietic stem cell transplantation) are at risk for accelerated physiological aging (14). That said, there is very little known about the incidence of COVID-19 and its clinical course in CAYA cancer survivors, or whether preventive measures are warranted above and beyond those recommended for the general population. The high burden of chronic comorbidities experienced by CAYA cancer survivors raises concern that they may be at increased risk for severe COVID-19.

Establishing a statement to guide healthcare providers (HCPs), long-term follow-up clinics, and CAYA cancer survivors about how a history of cancer may affect the course of COVID-19 is key to ensuring that survivors take optimal precautions during the current pandemic. With this in mind, we organized an international working group within the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) (15). We aimed (1) to summarize existing evidence and worldwide recommendations regarding relevant factors and conditions associated with risk for a severe course of COVID-19, and (2) to develop a consensus statement to provide guidance for HCPs and CAYA cancer survivors regarding COVID-19.

Methods

For this report, CAYA cancer survivors were defined as individuals of any age who were diagnosed with cancer before age 25 years and were at least one year following completion of primary cancer therapy.

The IGHG COVID-19 working group

IGHG is an international collaboration focused on developing widely applicable guidance for the long-term follow-up of CAYA cancer survivors. The main goal of the IGHG is to establish a common vision and integrated strategy for the surveillance of chronic health conditions in CAYA cancer survivors (15-21). The IGHG COVID-19 working group was assembled by the co-chairs of the IGHG (MH, LK), and currently consists of pediatric oncologists, late effects clinicians, supportive care specialists, infectious disease specialists, psychologists, patient representatives, and survivorship researchers from the following fifteen countries: Australia, Austria, Belgium, Canada, China, Czech Republic, France, Germany, Italy, Japan, Sweden, Switzerland, the Netherlands, the United Kingdom, and the United States. We used a stepwise approach to summarize the existing evidence and recommendations, and to develop recommendations for the IGHG COVID-19 statement.

Summary of the evidence

We defined two clinical questions: "What is the evidence on COVID-19 infections in survivors of CAYA cancer?", and "Which factors are associated with severe course among patients with confirmed/suspected COVID-19 in the general population?"

In collaboration with Cochrane Childhood Cancer, we first performed a literature search to examine the published data on COVID-19 in CAYA cancer survivors (Supplemental table S1a), and a second literature search on factors that are associated with severe course among patients with confirmed/suspected COVID-19 in the general population (Supplemental table S1b). For the first question, we planned to include all published studies. For the second question, we included studies that used multivariable analysis to evaluate factors or comorbidities associated with a severe course of disease, including: hospitalization, intensive care unit (ICU) admission, mechanical ventilation, and death. We excluded all case reports, reviews, and articles not written in English. We checked the reference lists of systematic reviews to find additional studies. The searches were performed in PubMed from December 1, 2019 and April 20, 2020. Two independent reviewers first screened titles and abstracts to identify potentially eligible articles. Two independent reviewers then screened full text articles. For all included articles, evidence tables were prepared. The evidence was organized in summary tables

and conclusions of evidence were formulated. We defined a high level of evidence as having a risk factor or comorbidity associated with a specific outcome based on multivariable analyses in three or more studies, a moderate level of evidence if this factor was identified in two studies, and a low level of evidence if only one study identified the risk factor or comorbidity (15).

Summary of existing recommendations for high risk groups for a severe course of COVID-19 in the general population

We collected information from the websites of national health institutions and the WHO about recommendations for risk factors and comorbidities associated with higher risk of a severe course of COVID-19 in the general population (Supporting information file S2). We summarized the risk factors and comorbidities associated with higher risk for a severe course of COVID-19 and identified (dis)concordances.

Development of recommendations for the IGHG COVID-19 statement

During weekly working group discussion sessions, we evaluated the results of the conclusions of evidence and summary of recommendations on risk groups for the general population, and the relevance of the identified risk factors and comorbidities in the general population for CAYA cancer survivors. Consensus was reached to designate comorbidities and risk factors that were identified in recommendations for the general population by >70% of the organizations as high risk. We extrapolated these risk factors to CAYA cancer survivors and assumed that same conditions, even when cancer treatment-related (e.g. radiation-related cardiovascular disease), may similarly increase the risk for a severe course of COVID-19 in CAYA cancer survivors. Subsequently, we formulated recommendations for measures that all CAYA cancer survivors should take to reduce the risk of infection, the additional measures that survivors at high risk should take, and what should be done if a survivor at high risk develops symptoms suggestive of COVID-19.

The websites of the national health organizations of the involved countries were consulted weekly between March 20 and May 14, 2020. New information was discussed on a weekly basis and the statement was modified accordingly.

The statement and updates are published at the IGHG website (www.ighg.org), and working group members disseminated the IGHG COVID-19 statement on the Cochrane Childhood Cancer website and to societies such as the American Society of Pediatric Hematology Oncology, the Japanese Society of Pediatric Hematology/ Oncology, the Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer, the Childhood Cancer International-Europe organization, and

the European branch of the International Society of Pediatric Oncology Europe (SIOPE) to reach as many CAYA cancer survivors as possible. The IGHG COVID-19 statement was developed in English and translated into the following languages: Chinese, Croatian, Czech, Dutch, French, German, Greek, Italian, Japanese, Polish, Portuguese, Spanish and Turkish. Translations of the latest statement are available at www.ighg.org. Additional translations will also be posted on the website as they become available.

Results

Summary of the evidence

In the systematic literature search concerning COVID-19 among cancer survivors, there were only three studies identified and none reported on the effects of COVID-19 on CAYA cancer survivors. The systematic literature search on severe course among patients with confirmed/suspected COVID-19 in the general population identified 14 studies that were included after full text review. Supporting information file S3 shows the flow chart of inclusion of articles and the summary of evidence. The conclusions of evidence from identified studies and reporting of risk factors for a severe course of disease are presented in Table 1. No studies examined risk factors or comorbidities with increased risk of hospitalization as an outcome. For ICU admission and mechanical ventilation, only low level of evidence was identified (e.g., older age, male sex, and body mass index ≥35). For mortality, high level of evidence was identified for older age and moderate evidence for male sex and heart disease. For a combined outcome (i.e. ICU admission, mechanical ventilation, and mortality) moderate level of evidence was identified for older age, hypertension, diabetes, chronic obstructive pulmonary disease, and malignancies.

Summary of existing recommendations for high-risk groups for a severe course of COVID-19 in the general population

Sixteen conditions have been reported to be associated with a higher risk of a severe course of COVID-19 in the general population (Table 2 and Supplemental table S4). Among these, older age, endocrine disease, heart disease, lung disease, oncologic disease, immune disorders or organ transplantation were mentioned by more than 70% of the organizations.

Development of recommendations for the IGHG COVID-19 statement

The IGHG statement advises that all CAYA cancer survivors adhere to their local and/or national authorities' recommendations for the general population regarding social distancing, frequent handwashing, and wearing masks in specific situations.

Based on the recommendations of (inter)national organizations, we concluded that survivors who have the following characteristics or comorbidities may be at increased risk for a severe course of COVID-19: (1) age ≥60 years; (2) cardiovascular disease (e.g., following anthracycline therapy and/or chest radiation); (3) chronic lung disorders (e.g., following chest radiation); (4) diabetes (e.g., following radiation to abdomen or pancreas); and (5) conditions or active treatments that affect the immune system (e.g., CAYA cancer survivors undergoing treatment for new adult-onset cancer, history of organ transplantation, chronic graft versus host disease). Original studies supported this conclusion, with evidence that these conditions have an increased risk of a severe course of COVID-19 in the general population. For these high-risk survivors, we recommend additional precautionary measures to reduce risk of COVID-19 exposure/infection in the workplace or home (see fig. 1 for the v3.0 IGHG COVID-19 statement). Moreover, survivors who develop symptoms consistent with COVID-19 or those who test positive for COVID-19 are advised to seek medical advice early and alert HCPs about their cancer history and other health conditions that may increase their risk for a severe course of disease.

Recognizing that the impact of the pandemic extends beyond physical health, IGHG also provides guidance about measures to take to cope with stress, anxiety, and the emotional effects of COVID-19 and refers survivors to local mental health services.

The IGHG COVID-19 statement has been updated each time new information has emerged (Supplemental figure S5: Version 1.0, Supplemental figure S6: version 2.0, Fig. 1: current version 3.0). The latest version is posted at www.ighg.org, and is available in 14 languages. As of July 1, 2020 the website has been viewed 9024 times since April 6, 2020.

Table 1. Conclusions of identified evidence for comorbidities and risk factors associated with increased risk for severe course of disease in the general population based on a systematic search (see for complete Table of all risk factors and outcomes Supporting information file S3)

What are risk factors or comorbidities with increased risk of hospitalization?		
	Studies	**Level of evidence**
	No studies	No evidence
What are risk factors or comorbidities with increased risk of ICU admission?		
	Studies	**Level of evidence**
Increased risk of *older age* vs. younger age	Reported in 1 study [25]	Low
No significant effect of *male* vs. female	Reported in 1 study [25]	Low
No significant effect of any comorbidity vs. no comorbidity	Reported in 1 study [25]	Low
What are risk factors or comorbidities with increased risk of mechanical ventilation?		
	Evidence	**Level of evidence**
No significant effect of older age vs. younger age	Reported in 1 study [4]	Low
Increased risk of *male* vs. female	Reported in 1 study [4]	Low
No significant effect of BMI 25-35 vs. <25	Reported in 1 study [4]	Low
Increased risk of *BMI≥35* vs. <25	Reported in 1 study [4]	Low
No significant effect of hypertension vs no hypertension	Reported in 1 study [4]	Low
No significant effect of diabetes vs. no diabetes	Reported in 1 study [4]	Low
What are risk factors or comorbidities with increased risk of mortality?		
	Studies	**Level of evidence**
Increased risk of *older age* vs. younger age	Reported in 7 studies [6, 26-31] out of 8 (1 study reported no significant result [32])	High
Increased risk of *male* vs. female	Reported in 2 studies [30, 33] out of 6 (4 studies reported no significant results [6, 26, 27, 32])	Moderate
Increased risk of *heart disease* vs no heart disease	Reported in 2 studies [26, 29] out of 5 (3 studies reported no significant result [6, 31, 32])	Moderate
Increased risk of *hypertension* vs no hypertension	Reported in 1 study with univariable analyses [6] out of 5 (4 studies reported no significant results [26, 28, 31, 32])	Low
Increased risk of *cerebrovascular disease* vs. no cerebrovascular disease	Reported in 1 study [29] out of 3 (2 studies reported no significant results [26, 28])	Low
Increased risk of *diabetes* vs. no diabetes	Reported in 1 study with univariable analyses [6] out of 4 (3 studies reported no significant results [26, 31, 32])	Low

Table 1. Conclusions of identified evidence for comorbidities and risk factors associated with increased risk for severe course of disease in the general population based on a systematic search (see for complete Table of all risk factors and outcomes Supporting information file S3) (continued)

Increased risk of *COPD* vs. no COPD	Reported in 1 study [26] out of 3 (2 studies reported no significant results [6, 32])	Low
No significant effect of malignancy vs. no malignancy	Reported in 1 study with univariable analyses [26]	Low
Increased risk of smoking vs. no smoking	Reported in 1 study with univariable analyses [6]	Low
No significant effect of liver disease vs. no liver disease	Reported in 1 study with univariable analyses [26]	Low
No significant effect of any comorbidity vs. no comorbidity	Reported in 2 studies [27, 33]	Moderate
No significant effect of kidney disease vs. no kidney disease	Reported in 1 study with univariable analyses [26]	Low
No significant effect of autoimmune disease vs. no autoimmune disease	Reported in 1 study with univariable analyses [26]	Low
What are risk factors or comorbidities with increased risk of combined outcome severe events including hospitalization, ICU admission, mechanical ventilation and/or mortality?		
	Studies	**Level of evidence**
Increased risk of *older age* vs. younger age	Reported in 2 studies [3, 34] out of 3 (1 study reported no significant results [25])	Moderate
Increased risk of *male* vs. female	Reported in 1 study [34] out of 2 (1 study reported not significant results [35])	Low
Increased risk of *hypertension* vs no hypertension	Reported in 2 studies [3, 34]	Moderate
Increased risk of *diabetes* vs. no diabetes	Reported in 2 studies [3, 34]	Moderate
Increased risk of *COPD* vs. no COPD	Reported in 2 studies [3, 34]	Moderate
Increased risk of malignancy vs. no malignancy	Reported in 2 studies [3, 34]	Moderate
Increased risk of last antitumor treatment ≤14 days vs. last antitumor treatment ≥14 days	Reported in 1 study [35]	Low
Increased risk of smoking vs. no smoking	Reported in 1 study [3]	Low
Increased risk of any comorbidity vs. no comorbidity	Reported in 1 study [3]	Low

Abbreviations: BMI = body mass index; COPD = Chronic obstructive pulmonary disease; ICU = intensive care unit

Table 2. Conclusions for comorbidities and risk factors associated with increased risk for severe course of disease in the general population according to recommendations in 15 national health organizations and the WHO*

Comorbidity or Risk factor associated with increased risk for severe course of disease of COVID-19	Number of organizations that mentioned this risk factor
Older age	16 *
Endocrine disease	14 *
Heart disease	14 *
Lung disease	14 *
Oncologic disease	13 *
Immune disorders or organ transplantation	11 *
Kidney disease	10
High blood pressure	9
Liver disease	8
Pregnancy	6
Overweight	6
Neurological condition	5
Hematological (blood) disease	4
Problems with the spleen	3
Smoking	3
Males	1

*The following 15 countries and the WHO are involved: Australia, Austria, Belgium, Canada, China, Czech Republic, France, Germany, Italy, Japan, Sweden, Switzerland, the Netherlands, the United Kingdom, and the United States. Selected comorbidity or risk factor for the high risk group of survivors for a severe course of disease of COVID-19 because more than 70% of the organization mentioned these factors as comorbidity or risk factor associated with increased risk for severe course of disease of COVID-19.

Figure 1 IGHG statement for COVID-19 V3.0 14 May 2020 (Updated v1.0 published 7 April 2020)

IGHG Statement COVID-19 v3.0 14 May 2020 (Updated v1.0 published 7 April 2020) for survivors of childhood, adolescent and young adult cancer

The IGHG and Cochrane Childhood Cancer are carefully monitoring the rapidly emerging medical information about COVID-19 and will update this guidance as new information becomes available. See www.ighg.org for future updates of this statement.

Purpose

The purpose of this statement is to provide guidance to childhood, adolescent and young adult cancer survivors related to risk and additional preventive measures for Coronavirus Disease 2019 (COVID-19). For this guidance, childhood, adolescent and young adult (CAYA) cancer survivors are defined as individuals of any age who were diagnosed with cancer before age 25 years and are at least one year following completion of primary cancer therapy.

Knowledge

Survivors, their caregivers, and health care providers should be mindful that the risk and course of COVID-19 in childhood, adolescent and young adult cancer survivors is not currently known. Thus, the information provided in this guidance is largely extrapolated from medical information from national health services and the World Health Organization (WHO) about COVID-19 in the general population.

Recommendation 1

Who is at higher risk?

Based on medical information about COVID-19 in the general population, cancer survivors with the specific health conditions below may have a higher risk for a severe course of COVID-19, especially if they have more than one of these conditions.

In addition to these comorbid conditions, a more severe course has been observed in older individuals, especially those 60 years of age or older, which may be because older individuals are more likely to have the chronic health conditions listed in the table. Individuals with conditions and/or use of drugs that affect immune system function may also be at risk for a more severe course of COVID-19 because of their overall higher risk of infection.

Conditions[1] most frequently identified by national health services and WHO to increase risk for a severe course of COVID-19	Examples of cancer treatment-related conditions that may increase a CAYA cancer survivor's risk for a severe course of COVID-19
Heart disease, including but not limited to: • Heart failure requiring medication • History of myocardial infarction (heart attack)	Heart disease, including but not limited to: • Cardiomyopathy (heart muscle disease) following anthracycline therapy • Coronary artery disease following chest radiation
Chronic lung disorders, including but not limited to: • Chronic obstructive pulmonary disease (COPD) • Severe asthma • Any lung disease causing chronic shortness of breath, difficulty breathing or requiring oxygen therapy	Chronic lung disorders, including but not limited to: • Lung fibrosis (scarring) following bleomycin or chest radiation • Chronic lung disease after bone marrow transplant
Diabetes	Diabetes following radiation to abdomen or pancreas
Conditions and/or use of drugs that affect immune system function, including but not limited to: • Anticancer treatment • Organ transplantation • Immune disorders	Conditions and/or use of drugs that affect immune system function, including but not limited to: • Ongoing treatment for a new or recurrent adult-onset cancer • History of organ transplant because of cancer or damage from cancer treatment (for heart, kidney or liver) • Chronic graft versus host disease

[1] *The following conditions/factors, which have been reported to increase risk for a severe course of COVID-19, were less frequently mentioned by national health services or medical reports: kidney disease, hypertension, liver disease, obesity, pregnancy, blood disorders, neurological dysfunction, asplenia, hyposplenia, high BMI, male sex, and use of ACE inhibitors or ibuprofen. The IGHG and Cochrane Childhood Cancer will monitor the medical literature about all of these conditions/factors and revise recommendations as new information becomes available.*
The higher risk of secondary bacterial infections should be considered for survivors with asplenia and hyposplenia.

Cochrane Childhood Cancer | International Guideline Harmonization Group for Late Effects of Childhood Cancer | IGHG COVID-19 Statement v 3.0 14 May 2020

Discussion

The IGHG COVID-19 working group developed harmonized COVID-19 recommendations for CAYA cancer survivors within a relatively short period of time, through an internationally collaborative approach that utilized methods that balanced the paucity of information regarding the incidence and clinical course of COVID-19 in CAYA cancer survivors with the rapidly emerging need for guidance within the survivorship community and beyond. Information was then disseminated to the public through the IGHG website and a variety of national/institutional pediatric cancer forums. This effort was facilitated by the existing IGHG collaborative platform, and the recognition by its members of the urgent need to summarize existing knowledge during a time of great uncertainty. Because evidence about the course of COVID-19 in CAYA cancer survivors was lacking, we extrapolated knowledge from evidence on risk factors for a severe course of COVID-19 in the general population, as well as recommendations from national health organizations and the WHO about relevant risk factors and comorbidities associated with a severe course of COVID-19 in the general population to CAYA cancer survivors. As shown in Table 1, the evidence for risk factors for a severe outcome in the general population was also very limited; only older age and a higher risk of mortality were identified in three or more studies. The recommendations of the different (inter)national organizations varied substantially among the different sources (Table 2). References to original studies underpinning many of the national recommendations were often lacking, and recommendations were frequently based on expert consensus. This is likely due to the rapidly emerging nature of the pandemic and subsequent lack of large cohort studies characterizing the magnitude of risk for comorbidities and risk factors associated with a severe course of COVID-19 in either CAYA cancer survivors or the general population. The IGHG COVID-19 working group will continue to monitor the literature quarterly and update recommendations as new data emerge.

The IGHG COVID-19 working group also identified a critical knowledge gap regarding the impact of COVID-19 on CAYA cancer survivors. Registration of CAYA cancer patients and CAYA cancer survivors with COVID-19 will increase our knowledge on the clinical course of COVID-19 in these populations (22). Towards this end, registries have been organized by institutional, national and pediatric cooperative groups. Among these, the open registry established by the International Society of Pediatric Oncology and the St. Jude Children's Research Hospital provides a forum to share resources and experiences about COVID-19 and to collect data on both CAYA cancer patients receiving cancer treatment and CAYA cancer survivors across different age groups who have completed therapy (23). This registry will facilitate a global observatory where the data of CAYA cancer survivors with COVID-19 can be updated in real time.

The COVID-19 pandemic has challenged the delivery of healthcare across the world and will also have consequences for long-term follow-up services for CAYA cancer survivors. Off therapy clinical evaluations have been limited to increase availability of medical and nursing staff for frontline clinical care at many cancer centers (24). Consequently, this has resulted in deferral of elective long-term follow-up and primary care appointments for CAYA cancer survivors, who as a group represent a medically vulnerable population. At this point, the long-term impact of these disruptions for CAYA cancer survivors is unclear. To begin to address this concern, a global survey of survivorship clinics is planned to evaluate the impact of COVID-19 on long-term follow-up services and identify ongoing initiatives to facilitate CAYA cancer survivors' access to health resources and services during the current pandemic. It remains to be seen whether recent efforts to expeditiously implement novel healthcare delivery platforms such as telehealth and remote patient monitoring can adequately address healthcare access gaps created by this global pandemic.

In conclusion, the IGHG COVID-19 working group provides guidance to CAYA cancer survivors, who in many cases may have comorbid conditions linked to a high risk of a severe course of COVID-19. Our ongoing monitoring of emerging COVID-19 data and recommendations will facilitate modification of guidance relevant to the survivor population.

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23. The global COVID-19 Observatory and Resource Center for Childhood Cancer. https://global.stjude.org/en-us/global-covid-19-observatory-and-resource-center-for-childhood-cancer.html
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Supplemental material

Supplemental table S1a
Search strategy to identify studies on survivors of cancer and COVID-19 infection in PubMed

Query	Items found
Search the below combination Filters: Publication date from 2019/12/01 to 2020/04/20	3 results
Search coronavirus OR Covid* OR COVID-19 OR SARS-Cov-2 OR 2019-nCov Filters: Publication date from 2019/12/01 to 2020/04/20	6,207 results
((mortality OR death) OR (hospitalization OR hospitalisation OR ("hospital admission") OR (ICU OR ("intensive care") OR (epidemiol* OR "course" OR prognosis OR clinic*)) Filters: Publication date from 2019/12/01 to 2020/04/20	237,706 results
Cancer AND survivor Filters: Publication date from 2019/12/01 to 2020/04/20	1,545 results

Supplemental table S1b
Search strategy to identify studies on comorbidities/risk factors associated with poor outcomes among adults and children with confirmed/suspected COVID-19 in the general population in PubMed

Query	Items found
Search the below combination Filters: Publication date from 2019/12/01 to 2020/04/20	3,050 results
Search coronavirus OR Covid* OR COVID-19 OR SARS-Cov-2 OR 2019-nCov Filters: Publication date from 2019/12/01 to 2020/04/20	6,207 results
((mortality OR death) OR (hospitalization OR hospitalisation OR ("hospital admission") OR (ICU OR ("intensive care") OR (epidemiol* OR "course" OR prognosis OR clinic*)) Filters: Publication date from 2019/12/01 to 2020/04/20	237,706 results

Supporting information file S2
IGHG COVID-19 background information: Websites with information from nationwide health institutions and WHO on higher risk for severe course of disease

WHO:

- https://www.who.int/westernpacific/emergencies/covid-19/information/high-risk-groups
- https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51covid-19.pdf?sfvrsn=1ba62e57_10
- https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen
- https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answershub/q-a-detail/q-a-coronaviruses
- https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answershub/q-a-detail/q-a-on-covid-19-pregnancy-and-childbirth

1. UK:

- https://www.gov.uk/government/publications/staying-alert-and-safe-social-distancing/stayingalert-and-safe-social-distancing
- https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremelyvulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerablepersons-from-covid-19

2. US:

- https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html
- https://www.cdc.gov/cancer/survivors/staying-well-at-home.htm

3. NL:

- https://lci.rivm.nl/testbeleid-risicogroepen-covid-19https://lci.rivm.nl/testbeleid-risicogroepencovid-19

4. Swiss:

- https://www.bag.admin.ch/bag/en/home/krankheiten/ausbrueche-epidemienpandemien/aktuelle-ausbrueche-epidemien/novel-cov/selbst-isolierung-und-selbstquarantaene.html

5. China:

- http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989/files/ce3e6945832a438eaae415350a8ce964.pdf
- http://www.chinacdc.cn/jkzt/crb/zl/szkb_11803/jszl_2275/202002/t20200201_212138.html
- http://www.gov.cn/fuwu/2020-03/10/5489535/files/a3e521acbbb84e82a132c4f15b569470.pdf

6. France:

- https://solidarites-sante.gouv.fr/actualites/actualites-du-ministere/article/coronavirus-qui-sontles-personnes-fragiles

7. Japan:

- https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/dengue_fever_qa_00004.html
- https://www.j-circ.or.jp/cms/wp-content/uploads/2020/04/JCS_COVID19_QA.pdf
- https://www.jrs.or.jp/modules/information/index.php?content_id=1468, https://www.jsaweb.jp/uploads/files/新型コロナウイルス感染における気管支喘息患者への対応 Q%26A（医療従事者向け）.pdf
- http://www.jds.or.jp/modules/important/index.php?content_id=137
- https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/dengue_fever_qa_00004.html
- http://www.jca.gr.jp/public/c_q_and_a.html
- https://www.jsn.or.jp/topics/covid19/_3688.php,
- https://www.jsiad.org/covid19/
- https://www.neurology-jp.org/covid/20200330_01.html
- http://jsidog.kenkyuukai.jp/images/sys/information/20200526112133-513E115CF9950683BA78242CDEA323EB4689CB6827758DD8B5C87B341507D402.pdf
- https://www.jrs.or.jp/uploads/uploads/files/koronatotabako.pdf

8. Canada:

- https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirusinfection/prevention-risks.html

- https://www.canada.ca/en/public-health/services/publications/diseases-conditions/vulnerablepopulations-covid-19.html

9. Italy:
- https://www.epicentro.iss.it/coronavirus/
- http://www.simit.org/IT/index.xhtml
- https://www.airc.it/news/covid-19-e-malati-di-cancro-le-precauzioni-da-tenere-nelle-rispostedegli-esperti-0220

10. Czech Republic:
- https://onemocneni-aktualne.mzcr.cz/covid-19
- https://www.uzis.cz/index.php?pg=covid-19
- https://nzis-open.uzis.cz/prezentace-2020/12-jarkovsky.pdf

11. Germany:
- https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Steckbrief.html#doc13776792bodyText2
- https://www.gpoh.de/fileadmin/user_upload/STellungnahme_der_GPOH_und_der_DGPI_zu_Kindern_mit_hämatologisch-onkologischen_Erkrankungen_zu_COVID-19_Infektionen.pdf
- https://dgpi.de/sars-cov-2-und-covid-19-erkrankung-an-sars-cov-2-in-der-ambulanten-kinderund-jugendmedizin/
- https://www.infektionsschutz.de/coronavirus/verhaltensregeln.html
- https://www.infektionsschutz.de/coronavirus/fragen-und-antworten/ansteckung-undkrankheitsverlauf.html

12. Austria:
- https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Risikogruppen.html

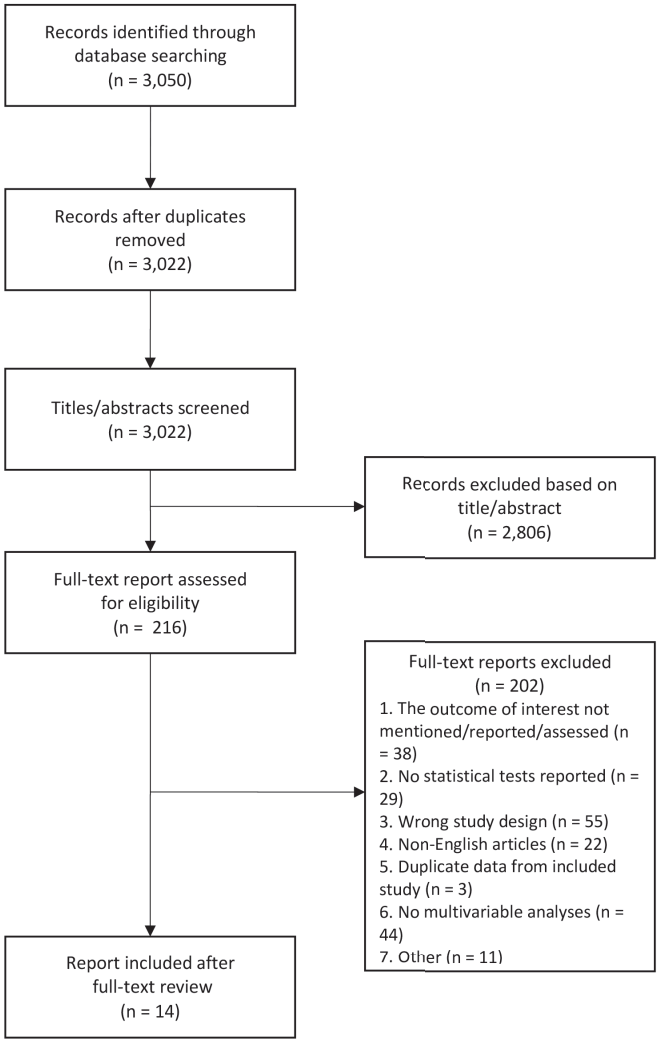
13. Australia:
- https://covid19evidence.net.au
- https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/advicefor-people-at-risk-of-coronavirus-covid-19/coronavirus-covid-19-advice-for-older-people
- https://anzchog.org/covid-19-guidance-for-children-and-young-people-undergoing-cancertreatment-2/
- https://www.asid.net.au/documents/item/1897

14. Sweden:
- https://www.folkhalsomyndigheten.se/nyheter-och-press/nyhetsarkiv/2020/april/nya-allmannarad-hall-avstand-och-ta-personligt-ansvar/
- https://www.folkhalsomyndigheten.se/publicerat-material/publikationsarkiv/h/hslf-fs-202012/
- https://www.folkhalsomyndigheten.se/smittskydd-beredskap/utbrott/aktuella-utbrott/covid19/fragor-och-svar/

15. Belgium:
- https://www.info-coronavirus.be
- https://www.kanker.be/coronavirus
- https://bpidg.be/nl/covid19-richtlijnen/

Supporting information file S3

Flow chart of inclusion of articles from the search on factors associated with poor outcomes in the general population



Summary of the evidence[#]

Comorbidity/Risk factors	Outcomes	Details	Risk
Age	**ICU admission**	Unclear (older age)	**OR 1.06 (95% CI 1.00-1.12)**
	Mechanical ventilation	Per yr	OR 1.00 (95% CI 0.97-1.04)
	Mortality	≥65 yr vs. <65 yr	**HR 1.72 (95% CI 1.09-2.73)**
		≥75 yr vs. <65 yr	**HR 7.86 (95% CI 2.44-25.35)**
		65-74 yr vs. <65 yr	**HR 3.43 (95% CI 1.24-9.5)**
		Per yr	**OR 1.10 (95% CI 1.03-1.17)**
		Not specified	**HR 1.06 (95% CI 1.03-1.10)**
		Per 10 yr	HR 1.18 (95% CI 0.72-1.92)
		Not specified	**OR 1.03 (95% CI 1.01-1.06)**
		≥ 65 yr vs. <65 yr	**OR 3.77 (95% CI 1.15-17.39)**
		≥75 yr vs. <75 yr	**HR 6.07 (95% CI 1.65-22.35)**
	Combined outcome severe events*	>65 vs <=65	HR 1.46 (95% CI 0.48-4.43)
		Per yr	**HR 1.04 (95% CI 1.02-1.05)**
		Per yr	**OR 1.05 (95% CI 1.03-1.06)**
Sex	**ICU admission**	Male vs. female	OR 3.38 (95% CI 0.77-14.9)
	Mechanical ventilation	Male vs. female	**OR 2.83 (95% CI 1.02-7.85)**
	Combined outcome severe events*	Male vs female	HR 0.57 (95% CI 0.16-2.04)
		Female vs. male	**OR 0.61 (95% CI 0.41-0.92)**
	Mortality	Male vs. female	**HR 1.72 (95% CI 1.05-2.82)**
		Female vs. Male	HR 1.08 (95% CI 0.33-3.52)
		Not specified	OR 0.68 (95% CI 0.43-1.08)
		Male vs. female	**OR 13.8 (95% CI 1.41-136.1)**

Adjustment	Additional information	Article
Adjusted for sex and comorbidity		J. Chen (2020)
Adjusted for sex, diabetes, hypertension, dyslipidemia, BMI		A. Simonnet (2020)
Adjusted for sex, blood leukocyte count, lactose dehydrogenase, cardiac injury, hyperglycemia, and administration of corticosteroids, lopinavir/ritonavir, and umifenovir		X. Li (2020)
The model adjustments were not specifically mentioned in the article. We assumed all the variables in the model were adjusted, including age, CHD, CVD, dyspnea, PCT, AST, TBIL, creatinine.		R. Chen (2020)
Adjusted for lymphocyte count, d-dimer, SOFA score (Sequential Organ Failure Assessment), coronary heart disease		F. Zhou (2020)
Adjusted for cardiovascular disease, cerebrovascular disease, COPD	No definition provided	L. Wang (2020)
Adjusted for NT-proBNP and sex		L. Gao (2020)
Adjusted for sex and presence of underlying disease	No definition provided	N. Tang (2020)
Adjusted for hypertension, cardiovascular or cerebrovascular diseases, dyspnea, fatigue, sputum production, headache, white blood cell counts, neutrophils, CD3+CD8+ T cells, cardiac troponin I, myoglobin, creatinine, D-dimer, PaO2		R. Du (2020)
The article didn't mention the specific adjustments of the model. Thus, all variables in the table were assumed as adjustments, including age, lymphocyte count, D-dimer, creatine kinase, LDH, hypertension, cardiovascular disease, and diabetes		Y. Feng (2020)
Adjusted for sex, receiving last antitumour treatment ≤14 days, and patchy consolidation on CT on admission		L. Zhang (2020)
Adjusted for smoking status		W. Guan (2020)
Adjusted for other risk factors, including smoking history, and other comorbidities		W. Liang (2020)
Adjusted for age and comorbidity		J. Chen (2020)
Adjusted for age, diabetes, hypertension, dyslipidemia, BMI		A. Simonnet (2020)
Adjusted for age, receiving last antitumour treatment ≤14 days, and patchy consolidation on CT on admission		L. Zhang (2020)
Adjusted for other risk factors, including age, smoking history, and other comorbidities		W. Liang (2020)
Adjusted for age, blood leukocyte count, lactose dehydrogenase, cardiac injury, hyperglycemia, and administration of corticosteroids, lopinavir/ritonavir, and umifenovir.		X. Li (2020)
Adjusted for NT-proBNP and age		L. Gao (2020)
Adjusted for age and presence of underlying disease		N. Tang (2020)
Adjusted for breath shortness, time from illness to first hospital admission and blood tests		T. Chen (2020)

Summary of the evidence[#] (continued)

Comorbidity/Risk factors	Outcomes	Details	Risk
Sex	**Mortality**	Not included in multivariable analysis, the following association was found with in-hospital death on univariable analysis: Female sex	OR 0.61 (95% CI 0.31-1.20)
		Not included in multivariable analysis, the following association was found in univariate Cox regression analysis of risk factors associated with fatality: Female Gender	HR 0.61 (p = 0.053)
BMI	**Mechanical ventilation**	BMI 25-30 kg/m2 vs. <25 kg/m2	OR 1.69 (95% CI 0.52-5.48)
		BMI 30-35 vs. <25	OR 3.45 (95% CI 0.83-14.31)
		BMI ≥35 vs. <25	**OR 7.36 (95% CI 1.63-33.14)**
Heart disease	**Mortality**	Coronary heart disease, yes vs. no	**HR 4.28 (95% CI 1.14-16.13)**
		Coronary heart disease, yes vs. no	OR 2.14 (95% CI 0.26-17.79)
		Cardiovascular disease, yes vs. no	**HR 1.86 (95% CI 1.06-3.26)**
		Coronary heart disease, yes vs. no	HR 1.22 (95% CI 0.42-3.52)
		Cardiovascular disease, yes vs. no	HR 0.59 (95% CI 0.1-3.63)
		Cardiovascular or cerebrovascular disease, yes vs. no	OR 2.46 (95% CI 0.76-8.04)
Cerebrovascular disease	**Mortality**	Yes vs. no	**HR 3.10 (95% CI 1.07-8.94)**
		Yes vs. no	HR 1.38 (95% CI 0.65-2.93)
		Cardiovascular or cerebrovascular disease, yes vs. no	OR 2.46 (95% CI 0.76-8.04)
Hypertension	**Mechanical ventilation**	Yes vs. no	OR 2.29 (95% CI 0.89-5.84)
	Mortality	Yes vs. no	HR 1.61 (95% CI 0.59-4.41)
		Yes vs. no	Not significant; no results reported

Adjustment	Additional information	Article
		F. Zhou (2020)
		L. Wang (2020)
Adjusted for age, sex, diabetes, hypertension, dyslipidemia		A. Simonnet (2020)
The model adjustments were not specifically mentioned in the article. We assumed all the variables in the model were adjusted, including age, CHD, CVD, dyspnea, PCT, AST, TBIL, creatinine.	No further definition provided	R. Chen (2020)
Adjusted for lymphocyte count, d-dimer, SOFA score (Sequential Organ Failure Assessment), and age	No further definition provided	F. Zhou (2020)
Adjusted for age, cerebrovascular disease, COPD	No further definition provided	L. Wang (2020)
Adjusted for NT-proBNP and hypertension	No further definition provided	L. Gao (2020)
The article didn't mention the specific adjustments of the model. Thus, all variables in the table were assumed as adjustments, including age, lymphocyte count, D-dimer, creatine kinase, LDH, hypertension, cardiovascular disease, and diabetes	No further definition provided	Y. Feng (2020)
Adjusted for age, hypertension, dyspnea, fatigue, sputum production, headache, white blood cell counts, neutrophils, CD3+CD8+ T cells, cardiac troponin I, myoglobin, creatinine, D-dimer, PaO2	No further definition provided	R. Du (2020)
The model adjustments were not specifically mentioned in the article. We assumed all the variables in the model were adjusted, including age, CHD, CVD, Dyspnea, PCT, AST, TBIL, Creatinine.	No further definition provided	R. Chen (2020)
Adjusted for age, Cardiovascular disease, COPD	No further definition provided	L. Wang (2020)
Adjusted for age, hypertension, dyspnea, fatigue, sputum production, headache, white blood cell counts, neutrophils, CD3+CD8+ T cells, cardiac troponin I, myoglobin, creatinine, D-dimer, PaO2	No further definition provided	R. Du (2020)
Adjusted for age, sex, diabetes, BMI, dyslipidemia		A. Simonnet (2020)
Adjusted for NT-proBNP and coronary heart disease		L. Gao (2020)
Adjusted for age, hypertension, cardiovascular or cerebrovascular diseases, dyspnea, fatigue, sputum production, headache, white blood cell counts, neutrophils, CD3+CD8+ T cells, cardiac troponin I, myoglobin, creatinine, D-dimer, PaO2		R. Du (2020)

Summary of the evidence# (continued)

Comorbidity/Risk factors	Outcomes	Details	Risk
Hypertension	**Mortality**	Yes vs. no	HR 1.56 (95% CI 0.42-5.83)
		Not included in multivariable analysis, the following association was found with in-hospital death on univariable analysis	**OR 3.05, (95% CI 1.57-5.92)**
		Not included in multivariable analysis, the following association was found in univariate Cox regression analysis of risk factors associated with fatality: Hypertension	HR 1.49 (p = 0.109)
	Combined outcome severe events*	Yes vs. no	**HR 1.58 (95% CI 1.07-2.32)**
		Yes vs. no	**OR 1.88 (95% CI 1.22-2.90)**
Diabetes	**Mechanical ventilation**	Yes vs. no	OR 1.60 (95% CI 0.44-5.83)
	Mortality	Yes vs. no	HR 1.68 (95% CI 0.34-8.16)
		Not included in multivariable analysis, the following association was found with in-hospital death on univariable analysis	**OR 2.85 (95% CI 1.35-6.05)**
		Not included in multivariable analysis, the following association was found in univariate Cox regression analysis of risk factors associated with fatality: Diabetes	HR 1.08 (p = 0.799)
		Not included in multivariable analyses univariate Cox proportional-hazards regression analyzing the effect of baseline variables on in-hospital death showed the following association: History of DM no vs yes	HR 0.96 (95%CI 0.28-3.31)
	Combined outcome severe events*	Yes vs. no	**HR 1.59 (95% CI 1.03-2.45)**
		Yes vs. no	**OR 2.21 (95% CI 1.33-3.66)**

Adjustment	Additional information	Article
The article didn't mention the specific adjustments of the model. Thus, all variables in the table were assumed as adjustments, including age, lymphocyte count, D-dimer, creatine kinase, LDH, hypertension, cardiovascular disease, and diabetes		Y. Feng (2020)
		F. Zhou (2020)
		L. Wang (2020)
Adjusted for age and smoking status		W. Guan (2020)
Adjusted for other risk factors, including age, smoking history, and other comorbidities		W. Liang (2020)
Adjusted for age, sex, hypertension, dyslipidemia, BMI		A. Simonnet (2020)
The article didn't mention the specific adjustments of the model. Thus, all variables in the table were assumed as adjustments, including age, lymphocyte count, D-dimer, creatine kinase, LDH, hypertension, cardiovascular disease, and diabetes		Y. Feng (2020)
		F. Zhou (2020)
		L. Wang (2020)
		L. Gao (2020)
Adjusted for age and smoking status		W. Guan (2020)
Adjusted for other risk factors, including age, smoking history, and other comorbidities		W. Liang (2020)

Summary of the evidence# (continued)

Comorbidity/Risk factors	Outcomes	Details	Risk
COPD	**Mortality**	Yes vs. no	**HR 2.24 (95% CI 1.12-4.50)**
		Not included in multivariable analysis, the following association was found with in-hospital death on univariable analysis	OR 5.40 (95% CI 0.96-30.40)
		Not included in multivariable analysis, the following association was found with in-hospital death on univariable analysis	HR 4.13 (95%CI 0.95-18.02)
	Combined outcome severe events*	Yes vs. no	**HR 2.68 (95% CI 1.42-5.05)**
		Yes vs. no	**OR 3.40 (95% CI 1.37-8.41)**
Malignancy	**Combined outcome severe events***	Yes vs. no	**HR 3.50 (95% CI 1.60-7.64)**
		Yes vs. no	**HR 3.56 (95% CI 1.65-7.69)**
			OR 5.34 (95% CI 1.80-16.18)
	Mortality	Not included in multivariable analysis, the following association was found in univariate Cox regression analysis of risk factors associated with fatality: Malignancy	HR 0.98 (p = 0.976)
Comorbidity	**ICU admission**	Yes vs. no	OR 1.83 (95% CI 0.50-6.75)
	Mortality	Yes vs. no	**OR 16.1 (95% CI 1.9-133.8)**
		Yes vs. no	OR 0.86 (95% CI 0.54-1.38)

Adjustment	Additional information	Article
Adjusted for age, cardiovascular disease, cerebrovascular disease		L. Wang (2020) F. Zhou (2020) L. Gao (2020)
Adjusted for age and smoking status		W. Guan (2020)
Adjusted for other risk factors, including age, smoking history, and other comorbidities		W. Liang (2020)
Adjusted for age and smoking status		W. Guan (2020)
Adjusted for age		W. Liang (2020)
Adjusted for other risk factors, including age, smoking history, and other comorbidities		L. Wang (2020)
Adjusted for age and sex	Including cardiovascular and cerebrovascular diseases (21.7%,) endocrine system diseases (10.0%), digestive system diseases (3.6%), respiratory system diseases (2.0%), chronic hepatitis B virus infection (0.8%), malignant tumor (0.4%)	J. Chen (2020)
Adjusted for breath shortness, time from illness to first hospital admission and blood tests	Comorbidities include hypertension, diabetes, cardiovascular disease, cerebrovascular disease, malignancy, chronic liver disease, chronic renal disease, COPD, tuberculosis, HIV	T. Chen (2020)
Adjusted for age and sex		N. Tang (2020)

Summary of the evidence# (continued)

Comorbidity/Risk factors	Outcomes	Details	Risk
Comorbidity	**Combined outcome severe events***	Patients with 1 comorbidity, vs. none	**HR 1.79 (95% CI 1.16-2.77)**
		Patients with 2 or more comorbidities, vs. none	**HR 2.59 (95% CI 1.61-4.17)**
Last antitumour treatment ≤14 days	**Combined outcome severe events***	<=14 days vs > 14 days	**HR 4.08 (95% CI 1.09 -15.32)**
Smoking	**Combined outcome severe events***	Yes vs. no	**HR 1.67 (95% CI 1.01-2.76)**
	Mortality	Not included in multivariable analysis, the following association was found with in-hospital death on univariable analysis: Current smoker	**OR 2.23 (95% CI 0.65-7.63)**
Liver disease	**Mortality**	Not included in multivariable analysis, the following association was found in univariate Cox regression analysis of risk factors associated with fatality: Chronic liver disease	HR 2.90 (p = 0.291)
Chronic renal disease	**Mortality**	Not included in multivariable analysis, the following association was found in univariate Cox regression analysis of risk factors associated with fatality	HR 1.73 (p = 0.289)
Autoimmune disease	**Mortality**	Not included in multivariable analysis, the following association was found in univariate Cox regression analysis of risk factors associated with fatality	HR 1.10 (p = 0.927)

* Combined outcome severe events defined as a condition requiring admission to an intensive care unit, the use of mechanical ventilation, or death
# Abbreviations: BMI = body mass index; CHD = coronary heart disease; CVD = cerebrovascular disease; PCT = procalcitonin; AST = aspartate aminotransferase; TBIL = total bilirubin; COPD = chronic obstructive pulmonary disease; NT-proBNP = N-terminal pro-brain natriuretic peptide; CT = computed tomography; ICU = intensive care unit
^ Risks in bold indicate significant results

Adjustment	Additional information	Article
Adjusted for age and smoking status	Comorbidities defined as COPD, diabetes, hypertension, cardiovascular disease, cerebrovascular disease, hepatitis B infection, malignancy, chronic kidney disease, immunodeficiency	W. Guan (2020)
Adjusted for age, sex and patchy consolidation on CT on admission		L. Zhang (2020)
Adjusted for age		W. Guan (2020)
		F. Zhou (2020)
		L. Wang (2020)
		L. Wang (2020)
		L. Wang (2020)

Supplemental table S4
Comorbidities and risk factors associated with increased risk for severe course of disease according to 15 national health organizations and the WHO*

	Comorbidity/Risk factor associated with increased risk for severe course of disease of COVID-19	Countries/WHO
Age	50+ years	DE, AT
	60+ years	WHO, CZ
	65+ years	US, CN, CAN, BE
	70+ years	UK, NL, IT, FR, SE, AUS
	People who live in a nursing home or long-term care facility.	US, AT
	People aged 65+ years with chronic medical conditions People with compromised immune systems, and Aboriginal and Torres Strait Islander people over the age of 50	AUS
	Older age	CN, JP, AT
Weight	Being seriously overweight	UK, US, FR, NL, IT, CZ
	- In particular in patients younger 40 year	IT
	- a body mass index (BMI) of 40 or above	UK, US, FR, NL
Sex	Male sex	IT
Cardiovascular disease	Chronic heart disease	UK, CZ, AT, BE, IT, WHO, DE, SE
	Atrial fibrillation	IT
	Ischemic heart disease	IT, FR
	Heart surgery or heart failure	FR
	Under treatment of a cardiologist because of the severity of disease	NL
	Heart disease with complications	AT
	People who have serious heart conditions	US
	Cardiovascular disease	CN, DE, AT, AUS
	Heart disease with immunocompromised state (post-transplantation etc), on chemotherapy of radiation therapy for cancer, complicated with leukemia or lymphoma, older age, hypokinesia due to aging, pregnant women, heart failure, dilated cardiomyopathy, progressive arrhythmogenic right ventricular cardiomyopathy, cyanotic congenital heart disease, obstructive hypertrophic cardiomyopathy	JP
Blood pressure	High blood pressure	CN, WHO, IT, JP, CZ, DE, AT, SE
	Complicated high blood pressure	FR

Supplemental table S4
Comorbidities and risk factors associated with increased risk for severe course of disease according to 15 national health organizations and the WHO* (continued)

	Comorbidity/Risk factor associated with increased risk for severe course of disease of COVID-19	Countries/WHO
Lung disease	Chronic (long-term) respiratory diseases, such as asthma, chronic obstructive pulmonary disease (COPD), emphysema or bronchitis	UK, US, CN, IT, CZ, DE, AUS, WHO, AT, SE
	Extremely vulnerable: people with severe respiratory conditions including all cystic fibrosis, severe asthma and severe COPD	UK
	Abnormalities and dysfunctions of the respiratory tract and lungs	BE
	Chronic abnormalities and dysfunctions of the respiratory tract and lungs under treatment of a lung specialist because of the severity of disease	NL
	A chronic respiratory condition that may decompensate in the event of a viral infection	FR
	Respiratory disease (interstitial pneumonia, asthma) Long-term Steroid use	JP
	Maybe: Asthma	US, JP
Endocrine disease	Diabetes	UK, CN, WHO, IT, CZ, AT, AUS, BE, US, JP, DE, SE
	(Insulin-dependent) diabetics who are not well controlled or have complications	FR, NL
Oncologic disease	Extremely vulnerable individuals include those: • undergoing active chemotherapy or radical radiotherapy for lung cancer • with cancers of the blood or bone marrow such as leukaemia, lymphoma or myeloma who are at any stage of treatment • receiving immunotherapy or other continuing antibody treatments for cancer • receiving other targeted cancer treatments which can affect the immune system, such as protein kinase inhibitors or PARP inhibitors • treated with a bone marrow or stem cell transplant in the last 6 months, or who are still taking immunosuppression drugs	UK
	Cancer	CN, WHO, DE, AT, AUS
	History of active disease (cancer) in the previous 5 years	IT
	Cancer patients undergoing treatment	FR, BE, CZ
	In case of active treatment or < 3 months after finishing chemotherapy and / or radiation therapy	NL
	Children at increased risk include those: • receiving chemotherapy or radiotherapy, • treated with a bone marrow transplant within the past 12 months, • receiving active treatment for GVHD • who have heart or lung problems as a result of their cancer treatment are at some increased risk of more severe infection	AUS
	Cancer or those undergoing active treatment may be at risk	JP, SE

Supplemental table S4
Comorbidities and risk factors associated with increased risk for severe course of disease according to 15 national health organizations and the WHO* (continued)

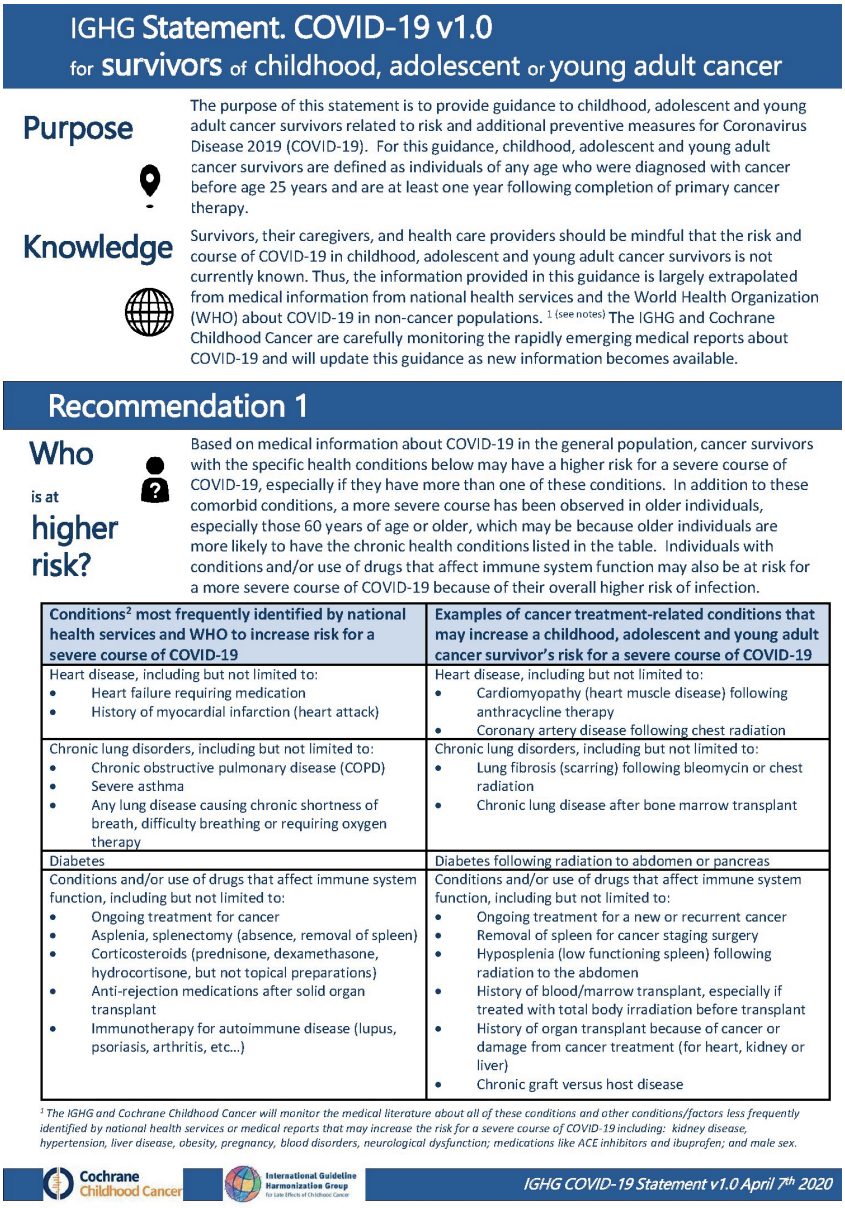
	Comorbidity/Risk factor associated with increased risk for severe course of disease of COVID-19	Countries/WHO
Kidney disease	Chronic kidney disease	UK, AT, IT, CZ, JP,
	Kidney disease	BE
	Patients with chronic renal failure on dialysis	FR, US
	Severe kidney disease leading to dialysis or kidney transplant	NL
	Renal failure might be at risk	SE
Immune disorders	Conditions and therapies that weaken the immune system	CN, DE, AT, BE, AUS, US
	HIV or AIDS	UK
	Poorly controlled HIV or AIDS	US, FR, NL
	Medicines such as steroid tablets	UK, US, FR, NL
	Problems with spleen – e.g., sickle cell disease or hypo/asplenia	UK, NL
	Following a solid organ or hematopoietic stem cell transplant	FR, US, NL
	Extremely vulnerable individuals are those : with rare diseases and inborn errors of metabolism that significantly increase the risk of infections (such as severe combined immunodeficiency (SCID), homozygous sickle cell) people on immunosuppression therapies sufficient to significantly increase risk of infection. who received a solid organ transplant recipients	UK
	Immunocompromised including cancer treatment	US
	Immunocompromised including smoking	US
	People with congenital or acquired immunosuppression related to a malignant haemopathy being treated	FR
	Possible; patients with suppressed T-lymphocyte function	JP
	Maybe at risk: Immunocompromised including cancer treatment HIV Following a solid organ or hematopoietic stem cell transplant Risk of functional hyposplenia (Radiation to the spleen > 10 Gy or splenectomy)	SE
Neurological conditions	Chronic neurological conditions	UK
	Dementia Stroke	IT
	History of stroke	FR, CZ
	Those with neurological disease may be at risk	JP

Supplemental table S4
Comorbidities and risk factors associated with increased risk for severe course of disease according to 15 national health organizations and the WHO* (continued)

	Comorbidity/Risk factor associated with increased risk for severe course of disease of COVID-19	Countries/WHO
Liver disease	Chronic liver disease	UK, DE, AT, US
	Patients with cirrhosis at stage B or C of the Child-Pugh classification	FR
	Patients at stage B or C of the Child-Pugh classification	NL
	Chronic liver disease reported in 4% of deceased subjects	IT
	Those with liver disease might be at risk	SE
Hematological disease	Hematological diseases	US, NL, BE, UK
Pregnancy	Higher risk: Those who are pregnant Extremely vulnerable: Pregnant women with significant heart disease, congenital or acquired	UK
	No data for increased risk for severe illness. However, pregnant women may be at risk.	US, WHO, AUS, SE
	From the third trimester onwards	FR
Smoking	Smoking	DE, JP
	Immunocompromised including smoking	US
Other	People under 70 who based on underlying health problems are eligible for the flu vaccination	NL, UK

***AUS=Australia, AT=Austria, BE=Belgium, CAN=Canada, CZ=Czech Republic, FR=France, DE=Germany, CN=China, CH=Switzerland, IT=Italy, JP=Japan, NL=Netherlands, SE=Sweden, UK=United Kingdom, US=United States of America, WHO= World Health Organization*
 # Comorbidities mentioned in the table for NL are for persons of 18 years or older

Supplemental figure S5 IGHG COVID-19 statement Version 1.0



IGHG Statement. COVID-19 v1.0
for survivors of childhood, adolescent or young adult cancer

Purpose

The purpose of this statement is to provide guidance to childhood, adolescent and young adult cancer survivors related to risk and additional preventive measures for Coronavirus Disease 2019 (COVID-19). For this guidance, childhood, adolescent and young adult cancer survivors are defined as individuals of any age who were diagnosed with cancer before age 25 years and are at least one year following completion of primary cancer therapy.

Knowledge

Survivors, their caregivers, and health care providers should be mindful that the risk and course of COVID-19 in childhood, adolescent and young adult cancer survivors is not currently known. Thus, the information provided in this guidance is largely extrapolated from medical information from national health services and the World Health Organization (WHO) about COVID-19 in non-cancer populations. [1 (see notes)] The IGHG and Cochrane Childhood Cancer are carefully monitoring the rapidly emerging medical reports about COVID-19 and will update this guidance as new information becomes available.

Recommendation 1

Who is at higher risk?

Based on medical information about COVID-19 in the general population, cancer survivors with the specific health conditions below may have a higher risk for a severe course of COVID-19, especially if they have more than one of these conditions. In addition to these comorbid conditions, a more severe course has been observed in older individuals, especially those 60 years of age or older, which may be because older individuals are more likely to have the chronic health conditions listed in the table. Individuals with conditions and/or use of drugs that affect immune system function may also be at risk for a more severe course of COVID-19 because of their overall higher risk of infection.

Conditions[2] most frequently identified by national health services and WHO to increase risk for a severe course of COVID-19	**Examples of cancer treatment-related conditions that may increase a childhood, adolescent and young adult cancer survivor's risk for a severe course of COVID-19**
Heart disease, including but not limited to: • Heart failure requiring medication • History of myocardial infarction (heart attack)	Heart disease, including but not limited to: • Cardiomyopathy (heart muscle disease) following anthracycline therapy • Coronary artery disease following chest radiation
Chronic lung disorders, including but not limited to: • Chronic obstructive pulmonary disease (COPD) • Severe asthma • Any lung disease causing chronic shortness of breath, difficulty breathing or requiring oxygen therapy	Chronic lung disorders, including but not limited to: • Lung fibrosis (scarring) following bleomycin or chest radiation • Chronic lung disease after bone marrow transplant
Diabetes	Diabetes following radiation to abdomen or pancreas
Conditions and/or use of drugs that affect immune system function, including but not limited to: • Ongoing treatment for cancer • Asplenia, splenectomy (absence, removal of spleen) • Corticosteroids (prednisone, dexamethasone, hydrocortisone, but not topical preparations) • Anti-rejection medications after solid organ transplant • Immunotherapy for autoimmune disease (lupus, psoriasis, arthritis, etc...)	Conditions and/or use of drugs that affect immune system function, including but not limited to: • Ongoing treatment for a new or recurrent cancer • Removal of spleen for cancer staging surgery • Hyposplenia (low functioning spleen) following radiation to the abdomen • History of blood/marrow transplant, especially if treated with total body irradiation before transplant • History of organ transplant because of cancer or damage from cancer treatment (for heart, kidney or liver) • Chronic graft versus host disease

[1] The IGHG and Cochrane Childhood Cancer will monitor the medical literature about all of these conditions and other conditions/factors less frequently identified by national health services or medical reports that may increase the risk for a severe course of COVID-19 including: kidney disease, hypertension, liver disease, obesity, pregnancy, blood disorders, neurological dysfunction; medications like ACE inhibitors and ibuprofen; and male sex.

Cochrane Childhood Cancer | International Guideline Harmonization Group for Late Effects of Childhood Cancer

IGHG COVID-19 Statement v1.0 April 7th 2020

Recommendation 2

What Measures should be taken by survivors?

All childhood, adolescent and young adult cancer survivors should adhere to recommendations, like social distancing, frequent hand washing, etc, as advised by national and/or local authorities.

Recommendation 3

What additional measures should be taken by **survivors** at **high risk?**

Survivors at higher risk of a severe course of COVID-19 (as described in the above list) should:

- Shelter at home and minimize all non-essential contact with household members.
- Request reassignment to remote work activities (for you and for household members if possible) if your work is typically performed in public spaces.
- Encourage household members who are visiting or working in public spaces to take extra care to avoid exposure and transmission of COVID-19.
- Take extra care to avoid exposure to household members who have symptoms or have been diagnosed with COVID-19.
  - Isolate ill household members in the home or move to another location if possible.
  - If isolation or relocation is not possible, have ill household members wear masks.
  - Increase the frequency of hand washing and cleaning of hard surfaces with disinfectants.
  - Clean shared toilet and bathroom surfaces after every use.

Recommendation 4

What should be done by a survivor at high risk, who **is ill?**

Survivors at higher risk of a severe course of COVID-19 should:

- Seek medical advice early if you develop symptoms that could be related to COVID-19.
- Alert health care providers about your cancer history and other health conditions that have been linked to higher risk for a severe course of COVID-19.
- Call your doctor or emergency department for instructions if your symptoms worsen (e.g., fever, shortness of breath, difficulty breathing, confusion, etc...) and you feel you need to be evaluated.

Notes

IGHG: *International Late Effects of Childhood Cancer Guideline Harmonization Group (www.ighg.org)*
IGHG COVID-19 working group: Chairs: *Leontien Kremer, Melissa Hudson.* ***Core group:*** *Saro Armenian, Rod Skinner, Matt Ehrhardt, Claudia Kuehni, Renée Mulder, Elvira van Dalen, Helena van der Pal.* ***Coordinators:*** *Lisanne Verbruggen, Yuehan Wang.* ***Members:*** *Edit Bardi, Claire Berger, Elio Castagnola, Adam Glaser, Riccardo Haupt, Lars Hjorth, Miho Kato, Miho Maeda, Monica Muraca, Paul Nathan, Vesna Pavasovic, Satomi Sato, Lillian Sung, Anne Uyttebroeck.* ***Reviewers v1.0 and members for next version:*** *Judith Gebauer, Jaap den Hartogh, Thorsten Langer, Wim Tissing, Tomas Kepak.*
For more information contact: *L.C.M.Kremer@prinsesmaximacentrum.nl & Melissa.hudson@stjude.org*

[1]***Summary of risk factors for severe course of COVID-19 in the general population,*** *reported in medical information from 9 national health services and the World Health Organization (WHO).*

n=10 Older age (United Kingdom, United States of America, The Netherlands, Switzerland, WHO, Canada, Italy, France, Japan, China)
n=8 Heart disease (UK, US, NL, CH, WHO, IT, FR, JP)
n=8 Lung disease (UK, US, NL, CH, WHO, IT, FR, JP)
n=8 Diabetes (UK, US, NL, CH, WHO, IT, FR, JP)
n=7 Active Cancer treatment (UK, NL, CH, WHO, IT, FR, JP)
n=6 Immune disorders or Organ transplant (UK, US, NL, CH, FR, JP)
n=6 Kidney disease (UK, US, NL, IT, FR, JP)
n=5 High blood pressure (CH, WHO, IT, FR, JP)
n=3 Liver disease (UK, US, FR)
n=4 Overweight (UK, US, IT, FR)
n=4 Pregnant women (UK, US, WHO, FR)
n=3 Hematological (blood) disease (UK, NL, US)
n=3 Chronic neurological condition (UK, FR, IT).
n=1 Males (IT)

Supplemental figure S6 IGHG COVID-19 statement Version 2.0

IGHG Statement. COVID-19 v 2.0 17 April 2020 (Updated v1.0 published 7 April 2020) for survivors of childhood, adolescent or young adult cancer

The IGHG and Cochrane Childhood Cancer are carefully monitoring the rapidly emerging medical information about COVID-19 and will update this guidance as new information becomes available. See www.ighg.org for future updates of this statement.

Purpose

The purpose of this statement is to provide guidance to childhood, adolescent and young adult cancer survivors related to risk and additional preventive measures for Coronavirus Disease 2019 (COVID-19). For this guidance, childhood, adolescent and young adult cancer survivors are defined as individuals of any age who were diagnosed with cancer before age 25 years and are at least one year following completion of primary cancer therapy.

Knowledge

Survivors, their caregivers, and health care providers should be mindful that the risk and course of COVID-19 in childhood, adolescent and young adult cancer survivors is not currently known. Thus, the information provided in this guidance is largely extrapolated from medical information from national health services and the World Health Organization (WHO) about COVID-19 in the general population.

Recommendation 1

Who is at higher risk?

Based on medical information about COVID-19 in the general population, cancer survivors with the specific health conditions below may have a higher risk for a severe course of COVID-19, especially if they have more than one of these conditions. In addition to these comorbid conditions, a more severe course has been observed in older individuals, especially those 60 years of age or older, which may be because older individuals are more likely to have the chronic health conditions listed in the table. Individuals with conditions and/or use of drugs that affect immune system function may also be at risk for a more severe course of COVID-19 because of their overall higher risk of infection.

Conditions[1] most frequently identified by national health services and WHO to increase risk for a severe course of COVID-19	Examples of cancer treatment-related conditions that may increase a childhood, adolescent and young adult cancer survivor's risk for a severe course of COVID-19
Heart disease, including but not limited to: • Heart failure requiring medication • History of myocardial infarction (heart attack)	Heart disease, including but not limited to: • Cardiomyopathy (heart muscle disease) following anthracycline therapy • Coronary artery disease following chest radiation
Chronic lung disorders, including but not limited to: • Chronic obstructive pulmonary disease (COPD) • Severe asthma • Any lung disease causing chronic shortness of breath, difficulty breathing or requiring oxygen therapy	Chronic lung disorders, including but not limited to: • Lung fibrosis (scarring) following bleomycin or chest radiation • Chronic lung disease after bone marrow transplant
Diabetes	Diabetes following radiation to abdomen or pancreas
Conditions and/or use of drugs that affect immune system function, including but not limited to: • Ongoing treatment for cancer • Organ transplant • Immune disorders	Conditions and/or use of drugs that affect immune system function, including but not limited to: • Ongoing treatment for a new or recurrent cancer • History of organ transplant because of cancer or damage from cancer treatment (for heart, kidney or liver) • Chronic graft versus host disease

[1] The following conditions/factors, which have been reported to increase risk for a severe course of COVID-19, were less frequently mentioned by national health services or medical reports: kidney disease, hypertension, liver disease, obesity, pregnancy, blood disorders, neurological dysfunction, asplenia, hyposplenia, high BMI, male sex, and use of ACE inhibitors or ibuprofen. The IGHG and Cochrane Childhood Cancer will monitor the medical literature about all of these conditions/factors and revise recommendations as new information becomes available.
The higher risk of secondary bacterial infections should be considered for survivors with asplenia and hyposplenia.

Cochrane Childhood Cancer | International Guideline Harmonization Group for Late Effects of Childhood Cancer | *IGHG COVID-19 Statement v2.0 April 17th 2020*

Recommendation 2

What Measures should be taken by survivors?

All childhood, adolescent and young adult cancer survivors should adhere to recommendations, like social distancing, frequent hand washing, etc, as advised by national and/or local authorities.

Recommendation 3

What additional measures should be taken by **survivors** at **high risk?**

Survivors at higher risk of a severe course of COVID-19 (as described in the above list) should:

- Shelter at home and minimize all non-essential contact with household members.
- Request reassignment to remote work activities (for you and for household members if possible) if your work is typically performed in public spaces.
- Encourage household members who are visiting or working in public spaces to take extra care to avoid exposure and transmission of COVID-19.
- Take extra care to avoid exposure to household members who have symptoms or have been diagnosed with COVID-19.
  - Isolate ill household members in the home or move to another location if possible.
  - If isolation or relocation is not possible, have ill household members wear masks.
  - Increase the frequency of hand washing and cleaning of hard surfaces with disinfectants.
  - Clean shared toilet and bathroom surfaces after every use.

Recommendation 4

What should be done by a survivor at high risk, who **is ill?**

Survivors at higher risk of a severe course of COVID-19 should:

- Seek medical advice early if you develop symptoms that could be related to COVID-19.
- Alert health care providers about your cancer history and other health conditions that have been linked to higher risk for a severe course of COVID-19.
- Call your doctor or emergency department for instructions if your symptoms worsen (e.g., fever, shortness of breath, difficulty breathing, confusion, etc...) and you feel you need to be evaluated.

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Summary of risk factors for severe course of COVID-19 in the general population, *reported in medical information from 15 national health services and the World Health Organization (WHO):*

n=16 Older age (GER, AUT, WHO, CZ, US, CH, CAN, BE, UK, NL, IT, FR, SE, AUS, China, JP)
n=14 Diabetes (UK, CH, WHO, IT, FR, CZ, AUT, AUS, BE, US, NL, JP, GER, SE)
n=14 Heart disease (UK, NL, CZ, AUT, BE, US, CH, GER, AUS, WHO, JP, SE, IT, FR)
n=14 Lung disease (UK, US, NL, BE, CH, IT, CZ, GER AUS, WHO, AUT, SE, FR, JP)
n=13 Active Cancer treatment (UK, NL, CH, WHO, GER, AUT, AUS, IT, FR, BE, JP, CZ, SE)
n=11 Immune disorders or organ transplant (UK, SE, US, NL, CH, GER, AUT, FR, JP, BE, AUS)
n=10 Kidney disease (UK, AUT, SE, NL, BE, IT, FR, US, CZ, JP)
n=9 High blood pressure (CH, WHO, IT, JP, CZ, GER, AUT, SE, FR)
n=7 Liver disease (UK, GER, AUT, SE, US, IT, FR)
n=6 Pregnant women (UK, US, WHO, AUS, SE, FR)
n=5 Overweight (UK, US, FR, IT, CZ)
n=4 Hematological (blood) disease (UK, US, NL, BE)
n=2 Chronic neurological condition (UK, IT)
n=2 Problems with the spleen (UK, SE)
n=1 Males (IT)

AUS= Australia, AUT=Austria, BE=Belgium, CAN=Canada, CZ=Czech Republic, FR=France, GER= Germany, China=China, CH=Switzerland, IT=Italy, JP=Japan, NL=Netherlands, SE=Sweden, UK=United Kingdom, US=United States of America

CHAPTER 6

Summary and general discussion

Overall, this thesis aims to provide expanded knowledge regarding the risk of and risk factors for subsequent breast cancer (SBC) after treatment for childhood cancer in both females and males. This thesis also provides recommendations established to guide healthcare providers and childhood cancer survivors during the abrupt COVID-19 pandemic. In this chapter, the findings are summarized and compared with relevant literature. Furthermore, the strengths and limitations of our studies and the associated clinical impact of our findings are discussed.

Main findings of the studies in this thesis

In **Chapter 2**, we address the methodology and characteristics of the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer, which initially focused on SBC-related objectives. This cohort profile summarized the data collected from each included cohort, including childhood cancer diagnostic information and treatment details (i.e., radiotherapy fields and cumulative doses, and chemotherapy agents and cumulative doses for each agent). In the consortium database, data was pooled from seven cohorts (three from the United States, two from the Netherlands, one from France, and one from Switzerland). Included cohorts' follow-up started between 1951 and 1981 and ended between 2013 and 2021 for a median follow-up duration of 24.3 (interquartile range (IQR) 18.0-32.8) years after primary cancer diagnosis. The median age at primary cancer diagnosis was 5.4 (IQR 2.5-11.9) years and the median attained age at last follow-up was 32.2 (IQR 24.0-40.4) years. In all, 4,240 (19.4%) survivors were treated with radiotherapy of the chest, and 9,308 (42.5%) with anthracyclines. At the end of the follow-up, 835 females had developed a first SBC, including 635 with invasive breast cancer only, 184 with carcinomas in situ of the breast only (172 ductal carcinomas in situ and 12 with lobular carcinomas in situ), and 16 with both an invasive and in situ diagnosis at the same time. The cumulative incidences of SBC (both invasive and in situ) 25 and 35 years after primary cancer diagnosis were 2.2% and 6.2%, respectively. The consortium is meant to serve as a model and robust source of childhood cancer survivor data for elucidating other knowledge gaps on SBC risk, and risk of other subsequent malignancies in the future.

In **Chapter 3**, we analyze dose-dependent effects of individual anthracycline agents on developing SBC and their interactions with chest radiotherapy in our international consortium database. Among 17,903 survivors of childhood cancer with a median follow-up of 24.9 years (IQR 19.1-33.2) after the primary cancer diagnosis, 782 developed a first SBC. An increased SBC risk was seen for doxorubicin (hazard ratio (HR) per 100 mg/m^2: 1.24, 95% confidence interval (CI):

1.18-1.31), and a non-statistically significant increase in SBC risk was observed for daunorubicin (HR per 100 mg/m²: 1.10, 95% CI: 0.95-1.29). Epirubicin was also associated with an increased SBC risk (yes vs. no HR: 3.25, 95% CI: 1.59-6.63). Both among survivors with and without chest radiotherapy, a dose-dependent effect of doxorubicin on SBC risk was observed. Joint effects of doxorubicin and chest radiation were less than multiplicative ($HR_{multiplicative\ interaction}$ 0.86, 95% CI: 0.78-0.96, $P_{multiplicative\ interaction}$=0.006) and compatible with additivity ($P_{additive\ interaction}$=0.99). Our findings support that early initiation of breast cancer surveillance is reasonable for childhood cancer survivors who received ≥200 mg/m² cumulative doxorubicin dose. The results of our study should be implemented in SBC surveillance guidelines for survivors and will inform future treatment protocols for newly diagnosed childhood cancer patients.

In **Chapter 4**, we conduct a systematic review and analyses in a large Pan-European cohort on male breast cancer risk in five-year childhood cancer survivors. In the systematic review, we searched Medline/PubMed for cohort studies and case reports/series that assessed subsequent male breast cancer (SMBC) after childhood cancer (≤21 years) and summarized the existing evidence on SMBC in childhood cancer survivors. Furthermore, we analyzed data on SMBC in the PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup) cohort, reporting standardized incidence ratios (SIRs), absolute excess risks (AERs), and five- and ten-year survival rates. The systematic review included 38 of 7,080 potentially eligible articles. Cohort-specific SMBC frequencies were 0-0.40% (31 studies). SMBC occurred after a follow-up ranging from 24.0-42.0 years. Nine case reports/series described 11 SMBC cases, occurring 11.0-42.5 years after primary childhood cancer. In the PanCareSurFup cohort (16 SMBC/37,738 males; 0.04%), we observed a 22.3-fold increased risk of SMBC relative to the general male population (95% CI 12.7-36.2; AER/100,000 person-years: 2.3, 95% CI 1.3-3.7). Cumulative incidences of SMBC were 0.02%, 0.04%, and 0.10% by age 30, 40, and 50, respectively. The five- and ten-year survival rates after SMBC diagnosis were 60.3% (95% CI 35.6%-85.0%) and 43.0% (95% CI 16.1%-69.9%), respectively. Clear evidence of risk factors did not emerge from these comprehensive efforts. We concluded that compared to the general population, childhood cancer survivors have an elevated risk of developing SMBC, although the absolute risk is low. Health care providers should be aware of this rare yet serious late effect; male survivors with symptoms potentially related to SMBC warrant careful examination.

In **Chapter 5**, to cope with the abrupt and unexpected COVID-19 pandemic, we organized an international working group to summarize existing evidence and worldwide recommendations regarding relevant factors and conditions associated

with risk of a severe course of COVID-19 and develop a consensus statement to provide guidance for health care providers and childhood cancer survivors regarding COVID-19 within a relatively short period of time. Information was then disseminated to the public through the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) website and a variety of national/institutional pediatric cancer forums. We provided guidance in a timely manner to childhood cancer survivors, who in many cases may have had comorbid conditions linked to a high risk of a severe course of COVID-19 at the beginning of COVID-19 pandemic.

Strengths and limitations of the studies in this thesis

This thesis has carried the studies on the treatment-associated risk of SBC in childhood cancer survivors an important step forward, in both females and males. To our knowledge, both of our pooled analyses in females and males represent the most extensive studies ever on SBC risk in childhood cancer survivors with comprehensive and long-term follow-up. The tremendous effort of pooling individual patient observations from eligible cohorts worldwide improves statistical power to identify risks of SBC associated with specific treatments, which has often been insufficient in previous individual cohort studies.

Additionally, combining data increases the sample size of childhood cancer survivors who have attained an older age, which enables a more precise estimation of the risk for SBC in this aging population. Moreover, our studies may have more heterogeneity in treatment exposures than in single cohorts, given that childhood cancer treatment protocols differ among the various countries that have contributed to this consortium.

The most remarkable and unique aspect of our female international pooled cohort study in **Chapter 2 & 3** is that detailed treatment information has been collected, including specific chest radiotherapy fields, chemotherapeutic agents, and their corresponding doses. Furthermore, we converted the received data into a uniform format of categories while maintaining their medical and clinical relevance. Therefore, our international database creates a better opportunity to disentangle single treatment exposures in the pooling effort to account for the heterogeneity of treatment exposure, in particular regarding variation in treatment combinations across countries, because better adjustments can be made for other treatments.

In **Chapter 4**, our SMBC study includes the largest ever cohort of male childhood cancer survivors with comprehensive and long follow-up and, therefore, also

includes a comparatively large number of SMBC cases compared to other studies. In addition, our systematic review used a very comprehensive search strategy, thereby limiting the possibility of missing eligible studies, and thoroughly evaluating the existing evidence on SMBC in childhood cancer survivors.

Additionally, at the beginning of the unexpected COVID-19 pandemic, in the new landscape of healthcare that was so dramatically reshaped, we developed the first guidance for childhood cancer survivors and their care providers, together with late effects experts from around the world. Our recommendations for navigating through the COVID-19 pandemic (**Chapter 5**) have also been translated into several languages to reach different populations as widely as possible and help people who need the corresponding support during the pandemic.

However, some limitations should also be taken into account when interpreting our study findings.

The participants in our studies (both females and males) were recruited exclusively from North American and European cohorts, and consisted predominantly of individuals of European ancestry. In this respect, the homogeneity of our sample may limit the generalizability of the results to other populations.

Furthermore, even though the studies included in this thesis represent the largest effort to assess SBC risk in female and male childhood cancer survivors, the power of conducting specific analyses may still be limited. For our female pooled analyses in **Chapter 2 & 3**, we were not able to examine the dose effect of two anthracycline agents, epirubicin and idarubicin, on SBC risk due to the fact that limited number of survivors and SBC cases had these specific exposures. For our SMBC study in **Chapter 4**, the pooled database we utilized for analyses, PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup), only has specific information on radiation field and chemotherapy agents for SMBC cases. Therefore, we could not clearly identify treatment-related risk factors for SMBC in this study.

Moreover, as we had incomplete information on genetic cancer predispositions in our studies presented in **Chapter 2 & 3**, we were not able to evaluate potential gene-treatment interactions. While initial analyses of our studies focus on treatment-related research questions, the infrastructure of these individual pooled data projects will facilitate investigations of additional effects (e.g., lifestyle, specific reproductive and genetic factors), which are available for varying subgroups of the combined individual pooled data cohort, and which will be considered in future efforts.

General discussion

The most distinctive aspect of our female breast cancer international consortium database is that we pooled and merged well-established cohort data with specific treatment information into one database, which required a great deal of effort. Regarding the merging and harmonizing procedures, the most challenging variable to analyze concerned the chest radiotherapy fields. During the data collection phase, we requested that data providers from each cohort provided their respective data in its original format, to accelerate the data collection procedures; subsequently we would convert the data into a uniform format. After we received the data and examined it closely, we concluded that the data, especially regarding radiotherapy, differed significantly between cohorts because the treatment protocols varied in different countries, and all studies defined the radiotherapy treatment fields in their own way. Figuring out these variables was like solving a puzzle. We, therefore, concluded that there were, in total, two critical steps to harmonize the radiotherapy variables. First, we determined whether the fields in the received data involved the chest, then cross-checked this specific field against other data to ensure that the definition of "chest radiotherapy" was consistent among all cohort data; second, if the provided fields involve the chest, it was necessary to categorize them uniformly to maintain the medical and clinical relevance. Before we arrived at a uniform format of categories across the data, careful inspection of the data received as well as extensive consultation with the individual investigators were required. Eventually, we arrived at the following categories: whole lung, total body irradiation, mantle, mediastinal, axilla, spine, and other chests areas without axilla. After we created a system to modify the chest radiotherapy fields to fit our uniform format, we double- or triple-checked our conversions with each data provider and their radiation experts to arrive at an agreement on our conversions. The procedures described above for merging and harmonizing data in different formats were among the most complicated and time-intensive steps in our pooled analyses. Therefore, our data pooling experience can serve as a useful tool for future studies by providing a standard protocol to manage databases more efficiently. Additionally, our pooled data analysis provides new research opportunities and tools to re-examine the currently available data rather than establishing new studies to investigate research questions that are hard to examine in single cohorts. Pooling data can save significant resources (e.g., manpower, time, and funding) compared with initiating new studies and can also take heterogeneity across cohorts into account.

We collected *prescribed* radiotherapy dose information in our subsequent female breast cancer international consortium database. It is worth noting that most studies on the effect of chest radiotherapy dose on SBC in both adult and

childhood cancer survivors are based on reconstructed *absorbed* radiotherapy doses to the breast (1-4). However, it is relatively impractical to apply the *absorbed* dose information in clinical practice since this information is usually not available for survivors treated in the past. Therefore, to adapt our research results to clinical practice without creating additional barriers, we intentionally collected prescribed radiotherapy doses in our study, generating slightly different radiation exposure measures than previous studies.

In **Chapter 3**, our findings indicate that the joint effects of doxorubicin and chest radiation were sub-multiplicative and compatible with additive effects, which implies that the combined effects of doxorubicin and chest radiation are equal to the sum of their individual effects. In contrast, a previous Childhood Cancer Survivor Study (CCSS) case-control study showed that the joint effects of radiotherapy dose to the breast and anthracycline exposure (yes/no) were more than additive (5). Despite the inclusion of the CCSS cohort data in our pooled study, the results of these two studies are difficult to compare. Our pooled cohort analyses examined the interaction of doxorubicin and daunorubicin with chest radiotherapy, instead of using a case-control design and investigating the interaction between estimated radiation dose to the breast cancer location and any anthracycline exposure (yes/no).

Although the pelvic radiotherapy effect on SBC risk is not our primary focus in **Chapter 3**, we compared our results on the effects of pelvic radiotherapy on SBC to previous studies. While reduced SBC risk associated with absorbed ovarian radiation dose ≥5 Gy has been reported in survivors treated with chest radiation (1), we did not observe a statistically significant reduction of SBC risk in those with radiotherapy delivered to the pelvic region (≥5 Gy vs. no pelvic radiotherapy or <5 Gy) in our entire cohort, which aligns with a SJLIFE study (pelvic radiotherapy yes vs. no) that was also included in our pooled cohort (6). However, when we restricted our analyses to survivors who received chest radiotherapy, we found a decreased SBC risk associated with pelvic radiotherapy, as expected.

A previous CCSS study, which was also included in our international consortium, demonstrated that women treated with lower doses of radiotherapy to the whole volume of breast tissue appeared to have a higher risk of breast cancer than women treated with high dose radiotherapy to only part of the breast tissue (3). Our pooled analysis results showed that survivors who received, for example, total body irradiation or whole lung irradiation had a higher risk of SBC development compared with survivors who received mediastinal irradiation, which confirmed that female survivors with more extensive chest area irradiation have an increased risk of developing SBC than survivors who had a smaller chest field irradiated.

While we observed a statistically significant dose-dependent effect on SBC risk for doxorubicin, as previously suggested in smaller single cohorts also represented in our data, we did not observe a clear dose-dependent association with daunorubicin (5, 7). We also found an increased SBC risk associated with epirubicin exposure (yes vs. no). Potential differences in the mechanisms of developing subsequent neoplasms between different anthracycline agents are unclear. Daunorubicin was also reported to be less cardiotoxic than doxorubicin among childhood cancer survivors (8). Animal studies indicate that both doxorubicin and daunorubicin can induce mammary tumors (9, 10). The antineoplastic properties of doxorubicin and daunorubicin have both been assumed to result from DNA damage and chromatin damage (11). Based on limited studies, the anticancer efficacies are thought to be similar (12, 13). Evidence suggests that chemically separating those activities by reducing the effect of DNA damage while retaining the chromatin damage could detoxify the anthracycline variants, while maintaining anticancer efficacy (14). Possible factors that might underlie the differences in the dose effects we observed between doxorubicin and daunorubicin include genetic factors, which were not examined in our current study. And the low number of individuals and SBC cases with daunorubicin exposure may have limited the statistical power to detect a significant dose-response relationship. For epirubicin (nine SBC cases exposed) and idarubicin (one SBC case exposed), patient numbers were too low to evaluate their dose effects.

Regarding SMBC risk in childhood cancer survivors explored in **Chapter 4**, a previous study reported that all four SMBC cases after childhood cancer in their cohort had received radiotherapy involving breast tissue and chemotherapy as the primary cancer treatments (15). In the reviewed case-reports/series (also including the four SMBC cases from Demoor-Goldschmidt, et al. (15)), we observed that all but one case had both chest-/breast-exposing radiotherapy and chemotherapy for primary cancer treatment (n=10, 91%). It should be kept in mind that the case reports/series are likely not a representative sample of all SMBC cases; it is not possible to draw conclusions regarding causal effects of potential risk factors from this type of evidence. Moreover, in the PanCareSurFup cohort, a history of chest radiotherapy was reported for only 38% of our SMBC cases (6/16). In our PanCareSurFup cohort, prior treatment with anthracyclines and alkylating agents was only documented for two and six SMBC patients, respectively. Of note, drug-specific information was incomplete for three SMBC cases and no cohort-wide information on type of chemotherapy was available. In summary, the collective data on male cancer survivors provided here does not yet allow for further investigation of treatments associated with SMBC risk.

Implication for care

Clinical practice guidelines for providers have been developed to promote optimal health-related outcomes by screening survivors (16, 17). In 2010, the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) was established (https://www.ighg.org/) to harmonize the guidelines available worldwide, according to a common methodology (18). In 2012, the IGHG formulated recommendations for breast cancer surveillance among high-risk groups (19), to which an update was recently provided (20). According to current breast cancer screening recommendations, female survivors treated with ≥10 Gy chest radiotherapy should initiate annual breast screening at age 25 or 8 years after radiation, whichever occurs last, to facilitate early detection of occult lesions (20).

Our findings support that it is reasonable to initiate early breast cancer screening in female childhood cancer survivors who have received ≥200 mg/m^2 cumulative doxorubicin dose. Regarding daunorubicin, increasing cumulative dose was not significantly associated with SBC risk in either survivors treated with chest radiotherapy or among those treated without chest radiotherapy. Therefore, for survivors treated with daunorubicin without doxorubicin or chest radiation, our results do not support the need for breast cancer surveillance earlier than recommended for the general population. For guiding survivorship care, it would be useful to refine current absolute risk calculators (21) for SBC by extending these to women treated without chest radiotherapy but with anthracyclines.

Although male childhood cancer survivors have a more than 20-fold elevated risk of developing SMBC compared to the expected risk in the general population, the absolute risk is low. Given the low absolute risk of SMBC and the relative shortage of evidence on which subgroups of survivors are particularly at increased risk, regular breast cancer screening for males does not seem warranted at this time. However, it is important that survivors and their caregivers are aware of signs and symptoms that might be indicative of male breast cancer and, considering the possibility of SMBC diagnosis, childhood cancer survivors with symptoms that might be related to SMBC should be carefully and comprehensively examined to avoid a delay in detection.

Future perspectives

We established the International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer to conduct individual patient data analyses aimed to address knowledge gaps regarding SBC, that have not been adequately addressed in individual cohort studies due to the limited number of

survivors and cases treated with specific modalities. Several analyses on clinically relevant questions regarding SBC are currently ongoing, including investigation of the effects of prescribed radiation dose and radiation field, as a proxy for exposed tissue volume, on the risk of SBC and whether relative and absolute excess risks of SBC remain increased across the lifespan, especially after age 50 and/or 60 years. Additionally, the consortium can serve as a model and robust resource of childhood cancer survivor data for elucidating other knowledge gaps on SBC risk, and risk of other subsequent malignancies (including data on males) in the future.

As specific treatment information will be collected for additional cohorts in the future, our international consortium in females can be expanded by including more studies and survivors with specific treatment information to gain substantial statistical power in answering specific research questions that require relatively large sample sizes. Moreover, as the survivors included in current studies are followed longer and reach advanced ages, we can investigate the late effect risks in survivors more thoroughly.

Expanding our international consortium from survivors recruited exclusively from North American and European cohorts, predominantly consisting of individuals of European ancestry, to a more diverse population with different racial backgrounds will allow us to better generalize our findings and take the heterogeneity of treatment modalities in different regions further into account.

It is also of great importance to include genetic data in our international consortium, so that the gene-treatment associations with SBC risk can be examined. Future studies with complete genome and exome sequencing data may further elucidate the effects of individual chemotherapeutic agents on SBC risk among genetically susceptible individuals and may provide novel insights into SBC development at genetic and molecular levels.

Potential differences in the mechanisms of subsequent neoplasms development between different anthracycline agents are unclear. Future studies that elucidate mechanisms underlying carcinogenicity and anticancer efficacy among the various anthracycline agents are warranted. If anticancer efficacy is equivalent in doxorubicin and daunorubicin in childhood cancer and specific late effects have been demonstrated to be less frequent after daunorubicin, preference for daunorubicin over doxorubicin in childhood cancer treatment might reduce the risk of adverse effects without compromising anticancer efficacy.

In recent decades, there have been trends in radiotherapy of transitions from 2-Dimensional radiation therapy to 3-Dimensional conformal radiation therapy, intensity modulated radiation therapy, and/or proton radiotherapy, to deliver radiation to the target tissues more precisely while avoiding the unrelated body regions (22-24). It is of great importance to conduct collaborative studies to monitor the potential late effects caused by these new techniques since the number of childhood cancer patients who received these treatments is still relatively small in individual studies. In addition, evaluating the cost-effectiveness of these new techniques is essential as it will guide future treatment protocol establishment (25).

Comparing latency period and clinical characteristics, such as hormonal receptor status, between SBCs occurring after chest radiotherapy and SBCs occurring after anthracyclines is relevant to inform surveillance guidelines and to provide a better understanding of the etiology of SBC.

Even though our study is the largest effort on SMBC risk in male childhood cancer survivors, specific treatment information on radiation fields and chemotherapy agents was limited to SMBC cases. Thus, we were not able to clearly identify treatment-related risk factors for SMBC. More studies are needed to investigate SMBC risk, particularly pooling of data at an international scale is of great importance to obtain sufficient power to study the relevant risk factors for this rare diagnosis.

Lastly, most late effects studies focus on either describing the trends of late effects in childhood cancer survivors or on targeting one late effect as an outcome to identify the corresponding risk and risk factors. The next step for future research could be combining late effect outcomes, such as, risk factors for SBC and cardiotoxicity in childhood cancer survivors, to examine whether the survivor groups with a higher risk of SBC are potentially also the survivor groups with a higher risk of developing cardiotoxicity in the long-term. Merging and harmonizing the datasets with different outcomes can create innovative opportunities for these types of pooled analyses and give both healthcare providers and survivors a bigger and more detailed picture of the overall risk of late effects in childhood cancer survivors.

Key messages from this thesis

- Pooling individual patient observations from eligible cohorts worldwide improves statistical power for the identification of subsequent breast cancer risks associated with specific treatments, for which power was previously insufficient in individual cohorts.
- The heterogeneity of treatment exposure, particularly related to variation in treatment combinations across countries, creates a better opportunity to disentangle effects of single treatment exposures in the pooling effort.
- Our study provides evidence that doxorubicin is associated with a dose-dependent increase of breast cancer risk, both in survivors treated with and without chest radiotherapy. Epirubicin (yes vs. no) was also associated with an increased breast cancer risk.
- Breast cancer risk in survivors who had both doxorubicin and chest radiation was equal to the sum of their individual effects.
- Our findings support that it is reasonable to initiate early breast cancer screening in female childhood cancer survivors who have received ≥200 mg/m^2 cumulative doxorubicin dose. The results of our study should be implemented in subsequent breast cancer surveillance guidelines for survivors and will inform future treatment protocols for newly diagnosed childhood cancer patients.
- The resources of the internationally pooled female breast cancer study can be used for future studies on breast cancer risk and risk of other subsequent malignant neoplasms, after including male survivors.
- Male childhood cancer survivors have a strongly elevated risk of developing subsequent male breast cancer compared to the expected risk in the general population, although the absolute risk is low. Risk factors for subsequent breast cancer in male survivors remain unclear.
- Given the low absolute risk of subsequent male breast cancer and the lack of evidence about responsible treatment factors, regular breast cancer screening for males does not appear to be warranted at this time.
- Considering the increased risk of subsequent male breast cancer in survivors, childhood cancer survivors with symptoms that may be related to subsequent male breast cancer should be carefully and comprehensively examined to avoid a delay in detection.
- The IGHG (International Late Effects of Childhood Cancer Guideline Harmonization Group) COVID-19 working group provides guidance to childhood cancer survivors, who in many cases may have comorbid conditions linked to a high risk of a severe course of COVID-19. Our ongoing monitoring of emerging COVID-19 data and recommendations will facilitate modification of guidance relevant to the survivor population.

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CHAPTER 7

Nederlandse samenvatting

Nederlandse samenvatting / Summary in Dutch

In Nederland worden jaarlijks 550-600 kinderen gediagnosticeerd met kanker. De overleving is de afgelopen decennia sterk verbeterd. Overlevenden van kinderkanker hebben echter een hogere kans op het krijgen van gezondheidsproblemen later in hun leven door hun eerdere kanker en de behandeling daarvan. Één van de meest ernstige gezondheidsproblemen die kunnen optreden zijn nieuwe tumoren. Borstkanker is een van de meest voorkomende nieuwe tumoren bij overlevenden van kinderkanker. Het is belangrijk dat overlevenden van kinderkanker, en hun zorgverleners bewust zijn van hun verhoogde kans op het krijgen van borstkanker door hun behandeling. Om goed inzicht te krijgen welke overlevenden van kinderkanker vooral een verhoogde kans hebben op het krijgen van borstkanker is het belangrijk om risicofactoren voor borstkanker te identificeren. Het doel van dit proefschrift is om onze kennis over het risico op en de risicofactoren voor borstkanker na kinderkanker te vergroten. In het proefschrift worden ook aanbevelingen gedaan voor overlevenden van kinderkanker en hun zorgverleners met betrekking tot COVID-19.

Belangrijkste bevindingen in het proefschrift

In **Hoofdstuk 2** hebben we de methodologie en karakteristieken van ons internationaal consortium "International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer" beschreven. Dit consortium richt zich in eerste instantie op onderzoeksvragen gerelateerd aan borstkanker als nieuwe tumor. In dit hoofdstuk hebben we samengevat hoe de gegevens van de verschillende cohorten zijn verzameld, waaronder gegevens over de diagnose van de kinderkanker en de behandeling (bestralingsvelden, cumulatieve bestralingsdosis, chemotherapiemiddelen en dosis voor elk middel). Data zijn gepoold van zeven cohorten (die uit de Verenigde Staten, twee uit Nederlands, één uit Frankrijk en één uit Zwitserland). In totaal zijn er 21982 vrouwelijke vijf-jaars overlevenden van kinderkanker geïncludeerd in het gepoolde cohort. Het startjaar voor follow-up voor de cohorten varieerde tussen 1951 en 1981 en eindigde tussen 2013 en 2021, waarbij de mediane follow-up duur 24,3 jaar na kinderkankerdiagnose was (interkwartielafstand: 18,0-32,8). De mediane leeftijd ten tijde van kinderkankerdiagnose was 5,4 jaar (interkwartielafstand: 2,5-11,9 jaar) en de mediane bereikte leeftijd op einde van follow-up was 32,3 jaar (interkwartielafstand: 24,0-40,4 jaar). In totaal waren 4240 (19,4%) vrouwelijke overlevenden van kinderkanker behandeld met radiotherapie op de borst en 9308 (42,5%) behandeld met anthracyclines. Op het einde van de follow-up hadden 835 vrouwen een borstkanker als nieuwe tumor ontwikkeld, waarbij 635 van de vrouwen alleen een invasieve vorm van borstkanker hadden ontwikkeld,

184 alleen een in situ borstkanker (172 ductaal carcinoma in situ en 12 lobular carcinoma in situ) en 16 hadden een invasieve vorm van borstkanker en een in situ borstkanker. The cumulatieve incidenties voor borstkanker (invasief en in situ samen) 25 en 35 jaar na diagnose van de kinderkanker waren respectievelijk 2,2% en 6,2%. Het is de bedoeling dat het consortium als model en robuuste bron van gegevens over overlevenden van kinderkanker zal dienen voor het beantwoorden van andere kennishiaten over borstkanker als nieuwe tumor na kinderkanker en, in de toekomst, ook van het risico op andere soorten nieuwe tumoren.

In **Hoofdstuk 3** hebben we in onze internationale consortium database de dosis-respons relaties voor verschillende typen anthracyclines op het ontwikkelen van borstkanker als nieuwe tumor geanalyseerd en ook de interactie van anthracyclines met radiotherapie op de thorax. Onder de 17903 vrouwelijke overlevenden van kinderkanker die in deze studie waren geïncludeerd hadden na een mediane follow-up tijd van 24,9 jaar (interkwartielafstand: 19,1-33,2 jaar) in totaal 782 een borstkanker als nieuwe tumor ontwikkeld. We vonden een verhoogd risico op borstkanker na behandeling met doxorubicine (hazard ratio (HR) per 100 mg/m²: 1,24, 95% betrouwbaarheidsinterval (BI) 1,18-1,31), en een niet-statistisch significant verhoogd risico na behandeling met daunorubicine (HR per 100 mg/m²: 1,10, 95% BI: 0,95-1,29). Epirubicine was ook geassocieerd met een verhoogd risico op borstkanker (HR voor ja vs. nee: 3,25, 95% BI: 1,59-6,63). Onder survivors met en zonder radiotherapie op de thorax zagen we beide een dosis-afhankelijk effect van doxorubicine op het risico op borstkanker. De gezamenlijke effecten van doxorubicine en radiotherapie op de thorax waren minder dan multiplicatief ($HR_{multiplicatieve\ interactie}$ 0,86, 95% BI: 0,78-0,96, $P_{multiplicatieve\ interactie}$=0,006) en compatibel met een additief effect ($P_{additieve\ interactie}$=0,99). Onze bevindingen ondersteunen dat vroege initiatie van borstkanker surveillance redelijk is bij vrouwelijke overlevenden van kinderkanker die ≥200 mg/m² cumulatieve dosis doxorubicine hebben gehad. De resultaten van onze studie zouden moeten geïmplementeerd worden in richtlijnen voor borstkankersurveillance bij overlevenden van kinderkanker en zijn belangrijke informatie voor het ontwikkelen van behandelprotocollen voor nieuwe kinderkankerpatiënten.

In **Hoofdstuk 4** hebben we een systematisch literatuuronderzoek en analyse in een Pan-Europees cohort gedaan naar het risico op borstkanker bij mannen na kinderkanker. In het systematisch literatuuronderzoek hebben we in Medline/Pubmed gezocht naar artikelen die cohortstudies of case reports/series beschreven over borstkanker bij mannen na kinderkanker (≤21 years) om zo de huidige kennis over borstkanker bij mannen na kinderkanker samen te vatten. Daarnaast hebben we gegevens geanalyseerd over borstkanker bij mannen na kinderkanker van het

PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup) cohort. We hebben standardized incidence ratio's (SIR's), absolute excess risico's (AER's) en vijf- en tien-jaar overlevingskansen berekend. In het systematische literatuuronderzoek hebben we 38 artikelen uiteindelijk geïncludeerd van de 7080 potentieel in aanmerking komende artikelen. De frequenties van borstkanker bij mannen na kinderkanker tussen de verschillende studies varieerde van 0% tot 0,4% (31 studies). De tijd dat borstkanker optrad na kinderkanker varieerde van 24,0-42,0 jaar. In totaal waren er negen case reports/series die 11 gevallen van borstkanker bij mannen na kinderkanker beschreven; de borstkankers traden op tussen 11,0-42,5 jaar na kinderkanker diagnose. In het PanCareSurFup cohort analyseerden we gegevens van 37738 mannen waarbij in totaal 16 mannen een borstkanker hadden ontwikkeld. We vonden dat de mannelijke overlevenden van kinderkanker een 22,3 (95% BI: 12,7-36,2) keer hogere kans hadden op het krijgen van borstkanker dan de algemene mannelijke bevolking en de AER/100000 persoonsjaren was 2,3 (95% BI: 1,3-3,7). De cumulatieve incidentie voor het krijgen van borstkanker waren 0,02%, 0,04% en 0,10% respectievelijk op de leeftijd van 30, 40 en 50 jaar. De vijf- en tien-jaars overleving na borstkanker waren 60,3% (95% BI: 35,6%-85,0%) en 43,0% (95% BI: 16,1%-69,9%), respectievelijk. We vonden geen duidelijke risicofactoren op het krijgen van borstkanker bij mannen na kinderkanker in ons literatuuronderzoek en onze analyses. We concluderen dat mannelijke overlevenden van kinderkanker een verhoogde kans hebben op het krijgen van borstkanker ten opzichte van de algemene bevolking, maar dat het absoluut risico laag is. Zorgverleners voor overlevenden van kinderkanker moeten zich bewust zijn van de kans op dit zeldzame, maar ernstige gezondheidsprobleem en zorgvuldig onderzoek is nodig bij mannelijke overlevenden van kinderkanker die symptomen hebben die mogelijk kunnen duiden op borstkanker.

In **Hoofdstuk 5** hebben we een internationale werkgroep opgezet om de bestaande kennis samen te vatten en wereldwijde aanbevelingen te maken wat betreft relevante factoren en omstandigheden die geassocieerd zijn met een ernstig verloop van COVID-19. Bovendien hebben we in een relatief korte tijdsperiode een consensus statement gemaakt als leidraad voor zorgverleners en overlevenden van kinderkanker over COVID-19. Daarna hebben we informatie verspreid naar het publiek via de website van de International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) en verschillende nationale/institutionele kinderkanker forums. We hebben daarmee tijdig, in het begin van de COVID-19 pandemie, aanknopingspunten geboden aan overlevenden van kinderkanker, die vaak te maken hebben met comorbide problemen die een hogere kans geven op een ernstig verloop van COVID-19.

Dit proefschrift heeft de kennis over het risico op borstkanker bij zowel mannelijke als vrouwelijke overlevenden van kinderkanker een belangrijke stap voorwaarts gebracht. Voor zover wij weten, zijn onze beide gepoolde analyses, bij vrouwen en mannen, de meest uitgebreide onderzoeken met langdurige follow-up ooit naar het risico op borstkanker bij overlevenden van kinderkanker. Individuele cohorten hebben niet de statistische power om bepaalde belangrijke onderzoeksvragen te bestuderen. Door de enorme inspanning om individuele patiëntdata van cohorten wereldwijd te bundelen hebben we een grotere statistische power verkregen om risico's op het krijgen van borstkanker na kinderkanker te kwantificeren en om de specifieke kinderkankerbehandelingen te identificeren die geassocieerd zijn met het risico op borstkanker.

Hoofdboodschappen van dit proefschrift

- Het poolen van individuele patiënten data van geschikte cohorten wereldwijd verbetert de statistische power om risico's voor verschillende kinderkankerbehandelingen te bepalen op het krijgen van borstkanker, waarbij de power niet groot genoeg is in individuele studies.
- De heterogeniteit van de behandelingsblootstellingen in het gepoolde cohort, vooral gerelateerd aan variatie in behandelingscombinaties tussen landen, creëert betere mogelijkheden om de effecten van individuele behandelingen te ontrafelen.
- Onze studies levert bewijs dat doxorubicine geassocieerd is met dosis-afhankelijk verhoogd risico op het krijgen van borstkanker bij vrouwelijke overlevenden van kinderkanker, zowel bij vrouwen die ook op de thorax zijn bestraald als vrouwen die niet op de thorax zijn bestraald. Epirubicine (ja vs. nee) was ook geassocieerd met een verhoogd risico op borstkanker.
- Het risico op borstkanker bij vrouwen die doxorubicine en radiotherapie op de thorax hebben gehad was gelijk aan de som van hun individuele effecten.
- Onze bevindingen ondersteunen dat vroege initiatie van borstkanker surveillance redelijk is bij vrouwelijke overlevenden van kinderkanker die ≥200 mg/m^2 cumulatieve dosis doxorubicine hebben gehad. De resultaten van onze studie zouden moeten geïmplementeerd worden in richtlijnen voor borstkankersurveillance bij overlevenden van kinderkanker en zijn belangrijke informatie voor het ontwikkelen van behandelprotocollen voor nieuwe kinderkankerpatiënten.
- De infrastuctuur en gegevens over overlevenden van kinderkanker in het gepoolde internationale cohort kunnen gebruikt worden voor het beantwoorden van andere kennishiaten over borstkanker als nieuwe tumor na kinderkanker en, in de toekomst na het toevoegen van mannelijke overlevenden van kinderkanker, ook van kennishiaten over het risico op andere soorten nieuwe tumoren.

- Mannelijke overlevenden van kinderkanker hebben een sterk verhoogd risico op het krijgen van borstkanker ten opzichte van de algemene mannelijke bevolking, maar het absolute risico is laag. Risicofactoren voor borstkanker bij mannelijke overlevenden van kinderkanker zijn onbekend.
- Gezien het lage absolute risico op borstkanker bij mannelijke overlevenden van kinderkanker en het gebrek aan bewijs voor de bijdrage van behandelingsfactoren van kinderkanker aan dit risico, lijkt regelmatige borstkankerscreening voor mannen op dit moment niet gerechtvaardigd.
- Mannelijke overlevenden van kinderkanker met symptomen die mogelijk kunnen duiden op borstkanker moeten zorgvuldig en uitvoerig worden onderzocht om een vertraging in de opsporing te voorkomen.
- De IGHG (International Late Effects of Childhood Cancer Guideline Harmonization Group) COVID-19 werkgroep heeft aanknopingspunten geboden aan overlevenden van kinderkanker, die vaak te maken hebben gehad met comorbide problemen die een hogere kans geven op een ernstig verloop van COVID-19. Door het voortdurend in de gaten houden van nieuwe data en aanbevelingen over COVID-19 zullen aanpassingen van de aanbevelingen die relevant zijn voor de overlevenden van kinderkanker snel worden gedaan.

ADDENDUM

List of abbreviations
Curriculum Vitae
List of publications
PhD portfolio
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List of abbreviations

ALL	Acute lymphoblastic leukemia
AR	Androgen receptor
BMI	Body mass index
CAYA	Childhood, adolescent and young adult
CCS	Childhood cancer survivor
CCSS	Childhood Cancer Survivor Study
CED	Cyclophosphamide equivalent dose
CHD	Coronary heart disease
CI	Confidence interval
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CVD	Cerebrovascular disease
DCCSS LATER	Dutch Childhood Cancer Survivor Study LATER / Dutch Long-term Effects After Childhood Cancer Study
DCIS	Ductal carcinoma in situ
DHL	Dutch Hodgkin Late Effects cohort study
EAR/AER	Excess absolute risk / Absolute excess risk
ER	Estrogen receptor
FCCSS	French Childhood Cancer Survivor Study
Gy	Gray
HCP	Healthcare provider
HCT	Hematopoietic cell transplantation
HER2	Human epidermal growth factor receptor 2
HL	Hodgkin lymphoma
HR	Hazard ratio
IBC	Invasive breast cancer
ICCC	International Classification of Childhood Cancer
ICD-O-3	International Classification of Diseases for Oncology, Third Edition
ICU	Intensive care unit
IGHG	International Late Effects of Childhood Cancer Guideline Harmonization Group
IPD	Individual patient data

IQR	Interquartile range
LCIS	Lobular carcinoma in situ
LFS	Li-Fraumeni syndrome
mo	month
N/I	No information available
NA	Not applicable
NM	Not mentioned
NWTSG	US National Wilms' Tumor Study Group
OR	Odds ratio
PanCareSurFup	PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies
PR	Progesterone receptor
RR	Relative risk
RT	Radiotherapy
SBC	Subsequent breast cancer
SCCSS	Swiss Childhood Cancer Survivor Study
SD	Standard deviation
SEER	Surveillance, Epidemiology, and End Results
SEM	Standard error of the mean
SIOPE	European branch of the International Society of Pediatric Oncology Europe
SIR	Standardized incidence ratio
SJCRH	St Jude Childrens' Research Hospital, Memphis TN, USA
SJLIFE	St. Jude Lifetime Cohort Study
SMBC	Subsequent male breast cancer
SMN	Subsequent malignant neoplasm
STS	Soft tissue sarcoma
TBI	Total body irradiation
WHO	World Health Organization
yr	year

Curriculum Vitae

Yuehan Wang (王悦涵) was born in Juelich, Germany, on May 24th 1993. When she was one-year-old, her family moved to Toyko, Japan, where she spent her early childhood and was deeply influenced by the eating culture there. Yuehan finished her education from elementary school through college in Beijing, China, which she regards as her hometown. In 2011, Yuehan earned her Bachelor of Medicine degree in Preventive Medicine from China Capital Medical University in Beijing. In 2016, she moved to Nijmegen, the Netherlands, for her master's studies at Radboud University, majoring in biomedical science, specializing in epidemiology. During her master's studies, she completed her first research internship on physical activity epidemiology to identify the impact of cardiovascular disease diagnosis on physical activity behavior, under the supervision of Dr. Martijn Maessen, Dr. Thijs Eijsvogels, and Prof. André Verbeek, at the Department of Physiology, Radboud University Medical Center (RadboudUMC). She found her passion for research during her internship. She then went to the US for her second research internship, also focused on physical activity epidemiology, under the supervision of Dr. Duck-chul Lee at Iowa State University, Ames, Iowa. During this 10-month internship, she independently finished and published two research projects by conducting data analyses on the Aerobics Center Longitudinal Study (ACLS), and was also involved in two ongoing projects as a research assistant. Yuehan finished her Master's Degree, *cum laude*, in 2018.

Yuehan started her Ph.D. journey in 2019 at the Prinses Maxima Centrum, Utrecht, the Netherlands. There, she researched late effects in childhood cancer survivors, especially for second breast cancer risk in both females and males, and trained as an epidemiologist. Meanwhile, she has been also a member of the Vereniging voor Epidemiologie (VvE) and the Mentorship Initiative Network of ISoRED (International Society of Radiation Epidemiology and Dosimetry).

Yuehan currently plans to move to the US for her post-doc training at the National Cancer Institute (NCI) to continue the late effects research in second cancer.

List of publications

This thesis

Wang Y, Ronckers CM, van Leeuwen FE, Moskowitz CS, Leisenring W, Armstrong GT, de Vathaire F, Hudson MM, Kuehni CE, Arnold MA, Demoor-Goldschmidt C, Green DM, Henderson TO, Howell RM, Ehrhardt MJ, Neglia JP, Oeffinger KC, van der Pal HJH, Robison LL, Schaapveld M, Turcotte LM, Waespe N, Kremer LCM, Teepen JC; Subsequent female breast cancer risk associated with anthracycline chemotherapy for childhood cancer [Accepted for publication in *Nature Medicine*]

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Wang Y, Lee DC, Brellenthin AG, Eijsvogels TMH, Sui X, Church TS, Lavie CJ, Blair SN. Leisure-Time Running Reduces the Risk of Incident Type 2 Diabetes. Am J Med. 2019 Oct;132(10):1225-1232. doi: 10.1016/j.amjmed.2019.04.035. Epub 2019 May 17. PMID: 31103650; PMCID: PMC6832784.

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Liu W, **Wang Y**, Zhou Y. Progress of Stem Cell Therapy in End-stage Ischemic Cardiomyopathy. Journal of Cardiovascular and Pulmonary Diseases. 2015 (2):141-143. [Chinese]

PhD Portfolio

Name PhD candidate: Yuehan Wang
Institute: Princess Máxima Center for Pediatric Oncology
PhD period: 2019 March - 2023 January
Graduate school: Graduate School of Life Sciences (GSLS), Utrecht University
PhD programme: Epidemiology
Promotors: Prof. dr. L.C.M. Kremer & Prof. dr. ir. F.E. van Leeuwen
Co-promotors: Dr. J.C. Teepen & Dr. C.M. Ronckers

PhD training	Year
Courses within the PhD programme, Julius center, UMC Utrecht	
Advanced Topics in Causal Research: Confounding and Effect Modification	2020
Mixed Models	2020
Survival Analysis	2020
Missing Data	2020
Machine Learning & Application in Medicine	2021
General courses, Graduate School of Life Sciences (GSLS), UMC Utrecht	
Mindfulness and Stress Reduction	2020
Supervising Research of MSc Students	2021
Other courses	
Cancer epidemiology, National Institute for Health Sciences (NIHES), Amsterdam	2019
Radiation Epidemiology & Dosimetry Course, National Cancer Institute (NCI), Rockville, Maryland, USA	2019
Presentation course and storytelling, Princess Máxima Center for Pediatric Oncology, Utrecht	2019
Introduction to Breast Cancer, Coursera	2020
Seminars and workshops	
LATER research meetings & Journal clubs (chair 2019-2020)	2019-2023
Team research meetings	2019-2023
Princess Máxima Research meetings & seminars	2019-2023
Kika site visit	2019

PhD training	Year
Princess Máxima Retreat	2019 & 2021
Working consciously & effectively	2020
LinkedIn Basics workshop	2021
Explore your career from home	2021
VvE Webinar series COVID-19: Modeling data in COVID 19 time	2021
PhACE (PhD Activating Career Event)	2021
Educational day PanCare, Utrecht	2021
The Science of Childhood Cancer lecture series	2021-2022
The International Society of Radiation Epidemiology and Dosimetry (ISoRED) seminars	2021-2022
Mentorship Initiative Network of ISoRED (MINI) Events	2021-2022
St. Jude-VIVA Survivorship webinars	2022
Kika speechcoaching workshop (for nominees of Tom Voûte young investigator award)	2022
Best Practices for Writing Reproducible Code	2022
Writing a Reproducible Paper in R with WORCS	2023
(Inter)national confereces and meetings	
North American Symposium on Late Complications After Childhood Cancer (NASLCCC) 2019, Atlanta, Georgia, USA	2019
25th Pan-European Network For Care of Survivors after Childhood and Adolescent Cancer (PanCare) Spring Meeting 2021, Utrecht (oral presentation)	2021
Máxima research meeting, Utrecht (oral presentation)	2021
International Symposium on Late Complications after Childhood Cancer (ISLCCC) 2022, Utrecht (oral and poster presentation)	2022
National Cancer Institute seminar, online (oral presentation)	2022
Tom Voûte young investigator awards, Utrecht (oral presentation)	2022
The International Society of Radiation Epidemiology and Dosimetry 1st meeting	2023
International Symposium on Late Complications after Childhood Cancer (ISLCCC) 2023, Atlanta, Georgia, USA (oral presentation)	2023

PhD training	Year
Others	
BROK training & certificate	2021
Supervision of master student -- Loraine Cahn: Attained age-related risks of subsequent breast cancer in childhood cancer survivors	2021
MINI Organizing committee	2022-2023

Dankwoord

If someone ever told me ten years ago that I would be where I am now. I would definitely say, “no way”. Honestly, I could never imagine that I could make it that far! Ph.D. journey has never been easy. Undoubtedly, It’s impossible to achieve all of this by myself without love, help, and support from many people. Therefore, I want to thank everyone who has been involved in my Ph.D. journey here.

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Cécile, you always impress me with your passion and enthusiastic characteristics. Every meeting, you start it with “what can I help you?”, which makes me feel that I am an “independent-to-be adult” in the research field. You are the person I admire a lot. I will follow what you have done before, going to the place you have worked, the NCI, to continue a post-doc training. Thank you for trusting me with the IPD project. Every achievement that I’ve made started there.

Leontien, I’m extremely grateful to have you as my PI. Project-wise, I’m impressed by your big picture of the late effects field. During the meeting, you can pick up our struggles immediately and precisely every time. Life-wise, I really appreciated how much effort you have been putting in to gather our group to connect, especially during the corona time. Thanks for your exceptional work ethic on our group together. And I really appreciated your help and support during my Ph.D.

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