BMJ Open

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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To cite: Wang Y, Kremer LCM, van Leeuwen FE, *et al*. Cohort profile: Risk and risk factors for female breast cancer after treatment for childhood and adolescent cancer: an internationally pooled cohort. *BMJ Open* 2022;**12**:e065910. doi:10.1136/bmjopen-2022-065910

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-065910).

Received 24 June 2022
Accepted 13 October 2022

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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 summarised the data collected from each included cohort, including childhood cancer diagnosis information and treatment details (ie, 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, 4240 (19.4%) survivors were treated with radiotherapy to the chest and 9308 (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.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study 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.
⇒ The heterogeneity of treatment exposure, in particular related to variation in treatment combinations across countries, creates a better possibility to disentangle single treatment exposures in the pooling effort.
⇒ 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 generalisability of the results to other populations.

INTRODUCTION

Although cancer remains a leading cause of death for children worldwide,[1] the long-term survival of childhood, adolescent and young adult patients with cancer 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-recognised late adverse effect among women exposed to ionising 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 Harmonisation Group (IGHG) was established (https://www.ighg.org/) to harmonise 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 harmonisation 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]: (1) 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; (2) to examine the role of anthracyclines and the contributions of single anthracycline drugs regarding risk of subsequent breast cancer and (3) 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 use lower doses and smaller radiation volumes than cancer treatments from earlier years. In addition, 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 ionising radiation exposure in other circumstances (eg, 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 (eg, whole lung irradiation, median delivered dose, 14 Gy; range, 2–20 Gy) appeared to have excess risk of breast cancer; standardised incidence ratio (SIR), 43.6; 95% CI 27.2 to 70.3). This exceeds the reported risk for females treated with high dose radiotherapy exposures to only part of the breast tissue (eg, mantle irradiation, median delivered dose 40 Gy; range, 5–54 Gy; SIR, 24.2; 95% CI 20.7 to 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 fourfold increase in breast cancer risk compared with the general population at a similar age (SIR 4.0; 95% CI 3.0 to 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 HRs of 1.1 (95% CI 0.4 to 2.9), 2.6 (95% CI 1.1 to 6.5) and 5.8 (95% CI 2.7 to 12.5) for ≤270, 271–443, and >443 mg/m^2

doxorubicin dose, respectively (P_{trend}<0.001).[10] In both, the CCSS and DCCSS LATER reports, the association between anthracyclines and subsequent breast cancer was stronger among survivors of tumour types known to be associated with Li-Fraumeni syndrome, that is, leukaemia, central nervous system tumours 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 (ie, 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 (eg, ≥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 with 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 with 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 postmenopausal ages in the existing studies is too limited to demonstrate whether the risk of subsequent breast cancer remains elevated beyond postmenopausal 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 online 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 Tumour 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 harmonised data protocol, and are stored at the Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands (see online supplemental table 1 for an overview per data provider).

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, behaviour 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

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, behaviour code and topography code ▶ Laterality (left/right/bilateral/not applicable/unknown)	SJLIFE: no ICD-O-3 coding, but detailed description of tumour 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 tumour up to five years following primary diagnosis SJLIFE/NWTSG/DCCSS LATER/ FCCSS/SCCSS/DHL: all known treatments for primary tumours 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
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. 1. For analyses, if patients had multiple fields to the same region, the dose was summed, with two exceptions: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 behaviour code ▶ ICD-O-3 topography code ▶ Laterality (left/right/bilateral/unknown) ▶ Year and month of diagnosis ▶ Tumour receptor status: Oestrogen, human epidermal growth factor receptor 2 and progesterone status (negative/positive/unknown)	DCCSS LATER: no information on tumour receptor status
Other subsequent malignant neoplasms	▶ ICD-O-3 morphology code, behaviour 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

Continued

Table 1 Continued

Data information	Requested items for consortium database	Comments
Reproductive factors	▶ Age at menarche ▶ Menopausal status (premenopausal/ 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	SCCSS: not available NWTSG/DHL: only available for first-degree relatives
	▶ Race	DCCSS LATER/FCCSS/SCCSS/DHL: not available
	▶ Treatment protocol name	DCCSS LATER/FCCSS/DHL: not available
	▶ Ovarian transplantation before pelvic field irradiation	SJLIFE/NWTSG/DCCSS LATER/SCCSS/DHL: not available
	▶ Breast dosimetry performed, absorbed breast dose, ovarian dosimetry performed, absorbed ovarian dose	NWTSG/DCCSS LATER/SCCSS/DHL: not available

*Spine irradiation fields not involving a thoracic part of the spine were not considered chest radiotherapy.
CCSC, Childhood Cancer Survivor Study; DCCSS LATER, Dutch Long-term Effects After Childhood Cancer Study; DHL, Dutch Hodgkin Late Effects cohort; FCCSS, French Childhood Cancer Survivor Study; ICCC, International Classification of Childhood Cancer, Third Edition; ICD-O-3, International Classification of Diseases for Oncology, Third Edition; NWTSG, US National Wilms Tumour Study group; SCCSS, Swiss Childhood Cancer Survivor Study; SJLIFE, St. Jude Lifetime Cohort Study.

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 (eg, 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.

Outcome ascertainment

The process of ascertainment of subsequent (invasive and in situ) breast cancer and other subsequent malignancies for each participating cohort is summarised in table 2. For all subsequent malignancies, information of morphology,

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

Participating studies	Subsequent breast cancer ascertainment			Subsequent breast cancer case validation
	Medical files	Record linkage	Other sources for SMN ascertainment	
CCSS	None	National Death Index	Initial self-reports 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

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

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							Overall		
	CCSS (n=9671)	NWTS (n=3989)	FCCSS (n=3415)	SJLIFE (n=2236)	LATER (n=2237)	DHL (n=265)	SCCSS (n=79)	Total (n=21 892)	Non-SBC patients (n=21 057)	SBC* patients (n=835)
Primary childhood cancer type										
Leukaemia	2987 (30.9%)	–	–	802 (35.9%)	770 (34.4%)	–	15 (19.0%)	4574 (20.9%)	4492 (21.3%)	82 (9.8%)
Non-Hodgkin's lymphoma	586 (6.1%)	–	235 (6.9%)	115 (5.1%)	157 (7.0%)	–	4 (5.1%)	1097 (5.0%)	1060 (5.0%)	37 (4.4%)
Hodgkin lymphoma	1276 (13.2%)	–	189 (5.5%)	227 (10.2%)	125 (5.6%)	265 (100%)	19 (24.1%)	2101 (9.6%)	1692 (8.0%)	409 (49.0%)
CNS tumour	1841 (19.0%)	–	498 (14.6%)	287 (12.8%)	312 (13.9%)	–	8 (10.1%)	2946 (13.5%)	2932 (13.9%)	14 (1.7%)
Neuroblastoma	901 (9.3%)	–	505 (14.8%)	101 (4.5%)	145 (6.5%)	–	5 (6.3%)	1657 (7.6%)	1642 (7.8%)	15 (1.8%)
Retinoblastoma	–	–	293 (8.6%)	119 (5.3%)	14 (0.6%)	–	–	426 (1.9%)	424 (2.0%)	2 (0.2%)
Renal tumour	389 (4.0%)	3989 (100%)	558 (16.3%)	170 (7.6%)	250 (11.2%)	–	5 (6.3%)	5361 (24.5%)	5270 (25.0%)	91 (10.9%)
Hepatic tumour	–	–	32 (0.9%)	10 (0.4%)	19 (0.8%)	–	–	61 (0.3%)	60 (0.3%)	1 (0.1%)
Bone tumour	884 (9.1%)	–	295 (8.6%)	133 (5.9%)	141 (6.3%)	–	6 (7.6%)	1459 (6.7%)	1352 (6.4%)	107 (12.8%)
Soft tissue tumour	763 (7.9%)	–	361 (10.6%)	127 (5.7%)	151 (6.8%)	–	3 (3.8%)	1405 (6.4%)	1350 (6.4%)	55 (6.6%)
Germ cell tumour	20 (0.2%)	–	249 (7.3%)	68 (3.0%)	101 (4.5%)	–	2 (2.5%)	440 (2.0%)	431 (2.0%)	9 (1.1%)
Other malignant epithelial neoplasms	–	–	187 (5.5%)	49 (2.2%)	50 (2.2%)	–	11 (13.9%)	297 (1.4%)	286 (1.4%)	11 (1.3%)
Other and unspecified	–	–	7 (0.2%)	28 (1.3%)	2 (0.1%)	–	1 (1.3%)	38 (0.2%)	37 (0.2%)	1 (0.1%)
Unclassified	24 (0.2%)	–	6 (0.2%)	–	–	–	–	30 (0.1%)	29 (0.1%)	1 (0.1%)
Age at primary childhood cancer diagnosis (year) category										
<5	3666 (37.9%)	2990 (75.0%)	1671 (48.9%)	973 (43.5%)	1049 (46.9%)	–	17 (21.5%)	10 366 (47.4%)	10 282 (48.8%)	84 (10.1%)
5–9	2027 (21.0%)	869 (21.8%)	707 (20.7%)	468 (20.9%)	569 (25.4%)	7 (2.6%)	10 (12.7%)	4657 (21.3%)	4574 (21.7%)	83 (9.9%)
10–14	2204 (22.8%)	115 (2.9%)	744 (21.8%)	472 (21.1%)	471 (21.1%)	21 (7.9%)	18 (22.8%)	4045 (18.5%)	3759 (17.9%)	286 (34.3%)
15–21	1774 (18.3%)	15 (0.4%)	293 (8.6%)	323 (14.4%)	148 (6.6%)	237 (89.4%)	34 (43.0%)	2824 (12.9%)	2442 (11.6%)	382 (45.7%)
Period of childhood cancer diagnosis category										
<1960	–	–	60 (1.8%)	–	–	–	–	60 (0.3%)	51 (0.2%)	9 (1.1%)
1960–1969	–	3 (0.1%)	264 (7.7%)	42 (1.9%)	49 (2.2%)	29 (10.9%)	–	387 (1.8%)	352 (1.7%)	35 (4.2%)
1970–1979	2639 (27.3%)	612 (15.3%)	693 (20.3%)	274 (12.3%)	386 (17.3%)	81 (30.6%)	8 (10.1%)	4693 (21.4%)	4326 (20.5%)	367 (44.0%)
1980–1989	3737 (38.6%)	1440 (36.1%)	1035 (30.3%)	535 (23.9%)	711 (31.8%)	76 (28.7%)	27 (34.2%)	7561 (34.5%)	7254 (34.4%)	307 (36.8%)
1990–1999	3295 (34.1%)	1562 (39.2%)	1233 (36.1%)	633 (28.3%)	871 (38.9%)	76 (28.7%)	26 (32.9%)	7696 (35.2%)	7585 (36.0%)	111 (13.3%)
2000–2011	–	372 (9.3%)	130 (3.8%)	752 (33.6%)	220 (9.8%)	3 (1.1%)	18 (22.8%)	1495 (6.8%)	1489 (7.1%)	6 (0.7%)
Duration of follow-up since 5-year survival (year)†										
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)	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)
Duration of follow-up since 5-year survival (year)† category										
<10	1096 (11.3%)	1308 (32.8%)	251 (7.4%)	543 (24.3%)	482 (21.5%)	40 (15.1%)	36 (45.6%)	3756 (17.2%)	3690 (17.5%)	66 (7.9%)
10–19	3672 (38.0%)	1145 (28.7%)	1130 (33.1%)	703 (31.4%)	859 (38.4%)	116 (43.8%)	24 (30.4%)	7649 (34.9%)	7326 (34.8%)	323 (38.7%)

Continued

Table 3 Continued

	Participating study							Overall		
	CCSS (n=9671)	NWTS (n=3989)	FCCSS (n=3415)	SJLIFE (n=2236)	LATER (n=2237)	DHL (n=265)	SCCSS (n=79)	Total (n=21 892)	Non-SBC patients (n=21 057)	SBC* patients (n=835)
20–29	3014 (31.2%)	1007 (25.2%)	1019 (29.8%)	570 (25.5%)	645 (28.8%)	69 (26.0%)	18 (22.8%)	6342 (29.0%)	5995 (28.5%)	347 (41.6%)
≥30	1889 (19.5%)	529 (13.3%)	1015 (29.7%)	420 (18.8%)	251 (11.2%)	40 (15.1%)	1 (1.3%)	4145 (18.9%)	4046 (19.2%)	99 (11.9%)
Attained age at last follow-up (year)†										
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)	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)
Attained age at last follow-up age (year)† category										
<20	838 (8.7%)	1484 (37.2%)	242 (7.1%)	380 (17.0%)	395 (17.7%)	1 (0.4%)	14 (17.7%)	3354 (15.3%)	3350 (15.9%)	4 (0.5%)
20–29	2552 (26.4%)	1128 (28.3%)	862 (25.2%)	614 (27.5%)	798 (35.7%)	26 (9.8%)	30 (38.0%)	6010 (27.5%)	5929 (28.2%)	81 (9.7%)
30–39	3314 (34.3%)	921 (23.1%)	1069 (31.3%)	688 (30.8%)	666 (29.8%)	93 (35.1%)	18 (22.8%)	6769 (30.9%)	6413 (30.5%)	356 (42.6%)
≥40	2967 (30.7%)	456 (11.4%)	1242 (36.4%)	554 (24.8%)	378 (16.9%)	145 (54.7%)	17 (21.5%)	5759 (26.3%)	5365 (25.5%)	394 (47.2%)
Any subsequent breast cancer (invasive or in situ)‡										
No	9214 (95.3%)	3943 (98.8%)	3287 (96.3%)	2158 (96.5%)	2196 (98.2%)	200 (75.5%)	59 (74.7%)	21 057 (96.2%)	21 057 (100%)	–
Yes	457 (4.7%)	46 (1.2%)	128 (3.7%)	78 (3.5%)	41 (1.8%)	65 (24.5%)	20 (25.3%)	835 (3.8%)	–	835 (100%)
First subsequent breast cancer type										
Only invasive	336 (73.5%)	30 (65.2%)	110 (85.9%)	52 (66.7%)	36 (87.8%)	51 (78.5%)	20 (100%)	635 (76.1%)§	–	635 (76.1%)§
Only in situ	113 (24.7%)	12 (26.1%)	16 (12.5%)	24 (30.8%)	5 (12.2%)	14 (21.5%)	–	184 (22.0%)¶**	–	184 (22.0%)¶**
Invasive and in situ diagnosed at the same moment	8 (1.8%)	4 (8.7%)	2 (1.6%)	2 (2.6%)	–	–	–	16 (1.9%)††	–	16 (1.9%)††
Vital status at last point of contact										
Alive	8174 (84.5%)	3802 (95.3%)	2759 (80.8%)	2171 (97.1%)	1928 (86.2%)	178 (67.2%)	68 (86.1%)	19 080 (87.2%)	18 489 (87.8%)	591 (70.8%)
Deceased	1497 (15.5%)	187 (4.7%)	656 (19.2%)	65 (2.9%)	309 (13.8%)	87 (32.8%)	11 (13.9%)	2812 (12.8%)	2568 (12.2%)	244 (29.2%)

*Includes patients with invasive and/or in situ breast cancer
†Follow-up time was calculated from 5 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 online supplemental material.
§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 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, two developed DCIS as a third subsequent breast cancer.
CCSS, Childhood Cancer Survivor Study; 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; LCIS, lobular carcinoma in situ; NWTSG, US National Wilms Tumour Study group; SBC, subsequent breast cancer; SCCSS, Swiss Childhood Cancer Survivor Study; SJLIFE, St. Jude Lifetime Cohort Study.

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							Overall		
	CCSS (n=9671)	NWTS (n=3989)	FCCSS (n=3415)	SJLIFE (n=2236)	LATER (n=2237)	DHL (n=265)	SCCSS (n=79)	Total (n=21 892)	Non-SBC patients (n=21 057)	SBC* patients (n=835)
Radiotherapy exposure to the chest										
No	6607 (68.3%)	3415 (85.6%)	2728 (79.9%)	1706 (76.3%)	1892 (84.6%)	22 (8.3%)	49 (62.0%)	16 419 (75.0%)	16 145 (76.7%)	274 (32.8%)
Yes	2098 (21.7%)	547 (13.7%)	482 (14.1%)	506 (22.6%)	341 (15.2%)	243 (91.7%)	23 (29.1%)	4240 (19.4%)	3735 (17.7%)	505 (60.5%)
Unknown	966 (10.0%)	27 (0.7%)	205 (6.0%)	24 (1.1%)	4 (0.2%)	–	7 (8.9%)	1233 (5.6%)	1177 (5.6%)	56 (6.7%)
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)	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)
Chest radiation dose (Gy) category										
No chest radiation	6607 (68.3%)	3415 (85.6%)	2728 (79.9%)	1706 (76.3%)	1892 (84.6%)	22 (8.3%)	49 (62.0%)	16 419 (75.0%)	16 145 (76.7%)	274 (32.8%)
<10	73 (0.8%)	4 (0.1%)	7 (0.2%)	5 (0.2%)	48 (2.1%)	–	–	137 (0.6%)	132 (0.6%)	5 (0.6%)
10–19	403 (4.2%)	509 (12.8%)	102 (3.0%)	133 (5.9%)	69 (3.1%)	2 (0.8%)	6 (7.6%)	1224 (5.6%)	1151 (5.5%)	73 (8.7%)
20–29	533 (5.5%)	19 (0.5%)	148 (4.3%)	210 (9.4%)	60 (2.7%)	11 (4.2%)	2 (2.5%)	983 (4.5%)	906 (4.3%)	77 (9.2%)
30–39	542 (5.6%)	12 (0.3%)	92 (2.7%)	85 (3.8%)	82 (3.7%)	90 (34.0%)	5 (6.3%)	908 (4.1%)	762 (3.6%)	146 (17.5%)
≥40	511 (5.3%)	3 (0.1%)	133 (3.9%)	41 (1.8%)	68 (3.0%)	85 (32.1%)	6 (7.6%)	847 (3.9%)	650 (3.1%)	197 (23.6%)
Unknown	1002 (10.4%)	27 (0.7%)	205 (6.0%)	56 (2.5%)	18 (0.8%)	55 (20.8%)	11 (13.9%)	1374 (6.3%)	1311 (6.2%)	63 (7.5%)
Chest radiation field										
No chest radiation	6607 (68.3%)	3415 (85.6%)	2728 (79.9%)	1706 (76.3%)	1892 (84.6%)	22 (8.3%)	49 (62.0%)	16 419 (75.0%)	16 145 (76.7%)	274 (32.8%)
Axilla	12 (0.1%)	–	–	5 (0.2%)	15 (0.7%)	2 (0.8%)	–	34 (0.2%)	31 (0.1%)	3 (0.4%)
Mantle	723 (7.5%)	–	86 (2.5%)	191 (8.5%)	39 (1.7%)	192 (72.5%)	11 (13.9%)	1242 (5.7%)	911 (4.3%)	331 (39.6%)
Mediastinal	227 (2.3%)	1 (0.0%)	134 (3.9%)	23 (1.0%)	36 (1.6%)	45 (17.0%)	4 (5.1%)	470 (2.1%)	437 (2.1%)	33 (4.0%)
Others	177 (1.8%)	19 (0.5%)	117 (3.4%)	33 (1.5%)	49 (2.2%)	–	1 (1.3%)	396 (1.8%)	344 (1.6%)	52 (6.2%)
Spine	598 (6.2%)	–	98 (2.9%)	131 (5.9%)	109 (4.9%)	–	3 (3.8%)	939 (4.3%)	927 (4.4%)	12 (1.4%)
Total body irradiation	223 (2.3%)	–	10 (0.3%)	67 (3.0%)	69 (3.1%)	–	2 (2.5%)	371 (1.7%)	348 (1.7%)	23 (2.8%)
Whole lung	79 (0.8%)	527 (13.2%)	37 (1.1%)	44 (2.0%)	22 (1.0%)	–	2 (2.5%)	711 (3.2%)	663 (3.1%)	48 (5.7%)
Unknown	1025 (10.6%)	27 (0.7%)	205 (6.0%)	36 (1.6%)	6 (0.8%)	4 (1.5%)	7 (8.9%)	1310 (6.0%)	1251 (5.9%)	59 (7.1%)
Radiotherapy exposure to the pelvis										
No	7191 (74.4%)	1922 (48.2%)	2287 (67.0%)	1873 (83.8%)	2129 (95.2%)	179 (67.5%)	68 (86.1%)	15 649 (71.5%)	15 133 (71.9%)	516 (61.8%)
Yes	1515 (15.7%)	–	923 (27.0%)	337 (15.1%)	105 (4.7%)	81 (30.6%)	3 (3.8%)	2964 (13.5%)	2740 (13.0%)	224 (26.8%)
Unknown	965 (10.0%)	2067 (51.8%)	205 (6.0%)	26 (1.2%)	3 (0.1%)	5 (1.9%)	8 (10.1%)	3279 (15.0%)	3184 (15.1%)	95 (11.4%)
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)	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)
Pelvic radiation dose (Gy) category										
No pelvic radiation	7191 (74.4%)	1922 (48.2%)	2287 (67.0%)	1873 (83.8%)	2129 (95.2%)	179 (67.5%)	68 (86.1%)	15 649 (71.5%)	15 133 (71.9%)	516 (61.8%)

Continued

Table 4 Continued

	Participating study							Overall		
	CCSS (n=9671)	NWTS (n=3989)	FCCSS (n=3415)	SJLIFE (n=2236)	LATER (n=2237)	DHL (n=265)	SCCSS (n=79)	Total (n=21 892)	Non-SBC patients (n=21 057)	SBC* patients (n=835)
<10	66 (0.7%)	–	25 (0.7%)	4 (0.2%)	47 (2.1%)	–	–	142 (0.6%)	136 (0.6%)	6 (0.7%)
10–19	369 (3.8%)	–	114 (3.3%)	89 (4.0%)	20 (0.9%)	–	2 (2.5%)	594 (2.7%)	570 (2.7%)	24 (2.9%)
20–29	365 (3.8%)	–	232 (6.8%)	120 (5.4%)	2 (0.1%)	–	–	719 (3.3%)	681 (3.2%)	38 (4.6%)
30–39	398 (4.1%)	–	216 (6.3%)	66 (3.0%)	6 (0.3%)	81 (30.6%)‡	–	767 (3.5%)	684 (3.2%)	83 (9.9%)
≥40	295 (3.1%)	–	336 (9.8%)	57 (2.5%)	25 (1.1%)	–	–	713 (3.3%)	641 (3.0%)	72 (8.6%)
Unknown	987 (10.2%)	2067 (51.8%)	205 (6.0%)	27 (1.2%)	8 (0.4%)	5 (1.9%)	9 (11.4%)	3308 (15.1%)	3212 (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.
CCSS, Childhood Cancer Survivor Study; CNS, central nervous system; DCCSS LATER, Dutch Long-term Effects After Childhood Cancer Study; DHL, Dutch Hodgkin Late Effects cohort; FCCSS, French Childhood Cancer Survivor Study; NA, not applicable; NWTSG, US National Wilms Tumour Study group; SBC, subsequent breast cancer; SCCSS, Swiss Childhood Cancer Survivor Study; SJLIFE, St. Jude Lifetime Cohort Study.

topography, diagnosis year and month was collected. For subsequent breast cancer, laterality, hormone receptor status (ie, oestrogen 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 (oophoropexy) 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 organisations (eg, 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.

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=4145) of females were followed for ≥30 years since 5-year survival. The median attained age at last follow-up was 32.2 (IQR 24.0–40.4) years, and the consortium

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							Overall		
	CCSS (n=9671)	NWTS (n=3989)	FCCSS (n=3415)	SJLIFE (n=2236)	LATER (n=2237)	DHL (n=265)	SCCSS (n=79)	Total (n=21 892)	Non-SBC patients (n=21 057)	SBC* patients (n=835)
Anthracyclines†										
No	4889 (50.6%)	2237 (56.1%)	2095 (61.3%)	955 (42.7%)	1250 (55.9%)	155 (58.5%)	36 (45.6%)	11 617 (53.1%)	11 204 (53.2%)	413 (49.5%)
Yes	3990 (41.3%)	1738 (43.6%)	1201 (35.2%)	1263 (56.5%)	982 (43.9%)	98 (37.0%)	36 (45.6%)	9308 (42.5%)	8943 (42.5%)	365 (43.7%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)	5 (0.2%)	12 (4.5%)	7 (8.9%)	967 (4.4%)	910 (4.3%)	57 (6.8%)
Doxorubicin										
No	5729 (59.2%)	2237 (56.1%)	2300 (67.4%)	1377 (61.6%)	1541 (68.9%)	181 (68.3%)	42 (53.2%)	13 407 (61.2%)	12 954 (61.5%)	453 (54.3%)
Yes	3150 (32.6%)	1738 (43.6%)	996 (29.2%)	841 (37.6%)	691 (30.9%)	84 (31.7%)	30 (38.0%)	7530 (34.4%)	7205 (34.2%)	325 (38.9%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)	5 (0.2%)	–	7 (8.9%)	955 (4.4%)	898 (4.3%)	57 (6.8%)
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)	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)
Doxorubicin dose (mg/m²) category										
0	5729 (59.2%)	2237 (56.1%)	2300 (67.4%)	1377 (61.6%)	1541 (68.9%)	181 (68.3%)	42 (53.2%)	13 407 (61.2%)	12 954 (61.5%)	453 (54.3%)
<100	502 (5.2%)	–	95 (2.8%)	121 (5.4%)	188 (8.4%)	5 (1.9%)	1 (1.3%)	912 (4.2%)	896 (4.3%)	16 (1.9%)
100–199	769 (8.0%)	–	347 (10.2%)	414 (18.5%)	232 (10.4%)	20 (7.5%)	13 (16.5%)	1795 (8.2%)	1725 (8.2%)	70 (8.4%)
200–299	590 (6.1%)	–	207 (6.1%)	124 (5.5%)	62 (2.8%)	38 (14.3%)	5 (6.3%)	1026 (4.7%)	958 (4.5%)	68 (8.1%)
300–399	568 (5.9%)	–	203 (5.9%)	146 (6.5%)	77 (3.4%)	11 (4.2%)	7 (8.9%)	1012 (4.6%)	945 (4.5%)	67 (8.0%)
≥400	474 (4.9%)	–	137 (4.0%)	35 (1.6%)	124 (5.5%)	6 (2.3%)	3 (3.8%)	779 (3.6%)	721 (3.4%)	58 (6.9%)
Unknown	1039 (10.7%)	1752 (43.9%)	126 (3.7%)	19 (0.8%)	13 (0.6%)	4 (1.5%)	8 (10.1%)	2961 (13.5%)	2858 (13.6%)	103 (12.3%)
Daunorubicin										
No	7660 (79.2%)	3975 (99.6%)	3239 (94.8%)	1618 (72.4%)	1795 (80.2%)	253 (95.5%)	65 (82.3%)	18 605 (85.0%)	17 869 (84.9%)	736 (88.1%)
Yes	1219 (12.6%)	–	57 (1.7%)	600 (26.8%)	437 (19.5%)	–	7 (8.9%)	2320 (10.6%)	2278 (10.8%)	42 (5.0%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)	5 (0.2%)	12 (4.5%)	7 (8.9%)	967 (4.4%)	910 (4.3%)	57 (6.8%)
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)	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)
Daunorubicin dose (mg/m²) category										
0	7660 (79.2%)	3975 (99.6%)	3239 (94.8%)	1618 (72.4%)	1795 (80.2%)	253 (95.5%)	65 (82.3%)	18605 (85.0%)	17869 (84.9%)	736 (88.1%)
<100	263 (2.7%)	–	5 (0.1%)	339 (15.2%)	16 (0.7%)	–	–	623 (2.8%)	616 (2.9%)	7 (0.8%)
100–199	373 (3.9%)	–	17 (0.5%)	198 (8.9%)	361 (16.1%)	–	4 (5.1%)	953 (4.4%)	937 (4.4%)	16 (1.9%)
≥200	494 (5.1%)	–	35 (1.0%)	62 (2.8%)	51 (2.3%)	–	3 (3.8%)	645 (2.9%)	628 (3.0%)	17 (2.0%)
Unknown	881 (9.1%)	14 (0.4%)	119 (3.5%)	19 (0.8%)	14 (0.6%)	12 (4.5%)	7 (8.9%)	1066 (4.9%)	1007 (4.8%)	59 (7.1%)
Epirubicin										
No	8877 (91.8%)	3975 (99.6%)	3116 (91.2%)	2217 (99.2%)	2104 (94.1%)	251 (94.7%)	72 (91.1%)	20612 (94.2%)	19843 (94.2%)	769 (92.1%)

Continued

Table 5 Continued

	Participating study							Overall		
	CCSS (n=9671)	NWTS (n=3989)	FCCSS (n=3415)	SJLIFE (n=2236)	LATER (n=2237)	DHL (n=265)	SCCSS (n=79)	Total (n=21 892)	Non-SBC patients (n=21 057)	SBC* patients (n=835)
Yes	2 (0.0%)	–	180 (5.3%)	1 (0.0%)	128 (5.7%)	14 (5.3%)	–	325 (1.5%)	316 (1.5%)	9 (1.1%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)	5 (0.2%)	–	7 (8.9%)	955 (4.4%)	898 (4.3%)	57 (6.8%)
Idarubicin										
No	8814 (91.1%)	3975 (99.6%)	3296 (96.5%)	2198 (98.3%)	2212 (98.9%)	253 (95.5%)	70 (88.6%)	20 818 (95.1%)	20 041 (95.2%)	777 (93.1%)
Yes	65 (0.7%)	–	–	20 (0.9%)	20 (0.9%)	–	2 (2.5%)	107 (0.5%)	106 (0.5%)	1 (0.1%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)	5 (0.2%)	12 (4.5%)	7 (8.9%)	967 (4.4%)	910 (4.3%)	57 (6.8%)
Alkylating agents										
No	4003 (41.4%)	3666 (91.9%)	1597 (46.8%)	947 (42.4%)	1152 (51.5%)	100 (37.7%)	33 (41.8%)	11 498 (52.5%)	11 167 (53.0%)	331 (39.6%)
Yes	4876 (50.4%)	309 (7.7%)	1699 (49.8%)	1271 (56.8%)	1080 (48.3%)	153 (57.7%)	39 (49.4%)	9427 (43.1%)	8980 (42.6%)	447 (53.5%)
Unknown	792 (8.2%)	14 (0.4%)	119 (3.5%)	18 (0.8%)	5 (0.2%)	12 (4.5%)	7 (8.9%)	967 (4.4%)	910 (4.3%)	57 (6.8%)
CED§ dose (mg/m²)										
0	4093 (42.3%)	3666 (91.9%)	1608 (47.1%)	956 (42.8%)	1160 (51.9%)	100 (37.7%)	34 (43.0%)	11 617 (53.1%)	11 272 (53.5%)	345 (41.3%)
<6000	1687 (17.4%)	–	606 (17.7%)	489 (21.9%)	265 (11.8%)	–	22 (27.8%)	3069 (14.0%)	2972 (14.1%)	97 (11.6%)
6000–17999	1876 (19.4%)	–	819 (24.0%)	631 (28.2%)	563 (25.2%)	–	10 (12.7%)	3899 (17.8%)	3706 (17.6%)	193 (23.1%)
≥18 000	561 (5.8%)	–	222 (6.5%)	139 (6.2%)	192 (8.6%)	–	3 (3.8%)	1117 (5.1%)	1070 (5.1%)	47 (5.6%)
Unknown	1454 (15.0%)	323 (8.1%)	160 (4.7%)	21 (0.9%)	57 (2.5%)	165 (62.3%)	10 (12.7%)	2190 (10.0%)	2037 (9.7%)	153 (18.3%)

*Includes patients with invasive and/or in situ breast cancer.
†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 (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)).
CCSS, Childhood Cancer Survivor Study; CED, cyclophosphamide equivalent dose; CNS, central nervous system; DCCSS LATER, Dutch Long-term Effects After Childhood Cancer Study; DHL, Dutch Hodgkin Late Effects cohort; FCCSS, French Childhood Cancer Survivor Study; NA, not applicable; NWTSG, US National Wilms Tumour Study group; SBC, subsequent breast cancer; SCCSS, Swiss Childhood Cancer Survivor Study; SJLIFE, St. Jude Lifetime Cohort Study.

cohort included 1592 (7.3%) survivors who reached age 50 years, and 211 (1.0%) survivors who reached age 60 years. In all, 4240 (19.4%) childhood/adolescent cancer survivors were treated with radiotherapy to the chest, and 9308 (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 tumour 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 tumour survivors. Tables 4 and 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 online supplemental 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 summarised in online supplemental table 3. In addition, selected other cohort-specific findings relating to subsequent breast cancer risk are highlighted.

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 ageing population. The differences between studies (eg, primary cancer types, cancer treatment and 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 generalisability 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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Acknowledgements We thank Giulio J. D'Angio and Norman E. Breslow for their contribution to the set up of the NWTSG. We also thank Susan Smith for critical review of the manuscript.

Collaborators The International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer includes the listed co-authors and the following collaborators: K. Scott Baker, Fred Hutchinson Cancer Research Center, Seattle, WA, USA and University of Washington, Seattle, WA, USA; Amy Berrington de González, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; Miriam R. Conces, Department of Pathology and Laboratory Medicine, Nationwide Children's Hospital, Columbus, Ohio, USA and Department of Pathology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA; Louis S. Constine, University of Rochester Medical Center, Rochester, NY, USA; Daniel M. Green, St. Jude Children's Research Hospital, Memphis, TN, USA; Mike Hawkins, Centre for Childhood Cancer Survivor Studies, University of Birmingham, Birmingham, UK; Tara O. Henderson, University of Chicago Medicine Comer Children's Hospital, Chicago, IL, USA; Geert O. Janssens, University Medical Centre Utrecht, Utrecht, The Netherlands and Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands; Lene Mellemkjaer, Danish Cancer Society Research Center, Copenhagen, Denmark; Kevin C. Oeffinger, Duke University Medical Center, Durham, NC, USA; Raoul Reulen, Centre for Childhood Cancer Survivor Studies, University of Birmingham, Birmingham, UK; Jeanette F. Winther, Childhood Cancer Research Group, Danish Cancer Society Research Center, Copenhagen, Denmark and Department of Clinical Medicine, Faculty of Health, Aarhus University and Aarhus University Hospital, Aarhus, Denmark.

Contributors YW and JCT performed the analyses. YW, JCT and CMR drafted the manuscript. YW, JCT, CMR, LCMK, FEvL, GTA, WL, FdV, MMH, CEK, MAA, NH, CD-G, ID, RMH, MJE, CSM, JPN, HJHvdP, LLR, MS, LMT and NW contributed to the conception or design of the work, critically revised the manuscript, and approved the final version. JCT is the guarantor for this study. CMR and JCT are joint last authors.

Funding This work was supported by the Children Cancer Free Foundation (KiKa, Grant No. 325 title: Risk factors for female breast cancer after treatment for childhood and adolescent cancer: individual patient data analyses of an internationally pooled cohort; CMR, FEvL, LCMK, principal investigators). The CCSS and SJLIFE cohorts are supported by the National Cancer Institute (CA55727, GTA, principal investigator; CA195547, MMH and LLR, principal investigators) as well as support to St. Jude Children's Research Hospital also provided by the Cancer Center Support (CORE) grant (CA21765, C. Roberts, principal investigator) and the American Lebanese Syrian Associated Charities (ALSAC). The NWTSG was supported by the National Cancer Institute (CA054498, N.E. Breslow and WL, principal investigator). The DCCSS LATER is supported by the Dutch Cancer Society (DCOG2011-5027, CMR, FEvL, Wim Tissing, principal investigators and UVA2012-5517, CMR, LCMK, principal investigators). The FCCSS is funded by the Fondation ARC (PopHARC Grant) and the Agence Nationale pour la Recherche Médicale (ANR, Hope-Epi Grant). 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 Kinderkrebshilfe Schweiz (www.kinderkrebshilfe.ch). The DHL has been supported by Dutch Cancer Society (NKI 2010-4720).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The contributing cohort-study teams obtained IRB and/or Ethics Committee approval or exemption in their respective contributing institute. 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.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer database is not an open-access database due to ethical and data protection constraints. The pseudonymised data is managed by the Princess Máxima Center for Pediatric Oncology in the Netherlands and cannot be shared with investigators outside the institute without consent from all involved parties. However, potential collaborators are welcome to submit proposals to JCT (J.C.Teepen@prinsesmaximacentrum.nl), which will be considered by the consortium.

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