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Male Breast Cancer After Childhood Cancer: Systematic Review and Analyses in the Pan-CareSurFup Cohort

Yuehan Wang	Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands
Raoul C. Reulen	Centre for Childhood Cancer Survivor Studies, University of Birmingham, Birmingham, UK
Leontien C.M. Kremer	Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands University Medical Center Utrecht, Wilhelmina Children's Hospital, Utrecht, The Netherlands Emma Children's Hospital, Amsterdam University Medical Center (UMC), University of Amsterdam, Amsterdam, The Netherlands
Florent de Vathaire	Radiation Epidemiology Team, INSERM U1018, Gustave Roussy, Université Paris-Saclay, Villejuif, France
Riccardo Haupt	DOPO Clinic, Division of Pediatric Hematology/Oncology, IRCCS Istituto Giannina Gaslini, Genova, Italy
Lorna Zadravec Zaletel	Division of Radiotherapy, Institute of Oncology, Ljubljana, Slovenia Faculty of medicine, University of Ljubljana, Ljubljana, Slovenia
Francesca Bagnasco	Epidemiology and Biostatistics Unit, Scientific Directorate, IRCCS Istituto Giannina Gaslini, Genova, Italy
Charlotte Demoor-Goldschmidt	Radiation Epidemiology Team, INSERM U1018, Gustave Roussy, Université Paris-Saclay, Villejuif, France Department of Pediatric Hematology and Oncology, University-Hospital of Angers, Angers, France Radiotherapy department, Francois Baclesse center, Caen, France
Willem J. van Dorp	Amsterdam University Medical Center (UMC), University of Amsterdam, Amsterdam, The Netherlands
Nadia Haddy	Radiation Epidemiology Team, INSERM U1018, Gustave Roussy, Université Paris-Saclay, Villejuif, France

Lars Hjorth	Lund University, Skane University Hospital, Department of Clinical Sciences Lund, Paediatrics, Lund, Sweden
Zsuzsanna Jakab	Hungarian Childhood Cancer Registry, 2nd Department of Pediatrics, Semmelweis University, Budapest, Hungary
Claudia E. Kuehni	Childhood Cancer Registry (ChCR), Institute for Social and Preventive Medicine, University of Bern, Bern, Switzerland Pediatric Hematology and Oncology, University Children's Hospital Bern, University of Bern, Bern, Switzerland
Päivi Maria Lähteenmäki	Department of Pediatric and Adolescent Medicine, Turku University, FICAN-West, and Turku University Hospital, Turku, Finland
Helena J.H. van der Pal	Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands
Carlotta Sacerdote	Childhood Cancer Registry of Piedmont, Cancer Epidemiology Unit, Citta' della Salute e della Scienza Hospital-University of Turin and Center for Cancer Prevention (CPO), Turin, Italy
Roderick Skinner	Department of Paediatric and Adolescent Haematology/Oncology, Great North Children's Hospital, Newcastle upon Tyne, UK Translational and Clinical Research Institute, Newcastle University Centre for Cancer, Newcastle University, Newcastle upon Tyne, UK
Monica Terenziani	Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy
Finn Wesenberg	Norwegian Cancer Register Department of Pediatric Medicine, Faculty of Medicine, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Oslo, Norway
Jeanette F. Winther	Childhood Cancer Research Group, Danish Cancer Society Research Center, Copenhagen, Denmark Department of Clinical Medicine, Faculty of Health, Aarhus University and Aarhus University Hospital, Aarhus, Denmark
Flora E. van Leeuwen	Netherlands Cancer Institute, Amsterdam, The Netherlands
Mike M. Hawkins	Centre for Childhood Cancer Survivor Studies, University of Birmingham, Birmingham, UK
Jop C. Teepen †	Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands
Elvira C. van Dalen †	Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

Cécile M. Ronckers †

Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands
Brandenburg Medical School Theodor Fontane, Neuruppin, Germany

† Joint last authors

Corresponding author:
Yuehan Wang
Princess Máxima Center for Pediatric Oncology, Heidelberglaan 25, 3584 CS Utrecht, the Netherlands
Telephone: +31-88-9725192
Email address: y.wang-2@prinsesmaximacentrum.nl

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Abbreviations

CCSs	Childhood cancer survivors
SMBC	Subsequent male breast cancer
SIR	Standardized incidence ratio
AER	Absolute excess risk
PanCareSurFup	PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies
SMN	Subsequent malignant neoplasm
CI	Confidence interval
ER	Estrogen receptor
PR	Progesterone receptor
HER 2	Human epidermal growth factor receptor 2

IQR	Interquartile range

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.

Keywords: Late effects; Childhood cancer survivors; Male breast cancer; Second cancer; Systematic review; Data analyses; Cohort study

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 5-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.

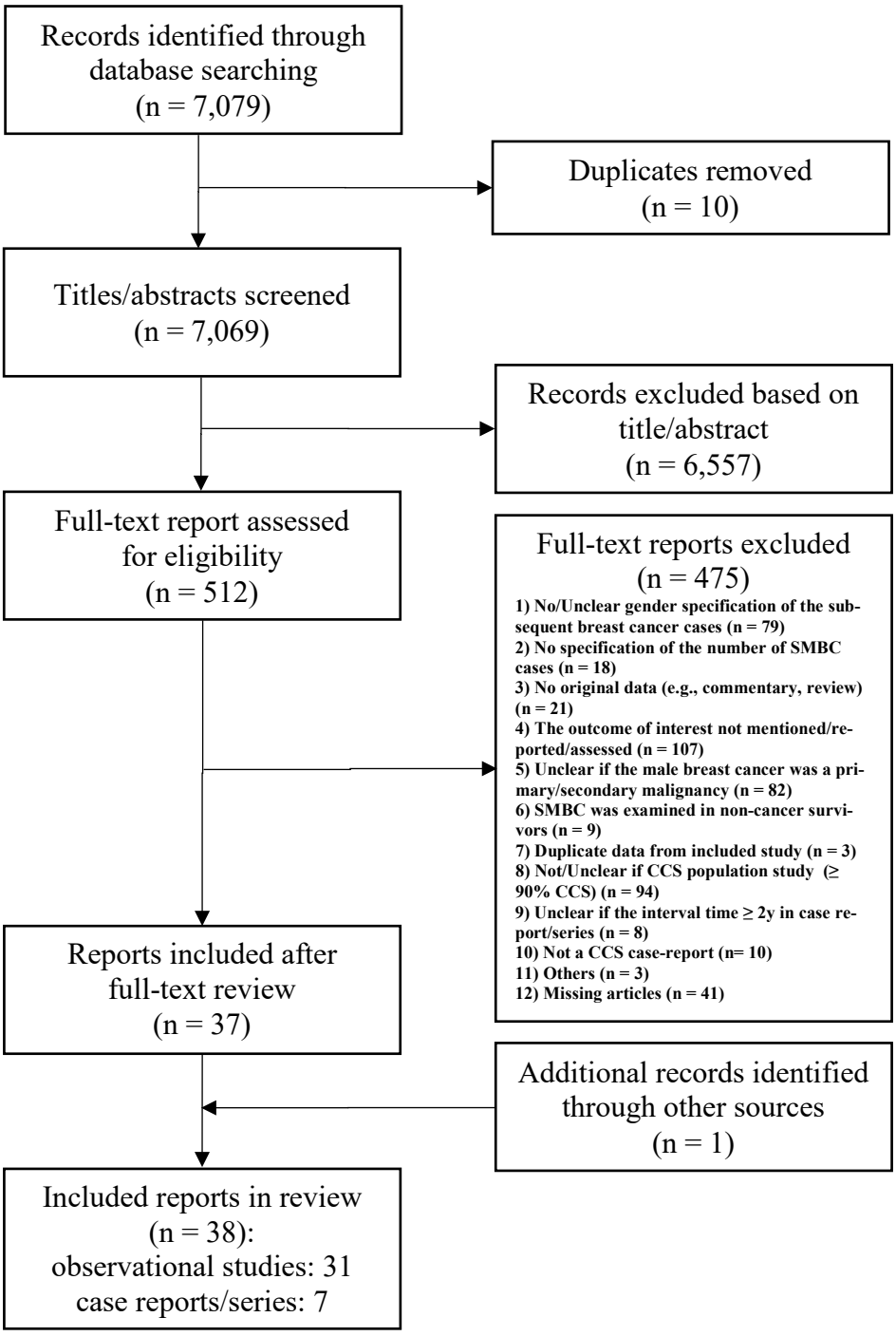
Results

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.

Figure 1. Flow chart of study selection



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 5-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.

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 HER 2- tumor out of five cases with HER 2 status reported, and two had a HER 2+ 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].

Part 2. PanCareSurFup Cohort

In the PanCareSurFup cohort, 37,738 male 5-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.

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.

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 5-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.

Author contributions: YW: Formal analysis; Investigation; Methodology; Writing - original draft; Writing - review & editing. RCR: Conceptualization; Formal analysis; Investigation; Methodology; Writing - review & editing. LCMK: Investigation; Writing - review & editing. FdV: Investigation; Writing - review & editing. RH: Investigation; Writing - review & editing. LZZ: Investigation; Writing - review & editing. FB: Investigation; Writing - review & editing. CD-G: Investigation; Writing - review & editing. WJvD: Investigation; Writing - review & editing. NH: Investigation; Writing - review & editing. LH: Investigation; Writing - review & editing. ZJ: Investigation; Writing - review & editing. CEK: Investigation; Writing - review & editing. PML: Investigation; Writing - review & editing. HJHvdP: Investigation; Writing - review & editing. CS: Investigation; Writing - review & editing. RS: Conceptualization; Investigation; Writing - review & editing. MT: Investigation; Writing - review & editing. FW: Investigation; Writing - review & editing. JFW: Investigation; Writing - review & editing. FEvL: Investigation; Writing - review & editing. MMH: Investigation; Writing - review & editing. JCT: Formal analysis; Investigation; Methodology; Writing - review & editing. ECvD: Formal analysis; Investigation; Methodology; Writing - review & editing. CMR: Conceptualization; Formal analysis; Investigation; Methodology; Writing - review & editing.

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References

1. Wang Z, Liu Q, Wilson CL*, et al.* Polygenic Determinants for Subsequent Breast Cancer Risk in Survivors of Childhood Cancer: The St Jude Lifetime Cohort Study (SJLIFE). Clin Cancer Res 2018;24(24):6230-6235.
2. Friedman DL, Whitton J, Leisenring W*, et al.* Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 2010;102(14):1083-95.
3. Inskip PD, Robison LL, Stovall M*, et al.* Radiation dose and breast cancer risk in the childhood cancer survivor study. J Clin Oncol 2009;27(24):3901-7.
4. Moskowitz CS, Chou JF, Wolden SL*, et al.* Breast cancer after chest radiation therapy for childhood cancer. J Clin Oncol 2014;32(21):2217-23.
5. Ehrhardt MJ, Howell CR, Hale K*, et al.* Subsequent Breast Cancer in Female Childhood Cancer Survivors in the St Jude Lifetime Cohort Study (SJLIFE). J Clin Oncol 2019;37(19):1647-1656.

6. Veiga LH, Curtis RE, Morton LM*, et al.* 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. JAMA Pediatr 2019; 10.1001/jamapediatrics.2019.3807.
7. Yalaza M, Inan A, Bozer M. Male Breast Cancer. J Breast Health 2016;12(1):1-8.
8. Fentiman IS, Fourquet A, Hortobagyi GN. Male breast cancer. Lancet 2006;367(9510):595-604.
9. Mulder RL, Kremer LC, Hudson MM*, et al.* Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol 2013;14(13):e621-9.
10. Mulder RL, Hudson MM, Bhatia S*, et al.* Updated Breast Cancer Surveillance Recommendations for Female Survivors of Childhood, Adolescent, and Young Adult Cancer From the International Guideline Harmonization Group. J Clin Oncol 2020;38(35):4194-4207.
11. Byrne J, Alessi D, Allodji RS*, et al.* The PanCareSurFup consortium: research and guidelines to improve lives for survivors of childhood cancer. Eur J Cancer 2018;103:238-248.
12. Grabow D, Kaiser M, Hjorth L*, et al.* The PanCareSurFup cohort of 83,333 five-year survivors of childhood cancer: a cohort from 12 European countries. Eur J Epidemiol 2018;33(3):335-349.
13. Bright CJ, Hawkins MM, Winter DL*, et al.* Risk of Soft-Tissue Sarcoma Among 69 460 Five-Year Survivors of Childhood Cancer in Europe. J Natl Cancer Inst 2018;110(6):649-660.
14. Reulen RC, Wong KF, Bright CJ*, et al.* Risk of digestive cancers in a cohort of 69 460 five-year survivors of childhood cancer in Europe: the PanCareSurFup study. Gut 2020; 10.1136/gutjnl-2020-322237.
15. Magnani C, Terracini B, Cordero Di Montezemolo L*, et al.* Incidence of second primary malignancies after a malignant tumor in childhood: a population-based survey in Piedmont (Italy). Int J Cancer 1996;67(1):6-10.
16. Demoor-Goldschmidt C, Allodji RS, Jackson A*, et al.* Breast Cancer, Secondary Breast Cancers in Childhood Cancer Male Survivors-Characteristics and Risks. Int J Radiat Oncol Biol Phys 2018;102(3):578-583.
17. Holmqvist AS, Chen Y, Berano Teh J*, et al.* Risk of solid subsequent malignant neoplasms after childhood Hodgkin lymphoma-Identification of high-risk populations to guide surveillance: A report from the Late Effects Study Group. Cancer 2019;125(8):1373-1383.
18. Reulen RC, Frobisher C, Winter DL*, et al.* Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. Jama 2011;305(22):2311-9.
19. Li FP, Corkery J, Vawter G*, et al.* Breast carcinoma after cancer therapy in childhood. Cancer 1983;51(3):521-3.
20. Little MP, Schaeffer ML, Reulen RC*, et al.* Breast cancer risk after radiotherapy for heritable and non-heritable retinoblastoma: a US-UK study. Br J Cancer 2014;110(10):2623-32.
21. Teepen JC, van Leeuwen FE, Tissing WJ*, et al.* Long-Term Risk of Subsequent Malignant Neoplasms After Treatment of Childhood Cancer in the DCOG LATER Study Cohort: Role of Chemotherapy. J Clin Oncol 2017;35(20):2288-2298.
22. Beaty O, 3rd, Hudson MM, Greenwald C*, et al.* Subsequent malignancies in children and adolescents after treatment for Hodgkin's disease. J Clin Oncol 1995;13(3):603-9.

23. Cohen RJ, Curtis RE, Inskip PD*, et al.* The risk of developing second cancers among survivors of childhood soft tissue sarcoma. Cancer 2005;103(11):2391-6.
24. Constine LS, Tarbell N, Hudson MM*, et al.* Subsequent malignancies in children treated for Hodgkin's disease: associations with gender and radiation dose. Int J Radiat Oncol Biol Phys 2008;72(1):24-33.
25. Dottorini ME, Vignati A, Mazzucchelli L*, et al.* Differentiated thyroid carcinoma in children and adolescents: a 37-year experience in 85 patients. J Nucl Med 1997;38(5):669-75.
26. Gold DG, Neglia JP, Dusenbery KE. Second neoplasms after megavoltage radiation for pediatric tumors. Cancer 2003;97(10):2588-96.
27. Green DM, Hyland A, Barcos MP*, et al.* Second malignant neoplasms after treatment for Hodgkin's disease in childhood or adolescence. J Clin Oncol 2000;18(7):1492-9.
28. Hisada M, Garber JE, Fung CY*, et al.* Multiple primary cancers in families with Li-Fraumeni syndrome. J Natl Cancer Inst 1998;90(8):606-11.
29. Inskip PD, Curtis RE. New malignancies following childhood cancer in the United States, 1973-2002. Int J Cancer 2007;121(10):2233-40.
30. Kushner BH, Zauber A, Tan CT. Second malignancies after childhood Hodgkin's disease. The Memorial Sloan-Kettering Cancer Center experience. Cancer 1988;62(7):1364-70.
31. MacArthur AC, Spinelli JJ, Rogers PC*, et al.* Risk of a second malignant neoplasm among 5-year survivors of cancer in childhood and adolescence in British Columbia, Canada. Pediatr Blood Cancer 2007;48(4):453-9.
32. Macklis RM, Oltikar A, Sallan SE. Wilms' tumor patients with pulmonary metastases. Int J Radiat Oncol Biol Phys 1991;21(5):1187-93.
33. Neglia JP, Friedman DL, Yasui Y*, et al.* Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. J Natl Cancer Inst 2001;93(8):618-29.
34. Olsen JH, Moller T, Anderson H*, et al.* Lifelong cancer incidence in 47,697 patients treated for childhood cancer in the Nordic countries. J Natl Cancer Inst 2009;101(11):806-13.
35. Ottaviani G, Robert RS, Huh WW*, et al.* Sociooccupational and physical outcomes more than 20 years after the diagnosis of osteosarcoma in children and adolescents: limb salvage versus amputation. Cancer 2013;119(20):3727-36.
36. Paulino AC, Wen BC, Brown CK*, et al.* Late effects in children treated with radiation therapy for Wilms' tumor. Int J Radiat Oncol Biol Phys 2000;46(5):1239-46.
37. Paulino AC, Fowler BZ. Secondary neoplasms after radiotherapy for a childhood solid tumor. Pediatr Hematol Oncol 2005;22(2):89-101.
38. Sankila R, Garwicz S, Olsen JH*, et al.* Risk of subsequent malignant neoplasms among 1,641 Hodgkin's disease patients diagnosed in childhood and adolescence: a population-based cohort study in the five Nordic countries. Association of the Nordic Cancer Registries and the Nordic Society of Pediatric Hematology and Oncology. J Clin Oncol 1996;14(5):1442-6.
39. Schellong G, Riepenhausen M. Late effects after therapy of Hodgkin's disease: update 2003/04 on overwhelming post-splenectomy infections and secondary malignancies. Klin Padiatr 2004;216(6):364-9.
40. Strong LC, Stine M, Norsted TL. Cancer in survivors of childhood soft tissue sarcoma and their relatives. J Natl Cancer Inst 1987;79(6):1213-20.
41. Tarbell NJ, Gelber RD, Weinstein HJ*, et al.* Sex differences in risk of second malignant tumours after Hodgkin's disease in childhood. Lancet 1993;341(8858):1428-32.

42. Terracini B, Pastore G, Zurlo MG*, et al.* Late deaths and second primary malignancies among long-term survivors of childhood cancer: an Italian multicentre study. Eur J Cancer Clin Oncol 1987;23(5):499-504.
43. Tukenova M, Diallo I, Hawkins M*, et al.* Long-term mortality from second malignant neoplasms in 5-year survivors of solid childhood tumors: temporal pattern of risk according to type of treatment. Cancer Epidemiol Biomarkers Prev 2010;19(3):707-15.
44. Wolden SL, Lamborn KR, Cleary SF*, et al.* Second cancers following pediatric Hodgkin's disease. J Clin Oncol 1998;16(2):536-44.
45. de Vathaire F, Shamsaldin A, Grimaud E*, et al.* Solid malignant neoplasms after childhood irradiation: decrease of the relative risk with time after irradiation. C R Acad Sci III 1995;318(4):483-90.
46. Alazhri J, Saclarides C, Avisar E. A rare complication resulting in a rare disease: radiation-induced male breast cancer. BMJ Case Rep 2016;2016:10.1136/bcr-2015-211874.
47. Boussen H, Kochbati L, Besbes M*, et al.* [Male secondary breast cancer after treatment for Hodgkin's disease. Case report and review of the literature]. Cancer Radiother 2000;4(6):465-8.
48. Hagelstrom RT, Ford J, Reiser GM*, et al.* Breast Cancer and Non-Hodgkin Lymphoma in a Young Male with Cowden Syndrome. Pediatr Blood Cancer 2016;63(3):544-6.
49. Latz D, Alfrink M, Nassar N*, et al.* Breast cancer in a male patient after treatment of acute lymphoblastic leukemia including total body irradiation and bone marrow transplantation. Onkologie 2004;27(5):477-9.
50. Lowe T, Luu T, Shen J*, et al.* Male breast cancer 15 years after allogeneic hematopoietic cell transplantation including total body irradiation for recurrent acute lymphoblastic leukemia. Onkologie 2008;31(5):266-9.
51. O'Flynn EA, Wilson R, Nerurkar A*, et al.* Metastatic breast cancer in a young adult man after total-body irradiation for acute lymphoblastic leukemia. J Clin Oncol 2011;29(20):e607-9.
52. Thompson DK, Li FP, Cassady JR. Breast cancer in a man 30 years after radiation for metastatic osteogenic sarcoma. Cancer 1979;44(6):2362-5.
53. Ron E, Ikeda T, Preston DL*, et al.* Male breast cancer incidence among atomic bomb survivors. J Natl Cancer Inst 2005;97(8):603-5.
54. Little MP, McElvenny DM. Male Breast Cancer Incidence and Mortality Risk in the Japanese Atomic Bomb Survivors - Differences in Excess Relative and Absolute Risk from Female Breast Cancer. Environ Health Perspect 2017;125(2):223-229.
55. Henderson TO, Moskowitz CS, Chou JF*, et al.* Breast Cancer Risk in Childhood Cancer Survivors Without a History of Chest Radiotherapy: A Report From the Childhood Cancer Survivor Study. J Clin Oncol 2016;34(9):910-8.
56. Travis LB, Hill DA, Dores GM*, et al.* Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA 2003;290(4):465-75.
57. van Leeuwen FE, Klokman WJ, Stovall M*, et al.* Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. J Natl Cancer Inst 2003;95(13):971-80.
58. van Leeuwen FE, Ronckers CM. Anthracyclines and Alkylating Agents: New Risk Factors for Breast Cancer in Childhood Cancer Survivors? J Clin Oncol 2016;34(9):891-4.

59. Sasco AJ, Lowenfels AB, Pasker-de Jong P. Review article: epidemiology of male breast cancer. A meta-analysis of published case-control studies and discussion of selected aetiological factors. Int J Cancer 1993;53(4):538-49.
60. Fackenthal JD, Marsh DJ, Richardson AL*, et al.* Male breast cancer in Cowden syndrome patients with germline PTEN mutations. J Med Genet 2001;38(3):159-64.
61. Breast Cancer in Men. Annals of Internal Medicine 2002;137(8):678-687.
62. Wang F, Shu X, Meszoely I*, et al.* Overall Mortality After Diagnosis of Breast Cancer in Men vs Women. JAMA Oncol 2019;5(11):1589-96.
63. Johansen Taber KA, Morisy LR, Osbahr AJ, 3rd*, et al.* Male breast cancer: risk factors, diagnosis, and management (Review). Oncol Rep 2010;24(5):1115-20.

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	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)
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	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]
Holmqvist (2019) [17]	Late Effects Study Group cohort	Diagnosed between 1955 - 1986	1,136	At least 744 [d]	HL	Medical records + Pathology reports confirmation	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)
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	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
Li (1983) [19]	NM	Diagnosed between 1931 - 1974	910 5-yr survivors	504	Any diagnosis	Medical records	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]

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	NM	Mean 1.3 yr	Mean 26.9 yr	Since one year after first diagnosis	1 (0.12%)	NM
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	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

Beaty III (1995) [22]	NM	Treated between 1962 - 1993	499	289	HL	- Medical records - Medical information from local physicians	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
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	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
Constine (2008) [24]	NM	Treated between 1960 - 1990	930	532	HL	Medical records	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
Dottorini (1996) [25]	NM	Treated between 1958 - 1995	85	22	Differentiated thyroid carcinoma	- Clinical examinations - Telephone contacts - Information from family/referring physicians	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
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	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

						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	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
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	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
Inskip (2007) [29]	SEER	Diagnosed between 1973 - 2002	25,965 2-mo survivors	14,043	Any diagnosis	Cancer registry	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
Kushner (1988) [30]	Memorial Sloan-Kettering Cancer Center tumor registry	Diagnosed between 1949 - 1983	254 1-yr survivors	156	HL	NM	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
MacArthur (2007) [31]	Population-based British Columbia Cancer Registry	Diagnosed between 1970 - 1995	2,322 5-yr survivors	1,217	Any diagnosis	Cancer registry	NM	Mean (± SD) 10 (± 6.5) yr	Mean 11.2 yr [i]	Starting point not mentioned	0	NA
Macklis (1991) [32]	National Wilms' Tumor Study	Evaluated between 1968 - 1988	51	22	Wilms' tumor	- Medical records - Questionnaires - Telephone contacts - Autopsy reports	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%)	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

							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%)					
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	NM	0 - 14 yr	Mean 6.6 yr [i]	Starting point not mentioned	0	NA
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	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
Olsen (2009) [34]	Five Nordic cancer registries	Reported between 1943 - 2005	47,697	26,168	Any diagnosis	Cancer registry	Some had CT but no further information provided	0 - 19 yr	Mean 10.0 yr [i]	Starting point not mentioned	0	NA
Ottaviani (2013) [35]	NM	Treated between	38	14	Osteosarcoma	- Questionnaires	CT: 38 (100%); RT: 9 (24%)	Mean ± the SEM: 13.2 ± 0.7	Mean ± the SEM: 24.3 ± 0.7 yr	Since first diagnosis	0	NA

		1972 - 2005 [k]	20-yr survivors			- Medical records - National and international databases		yr (range, 3 - 19 yr)	(range, 20 - 39 yr)			
Paulino (2000) [36]	NM	Treated between 1968 - 1994	42 5-yr survivors	17	Wilms' tumor	- Clinical follow-up - Questionnaires to patients and physicians	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
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	All received RT, some had CT, but no further information provided	≤ 21 yr	Median 9.6 yr	Starting point not mentioned	0	NA
Sankila (1996) [38]	Five Nordic cancer registries	Diagnosed and registered between 1943 - 1987	1,641	971	HL	Medical records	Some had RT, no specific treatment information mentioned	Median 16 yr (< 20 yr)	Mean 10.4 yr	Starting point not mentioned	0	NA
Schellong (2004) [39]	Hodgkin disease late effects project of the GPOH	Enrolled between 1978 - 1995	1,245	737	HL	- Submitted by centers - Mailing questionnaires	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

						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	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
Tarbell (1993) [41]	NM	Treated between 1969 - 1988	191	125	HL	NM	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
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	11 patients with subsequent malignancies received both RT (2,400 - 9,600 rads) and CT	NM	NM	NM	0	NA
Tukenova (2010) [43] [l]	Multicentric French-UK cohort	Diagnosed between 1942 - 1986	4,230 5-yr survivors	NM	Any solid malignant tumor	Medical records	RT: Integral dose mean (min - max): 160.3 (0.1 - 1,247.9) J [m] CT categories included anthracyclines, alkylating	< 17 yr	Median 28 yr (range, 5 - 63 yr)	Since first diagnosis	0	NA

							agents, epipodophyllotoxins, antimetabolites, vinca alkaloids, and other drugs					
Wolden (1998) [44]	NM	Treated between 1960 - 1995	694 1-yr survivors	387	HL	Medical records	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
de Vathaire (1995) [45]	NM	Treated between 1942 - 1985	1,055 2-yr survivors	546	Any diagnosis	Medical records	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

[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

15. Magnani C, Terracini B, Cordero Di Montezemolo L*, et al.* Incidence of second primary malignancies after a malignant tumor in childhood: a population-based survey in Piedmont (Italy). Int J Cancer 1996;67(1):6-10.
16. Demoor-Goldschmidt C, Allodji RS, Jackson A*, et al.* Breast Cancer, Secondary Breast Cancers in Childhood Cancer Male Survivors-Characteristics and Risks. Int J Radiat Oncol Biol Phys 2018;102(3):578-583.
17. Holmqvist AS, Chen Y, Berano Teh J*, et al.* Risk of solid subsequent malignant neoplasms after childhood Hodgkin lymphoma-Identification of high-risk populations to guide surveillance: A report from the Late Effects Study Group. Cancer 2019;125(8):1373-1383.
18. Reulen RC, Frobisher C, Winter DL*, et al.* Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. Jama 2011;305(22):2311-9.

19. Li FP, Corkery J, Vawter G*, et al.* Breast carcinoma after cancer therapy in childhood. Cancer 1983;51(3):521-3.
20. Little MP, Schaeffer ML, Reulen RC*, et al.* Breast cancer risk after radiotherapy for heritable and non-heritable retinoblastoma: a US-UK study. Br J Cancer 2014;110(10):2623-32.
21. Teepen JC, van Leeuwen FE, Tissing WJ*, et al.* Long-Term Risk of Subsequent Malignant Neoplasms After Treatment of Childhood Cancer in the DCOG LATER Study Cohort: Role of Chemotherapy. J Clin Oncol 2017;35(20):2288-2298.
22. Beaty O, 3rd, Hudson MM, Greenwald C*, et al.* Subsequent malignancies in children and adolescents after treatment for Hodgkin's disease. J Clin Oncol 1995;13(3):603-9.
23. Cohen RJ, Curtis RE, Inskip PD*, et al.* The risk of developing second cancers among survivors of childhood soft tissue sarcoma. Cancer 2005;103(11):2391-6.
24. Constine LS, Tarbell N, Hudson MM*, et al.* Subsequent malignancies in children treated for Hodgkin's disease: associations with gender and radiation dose. Int J Radiat Oncol Biol Phys 2008;72(1):24-33.
25. Dottorini ME, Vignati A, Mazzucchelli L*, et al.* Differentiated thyroid carcinoma in children and adolescents: a 37-year experience in 85 patients. J Nucl Med 1997;38(5):669-75.
26. Gold DG, Neglia JP, Dusenbery KE. Second neoplasms after megavoltage radiation for pediatric tumors. Cancer 2003;97(10):2588-96.
27. Green DM, Hyland A, Barcos MP*, et al.* Second malignant neoplasms after treatment for Hodgkin's disease in childhood or adolescence. J Clin Oncol 2000;18(7):1492-9.
28. Hisada M, Garber JE, Fung CY*, et al.* Multiple primary cancers in families with Li-Fraumeni syndrome. J Natl Cancer Inst 1998;90(8):606-11.
29. Inskip PD, Curtis RE. New malignancies following childhood cancer in the United States, 1973-2002. Int J Cancer 2007;121(10):2233-40.
30. Kushner BH, Zauber A, Tan CT. Second malignancies after childhood Hodgkin's disease. The Memorial Sloan-Kettering Cancer Center experience. Cancer 1988;62(7):1364-70.
31. MacArthur AC, Spinelli JJ, Rogers PC*, et al.* Risk of a second malignant neoplasm among 5-year survivors of cancer in childhood and adolescence in British Columbia, Canada. Pediatr Blood Cancer 2007;48(4):453-9.
32. Macklis RM, Oltikar A, Sallan SE. Wilms' tumor patients with pulmonary metastases. Int J Radiat Oncol Biol Phys 1991;21(5):1187-93.
33. Neglia JP, Friedman DL, Yasui Y*, et al.* Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. J Natl Cancer Inst 2001;93(8):618-29.
34. Olsen JH, Moller T, Anderson H*, et al.* Lifelong cancer incidence in 47,697 patients treated for childhood cancer in the Nordic countries. J Natl Cancer Inst 2009;101(11):806-13.
35. Ottaviani G, Robert RS, Huh WW*, et al.* Sociooccupational and physical outcomes more than 20 years after the diagnosis of osteosarcoma in children and adolescents: limb salvage versus amputation. Cancer 2013;119(20):3727-36.

36. Paulino AC, Wen BC, Brown CK*, et al.* Late effects in children treated with radiation therapy for Wilms' tumor. Int J Radiat Oncol Biol Phys 2000;46(5):1239-46.
37. Paulino AC, Fowler BZ. Secondary neoplasms after radiotherapy for a childhood solid tumor. Pediatr Hematol Oncol 2005;22(2):89-101.
38. Sankila R, Garwicz S, Olsen JH*, et al.* Risk of subsequent malignant neoplasms among 1,641 Hodgkin's disease patients diagnosed in childhood and adolescence: a population-based cohort study in the five Nordic countries. Association of the Nordic Cancer Registries and the Nordic Society of Pediatric Hematology and Oncology. J Clin Oncol 1996;14(5):1442-6.
39. Schellong G, Riepenhausen M. Late effects after therapy of Hodgkin's disease: update 2003/04 on overwhelming post-splenectomy infections and secondary malignancies. Klin Padiatr 2004;216(6):364-9.
40. Strong LC, Stine M, Norsted TL. Cancer in survivors of childhood soft tissue sarcoma and their relatives. J Natl Cancer Inst 1987;79(6):1213-20.
41. Tarbell NJ, Gelber RD, Weinstein HJ*, et al.* Sex differences in risk of second malignant tumours after Hodgkin's disease in childhood. Lancet 1993;341(8858):1428-32.
42. Terracini B, Pastore G, Zurlo MG*, et al.* Late deaths and second primary malignancies among long-term survivors of childhood cancer: an Italian multicentre study. Eur J Cancer Clin Oncol 1987;23(5):499-504.
43. Tukenova M, Diallo I, Hawkins M*, et al.* Long-term mortality from second malignant neoplasms in 5-year survivors of solid childhood tumors: temporal pattern of risk according to type of treatment. Cancer Epidemiol Biomarkers Prev 2010;19(3):707-15.
44. Wolden SL, Lamborn KR, Cleary SF*, et al.* Second cancers following pediatric Hodgkin's disease. J Clin Oncol 1998;16(2):536-44.
45. de Vathaire F, Shamsaldin A, Grimaud E*, et al.* Solid malignant neoplasms after childhood irradiation: decrease of the relative risk with time after irradiation. C R Acad Sci III 1995;318(4):483-90.
64. Hawkins MM, Lancashire ER, Winter DL, et al. The British Childhood Cancer Survivor Study: Objectives, methods, population structure, response rates and initial descriptive information. Pediatr Blood Cancer 2008;50(5):1018-25.
65. Ottaviani G, Robert RS, Huh WW, et al. Late Events in Osteosarcoma Survivors: What Can We Learn From Clinical Trials in Amputation Versus Limb Salvage? In. Proceedings of the 34th Meeting of the Scandinavian Sarcoma Group 30 Years' Jubilee. Oslo, Norway; 2009.

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 co-hort/stud y	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 inci-dence among males
Demoor-Gold-schmidt (2018) [16]	3,893	Any solid malig-nant tumor	For the male popu-lation: Me-dian 25 yr (range, 5 - 67 yr)	Since first diagnosis	4 (0.10%)	NM	NM	- 30 years after di-agnosis: 0.2% (95% CI 0.01% - 0.4%) - 50 years after di-agnosis: 0.7% (95% CI 0.2% - 2.8%)
Holmqvi st (2019) [17]	At least 744 [b]	Hodgkin lym-phoma	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 di-agnosis: 0.2% (95% CI 0% - 1.3%) - 40 years after di-agnosis: 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 -	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 per-son-years	NM

			75th per-centile, 17.9 - 32.4 yr					
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

16. Demoor-Goldschmidt C, Allodji RS, Jackson A*, et al.* Breast Cancer, Secondary Breast Cancers in Childhood Cancer Male Survivors-Characteristics and Risks. Int J Radiat Oncol Biol Phys 2018;102(3):578-583.
17. Holmqvist AS, Chen Y, Berano Teh J*, et al.* Risk of solid subsequent malignant neoplasms after childhood Hodgkin lymphoma-Identification of high-risk populations to guide surveillance: A report from the Late Effects Study Group. Cancer 2019;125(8):1373-1383.
18. Reulen RC, Frobisher C, Winter DL*, et al.* Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. Jama 2011;305(22):2311-9.
19. Li FP, Corkery J, Vawter G*, et al.* Breast carcinoma after cancer therapy in childhood. Cancer 1983;51(3):521-3.
21. Teepen JC, van Leeuwen FE, Tissing WJ*, et al.* Long-Term Risk of Subsequent Malignant Neoplasms After Treatment of Childhood Cancer in the DCOG LATER Study Cohort: Role of Chemotherapy. J Clin Oncol 2017;35(20):2288-2298.

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	Age at SMBC diagnosis (yr)	Interval primary cancer - SMBC (yr)	Type of SMBC	SMBC receptor status	History of familial cancers	Genetic predisposition	Outcome	Others
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)	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
Boussen (2000) [47]	HL	13.0	Mantle field (44 Gy) [a]	Vinblastine (10 mg/week for 13 months)	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
Demoor-Goldschmidt (2018) [16]	Neuroblastoma	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)	43.0	42.5	Invasive ductal carcinoma, SBR I	ER+, PR+, HER2-	No	Not performed	NM	
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)	34.0	26.5	Invasive ductal carcinoma, pT2N0	ER+, PR+	Yes: liver cancer grandfather	BRCA and p53 mutations negative	NM	
Demoor-Goldschmidt (2018) [16]	Malignant mesenchymoma 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);	38.0	24.0	Invasive ductal carcinoma, SBRIII, pT2N1	ER+, PR+	No	Not performed	NM	
Demoor-Goldschmidt	Medulloblastoma	14.4	Estimated dose received by the breast mean 1.98 Gy; Max	Cyclophosphamide (1800 mg/m^2), Procarbazine (450	42.0	27.6	Invasive ductal carcinoma, SBRIII,	ER+, PR+	Yes: father family: several leukemia,	Not performed	NM	

(2018) [16]			(D5%) 2.3 Gy; Min (D95%) 1.4 Gy	mg/m^2), steroids, Vincristine ($8 mg/m^2$), Methotrexate ($30 mg/m^2$), Hydrea ($1500 mg/m^2$)			pT2N2		solid cancers			
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	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%
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 prednisone	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
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	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)	

Lowe (2008) [50]	ALL	17.0	TBI (1320 cGy)	Vincristine, prednisone, doxorubicin, intrathecal chemotherapy, methotrexate, 6-mercaptopurine, daunorubicin, and etoposide	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
O'Flynn (2011) [51]	ALL	7.0	TBI (12 Gy with boosts to the brain and spine)	Yes but no further information provided	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

[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

16. Demoor-Goldschmidt C, Allodji RS, Jackson A*, et al.* Breast Cancer, Secondary Breast Cancers in Childhood Cancer Male Survivors-Characteristics and Risks. Int J Radiat Oncol Biol Phys 2018;102(3):578-583.
19. Li FP, Corkery J, Vawter G*, et al.* Breast carcinoma after cancer therapy in childhood. Cancer 1983;51(3):521-3.
46. Alazhri J, Saclarides C, Avisar E. A rare complication resulting in a rare disease: radiation-induced male breast cancer. BMJ Case Rep 2016;2016:10.1136/bcr-2015-211874.
47. Boussen H, Kochbati L, Besbes M*, et al.* [Male secondary breast cancer after treatment for Hodgkin's disease. Case report and review of the literature]. Cancer Radiother 2000;4(6):465-8.
48. Hagelstrom RT, Ford J, Reiser GM*, et al.* Breast Cancer and Non-Hodgkin Lymphoma in a Young Male with Cowden Syndrome. Pediatr Blood Cancer 2016;63(3):544-6.
49. Latz D, Alfrink M, Nassar N*, et al.* Breast cancer in a male patient after treatment of acute lymphoblastic leukemia including total body irradiation and bone marrow transplantation. Onkologie 2004;27(5):477-9.
50. Lowe T, Luu T, Shen J*, et al.* Male breast cancer 15 years after allogeneic hematopoietic cell transplantation including total body irradiation for recurrent acute lymphoblastic leukemia. Onkologie 2008;31(5):266-9.
51. O'Flynn EA, Wilson R, Nerurkar A*, et al.* Metastatic breast cancer in a young adult man after total-body irradiation for acute lymphoblastic leukemia. J Clin Oncol 2011;29(20):e607-9.

52. Thompson DK, Li FP, Cassady JR. Breast cancer in a man 30 years after radiation for metastatic osteogenic sarcoma. Cancer 1979;44(6):2362-5.

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)
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

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	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15	Patient 16
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	5-9 yrs	0-4 yrs	10-14 yrs	10-14 yrs	0-4 yrs	5-9 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	1980-89	<1970	1990-2008	1980-89	<1970	1970-79	1970-79	1970-79
Type of primary cancer	HL	STS	Malignant teratoma	Retinoblastoma	ALL	Nephroblastoma	ALL	ALL	Non-HL	Nephroblastoma	Bone sarcoma	HL	Neuroblastoma and ganglioneuroblastoma	HL	Rhabdomyosarcoma	Nephroblastoma
Chest field RT, yes/no	Yes	No	Yes	No	No	Yes	No	Yes	N/I	N/I	No	No	No	Yes	Yes	No
Chest radiation fields	Mediastinum, axillae	N/A	Chest right, chest left (posterior only)	N/A	N/A	Chest	N/A	TBI	N/I	N/I	N/A	N/A	N/A	N/I	N/I	N/A
Chest field radiation dose, Gy	20	N/A	30	N/A	N/A	15	N/A	N/I	N/I	N/I	N/A	N/A	N/A	N/I	N/I	N/A
Other radiation fields	Neck (R)	Thigh (L)	Para-aortic nodes anterior and posterior	Eye (L) Radon seeds	Testes, cranium	Abdominal field	No	No	N/I	N/I	No	Neck, spleen, paraaortal and billateral iliac regions	Abdominal field	Abdominal field	No	Abdominal field
Chemotherapy drug/dose, mg/m^2	Procarbazine 14302,1 mg/m^2, Vinblastine 190,5 mg/m^2, Mustine 34,2 mg/m^2, Cyclophosphamide 8992,4 mg/m^2, Prednisolone 9699,2 mg/m^2	No	Vinblastine, Bleomycin, Vepesid, Cisplatin (dose N/I)	No	Prednisolone, Vincristine, Cyclophosphamide, Cytosine arabinoside, Asparaginase, Adriamyicin, Mercaptopurine, Methotrexate (dose N/I)	Vincristine, Actinomycin D, Cyclophosphamide (dose N/I)	Yes (information N/I)	N/I	Yes (information 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)	Cyclophosphamide 413 mg/m^2	Vinblastine 305 mg/m^2	Actinomycin D 3 mg/m^2, Vincristine 8 mg/m^2, Cyclophosphamide 1601 mg/m^2, Procarbazine 2775 mg/m^2, Doxorubicin 178 mg/m^2	Vincristine, Actinomycin D (dose N/I)
HCT	No	No	No	No	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No
Age at SMBC diagnosis, yr	50+ yrs	50+ yrs	40-49 yrs	50+ yrs	<30 yrs	<30 yrs	40-49 yrs	<30 yrs	30-39 yrs	40-49 yrs	<30 yrs	30-39 yrs	40-49 yrs	30-39 yrs	30-39 yrs	40-49 yrs

Year of SMBC diagnosis	2010-2019	2010-2019	2000-2009	2010-2019	<2000	2000-2009	2000-2009	2010-2019	2010-2019	2000-2009	2000-2009	2000-2009	2000-2009	<2000	<2000	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	20-29 yrs	40-49 yrs	10-19 yrs	20-29 yrs	40-49 yrs	20-29 yrs	20-29 yrs	30-39 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 information provided)	Invasive ductal carcinoma	Invasive ductal carcinoma	Invasive ductal carcinoma	Invasive ductal carcinoma	Invasive ductal carcinoma	Invasive ductal carcinoma	Invasive ductal carcinoma	Invasive ductal carcinoma	Invasive ductal carcinoma
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	N/I	N/I	T1c, N0, Stage I, grade 2	T3 (8 cm), N0, Stage lll B, grade 3	Grade 1	N/I	T2 (25mm), grade 3	T4N+, 6x7 cm
SMBC receptor status [a]	N/I	N/I	N/I	N/I	ER+	ER+	N/I	N/I	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%+
SMBC laterality	N/I	N/I	N/I	Bilateral	Right	Left	N/I	N/I	N/I	N/I	Left	Left	Left	Left	Right	Left
SMBC location	Central	Overlapping lesion of breast	Nipple & areola/central portion of breast	N/I	N/I	N/I	N/I	N/I	N/I	N/I	N/I	Central	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	N/I	N/I	N/I	No	N/I	N/I	N/I	Negative for breast cancer, prostate carcinoma and ovarian carcinoma
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	Deceased, 01/2015	Alive, 12/2015	Deceased, 05/2007	Alive, 12/2019	Deceased, 9/2009	Deceased, 4/2004	Deceased, 2/2007	Deceased, 8/2012

[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