# Risk factors for subsequent endocrine-related cancer in childhood cancer survivors

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## Abstract

Long-term adverse health conditions, including secondary malignant neoplasms, are common in childhood cancer survivors. Although mortality attributable to secondary malignancies declined over the past decades, the risk for developing a solid secondary malignant neoplasm did not. Endocrine-related malignancies are among the most common secondary malignant neoplasms observed in childhood cancer survivors. In this systematic review, we describe risk factors for secondary malignant neoplasms of the breast and thyroid, since these are the most common secondary endocrine-related malignancies in childhood cancer survivors. Radiotherapy is the most important risk factor for secondary breast and thyroid cancer in childhood cancer survivors. Breast cancer risk is especially increased in survivors of Hodgkin lymphoma who received moderate- to high-dosed mantle field irradiation. Recent studies also demonstrated an increased risk after lower-dose irradiation in other radiation fields for other childhood cancer subtypes. Premature ovarian insufficiency may protect against radiation-induced breast cancer. Although evidence is weak, estrogen–progestin replacement therapy does not seem to be associated with an increased breast cancer risk in premature ovarian-insufficient childhood cancer survivors. Radiotherapy involving the thyroid gland increases the risk for secondary differentiated thyroid carcinoma, as well as benign thyroid nodules. Currently available studies on secondary malignant neoplasms in childhood cancer survivors are limited by short follow-up durations and assessed before treatment regimens. In addition, studies on risk-modifying effects of environmental and lifestyle factors are lacking. Risk-modifying effects of premature ovarian insufficiency and estrogen–progestin replacement therapy on radiation-induced breast cancer require further study.

**Key Words**
- childhood cancer survivors
- secondary malignant neoplasms
- endocrine-related cancer
- breast cancer
- thyroid cancer

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## Introduction

Childhood cancer survival has increased substantially over the past five decades due to advances in therapy, risk-based treatment stratification, and supportive care (Hudson *et al*. 2014). To date, approximately 80% of children and adolescents survive at least 5 years following a diagnosis of childhood cancer (Gatta *et al*. 2014, Howlader *et al*. 2015), and are thereby subsequently considered childhood cancer survivors. This percentage is anticipated to grow

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due to further improvements in childhood cancer care (Hudson *et al.* 2014), and a slow increase in childhood cancer incidence as reported by some investigators (Siegel *et al.* 2014, Steliarova-Foucher *et al.* 2004). Accordingly, awareness of and insight in side effects and long-term consequences of childhood cancer treatment have become increasingly important (Hewitt *et al.* 2003, Oeffinger *et al.* 2006, Geenen *et al.* 2007, Armstrong *et al.* 2009, Hudson *et al.* 2013, Hjorth *et al.* 2015). At an attained age of 45 years, approximately 95% of childhood cancer survivors suffer from at least one chronic health condition related to their former cancer treatment; in approximately 75%, this concerns a serious/disabling or life-threatening condition (Hudson *et al.* 2013). Over the past decades, childhood cancer treatment protocols have been modified, aiming to reduce the occurrence and severity of long-term treatment-related complications. Recently, Armstrong and coworkers demonstrated that these efforts resulted in improved long-term survival (Armstrong *et al.* 2016).

Secondary neoplasms are among the most serious long-term adverse health conditions in childhood cancer survivors, and can be defined as histologically distinct tumors developing after primary cancer therapy. They have been estimated to affect approximately 21% of childhood cancer survivors after 30 years of follow-up since primary cancer diagnosis (Friedman *et al.* 2010). This estimation includes both benign and malignant secondary neoplasms. The 30-year cumulative incidence of secondary malignant neoplasms solely is approximately 8%, and represents a six-fold increased risk in comparison with the general population (Friedman *et al.* 2010). The increased risk for secondary malignancies in childhood cancer survivors seems to persist even after 40 years of follow-up since primary cancer diagnosis (Olsen *et al.* 2009). At an attained survivor's age of 60 years, the cumulative incidence of secondary malignant neoplasms varies between 14 and 18% (Olsen *et al.* 2009, Reulen *et al.* 2011). The risk for secondary malignant neoplasms in older childhood cancer survivors remains unknown. Although most secondary malignant neoplasms are diagnosed during the first 10–20 years following childhood cancer treatment (Friedman *et al.* 2010, Choi *et al.* 2014), they may present within months to decades following the completion of former cancer therapy (Choi *et al.* 2014). Risk factors for the development of secondary malignancies in childhood cancer survivors include host factors, primary cancer diagnosis, types and timing of primary cancer treatment, environmental factors, and lifestyle factors (Ng *et al.* 2010). Secondary malignant neoplasms appear to be an important cause of death in childhood cancer survivors. Recent cohort studies demonstrated that 12–19% of mortality in individuals who survived at least 5 years following a diagnosis of childhood cancer was attributable to secondary malignancies (Mertens *et al.* 2008, Reulen *et al.* 2010, Garwicz *et al.* 2012). After 25 years of follow-up since primary cancer diagnosis, secondary malignant neoplasms even become the most important cause of death in survivors of childhood cancer (Mertens *et al.* 2008, Reulen *et al.* 2010). Although mortality attributable to secondary malignancies in childhood cancer survivors declined over the past treatment eras (Armstrong *et al.* 2016), the risk for developing a solid secondary malignant neoplasm did not (Schaapveld *et al.* 2015). Endocrine-related cancers are among the most common secondary malignancies in childhood cancer survivors (Inskip & Curtis 2007, Olsen *et al.* 2009, Friedman *et al.* 2010, Reulen *et al.* 2011). In the Childhood Cancer Survivor Study, they represent 40% of the invasive

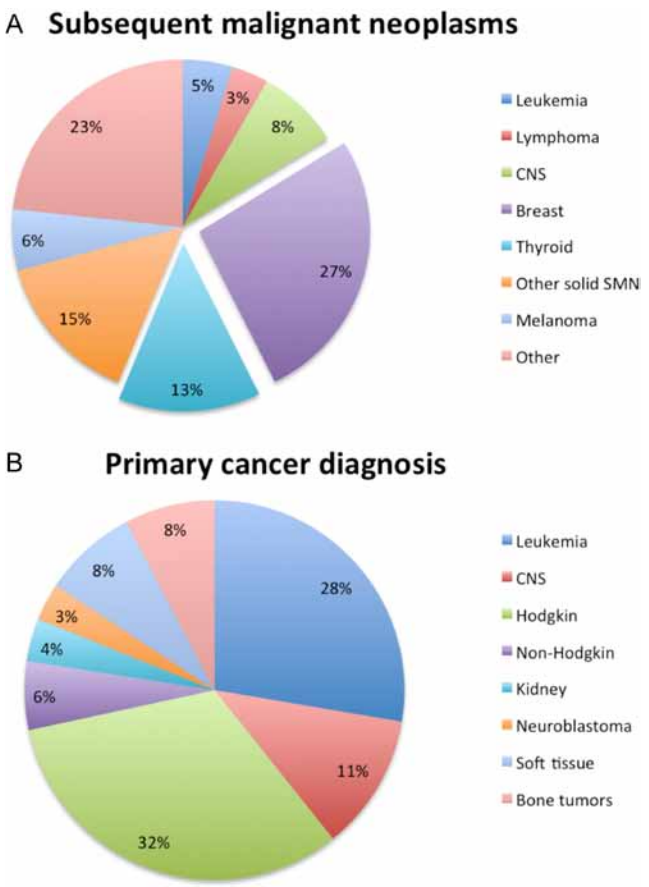


**Figure 1**
Distribution of secondary malignant neoplasms and primary cancer diagnoses among childhood cancer survivors who developed a secondary neoplasm as observed in the Childhood Cancer Survivor Study by Friedman *et al.* (2010). (A) Secondary malignant neoplasms (nonmelanoma skin cancers excluded). (B) Primary cancer diagnoses. CNS, central nervous system; SMN, secondary malignant neoplasm.



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secondary malignant neoplasms observed (Fig. 1A) (Friedman *et al*. 2010).

In this review, we will discuss risk factors for secondary endocrine-related malignant neoplasms in childhood cancer survivors. A special focus will be on breast and thyroid cancer, since these are the most common secondary endocrine-related malignancies in survivors of childhood cancer (Olsen *et al*. 2009, Friedman *et al*. 2010, Reulen *et al*. 2011).

## Search strategy

We systematically searched the MEDLINE-database (United States National Library of Medicine, Washington, DC, USA) until January 2016 for relevant articles on secondary cancer risk in survivors of pediatric malignancies. The keywords 'childhood cancer survivors', 'second malignant neoplasms', 'secondary malignant neoplasms', 'subsequent neoplasms', 'endocrine cancers', 'breast cancer', 'thyroid cancer', 'risk factors', 'radiotherapy', 'radiation', 'irradiation', 'chemotherapy', 'stem cell transplantation', 'total body irradiation', 'conformal radiotherapy', 'intensity-modulated radiation therapy' and 'proton-beam therapy' were used. Only articles written in English were included in the review. Reference lists of included articles were checked for additional relevant publications. In case two or more articles described the same patient cohort, the most recent or relevant article was included.

## Risk factors for secondary malignant neoplasms in childhood cancer survivors

In the Childhood Cancer Survivor Study, host-, disease- and treatment-related risk factors for the development of secondary neoplasms in childhood cancer survivors have been identified (Friedman *et al*. 2010). The Childhood Cancer Survivor Study is a multi-institutional study conducted in the United States and Canada, and involves 14,363 individuals treated for cancer <21 years of age (Robison *et al*. 2002). Female gender and older age at initial cancer diagnosis were associated with an increased risk for secondary malignant neoplasms after childhood cancer (relative risk (RR) 1.4 (95% confidence interval (CI): 1.2–1.6) for females vs males; RR 1.5 (95% CI: 1.2–1.9) for age at diagnosis ≥15 years vs 0–4 years) (Friedman *et al*. 2010). The Surveillance,

**Table 1** High-penetrance genetic cancer predisposition syndromes associated with endocrine-related malignancies.

| Name | Genes | Associated cancers | References |
|---|---|---|---|
| Hereditary breast and ovarian cancer syndrome | *BRCA1*<br>*BRCA2* | Breast cancer, ovarian cancer, prostate cancer, pancreatic cancer, biliary cancer, melanoma | Shiovitz & Korde (2015) |
| Cowden syndrome (also known as multiple hamartoma syndrome) | *PTEN* | Breast cancer, nonmedullary thyroid cancer, endometrial cancer, genitourinary tumors | Pilarski & Nagy (2012), Shiovitz & Korde (2015) |
| Li–Fraumeni syndrome (LFS) | *TP53* | Breast cancer, sarcoma, brain tumor, adrenocortical tumor, leukemia, lung cancer | Shiovitz & Korde (2015) |
| Hereditary diffuse gastric cancer | *CDH1* | Breast cancer, gastric cancer, colorectal cancer | Shiovitz & Korde (2015) |
| Peutz–Jeghers syndrome | *STK11* | Gastro-intestinal cancer, breast cancer, ovarian cancer, pancreatic cancer | Shiovitz & Korde (2015), Strahm & Malkin (2006) |
| Multiple endocrine neoplasia type 1 (MEN1) | *MEN1* | Parathyroid adenoma, pancreatic endocrine tumors, pituitary adenoma | Pilarski & Nagy (2012), Strahm & Malkin (2006) |
| Multiple endocrine neoplasia type 2 (MEN2) | *RET* | Medullary thyroid carcinoma, pheochromocytoma, parathyroid hyperplasia | Pilarski & Nagy (2012), Strahm & Malkin (2006) |
| Succinate dehydrogenase complex (SDHX) | *SDHB*<br>*SDHC*<br>*SDHD* | Paraganglioma, pheochromocytoma | Pilarski & Nagy (2012) |
| von Hippel–Lindau syndrome (VHL) | *VHL* | Retinal and central nervous system hemangioblastoma, renal cell carcinoma, pheochromocytoma, pancreatic islet cell tumor, endolymphatic sac tumor | Pilarski & Nagy (2012) |
| Adenomatous polyposis of the colon | *APC* | Colon cancer, small intestine cancer, thyroid cancer, stomach cancer, hepatoblastoma | Strahm & Malkin (2006) |
| Beckwith–Wiedemann syndrome | *CDKN1C/NSD1* | Nephroblastoma, hepatoblastoma, adrenal carcinoma, rhabdomyosarcoma | Strahm & Malkin (2006) |
| DICER1 syndrome | *DICER1* | Pleuropulmonary blastoma, ovarian tumor, cystic nephroma, sarcoma, thyroid tumor, pituitary tumor | Foulkes *et al*. (2014) |



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Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) of the United States could not demonstrate this sex difference in the risk for secondary malignant neoplasms. However, it found a somewhat higher risk for secondary malignancies in black vs white people (standardized incidence ratio (SIR) 8.9 vs SIR 5.5; excess absolute risk (EAR) 18.4 vs 15.0 per 10,000 person-years) (Inskip & Curtis 2007). Genetic susceptibility might contribute to the development of secondary neoplasms in childhood cancer survivors, which is illustrated by high-penetrance genetic cancer predisposition syndromes (Table 1) (Strahm & Malkin 2006, Pilarski & Nagy 2012, Foulkes *et al*. 2014, Shiovitz & Korde 2015). However, germline mutations in known moderate- to high-penetrance cancer susceptibility genes are only found in 8.5% of pediatric and adolescent cancer patients (Zhang *et al*. 2015). Data from the Swedish general population suggest that less pathogenic low-penetrance familial cancer predisposition might be more important in the development of malignancies than high-penetrance genetic cancer susceptibility genes (Frank *et al*. 2015). This is illustrated by Friedman and coworkers, who observed an increased cancer risk in siblings of childhood cancer survivors in comparison with the general population (SIR 1.5 (95% CI: 1.3–1.7)), even after exclusion of families with suspected high-penetrance genetic cancer predisposition syndromes (SIR 1.3 (95% CI: 1.2–1.5)) (Friedman *et al*. 2005). In their study, siblings and offspring of childhood cancer survivors who developed a secondary malignant neoplasm were even at higher risk of developing cancer in comparison with relatives of childhood cancer survivors who did not develop a secondary malignancy (SIR 2.4 (95% CI: 1.5–3.7) for siblings; SIR 15.0 (95% CI: 5.3–42.9) for offspring) (Friedman *et al*. 2005).

Childhood cancer survivors at highest risk for secondary malignant neoplasms include survivors of Hodgkin lymphoma, leukemia, sarcoma, and central nervous system malignancies (Fig. 1B) (Inskip & Curtis 2007, Friedman *et al*. 2010, Reulen *et al*. 2011). This seems to be related to administered treatment modalities. Radiotherapy is the most important risk factor for the development of secondary neoplasms (Inskip & Curtis 2007, Friedman *et al*. 2010, Reulen *et al*. 2011). Risk for radiation-induced secondary malignant neoplasms depends on cumulative radiation dose, radiotherapy fractionation, radiation field, radiosensitivity, radiotherapy technique, quality of radiation, and other confounding factors (Kumar 2012). Besides radiotherapy, chemotherapeutic agents

**Table 2** Risk of secondary breast cancer following childhood cancer in recent large cohort studies.

| Study (year) | Study population | Treatment era | Patients | Age at primary cancer Dx (year) | Median FU (year) | Breast cancer cases | SIR (95% CI) | EAR per 10,000/year (95% CI) | Cumulative incidence at 30 year following primary cancer Dx (95% CI) | Median latency time (range) (year) |
|---|---|---|---|---|---|---|---|---|---|---|
| Inskip & Curtis (2007) | Population-based cohort from United States | 1973–2002 | ♂ 11,922<br>♀ 14,043 | <18 | 6.3 | 51 | 8.4 | 1.9 | NA | NA |
| Olsen *et al*. (2009) | Population-based cohort from Denmark, Finland, Iceland, Norway and Sweden | 1943–2005 | ♂ 26,168<br>♀ 21,529 | <20 | NA | 148 | 2.4 (2.0–2.8) | NA | NA | NA |
| Friedman *et al*. (2010) | Cohort from 26 institutions in United States and Canada | 1970–1986 | ♂ 7714<br>♀ 6645 | <21 | 22.9 | 252 | 9.8 (8.4–11.5) | NA | 5.0% (4.2–5.9%) | 21.3 (6.7–33.5) |
| Reulen *et al*. (2011) | Population-based cohort from Britain | 1940–1991 | ♂/♀ 17,981 | <15 | 24.3 | 97 | 2.2 (1.8–2.7) | 1.4 (0.9–2.0) | NA | NA |

♂, male; ♀, female; CI, confidence interval; Dx, diagnosis; EAR, excess absolute risk; FU, follow-up; NA, not available; SIR, standardized incidence ratio.

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**Table 3** Latency time between childhood cancer and secondary breast cancer.

| Study (year) | Study population | Treatment era | Patients | Age at primary cancer Dx (year) | Median follow-up (year) | Radiotherapy (%) | Breast cancers (*N*) | Latency period | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Median (year) | Range (year) |
| Gold *et al.* (2003) | Single-center cohort of survivors of several childhood cancers from Minnesota | 1954–1980 | ♂/♀ 446 | <18 | 19.5 | 100 | 8 | 20 | 10–32 |
| Taylor *et al.* (2007) | Population-based cohort of Hodgkin lymphoma survivors from Britain | 1940–1991 | ♀ 383 | <15 | 20.3[a] | 67.6 | 16 | 21.6* | 9.5–34.1 |
| Constine *et al.* (2008) | Cohort Hodgkin lymphoma survivors from 5 institutions in the United States | 1960–1990 | ♂ 532 | <19 | 16.8[a] | 91.2 | 29 | 17.2 | 9.4–36.1 |
| Taylor *et al.* (2008) | Population-based cohort of nephroblastoma survivors from Britain | 1940–1991 | ♀ 398<br>♂ 732 | <15 | 19.3[a] | 82.4 | 9 | 26.7* | 12.4–34.5 |
| Diallo *et al.* (2009) | Cohort of survivors of several childhood cancers from 8 institutions in France and Britain | 1942–1986 | ♀ 709<br>♂/♀ 4581 | <17 | 15.4 | NA | 13 | 21 | 9–37 |
| Friedman *et al.* (2010) | Cohort of survivors of several childhood cancers from 26 institutions in United States and Canada | 1970–1986 | ♂ 7714 | <21 | 22.9 | 68.0 | 252 | 21.3 | 6.7–33.5 |
| O'Brien *et al.* (2010) | Single-center cohort of Hodgkin lymphoma survivors from Stanford | 1970–1990 | ♀ 6645<br>♂ 75 | <19 | 20.6 | 100 | 6 | 16.6 | 12.1–29.9 |
| Lange *et al.* (2014) | Cohort of nephroblastoma survivors from the National Wilms Tumor Studies 1–4 | 1969–1995 | ♀ 35<br>♀ 2492 | <20 | NA | 50.7 | 28 | 27.1 | 7.9–35.7 |
| Dorffel *et al.* (2015) | Cohort from German, Austrian and Swiss pediatric Hodgkin lymphoma studies | 1978–2002 | ♂ 1424 | <19 | 14.3 | NA | 37 | 22.0 | 14.3–32.1 |
| Henderson *et al.* (2015) | Cohort of survivors of several childhood cancers from 26 institutions in United States and Canada | 1970–1986 | ♀ 1124<br>♀ 3768 | <21 | 25.5 | 0 | 47 | 24.0 | 10.0–34.0 |

[a], mean. ♂, male; ♀, female; Dx, diagnosis; N, number; NA, not available.

(i.e. alkylators, anthracyclines, and topoisomerase II inhibitors), as well as hematopoietic stem cell transplantation, have been associated with an increased risk for secondary malignant neoplasms in childhood cancer survivors (Meadows *et al*. 2009, Socie *et al*. 2012, Choi *et al*. 2014).

Besides the factors mentioned above, environmental and lifestyle determinants may also be important in secondary tumor development (Travis *et al*. 2002, Carpenter & Bushkin-Bedient 2013, Kamiya *et al*. 2015). However, studies specifically addressing the risk-modifying effects of these determinants in childhood cancer survivors have to be performed yet.

## Breast cancer

### Epidemiology and host-related risk factors

Breast cancer risk in childhood cancer survivors has recently been addressed in several large cohort studies (Table 2) (Inskip & Curtis 2007, Olsen *et al*. 2009, Friedman *et al*. 2010, Reulen *et al*. 2011). After 30 years of follow-up since childhood cancer diagnosis, secondary breast cancer affects approximately 5% of childhood cancer survivors (Friedman *et al*. 2010). This represents a standardized incidence ratio of 2.2–9.8 in comparison with the general population (Inskip & Curtis 2007, Olsen *et al*. 2009, Friedman *et al*. 2010, Reulen *et al*. 2011). Latency periods for the development of secondary breast cancer following childhood cancer vary between 6.7 and 39 years (average 21.8 years) (Table 3) (Gold *et al*. 2003, Taylor *et al*. 2007, 2008, Constine *et al*. 2008, Diallo *et al*. 2009, Friedman *et al*. 2010, O'Brien *et al*. 2010, Lange *et al*. 2014, Dorffel *et al*. 2015, Henderson *et al*. 2015). This is illustrated by Reulen and coworkers, who observed an increased risk for secondary breast cancer in female childhood cancer survivors during the first three decades following primary cancer diagnosis, which gradually declined to general population norms at an attained survivor's age of 50 years (Reulen *et al*. 2008).

Several studies identified pubertal age at primary cancer diagnosis to be an important risk factor for secondary breast cancer (Metayer *et al*. 2000, Constine *et al*. 2008, Inskip *et al*. 2009). In a study by Metayer and coworkers, risk for secondary breast cancer was highest in women aged 10–16 years at Hodgkin lymphoma diagnosis (Metayer *et al*. 2000). In addition, 114 of the 120 secondary breast cancers observed in a study by Inskip and coworkers were diagnosed in women aged 10–20 years at childhood cancer diagnosis (Inskip *et al*. 2009). Therefore, an increased susceptibility of proliferating breast tissue for carcinogenic factors in adolescent girls

**Table 4** Secondary breast cancer risk in childhood cancer survivors by follow-up since primary cancer diagnosis.

| Study (year) | Study population | Treatment era | Patients | Follow-up (year) | Breast cancers (*N*) | | Follow-up since Dx (SIR (95% CI)) | Follow-up since Dx (EAR per 10,000 per year (95% CI)) |
|---|---|---|---|---|---|---|---|---|
| Kenney *et al*. (2004) | Cohort from 26 institutions in United States and Canada | 1970–1986 | ♀ 6068 | Median 18.5 | 111 | 5–9 years | 6.3 (2.0–20.3) | NA |
| | | | | | | 10–14 years | 11.8 (7.0–19.8) | |
| | | | | | | 15–19 years | 9.2 (5.8–14.5) | |
| | | | | | | ≥20 years | 6.0 (3.8–9.4) | |
| Guibout *et al*. (2005) | Cohort of solid tumor survivors from 8 institutions in France and Britain | 1946–1986 | ♀ 1814 | Mean 16 | 16 | NA | NA | NA |
| Inskip & Curtis (2007) | Population-based cohort from United States | 1973–2002 | ♂ 11,922<br>♀ 14,043 | Median 6.3 | 51 | 0.16–<1 year | 0 | NA |
| | | | | | | 1–4 years | 0 | |
| | | | | | | 5–9 years | 7.6 | |
| | | | | | | 10–14 years | 15.1 | |
| | | | | | | 15–19 years | 11.8 | |
| | | | | | | ≥20 years | 5.0 | |
| Reulen *et al*. (2008) | Population-based cohort from Britain | 1940–1991 | ♀ 8093 | Mean 25.1 | 81 | 5–9 years | 9.3 (1.3–66.3) | 0.2 (0.0–2.0) |
| | | | | | | 10–19 years | 9.2 (6.1–14.0) | 1.9 (1.8–4.7) |
| | | | | | | 20–29 years | 2.6 (1.8–3.8) | 4.2 (2.2–8.0) |
| | | | | | | 30–39 years | 1.5 (1.0–2.3) | 4.9 (1.4–17.0) |
| | | | | | | ≥40 years | 1.0 (0.5–1.8) | 0.0 |

♀, female; CI, confidence interval; Dx, diagnosis; EAR, excess absolute risk; *N*, number; NA, not available; SIR, standardized incidence ratio.



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has been suggested (Metayer *et al*. 2000, Inskip *et al*. 2009, Barcellos-Hoff 2013). However, several other studies could not confirm a risk-modifying effect of age at childhood cancer diagnosis (Travis *et al*. 2003, Guibout *et al*. 2005, Reulen *et al*. 2008). This inconsistency might be explained by shorter follow-up durations since childhood cancer in studies reporting an increased secondary breast cancer risk by pubertal age compared with studies not reporting such an effect (average 11.0–16.8 vs 16–25.1 years) (Metayer *et al*. 2000, Guibout *et al*. 2005, Constine *et al*. 2008, Reulen *et al*. 2008). Secondary breast cancer risk in childhood cancer survivors by follow-up since childhood cancer diagnosis, attained survivor's age and age at childhood cancer diagnosis is represented in Tables 4 and 5 (Kenney *et al*. 2004, Guibout *et al*. 2005, Inskip & Curtis 2007, Reulen *et al*. 2008).

Genetic susceptibility might contribute to secondary breast cancer development in childhood cancer survivors. This is illustrated by studies reporting an increased secondary breast cancer risk in survivors of childhood cancer with a positive family history for breast and/or ovarian cancer (Kenney *et al*. 2004, Hill *et al*. 2005). However, germline mutations in known high- to moderate-penetrance breast cancer susceptibility genes like *BRCA1*, *BRCA2*, *TP53* and *ATM* are only found in a minority of childhood cancer survivors who develop a secondary breast malignancy (Broeks *et al*. 2000, Nichols *et al*. 2003). Therefore, less pathogenic low-penetrance genetic susceptibility might be more important. Recent studies identified allelic variants in *PRDM1* and *FGFR2* to predispose Hodgkin lymphoma survivors to radiation-induced breast cancer (Best *et al*. 2011, Ma *et al*. 2012).

Kenney and coworkers identified the presence of thyroid disease to be a risk factor for secondary breast cancer in childhood cancer survivors (RR 1.7 (95% CI: 1.1–2.6)) (Kenney *et al*. 2004). An association between thyroid disease and breast cancer has also been observed in the general population (Hardefeldt *et al*. 2012, Prinzi *et al*. 2014). Although no clear explanations for this finding have been found, stimulation of breast cancer cells by deregulated thyroid hormone receptors, estrogen-receptor activation by triiodothyronine, and a potential role of the sodium–iodide symporter expressed in breast cancer tissue have been proposed (Nogueira & Brentani 1996, Silva *et al*. 2002, Portulano *et al*. 2014).

### Treatment-related risk factors for secondary breast cancer

**Radiotherapy** Chest irradiation is the most important treatment-related risk factor for secondary breast cancer in

**Table 5** Secondary breast cancer risk in childhood cancer survivors by attained survivors' age and age at primary cancer diagnosis.

| Study | | Attained age (SIR (95% CI)) | Attained age (EAR per 10,000 per year (95% CI)) | | Age at Dx (SIR (95% CI)) | Age at Dx (EAR per 10,000 per year (95% CI)) |
|---|---|---|---|---|---|---|
| Kenney *et al*. (2004) | NA | NA | NA | 0–20 years | 24.7 (19.3–31.0) | NA |
| Guibout *et al*. (2005) | 3–9 years | 0 | NA | 0–16 years | 16.9 (9.9–26.6) | NA |
| | 10–19 years | 185.0 (30.8–572.6) | | | | |
| | 20–29 years | 18.8 (4.7–48.9) | | | | |
| | 30–39 years | 23.2 (11.6–40.6) | | | | |
| | ≥40 years | 2.9 (0.2–12.8) | | | | |
| Inskip & Curtis (2007) | NA | NA | NA | 0–17 years | 8.4 | 1.9 |
| Reulen *et al*. (2008) | 0–19 years | 10.9 (1.5–77.0) | 0.1 (0.0–1.2) | 0–4 years | 2.5 (1.7–3.6) | 1.7 (0.8–3.6) |
| | 20–29 years | 5.7 (3.3–9.8) | 1.9 (1.0–3.7) | 5–9 years | 1.1 (0.6–2.1) | 0.0 |
| | 30–39 years | 3.1 (2.3–4.3) | 8.5 (5.3–13.6) | 10–14 years | 2.5 (1.9–3.4) | 5.8 (3.5–9.7) |
| | 40–49 years | 1.5 (1.0–2.3) | 6.9 (2.0–23.7) | | | |
| | ≥50 years | 0.9 (0.5–1.8) | 0.0 | | | |

♀, female; CI, confidence interval; Dx, diagnosis; EAR, excess absolute risk; *N*, number; NA, not available; SIR, standardized incidence ratio.



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**Table 6** Secondary breast cancer risk after various radiation fields.

| **Study** (year) | **Study population** | **Treatment era** | **Patients** | **Age at primary cancer Dx** (year) | **Breast cancers** (*N*) | **Radiation field** | **Median radiation dose in Gy** (range) | **SIR** (95% CI) |
|---|---|---|---|---|---|---|---|---|
| De Bruin *et al.* (2009) | Cohort of Hodgkin lymphoma survivors from 5 institutions in the Netherlands | 1965–1995 | ♀ 1122 | <51 (27.7% <21 years) | 120 | Mantle | NA | 8.2 (6.6–10.1) |
| | | | | | | Mediastinal | | 3.7 (1.2–8.7) |
| | | | | | | Other supradiaphragmatic | | 1.6 (0.3–4.6) |
| | | | | | | Infradiaphragmatic | | 0.0 |
| Swerdlow *et al.* (2012) | Population-based cohort of England and Wales | 1956–2003 | ♀ 5002 | <36 (23.7% <20 years) | 373 | Mantle | 36 | 6.0 (5.3–6.7) |
| | | | | | | Two mantle component fields[a] | 31–33 | 3.4 (2.4–4.7) |
| | | | | | | One mantle component field[a] | 31–33 | 2.5 (1.7–3.7) |
| Lange *et al.* (2014) | Cohort of nephroblastoma survivors from the National Wilms Tumor Studies 1–4 | 1969–1995 | ♀ 2492 | <20 | 28 | Chest | NA | 27.6 (16.1–44.2) |
| | | | | | | Abdominal | | 6.0 (2.9–11.0) |
| Moskowitz *et al.* (2014) | Cohort of survivors of several childhood cancers from 26 institutions in United States and Canada | 1970–1986 | ♀ 1230 | <21 | 203 | Mantle | 40 (5–54) | 24.2 (20.7–28.3) |
| | | | | | | Mediastinal | 30 (3–54) | 13.0 (8.4–20.2) |
| | | | | | | Whole lung | 14 (2–20) | 43.6 (27.1–70.1) |
| | | | | | | Total body | 12 (4–16) | 19.3 (7.3–51.5) |
| | | | | | | Abdominal[b] | 20 (4–40) | 10.8 (2.7–43.2) |
| | | | | | | Posterior chest[c] | 31 (6–54) | 0.0 |
| | | | | | | Other one-sided anterior | 41 (10–61) | 9.9 (3.2–30.6) |

[a], mediastinum, axilla, neck or clavicle; [b], abdominal field extending above diaphragm; [c], posterior thoracic or paravertebral fields. ♂, male; ♀, female; CI, confidence interval; Dx, diagnosis; Gy, Gray; *N*, number; NA, not available; SIR, standardized incidence ratio.

childhood cancer survivors. In a recent review, Henderson and coworkers summarized the risk for secondary breast cancer after treatment with chest irradiation for pediatric cancer (Henderson *et al*. 2010). In the included higher quality cohort studies, standardized incidence ratios for secondary breast cancer varied between 13.3 and 55.5, excess absolute risks varied between 18.6 and 79.0 per 10,000 person-years, and cumulative incidences varied between 12 and 26% at 25–30 years follow-up since childhood cancer (Ng *et al*. 2002, Bhatia *et al*. 2003, Kenney *et al*. 2004, Taylor *et al*. 2007, Constine *et al*. 2008, De Bruin *et al*. 2009). These risk estimates are comparable to risks for breast cancer in women harboring a germline *BRCA1* or *BRCA2* gene mutation (Moskowitz *et al*. 2014).

Radiation fields associated with an increased secondary breast cancer risk in childhood cancer survivors include mantle field, whole lung, hemithorax, mediastinum, supradiaphragmatic abdomen, axilla, neck and clavicle, as well as total body (Table 6) (De Bruin *et al*. 2009, Swerdlow *et al*. 2012, Lange *et al*. 2014, Moskowitz *et al*. 2014). Smaller radiation fields seem to be associated with lower risks for radiation-induced breast cancer (De Bruin *et al*. 2009, Swerdlow *et al*. 2012, Schaapveld *et al*. 2015). However, despite an increased use of less extensive supradiaphragmatic radiation fields over the past decades, the incidence of radiation-induced breast cancer remained stable in Hodgkin lymphoma survivors (Schaapveld *et al*. 2015). This may be partly related to an earlier detection of secondary breast malignancies by improved screening practices (Ng *et al*. 2013). In a recent study on secondary breast cancer risk after craniospinal irradiation for pediatric central nervous system malignancies and leukemia, Moskowitz and coworkers observed an increased risk for secondary breast cancer in the subgroup of leukemia survivors solely (SIR 3.8 (95% CI: 1.2–11.7)) (Moskowitz *et al*. 2015). This observation might be related to genetic susceptibility, as illustrated by a population-based study in Italy that observed an increased standardized mortality ratio attributable to breast cancer in mothers of children diagnosed with leukemia (Zuccolo *et al*. 2007).

The relationship between chest radiation dose and breast cancer risk has been investigated by several studies (Table 7) (Travis *et al*. 2003, van Leeuwen *et al*. 2003, Guibout *et al*. 2005, Hill *et al*. 2005, Inskip *et al*. 2009). A linear dose–response curve has been established (Fig. 2A) (Inskip *et al*. 2009, Berrington de Gonzalez *et al*. 2013). Risk for radiation-induced breast cancer was traditionally studied after moderate- to high-dosed chest irradiation (i.e. ≥20 Gy) (Henderson *et al*. 2010). However, recent studies also demonstrated an increased secondary breast cancer risk after lower dosed chest irradiation (Lange *et al*. 2014, Moskowitz *et al*. 2014). Lange and coworkers observed an increased breast cancer risk of 14.4% (95% CI: 7.6–30.1) at an attained survivors' age of 40 years after 1–12 Gy chest irradiation for nephroblastoma (Lange *et al*. 2014). In a recent study by Moskowitz and coworkers, breast cancer risk was 30.6-fold increased (95% CI: 18.4–50.7) in comparison with the United States general

**Table 7** Estimated excess relative risk for secondary breast cancer per Gy chest irradiation in childhood cancer survivors.

| **Study** (year) | **Study population** | **Treatment era** | **Patients**[a] | **Age at primary cancer Dx** (year) | **ERR for subsequent breast cancer per Gy** (95% CI) |
|---|---|---|---|---|---|
| Travis *et al*. (2003) | Nested case–control study in a cohort of Hodgkin lymphoma survivors from 6 population-based cohorts | 1965–1994 | Cases 105<br>Controls 266 | <31 | 0.15 (0.04–0.73) |
| van Leeuwen *et al*. (2003) | Nested case–control study in a cohort of Hodgkin lymphoma survivors from 4 institutions in the Netherlands | 1965–1988 | Cases 48<br>Controls 175 | <41 | 0.03 (0.002–0.06) |
| Guibout *et al*. (2005) | Cohort of solid tumor survivors from 8 institutions in France and Britain | 1946–1986 | 1814 | <17 | 0.13 (<0.00–0.75) |
| Hill *et al*. (2005) | Nested case–control study in 6 population-based cohorts of Hodgkin lymphoma survivors | 1965–1999 | Cases 105<br>Controls 266 | <31 | 1.04 (1.00–1.07)[b] |
| Inskip *et al*. (2009) | Nested case–control study in a cohort of survivors of several childhood cancers from 26 institutions in United States and Canada | 1970–1986 | Cases 120<br>Controls 464 | <21 | 0.36 (0.14–0.93) |

[a], all patients were females. [b], relative risk per Gy. CI, confidence interval; Dx, diagnosis; ERR, excess relative risk.



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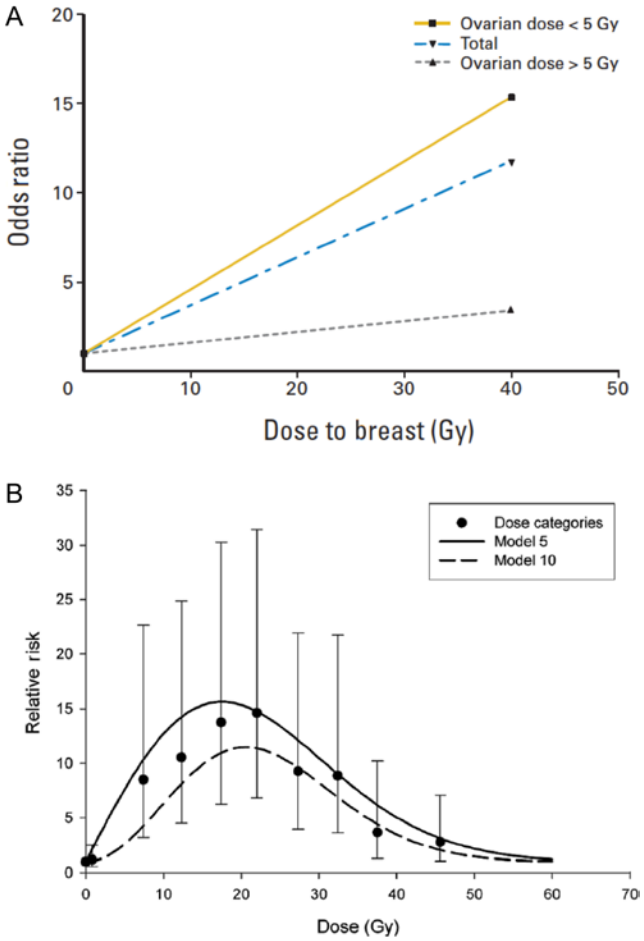


**Figure 2**
Fitted radiation dose–response relationships for chest irradiation and breast cancer, as well as thyroid gland irradiation and thyroid cancer as observed as in the Childhood Cancer Survivors Study by Inskip *et al.* (2009) and Bhatti *et al.* (2010), respectively. (A) Fitted dose–response relationship between chest radiation and breast cancer risk by radiation dose to the chest and ovaries. Reproduced from Inskip PD *et al.*: *Journal of Clinical Oncology* Vol. **27**(24), 2009: 3901–3907. Reprinted with permission. Copyright 2009 American Society of Clinical Oncology. All rights reserved. (B) Fitted dose–response relationship for thyroid gland irradiation and thyroid cancer risk (based on two constructed models (model 5 and 10) and adjusted for attained age, gender, and primary childhood cancer subtype). Reproduced from Bhatti P *et al.*: *Radiation Research* Vol. **174**(6), 2010: 741–752. Reprinted with permission. Copyright 2010 Radiation Research Society. All rights reserved.

population after 10–19 Gy chest irradiation for various childhood cancer subtypes (Moskowitz *et al.* 2014). Currently, there is no evidence of a significant effect of radiotherapy fractionation on secondary breast cancer risk following childhood cancer (Guibout *et al.* 2005).

Studies investigating radiation-related secondary cancer risk in childhood cancer survivors have predominantly assessed older radiotherapeutic modalities (Kumar 2012). Contemporary radiotherapeutic techniques like conformal radiotherapy, intensity-modulated radiation therapy and proton-beam therapy allow for more precise radiation delivery to the tumor target, thereby sparing healthy surrounding tissue. Therefore, these techniques may yield lower risks for secondary malignant neoplasm development compared with older radiotherapeutic modalities of earlier treatment eras (Armstrong *et al.* 2010, Kumar 2012). However, there are also concerns of a potentially increased secondary cancer risk following modern radiotherapeutic techniques due to a larger amount of leakage radiation (Kumar 2012). To our knowledge, observational studies on secondary breast cancer risk in childhood cancer survivors following modern radiotherapeutic techniques have to be performed yet.

**Hematopoietic stem cell transplantation** Childhood cancer survivors who received hematopoietic stem cell transplantation are at increased risk for secondary breast cancer (Friedman *et al.* 2008, Danner-Koptik *et al.* 2013). Friedman and coworkers, observed a standardized incidence ratio of 2.2 (95% CI: 1.7–2.9) for secondary breast cancer following allogeneic hematopoietic stem cell transplantation. In their study, secondary breast cancer risk was associated with total-body irradiation, follow-up duration, and age at stem cell transplantation (Friedman *et al.* 2008). In addition, Danner-Koptik and coworkers observed a standardized incidence ratio of 93 (95% CI 11–336) for secondary breast cancer following autologous hematopoietic stem cell transplantation. However, they could not demonstrate an association between secondary breast cancer risk and age, gender, childhood cancer subtype, follow-up duration, response to primary cancer treatment, and use of total-body irradiation or etoposide as part of pretransplant conditioning regimen (Danner-Koptik *et al.* 2013). Intriguingly, three cases of secondary breast cancer in male childhood cancer survivors following total-body irradiation and hematopoietic stem cell transplantation have been described (Latz *et al.* 2004, Lowe *et al.* 2008, O'Flynn *et al.* 2011).

**Chemotherapy** Most studies in cohorts of solely childhood cancer survivors and childhood- and adult-onset cancer survivors combined did not observe a relationship between chemotherapy and secondary breast cancer risk (Guibout *et al.* 2005, Reulen *et al.* 2008, Alm El-Din *et al.* 2009, Little *et al.* 2014), or observed a protective effect of certain chemotherapeutic agents on the development of radiation-related breast cancer (van Leeuwen *et al.* 2003,



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Travis *et al*. 2003, 2005, De Bruin *et al*. 2009, Swerdlow *et al*. 2012, Schaapveld *et al*. 2015). However, two studies reported an increased risk for secondary breast cancer attributable to chemotherapy (Hancock *et al*. 1993, Henderson *et al*. 2015). In a combined cohort of childhood- and adult-onset Hodgkin lymphoma survivors, Hancock and coworkers observed a higher risk for secondary breast cancer following treatment with mechlorethamine, vincristine, procarbazine and prednisone in combination with radiotherapy compared with treatment with radiotherapy alone during the first 15 years following Hodgkin lymphoma (SIR 6.3 (95% CI: 3.1–11.6) for combination chemoradiation therapy vs SIR 0.8 (95% CI: 0.1–2.5) for radiotherapy alone). After 15 years of follow-up since Hodgkin lymphoma, secondary breast cancer risk became equivalently increased in both treatment groups (SIR 14.8 (95% CI: 3.7–40.4) for combination chemoradiation therapy vs SIR 13.0 (95% CI: 6.6–23.1) for radiotherapy alone) (Hancock *et al*. 1993). In addition, in a recent Childhood Cancer Survivor Study report by Henderson and coworkers on the risk for secondary breast cancer in childhood cancer survivors not treated with chest irradiation, exposure to anthracyclines and alkylating agents was associated with an increased secondary breast cancer risk (relative SIR 3.8 (95% CI: 1.7–8.3) for anthracyclines dosed ≥250 mg/m$^2$, and relative SIR 3.0 (95% CI: 1.2–7.7) for alkylating agents dosed ≥18,000 mg/m$^2$ compared with no treatment with anthracyclines or alkylating agents) (Henderson *et al*. 2015). As suggested by Van Leeuwen and coworkers, the observed increased risk for secondary breast cancer attributable to anthracyclines and alkylating agents in childhood cancer survivors not treated with chest irradiation might be partly related to genetic susceptibility (van Leeuwen & Ronckers 2016).

### Primary cancer diagnosis and secondary breast cancer risk

In a series of three articles, Maule and coworkers reported standardized incidence ratios and excess absolute risks for secondary malignant neoplasms in childhood cancer survivors derived from 13 population-based cancer registries (Maule *et al*. 2007, 2008, 2011). They observed an increased risk for secondary breast cancer after several childhood cancer subtypes (Table 8). The highest risk for secondary breast cancer was observed in survivors of Hodgkin lymphoma (Maule *et al*. 2007), which likely reflect treatment with mantle field irradiation. However, Guibout and coworkers also observed an increased risk for secondary breast cancer in Hodgkin lymphoma survivors after adjustment for chest irradiation and treatment with chemotherapy (RR 7.01 (95% CI: 1.4–30.9) compared with survivors of other childhood cancer subtypes) (Guibout *et al*. 2005). This supports the idea that factors other than treatment exposures, like genetic determinants, may also contribute to secondary breast cancer development in Hodgkin lymphoma survivors. Although Maule and coworkers did not observe a significantly increased risk for secondary breast cancer in survivors of soft-tissue sarcoma, retinoblastoma, nephroblastoma, neuroblastoma, germ cell tumors and non-Hodgkin lymphoma, other studies did (Kenney *et al*. 2004, Guibout *et al*. 2005, Inskip & Curtis 2007, Marees *et al*. 2008, Reulen *et al*. 2011, Lange *et al*. 2014, Little *et al*. 2014). The increased risk for secondary breast cancer in survivors of sarcoma might also be partly related to genetic factors. Data from the Childhood Cancer Survivor Study demonstrated an increased standardized incidence ratio for secondary breast cancer in sarcoma survivors not treated with chest irradiation (5.3 (95% CI: 3.6–7.8)) (Henderson *et al*. 2015). In addition, a positive family history for sarcoma was associated with an increased secondary breast cancer risk (RR 5.3 (95% CI: 1.3–21.5)) (Kenney *et al*. 2004). The increased risk for secondary breast cancer after retinoblastoma is observed in both heritable and nonheritable retinoblastoma survivors (Little *et al*. 2014), and seems to become apparent after ≥40 years of follow-up since primary cancer diagnosis in heritable retinoblastoma survivors (Marees *et al*. 2008).

**Table 8** Risk for secondary breast cancer by childhood cancer subtype.

| Primary childhood cancer diagnosis | SIR (95% CI) | EAR per 100,000 person-years |
|---|---|---|
| Leukemia | 2.42 (0.06–13.5) | 0.8 |
| Hodgkin lymphoma | 20.9 (7.66–45.4) | 40.6 |
| Non-Hodgkin lymphoma | 0.00 (0.00–0.33) | −1.7 |
| Glioma | 1.4 (0.2–5.2) | 1.3 |
| Other central nervous system tumors | 1.3 (0.0–7.4) | 2.5 |
| Retinoblastoma | 1.5 (<0.1–8.5) | 1.6 |
| Renal tumors | 3.0 (0.1–16.7) | 2.7 |
| Bone sarcomas | 6.8 (1.9–17.5) | 26.9 |
| Soft-tissue sarcomas | 1.3 (<0.1–7.4) | 1.1 |
| Epithelial tumors | 1.8 (0.5–4.6) | 8.7 |

CI, confidence interval; EAR, excess absolute risk; SIR, standardized incidence ratio.

### Hormonal influences on secondary breast cancer risk

In the general population, prolonged exposure to estrogens has been associated with an increased breast



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cancer risk (Clemons & Goss 2001). Therefore, several studies investigated the risk-modifying effects of age at menarche, menopausal age, and age at first childbirth on secondary breast cancer in childhood- and young-adult-onset cancer survivors (Travis *et al*. 2003, van Leeuwen *et al*. 2003, Kenney *et al*. 2004, Hill *et al*. 2005, De Bruin *et al*. 2009, Cooke *et al*. 2013). In contrast to observations in the general population, Cooke and coworkers demonstrated an increased risk for secondary breast cancer in Hodgkin lymphoma survivors experiencing a late menarche (OR 3.74 (95% CI: 1.08–12.98) for age at menarche 17 vs 13 years) (Cooke *et al*. 2013). In addition, they observed a relationship between timing of chest irradiation in relation to menarche and secondary breast cancer risk. Secondary breast cancer risk was significantly increased in survivors treated with chest irradiation within 5 years of menarche; the smaller the interval between chest irradiation and menarche, the higher the risk for secondary breast cancer ($P < 0.001$ for trend) (Cooke *et al*. 2013). Other studies could not demonstrate an association between age at menarche and secondary breast cancer risk (van Leeuwen *et al*. 2003, Kenney *et al*. 2004, Hill *et al*. 2005). In addition, no studies observed a risk-modifying effect of age at first childbirth on secondary breast cancer development in childhood- and young-adult-onset cancer survivors (van Leeuwen *et al*. 2003, Kenney *et al*. 2004, Hill *et al*. 2005). However, Hill and coworkers demonstrated a relationship between timing of childbirth in relation to Hodgkin lymphoma diagnosis and secondary breast cancer risk. Women not treated with alkylating agents or ovarian irradiation ≥5 Gy who had childbirth within 5 years following Hodgkin lymphoma diagnosis demonstrated an increased secondary breast cancer risk compared with women who had childbirth at least 5 years after Hodgkin lymphoma diagnosis (OR 2.6 (95% CI: 1.0–6.7)) (Hill *et al*. 2005). An increased risk for breast cancer shortly after childbirth has also been observed in the general population, and is thought to be related to gestational hormone exposure, immunosuppressive effects of pregnancy and postpartum breast involution (Lyons *et al*. 2009).

Several studies investigated the risk-modifying effects of age at menopause, premature ovarian insufficiency, alkylating agents and ovarian irradiation on radiation-induced breast cancer in survivors of childhood- and young-adult-onset cancer (Table 9) (Travis *et al*. 2003, van Leeuwen *et al*. 2003, Kenney *et al*. 2004, Hill *et al*. 2005, Taylor *et al*. 2007, De Bruin *et al*. 2009, Cooke *et al*. 2013, Schaapveld *et al*. 2015). Studies in combined cohorts of childhood- and adult-onset Hodgkin lymphoma survivors consistently reported a protective effect of premature ovarian insufficiency on radiation-induced breast cancer risk (Travis *et al*. 2003, van Leeuwen *et al*. 2003, Hill *et al*. 2005, De Bruin *et al*. 2009, Cooke *et al*. 2013). Risk for radiation-induced breast cancer seems to be lower in women experiencing less premenopausal years following Hodgkin lymphoma treatment (De Bruin *et al*. 2009, Cooke *et al*. 2013). Alkylating agent chemotherapy and ovarian irradiation are known to potentially induce premature ovarian insufficiency. Therefore, several studies investigated the risk-modifying effects of these therapies on radiation-induced breast cancer development. A protective effect of alkylating agent chemotherapy on radiation-induced breast cancer has been observed in combined cohorts of childhood- and adult-onset Hodgkin lymphoma survivors (Travis *et al*. 2003, 2005, van Leeuwen *et al*. 2003, De Bruin *et al*. 2009, Swerdlow *et al*. 2012, Schaapveld *et al*. 2015). In the studies by Travis and coworkers, and Van Leeuwen and coworkers, increasing cycles of alkylating agent chemotherapy and a high dose of procarbazine were significantly associated with a decreased risk for radiation-induced breast cancer (Travis *et al*. 2003, van Leeuwen *et al*. 2003). Note that no studies in cohorts of childhood cancer survivors solely could demonstrate a beneficial effect of alkylating agents on radiation-induced breast cancer risk. In addition, several studies in cohorts of childhood cancer survivors solely and childhood- and adult-onset cancer survivors combined observed a protective effect of ovarian irradiation on radiation-induced breast cancer (Fig. 2A) (Kenney *et al*. 2004, Constine *et al*. 2008, Inskip *et al*. 2009, Swerdlow *et al*. 2012, Moskowitz *et al*. 2014).

Although the aforementioned studies suggest protective effects of premature ovarian insufficiency and gonadotoxic therapies on radiation-induced breast cancer development, it is important to keep in mind that most of these studies were performed in combined cohorts of childhood- and adult-onset Hodgkin lymphoma survivors (Travis *et al*. 2003, 2005, van Leeuwen *et al*. 2003, Hill *et al*. 2005, De Bruin *et al*. 2009, Swerdlow *et al*. 2012, Cooke *et al*. 2013, Schaapveld *et al*. 2015). The beneficial effect of gonadotoxic treatment on radiation-induced breast cancer risk seems less pronounced in childhood- compared with adult-onset cancer survivors. This is underscored by a recent study in survivors of Hodgkin lymphoma by Swerdlow and coworkers which observed a beneficial effect of gonadotoxic therapy on radiation-induced breast cancer risk only in women aged ≥20 years at primary cancer treatment (Swerdlow *et al*. 2012).



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**Table 9** Risk-modifying effects of gonadotoxic treatment, premature ovarian insufficiency and age at menopause on secondary breast cancer risk in childhood cancer survivors.

| **Study** (year) | **Study population** | **Treatment era** | **Patients** | **Age at primary cancer Dx** (year) | **RR** (95% CI) **associated with alkylating agents** (yes vs no) | **RR** (95% CI) **associated with ovarian irradiation** (yes vs no) | **RR** (95% CI) **associated with premature ovarian insufficiency** (yes vs no)[a] |
|---|---|---|---|---|---|---|---|
| **Studies in combined cohorts of childhood- and adult-onset Hodgkin lymphoma survivors** | | | | | | | |
| Travis *et al.* (2003) | Nested case–control study in a cohort of Hodgkin lymphoma survivors from 6 population-based cohorts | 1965–1994 | Cases 105 | <31 | 0.7 (0.3–1.7) 1–4 cycles | 0.4 (0.1–1.1)[b] | 0.2 (0.05–0.6) <30 years |
| | | | Controls 266 | | 0.6 (0.3–1.1) 5–8 cycles | | 0.3 (0.1–0.8) 30–39 years |
| van Leeuwen *et al.* (2003) | Nested case–control study in a cohort of Hodgkin lymphoma survivors from 4 institutions in the Netherlands | 1965–1988 | Cases 48 | <41 | 0.2 (0.1–0.7) ≥9 cycles<br>0.31 (0.09–1.05) <6 cycles | 0.13 (0.02–1.08)[b] | 0.09 (0.01–0.81) 19–30 years |
| | | | Controls 175 | | 0.33 (0.13–0.86) ≥6 cycles | | 0.25 (0.07–0.92) 31–40 years<br>0.84 (0.23–3.05) ≥41 years |
| Hill *et al.* (2005) | Nested case–control study in 6 population-based cohorts of Hodgkin lymphoma survivors | 1965–1999 | Cases 105 | <31 | NA | NA | 0.3 (0.2–0.7)[c] |
| | | | Controls 266 | | | | |
| De Bruin *et al.* (2009)[d] | Cohort of Hodgkin lymphoma survivors from 5 institutions in the Netherlands | 1965–1995 | ♀ 1122 | <51 (27.7% <21 years) | 0.6 (0.3–0.9)[e,f]<br>0.4 (0.1–1.3)[e,g] | 0.4 (0.1–1.4)[e] | 0.4 (0.2–0.8)[e] |
| Cooke *et al.* (2013) | Nested case–control study in a cohort of Hodgkin lymphoma survivors from Wales and Britain treated with chest irradiation | 1956–2003 | Cases 260 | <36 | NA | NA | 0.65 (0.44–0.94)[c] |
| | | | Controls 2237 | | | | |
| Schaapveld *et al.* (2015) | Cohort of Hodgkin lymphoma survivors from 7 institutions in the Netherlands | 1965–2000 | ♂ 2207 | 15–50 | 0.84 (0.52–1.36)[e,h] | NA | NA |
| | | | ♀ 1698 | | 0.71 (0.47–1.07)[e,i]<br>0.33 (0.16–0.68)[e,g] | | |
| **Studies in cohorts childhood cancer survivors solely** | | | | | | | |
| Kenney *et al.* (2004) | Cohort from 26 institutions in United States and Canada | 1970–1986 | ♀ 6068 | <21 | 0.8 (0.4–1.6) AA-score 1–2<br>0.8 (0.4–1.4) AA-score 3–4<br>1.11 (0.6–2.0) AA-score ≥5 | 0.6 (0.4–0.9) | NA |
| Taylor *et al.* (2007) | Population-based cohort of Hodgkin lymphoma survivors from Britain | 1940–1991 | ♀ 383 | <15 | 0.49 (0.18–1.33) | NA | NA |

[a], premature ovarian insufficiency is defined as menopause <40 years of age. [b], ≥5 Gy ovarian irradiation. [c], odds ratio. [d], analyses of risk-modifying effects restricted to women <41 years of age at Hodgkin lymphoma diagnosis. [e], hazard ratio. [f], ≤8.4 g/m² procarbazine. [g], >8.4 g/m² procarbazine. [h], ≤4.2 g/m² procarbazine. [i], 4.2–8.4 g/m² procarbazine. ♂, male; ♀, female; AA-score, alkylating agent score (i.e. a categorical variable accounting for exposure to various alkylating agents and a range of doses developed by Tucker *et al.* (1987)); CI, confidence interval; Dx, diagnosis; Gy, Gray; NA, not available; RR, relative risk.

The less pronounced protective effect of gonadotoxic therapy in childhood- compared with adult-onset cancer survivors may be explained by a greater reserve of follicles in young women, which might be less likely to deplete following ovarian toxic treatment (Sklar 2005). Note that in a recent study in childhood cancer survivors not treated with chest irradiation, Henderson and coworkers could not demonstrate a protective effect of ovarian irradiation or alkylating agent chemotherapy on secondary breast cancer risk (Henderson *et al*. 2015). This indicates that gonadotoxic treatment only protects for radiation-induced breast cancer development.

Currently, there is no evidence of a harmful effect of estrogen–progestin replacement therapy on secondary breast cancer risk in premature ovarian-insufficient childhood cancer survivors (Travis *et al*. 2003, van Leeuwen *et al*. 2003, De Bruin *et al*. 2009). However, the number of women using estrogen–progestin replacement therapy in the available studies addressing this issue is too small to reliably evaluate this topic. Only recently, estrogen–progestin replacement therapy is prescribed commonly in premature ovarian-insufficient childhood cancer survivors (van Leeuwen *et al*. 2003). Since potential benefits of premature ovarian insufficiency on radiation-induced breast cancer risk have not been demonstrated in cohorts of solely childhood cancer survivors, and harms of estrogen–progestin replacement therapy on radiation-induced breast cancer risk in premature ovarian-insufficient childhood cancer survivors have not been described thus far, castration of female childhood cancer survivors at high risk for radiation-induced breast cancer should not be performed. This is underscored by the clearly demonstrated beneficial effects of estrogen–progestin replacement therapy on bone and cardiovascular health, as well as quality of life in women from the general population experiencing premature ovarian insufficiency (National Collaborating Centre for Women's and Children's Health 2015). The effect of oral contraceptives on secondary breast cancer risk in childhood cancer survivors has only been studied in combined cohorts of childhood- and adult-onset Hodgkin lymphoma survivors. No risk-modifying effects have been demonstrated (van Leeuwen *et al*. 2003, Hill *et al*. 2005, De Bruin *et al*. 2009).

## Thyroid cancer

### Epidemiology and host-related risk factors

Several recent large cohort studies in childhood cancer survivors observed significantly increased standardized incidence ratios for secondary thyroid carcinoma between 5.4 and 18.0 in comparison with the general population (Inskip & Curtis 2007, Olsen *et al*. 2009, Taylor *et al*. 2009, Friedman *et al*. 2010). This represents a 30-year cumulative incidence of 1.4% (95% CI: 1.1–1.6) since childhood cancer diagnosis (Friedman *et al*. 2010). The increased risk for secondary thyroid cancer in childhood cancer survivors involves predominantly differentiated thyroid carcinoma (i.e. papillary or follicular thyroid carcinoma) (Black *et al*. 1998, Taylor *et al*. 2009). Latency periods for the development of secondary thyroid carcinoma in childhood cancer survivors vary between 0.6 and 38 years (average 12.3 years) (Table 10) (Black *et al*. 1998, Bhatia *et al*. 2002, Acharya *et al*. 2003, Cohen *et al*. 2007, Constine *et al*. 2008, Diallo *et al*. 2009, Taylor *et al*. 2009, Veiga *et al*. 2012*a*, Danner-Koptik *et al*. 2013, Dorffel *et al*. 2015, Finke *et al*. 2015, Brignardello *et al*. 2016). A recent study by Veiga and coworkers included pooled data from the Childhood Cancer Survivor Study cohort (Bhatti *et al*. 2010), the Late Effects Study Group cohort (Tucker *et al*. 1991), the Nordic countries cohort (Svahn-Tapper *et al*. 2006) and a combined French and British cohort (de Vathaire *et al*. 1999). The study found that female gender (RR 2.0 (95% CI: 1.5–2.8)), younger age at primary cancer ($P<0.01$ for trend), longer follow-up since primary cancer ($P=0.01$ for trend), older attained survivor's age ($P<0.01$ for trend), and treatment with radiotherapy (RR 5.5 (95% CI: 3.1–9.7)) were significantly associated with secondary thyroid carcinoma risk in childhood cancer survivors (Veiga *et al*. 2012*b*). A risk-modifying effect of gender and age at childhood cancer diagnosis has also been observed in other studies (Cohen *et al*. 2007, Constine *et al*. 2008), but not all (Somerville *et al*. 2002, Taylor *et al*. 2009). A recent study by De Vathaire *et al*. investigated the influence of smoking and overweight on secondary thyroid cancer risk in childhood cancer survivors, but could not demonstrate a significant effect (RR 0.75 (95% CI: 0.32–1.6) for smoking; RR 1.4 (95% CI: 0.7–2.80 for overweight)) (de Vathaire *et al*. 2015). Best and coworkers identified allelic variants in *PRDM1* to predispose Hodgkin lymphoma survivors to radiation-induced thyroid cancer (Best *et al*. 2011). In addition, several studies identified allelic variants in *TP53*, *ATM* and *FOXE1* to be associated with radiation-induced papillary thyroid carcinoma in survivors of the Chernobyl nuclear accident (Akulevich *et al*. 2009, Takahashi *et al*. 2010, Damiola *et al*. 2014).



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**Table 10** Latency time between childhood cancer and secondary thyroid cancer.

| Study (year) | Study population | Treatment era | Patients | Age at primary cancer Dx (year) | Median follow-up (year) | Radiotherapy (%) | Thyroid cancers (*N*) | Latency period | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Median (year) | Range (year) |
| Black *et al.* (1998) | Population-based study in Germany, Austria and Switzerland | 1980–1997 | NA | <16 | NA | NA | 18 | 8 | 4–19 |
| Bhatia *et al.* (2002) | Cohort of leukemia survivors from 122 institutions in United States and Canada | 1983–1995 | ♂ 5034 | <21 | 15 | 38 | 4 | 9.7 | 5.5–11.8 |
| Acharya *et al.* (2003) | Single-center cohort of survivors of several childhood cancers from the United States | 1970–1998 | ♀ 3797<br>♂ 10 | <21 | NA | 100 | 33 | 13.0 | 6.2–30.1 |
| Cohen *et al.* (2007) | Cohort of hematopoietic stem cell transplantation survivors from 166 institutions participating in the European Group for Blood and Marrow Transplantation (EBMT) registry | 1985–2003 | ♀ 23<br>♂ 40,148 | <52 (27.5% <21 years) | 12.7 | 75.0 | 32 | 8.5 | 0.6–18.5 |
| Constine *et al.* (2008) | Cohort of Hodgkin lymphoma survivors from 5 institutions in the United States | 1960–1990 | ♀ 30,538<br>♂ 532 | <19 | 16.8[a] | 91.2 | 14 | 14.4 | 8.5–23.0 |
| Diallo *et al.* (2009) | Cohort of survivors of several childhood cancers from 8 institutions in France and Britain | 1942–1986 | ♀ 398<br>♂/♀ 4581 | <17 | 15.4 | NA | 17 | 18 | 8–38 |
| Taylor *et al.* (2009) | Population-based cohort from Britain | 1940–1991 | ♂/♀ 17,980 | <15 | 17.4 | NA | 50 | 19.5 | 6–38 |
| Veiga *et al.* (2012) | Cohort from 26 institutions in United States and Canada | 1970–1986 | ♂ 6621 | <21 | 16[a] | 68.0 | 119 | 14.3[a] | 5–34 |
| Danner-Koptik *et al.* (2013) | Cohort of survivors of autologous hematopoietic stem cell transplantation survivors from >450 institutions participating in the Center for International Blood and Marrow Transplantation (CIBMT) | 1987–2003 | ♀ 5926<br>♂ 895 | <21 | 8 | 22[b] | 5 | 6.8 | 1.9–12.5 |
| Dorffel *et al.* (2015) | Cohort from German, Austrian and Swiss pediatric Hodgkin lymphoma studies | 1978–2002 | ♀ 592<br>♂ 1424 | <19 | 14.3 | NA | 47 | 13.2 | 4.0–29.2 |
| Finke *et al.* (2015) | Population-based cohort from German Childhood Cancer Registry | 1980–2002 | ♀ 1124<br>♂/♀ 33,809 | <15 | NA | NA | 17 | 9.3 | 4.0–17.6 |
| Brignardello *et al.* (2016) | Single-center cohort of survivors of several childhood cancers from Italy | 1985–2007 | ♂ 113<br>♀ 84 | <18 | 15.19 | 100 | 14 | 13.08 | 8.22–23.65 |

[a], mean. [b], radiotherapy as part of conditioning regimen for hematopoietic stem cell transplantation. ♂, male; ♀, female; Dx, diagnosis; *N*, number; NA, not available.

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**Table 11** Detection and presence of benign and malignant thyroid nodules in childhood cancer survivors.

| Study (year) | Study population | Treatment era | Patients | Age at primary cancer Dx (year) | Median follow-up (year) | RTx (%) | Method of nodule detection | Benign nodules (%) | Malignant nodules (%) |
|---|---|---|---|---|---|---|---|---|---|
| Acharya *et al.* (2003) | Single-center cohort of survivors of several childhood cancers from the United States | 1970–1998 | ♂ 10<br>♀ 23 | <21 | NA | 100 | Retrospective search in hospital-based databases for thyroid nodules in childhood cancer survivors and histological confirmation by pathologist | 20 (60.6) | 13 (39.4) |
| Agrawal *et al.* (2016) | Single-center cohort of survivors of several childhood cancers from the United States | NA | ♂ 58<br>♀ 61 | <21 | NA | 50.4 | Ultrasonography and histological examination in suspected nodules | 31 (93.9) | 2 (6.1) |
| Brignardello *et al.* (2016) | Single-center cohort of survivors of several childhood cancers from Italy | 1985–2007 | ♂ 113<br>♀ 84 | <18 | 15.19 | 100 | Ultrasonography and histological examination in suspected nodules | 60 (81.1) | 14 (18.9) |
| Caglar *et al.* (2014) | Single-center cohort of survivors of several childhood cancers from Turkey | NA | ♂ 84<br>♀ 36 | <18 | 7.8[a] | 56.7 | Ultrasonography and histological examination in suspected nodules | 24 (88.9) | 3 (11.1) |
| Crom *et al.* (1997) | Single-center cohort of survivors of several childhood cancers from the United States | NA | ♂ 53<br>♀ 43 | <22 | 10.6 | 100 | Ultrasonography and histological examination in suspected nodules | 21 (95.5) | 1 (4.5) |
| Haddy *et al.* (2012) | Cohort of survivors of several childhood cancers from 5 institutions in France | 1940–1985 | ♂ 1831<br>♀ 1423 | <16 | 25 | 70.3 | Self-reported questionnaire or retrospective search in medical records for histologically confirmed thyroid adenomas | 71 (2.2) | NA |
| Healy *et al.* (1996) | Single-center cohort of Hodgkin lymphoma survivors from Britain | NA | 46 | NA | 10.3 | 100 | Ultrasonography and histological examination in suspected nodules | 28 (93.3) | 2 (6.7) |
| Kelly *et al.* (2013) | Single-center cohort of survivors of several childhood cancers from the United States | 1987–2007 | ♂ 17<br>♀ 30 | <18 | 8 | 100 | Ultrasonography and histological examination in suspected nodules | 43 (91.5) | 4 (8.5) |
| Li *et al.* (2014) | Single-center cohort of survivors of several childhood cancers from Canada | NA | ♂ 44<br>♀ 34 | <19 | 17.90 | 100 | Retrospective search in medical records for childhood cancer survivors who received ultrasonography and histological examination for suspected nodules | 41 (89.1) | 5 (10.9) |
| Somerville *et al.* (2002) | Single-center cohort of survivors of several childhood cancers from Australia | NA | ♂ 72<br>♀ 70 | NA | 14.0[a] | 100 | Ultrasonography and histological examination in suspected nodules | 81 (81.8) | 18 (18.2) |
| Vivanco *et al.* (2012) | Single-center cohort of survivors of several childhood cancers treated with total-body irradiation preceding hematopoietic stem cell transplantation from France | 1989–2009 | ♂ 43<br>♀ 33 | <18 | 5.1 | 100 | Ultrasonography and histological examination in suspected nodules | 15 (71.4) | 6 (28.6) |

[a], mean. ♂, male; ♀, female; %, percentage; Dx, diagnosis; NA, not available; RTx, radiotherapy.

### Treatment-related risk factors for secondary thyroid carcinoma

Radiotherapy involving the thyroid gland is the most important risk factor for secondary thyroid carcinoma in childhood cancer survivors, and seems to exert its effect via a sigmoidal dose–response relationship (Veiga *et al.* 2012*b*, de Vathaire *et al.* 2015). In the aforementioned pooled study by Veiga and coworkers, the dose–response relationship for thyroid carcinoma in survivors of pediatric cancer increased linearly until a radiation dose of approximately 10 Gy, leveled off at a radiation dose of approximately 10–30 Gy, and declined again at a radiation dose >30 Gy. However, the risk for thyroid cancer still remained increased at a radiation dose >50 Gy (Veiga *et al.* 2012*b*). The downturn in the dose–response relationship for radiation-induced thyroid carcinoma is thought to be related to a cell-killing effect (Sigurdson *et al.* 2005). In Fig. 2B, the dose–response curve for secondary thyroid carcinoma following thyroid gland irradiation as reported by Bhatti and coworkers is shown (Bhatti *et al.* 2010). This study by Bhatti and coworkers is also included in the pooled analysis by Veiga and coworkers (Veiga *et al.* 2012*b*). Besides increasing the risk for differentiated thyroid carcinoma, radiotherapy involving the thyroid gland is also known to promote the occurrence of benign thyroid nodules in childhood cancer survivors (Table 11). Clinically, it may be difficult to distinguish malignant from benign thyroid nodules (Healy *et al.* 1996, Crom *et al.* 1997, Somerville *et al.* 2002, Acharya *et al.* 2003, Haddy *et al.* 2012, Vivanco *et al.* 2012, Kelly *et al.* 2013, Caglar *et al.* 2014, Li *et al.* 2014, Agrawal *et al.* 2016, Brignardello *et al.* 2016). Studies investigating radiation-related thyroid carcinoma risk after childhood cancer treatment have predominantly assessed older radiotherapeutic modalities. To our knowledge, observational studies on secondary thyroid carcinoma risk in childhood cancer survivors treated with modern radiotherapeutic techniques like conformal radiotherapy, intensity-modulated radiation therapy and proton-beam therapy have to be performed yet.

A few studies demonstrated an increased risk for secondary thyroid carcinoma in childhood cancer survivors attributable to chemotherapy (Veiga *et al.* 2012*a*,*b*, de Vathaire *et al.* 2015). Veiga and coworkers observed a 2.4-fold increased risk (95% CI: 1.3–4.5) for secondary thyroid cancer in childhood cancer survivors treated with a combination of alkylating agents and ≤20 Gy thyroid gland irradiation; the contribution of chemotherapy to secondary thyroid cancer risk declined with increasing thyroid gland irradiation dose ($P=0.03$ for trend) (Veiga *et al.* 2012*a*). In another study, Veiga and coworkers observed a 4.5-fold increased risk (95% CI: 1.4–17.8) for secondary thyroid carcinoma in childhood cancer survivors treated with anthracyclines without thyroid gland irradiation (Veiga *et al.* 2012*b*). A recent study by De Vathaire and coworkers demonstrated an increased secondary thyroid carcinoma risk in childhood cancer survivors treated with nitrosourea chemotherapy (RR 6.6 (95% CI: 2.5–15.7)) (de Vathaire *et al.* 2015). Interestingly, in this study by De Vathaire and coworkers, childhood cancer treatment with splenectomy was also associated with an increased risk for secondary thyroid cancer (RR 2.3 (95% CI: 1.3–4.0)), while pituitary irradiation >10 Gy decreased secondary thyroid carcinoma risk (RR 0.2 (95% CI: 0.1–0.6)) (de Vathaire *et al.* 2015). In our institution, we could not demonstrate an increased risk for secondary thyroid cancer in survivors of childhood Hodgkin lymphoma treated with chemotherapy solely (van Beek *et al.* 2009, van Dorp *et al.* 2012).

Autologous and allogeneic hematopoietic stem cell transplantations are also associated with an increased secondary thyroid cancer risk (Socie *et al.* 2000, Cohen *et al.* 2007, Vivanco *et al.* 2012, Danner-Koptik *et al.* 2013). In a cohort of childhood- and adult-onset autologous and allogeneic hematopoietic stem cell transplantation survivors, Cohen and coworkers identified young age at transplantation (RR 24.61 (95% CI: 4.45–136.25) for age 0–10 vs >20 years), pretransplant conditioning with total-body irradiation (RR 3.44 (95% CI: 1.41–8.37)), and chronic graft-versus-host disease (RR 2.94 (95% CI: 1.21–7.15)) to increase the risk for secondary thyroid cancer (Cohen *et al.* 2007).

### Primary cancer diagnosis and secondary thyroid carcinoma risk

Several childhood cancer subtypes have been associated with an increased secondary thyroid cancer risk (Table 12). Particularly, high risks for secondary thyroid carcinoma have been observed in survivors of neuroblastoma, Hodgkin lymphoma, non-Hodgkin lymphoma, brain tumors, and leukemia (Maule *et al.* 2007, 2008, 2011). In addition, De Vathaire and coworkers observed an increased risk for secondary thyroid carcinoma in survivors of gonadal tumors (SIR 16.0 (95% CI: 4.0–41.4)) and soft-tissue sarcoma (SIR 8.2 (95% CI 2.0–21.2)) (de Vathaire *et al.* 2015). Administered treatment modalities, like $^{131}$I-MIBG and radiotherapy involving the thyroid gland, may conceivably explain the increased risks for secondary thyroid cancer.

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**Table 12** Risk for secondary thyroid cancer by childhood cancer subtype.

| Primary childhood cancer diagnosis | SIR (95% CI) | EAR per 100,000 person-years |
|---|---|---|
| Leukemia | 18.8 (8.60–35.7) | 11.3 |
| Hodgkin lymphoma | 52.5 (24.0–99.6) | 62.7 |
| Non-Hodgkin lymphoma | 40.4 (14.8–88.0) | 31.0 |
| Glioma | 6.8 (1.9–18.0) | 7.2 |
| Embryonal central nervous system tumors | 30 (8.2–77) | 25 |
| Other central nervous system tumors | 7.7 (0.2–43) | 8.8 |
| Sympathetic nervous system tumors | 143.7 (29.6–419.8) | 60.8 |
| Retinoblastoma | 5.3 (0.1–29.6) | 3.8 |
| Renal tumors | 13.9 (2.9–40.5) | 11.1 |
| Bone sarcomas | 10.8 (1.3–38.9) | 14.3 |
| Soft-tissue sarcomas | 4.1 (0.1–22.6) | 3.6 |
| Epithelial tumors | 3.3 (0.1–18.4) | 3.4 |

CI, confidence interval; EAR, excess absolute risk; SIR, standardized incidence ratio.

$^{131}$I-MIBG (131-iodine metaiodobenzylguanidine) may be used to treat neuroblastoma, and involves administering a radioiodine-labeled guanidine derivate (Kayano & Kinuya 2015). Approximately 2–5% of the administered $^{131}$I-MIBG enters the circulation as free radioiodine, and may affect thyroid functioning and induce thyroid nodules as well as secondary thyroid carcinoma (Clement *et al*. 2015).

## Limitations of currently available literature, and recommendations for future research

The currently available literature on secondary endocrine-related cancer risk in childhood cancer survivors has some limitations. Follow-up durations since childhood cancer are generally too short to assess the risk for secondary malignant neoplasms in aging childhood cancer survivors. Average follow-up durations since childhood cancer vary between 6.3 and 27.3 years in studies assessing secondary breast cancer risk (Hancock *et al*. 1993, Metayer *et al*. 2000, Ng *et al*. 2002, Bhatia *et al*. 2003, Gold *et al*. 2003, Guibout *et al*. 2005, Inskip & Curtis 2007, Constine *et al*. 2008, Friedman *et al*. 2008, Marees *et al*. 2008, Alm El-Din *et al*. 2009, De Bruin *et al*. 2009, Maule *et al*. 2011, Reulen *et al*. 2011, Cooke *et al*. 2013, Danner-Koptik *et al*. 2013, Little *et al*. 2014, Dorffel *et al*. 2015, Moskowitz *et al*. 2015, Schaapveld *et al*. 2015), and 5.1–27 years in studies investigating secondary thyroid carcinoma risk (Crom *et al*. 1997, Bhatia *et al*. 2002, Cohen *et al*. 2007, Inskip & Curtis 2007, Constine *et al*. 2008, Taylor *et al*. 2009, van Beek *et al*. 2009, Friedman *et al*. 2010, Maule *et al*. 2011, Vivanco *et al*. 2012, Danner-Koptik *et al*. 2013, Caglar *et al*. 2014, Li *et al*. 2014, Clement *et al*. 2015, de Vathaire *et al*. 2015, Dorffel *et al*. 2015, Brignardello *et al*. 2016). Specific subtypes of secondary malignant neoplasms and potential risk-modifying factors yet unknown may become apparent at an advanced survivor's age. Therefore, it is important to prospectively evaluate the growing cohort of aging childhood cancer survivors.

Furthermore, a large amount of the evidence on secondary breast cancer risk in childhood cancer survivors (Kenney *et al*. 2004, Marees *et al*. 2008, Inskip *et al*. 2009, Friedman *et al*. 2010, O'Brien *et al*. 2010, Moskowitz *et al*. 2014, 2015, Dorffel *et al*. 2015, Henderson *et al*. 2015) and, to a lesser extent, on secondary thyroid cancer risk in childhood cancer survivors (Sigurdson *et al*. 2005, Bhatti *et al*. 2010, Friedman *et al*. 2010, Veiga *et al*. 2012*a*, de Vathaire *et al*. 2015, Dorffel *et al*. 2015) has been derived from retrospective cohort studies using self-reported data to ascertain secondary malignant neoplasms, which may predispose to selection bias. Another source for selection bias may be the nature of the cohort. This is illustrated by Ness *et al*., who observed an overestimation of the prevalence of long-term adverse health conditions by 9.3% (95% CI: 7.0–11.6) in childhood cancer survivors ascertained in a hospital- compared with a population-based setting (Ness *et al*. 2009). Future studies on secondary endocrine-related malignancies after childhood cancer could be prospective, based on national registries, and use objective methods to collect data on secondary malignant neoplasms.

Although several studies reported a protective effect of gonadotoxic therapies and premature ovarian insufficiency on radiation-induced breast cancer (Travis *et al*. 2003, 2005, van Leeuwen *et al*. 2003, Kenney *et al*. 2004, Hill *et al*. 2005, Constine *et al*. 2008, De Bruin *et al*. 2009, Inskip *et al*. 2009, Cooke *et al*. 2013, Moskowitz *et al*. 2014, Schaapveld *et al*. 2015), it is important to consider that most of these studies were performed in combined cohorts of childhood- and adult-onset Hodgkin lymphoma survivors (Travis *et al*. 2003, 2005, van Leeuwen *et al*. 2003, Hill *et al*. 2005, De Bruin *et al*. 2009, Cooke *et al*. 2013, Schaapveld *et al*. 2015). Since the beneficial effects of gonadotoxic treatments on radiation-induced breast cancer risk seem less pronounced in childhood- compared with adult-onset cancer survivors (Swerdlow *et al*. 2012), and no studies assessed the risk-modifying effect of a diagnosis of premature ovarian insufficiency on radiation-induced breast cancer in



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childhood cancer survivors solely, more studies should be performed. Future studies may also address the potential harms and benefits of estrogen–progestin replacement therapy on radiation-induced breast cancer risk in women experiencing childhood cancer treatment-related premature ovarian insufficiency.

Studies on secondary malignant neoplasms after childhood cancer concern predominantly survivors treated with old-fashioned treatment regimens. Although childhood cancer therapy has changed considerably over the past five decades (Kumar 2012, Hudson *et al*. 2014), results described in this review are still highly valuable for those individuals treated in earlier treatment eras. Since the effects of modern radiotherapeutic techniques like conformal radiotherapy, intensity-modulated radiation therapy and proton-beam therapy on secondary endocrine-related cancer risk remain unknown, future studies should address the potential risks and benefits associated with these contemporary radiotherapeutic modalities. Risks for radiation-induced malignant neoplasms may be greater in small compared with large children due to a more significant contribution of scatter radiation (Hall 2006). Currently, no studies on secondary endocrine-related malignancies after childhood cancer accounted for this issue. Future studies may investigate radiation-induced cancer risks by dosimetry according to body size at cancer treatment.

Finally, there is a lack of studies specifically investigating the influence of environmental and lifestyle factors on secondary endocrine-related cancer risk in childhood cancer survivors. Future studies should address these potentially risk-modifying factors.

## Conclusion

Secondary malignant neoplasm development in childhood cancer survivors depends on host factors, primary cancer diagnosis, and types and timing of primary cancer treatment. In addition, environmental factors and lifestyle factors may play a contributing role. Radiotherapy is the most important risk factor for secondary breast and thyroid cancer in childhood cancer survivors. Premature ovarian insufficiency may protect against radiation-induced breast cancer. Although evidence is weak, there seems to be no harmful effect of estrogen–progestin replacement therapy on radiation-induced breast cancer risk in premature ovarian-insufficient childhood cancer survivors. Childhood cancer survivors at risk for secondary endocrine-related malignancies should be regularly screened in a risk-based fashion, preferably by endocrinologists in close collaboration with physicians experienced in long-term complications of childhood cancer treatment.

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The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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