JAMA | Review

Clinical Care for People Who Survive Childhood Cancer
A Review

Smita Bhatia, MD, MPH; Emily S. Tonorezos, MD, MPH; Wendy Landier, PhD, CRNP

IMPORTANCE An estimated 15 000 children and adolescents aged 0 to 19 years are diagnosed with cancer each year in the US, and more than 85% survive for at least 5 years. By 45 years of age, approximately 95% of people who survive childhood cancer will develop a significant health problem related to the childhood cancer diagnosis or its treatment.

OBSERVATIONS Approximately 500 000 people currently alive in the US have survived childhood cancer. The most common severe or life-threatening chronic health problems related to childhood cancer or its treatment are endocrine disorders such as hypothyroidism or growth hormone deficiency (44%), subsequent neoplasms such as breast cancer or thyroid cancer (7%), and cardiovascular disease such as cardiomyopathy or congestive heart failure, coronary artery disease, and cerebrovascular disease (5.3%). Medical conditions related to a cancer diagnosis during childhood or adolescence are most commonly caused by the radiation therapy and the chemotherapies used to treat cancer and may develop at varying lengths of time after exposure to these treatments. Individuals at highest risk for developing treatment-related health problems include patients with brain cancer treated with cranial irradiation (approximately 70% develop severe or life-threatening health problems) and allogeneic hematopoietic stem cell transplant recipients (approximately 60% develop severe or life-threatening health problems). Individuals at the lowest risk for developing treatment-related health problems include those who survived solid tumors (such as Wilms tumor) treated with surgical resection alone or with minimal chemotherapy, for whom the prevalence of subsequent health problems is similar to people who did not have cancer during childhood or adolescence. People diagnosed with childhood cancer in the 1990s who survived for at least 5 years after the cancer diagnosis have a shorter lifespan (by about 9 years) vs children who were not diagnosed with cancer in the 1990s.

CONCLUSIONS AND RELEVANCE Approximately 500 000 individuals currently alive in the US have survived childhood cancer. The most common adverse effects in individuals who survived childhood cancer are endocrine disorders, subsequent neoplasms, and cardiovascular disease. There is a need for clinicians and patients to have heightened awareness of these complications.

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Author Affiliations: Institute for Cancer Outcomes and Survivorship, Heersink School of Medicine, University of Alabama at Birmingham (Bhatia, Landier); Department of Pediatrics, Division of Pediatric Hematology/Oncology, Heersink School of Medicine, University of Alabama at Birmingham (Bhatia, Landier); Office of Cancer Survivorship, Division of Cancer Control and Population Sciences, National Cancer Institute, Rockville, Maryland (Tonorezos).

Corresponding Author: Smita Bhatia, MD, MPH, University of Alabama at Birmingham, 1600 Seventh Ave S, Birmingham, AL 35233 (smitabhatia@uabmc.edu).

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Approximately 500 000 individuals currently alive in the US have survived childhood cancer, and this number increases each year.[1] More than 95% of people who survive childhood cancer will have a significant health-related problem by 45 years of age, and approximately one-third will experience severe or potentially life-threatening chronic health problems.[2] The most common severe or life-threatening chronic health problems include endocrine disorders (such as hypothyroidism or growth hormone deficiency), subsequent neoplasms (such as breast cancer or thyroid cancer), and cardiovascular disease (such as cardiomyopathy or congestive heart failure, coronary artery disease, and cerebrovascular disease) (**Table 1**). These conditions can cause premature death. This review summarizes current evidence regarding adverse outcomes and optimal management of people who survive childhood cancer.

Methods

PubMed was searched from January 1, 2000, through July 23, 2023, for English-language studies using the following key terms and their associated Medical Subject Headings and expansions: *childhood cancer* and *survivor* and *late health outcomes* or *late effects*. We prioritized studies relevant to generalist clinicians. We identified 2468 studies, of which 73 studies were included, consisting of 39 cohort studies, 10 case-control studies, 10 cross-sectional studies, 5 systematic reviews,

Table 1. Common Sequelae of Treatment for Childhood Cancer

Body system	Potential late effect	Therapy-related exposures
Psychosocial	Anxiety, depression, financial hardship	Any cancer experience
Central nervous system	Neurocognitive impairment	Cranial radiation and high-dose or intrathecal methotrexate
Sensory	Cataracts, ocular toxicity	Radiation to the eye, corticosteroids
	Hearing loss, tinnitus, or both	Platinum-based chemotherapy, high-dose cranial radiation (≥30 Gy)
Endocrine	Growth hormone deficiency	Cranial radiation, total body irradiation
	Central adrenal insufficiency, hypopituitarism, gonadotropin deficiency	Cranial radiation (involving pituitary region)
	Hypothyroidism	Neck radiation, total body irradiation
	Diabetes	Abdominal radiation, total body irradiation
Cardiac	Cardiomyopathy	Anthracycline chemotherapy, chest radiation
	Cardiovascular disease (eg, valvular disease, pericardial disease, coronary artery disease, atherosclerosis)	Chest radiation
Pulmonary	Restrictive pulmonary disease	Chest radiation, bleomycin, busulfan, nitrosoureas, pulmonary surgery
Musculoskeletal	Reduced bone mineral density	Corticosteroids, allogeneic hematopoietic stem cell transplantation
	Muscular atrophy, skeletal hypoplasia, scoliosis, kyphosis	Radiation (especially to abdomen, chest, extremities, total body)
	Osteonecrosis	Corticosteroids, allogeneic hematopoietic stem cell transplantation
Neurological	Peripheral neuropathies (motor and sensory)	Vinca alkaloids, platinum-based chemotherapy
Reproductive	Primary gonadal insufficiency, testicular or ovarian hormone deficiency, premature ovarian failure	Pelvic radiation, testicular radiation, alkylating agent chemotherapy (especially in higher doses), total body irradiation
	Reduced fertility, infertility, shortened lifetime period of fertility	Pelvic radiation, testicular radiation, alkylating agent chemotherapy (especially in higher doses), total body irradiation
Subsequent neoplasms	Basal cell carcinoma	Any radiation
	Thyroid cancer	Head radiation, neck radiation
	Breast cancer	Chest radiation, anthracycline and alkylating agent chemotherapies
	Colorectal cancer	Abdominal radiation, pelvic radiation, total body irradiation
	Glioma	Cranial radiation
	Meningioma	Cranial radiation
	Sarcoma	Anthracycline chemotherapy, radiation involving bones or soft tissue

3 nonsystematic reviews, 5 clinical practice guidelines or consensus statements, and 1 randomized clinical trial.

Discussion

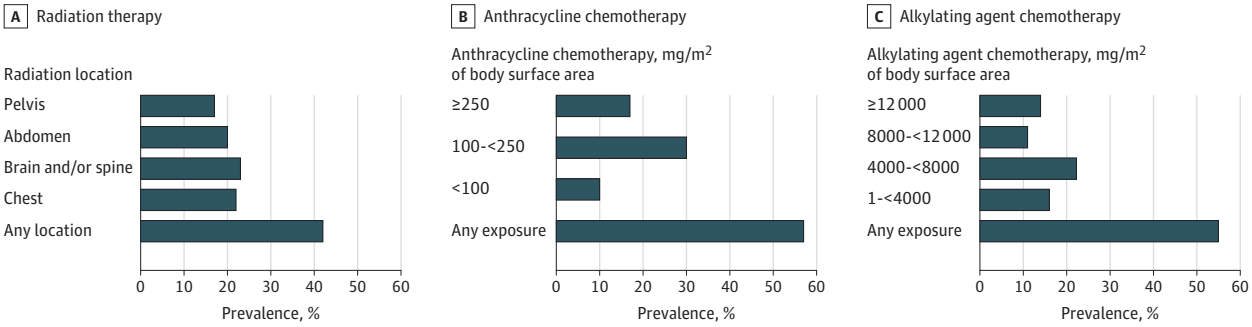
In the US, an estimated 15 000 people are diagnosed with cancer each year between birth and 19 years of age,[3] and more than 85% survive for at least 5 years.[4] The most common types of cancer diagnosed from birth through 14 years of age include central nervous system tumors such as medulloblastoma and glioma (26%) and acute lymphoblastic leukemia (21%). The most common types of cancer diagnosed in people 15 to 19 years of age include central nervous system tumors (21%), thyroid cancer (12%), Hodgkin lymphoma (11%), and germ cell and gonadal tumors (10%).[4] Other types of childhood cancer include non-Hodgkin lymphoma, acute myeloid leukemia, bone and soft tissue sarcomas, neuroblastoma, Wilms tumor, retinoblastoma, and hepatoblastoma. Treatment for childhood cancer may include chemotherapy, radiation, surgery, molecularly targeted therapy, immunotherapy, and hematopoietic stem cell transplant.

Among 22 150 people who survived for 5 years or longer after a childhood cancer diagnosis, life expectancy was 48.5 years (95% uncertainty interval [UI], 47.6-49.6 years) for those diagnosed from 1970 to 1979, 53.7 years (95% UI, 52.6-54.7 years) for those diagnosed from 1980 to 1989, and 57.1 years (95% UI, 55.9-58.1 years) for those diagnosed from 1990 to 1999.[5] Compared with individuals without a cancer history, this represented a gap in life expectancy (defined as the number of years that 5-year cancer survivors can expect to live) of 25% (95% UI, 24%-27%) for those diagnosed from 1970 to 1979, 19% (95% UI, 17%-20%) for those diagnosed from 1980 to 1989, and 14% (95% UI, 13%-16%) for those diagnosed from 1990 to 1999.[5]

In people who survive childhood cancer, subsequent complications may be related to the chemotherapy and radiation therapy used to treat cancer during childhood (**Figure 1**). Examples include anthracycline-related cardiomyopathy; radiation-related breast, thyroid, and brain tumors; radiation-related hypothyroidism and growth hormone deficiency; and radiation-related atherosclerosis. Chronic health conditions associated with childhood cancer treatment have varying latency periods from the time of therapeutic exposures (**Figure 2**).

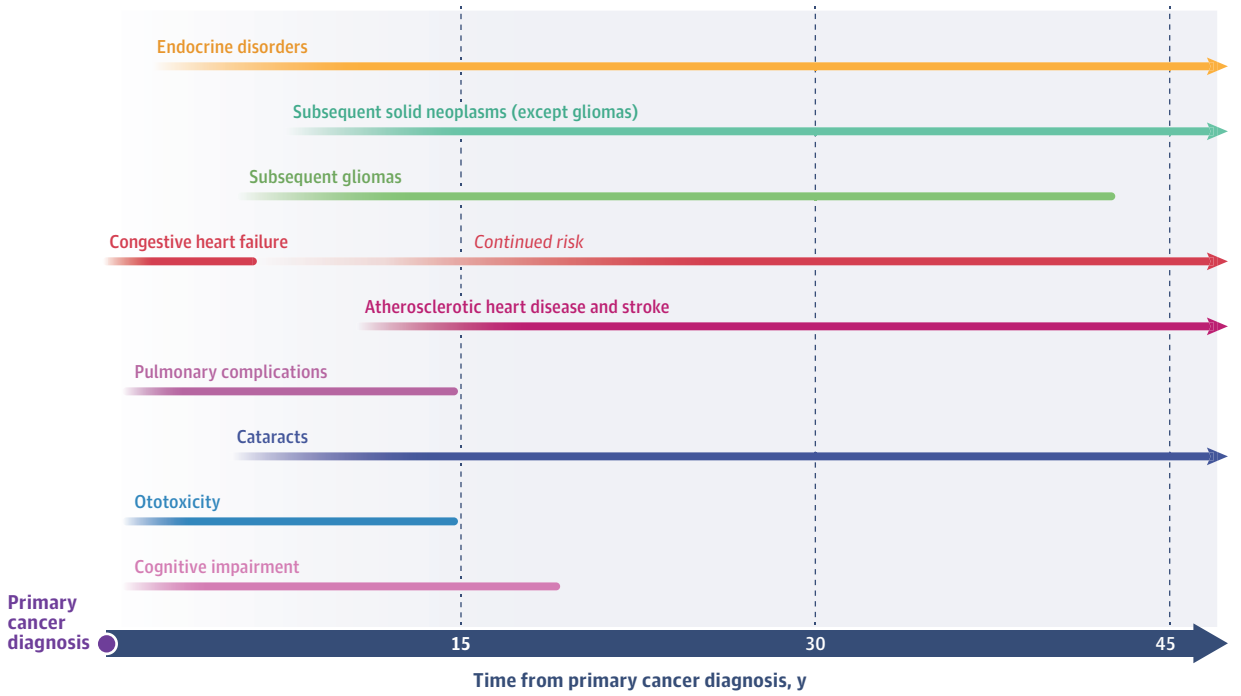
Radiation-related adverse effects usually develop within the radiation field (**Figure 3**A), are related to the dose, and are more likely to occur if radiation therapy is administered at a younger age. For example, a systematic review showed that patients who were treated with chest radiation before the age of 30 years were at high risk of breast cancer.[6] Chemotherapy-related risks are also dose- and age-related and may affect multiple organs due to the systemic nature of the exposure (Figure 3B). For example, in a case-control study of people who survived childhood cancer and either developed cardiomyopathy (n = 170) or did not develop cardiomyopathy (n = 317), the risk of anthracycline-related cardiomyopathy was higher when

Figure 1. Prevalence of Common Therapeutic Exposures in People Who Survived Childhood Cancer



In B, the units of measure are for the doxorubicin equivalent dose. Examples of anthracycline chemotherapy include doxorubicin and daunorubicin. In C, the units of measure are for the cyclophosphamide equivalent dose. Examples of alkylating agent chemotherapy include cyclophosphamide, procarbazine, and mechlorethamine.

Figure 2. Chronic Health Conditions Associated With Varying Latency Periods From the Time of Childhood Cancer Treatment



The direction of the arrows indicates that the risk continues beyond the attained age.

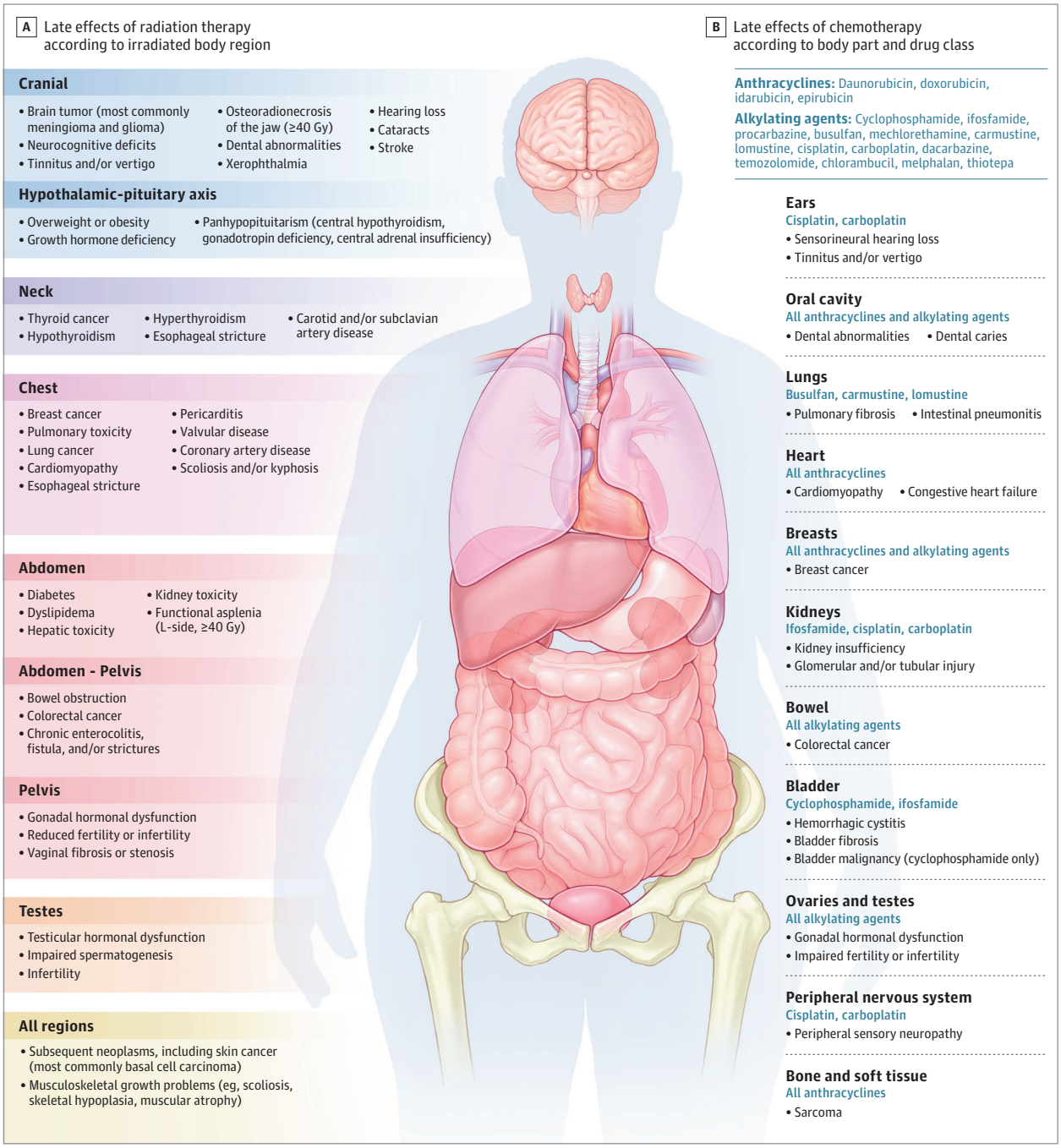
the cumulative exposure was greater than 250 mg/m^2 of body surface area.[7] The mechanisms of how specific treatments may cause these complications remain unclear. There are increasing efforts to examine these mechanisms. For example, anthracycline chemotherapy induces mitochondrial dysfunction that causes myocardial injury, which in turn may progress to myocardial necrosis and myocardial interstitial fibrosis.[8]

The generalist evaluating a person who survived childhood cancer should obtain a history that includes the type of cancer; the age at diagnosis; and the type, dose, and duration of therapy. When possible, generalists should obtain treatment records for radiation therapy and anthracycline and alkylating agent chemotherapies, such as doxorubicin, cyclophosphamide, and procarbazine. Guidelines from the Children's Oncology Group[9] provide suggested screening and health promotion recommendations when details of treatment are available. **Table 2** provides a summary of the suggested screening and health promotion recommendations for people in whom details of treatment are not available. No randomized clinical trials have been conducted to examine the benefit of screening for diseases on improved outcomes in people who survived childhood cancer.

Endocrine Disorders

People treated for childhood cancer have a higher prevalence of abnormal levels of growth hormone, thyroid hormone, adrenocorticotropin, and gonadotropin hormones.[10] Among 14 290 people who

Figure 3. Late Effects Related to Radiation Therapy, Anthracycline Chemotherapy, and Alkylating Agent Chemotherapy According to Body Region



survived for 5 years or longer after a childhood cancer diagnosis, 44% experienced at least 1 endocrine abnormality, 16.7% experienced at least 2 endocrine disorders, and 6.6% experienced 3 or more endocrine disorders.[10] In this study, exposure to neck radiation was associated with a 6.6-fold higher risk (95% CI, 5.6-7.8) of developing hypothyroidism compared with absence of such exposure.[10]

People exposed to a cranial irradiation dose of 18 Gy or greater had a relative risk (RR) of obesity of 1.4 (95% CI, 1.3-1.5) compared with those not exposed.[10] People treated with a cranial irradiation dose of 30 Gy or greater had a 4.5-fold greater risk (95% CI, 3.7-5.5) of central adrenal insufficiency compared with those treated with a dose of 0 to 29 Gy.[10] Total body irradiation or radiation to the abdomen with the pancreas within the field of radiation was associated with a 2.7-fold increased risk (95% CI, 2.1-3.6) of diabetes.[10] Risk of primary ovarian insufficiency was 6.3-fold higher (95% CI, 5.0-8.0) among females who received high doses of alkylating agent chemotherapy (cyclophosphamide equivalent dose ≥8 g/m^2 of body surface area) or pelvic irradiation.[10] Risk of ovarian dysfunction was 6-fold higher (95% CI, 4.2-8.5) among those exposed to pituitary irradiation at doses of 30 Gy or greater.[10]

Males treated with alkylating agent chemotherapy (cyclophosphamide equivalent dose >20 g/m^2 of body surface area) or testicular

Table 2. Suggested Screening for People Who Survived Childhood Cancer for Whom Treatment Information Is Not Available

Suggested screening based on primary diagnosis[a]	Frequency	Potential late effects	Indication													
			ALL	AML	CNS tumor	HL	NHL	Neuroblastoma	Wilms tumor	RMS	Osteosarcoma	Ewing sarcoma	Germ cell tumor	Hepatic tumor	Retinoblastoma	HSCT[b]
Thorough history and physical examination, general health screening (including measurement of blood pressure and body mass index), and psychosocial and mental health assessments. Age- and sex-appropriate preventive care per applicable US Preventive Services Task Force recommendations, including routine immunizations	Yearly	Health maintenance deficit; adverse psychosocial and/or mental health conditions	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dental evaluation	Every 6 mo	Dental developmental defects and/or dental caries	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Kidney[c] and liver function panel	Baseline and as clinically indicated	Kidney and/or hepatic dysfunction	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hemoglobin A_{1c}, fasting lipid profile	Every 2 y	Diabetes, dyslipidemia	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ophthalmology evaluation	Yearly	Cataracts, ocular toxicity	✓		✓	✓	✓			✓[d]					✓	✓
Formal neuropsychological evaluation	Baseline and as clinically indicated	Neurocognitive deficits	✓	✓	✓	✓	✓			✓[d]	✓					✓
Echocardiogram	Every 5 y	Cardiomyopathy, radiation-related valvulopathy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		
Thyroid function[e]	Yearly	Hypothyroidism	✓		✓	✓	✓	✓		✓						✓
Dual-energy x-ray absorptiometry	Baseline and as clinically indicated	Reduced bone mineral density	✓	✓	✓	✓	✓									✓
Pulmonary function testing	Baseline and as clinically indicated	Pulmonary toxicity			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Audiological evaluation	Every 5 y	Hearing loss, tinnitus			✓		✓	✓	✓	✓[d]	✓		✓	✓	✓	
Mammogram and breast MRI (at ≥25 y of age or 8 y after radiation, whichever comes last) for all women who received chest or axillary radiation and/or TBI[e]	Yearly	Breast cancer				✓	✓	✓	✓	✓		✓				✓

(continued)

Table 2. Suggested Screening for People Who Survived Childhood Cancer for Whom Treatment Information Is Not Available (continued)

Suggested screening based on primary diagnosis[a]	Frequency	Potential late effects	Indication													
			ALL	AML	CNS tumor	HL	NHL	Neuro-blastoma	Wilms tumor	RMS	Osteo-sarcoma	Ewing sarcoma	Germ cell tumor	Hepatic tumor	Retino-blastoma	HSCT[b]
Colorectal cancer screening (at ≥30 y of age or 5 y after radiation, whichever comes last) for all who received abdominal and/or pelvic radiation and/or TBI[e]	Every 3 y (multitarget stool DNA test) or every 5 y (colonoscopy)	Colorectal cancer			✓	✓	✓	✓	✓	✓		✓	✓	✓		✓
Asplenic precautions (survivors with splenectomy, L-sided abdominal radiation ≥40 Gy, or active chronic graft-vs-host disease only)[f]	As clinically indicated	Surgical or functional asplenia				✓				✓		✓				✓
Hepatitis B core antibody and surface antigen	Once if diagnosed prior to 1972	Hepatitis B	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HIV screening	Once if diagnosed between 1977 and 1985	HIV	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hepatitis C antibody, and if positive, polymerase chain reaction	Once if diagnosed prior to 1993	Hepatitis C	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CNS, central nervous system; HL, Hodgkin lymphoma; HSCT, hematopoietic stem cell transplant; MRI, magnetic resonance imaging; NHL, Non-Hodgkin lymphoma; RMS, rhabdomyosarcoma; TBI, total body irradiation.

[a] No randomized clinical trials have been conducted to demonstrate the benefit of the suggested screenings and follow-up care in improving outcomes.

[b] Suggested screening is only for exposures related to the HSCT. The suggested screening for the primary childhood cancer diagnosis also should be followed.

[c] Mononephric survivors should consider being screened for kidney function annually.

[d] Tumors involving the head and neck only.

[e] Omit in clear absence of radiation to targeted organ.

[f] Blood cultures and antibiotics when febrile and prophylactic vaccination against encapsulated organisms. Omit in clear absence of splenectomy or high-dose L-sided abdominal radiation.

radiation with a dose greater than 20 Gy had a 10.8-fold higher risk (95% CI, 8.2-14.2) of primary gonadal insufficiency (requiring testosterone replacement) compared with men who had not received these treatments.[10] Radiation to the hypothalamic-pituitary axis at a dose of 30 Gy or greater was associated with a 5.7-fold higher risk (95% CI, 4.2-7.7) of central gonadal dysfunction.[10] Limitations of this study include that health outcomes were based on patient report, and the absolute rates for these associations were not reported.

Among 2819 people who survived childhood cancer, premature ovarian failure (ie, cessation of menses prior to 40 years of age) was more common compared with siblings without childhood cancer (8% vs 0.8%).[11] Premature ovarian failure occurred in approximately 30% of people who received both alkylating agent chemotherapy and abdominopelvic radiation.[11] An analysis of 3 studies reported growth hormone deficiency in approximately 29.0% to 39.1% of childhood cancer survivors treated with cranial radiation therapy.[12] Higher cranial radiation doses were associated with an increased risk.[12]

Reproductive Health

High-dose alkylating agent chemotherapy (such as cyclophosphamide and procarbazine) and abdominopelvic and testicular radiation increase the risk of infertility.[13-15] In a study of 214 men treated with alkylating agent chemotherapy for childhood cancer and evaluated at a median age of 29 years, 48% had normospermia, 25% had azoospermia, and 28% had oligospermia.[16] In this cohort, each cyclophosphamide equivalent dose of 1000 mg/m^2 of body surface area was associated with a 1.22-fold increased risk (95% CI, 1.11-1.34) for azoospermia.[16] However, 89% of the people treated with less than a cyclophosphamide equivalent dose of 4000 mg/m^2 of body surface area had normospermia.[16]

In a cohort study,[17] 278 women who survived childhood cancer had higher rates of preeclampsia compared with 829 age-matched women from the general population (6.1% vs 1.9%, respectively), labor dystocia (4.3% vs 1.8%), fetal malpresentation (8.3% vs 5.2%), and imminent fetal asphyxia (10.8% vs 5.7%). Patients at highest risk for infertility from treatment with alkylating agent chemotherapy or gonadal radiation should be counseled regarding fertility preservation (ie, freezing of embryos, eggs, ovarian tissue, sperm, or testicular tissue for future reproduction) prior to treatment.[18,19] People at risk for impaired reproductive health as a result of the treatment for their childhood cancer should receive appropriate counseling.[9]

Neoplasms After Childhood Cancer Treatment

In people successfully treated for childhood cancer, subsequent neoplasms are defined as cases of histologically distinct cancer that occur after treatment for childhood cancer. In a retrospective cohort of 6155 people who survived for 5 years or longer after childhood cancer, the excess risk of subsequent neoplasms was 20.3 per 10 000 person-years after a median follow-up of 21 years.[20] Among 23 603 people who survived for 5 or more years after childhood cancer, the 15-year cumulative incidence of subsequent malignant neoplasms declined from 2.1% for those treated between 1970 and 1979 to 1.3% for those treated between 1990 and 1999.[21]

However, the risk of subsequent neoplasms among those who were treated in the 1990s was higher than in the general population (range of standardized incidence ratios, 3.1-3.6).[21] Subsequent neoplasms included skin cancer (commonly basal cell carcinoma), breast cancer, thyroid cancer (most commonly papillary thyroid cancer), central nervous system tumors (especially glioma and meningioma), bone tumors (osteosarcoma and Ewing sarcoma), and soft tissue sarcoma (**Table 3**).

Neoplasms After Chemotherapy Treatment During Childhood

Treatment with alkylating agent chemotherapy (eg, cyclophosphamide, procarbazine, mechlorethamine) or anthracycline chemotherapy (eg, doxorubicin, daunorubicin) for childhood cancer can increase the risk for subsequent neoplasms. Childhood cancer types commonly treated with anthracycline chemotherapy (doxorubicin equivalent dose of ≥250 mg/m^2 of body surface area) include bone tumors (85%) and soft tissue sarcoma (74%).[22] Childhood cancer types commonly treated with a cyclophosphamide equivalent dose of 8000 mg/m^2 of body surface area or higher include Hodgkin lymphoma (53%) and soft tissue sarcoma (82%).[22] A linear dose-response relationship has been reported between alkylating agent chemotherapy and subsequent neoplasms (relative rate, 1.2 [95% CI, 1.1-1.3] per cyclophosphamide equivalent dose of 5000 mg/m^2 of body surface area), and between anthracycline chemotherapy and breast cancer (relative rate, 1.3 [95% CI, 1.2-1.6] per doxorubicin equivalent dose of 100 mg/m^2 of body surface area).[20,23]

Subsequent Neoplasms in People Treated With Radiation During Childhood

The most common neoplasms after radiation treatment for childhood cancer are basal cell carcinoma, breast cancer, and thyroid cancer. Radiation fields of particular concern for subsequent neoplasms include the chest (risk of breast cancer in females and lung cancer in both sexes), brain (risk of central nervous system tumor), neck (risk of thyroid cancer), and abdomen or pelvis (risk of colorectal cancer). Lower doses and more focused fields of radiation have been used recently to treat childhood cancer, and radiation has been eliminated entirely from some treatment regimens.

For example, cranial radiation was commonly used to treat acute lymphoblastic leukemia throughout the 1980s, but it is currently used only for children with central nervous system leukemia or very high-risk disease. Similarly, until the 1990s, childhood Hodgkin lymphoma was treated primarily with radiation directed across multiple nodal fields, but it is now primarily treated with systemic chemotherapy or immunotherapy alone or combined with radiation limited to the involved fields. Clinicians caring for people who survived childhood cancer should note details regarding the field and dose of radiation therapy.

Basal Cell Carcinoma

Among 5843 people who survived childhood cancer, 259 developed 1061 cases of basal cell carcinoma, yielding a standardized incidence ratio of 29.8 and an absolute excess risk of 24.6 per 10 000 person-years.[24] Approximately 90% of basal cell carcinoma cases were located within the radiation field, and approximately 46% of patients had multiple cases of basal cell carcinoma.[25,26] In a study of 199 patients with basal cell carcinoma and 597 childhood cancer survivors without basal cell carcinoma, a radiation dose greater than 1 Gy demonstrated a linear dose-response relationship with basal cell carcinoma risk.[27] Even though it may be reasonable to advise people who were treated with radiation therapy for childhood cancer to

Table 3. Therapeutic Exposures Associated With Subsequent Neoplasms in Childhood Cancer Survivors

Therapeutic exposures	Subsequent neoplasms	Highest risk factors	Potential mitigating factors[a]
Radiation (all fields)	Skin cancer (primarily basal cell carcinoma)	• Higher radiation dose to skin • There is a linear dose-response relationship between radiation to the site and the risk of basal cell carcinoma	• Sun protective behaviors (eg, use of sunscreen and sun protective clothing, avoiding sun exposure at peak hours of intensity to reduce UV radiation exposure)
	Sarcoma	• Higher radiation dose (>10 Gy) • There is a linear dose-response relationship between radiation to the site and the development of sarcoma	• Regular physical examinations for early detection
Anthracycline chemotherapy[b]	Sarcoma	• Dose >300 mg/m^2 of body surface area	• Regular physical examinations for early detection
Anthracycline chemotherapy and alkylating agent chemotherapy	Breast cancer	• There is a linear dose-response relationship between cumulative anthracycline dose and risk of breast cancer • Anthracycline dose: >250 mg/m^2 of body surface area and chest radiation • Alkylating agent dose: cyclophosphamide equivalent dose >6000 mg/m^2 of body surface area (with or without chest radiation)	• Healthy diet and regular physical activity • Maintaining healthy weight
Chest radiation (eg, for the treatment of Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumor, bone and soft tissue sarcoma, neuroblastoma)	Breast cancer	• Higher radiation dose to the chest (>20 Gy) • Higher volume of breast tissue in the chest radiation field • Older age (>9 y) during treatment • Timing of radiation <1 y from onset of menarche • Primary cancer diagnosis of sarcoma or leukemia • Presence of breast cancer predisposition gene variants (such as *BRCA1*, *BRCA2*, *ATM*, *CDH1*, *CHEK2*, *PALB2*, *PTEN*, *STK11*, or *TP53*)	• Prophylactic mastectomy • Prophylactic oophorectomy • Healthy diet and regular physical activity • Maintaining healthy weight • Low-dose tamoxifen
Chest radiation (eg, for the treatment of Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumor, bone and soft tissue sarcoma, neuroblastoma)	Lung cancer	• Current or former smoker • Higher radiation dose (>10 Gy) • Primary cancer diagnosis of Hodgkin lymphoma or bone cancer	• Tobacco avoidance or cessation
Radiation to the neck	Thyroid cancer	• Increased risk with radiation dose of ≤29 Gy to the thyroid gland	• Regular physical examinations for early detection
Cranial radiation	Central nervous system tumors	• Younger age (<5 y) at radiation • Higher cranial radiation dose (>20 Gy)	• Regular physical examinations for early detection
Radiation to the abdomen or pelvis	Colorectal cancer	• Higher radiation dose to the abdomen or pelvis (risk of colorectal cancer increases by 70% for each 10-Gy increase in radiation dose)	• High-fiber, low-fat diet • Periodic screening for colorectal cancer per clinical practice guidelines
Alkylating agent chemotherapy[c]	Colorectal cancer	• Processed meat intake • Low-fiber diet • Family history of colorectal cancer	• High-fiber, low-fat diet • Periodic screening for colorectal cancer per guidelines from the Children's Oncology Group[9] on long-term follow-up for survivors of childhood, adolescent, and young adult cancers

[a] Based on expert opinion. No randomized clinical trials have been conducted to examine the benefit of these mitigating factors in improving outcomes for people who survived childhood cancer.

[b] Includes doxorubicin, daunorubicin, idarubicin, and epirubicin.

[c] Includes cyclophosphamide, ifosfamide, procarbazine, mechlorethamine, carmustine, lomustine, cisplatin, carboplatin, dacarbazine, temozolomide, chlorambucil, melphalan, thiotepa, and busulfan.

perform a monthly skin self-examination and have an annual dermatology evaluation, no randomized clinical trials have been conducted to demonstrate that these practices improve outcomes.[9] New, changing, or unusual skin growths should prompt referral to a dermatologist for an evaluation.[9,28]

Breast Cancer

Women treated with chest radiation during childhood cancer have an increased risk for breast cancer later in life[29] compared with women who were not treated with radiation. Among 11 550 females who survived childhood cancer, 489 (4.2%) developed breast cancer a median of 25.6 years after the childhood cancer diagnosis, which is consistent with an absolute excess risk of 1.8 per 1000 person-years (95% CI, 1.6-2.0).[29] Of those with breast cancer, 18% had bilateral disease.[29] By 55 years of age, the cumulative incidence of breast cancer was 18% among women who survived childhood cancer.[29]

Among 1230 women who underwent chest radiation and survived for 5 years or longer, the risk of breast cancer increased with dose of radiation and volume of tissue receiving a dose that was 50% or greater than the specified target dose.[30] All-cause mortality was higher after breast cancer among 274 women who survived childhood cancer (10-year cumulative mortality rate of 20% [95% CI, 15%-25%]) than among 1095 women with de novo breast cancer (10-year cumulative mortality rate of 13% [95% CI, 11%-16%]).[31]

Among 3768 females who had childhood cancer but did not receive radiation therapy, 47 (1.2%) developed breast cancer during a mean follow-up of 25.5 years (24 years between the childhood cancer diagnosis and the breast cancer diagnosis).[32] The standardized

incidence ratio was 4.0 (95% CI, 3.0-5.3) compared with the general population.[32] Treatment with anthracycline or alkylating agent chemotherapy was associated with higher risk among childhood survivors who had not received radiation therapy compared with women who had not received these chemotherapeutic agents.[32] Among 1467 females treated for childhood cancer, the presence of variants in breast cancer predisposition genes (such as *BRCA1, BRCA2, ATM, CDH1, CHEK2, PALB2, PTEN, STK11,* or *TP53*) also was associated with higher risk.[33]

Radiation-related breast cancer risk was mitigated by ovarian radiation in 6647 women who survived childhood cancer (excess odds ratio [OR] of 0.36 [per ovarian radiation dose of <5 Gy] vs 0.06 [per ovarian radiation dose of ≥5 Gy]; the absolute rates were not reported),[34] suggesting that endogenous estrogen contributes to higher risk and providing the rationale for low-dose tamoxifen as a risk-reduction strategy. In a double-blind, placebo-controlled randomized clinical trial, 72 female childhood cancer survivors exposed to chest radiation were randomized 1:1 to low-dose tamoxifen (5 mg/d) or identical placebo for 2 years.[35] Low-dose tamoxifen reduced the primary outcome of breast density, but the trial was not designed to assess the efficacy of tamoxifen on breast cancer rates.[35]

Current clinical practice guidelines[9] recommend that females treated with chest radiation for childhood cancer consider initiation of breast cancer screening annually with both mammogram and breast magnetic resonance imaging starting at 25 years of age or at 8 years after radiation, whichever occurs later. However, no randomized clinical trials have been conducted to examine the benefit of these methods for reducing breast cancer mortality in survivors of childhood cancer.

Thyroid Cancer

In 17 980 people who survived for 5 years or longer after childhood cancer, the absolute excess risk of thyroid cancer was 1.4 per 10 000 person-years.[36] The median time between the childhood cancer diagnosis and the diagnosis of thyroid cancer was 19.5 years.[36] Approximately two-thirds of these cancer cases were papillary thyroid cancer. Among 14 054 people who had survived for 5 years or longer after childhood cancer, the risk of thyroid cancer increased with radiation doses of 20 Gy to 29 Gy, and then declined at doses of 30 Gy or greater.[37]

Meningioma

Among 5843 people followed up for a median of 23.3 years after the childhood cancer diagnosis, 97 developed a histologically proven benign meningioma.[38] Cranial radiation was the primary risk factor (excess RR was 0.3 per 1-Gy cranial radiation dose; the absolute rates were not reported). Carboplatin also was associated with a 3.55-fold increased risk (95% CI, 1.62-7.78) of meningioma compared with no carboplatin exposure (the absolute rates were not reported).[38] Clinical manifestations of meningioma included severe headaches, seizures, and focal neurological deficits.[39]

Sarcoma

Among 69 460 people followed up for a median of 14.5 years after the childhood cancer diagnosis, 301 developed soft tissue sarcoma compared with 19 cases expected in the general population.[40] The specific types of sarcoma included malignant peripheral nerve sheath tumors, leiomyosarcoma, and fibromatous neoplasms. Although these individuals had a 15.7-fold higher risk (95% CI, 14.0-17.6) of developing a soft tissue sarcoma compared with the general population, the absolute excess risk was less than 1 per 10 000 person-years.[40]

In a nested case-control study of 105 people surviving childhood cancer who developed soft tissue sarcoma and 422 without sarcoma, a dose-response relationship with radiation was observed (OR, 15.6 [95% CI, 4.5-53.9] for a radiation dose of 10-29.9 Gy; OR, 16.0 [95% CI, 3.8-67.8] for 30-49.9 Gy; and OR, 114.1 [95% CI, 13.5-964.8] for >50 Gy; the reference group was a radiation dose of <10 Gy).[41] Anthracycline chemotherapy exposure also was associated with sarcoma risk (OR, 3.5 [95% CI, 1.6-77]) compared with no anthracycline exposure.[41]

Colorectal Cancer

Among 14 358 people followed up for a median of 22.8 years after the childhood cancer diagnosis, 24 developed colorectal carcinoma (standardized incidence ratio, 4.2 [95% CI, 2.8-6.3]) compared with the general population and the absolute excess risk was 7.0 per 100 000 person-years.[42] In a nested case-control study of 19 people with colorectal cancer and 220 without colorectal cancer, the median time to diagnosis of colorectal cancer after childhood cancer diagnosis was 24.9 years.[43] Higher doses of radiation were associated with increased colorectal cancer risk.[43]

Cardiovascular Disease

Commonly observed cardiovascular complications among people who survive childhood cancer include cardiomyopathy or congestive heart failure, valvular abnormalities, pericardial disease, and coronary artery disease. Among 14 358 people who had survived for 5 years or longer after childhood cancer and at a median age of 27.0 years, the age-adjusted rate was 9.7 per 10 000 person-years for cardiomyopathy or congestive heart failure, 6.4 per 10 000 person-years for valvular abnormalities, 5.8 per 10 000 person-years for pericardial disease, and 2.8 per 10 000 person-years for myocardial infarction.[44]

The prevalence of cardiomyopathy or congestive heart failure ranged from approximately 16% (symptomatic) to approximately 50% (echocardiographic evidence of decreased cardiac function) in people who received anthracycline chemotherapy for childhood cancer.[45,46] A systematic review demonstrated that coronary artery disease typically develops at least 10 years after exposure to radiation.[47] By 50 years of age, the cumulative incidence of coronary artery disease was approximately 8% in childhood cancer survivors compared with 1.2% among their cancer-free siblings.[47] Among 14 358 people followed up for a mean of 23.3 years after childhood cancer, 292 reported late-occurring stroke.[48] The age-adjusted stroke rate was 77 per 100 000 person-years among people who survived childhood cancer compared with 9.3 per 100 000 person-years among their cancer-free siblings.[48] The 30-year cumulative incidence of stroke was 12% after cranial radiation exposure with a dose of 50 Gy or greater.[48]

Among 571 people who survived childhood cancer for 5 years or longer, cardiovascular risk factors were more common compared with the general population (14.0% vs 4.9%, respectively, for dyslipidemia, 18% vs 11% for hypertension, and 6.5% vs 3.2% for diabetes).[49] Cardiovascular disease risk increases in the presence of cardiovascular risk factors.[50] Among 10 724 people who survived childhood cancer, having hypertension significantly increased

Box. Common Questions About Care of People Who Survive Childhood Cancer

What history should a generalist clinician obtain when caring for a person with a history of childhood cancer?
The generalist clinician should obtain information about the specific cancer diagnosis, time from diagnosis, and treatment, including details about field and doses of radiation therapy, anthracycline chemotherapy, and alkylating agent chemotherapy.

What are the most common chronic health conditions that affect people who survive childhood cancer?
The most common chronic health conditions affecting people treated for cancer during childhood include endocrine disorders (such as hypothyroidism and growth hormone deficiency), subsequent neoplasms (such as breast and thyroid cancer), and cardiovascular disease (such as coronary artery disease and cerebrovascular disease).

Which survivors of childhood cancer are at highest risk for developing treatment-related health problems?
People who were diagnosed with a brain tumor during childhood, those treated with cranial irradiation, and those who underwent allogeneic hematopoietic stem cell transplantation are at highest risk of developing complications related to the treatment of their childhood cancer.

the risk of coronary artery disease (RR, 6.1) and heart failure (RR, 19.4)[50]; the absolute rates were not reported. There was a significant interaction between chest radiation and hypertension for increased risk of coronary artery disease.[50]

Peripheral Nervous System Disorders

Among 531 people who had survived childhood cancer and were evaluated at a median age of 32 years, the prevalence of sensory neuropathy was 20% and the prevalence of motor neuropathy was 17.5%.[51] People treated with vinca alkaloids were at a 1.66-fold higher risk (95% CI, 1.04-2.64) of motor neuropathy, and those treated with platinum compounds were at a 1.62-fold greater risk (95% CI, 0.97-2.72) of sensory neuropathy compared with those not treated with the respective chemotherapies[51]; the absolute rates were not reported.

Musculoskeletal Complications

In a systematic review of childhood cancer survivors, radiation delivered before the age of 5 years was associated with higher rates of musculoskeletal growth problems, including muscular atrophy, skeletal hypoplasia, and scoliosis.[52] Among 1548 people who had survived childhood cancer and were evaluated at a mean age of 33.1 years for osteoporosis with dual-energy x-ray absorptiometry, 559 (36.1%) had low bone mineral density and 149 (9.6%) had very low–bone mineral density.[53] Male sex, underweight, high carboplatin dose, cranial radiation, hypogonadism, hyperthyroidism, low physical activity level, and severe vitamin D deficiency were associated with low bone mineral density.[53]

Osteonecrosis (defined as bone death caused by poor blood supply) is a debilitating complication of prolonged steroid therapy and is most commonly seen in children with acute lymphoblastic leukemia during treatment or soon thereafter.[54] The cumulative incidence of osteonecrosis ranged from 0.9% to 17.6% at completion of treatment for acute lymphoblastic leukemia.[54] Risk factors for osteonecrosis include an age older than 10 years at cancer diagnosis, female sex, and White race.[54]

Pulmonary Impairment

Approximately 15.6% of 1728 people who survived childhood cancer developed restrictive pulmonary disease (interstitial lung disease or pulmonary fibrosis) based on pulmonary function testing at a median follow-up of 24 years.[55] Radiation to the chest and particular chemotherapies (bleomycin, busulfan, and nitrosoureas) were associated with higher risk of pulmonary disease.[55]

Cataracts

Among 13 902 people followed up for an average of 21.4 years after childhood cancer, 483 (0.034%) developed presenile cataracts.[56] Radiation to the lens (a linear dose-response relationship) and corticosteroids were associated with increased risk.[56]

Ototoxicity

Of 451 people treated with platinum-based chemotherapy drugs without radiation therapy, 42% developed hearing loss at a median of 2.7 years (range, 0-28.4 years) after their cancer diagnosis.[57] In a study of 235 people treated with cranial radiation alone, 14% developed hearing loss, with a median time to onset of 3.6 years (range, 0.4-13.2 years).[58] Higher cumulative cisplatin dose,[57] younger age at diagnosis,[57,58] coadministration of furosemide,[57] history of cerebrospinal fluid shunts,[58] and higher doses of cranial radiation to the temporal bone (median, 54.0 Gy)[58] were associated with higher ototoxicity risk.

Cognition

Among 1426 people treated for childhood cancer, cognitive impairment was identified in more than 20% during a mean follow-up of 24 years.[59] Cognitive impairment was more common in people who received cranial radiation.[59] Manifestations included impairments in task efficiency, organization, emotional regulation, and memory. Adult survivors of childhood cancer who reported fatigue were more likely to have cognitive impairment compared with those without fatigue.[59] Other characteristics associated with cognitive impairment include sleep disruption,[59] cardiopulmonary disease and endocrine dysfunction,[60] higher cumulative anesthesia exposure,[61] exercise intolerance,[62] severe hearing impairment and seizures,[63] and missed school instruction while receiving treatment for childhood cancer. Consistent physical activity in adult survivors of childhood cancer has been associated with fewer cognitive problems.[64]

Mental Health

Among people who survive childhood cancer, approximately 2.3% to 40.8% reported having depression and approximately 1.2% to 27.6% reported having anxiety.[65] For comparison, the prevalence of major depression among young adults in the US has been 9.6%[66] and the prevalence of anxiety has been 19.1%.[66,67] Among 96 948 people with childhood cancer, 89 suicides occurred over a median follow-up of 7.2 years.[68] There were no differences in the suicide rates between people with vs without childhood cancer. However, among people older than 28 years of age, the suicide rates were elevated significantly among people with childhood cancer compared with the general population (22.43 per 100 000 person-years in the

childhood cancer population), resulting in a 1.4-fold higher risk (95% CI, 1.02-1.87) of death compared with the general population.[68]

Financial Hardship

Among 580 people who survived childhood cancer, 10% reported that their out-of-pocket medical costs exceeded 10% of their annual income compared with 2.9% of their cancer-free siblings. People who reported spending more than 10% of their annual income on medical bills were more likely to defer medical care, skip medical tests, and have difficulty paying medical bills compared with their cancer-free siblings.[69] The people at highest risk for financial hardship included those who were unemployed or had low incomes and those with severe medical conditions or hospitalizations during the past year.[69] People with these characteristics should be considered for programs to address medically related financial hardships.[69]

Care for People Who Survive Childhood Cancer

People who survive childhood cancer should receive lifelong care focused on health promotion and early detection of potential complications from their cancer treatment (**Box**). Individuals may be advised about long-term adverse effects of prior cancer treatment and provided with the recommendations regarding appropriate surveillance for early detection.[70] Guidelines for people in the US (eg, the Children's Oncology Group)[9,28] and internationally (eg, the International Guideline Harmonization Group)[71] recommend screening for early detection of treatment-related complications for those who survived childhood cancer and provide recommendations for follow-up care.[72,73] All survivors of childhood cancer should consider undergoing an annual thorough history and physical examination, psychosocial and mental health assessments, routine immunizations, and general age- and sex-appropriate health screenings and preventive care per applicable US Preventive Services Task Force recommendations.

Limitations

This review has several limitations. First, the quality of the included literature was not formally evaluated. Second, some relevant articles may have been missed. Third, the long-term adverse effects of newer therapeutic agents are unclear. Fourth, limited high-quality evidence is available regarding potential strategies to mitigate long-term risks after childhood cancer treatment.

Conclusions

Approximately 500 000 individuals currently alive in the US have survived childhood cancer. The most common adverse effects in individuals who survived childhood cancer are endocrine disorders, subsequent neoplasms, and cardiovascular disease. There is a need for clinicians and patients to have heightened awareness of these complications.

ARTICLE INFORMATION

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