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Impact of cancer therapy-related exposures on late mortality in childhood cancer survivors

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Abstract

Survival of children and adolescents diagnosed with cancer has improved dramatically in recent decades, but the substantial burden of late morbidity and mortality (i.e. more than five years after cancer diagnosis) associated with pediatric cancer treatments is increasingly being recognized. Progression or recurrence of the initial cancer is a primary cause of death in the initial post-diagnosis period, but as survivors age there is a dramatic shift in the cause-specific mortality profile. By 15 years post-diagnosis, the death rate attributable to health-related causes other than recurrence or external causes (e.g. accidents, suicide, assault) exceeds that due to primary disease, and by 30 years these causes account for the largest proportion of cumulative mortality. The two most prominent causes of treatment-related mortality in childhood cancer survivors are subsequent malignant neoplasms and cardiovascular problems, incidence of which can be largely attributed to the long-term toxicities of radiation and chemotherapy exposures. These late effects of treatment are likely to increase in importance as survivors continue to age, inspiring continued research to better understand their etiology and to inform early detection or prevention efforts.

INTRODUCTION

Survival of children and adolescents diagnosed with cancer has improved dramatically in recent decades due to advances in diagnosis, treatment, and supportive care. The most recent population-based data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program demonstrate that 83% of childhood cancer patients survive at least five years.¹ Among patients who survive five years, the vast majority (i.e. greater than 90%) will not experience a recurrence and are considered cured of their cancer. Estimates place the number of pediatric cancer survivors living in the United States at more than 420,000 at the end of 2013.² Unfortunately, the effects of cancer and its treatment are felt well beyond 5 years post-diagnosis, as evidenced by the growing body of literature detailing the significant morbidity and mortality in this population.³⁻⁵ Many of the studies examining late effects of cancer treatment have been conducted in the Childhood Cancer Survivor Study (CCSS), a large cohort study following over 12,000 5-year survivors of the most prominent childhood cancers (i.e. leukemia, central nervous system (CNS) malignancies, Hodgkin lymphoma, non-Hodgkin lymphoma, malignant renal tumors [Wilms],

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neuroblastoma, soft tissue sarcoma, and bone tumors) diagnosed from 1970-86 at one of 26 cancer centers around the US.⁶ Survivors in the CCSS experienced significantly greater mortality rates compared to those expected in the general population, even 30 years or more after their initial cancer diagnosis (Figure 1).³ The cumulative mortality among survivors was 18% by 30 years post-diagnosis, when the oldest survivors were entering their fifth decade of life. Compared to U.S. mortality data, the overall standardized mortality ratio for the CCSS survivor cohort was 8.4 (95% confidence interval: 8.0-8.7)

Progression or recurrence of the initial cancer is a primary cause of death in the initial post-diagnosis period, as illustrated in Figure 2A.³ However, as survivors age there is a dramatic shift in the cause-specific mortality profile. By 15 years post-diagnosis, the death rate attributable to health-related causes (i.e. not recurrence/progression of the original cancer or an external cause such as accident, suicide, or assault) exceeds that due to primary disease, and by 30 years these causes account for the largest proportion of cumulative mortality. Similar patterns have been reported in other childhood cancer survivor cohorts.⁷⁻⁹ The increasing slope of the cumulative mortality curve with time demonstrates the profound impact of late effects of therapy on survivors as they age through mid-life. As survivors of childhood cancer continue to age, mortality due to late effects will likely continue to increase.

A wide range of late effects of therapy have been identified in childhood cancer survivors, including fertility problems, metabolic dysfunction, psychological issues, and neurocognitive deficits.² However, the most prominent causes of late mortality are development of subsequent primary cancers and cardiovascular problems (Figure 2B).¹⁰ In the CCSS, subsequent malignant neoplasms (SMNs) accounted for 53% of deaths due to nonrecurrence, non-external causes (and 19% of deaths overall), whereas cardiovascular causes comprised 16% (7% overall).³ Many of these deaths are linked to the sequelae of childhood exposure to chemotherapeutic agents and ionizing radiation. Non-treatment factors such as genetics and lifestyle can contribute significantly to the substantial burden of late health effects faced by survivors as well, but here we focus primarily on the role of chemotherapy and radiation in risk of SMNs and cardiovascular problems.

TREATMENT-RELATED SUBSEQUENT NEOPLASMS

Development of SMNs is among the most serious therapy-related late effects in survivors of childhood cancer. Risk of invasive SMNs is elevated 4- to 6-fold in survivors compared to the age- and sex-matched general population,^{11, 12} resulting in even greater elevations in risk of mortality due to SMNs.⁸⁻¹⁰ Non-melanoma skin cancers were the most commonly diagnosed subsequent neoplasms, with a 30-year cumulative incidence approaching 10%. The most commonly diagnosed SMNs in the CCSS were breast, thyroid, CNS, and soft tissue sarcomas.¹¹ SMNs were diagnosed with a median latency of 18 years since the first cancer diagnosis, although secondary leukemias occur earlier, with the majority diagnosed within the first 10 years.

Ionizing radiation has long been recognized as a potent carcinogen, primarily due to direct deleterious effects on DNA.¹³ Radiation induces DNA damage, which if not properly

repaired by the cell can result in double-strand breaks and chromosomal aberrations. For these direct effects, the damage is proportional to energy deposition (dose), suggesting a linear dose-response for radiation carcinogenesis that has generally been supported in epidemiologic studies.¹⁴ Quantitative estimates of cancer risk due to radiation have largely been derived from studying survivors of the atomic bombings in Japan,¹⁵ people affected by the Chernobyl disaster,¹⁶ and cohorts with occupational or medical radiation exposures.^{14, 17} Notably, these studies indicate a substantial latency period between radiation exposure and emergence of cancer, with the first cases diagnosed a decade or more after the exposure.¹⁴ The effects of low dose radiation are difficult to enumerate in epidemiologic studies, so risks are generally derived by assuming a linear relationship and modeling expected effects at low doses. Indirect effects of radiation on non-cancer cells and the microenvironment are being identified as well, potentially complicating the accurate modeling of low dose and chronic radiation exposures.¹⁸

Radiation-induced genetic damage has the greatest impact on rapidly dividing cells, a property that has been harnessed to treat both childhood and adult cancers. Radiation therapy was a crucial component of the impressive advances in childhood cancer survival achieved in recent decades.^{19, 20} However, as more children treated for cancer survived into adulthood, it became clear that damage to non-cancer cells resulted in elevated risks of subsequent neoplasms. In the CCSS, exposure to any radiation therapy was associated with a 2.6-fold increased risk of SMNs compared to no radiation exposure.¹¹ However, the impact of radiation varied by site and dose, as evidenced by in-depth dosimetric analyses conducted for risks of thyroid, breast and CNS cancers²¹⁻²⁴.

A linear association between radiation dose to the breast during cancer treatment and risk of breast cancer has been reported,^{21, 25} with 6-fold and 11-fold increased risks after exposure to 20 Gy and 40 Gy, respectively. Notably, Hodgkin lymphoma survivors who received chest radiation were found to have a risk of breast cancer by age 50 years comparable to that of *BRCA1* mutation carriers.^{26, 27} Concomitant irradiation of the ovaries appears to attenuate the radiation-associated breast cancer risk, presumably due to alterations in hormone production.^{21, 26, 27} A linear dose-response with radiation has also been reported for risk of CNS neoplasms, with evidence suggesting a stronger association for meningioma compared to glioma, as well as increased susceptibility to the effects of cranial radiation in those exposed at very young ages.^{22, 28, 29}

Studies in atomic bomb survivors and those affected by the Chernobyl disaster showed that the thyroid is exquisitely sensitive to the carcinogenic effects of radiation, and indeed, risk of subsequent thyroid cancers is greatly increased in childhood cancer survivors with radiation fields in and around the neck.³⁰ In contrast to most other solid cancers,¹⁴ analyses of thyroid cancer risk show evidence of a linear exponential association with radiation dose, in which risk increases with dose up to 20-30 Gy, but then levels off or decreases at doses exceeding 30 Gy.^{23, 24, 30} This attenuation of risk at high doses supports a cell-killing model in which high doses of radiation cause sufficient damage to induce cell death, thereby precluding the development of malignancy.³¹ However, thyroid cancer risk after high radiation doses still significantly exceeds that in the non-irradiated population.

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Radiosensitivity varies across tissues, but recent evidence suggests significant associations between pediatric radiation exposure and risk of a number of other cancers, including renal carcinoma, sarcoma, and gastrointestinal malignancies such as colorectal and stomach cancer.^{12, 32-36} Notably, evidence from the British Childhood Cancer Survivor study, which includes an older population, indicated that digestive SMNs contribute the largest excess absolute risk of any cancer in survivors older than 40 years.¹² Thus, the importance of radiation associations with these less-recognized second cancers may increase as survivors reach the older ages more typically associated with cancer in the general population.

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The carcinogenic effects of exposure to both high- and low-dose radiation have inspired efforts to modify childhood cancer treatment protocols to reduce or even eliminate the need for radiation therapy. In addition, technology improvements such as the development of intensity-modulated radiotherapy (IMRT) and proton beam therapy have reduced direct exposure to non-target organs or tissues, although the ultimate impact of these changes on cancer risk have yet to be elucidated.

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Recognition of the harmful long-term effects of radiation has driven increasing reliance on intensification of combination chemotherapy regimens in the treatment of childhood cancers, but these drugs have also been associated with a wide range of adverse late effects. Chemotherapeutic agents are cytotoxic, usually targeting rapidly-dividing cells by impairing DNA replication, so it is not surprising that many have been recognized as human carcinogens.³⁷ The prime example of chemotherapy-induced carcinogenesis is therapy-related acute myeloid leukemia (t-AML)/myelodysplastic syndrome (MDS), for which incidence has increased in recent decades and prognosis is notably poor.³⁸ Two molecularly distinct subgroups of t-AML have been delineated based on the type of chemotherapeutic agent previously received by the patient.³⁹ Alkylating agents such as cyclophosphamide and nitrosoureas, which damage DNA by covalent bonding of alkyl groups and formation of DNA cross-links, have been associated with t-AML marked by deletions on chromosome 5 and 7, a typical latency period of 5-10 years, and presence of a myelodysplastic phase. A different subgroup of t-AML, characterized by a shorter latency (2-3 years) and balanced translocations involving chromosome band 11q23, has been associated with exposure to epipodophyllotoxins. These compounds interfere with the activity of DNA topoisomerase II and result in single- and double-strand breaks in DNA, ultimately resulting in chromosomal aberrations and mutagenesis. Anthracyclines have also been associated with risk of t-AML, likely via similar mechanisms involving topoisomerase II.³⁹

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Solid tumors have also been linked to chemotherapy exposure, although it is difficult to disentangle the independent effects of chemotherapy because most survivors in CCSS and other cohorts received combination therapy that also included radiation. A British study examined Hodgkin lymphoma survivors not treated with radiation and found chemotherapy exposure was associated with increased risks of leukemia, lung cancer, and NHL; but they concluded that risks were lower than after combined modalities and that risk was slight or negligible beyond 15 years of follow-up.⁴⁰ In the CCSS, thyroid cancer risk was significantly associated with chemotherapy exposures, but only in the subgroup exposed to radiation doses of 20 Gy or less.⁴¹ It is likely that independent effects of chemotherapy are dominated by the strong effects of high-dose radiation. Additionally, exposure to

chemotherapeutic agents such as procarbazine and platinum agents may potentiate the carcinogenic effects of radiation therapy.^{33, 35}

Patterns of use for chemotherapeutic agents have varied considerably over time, and few patients in earlier treatment eras were treated with chemotherapy alone, so additional research is needed to elucidate potential carcinogenic effects of chemotherapy, including newer agents such as kinase inhibitors and immunomodulators.

Pediatric exposure to cancer treatments clearly increases risk of subsequent neoplasms, but many survivors treated with high doses of radiation and/or chemotherapy do not develop additional cancers. This implies that in addition to treatment factors such as modality, dose and age at treatment, survivors have varying genetic susceptibility to treatment-related carcinogenesis. Numerous studies have examined the impact of genetic polymorphisms on second cancer risk, with particular focus on genes and pathways involved in DNA repair and drug metabolism.⁴² It is also important to note that not all subsequent cancers in survivors are attributable to the effects of treatment. Development of cancer early in life is often a marker of a cancer predisposition syndrome such as Li-Fraumeni syndrome, neurofibromatosis, or others, a hallmark of which is development of multiple neoplasms.⁴³

THERAPY-RELATED CARDIOVASCULAR COMPLICATIONS

When considering the occurrence of therapy-related morbidity and mortality among long-term survivors of childhood cancer, cardiovascular complications represent one of the more common and devastating sequelae.^{10, 44} Compared to siblings, childhood cancer survivors have been found to have a 15-fold increased risk of developing congestive heart failure (CHF),⁵ and compared to the U.S. population a 7-fold increased risk of cardiac-related mortality.¹⁰ Importantly, individuals with clinical CHF experience a high mortality rate with 5-year survival of less than 50%.^{45, 46}

Chemotherapy utilized in the successful treatment of children and adolescents with cancer can adversely impact a wide variety of organ systems, including the cardiovascular system.² Cardiovascular function may be impaired as a consequence of chemotherapeutic exposures through direct effects on the myocardium as well as the peripheral vasculature. While a number of anti-cancer drugs, including cyclophosphamide, cisplatin, and ifosfamide, are known to be associated with an increased risk of cardiovascular toxicity, the anthracyclines are most commonly associated with long-term cardiotoxicity. Anthracyclines, which include doxorubicin, daunorubicin, epirubicin and idarubicin, have been and continue to be frequently used in the treatment of a substantial proportion of pediatric malignancies.^{19, 20}

The cardiotoxic effect of anthracycline exposure was first characterized in the 1970s with observed occurrences of acute toxicities.⁴⁷ Over the subsequent decades the long-term impact of anthracyclines on cardiac function has been well-documented⁴⁸ and continues to be the topic of ongoing research.⁴⁹ Risk of long-term anthracycline-associated CHF, which may present as clinical CHF or asymptomatic cardiac abnormalities, is strongly dose dependent.^{50, 51} While there is general consensus that cumulative anthracycline exposures of less than 250 mg/m² are associated with a minimal risk for cardiac compromise,⁵¹ long-term follow-up and consideration of additional cardiovascular risk factors have identified

substantial risks with any anthracycline exposure.⁵² The mechanism by which anthracyclines damage myocardium is not fully understood; however, there is increasing evidence that oxidative stress is a major contributor through direct myocardial injury.⁵³ Also, anthracyclines can impact mitochondrial structure and function via changes in membrane permeability, which through reactive oxygen species can alter transport of calcium ions and contractility.⁵⁴

Within the setting of exposure to anthracycline, risk of CHF is also associated with younger age at exposure, female sex, and cardiac irradiation.^{55, 56} Independent of anthracycline exposure, radiation therapy involving the heart, either within or near the dose field, can damage key structural or functional components including the pericardium, myocardium, valves, conduction system and coronary arteries. Radiation-induced cardiovascular injury involves mechanisms related to formation of interstitial fibrosis and microcirculatory damage, with activation of inflammatory pathways leading to chronic inflammation.⁵⁷ One of the most striking associations between cardiac radiation and abnormal cardiac function is the high rate of heart valve disorders, which is estimated to have a cumulative prevalence approaching 100% by age 60 among radiation exposed childhood cancer survivors.⁴⁴

There is a growing body of literature regarding genetic determinants of cardiovascular structure, function and disease in the general population.^{58, 59} A topic of active investigation relating to treatment-related cardiotoxicity is the role of genetic determinants of risk. Specifically, while the documented risks associated with anthracycline and/or radiation exposure are substantial in magnitude, there are many heavily exposed survivors who do not develop cardiac dysfunction, in contrast to some survivors who received minimal exposures and do go on to develop cardiotoxicity. This raises the question of whether there are genetic determinants that, on an individual level, can influence the pharmacodynamics of anthracyclines or that might influence mechanisms of damage repair at the molecular or cellular level. Using candidate gene approaches, there are a limited number of studies that have investigated cancer survivors to identify host polymorphisms that may influence metabolism of anthracyclines. There has been interest in carbonyl reductases that catalyze reduction of anthracyclines to cardiotoxic alcohol metabolites. An early observation of an association with polymorphisms in *CBR1* and *CBR3* in a small population from the CCSS cohort was subsequently validated in a larger series conducted through the Children's Oncology Group.^{60, 61} Of interest, risk for cardiomyopathy was significantly associated with being homozygous for the G allele among survivors exposed to low (i.e., 100-150 mg/m²) or moderate-doses (i.e., 150-250 mg/m²) of anthracycline (Odds ratio, OR=3.3, 95% confidence interval, 95% CI=1.41-7.73). In contrast, no association with genotype was observed among survivors with exposure of 250 mg/m² (OR=1.37, 95% CI=0.66-2.84), suggesting that there is an exposure threshold effect where the influence on risk exerted by the anthracycline exposure dominates any influence of genetics. Using an array containing 2100 genes to investigate *de novo* cardiovascular disease, a variant in hyaluronan synthase 3 (*HAS3*) was found to be significantly associated with risk of anthracycline dose-dependent cardiomyopathy risk in survivors of childhood cancer.⁶² Those homozygous for the A allele at rs2232228 had slightly lower risk (OR=0.2, 95% CI=0.1-0.8) compared to those homozygous for the G allele when exposed to no or low

doses of anthracycline (250 mg/m²), whereas having the homozygous A genotype was associated with significantly increased risk (OR=8.9, 95% CI=2.1-37.5) with high anthracycline doses (>250 mg/m²). Importantly, the association with *HAS3* was replicated in an independent population of patients with anthracycline-associated cardiotoxicity. Hyaluronan is known to reduce reactive oxygen species-induced cardiac injury and is involved in the extracellular matrix and tissue remodeling. Thus, *HAS3* genotype may reflect one component of the overall pathophysiology of anthracycline-induced cardiomyopathy. With expanded investigations interrogating broader panels of single-nucleotide polymorphisms,⁶³ additional gene-chemotherapy associations will emerge and provide potential opportunities for risk profiling of survivors.

CONCLUSIONS

By 2020 it is conservatively projected that the number of survivors of childhood cancer in the U.S. population will approach 500,000.² While new approaches to treat childhood and adolescent cancer patients are continually being tested through the conduct of large-scale clinical trials,⁶⁴ it is likely that the vast majority of past and future survivors will have been exposed to chemotherapy and/or radiation that will place them at an increased risk for long-term morbidity and increased mortality. As the data from survivor cohorts and population-based registries continue to characterize the experience of this growing population, new insights will emerge regarding exposure-specific outcomes and associated risks. Newer targeted and/or non-genotoxic chemotherapies are being developed and used, but additional research is needed to understand the potential for late effects associated with these treatments (e.g. tyrosine kinase inhibitors).⁶⁵ Moreover, extended follow-up and research of this unique population will expand our understanding of the underlying pathophysiology of therapy-related toxicities. The estimated prevalence of childhood cancer survivors in the U.S. is 1 in 680, which from a health care and public health perspective has significant implications given the high magnitude of risk for therapy-related adverse risks and the large number of potential years of life over which to manifest long-term toxicities from treatment-related exposures. Accordingly, ongoing multidisciplinary research is needed to further characterize the long-term toxicity profiles of cancer therapy.

References

1. Howlader, N.; Noone, AM.; Krapcho, M.; Garshell, J.; Miller, D.; Altekruse, SF.; Kosary, CL.; Yu, M.; Ruhl, J.; Tatalovich, Z.; Cho, H.; Mariotto, A.; Lewis, DR.; Chen, HS.; Feuer, EJ.; Cronin, KA. SEER Cancer Statistics Review. National Cancer Institute; Bethesda, MD: 1975-2010. http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014
2. Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. *Nat Rev Cancer*. 2014; 14:61–70. [PubMed: 24304873]
3. Armstrong GT, Liu Q, Yasui Y, Neglia JP, Leisenring W, Robison LL, Mertens AC. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. *J Clin Oncol*. 2009; 27:2328–2338. [PubMed: 19332714]
4. Hudson MM, Mertens AC, Yasui Y, Hobbie W, Chen H, Gurney JG, Yeazel M, Recklitis CJ, Marina N, Robison LR, Oeffinger KC. Childhood Cancer Survivor Study, I. Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *JAMA*. 2003; 290:1583–1592. [PubMed: 14506117]

5. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, Friedman DL, Marina N, Hobbie W, Kadan-Lottick NS, Schwartz CL, Leisenring W, Robison LL, Childhood Cancer Survivor, S. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006; 355:1572–1582. [PubMed: 17035650]
6. Robison LL, Mertens AC, Boice JD, Breslow NE, Donaldson SS, Green DM, Li FP, Meadows AT, Mulvihill JJ, Neglia JP, Nesbit ME, Packer RJ, Potter JD, Sklar CA, Smith MA, Stovall M, Strong LC, Yasui Y, Zeltzer LK. Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. *Med Pediatr Oncol*. 2002; 38:229–239. [PubMed: 11920786]
7. Cardous-Ubbink MC, Heinen RC, Langeveld NE, Bakker PJ, Voute PA, Caron HN, van Leeuwen FE. Long-term cause-specific mortality among five-year survivors of childhood cancer. *Pediatr Blood Cancer*. 2004; 42:563–573. [PubMed: 15127410]
8. Garwicz S, Anderson H, Olsen JH, Falck Winther J, Sankila R, Langmark F, Tryggvadottir L, Moller TR. Association of the Nordic Cancer, R., and Nordic Society for Pediatric Hematology, O. Late and very late mortality in 5-year survivors of childhood cancer: changing pattern over four decades--experience from the Nordic countries. *Int J Cancer*. 2012; 131:1659–1666. [PubMed: 22170520]
9. Reulen RC, Winter DL, Frobisher C, Lancashire ER, Stiller CA, Jenney ME, Skinner R, Stevens MC, Hawkins MM. British Childhood Cancer Survivor Study Steering, G. Long-term cause-specific mortality among survivors of childhood cancer. *JAMA*. 2010; 304:172–179. [PubMed: 20628130]
10. Mertens AC, Liu Q, Neglia JP, Wasilewski K, Leisenring W, Armstrong GT, Robison LL, Yasui Y. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2008; 100:1368–1379. [PubMed: 18812549]
11. Friedman DL, Whitton J, Leisenring W, Mertens AC, Hammond S, Stovall M, Donaldson SS, Meadows AT, Robison LL, Neglia JP. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2010; 102:1083–1095. [PubMed: 20634481]
12. Reulen RC, Frobisher C, Winter DL, Kelly J, Lancashire ER, Stiller CA, Pritchard-Jones K, Jenkinson HC, Hawkins MM. British Childhood Cancer Survivor Study Steering, G. Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. *JAMA*. 2011; 305:2311–2319. [PubMed: 21642683]
13. Lomax ME, Folkes LK, O'Neill P. Biological consequences of radiation-induced DNA damage: relevance to radiotherapy. *Clin Oncol (R Coll Radiol)*. 2013; 25:578–585. [PubMed: 23849504]
14. Berrington de Gonzalez A, Gilbert E, Curtis R, Inskip P, Kleinerman R, Morton L, Rajaraman P, Little MP. Second solid cancers after radiation therapy: a systematic review of the epidemiologic studies of the radiation dose-response relationship. *Int J Radiat Oncol Biol Phys*. 2013; 86:224–233. [PubMed: 23102695]
15. Little MP. Cancer and non-cancer effects in Japanese atomic bomb survivors. *J Radiol Prot*. 2009; 29:A43–59. [PubMed: 19454804]
16. Cardis E, Hatch M. The Chernobyl accident--an epidemiological perspective. *Clin Oncol (R Coll Radiol)*. 2011; 23:251–260. [PubMed: 21396807]
17. Linet MS, Kim KP, Miller DL, Kleinerman RA, Simon SL, Berrington de Gonzalez A. Historical review of occupational exposures and cancer risks in medical radiation workers. *Radiat Res*. 2010; 174:793–808. [PubMed: 21128805]
18. Barcellos-Hoff MH. Integrative radiation carcinogenesis: interactions between cell and tissue responses to DNA damage. *Semin Cancer Biol*. 2005; 15:138–148. [PubMed: 15652459]
19. Green DM, Kun LE, Matthay KK, Meadows AT, Meyer WH, Meyers PA, Spunt SL, Robison LL, Hudson MM. Relevance of historical therapeutic approaches to the contemporary treatment of pediatric solid tumors. *Pediatr Blood Cancer*. 2013; 60:1083–1094. [PubMed: 23418018]
20. Hudson MM, Neglia JP, Woods WG, Sandlund JT, Pui CH, Kun LE, Robison LL, Green DM. Lessons from the past: opportunities to improve childhood cancer survivor care through outcomes investigations of historical therapeutic approaches for pediatric hematological malignancies. *Pediatr Blood Cancer*. 2012; 58:334–343. [PubMed: 22038641]

21. Inskip PD, Robison LL, Stovall M, Smith SA, Hammond S, Mertens AC, Whitton JA, Diller L, Kenney L, Donaldson SS, Meadows AT, Neglia JP. Radiation dose and breast cancer risk in the childhood cancer survivor study. *J Clin Oncol*. 2009; 27:3901–3907. [PubMed: 19620485]
22. Neglia JP, Robison LL, Stovall M, Liu Y, Packer RJ, Hammond S, Yasui Y, Kasper CE, Mertens AC, Donaldson SS, Meadows AT, Inskip PD. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2006; 98:1528–1537. [PubMed: 17077355]
23. Ronckers CM, Sigurdson AJ, Stovall M, Smith SA, Mertens AC, Liu Y, Hammond S, Land CE, Neglia JP, Donaldson SS, Meadows AT, Sklar CA, Robison LL, Inskip PD. Thyroid cancer in childhood cancer survivors: a detailed evaluation of radiation dose response and its modifiers. *Radiat Res*. 2006; 166:618–628. [PubMed: 17007558]
24. Sigurdson AJ, Ronckers CM, Mertens AC, Stovall M, Smith SA, Liu Y, Berkow RL, Hammond S, Neglia JP, Meadows AT, Sklar CA, Robison LL, Inskip PD. Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study. *Lancet*. 2005; 365:2014–2023. [PubMed: 15950715]
25. Guibout C, Adjadj E, Rubino C, Shamsaldin A, Grimaud E, Hawkins M, Mathieu MC, Oberlin O, Zucker JM, Panis X, Lagrange JL, Daly-Schveitzer N, Chavaudra J, de Vathaire F. Malignant breast tumors after radiotherapy for a first cancer during childhood. *J Clin Oncol*. 2005; 23:197–204. [PubMed: 15625374]
26. Moskowitz CS, Chou JF, Wolden SL, Bernstein JL, Malhotra J, Novetsky Friedman D, Mubdi NZ, Leisenring WM, Stovall M, Hammond S, Smith SA, Henderson TO, Boice JD, Hudson MM, Diller LR, Bhatia S, Kenney LB, Neglia JP, Begg CB, Robison LL, Oeffinger KC. Breast cancer after chest radiation therapy for childhood cancer. *J Clin Oncol*. 2014; 32:2217–2223. [PubMed: 24752044]
27. Travis LB, Hill D, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, Glimelius B, Andersson M, Pukkala E, Lynch CF, Pee D, Smith SA, Van't Veer MB, Joensuu T, Storm H, Stovall M, Boice JD Jr, Gilbert E, Gail MH. Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. *J Natl Cancer Inst*. 2005; 97:1428–1437. [PubMed: 16204692]
28. Bowers DC, Nathan PC, Constine L, Woodman C, Bhatia S, Keller K, Bashore L. Subsequent neoplasms of the CNS among survivors of childhood cancer: a systematic review. *Lancet Oncol*. 2013; 14:e321–328. [PubMed: 23816298]
29. Taylor AJ, Little MP, Winter DL, Sugden E, Ellison DW, Stiller CA, Stovall M, Frobisher C, Lancashire ER, Reulen RC, Hawkins MM. Population-based risks of CNS tumors in survivors of childhood cancer: the British Childhood Cancer Survivor Study. *J Clin Oncol*. 2010; 28:5287–5293. [PubMed: 21079138]
30. Veiga LH, Lubin JH, Anderson H, de Vathaire F, Tucker M, Bhatti P, Schneider A, Johansson R, Inskip P, Kleinerman R, Shore R, Pottern L, Holmberg E, Hawkins MM, Adams MJ, Sadetzki S, Lundell M, Sakata R, Damber L, Neta G, Ron E. A pooled analysis of thyroid cancer incidence following radiotherapy for childhood cancer. *Radiat Res*. 2012; 178:365–376. [PubMed: 22857014]
31. Gray, LH. Radiation biology and cancer. Proceedings of the Eighteenth Annual Symposium on Fundamental Cancer Research; University of Texas, and M.D Anderson Hospital and Tumor Inst. Baltimore: Williams & Wilkins; 1965. p. 7
32. Bhatia S, Yasui Y, Robison LL, Birch JM, Bogue MK, Diller L, DeLaat C, Fossati-Bellani F, Morgan E, Oberlin O, Reaman G, Ruymann FB, Tersak J, Meadows AT. Late Effects Study, G. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. *J Clin Oncol*. 2003; 21:4386–4394. [PubMed: 14645429]
33. Henderson TO, Oeffinger KC, Whitton J, Leisenring W, Neglia J, Meadows A, Crotty C, Rubin DT, Diller L, Inskip P, Smith SA, Stovall M, Constine LS, Hammond S, Armstrong GT, Robison LL, Nathan PC. Secondary gastrointestinal cancer in childhood cancer survivors: a cohort study. *Ann Intern Med*. 2012; 156:757–766. W–260. [PubMed: 22665813]
34. Henderson TO, Whitton J, Stovall M, Mertens AC, Mitby P, Friedman D, Strong LC, Hammond S, Neglia JP, Meadows AT, Robison L, Diller L. Secondary sarcomas in childhood cancer survivors:

a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2007; 99:300–308. [PubMed: 17312307]

35. van den Belt-Dusebout AW, Aleman BM, Besseling G, de Bruin ML, Hauptmann M, van't Veer MB, de Wit R, Ribot JG, Noordijk EM, Kerst JM, Gietema JA, van Leeuwen FE. Roles of radiation dose and chemotherapy in the etiology of stomach cancer as a second malignancy. *Int J Radiat Oncol Biol Phys.* 2009; 75:1420–1429. [PubMed: 19931732]
36. Nottage K, McFarlane J, Krasin MJ, Li C, Srivastava D, Robison LL, Hudson MM. Secondary colorectal carcinoma after childhood cancer. *J Clin Oncol.* 2012; 30:2552–2558. [PubMed: 22665546]
37. Grosse Y, Baan R, Straif K, Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Galichet L, Coglianò V. W.H.O. International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens-Part A: pharmaceuticals. *Lancet Oncol.* 2009; 10:13–14. [PubMed: 19115512]
38. Guillem V, Tormo M. Influence of DNA damage and repair upon the risk of treatment related leukemia. *Leuk Lymphoma.* 2008; 49:204–217. [PubMed: 18231906]
39. Pedersen-Bjergaard J, Pedersen M, Roulston D, Philip P. Different genetic pathways in leukemogenesis for patients presenting with therapy-related myelodysplasia and therapy-related acute myeloid leukemia. *Blood.* 1995; 86:3542–3552. [PubMed: 7579462]
40. Swerdlow AJ, Higgins CD, Smith P, Cunningham D, Hancock BW, Horwich A, Hoskin PJ, Lister TA, Radford JA, Rohatiner AZ, Linch DC. Second cancer risk after chemotherapy for Hodgkin's lymphoma: a collaborative British cohort study. *J Clin Oncol.* 2011; 29:4096–4104. [PubMed: 21969511]
41. Veiga LH, Bhatti P, Ronckers CM, Sigurdson AJ, Stovall M, Smith SA, Weathers R, Leisenring W, Mertens AC, Hammond S, Neglia JP, Meadows AT, Donaldson SS, Sklar CA, Friedman DL, Robison LL, Inskip PD. Chemotherapy and thyroid cancer risk: a report from the childhood cancer survivor study. *Cancer Epidemiol Biomarkers Prev.* 2012; 21:92–101. [PubMed: 22028399]
42. Allan JM, Rabkin CS. Genetic susceptibility to iatrogenic malignancy. *Pharmacogenomics.* 2005; 6:615–628. [PubMed: 16143001]
43. Travis LB, Demark Wahnefried W, Allan JM, Wood ME, Ng AK. Aetiology, genetics and prevention of secondary neoplasms in adult cancer survivors. *Nat Rev Clin Oncol.* 2013; 10:289–301. [PubMed: 23529000]
44. Hudson MM, Ness KK, Gurney JG, Mulrooney DA, Chemaitilly W, Krull KR, Green DM, Armstrong GT, Nottage KA, Jones KE, Sklar CA, Srivastava DK, Robison LL. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *JAMA.* 2013; 309:2371–2381. [PubMed: 23757085]
45. Armenian SH, Sun CL, Shannon T, Mills G, Francisco L, Venkataraman K, Wong FL, Forman SJ, Bhatia S. Incidence and predictors of congestive heart failure after autologous hematopoietic cell transplantation. *Blood.* 2011; 118:6023–6029. [PubMed: 21976673]
46. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, Baughman KL, Kasper EK. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med.* 2000; 342:1077–1084. [PubMed: 10760308]
47. Von Hoff DD, Layard MW, Basa P, Davis HL Jr, Von Hoff AL, Rozencweig M, Muggia FM. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med.* 1979; 91:710–717. [PubMed: 496103]
48. Lipshultz SE, Adams MJ, Colan SD, Constine LS, Herman EH, Hsu DT, Hudson MM, Kremer LC, Landy DC, Miller TL, Oeffinger KC, Rosenthal DN, Sable CA, Sallan SE, Singh GK, Steinberger J, Cochran TR, Wilkinson JD. American Heart Association Congenital Heart Defects Committee of the Council on Cardiovascular Disease in the Young, C. o. B. C. S. C. o. C., and Stroke Nursing, C. o. C. R. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention, and research directions: a scientific statement from the American Heart Association. *Circulation.* 2013; 128:1927–1995. [PubMed: 24081971]
49. Armenian SH, Robison LL. Childhood cancer survivorship: an update on evolving paradigms for understanding pathogenesis and screening for therapy-related late effects. *Curr Opin Pediatr.* 2013; 25:16–22. [PubMed: 23295717]

50. Hudson MM, Rai SN, Nunez C, Merchant TE, Marina NM, Zalamea N, Cox C, Phipps S, Pompeu R, Rosenthal D. Noninvasive evaluation of late anthracycline cardiac toxicity in childhood cancer survivors. *J Clin Oncol*. 2007; 25:3635–3643. [PubMed: 17704413]
51. Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, Donaldson SS, Green DM, Sklar CA, Robison LL, Leisenring WM. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ*. 2009; 339:b4606. [PubMed: 19996459]
52. Armstrong GT, Oeffinger KC, Chen Y, Kawashima T, Yasui Y, Leisenring W, Stovall M, Chow EJ, Sklar CA, Mulrooney DA, Mertens AC, Border W, Durand JB, Robison LL, Meacham LR. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. *J Clin Oncol*. 2013; 31:3673–3680. [PubMed: 24002505]
53. Tokarska-Schlattner M, Zaugg M, Zuppinger C, Wallimann T, Schlattner U. New insights into doxorubicin-induced cardiotoxicity: the critical role of cellular energetics. *J Mol Cell Cardiol*. 2006; 41:389–405. [PubMed: 16879835]
54. Outomuro D, Grana DR, Azzato F, Milei J. Adriamycin-induced myocardial toxicity: new solutions for an old problem? *Int J Cardiol*. 2007; 117:6–15. [PubMed: 16863672]
55. Lipshultz SE, Alvarez JA, Scully RE. Anthracycline associated cardiotoxicity in survivors of childhood cancer. *Heart*. 2008; 94:525–533. [PubMed: 18347383]
56. van der Pal HJ, van Dalen EC, van Delden E, van Dijk IW, Kok WE, Geskus RB, Sieswerda E, Oldenburger F, Koning CC, van Leeuwen FE, Caron HN, Kremer LC. High risk of symptomatic cardiac events in childhood cancer survivors. *J Clin Oncol*. 2012; 30:1429–1437. [PubMed: 22473161]
57. Hendry JH, Akahoshi M, Wang LS, Lipshultz SE, Stewart FA, Trott KR. Radiation-induced cardiovascular injury. *Radiat Environ Biophys*. 2008; 47:189–193. [PubMed: 18193445]
58. Preuss M, Konig IR, Thompson JR, Erdmann J, Absher D, Assimes TL, Blankenberg S, Boerwinkle E, Chen L, Cupples LA, Hall AS, Halperin E, Hengstenberg C, Holm H, Laaksonen R, Li M, Marz W, McPherson R, Musunuru K, Nelson CP, Burnett MS, Epstein SE, O'Donnell CJ, Quertermous T, Rader DJ, Roberts R, Schillert A, Stefansson K, Stewart AF, Thorleifsson G, Voight BF, Wells GA, Ziegler A, Kathiresan S, Reilly MP, Samani NJ, Schunkert H, Consortium CA. Design of the Coronary ARtery Disease Genome-Wide Replication And Meta-Analysis (CARDIoGRAM) Study: A Genome-wide association meta-analysis involving more than 22 000 cases and 60 000 controls. *Circ Cardiovasc Genet*. 2010; 3:475–483. [PubMed: 20923989]
59. Vasan RS, Glazer NL, Felix JF, Lieb W, Wild PS, Felix SB, Watzinger N, Larson MG, Smith NL, Dehghan A, Grosshennig A, Schillert A, Teumer A, Schmidt R, Kathiresan S, Lumley T, Aulchenko YS, Konig IR, Zeller T, Homuth G, Struchalin M, Aragam J, Bis JC, Rivadeneira F, Erdmann J, Schnabel RB, Dorr M, Zweiker R, Lind L, Rodeheffer RJ, Greiser KH, Levy D, Haritunians T, Deckers JW, Stritzke J, Lackner KJ, Volker U, Ingelsson E, Kullo I, Haerting J, O'Donnell CJ, Heckbert SR, Stricker BH, Ziegler A, Reffellmann T, Redfield MM, Werdan K, Mitchell GF, Rice K, Arnett DK, Hofman A, Gottdiener JS, Uitterlinden AG, Meitinger T, Blettner M, Friedrich N, Wang TJ, Psaty BM, van Duijn CM, Wichmann HE, Munzel TF, Kroemer HK, Benjamin EJ, Rotter JJ, Witteman JC, Schunkert H, Schmidt H, Volzke H, Blankenberg S. Genetic variants associated with cardiac structure and function: a meta-analysis and replication of genome-wide association data. *JAMA*. 2009; 302:168–178. [PubMed: 19584346]
60. Blanco JG, Leisenring WM, Gonzalez-Covarrubias VM, Kawashima TI, Davies SM, Relling MV, Robison LL, Sklar CA, Stovall M, Bhatia S. Genetic polymorphisms in the carbonyl reductase 3 gene CBR3 and the NAD(P)H:quinone oxidoreductase 1 gene NQO1 in patients who developed anthracycline-related congestive heart failure after childhood cancer. *Cancer*. 2008; 112:2789–2795. [PubMed: 18457324]
61. Blanco JG, Sun CL, Landier W, Chen L, Esparza-Duran D, Leisenring W, Mays A, Friedman DL, Ginsberg JP, Hudson MM, Neglia JP, Oeffinger KC, Ritchey AK, Villaluna D, Relling MV, Bhatia S. Anthracycline-related cardiomyopathy after childhood cancer: role of polymorphisms in carbonyl reductase genes—a report from the Children's Oncology Group. *J Clin Oncol*. 2012; 30:1415–1421. [PubMed: 22124095]

62. Wang X, Liu W, Sun CL, Armenian SH, Hakonarson H, Hageman L, Ding Y, Landier W, Blanco JG, Chen L, Quinones A, Ferguson D, Winick N, Ginsberg JP, Keller F, Neglia JP, Desai S, Sklar CA, Castellino SM, Cherrick I, Dreyer ZE, Hudson MM, Robison LL, Yasui Y, Relling MV, Bhatia S. Hyaluronan synthase 3 variant and anthracycline-related cardiomyopathy: a report from the children's oncology group. *J Clin Oncol*. 2014; 32:647–653. [PubMed: 24470002]
63. Visscher H, Ross CJ, Rassekh SR, Barhdadi A, Dube MP, Al-Saloos H, Sandor GS, Caron HN, van Dalen EC, Kremer LC, van der Pal HJ, Brown AM, Rogers PC, Phillips MS, Rieder MJ, Carleton BC, Hayden MR. Canadian Pharmacogenomics Network for Drug Safety, C. Pharmacogenomic prediction of anthracycline-induced cardiotoxicity in children. *J Clin Oncol*. 2012; 30:1422–1428. [PubMed: 21900104]
64. Adamson PC. The Children's Oncology Group's 2013 five year blueprint for research. *Pediatr Blood Cancer*. 2013; 60:955–956. [PubMed: 23255253]
65. Verma D, Kantarjian H, Strom SS, Rios MB, Jabbour E, Quintas-Cardama A, Verstovsek S, Ravandi F, O'Brien S, Cortes J. Malignancies occurring during therapy with tyrosine kinase inhibitors (TKIs) for chronic myeloid leukemia (CML) and other hematologic malignancies. *Blood*. 2011; 118:4353–4358. [PubMed: 21846902]

Figure 1.

A) All-cause mortality (survival function estimate) for the CCSS population compared to that expected in the age, calendar year, and sex-matched U.S. population. B) All-cause mortality (survival function estimate) by sex. Reprinted with permission. © 2009 American Society of Clinical Oncology. All rights reserved. Armstrong GT et al: J Clin Oncol Vol. 27, 2009: 2330.

Figure 2.

A) Cause-specific cumulative mortality for the CCSS population. B) Cumulative mortality in CCSS due to second malignant neoplasms or cardiac disease.