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Challenges and opportunities in the care of survivors of adolescent and young adult (AYA) cancers

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Abbreviations Key:

AYA	adolescents and young adults
CCSS	Childhood Cancer Survivor Study
ALiCCS	Adult Life after Childhood Cancer in Scandinavia

SPN	subsequent primary neoplasm
SIR	standard incidence ratio
SEER	Surveillance, Epidemiology and End Results
BCCSS	British Childhood Cancer Survivor Study
TYACSS	Teenage and Young Adult Cancer Survivor Study
HR	hazard ratio
YSRCCYP	Yorkshire Specialist Register of Cancer in Children and Young People
PTSD	post-traumatic stress disorder
NCCN	National Comprehensive Cancer Network
SCP	survivorship care plan
SCCSS	Swiss Childhood Cancer Survivor Study
DCOG	Dutch Childhood Oncology Group
IMPACT	Initiative to Maximize Progress in Adolescent and Young Adult Cancer Therapy
CAYACS	Childhood, Adolescent, and Young Adult Cancer Survivors Research Program
SJLIFE	St. Jude Lifetime Cohort Study
IGHG	International Guidelines Harmonization Group
COG	Children's Oncology Group
SIGN	Scottish Intercollegiate Guidelines Network
CCLG	Children's Cancer and Leukaemia Group
GPOH	German Society for Paediatric Oncology and Haematology
SALUB	Swedish Working Group for Long-term Follow-up after Childhood Cancer

Abstract

Adolescents and young adults (AYA) with cancer are an understudied group. Much of what is known about long-term outcomes after AYA cancer has been derived from cohorts of childhood cancer survivors, which seldom include patients at the older end of the AYA age spectrum. In general, AYA cancer survivors have a lower risk for premature mortality, subsequent primary neoplasms and chronic health conditions than childhood cancer survivors. However, AYA cancer survivors are vulnerable to psychosocial challenges, concerns about fertility and relationships, and financial toxicity. No single model is optimal for the care of these survivors, but it is generally agreed that all survivors require a survivor care plan that promotes their adherence to evidence-based surveillance guidelines. There is a need to create survivor cohorts that include the full range of AYA ages and diagnoses to be able to address the many pressing questions that remain unanswered in this vulnerable population.

Introduction

There are approximately 70,000 new cancer diagnoses in adolescents and young adults (AYA; aged 15-39 years[1]) in the United States each year, while globally, almost one million 20-39 year olds are diagnosed with a new cancer annually.[2] Cancer is the leading cause of disease-related (non-injury) death in AYA.[3,4] Although survival rates for many AYA cancers are good, improvements in survival have lagged behind those observed in children and older adults. This has been a focus of recent research;[4-7] however, less attention has been given to morbidity among long-term survivors. The number of survivors and their burden on the health care system continues to rise, but in many jurisdictions, health care professionals,[8,9] legislators and other stakeholders have limited knowledge about this population's special needs. Furthermore, resources to fund research, create specialized clinical programs including survivor programs and increase awareness are often inadequate.[10] In this article, we focus on key issues relating to survivors of AYA cancers. We compare the risk of late effects of therapy between survivors of AYA and childhood cancer and explore three critical challenges faced by AYA cancer survivors: fertility and sexuality, psychosocial outcomes, and financial consequences. We discuss the obstacles to providing lifelong, risk-based care to AYA cancer survivors. Lastly, we describe ongoing research into AYA survivor outcomes, and explore the research gaps and opportunities that should shape the future direction of AYA survivor research.

International cohorts available for the study of AYA cancer survivors

There is a large number of survivorship cohorts internationally, but most were established with the aim of assessing late effects among childhood cancer survivors, with the upper age band of the cohort often extending only to survivors of adolescent cancer. We identified only two large AYA survivorship cohorts (from the United Kingdom and Denmark) that covered the entire age

range of 15-39 years. Thus, while cohorts such as the North American *Childhood Cancer Survivor Study (CCSS)* and *Adult Life after Childhood Cancer in Scandinavia (ALiCCS)* have provided a wealth of knowledge regarding late effects for younger patients, their findings are largely driven by the often greater risks observed among survivors diagnosed before the age of 15 years, and not generalizable to the entire population of survivors of AYA cancer. Thus, there is a need to establish cohorts assessing AYA, particularly above the age of 25. We have highlighted some characteristics of selected survivorship cohorts in Table 1, which have informed our comparison of the risks of adverse outcomes in survivors of AYA and childhood cancers.

Risks of adverse physical outcomes in survivors of AYA cancer

AYA experience increased risks of premature mortality and morbidities compared to the general population. Serious late effects can occur in all organ systems depending on treatment exposures, and can impact mental health. Much of what is currently “known” about late effects in AYA has been extrapolated from childhood cancer survivors. It is important to recognize there are differences in risks between these two vulnerable populations. In this section we compare risks in survivors of childhood and AYA cancers for three of the most common late effects: late mortality, subsequent primary neoplasms (SPNs), and chronic health conditions.

Late mortality

Numerous investigations into mortality have been undertaken among survivors of childhood cancer, but little is known about the risks in AYA, with no study to date documenting the risk of all-cause mortality among those diagnosed between 34-39 years. Among the studies that were

identified, survivors of AYA cancers were generally observed to have lower risks compared to childhood cancer survivors. For example, in Scotland, the risk of all-cause mortality was 11.0 times higher in childhood cancer survivors compared to the general population, whilst the corresponding risk in those diagnosed aged 15-24 was 4.7 times higher.[11] Similar differences were observed in Finland when comparing survivors of cancer diagnosed at 0-19 years with those diagnosed at 20-34 years.[12] The risks were more comparable between survivors of childhood and AYA cancers in the institution-based CCSS.[13] Neoplastic-related deaths (relapse, SPN) are the main cause of premature mortality in both age groups, followed by infection and cardiovascular diseases.[12] Cause-specific mortality risks were also attenuated for AYA survivors compared to survivors of childhood cancer,[12,14,15] with standardized mortality ratios (SMRs) decreasing from 6.8 to 1.7 for respiratory deaths[14] and from 3.4 to 1.4 for cardiac deaths.[15,16]

Subsequent primary neoplasms

Radiotherapy, chemotherapy, and genetic predisposition have all been associated with increased SPN risks among cancer survivors. Compared to research in children, the vast majority of studies in AYA have been on specific diagnosis groups, such as testicular cancer,[17,18] breast cancer,[19-23] and Hodgkin lymphoma.[24-26] Only two studies[27][28] have addressed the risk of SPNs after each AYA cancer diagnosis, and only the former assessed the risks of specific types of SPNs after each particular AYA cancer.

While the SPN standardized incidence ratios (SIRs) in children range from three- to six-fold that expected,[28-36] the SIRs are substantially smaller in AYA, with the Surveillance,

Epidemiology, and End Results (SEER) program reporting an SIR of 1.6 among 15-39 year olds (corresponding SIR in children in SEER=4.3).[28] Excess risks of SPNs vary substantially when assessed by type of SPN and by interval from diagnosis of index cancer. For example, if we compare the SPN-specific risks in two United Kingdom population-based studies, the British Childhood Cancer Survivor Study (BCCSS) and the Teenage and Young Adult Cancer Survivor Study (TYACSS), we observe SIRs varying from 1.9 for genitourinary SPNs to 30.5 for bone SPNs in the BCCSS.[29] This is a far greater variation compared to AYA in the TYACSS where the SIRs varied from 1.1 for breast SPNs to 3.0 for meningiomas.[27] Similarly, if we compare the SIRs for breast cancer after Hodgkin lymphoma in female survivors, the estimate in the BCCSS was 8.9, over twice as high as the corresponding estimate in the TYACSS (SIR=3.2).[27,29] There are a number of factors which may be related to these differences including the potential for greater toxicity in tissue and organs exposed to cancer treatments whilst still developing and the different spectrum of malignant diseases predominating in childhood and AYA and the consequent different treatment exposures.

Chronic health conditions

Reports regarding chronic health conditions among AYA cancer survivors have largely focused on hospitalizations.[37-42] Childhood cancer survivors have been estimated to experience approximately twice as many hospitalizations compared to controls,[43] while the corresponding excess risk in AYA cancer survivors was 1.4.[39] Conditions associated with the greatest excess risks in AYA were hospitalizations for blood, infectious and parasitic disease, and SPNs, all of which were at least 50% more likely in AYA cancer survivors than comparative norms.[39] Greatest excess risks of hospitalizations among childhood cancer survivors were associated with

nervous system, blood, and endocrine diseases.[43] Again, childhood cancer survivors exhibited greater excess risks than AYA cancer survivors.

As only one study described above assessed all types of hospitalizations,[39] the remaining body of literature on chronic health conditions in AYA has focused on specific types of diseases, mostly circulatory outcomes. In the several reports from Finland comparing survivors of cancer diagnosed aged 0-19 years with those diagnosed aged 20-34 years, risk of cardiovascular morbidity was 13.5 times and 3.6 times higher respectively than expected from sibling controls.[37] The likelihood of purchasing cardiovascular medicines has been shown to be significantly higher in survivors of childhood (hazard ratio (HR) = 19.8) than AYA cancer (HR = 2.5).[44] These risks were more elevated than those observed in the Yorkshire Specialist Register of Cancer in Children and Young People (YSRCCYP) and Danish Cancer Registry, where AYA aged 15-39 years at diagnosis were only 1.3 times more at risk for a hospitalization for cardiovascular disease compared to the control group in the latter cohort.[38,42]

Hospitalizations due to endocrine diseases have also been studied in AYA in one study from Denmark, where survivors had a 70% greater risk than controls of having a condition;[41] this was substantially lower than the corresponding 4.8 times increased risk reported by the ALiCCS cohort.[45]

These initial reports provide important information, but the general lack of knowledge on the total burden of disease in AYA cancer survivors is concerning. With 99.9% of childhood cancer survivors experiencing a chronic health condition by age 50 years, and 96% of these survivors having a severe or disabling, life threatening or fatal condition by the same point,[46] it is critical

to understand the magnitude of morbidity in survivors of AYA cancers in order to provide evidence for clinical follow-up guidelines and preventative interventions.

Major challenges faced by AYA cancer survivors

AYA cancer patients face developmental challenges that are distinct from other age groups with cancer, and that exceed the challenges faced by other young people their age. These hardships arise from the fact that AYA are diagnosed with cancer during a period of development in which they form individual values and identity, and create strong personal relationships. Many AYA with cancer are still developing autonomy, and have less developed coping mechanisms and decision making skills which are critical when faced with a cancer diagnosis and medical decisions. As a result of their stage in life, AYA are likely to experience specific needs, particularly in relation to psychosocial problems, fertility, and financial stability.

Psychosocial outcomes

Adolescence and young adulthood are stages in life with increased vulnerability to stress. This vulnerability results in even greater psychosocial needs among AYA with a history of cancer,[47-50] with studies reporting poorer mental health,[48] health-related quality of life,[51-53] and social functioning,[54] as well as 2.5 times more fatigue.[55] These challenges, which occur throughout the cancer care continuum (i.e. from diagnosis to survivorship or end of life), span several domains of stress and coping,[56] and are likely related to multiple factors such as cancer-related distress in the short- and long-terms, altered relationships, and concerns about body-sexual image, interrupted future plans, and forced dependence.[57,58]

AYA live with a heightened awareness of the uncertainties in life due to their cancer diagnoses. Fears of recurrence, late effects of therapy, and death are common examples of cancer-related distress. While the availability of data on this topic remains limited, several studies have suggested that AYA survivors experienced higher levels of fear of recurrence than older cancer survivors.[59-62] These fears can impact mental health, self-perceptions, family concerns, and finances.[63,64] AYA survivors experience more depression compared to other survivors, with one study finding that 16% of AYA survivors met the clinical criteria for depression.[65] Elevated risks for suicidal ideation,[66,67] anxiety,[68] and post-traumatic stress disorder (PTSD)[69-71] have also been noted in this population. AYA survivors from a Norwegian cohort were 2.6 times more likely to commit suicide than their peers,[72] and separate studies have shown a 4-5 times higher risk of PTSD compared to siblings[73] or comparative norms.[74] Interventions have been developed to assist survivors with many of these psychosocial issues, but the inclusion of AYA in these studies remains limited, and more work is needed to design specific strategies for this age group.[75]

Fertility and interpersonal issues

Infertility and childbearing difficulties remain major concerns for all AYA cancer survivors who have not yet completed their families, regardless of their diagnosis, prognosis, or treatment.[76-78] Although health provider awareness of treatment-related fertility damage is improving,[1] many AYA lack awareness of gonadotoxic treatments and their related reproductive impact.[79] AYA have reported limited knowledge about their reproductive health,[80-82] and fertility information is one of the most cited unmet needs among AYA survivors.[83-85] This is particularly apparent in younger patients, where the overprotectiveness of parents and discomfort

among clinicians[79] may hinder the patient's ability to receive adequate information and support or be involved in fertility-related decisions.[86] Consequently, there have been numerous recommendations for increased counselling and referral of patients to reproductive specialists before treatment.[87-89] International guidelines for fertility in males and females have also advanced substantially in the past few years to support a common vision and integrated strategy for monitoring these patients,[90,91] though further work is necessary to provide family building support given the emotional and financial burdens faced by AYA survivors.

Cancer and its treatment can have a large impact on sexuality, intimacy and the formation of mature, committed relationships.[1] It can be difficult for the AYA cancer patient and their parents, partners and friends to discuss these issues. Numerous studies have highlighted the negative impact on interpersonal relationships of having a cancer, with it not being uncommon for these patients to experience isolation or changes in friendships.[1,57,92] However, one study did suggest that most young survivors report improved family relationships, which is a critical component of health and wellbeing.[1] Body image and sexuality can also be compromised among AYA cancer survivors.[57,92-95] For example, one study found that 52% of breast cancer survivors reported having a small problem in two or more areas of sexual functioning.[94] Whilst findings consistently show that AYA patients experience sexual problems and need support with sexual issues, one study found that 76% of AYA rated their relationship quality as high,[96] suggesting that AYA can cope with these struggles if sufficient information and support is provided.

Financial consequences

Cancer can interfere with educational and occupational goals both during treatment and for years afterwards. Diagnosis and treatment can have substantial effects on the AYA's ability to return to school or participate in the labour force.[1,97] As a result, cancer during adolescence and young adulthood can have a significant influence on the survivor's career development and potential earnings.[98] This is exemplified by the fact that cancer survivorship is associated with lost productivity due to fewer hours worked and more missed work days.[98-101] For example, in the United States, the annual excess economic burden of cancer survivorship was \$5,320 per AYA survivor;[98] 41.5% of this total was due to lost productivity, which was substantially higher than that observed in older cancer survivors.[98]

Financial worries and instability may also result in AYA avoiding routine medical care. Research has shown that AYA cancer survivors face higher out-of-pocket expenditures than their peers without cancer, with significantly higher costs noted for ambulatory care and prescriptions.[98] Similarly, AYA survivors may avoid care because it would require missing work and lower their income, making it then difficult to pay household bills. Indeed, in a study of AYA cancer survivors receiving financial assistance grants, 92% of the financial support provided was to support non-medical costs, of which rent/mortgage accounted for 62%.[102] Such findings suggest that AYA need additional support in order to maintain an appropriate income while receiving recommended care, particularly in settings without universal healthcare.[98]

Intervention studies aimed at prevention, earlier diagnosis or otherwise reducing the impact of late physical effects in AYA cancer survivors

We undertook a systematic review of the literature to identify interventions aimed at preventing, diagnosing or mitigating the impact of late effects in survivors of AYA cancer (see Appendix A for search strategy and study selection). We attempted to exclude studies which related exclusively to survivors of childhood cancer. Two previous systematic reviews of the literature have been completed addressing these issues.[103,104] In the first, Pugh et al identified 12 studies, nine of which were randomised clinical trials. They report that six of the 12 changed health behavior (see Table 2 for details). Physical activity, smoking, alcohol and diet were targeted by eight, five, four and three of the studies, respectively. In the second review, Kopp et al identified six studies, four of which were randomised clinical trials. Physical activity was targeted by all studies, while one also targeted smoking and alcohol, and another also targeted diet. Most survivors included in the studies comprising each systematic review had experienced a haematological neoplasm or a brain tumour, which are relatively uncommon among AYA survivors. With some notable exceptions, sample sizes were generally small with the inevitable consequences for statistical power. The duration of follow-up of many studies was limited.

We identified 11 primary studies, which did not appear in either systematic review, of which seven have been completed and four are on-going (Table 2). Nine of these targeted physical activity, one targeted sun protection and the remaining study targeted smoking. Again, sample sizes were relatively small except for two studies with at least 100 participants.[105,106] Gill et al concluded that a week-long outdoor adventure therapy camp increased physical activity levels during camp and for 3 months after camp termination. Emmons et al concluded that print and web format interventions yielded equivalent levels of success in smoking cessation; these were comparable to those found in a previous telephone-delivered intervention.

Given the potential role of lifestyle factors in the excess risk of strokes[40] and SPNs[27] reported among survivors of AYA cancer, further clarification is needed of the extent to which lifestyle factors are involved in the development of these outcomes and which interventions could target lifestyle factors with strongest effect.

Provision of care to survivors of AYA cancer

There is no single provider type or location of “risk-based” care that is ideal for all survivors of AYA cancer. Similar to models of care in place for young adult survivors of childhood cancers, several care models have been proposed for AYA cancer survivors,[107] including dedicated care at a specialized survivor clinic (in a cancer center) or shared care between a survivor clinic and a primary care physician, such as a family doctor or general internist.[108,109]

Unfortunately, there has been less focus on building specialized survivor clinics for AYA cancer survivors than there has been for childhood cancer survivors. Initiatives have been launched in several countries to develop systems for providing specialized care to AYA cancer survivors.

Canteen in Australia (<https://www.canteen.org.au/wp-content/uploads/2016/09/Adolescent-and-Young-Adult-Cancer-Survivorship-Report.pdf>) and the Teenage Cancer Trust

(<https://www.teenagecancertrust.org/sites/default/files/Blueprint-of-Care.pdf>) in the United

Kingdom are two examples, although neither caters to those in their late 20’s or 30’s. In

addition, numerous institutions around the world have developed specialized AYA survivor

clinics. However, most survivors of AYA cancers do not have access to such specialized

services. Some obtain their long-term follow-up in a general cancer clinic, often from the same

oncology team that provided their initial cancer therapy. Many survivors report feeling most

comfortable remaining with their treating oncologist given that physician’s familiarity with their

cancer treatment history.[110] However, these clinics often focus primarily on relapse detection rather than surveillance for late effects. After a certain period, survivors are frequently discharged back to their primary care physicians, who must then assume responsibility for long-term follow-up. This may be problematic given the professed discomfort and limited knowledge of many primary care physicians surrounding evidence-based follow-up care for young cancer survivors.[8,9] Finally, some survivors have no regular source of follow-up care at all. Thus, for many survivors of AYA cancer, long-term follow-up remains sub-optimal, and the extant literature does not clarify how best to care for this growing population in order to minimize chronic health conditions and maximize quality of life. Importantly, it has not been established that attendance at a specialized survivor clinic provides superior surveillance or long-term health outcomes compared to care in the general oncology system or from a knowledgeable family doctor.

Regardless of where an AYA cancer survivor receives their follow-up care, it is critical that their care focus on the specific risks arising from their prior cancer, and that survivors receive appropriate surveillance for late effects along with counselling around healthy lifestyle. To that end, the US Institute of Medicine has recognized the need for the development of evidence-based clinical practice guidelines for the care of survivors of childhood and adult cancers.[111,112]

Although numerous guidelines have been created, only a limited number (e.g. National Comprehensive Cancer Network [NCCN]) have been created specifically for survivors of AYA cancer. However, many of the guidelines written for survivors of childhood cancer include younger AYA survivors (e.g. diagnosed before age 21 or 25 years). These are listed in Table 3. An important tool for ensuring that survivors are aware of their specific risks and required

surveillance is the survivorship care plan (SCP) that contains a cancer history, a summary of their therapy, and a plan for surveillance for late effects. In fact, the American College of Surgeons Commission on Cancer has made provision of an SCP to at least 50% of eligible patients a requirement for designation as a cancer program.[113] Some controversy exists as to the effectiveness of an SCP[114] – a systematic review of 13 randomized and 11 non-randomized studies that assessed the impact of SCPs on health outcomes and health care delivery in adult cancer survivors generally showed no impact on physical, functional or psychological well-being, although individual studies showed positive effects on receipt of information, satisfaction with care and implementation of survivor care recommendations by physicians. Despite this, there remains a general consensus that all survivors should receive an SCP.

Future directions in AYA survivor research

Survival of AYA cancers continues to improve, and consequently the population of survivors of AYA cancers will continue to grow. As survivors age, the long-term consequences of their cancer therapies will combine with the normal aging process, and potentially accelerate the normal aging process, creating new challenges for survivors and their providers. Studies such as the Bone Marrow Transplant Survivor Study (BMTSS) and the St Jude Lifetime Cohort Study are examining outcomes such as premature frailty in cohorts that include survivors of AYA cancer. There are many gaps in our knowledge about long-term outcomes in this vulnerable population. Some opportunities for future research are suggested in Table 4. Since much of the “knowledge” about survivors of AYA cancers has been based on extrapolation of evidence from childhood cancer survivor cohorts, there is a need for the creation of survivor cohorts that span the full age range of AYA, and do not just focus on adolescents and younger adults. There was a recent systematic research prioritisation initiative undertaken in the UK involving AYA

survivors, their families, friends, parents, carers and healthcare professionals, which identified ten priorities for AYA research.[115] Priorities relevant to survivor care included studying psychological supports that can improve psychological well-being, social functioning and mental health; interventions to reduce late effects; interventions to support young people returning to work; and determining the optimal method and timing of follow-up in order to minimize psychological harm while ensuring early detection of late effects. Beyond research, there is a critical need for continued advocacy for AYA with cancer, not just during their therapy but in the years after their cure. Quality of survival must receive the same attention as quantity of survival.

Conflict of Interest Statement: The authors have no conflicts to declare.

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Table 1: International survivor cohorts that include survivors of AYA cancer

Cohort Name or Registry	Geographical location	Age at diagnosis (years)	Study Design	Calendar years of diagnosis	No. of Survivors Overall; No. of AYA^a	Survival interval at entry
Teenage and Young Adult Cancer Survivor Study (TYACSS)	England & Wales, United Kingdom	15-39	Population-based	1971-2006	200,945 AYA [14,15,27,40]	5-year survivors
Yorkshire Specialist Register of Cancer in Children and Young People (YSRCCYP)	Yorkshire and Humber region, England, United Kingdom	0-29	Population-based	1990-2012	5,902; 3,644 AYA 4,580; 2,857 AYA	No survivorship restriction 5-year survivors
Finnish Cancer Registry	Finland	0-34	Population-based	1971-2012	13,960; 10,770 AYA [37]	5-year survivors
Danish Cancer Registry	Denmark	15-39	Population-based	1943-2009 1943-2004	43,153 AYA [38] 33,555 AYA [39]	1-year survivors 5-year survivors
Scottish Cancer Registry	Scotland	0-24	Population-based	1981-2003	5,229; 3,053 AYA [11]	5-year survivors
Swiss Childhood Cancer Survivor Study (SCCSS)	Switzerland	0-20	Population-based	1976-2010	7,600; AYA [116]	5-year survivors
Adult Life after Childhood Cancer in Scandinavia (ALiCCS)	Denmark, Finland, Iceland, Norway, Sweden	0-19	Population-based	1943-2008	33,160; AYA [116]	1-year survivors
Dutch Childhood Oncology Group LATER (DCOG LATER)	The Netherlands	0-17	Nationwide hospital-based	1963-2002	6,165; 401 AYA [117]	5-year survivors
Initiative to Maximize Progress in Adolescent and Young Adult Cancer Therapy (IMPACT)	Ontario, Canada	15-21	Population-based	1992-2012	2,931 AYA	No survivorship time restriction, selected diagnoses ^b
Childhood, Adolescent, and Young Adult Cancer Survivors Research Program (CAYACS)	British Columbia, Canada	20-24	Population-based	1970-2010	4,776 AYA	No survivorship time restriction
Surveillance, Epidemiology, and End Results (SEER)	Connecticut, Detroit, Atlanta, San Francisco-Oakland, Hawaii, Iowa, New	15-39	Population-based	1973-2011	148,558 AYA [28]	5-year survivors

	Mexico, Seattle-Puget Sound, Utah					
Childhood Cancer Survivor Study (CCSS)	United States	0-20	Hospital-based	1970-1999	35,937; 5,600 AYA [116,118]	5-year survivors, selected diagnoses ^c
St. Jude Lifetime Cohort Study (SJLIFE)	St. Jude Children's Hospital, Tennessee, United States	0-24	Hospital-based	1962-2009	5,122; 793 AYA	5-year survivors

^aDiagnosed between 15-39 years age

^bAcute leukemia (acute lymphoblastic, acute myeloid), Hodgkin lymphoma, non-Hodgkin lymphoma, soft tissue sarcomas, bone sarcomas, and testicular cancer diagnoses

^cLeukemia, CNS tumors, Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumor, neuroblastoma, soft tissue sarcoma, and bone tumor diagnoses

Table 2: Previous intervention studies aimed at prevention, earlier diagnosis or otherwise reducing impact of physical late effects.

A. Previous systematic reviews:			
1. "Health behavior change interventions for teenage and young adult cancer survivors: A systematic review" Pugh et al (2016)[103] – contributing primary studies:			
Authors	Study Design	Participants	Target Behavior
Huang et al, 2014 ^{119*}	RCT	N=38, aged 8-18 years	Physical activity and diet
Bélangier et al, 2014 ^{120*}	RCT	N=212, aged 18-39 years	Physical activity
Berg et al, 2014 ^{121*}	One-arm feasibility	N=24, aged 18-34 years	Physical activity, smoking and alcohol
Valle et al, 2013 ^{122*}	RCT	N=86, aged 21-39 years	Physical activity
Li et al, 2013 ^{123*}	RCT	N=71, aged 9-16 years	Physical activity
Hollen et al, 2013 ^{124*}	RCT	N=243, aged 14-19 years	Smoking and alcohol
Järvelä et al, 2012 ^{125*}	One-arm feasibility	N=17, aged 16-30 years	Physical activity
Mays et al, 2011 ^{126*}	RCT	N=75, aged 11-21 years	Diet
Keats et al, 2008 ^{127*}	Repeated measures longitudinal	N=10, aged 14-18 years	Physical activity
Cox et al, 2005 ^{128*} & Hudson et al, 2002 ^{129*}	RCT	N=266, aged 12-18 years	Physical activity, diet, smoking and alcohol
Tyc et al, 2003 ^{130*}	RCT	N=103, aged 10-18 years	Smoking
Hollen et al, 1999 ^{131*}	RCT	N=64, aged 13-21 years	Smoking and alcohol
2. "Lifestyle behavior interventions delivered using technology in childhood, adolescent and young adult cancer survivors: A systematic review" Kopp et al (2017)[104] – contributing primary studies:			
Authors	Study Design	Participants	Target Behavior
Sabel et al, 2016 ^{132*}	RCT	N=13, aged 7-17 years	Physical activity
Berg et al, 2014 ^{121*}	One-arm feasibility	N=24, aged 18-34 years	Physical activity, smoking and alcohol
Huang et al, 2014 ^{119*}	RCT	N=38, aged 8-18 years	Physical activity and diet
Valle et al, 2013 ^{122*}	RCT	N=86, aged 21-39 years	Physical activity
Rabin et al, 2012 ^{133*}	RCT	N=18, aged 18-39 years	Physical activity
Gilliam et al, 2011 ^{134*}	Repeated measures longitudinal	N=20, aged 6-18 years	Physical activity
B. Primary research studies not appearing in the systematic reviews above			
Authors	Study Design	Participants	Target Behavior
Valle et al, 2017 ^{135*}	RCT	N=86, aged 21-39 years	Physical activity
Recklitis et al, 2017 ^{136*}	Feasibility	N=23, aged 15-39 years	Sun protection
Gill et al, 2016[105]	Non-randomised 2-group comparison	N=116, aged 18-39 years	Physical activity
Rabin et al, 2016 ^{137*}	RCT	N=35, aged 18-39 years	Physical activity and meditation
Valle et al, 2015 ^{138*}	RCT	N=86, aged 21-39 years	Physical activity
Emmons et al, 2013[106]	RCT	N=374, mean age 32 years	Smoking cessation
Schwartz et al, 2016 ^{139*}	RCT	N=62, mean age 17 years	Physical activity, smoking, sun protection and diet
Brunet ^{140*}	RCT	N=30, aged 15-44 years. Ongoing	Physical activity
Valle et al ^{141*}	RCT	N=64, aged 18-39 years. Ongoing	Physical activity
Devine et al ^{142*}	RCT	N=59, aged 13-25 years.	Physical activity

Salchow et al ^{143*}	RCT	Ongoing N=55, median age 23.9 years. Ongoing.	Physical activity
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* These references are in Appendix B

Table 3: Survivor guidelines applicable to AYA cancer survivors

Publisher	Age range at cancer diagnosis	Web link
International Guidelines Harmonization Group (IGHG)	Childhood, adolescence and young adulthood	www.ighg.org
Children's Oncology Group (COG)	Childhood, adolescence and young adulthood	http://survivorshipguidelines.org/
Scottish Intercollegiate Guidelines Network (SIGN)	<24 years	http://www.sign.ac.uk/assets/sign132.pdf
Children's Cancer and Leukaemia Group (CCLG)	Childhood	https://www.cclg.org.uk/write/MediaUploads/Member%20area/Treatment%20guidelines/LTFU-full.pdf
National Comprehensive Cancer Network (NCCN)	15-39 years	https://www.nccn.org/professionals/physician_gls/pdf/aya.pdf
Dutch Childhood Oncology Group (DCOG-LATER)	Pediatric	https://www.skion.nl/workspace/uploads/vertaling-richtlijn-LATER-versie-final-okt-2014_2.pdf
The Society for Paediatric Oncology and Haematology (GPOH; German)	Childhood, adolescence and young adulthood	https://www.awmf.org/leitlinien/detail/ll/025-003.html
Swedish Working Group for Long-term Follow-up after Childhood Cancer (SALUB)	Childhood	http://www.blf.net/onko/page6/page14/files/Salub_5_2010_Eng.pdf

Table 4: Gaps in research in AYA cancer survivors

Creation of cohorts that include the complete range of AYA ages (15-39 years)
Creation of cohorts that capture the full spectrum of cancers most common in AYA
Characterization and comparison of morbidity and mortality across the AYA age spectrum
Factors affecting AYA' decisions to undergo fertility preservation
Factors affecting transition of care after treatment
Factors affecting, and health outcomes related to, locus and provider of survivor care
The impact of survivor care plans on outcomes
Interventions to improve adherence to recommended surveillance for late effects
Study of barriers to completing school/obtaining employment after therapy
Health promotion intervention studies (e.g. diet, physical activity, smoking cessation)
Characterization of the psychosocial support needed by survivors
Characterization of the rehabilitation services needed by survivors
Characterization of financial toxicity and its risk factors
Factors affecting research investment in AYA

Appendix A

We performed a systematic search of the literature databases Medline/PubMed (1946–2018), Embase (1974–2018) and Ovid MEDLINE In-Process & Other Non-Indexed Citations (to November 05, 2018). Search terms for adolescent and young adult cancer survivors and interventions were combined in our search in these databases as detailed below.

The search terms and strategy used were:

A. Adolescent and young adult cancer:

1. *adolescent and young adult cancer survivor\$ (370)*
2. *AYA cancer survivor\$ (251)*
3. *survivor\$ of adolescent and young adult cancer (50)*
4. *survivor\$ of AYA cancer (30)*
5. *teenage and young adult cancer survivor\$ 24*
6. *TYA cancer survivor\$ (10)*
7. *survivor\$ of teenage and young adult cancer (9)*
8. *survivor\$ of TYA cancer (0)*
9. *young cancer survivor\$ (293)*

10. *1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 or 10 (838)*

B. Intervention, prevention, screening, early diagnosis, RCT, randomised control trial and clinical trial:

11. *prevent\$ (4666295)*
12. *early diagnosis (239994)*
13. *screen\$ (1880417)*
14. *intervention (1299072)*
15. *rct (49184)*
16. *randomi\$ controlled trial (1184603)*
17. *clinical trial (2104859)*

18. *11 OR 12 OR 13 OR 14 OR 15 OR 16 or 17 (9267603)*

C. Combined search adolescent and young adult cancer and subsequent cancers:

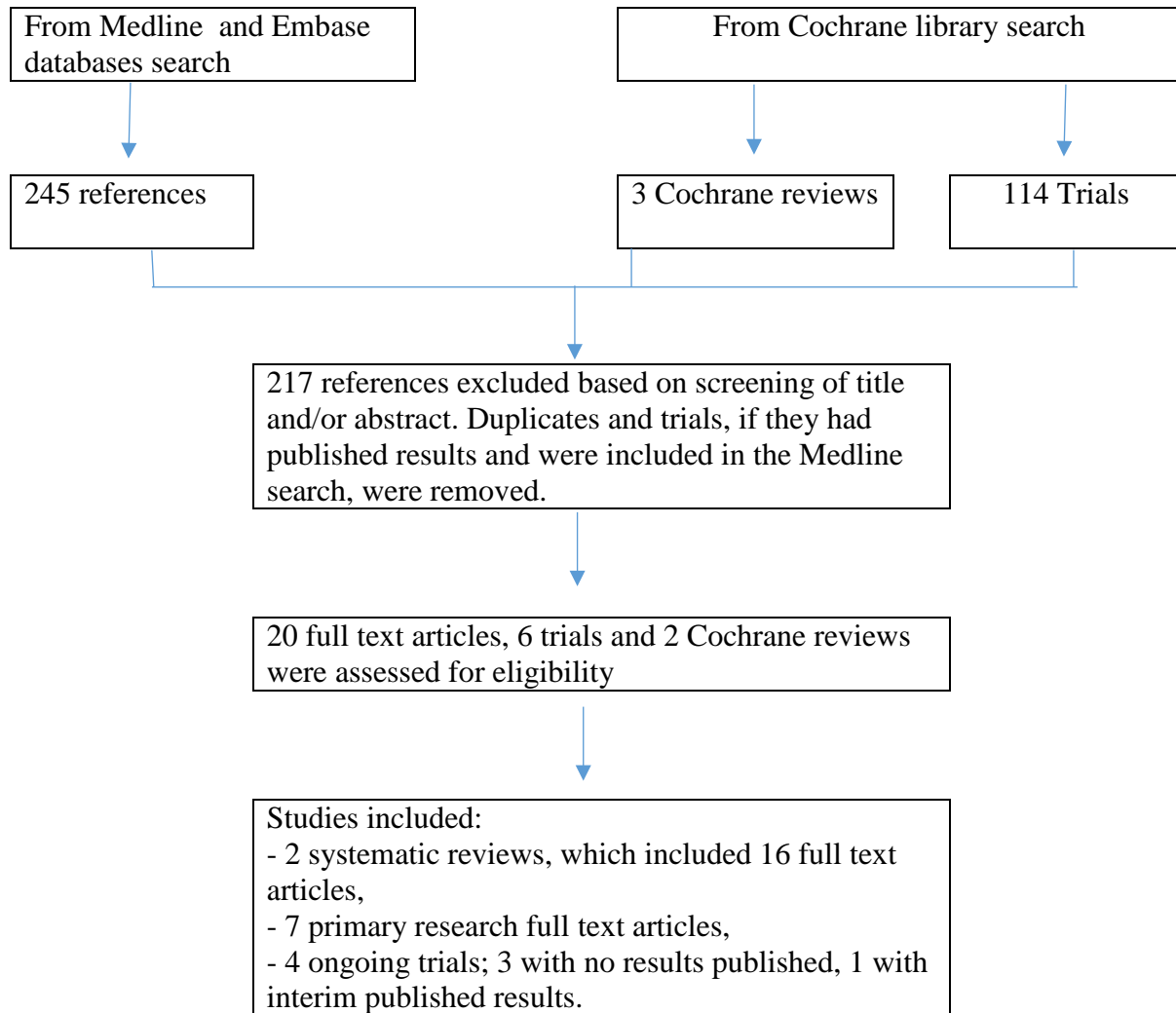
19. *10 AND 18 (245)*

The searches were performed as above on 06/11/18. The result was 245 references.

We also conducted a search within the Cochrane review library using the terms “adolescent and young adult cancer survivor\$” and “teenage and young adult cancer survivor\$”. The result was 3 Cochrane reviews and 114 trials.

From these resulting references, title and abstract were read for any interventions in AYA cancer survivors relating to physical effects, principally second cancers, cardiac, respiratory and fertility

outcomes. Irrelevant references were excluded for the following reasons: they were reporting solely the occurrence of late effects; the intervention was for psychological outcomes; they were not an intervention; they related exclusively to health care use and/or type of follow-up care. After excluding these studies, further exclusions were made if the participants were not AYA i.e. not in the age range of 15-39 years. Finally, duplicates were removed. Please see the flow chart below for further details on this process.



Appendix B

References from the review of the literature to identify interventions aimed at preventing, diagnosing or mitigating the impact of late effects in survivors of AYA cancer.

References:

119. Huang JS, Dillon L, Terrones L, et al. Fit4Life: a weight loss intervention for children who have survived childhood leukemia. *Pediatr Blood Cancer* 2014;61(5):894-900.
120. Bélanger LJ, Mummery WK, Clark AM, et al. Effects of targeted print materials on physical activity and quality of life in young adult cancer survivors during and after treatment: an exploratory randomized controlled trial. *J Adolesc Young Adult Oncol* 2014;3(2):83-91.
121. Berg CJ, Stratton E, Giblin J, et al. Pilot results of an online intervention targeting health promoting behaviors among young adult cancer survivors. *Psychooncology* 2014;23(10):1196-1199.
122. Valle CG, Tate DF, Mayer DK, et al. A randomized trial of a Facebook-based physical activity intervention for young adult cancer survivors. *J Cancer Surviv* 2013;7(3):355-368.
123. Li HW, Chung OKJ, Ho KY, et al. Effectiveness of an integrated adventure based training and health education program in promoting regular physical activity among childhood cancer survivors. *Psychooncology* 2013;22(11):2601-2610.
124. Hollen PJ, Tyc VL, Donnangelo MSF, et al. A substance use decision aid for medically-at-risk adolescents: results of a randomized controlled trial for cancer-surviving adolescents. *Cancer Nursing* 2013;36(5):355-367.
125. Järvelä LS, Kemppainen J, Niinikoski H, et al. Effects of a home-based exercise program on metabolic risk factors and fitness in long-term survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer* 2012;59(1):155-160.
126. Mays D, Black JD, Mosher RB, et al. Efficacy of the Survivor Health and Resilience Education (SHARE) program to improve bone health behaviors among adolescent survivors of childhood cancer. *Ann Behav Med* 2011;42(1):91-98.
127. Keats MR, Culos-Reed SN. A community-based physical activity program for adolescents with cancer (Project TREK): program feasibility and preliminary findings. *J Pediatr Hematol Oncol* 2008;30(4):272-280.
128. Cox CL, McLaughlin RA, Rai SN, et al. Adolescent survivors: A secondary analysis of a clinical trial targeting behaviour change. *Pediatr Blood Cancer* 2005;45(2):144-154.
129. Hudson MM, Tyc VL, Srivastava DK, et al. Multi-component behavioural intervention to promote health protective behaviours in childhood cancer survivors: The Protect Study. *Med Pediatr Oncol* 2002;39(1):2-11.

130. Tyc VL, Rai SN, Lensing S, et al. Intervention to reduce intentions to use tobacco among pediatric cancer survivors. *J Clin Oncol* 2003;21(7):1366-1372.
131. Hollen PJ, Hobbie WL, Finley SM. Testing the effects of a decision-making and risk-reduction program for cancer-surviving adolescents. *Oncol Nurs Forum* 1999;26(9):1475-1486.
132. Sabel M, Sjölund A, Broeren J, et al. Active video gaming improves body coordination in survivors of childhood brain tumours. *Disabil Rehabil* 2016;38(21):2073-2084.
133. Rabin C, Dunsiger S, Ness KK, et al. Internet-based physical activity intervention targeting young adult cancer survivors. *J Adolesc Young Adult Oncol* 2012;1(4):188-194.
134. Gilliam MB, Ross K, Futch L, et al. A pilot study evaluation of a web-based token economy to increase adherence with a community-based exercise intervention in child and adolescent cancer survivors. *Rehabil Oncol* 2011;29(2):16-22.
135. Valle CG, Tate DF. Engagement of young adult cancer survivors within a Facebook-based physical activity intervention. *Transl Behav Med* 2017;7(4):667-679.
136. Recklitis CJ, Bakan J, Werchaniak AE, et al. Using appearance-based messages to increase sun protection in adolescent young adult cancer survivors: A pilot study of ultraviolet light photography. *J Adolesc Young Adult Oncol* 2017;6(3):477-481.
137. Rabin C, Pinto B, Fava J. Randomized trial of a physical activity and meditation intervention for young adult cancer survivors. *J Adolesc Young Adult Oncol* 2016;5(1):41-47.
138. Valle CG, Tate DF, Mayer DK, et al. Exploring mediators of physical activity in young adult cancer survivors: evidence from a randomized trial of a Facebook-based physical activity intervention. *J Adolesc Young Adult Oncol* 2015;4(1):26-33.
139. Schwartz LA, Daniel LC, Butler E, et al. A pilot text messaging intervention for adolescents and young adults recently off treatment for cancer. *J Adolesc Health* 2016;58(2):S30.
140. Brunet J. Physical activity for adolescent and young adult cancer survivors. <https://clinicaltrials.gov/ct2/show/NCT03016728>. 2018.
141. Valle CG, Salsman JM. mHealth. Physical activity intervention for survivors of adolescent and young adult cancers (THRIVE). <https://clinicaltrials.gov/ct2/show/NCT03386383>. 2018.
142. Devine K. Mobile health fitness program for adolescent and young adult childhood cancer survivors (TLC FIT) <https://clinicaltrials.gov/ct2/show/NCT02688192>. 2018.
143. Salchow J, Jensen W, Koch B, et al. Effects of a structured intervention program to improve physical activity of adolescents and young adult cancer survivors (AYA) – Interim analysis of a randomized controlled trial – Motivate AYA – MAYA trial. *Oncol Res Treat* 2017;40(suppl 3):215;V730. DOI: 10.1159/000479566

References

1. Services USDoHaH. Closing the Gap: Research and Care Imperatives for Adolescents and Young Adults with Cancer – Report of the Adolescent and Young Adult Oncology Progress Review Group. 2006.
2. Fidler MM, Gupta S, Soerjomataram I, et al. Cancer incidence and mortality among young adults aged 20-39 years worldwide in 2012: a population-based study. *The Lancet Oncology* 2017;18(12):1579-1589.
3. Bleyer A, Barr R. Cancer in young adults: 20 to 39 years of age: Overview. *Semin Oncol* 2009;36(3):194-206.
4. Bleyer WA, O'Leary M, Barr R, et al. Cancer epidemiology in older adolescents and young adults 15 to 29 years of age, including SEER incidence and survival, 1975-2000. Bethesda, MD: National Cancer Institute; 2006.
5. Ellison LF, Pogany L, Mery LS. Childhood and adolescent cancer survival: A period analysis of data from the Canadian Cancer Registry. *Eur J Cancer* 2007;43:1967-1975.
6. Smith MA, Seibel NL, Altekruse SF, et al. Outcomes for children and adolescents with cancer: Challenges for the twenty-first century. *J Clin Oncol* 2010;28:2625-2634.
7. Bleyer A, Budd T, Montello M. Adolescents and young adults with cancer: the scope of the problem and criticality of clinical trials. *Cancer* 2006;107(7 Suppl):1645-1655.
8. Nathan PC, Daugherty CK, Wroblewski KE, et al. Family physician preferences and knowledge gaps regarding the care of adolescent and young adult survivors of childhood cancer. *Journal of cancer survivorship : research and practice* 2013.
9. Suh E, Daugherty CK, Wroblewski K, et al. General internists' preferences and knowledge about the care of adult survivors of childhood cancer: a cross-sectional survey. *Ann Intern Med* 2014;160(1):11-17.
10. Bleyer A, O'Leary M, Barr R, et al. Cancer Epidemiology in Older Adolescents and Young Adults 15 to 29 Years of Age, Including SEER Incidence and Survival: 1975-2000. National Cancer Institute, NIH Pub. No. 06-5767. Bethesda, MD 2006.
11. Brewster DH, Clark D, Hopkins L, et al. Subsequent mortality experience in five-year survivors of childhood, adolescent and young adult cancer in Scotland: a population based, retrospective cohort study. *European journal of cancer* 2013;49(15):3274-3283.
12. Kero AE, Jarvela LS, Arola M, et al. Late mortality among 5-year survivors of early onset cancer: a population-based register study. *International journal of cancer* 2015;136(7):1655-1664.

13. Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *Journal of the National Cancer Institute* 2008;100(19):1368-1379.
14. Fidler MM, Reulen RC, Bright CJ, et al. Respiratory mortality of childhood, adolescent and young adult cancer survivors. *Thorax* 2018;73(10):959-968.
15. Henson KE, Reulen RC, Winter DL, et al. Cardiac Mortality Among 200 000 Five-Year Survivors of Cancer Diagnosed at 15 to 39 Years of Age: The Teenage and Young Adult Cancer Survivor Study. *Circulation* 2016;134(20):1519-1531.
16. Fidler MM, Reulen RC, Henson K, et al. Population-Based Long-Term Cardiac-Specific Mortality Among 34 489 Five-Year Survivors of Childhood Cancer in Great Britain. *Circulation* 2017;135(10):951-963.
17. Travis LB, Fossa SD, Schonfeld SJ, et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. *Journal of the National Cancer Institute* 2005;97(18):1354-1365.
18. Richiardi L, Scelo G, Boffetta P, et al. Second malignancies among survivors of germ-cell testicular cancer: a pooled analysis between 13 cancer registries. *International journal of cancer* 2007;120(3):623-631.
19. Brown LM, Chen BE, Pfeiffer RM, et al. Risk of second non-hematological malignancies among 376,825 breast cancer survivors. *Breast cancer research and treatment* 2007;106(3):439-451.
20. Schonfeld SJ, Curtis RE, Anderson WF, et al. The risk of a second primary lung cancer after a first invasive breast cancer according to estrogen receptor status. *Cancer causes & control : CCC* 2012;23(10):1721-1728.
21. Schonfeld SJ, Berrington de Gonzalez A, Visvanathan K, et al. Declining second primary ovarian cancer after first primary breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013;31(6):738-743.
22. Mellemkjaer L, Friis S, Olsen JH, et al. Risk of second cancer among women with breast cancer. *International journal of cancer* 2006;118(9):2285-2292.
23. Schaapveld M, Visser O, Louwman MJ, et al. Risk of new primary nonbreast cancers after breast cancer treatment: a Dutch population-based study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2008;26(8):1239-1246.
24. Ibrahim EM, Abouelkhair KM, Kazkaz GA, et al. Risk of second breast cancer in female Hodgkin's lymphoma survivors: a meta-analysis. *BMC cancer* 2012;12:197.
25. Swerdlow AJ, Cooke R, Bates A, et al. Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: a National Cohort Study.

Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2012;30(22):2745-2752.

26. Schaapveld M, Aleman BM, van Eggermond AM, et al. Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma. *The New England journal of medicine* 2015;373(26):2499-2511.
27. Bright CR, R; Winter, D; Stark, D; McCabe, M; Edgar, A; Frobisher, C; Hawkins, M. Long-term risks of subsequent primary neoplasms among 200,945 five-year survivors of adolescent and young adult cancer: The Teenage and Young Adult Cancer Survivor Study (TYACSS). *Lancet Oncology* 2018:In press.
28. Lee JS, DuBois SG, Coccia PF, et al. Increased risk of second malignant neoplasms in adolescents and young adults with cancer. *Cancer* 2016;122(1):116-123.
29. Reulen RC, Frobisher C, Winter DL, et al. Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. *Jama* 2011;305(22):2311-2319.
30. Olsen JH, Moller T, Anderson H, et al. Lifelong cancer incidence in 47,697 patients treated for childhood cancer in the Nordic countries. *Journal of the National Cancer Institute* 2009;101(11):806-813.
31. Neglia JP, Friedman DL, Yasui Y, et al. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. *Journal of the National Cancer Institute* 2001;93(8):618-629.
32. Magnani C, Terracini B, Cordero Di Montezemolo L, et al. Incidence of second primary malignancies after a malignant tumor in childhood: a population-based survey in Piedmont (Italy). *International journal of cancer* 1996;67(1):6-10.
33. Cardous-Ubbink MC, Heinen RC, Bakker PJ, et al. Risk of second malignancies in long-term survivors of childhood cancer. *European journal of cancer* 2007;43(2):351-362.
34. Inskip PD, Curtis RE. New malignancies following childhood cancer in the United States, 1973-2002. *International journal of cancer* 2007;121(10):2233-2240.
35. Friedman DL, Whitton J, Leisenring W, et al. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *Journal of the National Cancer Institute* 2010;102(14):1083-1095.
36. Wilson CL, Cohn RJ, Johnston KA, et al. Late mortality and second cancers in an Australian cohort of childhood cancer survivors. *The Medical journal of Australia* 2010;193(5):258-261.
37. Kero AE, Jarvela LS, Arola M, et al. Cardiovascular morbidity in long-term survivors of early-onset cancer: a population-based study. *International journal of cancer* 2014;134(3):664-673.

38. Rugbjerg K, Mellemkjaer L, Boice JD, et al. Cardiovascular disease in survivors of adolescent and young adult cancer: a Danish cohort study, 1943-2009. *Journal of the National Cancer Institute* 2014;106(6):dju110.
39. Rugbjerg K, Olsen JH. Long-term Risk of Hospitalization for Somatic Diseases in Survivors of Adolescent or Young Adult Cancer. *JAMA oncology* 2016;2(2):193-200.
40. Bright CJ, Hawkins MM, Guha J, et al. Risk of Cerebrovascular Events in 178 962 Five-Year Survivors of Cancer Diagnosed at 15 to 39 Years of Age: The TYACSS (Teenage and Young Adult Cancer Survivor Study). *Circulation* 2017;135(13):1194-1210.
41. Jensen MR, K; de Fine Licht, S; Johansen, C; Schmiegelow, K; Andersen, KK; Winther, JF. Endocrine Late Effects in Survivors of Cancer in Adolescence and Young Adulthood. *JAMA Network Open* 2018;1:e180349.
42. van Laar M, Feltbower RG, Gale CP, et al. Cardiovascular sequelae in long-term survivors of young peoples' cancer: a linked cohort study. *British journal of cancer* 2014;110(5):1338-1341.
43. de Fine Licht S, Rugbjerg K, Gudmundsdottir T, et al. Long-term inpatient disease burden in the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study: A cohort study of 21,297 childhood cancer survivors. *PLoS medicine* 2017;14(5):e1002296.
44. Kero AE, Madanat-Harjuoja LM, Jarvela LS, et al. Cardiovascular medication after cancer at a young age in Finland: A nationwide registry linkage study. *International journal of cancer* 2016;139(3):683-690.
45. de Fine Licht S, Winther JF, Gudmundsdottir T, et al. Hospital contacts for endocrine disorders in Adult Life after Childhood Cancer in Scandinavia (ALiCCS): a population-based cohort study. *Lancet* 2014;383(9933):1981-1989.
46. Bhakta N, Liu Q, Ness KK, et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). *Lancet* 2017;390(10112):2569-2582.
47. Kazak AE, Derosa BW, Schwartz LA, et al. Psychological outcomes and health beliefs in adolescent and young adult survivors of childhood cancer and controls. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2010;28(12):2002-2007.
48. Tai E, Buchanan N, Townsend J, et al. Health status of adolescent and young adult cancer survivors. *Cancer* 2012;118(19):4884-4891.
49. Prasad PK, Hardy KK, Zhang N, et al. Psychosocial and Neurocognitive Outcomes in Adult Survivors of Adolescent and Early Young Adult Cancer: A Report From the Childhood Cancer Survivor Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2015;33(23):2545-2552.

50. Zebrack B, Kent EE, Keegan TH, et al. "Cancer sucks," and other ponderings by adolescent and young adult cancer survivors. *Journal of psychosocial oncology* 2014;32(1):1-15.
51. Quinn GP, Goncalves V, Sehovic I, et al. Quality of life in adolescent and young adult cancer patients: a systematic review of the literature. *Patient related outcome measures* 2015;6:19-51.
52. Husson O, Prins JB, Kaal SE, et al. Adolescent and young adult (AYA) lymphoma survivors report lower health-related quality of life compared to a normative population: results from the PROFILES registry. *Acta oncologica* 2017;56(2):288-294.
53. Smith AW, Bellizzi KM, Keegan TH, et al. Health-related quality of life of adolescent and young adult patients with cancer in the United States: the Adolescent and Young Adult Health Outcomes and Patient Experience study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013;31(17):2136-2145.
54. Husson O, Zebrack BJ, Aguilar C, et al. Cancer in adolescents and young adults: Who remains at risk of poor social functioning over time? *Cancer* 2017;123(14):2743-2751.
55. Daniel L, Kazak AE, Li Y, et al. Relationship between sleep problems and psychological outcomes in adolescent and young adult cancer survivors and controls. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2016;24(2):539-546.
56. Zebrack B, Isaacson S. Psychosocial care of adolescent and young adult patients with cancer and survivors. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2012;30(11):1221-1226.
57. Zebrack BJ. Psychological, social, and behavioral issues for young adults with cancer. *Cancer* 2011;117(10 Suppl):2289-2294.
58. Bellizzi KM, Smith A, Schmidt S, et al. Positive and negative psychosocial impact of being diagnosed with cancer as an adolescent or young adult. *Cancer* 2012;118(20):5155-5162.
59. Ziner KW, Sledge GW, Bell CJ, et al. Predicting fear of breast cancer recurrence and self-efficacy in survivors by age at diagnosis. *Oncology nursing forum* 2012;39(3):287-295.
60. Lebel S, Beattie S, Ares I, et al. Young and worried: Age and fear of recurrence in breast cancer survivors. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association* 2013;32(6):695-705.
61. Champion VL, Wagner LI, Monahan PO, et al. Comparison of younger and older breast cancer survivors and age-matched controls on specific and overall quality of life domains. *Cancer* 2014;120(15):2237-2246.

62. Shay LA, Carpentier MY, Vernon SW. Prevalence and correlates of fear of recurrence among adolescent and young adult versus older adult post-treatment cancer survivors. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2016;24(11):4689-4696.
63. Yi JS, K. Overview of cancer survivorship in adolescent and young adults. UpToDate 2018.
64. Beckjord EB, Reynolds KA, van Londen GJ, et al. Population-level trends in posttreatment cancer survivors' concerns and associated receipt of care: results from the 2006 and 2010 LIVESTRONG surveys. *Journal of psychosocial oncology* 2014;32(2):125-151.
65. Huang IC, Brinkman TM, Kenzik K, et al. Association between the prevalence of symptoms and health-related quality of life in adult survivors of childhood cancer: a report from the St Jude Lifetime Cohort study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013;31(33):4242-4251.
66. Recklitis CJ, Diller LR, Li X, et al. Suicide ideation in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2010;28(4):655-661.
67. Brinkman TM, Zhang N, Recklitis CJ, et al. Suicide ideation and associated mortality in adult survivors of childhood cancer. *Cancer* 2014;120(2):271-277.
68. Kinahan KE, Sharp LK, Seidel K, et al. Scarring, disfigurement, and quality of life in long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2012;30(20):2466-2474.
69. Smith SK, Zimmerman S, Williams CS, et al. Post-traumatic stress outcomes in non-Hodgkin's lymphoma survivors. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2008;26(6):934-941.
70. Kwak M, Zebrack BJ, Meeske KA, et al. Prevalence and predictors of post-traumatic stress symptoms in adolescent and young adult cancer survivors: a 1-year follow-up study. *Psycho-oncology* 2013;22(8):1798-1806.
71. Rourke MT, Hobbie WL, Schwartz L, et al. Posttraumatic stress disorder (PTSD) in young adult survivors of childhood cancer. *Pediatric blood & cancer* 2007;49(2):177-182.
72. Gunnes MW, Lie RT, Bjorge T, et al. Suicide and violent deaths in survivors of cancer in childhood, adolescence and young adulthood-A national cohort study. *International journal of cancer* 2017;140(3):575-580.
73. Stuber ML, Meeske KA, Krull KR, et al. Prevalence and predictors of posttraumatic stress disorder in adult survivors of childhood cancer. *Pediatrics* 2010;125(5):e1124-1134.

74. Schwartz L, Drotar D. Posttraumatic stress and related impairment in survivors of childhood cancer in early adulthood compared to healthy peers. *Journal of pediatric psychology* 2006;31(4):356-366.
75. Bradford NK, Chan RJ. Health promotion and psychological interventions for adolescent and young adult cancer survivors: A systematic literature review. *Cancer treatment reviews* 2017;55:57-70.
76. Crawshaw M. Psychosocial oncofertility issues faced by adolescents and young adults over their lifetime: a review of the research. *Human fertility* 2013;16(1):59-63.
77. Rosen A, Rodriguez-Wallberg KA, Rosenzweig L. Psychosocial distress in young cancer survivors. *Seminars in oncology nursing* 2009;25(4):268-277.
78. Schover LR. Motivation for parenthood after cancer: a review. *Journal of the National Cancer Institute Monographs* 2005(34):2-5.
79. Quinn GP, Vadaparampil ST, Bell-Ellison BA, et al. Patient-physician communication barriers regarding fertility preservation among newly diagnosed cancer patients. *Social science & medicine* 2008;66(3):784-789.
80. Eiser C, Arden-Close E, Morris K, et al. The legacy of sperm banking: how fertility monitoring and disposal of sperm are linked with views of cancer treatment. *Human reproduction* 2011;26(10):2791-2798.
81. Wright CI, Coad J, Morgan S, et al. 'Just in case': the fertility information needs of teenagers and young adults with cancer. *European journal of cancer care* 2014;23(2):189-198.
82. Perz J, Ussher J, Gilbert E. Loss, uncertainty, or acceptance: subjective experience of changes to fertility after breast cancer. *European journal of cancer care* 2014;23(4):514-522.
83. Wakefield CE, Butow P, Fleming CA, et al. Family information needs at childhood cancer treatment completion. *Pediatric blood & cancer* 2012;58(4):621-626.
84. McClellan W, Klemp JR, Krebill H, et al. Understanding the functional late effects and informational needs of adult survivors of childhood cancer. *Oncology nursing forum* 2013;40(3):254-262.
85. Zebrack B. Information and service needs for young adult cancer patients. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2008;16(12):1353-1360.
86. Benedict C, Shuk E, Ford JS. Fertility Issues in Adolescent and Young Adult Cancer Survivors. *Journal of adolescent and young adult oncology* 2016;5(1):48-57.

87. Logan S, Perz J, Ussher JM, et al. A systematic review of patient oncofertility support needs in reproductive cancer patients aged 14 to 45 years of age. *Psycho-oncology* 2018;27(2):401-409.
88. Barlevy D, Wangmo T, Elger BS, et al. Attitudes, Beliefs, and Trends Regarding Adolescent Oncofertility Discussions: A Systematic Literature Review. *Journal of adolescent and young adult oncology* 2016;5(2):119-134.
89. Shnorhavorian M, Harlan LC, Smith AW, et al. Fertility preservation knowledge, counseling, and actions among adolescent and young adult patients with cancer: A population-based study. *Cancer* 2015;121(19):3499-3506.
90. Skinner R, Mulder RL, Kremer LC, et al. Recommendations for gonadotoxicity surveillance in male childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. *The Lancet Oncology* 2017;18(2):e75-e90.
91. van Dorp W, Mulder RL, Kremer LC, et al. Recommendations for Premature Ovarian Insufficiency Surveillance for Female Survivors of Childhood, Adolescent, and Young Adult Cancer: A Report From the International Late Effects of Childhood Cancer Guideline Harmonization Group in Collaboration With the PanCareSurFup Consortium. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2016;34(28):3440-3450.
92. Hannah MG, ER; Wellisch, DK; Fobair, P; Hoppe, RT; Bloom, JR; Sun, GW; Varghese, A; Cosgrove, MD; Spiegel, D. Changes in marital and sexual functioning in long-term survivors and their spouses: Testicular cancer versus hodgkin's disease. *Psycho-oncology* 1992;1:89-103.
93. Carpentier MY, Fortenberry JD. Romantic and sexual relationships, body image, and fertility in adolescent and young adult testicular cancer survivors: a review of the literature. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine* 2010;47(2):115-125.
94. Fobair P, Stewart SL, Chang S, et al. Body image and sexual problems in young women with breast cancer. *Psycho-oncology* 2006;15(7):579-594.
95. Jonker-Pool G, Hoekstra HJ, van Imhoff GW, et al. Male sexuality after cancer treatment--needs for information and support: testicular cancer compared to malignant lymphoma. *Patient education and counseling* 2004;52(2):143-150.
96. Geue K, Schmidt R, Sender A, et al. Sexuality and romantic relationships in young adult cancer survivors: satisfaction and supportive care needs. *Psycho-oncology* 2015;24(11):1368-1376.

97. Guy GP, Jr., Yabroff KR, Ekwueme DU, et al. Estimating the health and economic burden of cancer among those diagnosed as adolescents and young adults. *Health affairs* 2014;33(6):1024-1031.
98. Guy GP, Jr., Ekwueme DU, Yabroff KR, et al. Economic burden of cancer survivorship among adults in the United States. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013;31(30):3749-3757.
99. Short PF, Moran JR, Punekar R. Medical expenditures of adult cancer survivors aged <65 years in the United States. *Cancer* 2011;117(12):2791-2800.
100. Finkelstein EA, Tangka FK, Trogdon JG, et al. The personal financial burden of cancer for the working-aged population. *The American journal of managed care* 2009;15(11):801-806.
101. Dowling EC, Chawla N, Forsythe LP, et al. Lost productivity and burden of illness in cancer survivors with and without other chronic conditions. *Cancer* 2013;119(18):3393-3401.
102. Muffly LS, Hlubocky FJ, Khan N, et al. Psychological morbidities in adolescent and young adult blood cancer patients during curative-intent therapy and early survivorship. *Cancer* 2016;122(6):954-961.
103. Pugh G, Gravestock HL, Hough RE, et al. Health behavior change interventions for teenage and young adult cancer survivors: a systematic review. *Journal of adolescent and young adult oncology* 2016;5(2):91-105.
104. Kopp LM, Gastelum Z, Guerrero CH, et al. Lifestyle behavior interventions delivered using technology in childhood, adolescent, and young adult cancer survivors: A systematic review. *Pediatric blood & cancer* 2017;64(1):13-17.
105. Gill E, Goldenberg M, Starnes H, et al. Outdoor adventure therapy to increase physical activity in young adult cancer survivors. *Journal of Psychosocial Oncology* 2016;34(3):184-199.
106. Emmons KM, Puleo E, Sprunck-Harrild K, et al. Partnership for health-2, a web-based versus print smoking cessation intervention for childhood and young adult cancer survivors: randomized comparative effectiveness study. *Journal of medical Internet research* 2013;15(11):e218.
107. Oeffinger KC, McCabe MS. Models for delivering survivorship care. *J Clin Oncol* 2006;24(32):5117-5124.
108. Blaauwbroek R, Tuinier W, Meyboom-de Jong B, et al. Shared care by paediatric oncologists and family doctors for long-term follow-up of adult childhood cancer survivors: a pilot study. *Lancet Oncol* 2008;9(3):232-238.

109. McCabe MS, Partridge AH, Grunfeld E, et al. Risk-based health care, the cancer survivor, the oncologist, and the primary care physician. *Semin Oncol* 2013;40(6):804-812.
110. Ramsay JM, Mann K, Kaul S, et al. Follow-Up Care Provider Preferences of Adolescent and Young Adult Cancer Survivors. *Journal of adolescent and young adult oncology* 2018;7(2):204-209.
111. Hewitt M, Weiner SL, Simone JC. *Childhood Cancer Survivorship: Improving Care and Quality of Life*. Washington, DC: The National Academies Press; 2003.
112. Hewitt M, Greenfield S, Stovall E, editors. *From Cancer Patient to Cancer Survivor: Lost in Transition*. Washington, D.C.: National Academies Press; 2005.
113. Surgeons ACo. 2017 June 27 Important information regarding CoC Survivorship Care Plan Standard. <<https://www.facs.org/quality-programs/cancer/news/survivorship>>. Accessed 2018 June 27
114. Jacobsen PB, DeRosa AP, Henderson TO, et al. Systematic Review of the Impact of Cancer Survivorship Care Plans on Health Outcomes and Health Care Delivery. *J Clin Oncol* 2018;36(20):2088-2100.
115. Institute NCR. 2018 05/12/2018. Top 10 research priorities for teenage and young adult cancer identified. <<https://www.ncri.org.uk/ncri-blog/top-10-research-priorities-for-teenage-and-young-adult-cancer-identified/>>. 05/12/2018.
116. Bhatia S, Armenian SH, Armstrong GT, et al. Collaborative Research in Childhood Cancer Survivorship: The Current Landscape. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2015;33(27):3055-3064.
117. Teepen JC, van Leeuwen FE, Tissing WJ, et al. Long-Term Risk of Subsequent Malignant Neoplasms After Treatment of Childhood Cancer in the DCOG LATER Study Cohort: Role of Chemotherapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2017;35(20):2288-2298.
118. Armstrong GT, Chen Y, Yasui Y, et al. Reduction in Late Mortality among 5-Year Survivors of Childhood Cancer. *The New England journal of medicine* 2016;374(9):833-842.