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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

[a] Diagnosed between 15-39 years age

[b] Acute leukemia (acute lymphoblastic, acute myeloid), Hodgkin lymphoma, non-Hodgkin lymphoma, soft tissue sarcomas, bone sarcomas, and testicular cancer diagnoses

[c] Leukemia, 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
Bélanger 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

* 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 7OR 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)

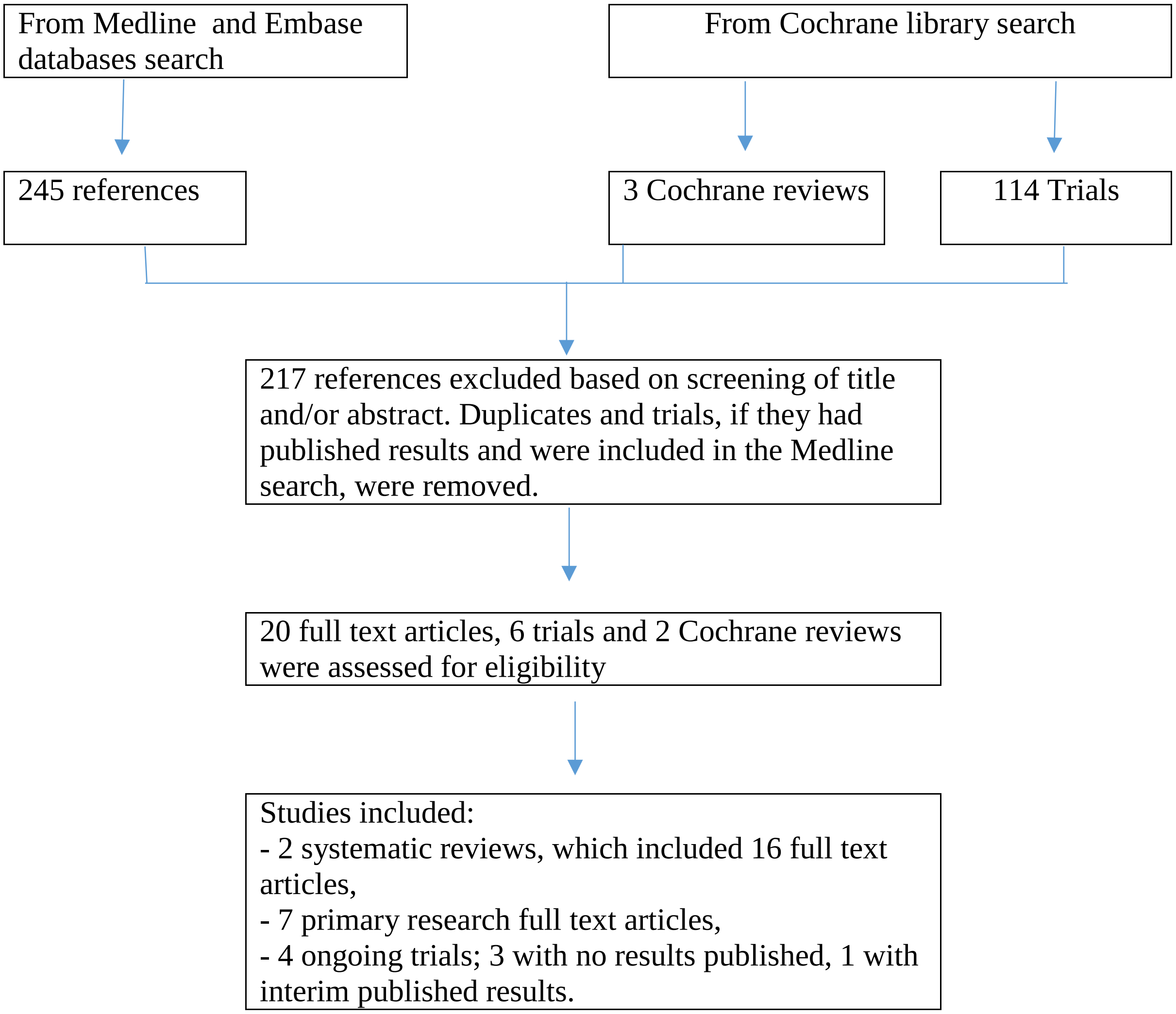
C. Combined search adolescent and young adult cancer and subsequent cancers:

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.



From Medline and Embase databases search

From Cochrane library search

245 references

3 Cochrane reviews

114 Trials

217 references excluded based on screening of title and/or abstract. Duplicates and trials, if they had published results and were included in the Medline search, were removed.

20 full text articles, 6 trials and 2 Cochrane reviews were assessed for eligibility

Studies included:
- 2 systematic reviews, which included 16 full text articles,
- 7 primary research full text articles,
- 4 ongoing trials; 3 with no results published, 1 with interim published results.

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.

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