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Survival from cancer in young people: An overview of late effects focussing on reproductive health

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ABSTRACT

This paper provides a summary of the areas of survival from childhood, teenage and young adult cancer and the significant late-effects that can arise from treatment with particular focus on the area of reproductive health and the impact on both fertility and pregnancy. To complete this review, Web of Science and MEDLINE were used. Search terms included: "survival AND childhood OR teenage OR young adult cancer", "late effects", "childhood cancer", "teenage and/or young adult cancer", "and fertility after cancer", "pregnancy after cancer" and "fertility preservation". Additionally, clinical expertise from the authors was drawn upon. Childhood cancer is thankfully a rare occurrence; however, the incidence is increasing. Survival rates remain high and this means that a growing population of childhood and young adult cancer survivors is reaching adulthood. For some of these adults, whilst cured of their cancer they are now facing a future with lasting effects on their health from their treatments. These effects, commonly referred to as Late Effects are defined as health problems related either directly to the underlying cancer or to its treatment and which occur months or years after treatment has finished. Reproductive health is an important consideration for these patients, and whilst many will be able to conceive naturally, some will exhibit impaired fertility after their treatments. This can include difficulties at all points along the path from conception to delivery of a live, healthy offspring. High quality, large population evidence is sparse in many areas relating to fertility risk from treatment and into the maternal and fetal health of childhood cancer survivors. Yet given the potential for complications the authors advocate consideration of fertility at the time of diagnosis and prior to potentially gonadotoxic treatment.

Keywords

childhood cancer, childhood cancer, teenage cancer, young adult cancer, survival, reproductive health, fertility, fertility preservation

Abbreviations

TYA – teenage and young adult

CYP – children and young people's

LEs – late effects

Key Message

Whilst childhood cancer is rare, survival from childhood cancer is thankfully high. Consideration of the impact of the disease itself and iatrogenic late effects of treatment are important factors in the long-term health of cancer survivors.

1. CHILDHOOD CANCER

Cancer in childhood is a rare entity, with those diagnosed before their fifteenth birthday accounting for 1% of total cancer diagnoses in the developed world[1 2]. However, over the past four decades there has been an increase of approximately 25% in the number of childhood cancer cases diagnosed across Europe and North America and[2 3 4]. Similarly, teenage and young adult (TYA) cancer (diagnosed between the ages of 15 and 24 years) has risen significantly in this time period[2 5 6]. TYA and childhood cancer are together known as children and young people's (CYP) cancer. Rates of CYP cancer vary widely. Age standardised rates of cancer in those under 20 years old across Europe range from 122.4 in some areas of Poland to 234.2 in parts of Italy, with similar ranges being seen across Oceania and North America[2].

Cancers in CYPs present an important health issue as a result of potential attendant mortality and morbidity. Cancer is the leading cause of death in children, accounting for around 20% of deaths in 1 to 14 year olds[7]. It is the leading cause of death in female TYAs, and the leading cause of death from disease in male TYAs, although transport accidents account for more deaths in this group[8]. The potential years of life lost to cancer and economic sequelae are much greater when it affects CYPs compared to older individuals[9]. Mortality rates vary significantly throughout Europe, from around eighteen deaths per million children in Norway to almost sixty deaths per million in the Ukraine[10]. Similar variability is seen in TYA cancers, where survival is significantly better in the Nordic countries compared to the United Kingdom, Spain and Italy[11]. As well as being a leading cause of mortality, CYP cancer results in significant morbidity and associated cost[12], with much of this morbidity persisting for the duration of the CYP's life[13].

1.1 Childhood Cancer Survival

Since the late 1970s, in the same time period that CYP cancer incidence has increased, survival rates for childhood cancer have more than doubled[2 14]. Over 80% of CYP diagnosed with cancer in the developed world are now expected to survive their illness[15]. Adult survivors of CYP cancer, therefore, account for an ever increasing proportion of the general population.

Despite medical and scientific advances resulting in CYP cancer being an increasingly survivable condition[13 14], survival often comes with associated morbidity and costs. Traditional cancer treatments, such as chemotherapy and radiotherapy, are generally both non-specific and frequently associated with adverse effects, meaning that many CYP cancer survivors will be at risk of developing subsequent health issues, some of which are not apparent until many years after treatment has ended[16]. Adults who have survived childhood cancer are 3 times more likely to die 35 years after diagnosis than age- and sex-matched controls who have not had a cancer diagnosis[17]. By 25 years post diagnosis, over two thirds of survivors will have at least one chronic health condition[18] and four in five will have at least one serious long-term illness by the age of 45[19] with some estimates being even higher[20].

1.2. Late Effects of Cancer and Treatment

The term "late effects" (LEs) from CYP's cancer refers to health problems related either directly to the underlying cancer or to its treatment and which occur months or years after treatment has finished. LEs affecting almost all systems have been described, with prevalence varying depending on cancer diagnosis and treatment modality as well as demographic and lifestyle factors.

Given the vastly improved survival now seen in CYP cancer, it is imperative that treatment aims not only to cure the underlying disease but to do so with minimal impact on future health: Large, multinational, studies have been set up aiming to fully explore the LEs of CYP cancer and to research how best to improve the lives of survivors[21 22]. Many contemporary trials are investigating the safety of reduced treatment intensities, which should help to reduce the incidence of LEs[23 24].

This review aims to provide a brief overview of the vast array of LEs experienced by survivors of CYP cancer in order to contextualise the issues they might experience whilst providing a more in-depth review of the reproductive health sequelae.

1.2.i Second Primary Neoplasms

Second primary neoplasms (SPNs) are further cancer diagnoses which are distinct from recurrence of the original tumour[25]. The possibility of SPNs causes significant anxiety to survivors and their families[26]. By 25 years post treatment, around 4% of survivors will have developed a further malignancy[27].

1.2.ii Cardiovascular Disease

Cardiovascular disease, including congestive cardiac failure, , myocardial infarction and vascular disease may affect survivors of CYP cancer, with prevalence of roughly 4-6 times that seen in the non-cancer population with the cumulative incidence continuing to increase 30 years after cancer diagnosis[28 29]. This increased risk is particularly notable amongst survivors of certain tumour types (eg lymphoma) and those receiving particular treatments (eg high dose anthracyclines or mediastinal/chest radiation)[21 22]. Stroke risk is additionally increased in CYP cancer survivors, with 12% reporting at least one stroke by 30 years post diagnosis[30], and a fifth of these experiencing recurrent strokes[31].

1.2.iii Endocrine Disorders

Endocrine disorders are particularly prevalent amongst survivors of CYP cancer, with one large study reporting that 44% of survivors had at least one endocrine disorder, with survivors of Hodgkin's lymphoma and central nervous system tumours being at greatest risk[32]. At least some of this endocrine pathology may relate to high rates of obesity and metabolic syndrome, which is associated with diabetes mellitus and seen in almost one third of cancer survivors[33]. Metabolic syndrome, alternatively known as the "cardiovascular risk factor cluster", due to its association with cardiovascular disease, is particularly prevalent in patients who are exposed to total body, chest or abdominal radiation[34].

1.2.iv Respiratory Disease

Respiratory disease has been less well studied than cardiovascular or endocrine disease, but nonetheless is known to disproportionately affect survivors of CYP cancer. 21% of survivors will have experienced at least one respiratory illness 35 years post diagnosis[35]. Patients who

have undergone chest radiation therapy have a cumulative incidence of 3.5% for pulmonary fibrosis 20 years after diagnosis[36]. Spinal and craniospinal irradiation is similarly associated with increased risk of respiratory pathology[37].

1.2.v Neurological Disorders

Neurological complications, other than strokes, are not especially prevalent amongst most CYP cancer survivors, but are increased in those who have been treated for central nervous system tumours; by 30 years post diagnosis, 41% will have experienced seizures, 35% will have motor impairment and 23% will have some degree of hearing loss[38].

1.2.vi Mental Health

CYP cancer survivors are known to be at increased risk of mental health problems; those survivors with ongoing physical health problems being amongst those at greatest risk of mental ill health[39]. Those who are diagnosed in the TYA period appear much more likely to suffer mental health problems than those diagnosed at younger ages[40].

1.2.vii Sexual and Reproductive Health

Problems with fertility[41 42] and sexual health[43] are strongly correlated with poor mental health. Equally, psychological factors are thought to be one reason why CYP cancer survivors develop problems with sexual function[44]. Sexual health problems are prevalent in survivors of CYP cancer; over 12% of males report erectile dysfunction, a rate around 4 times higher than non-cancer controls[45]. In females, decreased arousal, pleasure and overall satisfaction with sexual function occur at an increased rate amongst cancer survivors than the general population[46]. Survivors of TYA cancers, who are faced with cancer treatment at the same time as going through puberty and discovering their sexuality, are at particular risk of sexual health problems[47], despite having similar rates of engagement in sexual activity to their healthy peers[48]. Quality of life amongst survivors with reported sexual health problems is known to be reduced[49].

2. CANCER AND FERTILITY.

It is challenging to assess the full impact of cancer and treatment upon fertility. Classically amenorrhoea and pregnancy rates have been used as indicators amongst females and semen analysis or paternities have been used amongst male cancer survivors.

2.1. Impact in males (Table 1)

Although some forms of cancer itself, such as testicular, can have a significant direct impact on testicular health and function, for the purpose of this review the primary focus will be the impact of treatment rather than the disease process itself, accepting that it is not always possible to clearly differentiate these effects. It must be remembered that the psychological, endocrine and other physical LEs described previously in this review may significantly impact on fertility.

In males, the testis is the site of production of mature spermatozoa and testosterone. Given that cancer treatments can target both healthy and cancerous cell lines the spermatogonia and supporting cells are at risk of damage[50]. However, testosterone producing, Leydig cells are more resistant to anticancer treatments than the germinal cell lines[51 52 53] . Consequently most pre-pubertal male patients, who receive cancer treatment will achieve normal pubertal development [54 55 56]. Further research continues to try and establish the mechanisms by which different treatments lead to damage[57 58].

Green, et al, report that when compared with their siblings, survivors of childhood cancer were approximately half as likely to sire a pregnancy[59]. It remains unclear at present whether there is a long term generational impact on the fertility of children born from male cancer survivors with a Danish study reporting no significant association[60] but potential mechanisms of effect have been identified in animal work[61].

2.2. Impact in females (Table 1)

The incidence of premature ovarian insufficiency has been reported at 6.5% in female childhood cancer survivors[62]. The risk of premature ovarian insufficiency appears to be connected to the underlying diagnosis, the type of chemotherapy administered (alkylating agents appear to have one of the highest impacts), the total cumulative dose of chemotherapy, the dose and site of radiation (with abdominal and pelvic irradiation providing highest risk) and whether single or

combination agents are used.[63 64 65 66]. Should the menopause occur prior to the age of 40 it is defined as "premature". This has been reported at 8% in female cancer survivors (RR of 13.21 and 95% C.I 3.26-53.51; P<0.001) compared to sibling controls[67 68]. Even for women who do not fall into the category premature menopause evidence suggests that ovarian function ceases earlier within the group of childhood cancer survivors, at a median age of 44 years[69] compared to 51.4 years in the general population[70]. An expedited drop in the number of follicles in pre-pubertal females treated for cancer may be responsible for a narrower window of reproductive function in childhood cancer survivors[71].

It remains unclear the exact mechanism by which chemotherapy damages the ovary, and potential sites of damage include; primordial follicles, developing follicles, somatic support cells and ovarian vasculature[72 65]. Evidence exists to support different models of damage and potentially different agents and treatment modalities may cause damage via differing mechanisms[73 74 75 76].

Whilst ovarian function is vital for conception, it must not be regarded in isolation. To achieve a successful live, term birth a holistic approach must be considered. Uterine function along with overall physical, psychological and social health are important. A woman must be systemically healthy enough to cope successfully with the physiological changes of both the ante-natal and post-natal periods. In both sexes there are multiple potential sites for disruption and damage to occur in the process of reproduction and different treatments and modalities may impact fertility at different sites and in different ways.

Local effects on cancer treatment in both male and female survivors are summarised in Table 1.

2.3. Pregnancy rates in childhood cancer survivors.

Recently published population based data from Scotland (including patients up to the age of 40 at the time of cancer diagnosis) suggests that female cancer survivors achieve fewer pregnancies than age matched general population controls. SIR 0.62 (95% CI: 0.60, 0.63)[81]. These results are reflected in previous smaller studies across the Scandinavia with a Swedish population based – matched cohort study of patients aged <21 years at the time of their cancer diagnosis, reporting the probability of having a first live birth being significantly lower amongst survivors. In this study males were reported as having a lower hazard ratio [HR], than women (HR 0.65 v 0.79)[82].

3. FERTILITY PRESERVATION

3.1. Males

In the post-pubertal male, sperm cryopreservation remains the gold standard option for fertility preservation[83]. In adolescent males, it is possible to cryopreserve semen in >80% of cases[84]. In pre-pubertal boys the absence of mature sperm within the gonads means that this is not an option. Research is ongoing into the area of testicular tissue and spermatogonial stem cell cryopreservation and the development of techniques that will allow for the production and maturation of gametes after thawing of immature tissue [85 86]. Current strategies for restoring fertility after testicular or spermatogonial stem cell cryopreservation include; auto-transplantation, via intra-testicular spermatogonial stem cell injection or testicular tissue thaw and surgical graft[84]. Promising evidence exists in these areas, particularly in murine models[87 88 89 90].

3.2. Females

As with their male counterparts, post-pubertal females are potentially able to undergo mature gamete storage in the form of oocyte storage, or embryo (if appropriate) storage [83 91 92]. Both mature oocyte storage and embryo storage require an ovarian stimulation cycle to yield an increase in oocyte production in a single cycle. In some cases, this would cause a delay to a patient's cancer treatment that would put their health, and survival at risk and therefore may not be appropriate. In regard to pre-pubertal patients, unlike in the male, a girl is born with her full complement of primordial ovarian follicles, at an arrested stage of development, within her ovarian cortex (her ovarian reserve). This has led to the development of techniques to harvest and cryopreserve ovarian cortex with a view to autologous transplantation in adult life. There have been more than 100 babies born internationally from this technique [93 94 95 96] and whilst the vast majority have been from ovarian tissue cryopreserved after the onset of puberty there have been published reports of successful pregnancies and live births from ovarian tissue cryopreserved before the onset of puberty[97]. Ovarian tissue cryopreservation may also be an option for post-pubertal female patients for whom a stimulation cycle is inappropriate.

The ongoing research and successful outcomes in these areas are driving forward discussions and early fertility-preservation interventions with patients and their families at the point when they receive a diagnosis of cancer and their initial treatment plan is formulated.

3.3 Decision making in children in regard to fertility preservation.

As healthcare has shifted over recent decades from a paternalistic approach to a shared decision-making approach, tools are being developed to aid patients and their families when deciding upon options. In young adult survivors, studies have shown that fertility ranks highly amongst patients concerns[98], and adolescents have a strong desire to participate in decisions related to their cancer and treatment[99]. This must be taken into account by clinicians when discussing future reproductive health with children and young adults at the time of diagnosis of cancer and at later stages in their cancer journey including through adult survivorship. Clinical teams need to be considerate of the competence and ability of the child or young adult to understand their disease, treatment, potential side-effects and fertility preservation options. At the time of diagnosis with a life-threatening illness, patients and their families may find large volumes of information too much to deal with and it can be hard to focus on future considerations when faced with uncertainty regarding survival. Access to age-appropriate information may be beneficial and should be considered an essential part of clinical care provision[100].

Counselling and guidance of patients and their families is complicated by the difficulties in pin-pointing an individual patient's risk of infertility after treatment. The lack of specificity in clinical guidelines illustrate this[92 101 102]. Further research is required in this area.

4. CANCER AND PREGNANCY

Many survivors of childhood cancer are able to conceive naturally, whilst some may require assisted reproductive technologies. The maternal health of these patients should ideally be assessed and optimised prior to conception, with ongoing surveillance throughout the ante-natal and post-natal periods.

4.1 Late effects of cancer and cancer treatment on maternal health

As discussed previously cardiovascular, respiratory and metabolic factors are amongst the potential LEs facing survivors of childhood and young adult cancers. Pregnancy is known to increase the burden on the cardiorespiratory and endocrine systems and can lead to decompensation in women with pre-existing conditions [103 104 105].

Given the heterogeneity of cancer types and treatment regimes across the population of childhood cancer survivors it is important that patients are assessed on a one by one basis with regard to their diagnosis, treatment and potential LES (Table 2). Ideally preconception assessment and optimisation of known co-morbidities should occur. Antenatal care should be coordinated by an obstetrician and physician with expertise in their co-morbidities, if required[106].

When assessing a survivor of cancer preconceptionally or antenatally, one should be mindful that not all adverse effects will occur at the time of treatment and some may be delayed. For example, anthracycline related cardiotoxicity. Here the effects can occur many years later, and patients may be asymptomatic despite the damage[107 108]. For childhood cancer survivors treated with anthracyclines or radiation to the cardiac field regular assessment by echocardiography is recommended, particularly in the first and third trimester of pregnancy[101].

4.2. Late effects of cancer and cancer treatment on fetal health.

Maternal health itself can have a direct impact on fetal outcomes as well as treatments the mother receives during pregnancy to manage her LEs of prior cancer treatment (Table 3).

5. CONCLUSION

As CYP cancer survival continues to improve and the prevalence of cancer survivors increases, health services are providing care for a growing number of adults at risk of LEs of a malignancy treated in the CYP age range. Whilst the majority are free of their cancer and are not thought to be sub-fertile, they are not always free of LEs of their treatment. Reproductive health is commonly cited as an important consideration to survivors of cancer and it is essential that clinical teams consider any potential reproductive health sequelae both prior to commencing and following anti-cancer treatment. Recent advances in fertility preservation techniques provide a new array of interventions to potentially minimise adverse reproductive health consequences of cancers and their treatments in the CYP community. From the outset of a patient's cancer journey, close liaison between oncology and reproductive health multi-disciplinary teams is advocated to ensure optimal provision of advice and care.

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Table 1. Localised effects of cancer treatment in survivors

POTENTIAL SIDE EFFECT:	POTENTIAL IMPACT ON FERTILITY
MALE	
Testicular:	
Impaired spermatogenesis	Reduced semen quality or azoospermia resulting in male factor infertility[59, 77].
Disruption of hypothalamic – pituitary-gonadal axis	Central infertility resulting in impaired spermatogenesis[59].
FEMALE	
Ovarian:	
Primordial Follicle Loss or Damage	Premature ovarian insufficiency[78, 79, 80].
Uterine:	
Radiotherapy damage	Increased rates of early and late pregnancy loss[80].
Vaginal:	
Dryness/ strictures	Dyspareunia
Endocrine:	
Disruption of hypothalamic – pituitary-gonadal axis	Central infertility resulting in impaired folliculogenesis[78].

Based on Green et al. 2010[59], Green et al. 2014[77] , Green et al. 2009 [78], Green et al. 2009[79], Bath et al. 1999[80].

Table 2. Late effects of cancer treatment and potential obstetric complications

POTENTIAL LATE EFFECT:	POTENTIAL OBSTETRIC CONSIDERATION:
Cardiovascular:	
Increased rates of congestive heart failure OR cardiomyopathy	Pregnancy itself will increase strain on the cardiovascular system with changes to support the placental vasculature supply. The immediate post-partum period sees rapid changes in the circulating volume. These changes can lead to decompensation in a patient with cardiovascular mortality[106 119].
Increased risk of myocardial infarction	
Pericardial disease	
Valvar heart disease	
Increased coronary artery disease	
Endocrine and Metabolic:	
Diabetes	Diabetic control, even in previously well- controlled patients can become challenging in the antenatal period and there can be reduced awareness of hypoglycaemia[110 111].
Thyroid dysfunction	Patients often require review and adjustment of their thyroid medication throughout pregnancy to remain euthyroid[110 112].
Venous Thromboembolism:	
Recurrence in pregnancy	Given the prothrombotic state of pregnancy, patients predisposed to venous thrombo-embolism (VTE) are at risk of a recurrence. VTE remains one of the leading cause of maternal deaths worldwide[113].
Anticoagulation treatment	Due to fetal side effects from warfarin, pregnant patients are often converted to a low molecular weight heparin throughout pregnancy with a postnatal review and recommencement of prior therapy. Antepartum and postpartum haemorrhages are more common in anticoagulated patients. Anaesthetic and operative complications can occur and spinal or epidural anaesthesia are often contraindicated[113 115].
Recurrence or Secondary Malignancy in Pregnancy:	
Treatment in pregnancy	Increased pregnancy loss if treated in embryonal stage[114].
Ovarian tissue cryopreservation and transplant, and reintroduction of primary cancer risk	Patients with ovarian tissue cryopreserved prior to treatment who then receive this tissue back to restore fertility are at risk of the reintroduction of their primary cancer from the transplanted tissue[116].

Based on RCOG 2011[106], Wallace and Swallow 2016[109], Nelson-Piercy 2015 [110], Meacham et al. 2009[111], Jeffery et al. 2015 [112], RCOG. 2018[113], Basu et al. 2016[114], Esposito et al. 2016[115], Rosendahl et al. 2013[116].

Table 3. Potential fetal complications in pregnancies of female childhood cancer survivors

POTENTIAL FETAL COMPLICATIONS:	COMMENT:
Miscarriage	Increased rates have been reported in cancer survivors [117 118].
Intrauterine Growth Restriction	Increased rates have been reported in cancer survivors[118].
Prematurity	Increased rates have been reported in cancer survivors[118].
Intrauterine death	Not significantly increased unless high dose radiotherapy to pelvis[118].
Heritable cancer conditions	This will depend on the index malignancy. In appropriate cases genetic counselling will be required.
Congenital abnormalities	No direct increase is reported[118], although there are increased rates of congenital abnormalities amongst women with pre-existing diabetes[120 121].
Teratogenicity	Anticoagulants such as warfarin are known to cause teratogenicity and fetal warfarin syndrome[114]. Treatment for recurrence or secondary cancers may also lead to teratogenic effects.
Potential risk of congenital malformations or long-term health effects in offspring conceived with assisted reproductive technologies (ART).	Several studies report increased rates of fetal growth restriction, low birth weight, prematurity, increased cardiovascular malformations, leukaemia and Hodgkin lymphoma in ART offspring. With some studies indicating there can be metabolic effects in the long-term health of these children with increased incidences of elevated blood pressure, total body fat and fasting glucose being reported[122 123 124 125 126 127 128].

Based on Green et al. 2002[117], Critchley et al. 2005[118], Critchley et al. 1992[119], NICE. 2008[120], Metzger et al. 2002[121], Basu et al. 2016[114], Davies et al.[122], Pinborg et al. 2012[123], Huntriss et al. 2018[124], Hart et al. 2018[125], Giorgione et al. 2018[126], Källén et al. 2010 [127], Reigstad et al. 2016[128].