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Mental Health of Long Term Survivors of Childhood and Young Adult Cancer: A Systematic Review

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Novelty and Impact Statement:

This systematic review demonstrates the significant burden of mental ill health in long term survivors of childhood and young adult cancers. This highlights the extent of the problem whilst also demonstrating the clear need for further research to better identify those at risk and develop appropriate management strategies.

Abstract

Childhood cancer is increasing in prevalence whilst survival rates are improving. The prevalence of adult survivors of childhood cancer is consequently increasing. Many survivors suffer long-term consequences of their cancer treatment. Whilst many of these are well documented, relatively little is known about the mental health of survivors of childhood cancer.

This article aimed to describe the prevalence and spectrum of mental health problems found in adult survivors of childhood cancer using a systematic review methodology.

Our review included 67 papers, describing a number of problems, including depression, anxiety, behavioural problems and drug misuse. Factors increasing the likelihood of mental health problems included treatment with high dose anthracyclines, cranial irradiation, diagnoses of sarcoma or central nervous system tumours and ongoing physical ill health.

There were numerous limitations to the studies we found, including use of siblings of survivors as a control group, self-report methodology and lack of indications for prescriptions when prescribing data was used.

This review has identified many mental health problems experienced by survivors of childhood cancer, however the exact incidence, prevalence and risk-factors for their development remain unclear. Further work to identify childhood cancer patients who are at risk of developing late mental health morbidity is essential.

Introduction

Children and Young People's Cancer

Childhood cancer (diagnosed under the age of 15 years) is a rare entity, accounting for just 1% of all cancer cases[i][1]. However, incidence of cancer in children has been steadily rising globally since the late 1970s[ii][2]. Incidence rates of childhood cancer have increased by around a quarter in this period, rising slightly more in girls than boys, although cancer remains more common in boys[2]. Between 2012 and 2014, there were 164 new cancer cases for every million boys and 147 for every million girls in the UK[2]. Teenage and young adult (TYA) cancer (diagnosed between the ages of 15 and 24 years) has risen significantly in the same time period, with 280 new cancer cases for every million males and 307 for every million females in the UK between 2012 and 2014[iii][3].

Cancers in children and young people (CYPs) present an important health issue, not just because of their increasing number but because they result in significant mortality. The term "children and young people" in this context refers to children plus TYAs, i.e. all cancer patients 24 years of age and younger. Cancer is the leading cause of death in children, accounting for around 20% of deaths in 1 to 14 year olds.[iv][4] Cancer 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[v][5]. When cancer affects CYPs, there are potentially many more years of life lost than when it affects older adults[vi][6]. As well as being a leading cause of mortality, CYP cancer can result in significant morbidity and associated cost[vii][7], with much of this morbidity persisting for the duration of the CYP's life[viii][8].

Since the late 1970s, in the same time period that CYP cancer rates have increased, survival rates have dramatically improved with those for childhood cancer having more than doubled[ix][9] and those for TYA significantly improving[x][10]. More than 80% of children[9] and young adults diagnosed between 2006 and 2010 survived for at least 5 years[10] and three quarters of children diagnosed between 2001 and 2005 survived for at least 10 years[11]. Although TYA survival rates have not increased as sharply as childhood survival rates, this is offset against an already much higher baseline[14]. The prevalence of adult survivors of CYP cancer is consequently ever increasing. As a result any morbidity burden experienced by this population takes on increasing importance to health and social care economies.

Late Effects of Childhood Cancer

The frequently non-specific and toxic nature of many cancer treatments, such as systemic chemotherapy, result in the majority of children and young people who survive cancer developing treatment-related complications, which may occur many years after treatment has ended[xi][11]. Adults who have survived childhood cancer are at least 9 times more likely to die than matched controls in the 50 years after diagnosis[xii][12]. Data from American studies show that over two thirds of survivors will have at least 1 chronic health condition 25 years after diagnosis[xiii][13] and 80% have at least one serious chronic disease by the age of 45[xiv][14] with some estimates being even higher[xv][15]. It is possible that variation in these estimates is at least partially due to the majority of these data being obtained from self-reports rather than medical records, meaning it is difficult to know how accurate these data are as it may be affected by issues with recall and reporting bias. The majority of CYP cancer survivors will report decreased quality of life compared to the general population, which can be directly attributed to these ongoing health problems[xvi][16].

The term “late effects” (LEs) refers to health problems related either directly to the underlying cancer or to its treatment, which occur months or years after treatment has finished. Numerous LEs have been described, including cardiovascular disease[xvii][17], sub-fertility[xviii][18] and subsequent primary neoplasms (SPNs)[xix][19]. The term subsequent primary neoplasm refers to a further cancer which is unrelated to the initial diagnosis and therefore distinct from relapsed disease [23]. LEs vary depending on the treatment received; for example patients who received chest radiotherapy are at significantly increased risk of developing breast cancer[xx][20], whilst patients treated with anthracyclines may go on to develop cardiomyopathy[xxi][21].

Many LEs have been known about for many years and the majority are well documented. Cardiovascular[21], respiratory[xxii][22], renal[xxiii][23] and endocrine[xxiv][24] complications have all been comprehensively described in the literature. However, despite the obvious emotional impact of a cancer diagnosis[xxv][25], psychiatric late effects of childhood cancer have been less well studied. This may be for several reasons: Previous studies into LEs have focused on conditions with high rates of mortality, such as SPNs and cardiovascular disease[16]. Additionally, research has often looked at hospital admissions data[xxvi][26], despite the majority of contacts for mental health occurring in primary care [xxvii][27]. Thus, the majority of patients with mental health problems will not be detected by looking purely at hospital data. Additionally, self-reported data for LE description may potentially not be as accurate for sensitive and stigmatized conditions as for physical conditions such as cardiovascular ill-health[17,19,20]. Several previous systematic reviews have been carried out, however these have explicitly excluded survivors of young adult cancers (diagnosed over the age of 18)[xxviii][28],[xxix][29] and additionally in some cases are restricted to particular disease groups such as central nervous system (CNS) tumours[xxx][30].

Aims and Objectives

This work aimed to utilise a systematic review methodology to determine whether long term survivors of CYP cancer were at increased risk of mental health problems compared to their peers who had not experienced a cancer diagnosis. It also aimed to determine which mental health problems CYP cancer survivors were at risk of, and whether certain groups of cancer survivors were at higher risk of mental ill health than others.”

Methods

A standard systematic review was performed of the PubMed, Embase/OVID, CINAHL and Web of Science databases for papers published before April 2017 using the following strategy:

(child OR children OR childhood OR teen* OR adolescent* OR "young adult")

AND (cancer OR leukaemia OR tumour OR tumor)

AND survivor

AND "Mental health" or "mental illness" or "psychiatric" or "psychological" or "emotional" or "behavioural" or “behavioral”

AND "late effects" or "long term"

We included papers looking at the prevalence of mental health problems in long term survivors of CYP cancer. We included patients who had undergone bone marrow transplant for non-malignant conditions, on the basis that they will have been exposed to chemotherapeutic agents in their conditioning regimes and would be at risk of similar problems to cancer survivors. We excluded papers focussing only on cognitive function, as this is already relatively well reported [xxxi][31],[xxxii][32],[xxxiii][33]. We also excluded papers which included patients less than 5 years from diagnosis, as these would not be classed as “long term” survivors, and papers which included adult patients. We also excluded conference abstracts which did not provide sufficient information to allow us to determine inclusion criteria.

Each paper was reviewed separately by 2 authors to decide upon inclusion. Where the 2 initial authors disagreed on inclusion/exclusion, a third author reviewed the paper separately.

The reference lists of each included study were also reviewed to identify additional papers.

Results

The initial search returned 1530 papers: 320 papers underwent full text review, and 64 were included in the final review. Three additional papers were identified from screening reference lists of included studies. Diagram 1 describes the screening and identification of studies, based on the PRISMA method[xxxiv][34]. A full table with details of included studies can be found in Appendix 1.

Insert diagram 1 here

The qualitative synthesis suggested increased mental health problems in survivors of CYP cancers, with some papers finding that as many as half of survivors report a psychiatric diagnosis at some point since treatment and around a third report a current psychiatric diagnosis[xxxv][35]. Problems were still noted over 30 years after completion of treatment[xxxvi][36].

Mental Health of CYP Cancer Survivors

A wide variety of problems were reported. These included difficulties with interpersonal relationships[xxxvii][37], increased somatic distress/somatisation[xxxviii][38],[xxxix][39],[xl][40],[xli][41],[xlii][42],[xliii][43],[xliv][44], poor self-esteem[xlv][45], depression and other mood disorders[xlvi][46],[xlvii][47],[xlviii][48],[xlix][49],[l][50],[li][51],[lii][52],[liii][53],[liv][54],[lv][55],41,,42,62 , anxiety and other neurotic disorders[44,46,47,38,51,42], antisocial behaviour[44], post-traumatic stress disorder (PTSD)[lvi][56],[lvii][57],[lviii][58],[lix][59],[51], schizophrenia and other psychotic disorders[lx][60],[47], poor body image[48], difficulties fulfilling expected roles due to emotional disturbance[49], behavioural problems[lxi][61], mood swings[lxii][62], oppositional defiant disorder (ODD)[50], drug and alcohol misuse[lxiii][63],[lxiv][64], suicidal ideation[lxv][65],[lxvi][66] and unmet emotional and coping needs[lxvii][67].

One large study of hospital contacts found survivors of CYP cancers were more likely to have both in- and out-patient assessment and treatment for mental health problems. However, another study found that CYP cancer survivors were more likely to access healthcare for mental health problems than siblings with the same problems. It is therefore difficult to know whether increased hospital contact truly represents an increase in prevalence, or merely an increased likelihood of seeking help."

Some large studies found increased prescribing of antidepressants[lxviii][68] and psychotropic medication in general[lxix][69] amongst CYP cancer survivors compared to the wider population. Interestingly, the study reporting increased psychotropic medication use did not see a specific increase in antidepressant prescribing. Unfortunately, a reliance on self-reported data in one study and a lack of information on indications for prescriptions in the other mean that it is difficult to infer whether these increases in prescriptions truly represent increased prevalence of mental ill health. Furthermore, the study looking at overall psychotropic prescribing included analgesics in their defined "psychotropic" medications

Risk Factors for Poor Mental Health in Survivors

As well as finding details of the mental health problems CYP cancer survivors potentially faced, we found suggestions of groups who were particularly likely to have these problems.

a. Treatment

A number of studies reported on the effects of different treatment modalities on mental health outcomes.Cranial irradtion[lxx][70],[lxxi][71],[lxxii][72],[lxxiii][73], particularly at an early age[58], treatment with ≥300 mg/m2 of anthracyclines[38] and more intense treatment generally[58] was associated with greater likelihood of mental ill health, including creased PTSD risk. These differences were noted in older studies carried out when cranial irradiation was a routine part of ALL treatment, but also in more modern studies. However, we note that only 2 of these 5 studies also looked at a non-cancer control group.

Results of a small and somewhat dated study suggest that leukaemia survivors treated with BMT had no greater risk of distress than those treated with chemotherapy alone. [lxxiv][74]. However, timing of BMT was important, with another, much larger, study finding depression risk higher in survivors who underwent transplant in their teenage years than those transplanted as younger children[lxxv][75].

b. Pathology

Multiple studies investigated results for survivors of different tumour types. Evidence from several robust, large-scale studies indicates that solid tumour survivors (including central nervous system (CNS) tumour survivors) appeared to have poorer mental health outcomes than survivors of haematological malignancy. Although some of these studies used HADS scores, which are only validated in hospital inpatients, similar results were found in large scale studies using validated questionnaires. We found evidence that CNS tumour survivors had reduced social functioning[lxxvi][76],[lxxvii][77], increased psychological distress[lxxviii][78] and poorer psychosexual development[lxxix][79] as well as globally poorer quality of life scores[lxxx][80] than other survivors. Patients who had undergone brain surgery also reported more adverse mental health[lxxxi][81]. Amongst non-CNS tumour survivors, sarcoma survivors in particular had poor psychological outcomes[79,80].

c. Physical Health

The impact of ongoing poor physical health on mental health was explored in a number of studies. Perhaps unsurpriningly, survivors with more significant disability, chronic ill health and physical sequalae of cancer treatment reported more adverse mental health. Lack of health insurance and inability to work due to disability likely accounted for some of these effects Issues identified included problems with body image[lxxxii][82],[82,72, 50], , generally increased prevalence of distress and poor mental health[lxxxiii][83],[lxxxiv][84],[62], increased risk of PTSD[58] and increased risk of suicidal ideation[66]. . Whilst many of these results came from studies looking solely at survivors of CNS tumours or sarcoma, the increased likelihood of physical ill health in survivors means that this probably a reasonable sample group. We also noted some more specific findings, such as obesity being associated with higher risk of depression in patients treated with BMT[77] and fatigue and sleep problems being associated with higher levels of anxiety, depression and somatisation[lxxxv][85], although these came from smaller studies using self-reported diagnoses.

d. Demographic Factors

Different demographic factors were found to impact on risk of mental ill health in a number of studies. Female survivors appeared to have greater risk of mental health difficulties than males [lxxxvi][86][71,75,85,50]. PTSD also in particular was more common in female survivors [53].

A large scale study covering a diverse ethnic population found that, after adjustment for socioeconomic status, black survivors were less likely to report adverse mental health than white or Hispanic survivors[lxxxvii][87], although no non-cancer controls were used in this study.

Another large-scale study found that survivors without siblings were at higher risk of psychological distress than survivors with siblings, whilst immigrants were at higher risk of distress than those who had not immigrated[86].

Smaller studies of specific tumour survivors also found poor social support, reduced disease acceptance, exposure to other stressful life events and a more emotion-oriented coping strategy were associated with higher levels of distress[lxxxviii][88],[lxxxix][89] and a larger study of whole families found reduced family functioning to be associated with increased risk of PTSD[58,]

e. Later Health

Several very large cohort studies reported on the links between poor mental health and later physical health. We found evidence of links between poor psychological functioning and later risky health behaviours[xc][90], such as increased heavy and risky drinking in survivors with depression and anxiety [xci][91]. All-cause mortality was higher in survivors who had a history of suicidal ideation [66].

Alternative Viewpoints

Not all studies reported increased mental health problems, with some suggesting psychiatric disorder [69], work and educational attainment[37], poor body image and displeasure with current status[xcii][92] were no more common in CYP cancer survivors. Anxiety and depression[76,90,50] and sleep problems[88] were no more prevalent in some cohorts of survivors of CYP cancer. Some studiesof CYP cancer survivors found overall low levels of PTSD[100], depression[xciii][93] and other mental health problems[xciv][94], however lack of a control group makes it difficult to know whether these results simply reflect a lower prevalence of these diosrders in the population sampled. Some studies found no evidence of depression in their cohort[48]. Others found that increased anxiety and depression was no longer seen after adjustment for confounders such as physical ill health and socioeconomic status[39]. However, we note that some of these studies looked only at survivors of TYA and excluded childhood cancers[xcv][95] and tended to be smaller than studies which did find increased risk of mental health disorder[37,50,76,90,94].

Positive Mental Health Outcomes

As well as reports of significant difficulties, we found positive outcomes, with CYP cancer survivors less likely to drink alcohol heavily or in a risky fashion than the general population[93], although this may reflect recommended lifestyle advice to minimise the risk of other late effects. Reduced risk of mental health problems[xcvi][96] and behavioural problems[39,xcvii][97] were found in several very small studies[xcviii][98] These findings were replicated in 2 larger scale studies[xcix][99],[c][100], although use of sibling control groups limits the reliability of these findings.

Discussion

Our review highlights the wide variety of psychological, psychiatric and psychosocial difficulties which may be faced by many long term survivors of CYP cancer. The high prevalence of these conditions means that all healthcare providers looking after these patients should be competent in identification of these problems.

Some potential causative and associated factors were also noted.

The increased risk of psychological distress seen in patients who had undergone cranial irradiation[73,74,] and any form of brain surgery[84] may go some way to explaining why brain tumour survivors have greater mental health difficulties than survivors of other cancers[79]. However, these patients also had lower average IQ[74] and increased physical health problems[74] which may also account for at least some of the differences seen..

Higher risk of mental health problems in patients treated with anthracyclines[38] may be due to the significant LEs often seen in these patients, particularly cardiomyopathy and congestive cardiac failure[ci][101], and the association between chronic illness and poor mental health[87,68]. The anthracycline dose associated with increased risk of cardiotoxicity (>300mg/m^2) is the same as the dose associated with increased mental distress[106], which adds further weight to this theory.

Patients with sarcoma are often treated with high dose anthracyclines[cii[102],ciii[103]], and it may be that the link between anthracycline treatment and increased distress is responsible for the increased mental health difficulties in sarcoma survivors. Additionally, these patients may have experienced disfiguring surgery which can cause significant distress[civ[104]].

The complex nature of cancer biology and treatment means that it is difficult to attribute psychiatric morbidity to a single cause. In the case of CNS tumours, for example, it is not possible to clearly determine how much morbidity is due to brain surgery and how much is due to residual disability based on the currently available literature.

Some studies had seemingly conflicting findings, for example a study finding increased interpersonal difficulties but no difference in work or educational attainment[38]. There may be many reasons for this, but it is possible that, as a result of having to continue with education during treatment, survivors are used to persisting with work or study despite ongoing difficulties. However, whilst it is positive to find good function in patients despite their difficulties, reduction of distress remains an important goal.

There were a number of limitations to the studies we found. Many used siblings of survivors as a control group. Siblings will have similar genetics and upbringings to survivors and therefore allow good control for some confounding variables, however siblings have been shown to be at risk of significant psychological distress themselves[cv[105]]. These studies therefore risk underestimating any increased prevalence of problems in survivors. Several of the studies finding no difference between prevalence of mental health problems in survivors versus controls[70] used sibling controls and this may be the reason for the lack of difference found. Some studies reporting low levels of mental health problems had no control group at all[100,98,97], making interpretation of this result even more difficult.

Most of the data from included studies was obtained from self-reports and questionnaires rather than clinician-made diagnoses. Self-reporting of symptoms is known to have a low predictive value for psychiatric diagnoses such as depression[cvi[106]]and even well validated scores are less accurate in the presence of co-morbidity[cvii[107]].

Reports of secondary care contacts are helpful, however these also risk seriously underestimating the prevalence of mental health problems, which are largely looked after in a primary care setting[27].

Studies looking at antidepressant prescribing[71,72] did not provide information on the indication for prescription. Various antidepressants, including tricyclics and selective serotonin reuptake inhibitors

(SSRIs), have been used to treat neuropathic pain[cviii][108]. Pain is another commonly reported symptom in cancer survivors[cix][109] and therefore without data on indication for prescriptions of antidepressant medication, it is difficult to know how much increased prescribing is actually a result of increased prevalence of depression. Furthermore, antidepressant medications, in particular SSRIs, are also used for a number of psychiatric condition, such as obsessive-compulsive disorder (OCD)[cx][110], generalised anxiety disorder (GAD)[cxi][111] and bulimia nervosa[cxii][112], so whilst increased prescribing does likely indicate higher rates of psychiatric illness in this cohort, it would be useful to know specifically which conditions were more prevalent. In the United Kingdom, first line therapy for mild to moderate depression is psychological therapy such as cognitive behavioural therapy[cxiii][113]. It is therefore likely that looking at antidepressant prescribing alone would underestimate the prevalence of depression in our population. Additionally, other studies looking at prescriptions of psychotropic medications[68] included analgesics. As rates of pain and therefore higher levels of analgesic prescribing would be expected cancer survivors[105], these studies do not accurately help to ascertain prevalence of mental health problems.

We found no studies reporting on primary-care-diagnosed mental health problems, despite the evidence that this is the commonest place for them to be diagnosed and managed[27]. Although the studies we found reporting on prescribing data[71,72] did include prescriptions from primary care, diagnoses were not ascertained in these cases.

Many studies included mostly survivors of ALL; although this is reflective of survivorship patterns, it may be that because these patients are at lower risk of problems, issues seen in survivors of rarer malignancies, such as poor body image[85], were not present at a statistically significant level. Even in studies where there were overall no difference in prevalence of problems, there were some sub-groups with increased risk of anxiety and depression[76] and sleep problems[88].

The studies included in our review focussed mainly on survivors of childhood cancer. Of 65 included studies, only 5 either included only TYA survivors[96,48,47] or reported results for TYA survivors separately to childhood survivors[33,50]. Many other studies chose their age range such that many TYA would have been included (many included under 18s or under 21s), however these studies did not report separately on TYA outcomes. Additionally, we found no studies including young adults up to the age of 24. This highlights the striking lack of literature on TYA survivors, who have historically been excluded from many trials[cxiv][114].

Although this review included 67 studies, only 2 were carried out within the United Kingdom. Over half of the studies (n=35) were from North America. 26 were from mainland Europe, with 13 of these from Scandinavia, and the final 4 were from East Asia. Differences in the way healthcare is accessed, funded and paid for may well impact of the prevalence of diagnosed mental health problems and there is therefore a need for more local work to ascertain the true prevalence of these debilitating issues in our population.

Whilst this systematic review identified a large number of papers, the broad definition of "mental health" means that there were likely some papers on specific conditions which were not identified. Further reviews considering specific mental health conditions may be useful in ascertaining the state of knowledge regarding particular diagnoses. Additionally, it was outwith the scope of this review to look at intervention or treatment. A review of treatment options may enable the development of a clinical guideline which would assist clinicians caring for long term survivors of CYP cancer.

Conclusion

This systematic review has served to identify a wide range of mental health conditions experienced by survivors of CYP cancer. It is difficult to tease out the exact incidence, prevalence and risk-factors for their development from the existing literature. Given the potential for significant distress attendant on these conditions, further work is mandated. Comprehensive linkage of primary care/community health and hospital records may help to resolve this and support robust identification of those diagnosed with cancer at a young age who are at risk of developing late mental health morbidity.

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