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REVIEW ARTICLE

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Quality of life in young adult survivors of childhood cancer

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Abstract In recent years the necessity of measuring quality of life in childhood cancer survivors has been stressed. This paper gives an overview of the results of studies into the quality of life (QL) of young adult survivors of childhood cancer and suggest areas for future research. The review located 30 empirical studies published up to 2001. The results are described in terms of the following QL dimensions: physical functioning (QL, general health), psychological functioning (overall emotional functioning, depression and anxiety, self-esteem), social functioning (education, employment, insurance, living situation, marital status and family), and sexual functioning. Factors related to survivors' QL are reported: demographics and illness- and treatment related variables. Although the literature yields some inconsistent findings, a number of clear trends can be identified: (a) most survivors reported being in good health, with the exception of some bone tumour survivors; (b) most survivors function well psychologically; (c) survivors of CNS tumours and survivors of acute lymphoblastic leukaemia (ALL) are at risk for educational deficits; (d) job discrimination, difficulties in obtaining work and problems in obtaining health and life insurance were reported; (e) survivors have lower rates of marriage and parenthood; (f) survivors worry about their reproductive capacity and/or about future health problems their children might experience as a result of their cancer history. There is a need for methodological studies that measure QL among survivors of childhood cancer more precisely by taking into account the effects of the severity of the cancer and the long-term impact of different treatments. Additional data are needed to help us understand the needs of survivors and to identify those subgroups of survivors who are at greatest risk for the adverse sequelae of the disease and its treatment.

Keywords Childhood cancer · Young adult survivors · Quality of life · Psychosocial consequences · Review

Introduction

As a result of more effective treatment, improved supportive care and centralisation of care, the long-term survival rate of childhood cancer patients has risen dramatically during the past few decades. More than 70% of children newly diagnosed with acute lymphocytic leukaemia will be in continuous remission 5 years following their initial diagnosis, and the majority of these patients are probably cured of their disease. Survival has also increased for children with solid tumours: 93% of children with Hodgkin's disease, 84% of children with Wilms' tumour and 73% of children with non-Hodgkin's lymphoma will be alive 5 years after diagnosis [37].

The same treatments as have enabled long-term survival, however, can also cause potentially debilitating deficits, ranging from disruptions in day-to-day activities to such late effects as second primary cancers [13, 15, 36]. While numerous long-term physical effects of childhood cancer have been documented, the impact of such sequelae on patients' quality of life (QL) is much less well understood. Although a growing number of studies have documented the considerable impact of cancer diagnosis and treatment on QL in short-term survivors, less attention has focused on QL in long-term young adult survivors, partly because the rise in survival rates is relatively recent.

It is evident that long-term effects in young adults may differ from those experienced in childhood or adolescence. New issues may come up that were not of concern earlier on. For example, worries about fertility and health of offspring may not emerge until the survivor has reached a certain age and is in a stable relationship and both partners would really like to have children. Some of the late physical effects of childhood cancer treatment, such as those resulting from the cardiotoxic effects of some chemotherapeutic agents, are only just being identified, and how these sequelae may affect the survivors' QL is not known.

The research on QL in young adult survivors of childhood cancer is reviewed in this paper. The purpose of this article is to give investigators and other persons involved in childhood cancer care an overview of the research that has been conducted in this field. On the basis of the literature, limitations of the studies and methodological difficulties are described. Finally, suggestions for future research are given.

The concept of quality of life

Assessment of QL is complicated by the fact that there is no universally accepted definition for it. In the past, most researchers measured only one dimension, such as physical function, economic concern, or sexual function. More recently, researchers have attempted further definition of QL. The World Health Organization defines QL as "individuals' perceptions of their position in life in the context of the culture and value system in which they live and in relation to their goals, standards, and concerns" [44]. The definition includes six broad domains: physical health, psychological state, levels of independence, social relationships, environmental features, and spiritual concerns. The importance of this definition for childhood cancer survivors lies in the inclusion of both emotional and social dimensions of health in addition to physical aspects. While many survivors have no physical evidence of disease and appear to have made full recoveries, others have to come to terms with chronic, debilitating, or delayed effects of therapy. All remain at risk of the development of late sequelae of the former disease and/or treatment and of second malignancies. Furthermore, in most cases the life-threatening experience of cancer is never forgotten. In many ways, survival enhances appreciation of life, while at the same time reminding survivors of their vulnerability. The metaphor of the Damocles syndrome illustrates this dichotomy, and the way individual survivors interpret this metaphor for life will influence the quality of their survival [22].

Methods

A literature search of studies published up to 2001 was conducted using the databases of MEDLINE (National Library of Medicine), CINAHL (Cumulative Index to Nursing and Allied Health Literature), EMBASE and PsychINFO. The keywords 'childhood cancer', '(long-term) survivors', and 'late effects' were combined with dimensions that are often included as components of QL, including psychological/social adjustment, employment/health insurance, schools/learning, and quality of life/health status. Relevant articles were then hand-searched for further pertinent references. Studies published in English were included in the review. This review has been performed according to the methodological criteria defined by Eiser et al. [4] for the inclusion of studies in the field of psychosocial paediatric oncology. These standards are: (1) well-validated and reliable measures, (2) well-matched control group, or comparison with culturally appropriate measurement norms, (3) information about demographics and about illness and treatment factors (at least cancer diagnosis and time since diagnosis), (4) respondent rate, and (5) use of appropriate rigorous statistical tests. Additional selection criteria applied included: (6) survivors as the primary source of QL information, either by means of interviews or by completion of self-report questionnaires (studies with no more than 20% proxies as primary source of information were also included in this review), (7) original diagnoses of survivors made before they were 20 years of age, and (8) at least 5 years' survival after completion of therapy. Some studies, however, included survivors of 5 or more years after completion of therapy along with respondents who were closer to completion of therapy. We decided to include these studies as well because in most cases the mean or median time since completion of therapy ranged from 6 to 15 years. In addition, there is no consensus in the paediatric oncology literature about the definition of a survivor. Some authors define a survivor as a child or adolescent who has been disease free for at least 5 years, while others use disease-free survival for 2 years or more as their criterion. This may be partly due to the different survival perspectives for the different diagnoses in childhood cancer. We intended to limit this review to studies of survivors who were at least 18 years old at the time of investigation. However, a number of studies included survivors both under and over the age of 18 years. Studies of QL that included patients with very wide age ranges were excluded on the grounds that in these studies it is not possible to distinguish the impact of cancer on children from that on older adults. Studies in which results for the long-term survivors or time since completion of therapy were reported separately are included. In most study reports, however, this was not the case.

Initially, the studies featured in this review were selected by two reviewers on the basis of the above methodological criteria. However, we found that in most studies survivors' social functioning (e.g. education, employment) was not measured with the aid of standardised, well-validated instruments. Because we did not want to exclude the social aspects of survivors' QL we decided to include these studies in the review as well, while being aware of the methodological limitations. At the same time, these limitations meant that there was no possibility of doing a systematic review.

A total of 30 empirical studies that met the inclusion criteria were found. We found the results of one study in two different journals, and we have combined these findings in our review [8, 9]. The studies are summarised in Table 1. In this table, the fol-

Table 1 Summary of selected studies in young adult survivors of childhood cancer (*CNS* central nervous system, *ALL* acute lymphoblastic leukaemia, *CRT* cranial irradiation, *HD* Hodgkin's disease, *NHL* non-Hodgkin's lymphoma)

Study	Type of cancer	No. and sex of survivors	Age at evaluation (years)	Age at diagnosis and time since completion of therapy (years)	No., sex and age of control group	Instruments/measures	Results/outcome
[16] (1986)	Mixed	100: 58% men, 42% women	21 +: mean 33, median 32	Range 0–19, 5+	100 Sex-matched siblings: mean 33, median 32	Structured interview, in person or by telephone, about life and health insurance	Survivors had significantly more difficulty in obtaining life insurance an health insurance, because of their past health. Survivors were significantly less likely than siblings to be covered by health insurance
[21] (1986)	Mixed (excluding CNS tumours)	39: 49% men, 51% women	Mean age 23, range 16–33	Mean 13, range 10–18, 5+ since diagnosis: mean 7, range 0–18	Siblings	Structured interview, in person or by telephone, about family demographics, past and present medical problems, academic and career achievements, disease impact, issues related to separation, overall psychological adjustment	No significant difference in marital status, living arrangements, or academic and career attainment. A higher prevalence rate of episodes of treated depression, alcoholism, and/or suicide attempts in survivors than in the general population. Almost half reported that academic plans were altered, and 38% had made changes in their career goals because of the illness
[39] (1986)	Mixed	450: 48% men, 52% women	21+	<19; 5+ since diagnosis	587 sex-matched siblings: 47% men, 53% women	Structured interview in person or by telephone: Addendum to NCI questionnaire about depression, difficulties in obtaining entrance to armed forces or access to educational and employment opportunities, health and life insurance	No significant difference in depression between survivors and siblings, frequency was similar to the general population. No differences in reported frequencies of suicide attempts, running away or psychiatric hospitalisations. Survivors experienced significantly more job discrimination, more rejection from the armed forces and more difficulty in obtaining health and life insurance than their siblings. Depression was not associated with: age at diagnosis, year of diagnosis or type of treatment
[40] (1987)	Mixed	263: 52% men, 48% women	21+: mean 33, range 23–54	<20: 5+ since diagnosis	369 sex-matched siblings: 47% men, 53% women; mean age 33, range 20–59	Structured interview in person or by telephone: Part of NCI questionnaire including decisions about marriage and family planning, outcome of pregnancy	Survivors were less likely to marry. More survivors than controls cited their health as their reason for not marrying. More survivors than controls reported never having been pregnant and having no offspring. No significant difference was found between frequency of birth defects among the offspring of survivors and of controls

Table 1 (continued)

Study	Type of cancer	No. and sex of survivors	Age at evaluation (years)	Age at diagnosis and time since completion of therapy (years)	No., sex and age of control group	Instruments/measures	Results/outcome
[42] (1987)	Hodgkin's disease	40: 55% men, 45% women	Mean 25, range 10 –38	<20: mean 13, range 12–19; 5+ since diagnosis: mean 12, range 7–19	No control group, population norms available	Structured interview in person about perceptions of their cancer, reactions of family and friends, risk-taking behaviour, perceived benefits, education, employment, current medical problems; standardised questionnaire: Diagnostic and Statistical Manual of Mental Disorders	Survivors' educational levels exceeded those expected in sex-, age- and state-matched populations. Overall proportions of married and divorced did not differ from those in general population statistics. Male survivors had a higher rate of divorce than found in age- and race-specific statistics. Frequency of psychiatric diagnoses was no different from that found in the community
[18] (1988)	Mixed	2,283: 50% men 50% women	>21: mean 31, range 21–55	<20: range <5–19; 5+ since diagnosis	3,261 sex-matched siblings: 49% men, 51% women; mean 33, range 19–70	Structured interview in person or by telephone about demographic characteristics, medical and reproductive history, and social characteristics, including highest educational level achieved	No significant differences in educational achievement were found for survivors of non-CNS cancers. Survivors of CNS tumours were significantly less likely than controls to complete eight grades of school or, if they completed high school, to enter college. Educational deficit of brain tumour survivors was especially striking after tumours of the ventricles or cerebral hemispheres, and the deficit was more severe for those who were younger at diagnosis and those treated with radiation therapy than in those treated by surgery alone
[38] (1989)	Mixed (excluding CNS tumours)	40: 40% men, 60% women	Mean 26, range 18–35	Mean 16, range 13–19; 5+; mean 10 since diagnosis	40 healthy sex- and age-matched controls: 38% men, 63% women; mean 26, range 18–35	Semi-structured interview by telephone with standardised questionnaires: Rand Health Insurance Study Functional Limitations Battery (FLB), Physical Abilities Battery (PAB), vocational, insurance, social status, Rand Health Insurance study General Well-Being measure	No differences with regard to overall general well-being, although survivors were more concerned about their health and reported lower general spirits. Survivors' health limited their ability to engage in vigorous activities. Survivors reported disease-related discrimination in hiring, induction into military service, and obtaining health, life, and disability insurance. Survivors did not differ with respect to employment status, but they reported a higher average income than controls

Table 1 (continued)

Study	Type of cancer	No. and sex of survivors	Age at evaluation (years)	Age at diagnosis and time since completion of therapy (years)	No., sex and age of control group	Instruments/measures	Results/outcome
[2] (1989)	Mixed	2,170: sex not given	>21: mean age 31	<20; 5+ since diagnosis	3,138 sex-matched siblings; sex not given; mean 33	Structured interview, in person or by telephone, about demographic characteristics, personal medical history, marriage, divorce, pregnancies, offspring, fertility	Survivors were less likely to be married. Men treated for CNS tumours were the most seriously affected: not only were they less likely to be married, but also their first marriages were shorter and they were older at first marriage. Elevated divorce rate in male survivors of retinoblastoma
[25] (1989)	Mixed	95: 53% men, 47% women	>18: mean age 24, median 22, range 18–35	<16: mean 6; 5+	No. of siblings not given: median age 25	Structured interview by telephone about educational achievement, occupational status, interpersonal relationships, including marital status and progeny, benefits and insurance concerns, medical and health behaviours	Good overall functioning. No difference in the amount of education between survivors and their siblings. Siblings were significantly more likely to be married. Many survivors worried about recurrence of cancer. History of cancer sometimes affected their relationships. Age at diagnosis and type of treatment were not related to level of education
[24] (1989)	Solid tumours (excluding CNS tumours)	94: 51% men, 49% women	Median 23, range 11–15	Median 3, range 0–18	No control group, population norms available	Semi-structured interview in person: about education, occupation, social security, interests, marital status, disease-related opinions	Most survivors had good adjustment; some are at risk of developing emotional and social problems. Education level was similar to, or slightly above, level in general population. Some male survivors were rejected for military service because of the history of cancer. Fewer of the female patients and as many of the male ones were married compared with the general population
[46] (1990)	ALL	46: 52% men, 48% women	Mean 23, range 18–34	<20: mean 7, range 2–18; 5+ since diagnosis: mean 15	Population norms available; control group with survivors with HD + NHL	Standardised questionnaires in person or by mail: Multidimensional Personality Questionnaire (MPQ) Well-Being and Stress Reaction Scales, Minnesota Satisfaction Questionnaire-Short Form (MSQ), Long-Term Follow-Up Questionnaire (LFQ) (medical, employment, marital, and family history), occupational status	ALL survivors appeared to be well adjusted. Female survivors, however, had an greater tendency to experience anxiety in stressful situations. ALL survivors were marrying at a somewhat lower rate than the overall population. Vocational satisfaction did not differ from population norms. Vocational discrimination did not appear to be a problem. Cranial irradiation was negatively associated with well-being

Table 1 (continued)

Study	Type of cancer	No. and sex of survivors	Age at evaluation (years)	Age at diagnosis and time since completion of therapy (years)	No., sex and age of control group	Instruments/measures	Results/outcome
[11] (1991)	Mixed	227: 54% men, 46% women	Median age 27, range 18–44	<20: median 11, range 1–19; 5+ since diagnosis	No control group, population norms available	Self-report questionnaire in person or by mail: about marital status, employment history, current occupation and job duties, health and life insurance status, reproductive history, family history	The percentage of employed survivors was no different from US norms. Percentages of life and health insurances were lower than in the US population. The percentages of married men and women were significantly lower than US norms, especially among women aged 20–24. Women aged 35–44 had a significantly higher frequency of divorce than age-specific group norms. Male gender and age at study were positively associated with employment. Diagnosis, age at diagnosis and disease recurrence were not related to employment, marriage, divorce and insurance
[14] (1992)	Mixed	219; sex not given	30+	<19<, 2+	190 sex-matched siblings or friends	Structured interview, by telephone or mail, about insurance cover, demographic questions on race and ethnicity, occupation, education, employment, income	No differences in education, employment or insurance between non-CNS survivors and controls. Survivors of CNS tumours had limited educational achievements and lower rates of marriage and parenthood
[8, 9] (1992)	Mixed	62: 65% men, 35% women	>18; mean 26, range 18–37	<18: mean 11, range 1–18; 2+; mean 15, range 2–33	51 healthy age-matched peers 45% men 55% women Mean age 26	Standardised questionnaires, in person: Profile of Mood States, Desirability of Control Scale, Control Belief Scale, Locus of Control Scale, Rosenberg Self-Esteem Scale, Impact of Event Scale, projective story-telling technique, screening questionnaire (demographic factors, presence or absence of health-risk behaviours), experience-sampling technique	Survivors were similar to their peers in overall psychological adaptation, both within normal ranges. Survivors reported more positive affect, less negative affect, higher intimacy motivation, more perceived personal control and greater satisfaction with control in life situations. Survivors, especially CNS survivors, were more likely to have repeated school grades. Further, survivors worried more about issues of fertility and expressed more dissatisfaction with important relationships. No effects of time since illness, age at diagnosis, presence of recurrence and report of disability

Table 1 (continued)

Study	Type of cancer	No. and sex of survivors	Age at evaluation (years)	Age at diagnosis and time since completion of therapy (years)	No., sex and age of control group	Instruments/measures	Results/outcome
[29] (1992)	Osteo-sarcoma + Ewing's sarcoma	111: 50% men, 50% women	>21: mean age 33, range 21–51	<20; mean 15, range 3–19; 5+ since diagnosis; mean 18	151 sex- and age-matched siblings: 44% men, 56% women; mean 33, ange 21–66	Structured interview, in person or by telephone, about health status, activities of daily and disability, marriage, fertility, pregnancy, health of their offspring	Osteosarcoma survivors were more likely than their siblings to perceive their health as poor. Survivors were more likely than controls to have some difficulty climbing stairs and to have had employment disability. Marriage rate, fertility, employment status and annual income were similar. Amputation status was not associated with health perception
[12] (1994)	ALL	593: 51% men, 49% women	>18: mean 23, range 18–33	<20: median 10, range 0–20; 2+ since diagnosis	409 sex-matched siblings: 46% men, 54% women; mean 25, range 18–42	Structured interview by telephone about education (highest level of schooling, average grades during high school, enrolment into special programmes	On average, survivors had lower grades, were more likely to enter special education or a learning disabled programme and spent longer in these programmes. Survivors were at higher risk of missing school for long periods and/or repeating 1 year of school. Most survivors have similar rates of high school graduation, college entry, and college graduation to their siblings. Survivors treated with 24 Gy of CRT and those diagnosed at a preschool age were at higher risk for poor educational performance
[6] (1995)	Mixed	48: 54% men, 46% women	Mean 20, range 16–30	Information about age at diagnosis not given; <5 (16 survivors); 5 + (32 survivors)	38 siblings: mean 21, range 16–30	Unstructured interview, in person, about their experiences of cancer; structured interview: questions about their illness and current lifestyle; standardised questionnaire: Oxford Psychologists Press Adult Self-esteem Questionnaire	No significant difference in their educational achievements, employment status and salary earned, driving test achievements, establishment of relationships, participation in societies and competitive sports. Survivors were less likely to go on to higher education. Survivors' overall self-esteem was as high as their siblings

Table 1 (continued)

Study	Type of cancer	No. and sex of survivors	Age at evaluation (years)	Age at diagnosis and time since completion of therapy (years)	No., sex and age of control group	Instruments/measures	Results/outcome
[17] (1995)	Mixed	187: 47% men, 53% women	Range 19–39	<19; 5+ since diagnosis	108 siblings: 43% men, 57% women; range 19–39	Questionnaire by mail, about health insurance	Survivors were found to be more likely to be denied health insurance because of their cancer history and related medical history than their siblings. Survivors also more often had health insurance policies that excluded care for pre-existing medical conditions. Survivors reported more problems in obtaining health insurance coverage, were more likely to be covered by their parents' health insurance policies and had been turned down for a job more often because of their cancer history
[1], (1996)	Mixed (excluding CNS tumours)	168: 63% men, 37% women	Mean 23, range 16–35	Information about age at diagnosis not given, 1+; median 12	129 persons in general population: 47% men, 53% women; range 17–35	Standardised questionnaire by mail: 15-Dimensional questionnaire (15D) (mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity)	Survivors' QL was significantly better than that of controls. Both survivors and controls reported good levels of physical dimensions, sensory dimensions, usual activities and mental function. Although emotional dimensions (depression, distress, vitality, sleeping and discomfort) were less than satisfactory in both groups, survivors reported fewer problems than the controls. Younger survivors reported a better QL. BMT survivors reported a slightly lower QL. Type of cancer, follow-up time and gender were not associated with QL
[32] (1997)	Acute leukaemia	30: 100% women	>16: mean 20	Mean 9: 1+; mean 8	50 healthy age-matched controls: 100% women; mean 20	Self-report questionnaire, semi-structured interview, psychiatric evaluation, psychological tests, in person, about sexual attitudes, fears and behaviours, family and peer relationships, sexual experiences, health and illness concerns, ideals and expectations from life	Age at initiation of dating and sexual activity, frequency of sexual intercourse, and opinions on sexual behaviour were similar. Survivors differed significantly from controls with regard to inner sexuality; images of sexuality more restrictive, attitudes (concerning sexual pleasure) more negative. Sexual identity less often feminine and more often infantile in survivors. Sexual identity not associated with age at study, age at diagnosis, type of treatment or follow-up time

Table 1 (continued)

Study	Type of cancer	No. and sex of survivors	Age at evaluation (years)	Age at diagnosis and time since completion of therapy (years)	No., sex and age of control group	Instruments/measures	Results/outcome
[27] (1997)	ALL (without CRT)	94: 55% men, 45% women	Not given	Mean 5; 15+	90 sex-matched siblings/cousins: 59% men, 41% women	Standardised questionnaires by mail: SF-12 (physical and mental health), General HealthQuestionnaire (depression, strated anxiety, fatigue, social dysfunction), Eysenck's short scale of the EPQ-R (possible late effects on personality); author-developed questionnaire: demographic data, number of offspring, learning problems, level of athletic performance, education and work status	No statistical difference in physical and mental health or QL. The somatisation score on the GHQ involving items closely related to fatigue demon significantly higher scores for the ALL survivors. No significant differences with regard to performances issues, such as academic skills, level of education, work status and level of physical exercise. Male survivors had significantly fewer offspring than their male controls
[45] (1997)	ALL	580: 51% men, 49% women	Mean 23, median age 22, range 18–33	<20: 2+ since diagnosis	396 sex-matched siblings: 46% men, 54% women; mean 25, median 25, range 18–41	Structured interview, by telephone, about education, marital status, employment status, health, fertility, offspring, risk behaviours; standardised questionnaire: Profile of Mood States (POMS) (tension, anxiety, depression, anger, confusion, vigour, fatigue)	Marital differences between survivors and controls were not significant; however, older survivors were more likely never to have married. Survivors were more likely to be unemployed or working less than half-time. Survivors had a greater negative mood, reported more tension, depression, anger and confusion than controls, but scores were not as high as those found in a psychiatric sample. No differences on the vigour and fatigue subscale scores. Female, minority, and unemployed survivors reported highest total mood disturbance
[5] (1997)	Mixed	161: 53% men, 47% women	>15: median age 19, range 15–31	Median 10, range 0–21; 2+; median 7, range 2–15	No control group, population norms available	Standardised questionnaire in person: Symptom Checklist-90 Revised (SCL-90-R) (somatisation, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, distress, cosmetic and functional impairments)	Mean scores on all subscales of SCL-90-R were lower than those of the standardisation sample distributions of scores for anxiety, psychoticism, Global severity index and positive symptom total scores were significantly below normative values. Survivors appear significantly healthier than age- and gender-matched norms for the general population. Older age, disease relapse and functional impairment were risk factors for maladjustment. Not associated were diagnosis, age at diagnosis, type of treatment, cosmetic status, gender and socioeconomic status

Table 1 (continued)

Study	Type of cancer	No. and sex of survivors	Age at evaluation (years)	Age at diagnosis and time since completion of therapy (years)	No., sex and age of control group	Instruments/measures	Results/outcome
[30] (1997)	Ewing's sarcoma family tumours	89: 54% men, 46% women	Mean 29, range 10–48	Mean 15, range 4–34; mean 13, range 2–29	97 sex- and age-matched siblings: 47% men, 53% women; mean 31, range 10–57	Questionnaire, by mail, about education, job history, marital status, fertility, health status, diet, exercise habits, health insurance, health care needs; standardised instrument: Karnofsky performance scale (current functional status)	No difference in educational achievement. Survivors were less likely to be employed full-time, to be married and to have children. Survivors were more likely to be divorced than their siblings. No difference in self-rating of health status or in health care insurance status, but more problems in getting job-related health insurance. Functional status was adversely affected in survivors: they scored significantly worse than sibling controls. Having children was not related to treatment-related factors. Marriage was not associated with the treatment protocol or body irradiation
[7] (1998)	Osteosarcoma + Ewing's sarcoma	60: 43% men, 57% women	Mean 24, range 15–30	Mean 15, range 0–25; 1+ since diagnosis; mean 8, range 1–21	No control group, population norms available	Standardised questionnaires in person: Questionnaire on Subjective Well-Being (positive attitudes towards life, depressive mood, joy of life), State-Trait-Anxiety Inventory (trait-anxiety), Frankfurt Self-Concept Scales, Questionnaire on Life Goals and Satisfaction with Life; semi-structured interview about socioeconomic issues, life-style, problems and limitations due to disease and its consequences, overall QL	Survivors did not show a higher rate of serious personality disturbances or psychosocial problems than controls. Many, however, dealt with problems such as restricted mobility, catching up at school, changing jobs or job orientation. Survivors appeared to be married at a lower rate and seemed to live at home longer. Levels of education and income were similar. Survivors diagnosed in adolescence had more problems (especially with social well-being) than those diagnosed in childhood or early adulthood. Physical or functional sequelae and disease-related variables were not associated with psychosocial adjustment
[3] (1999)	Mixed	64: 47% men, 53% women	>18: mean 24, range 18–35	<18: mean 12, range 1–17; 3+; mean 10, range 3–21	51 age- and sex-matched controls: 53% men, 47% women; mean 23, range 18–32	Structured interview, in person, about level of functioning and achievement in the domains of education, employment, military service, social/family status, health status; standardised questionnaire: Mental Health Inventory (anxiety, depression, loss of control, general positive feeling, positive relationships)	No differences in education, employment, marital status or relationships with significant others. No evidence of increased psychological impairment or pathology. Survivors experienced military recruitment difficulties, lower income levels and higher rates of workplace rejection. Almost half reported feelings that their illness experience had impaired their achievement in education, social and family goals

Table 1 (continued)

Study	Type of cancer	No. and sex of survivors	Age at evaluation (years)	Age at diagnosis and time since completion of therapy (years)	No., sex and age of control group	Instruments/measures	Results/outcome
[33] (1999)	Mixed	10,425: 54% men, 46% women	Median 26, range 15–48	<21: median 7, range 0–21; 5+ since diagnosis	No control group, population norms available	Questionnaire, by mail, about marital status	Survivors, especially female and white survivors, were less likely ever to have married, but once married were less likely to divorce/separate. Black survivors were generally found to be more likely to have married, with men and blacks more likely to divorce/separate once married. Survivors of CNS tumours, particularly men, were less likely ever to have married and more likely to divorce/separate than those with other diagnoses and the general US population
[41] (2000)	Bone tumours	33: 55% men, 45% women	>16: mean 25, range 16–50	Information about age at diagnosis not given; 1+; mean 6, range 1–11	No control group, population norms available	Standardised questionnaires by mail: Two items EORTC-QLQ-C30, SF-36, shortened version Social Support List-Interactions and Social Support List-Discrepancies, items from EORTC QLQ-BR23, physical functioning and prosthesis, negative and positive effects of surgery	Survivors' physical functioning was poorer than that of healthy peers but better than chronically ill patients. Levels of psychosocial functioning, general QL and social support were highly comparable with healthy peers
[20] (2000)	ALL (with CRT)	94: 43% men, 57% women	Median 20, range 15–32	Median 5, range 1–15, mean 150	134 siblings: 49% men, 51% women; median 19, range 14–32	Questionnaire, by mail, about school career	Significantly more survivors than siblings were placed on special educational programmes. Survivors had also a lower level of secondary education. Younger age at diagnosis was negatively related to educational level. Gender and cranial irradiation dose were not associated with educational level
[23] (2000)	ALL + Wilms tumour	102: 56% men, 44% women	Mean 26, range 20–31	<16: mean 5, range 0–15; 5+; mean 16, range 5–29	102 healthy age- and sex-matched controls: 56% men, 45% women; mean 26, range 20–31	Standardised questionnaires in person; Schedule for Affective Disorder and Schizophrenia lifetime (SADS-L) with DSM-III-R, Adult Personality Functioning Assessment (APFA), Raven's standard progressive matrices	No elevated rates of psychiatric disorder for survivors. Mean scores were significantly higher (indicating poorer functioning) in survivors than in controls for love/sex relationships, friendships, non-specific social contacts and day-to-day coping. Mean overall work and educational performance scores did not differ between groups. Poor close relationship was related to longer duration of treatment and more recent illness, while age at diagnosis was not associated

lowing information is provided for each study: (a) the reference to our list and the year of publication; (b) type of cancer; (c) number and sex of survivors; (d) age at evaluation; (e) age at diagnosis and time since completion of therapy; (f) number, sex and age of subjects in control group; (g) instruments/measures used; and (h) results/outcome. These parameters are reviewed and summarised in the following five sections. The first section describes physical functioning, including QL and general health. The second section summarises the results relating to psychological functioning: overall emotional functioning, depression and anxiety, and self-esteem. No studies were found on the cognitive or neuropsychological aspects of psychological functioning in childhood cancer survivors. The third section describes social functioning, including education, employment, insurance, living situation, marital status and family. Sexual functioning is the topic of the fourth section, and in the fifth section factors related to survivors' functioning are summarised: demographics, and illness- and treatment-related factors.

Results

Of the 30 studies, 17 involved survivors of different cancers and did not attempt to distinguish between diagnostic groups in terms of outcome [1, 2, 3, 5, 6, 8, 11, 14, 16, 17, 18, 21, 25, 38, 39, 40]. Three of these studies excluded survivors of a CNS tumour [1, 21, 38]. Six studies focused specifically on leukaemia survivors [12, 20, 27, 32, 45, 46], and Mackie et al. [23] included survivors who had been treated for ALL and Wilms tumour. Four studies examined survivors treated for a bone tumour [7, 29, 30, 41]; one study investigated Hodgkin's disease survivors [42]; and one study was found in which survivors treated for solid tumours, except for CNS tumours, were investigated [24].

The majority of the studies discussed in this review were conducted in the United States [2, 5, 8, 11, 12, 14, 16, 17, 18, 21, 25, 28, 30, 33, 38, 39, 40, 42, 45, 46]. Three studies were conducted in Finland [1, 24, 32], 2 in the United Kingdom [6, 23], 2 in The Netherlands [20, 41], 1 in Norway [27], 1 in Austria [7], and 1 in Israel [3]. Sample sizes varied from 30 [32] to 10,425 [33]. Survivors differed in age at the time of evaluation (range from 10[1] [30, 42] to 55 years [18]), age at diagnosis, and time since completion of therapy. Twelve investigators used time since diagnosis as a criterion. Most investigators (*n*=22) compared the results in survivors with those in sex- and age-matched siblings, peers or healthy controls. Seven studies included comparison with population norms [5, 7, 11, 24, 33, 41, 42], and 1 study included both population norms and a control group of survivors with a different cancer diagnosis [46]. The instruments used in most of the studies were a mixture of standardised questionnaires and tests (see Table 2). In the remainder the instruments were mostly newly developed questionnaires with no information given on reliability and validity; some authors used less highly structured interviews.

Physical functioning

Four investigations asked survivors for a general evaluation of their health. The majority of the survivors (89%) in the study by Meadows et al. [25] reported being in good to excellent health. Nicholson et al. [29] investigated 111 bone tumour survivors, and 80% of osteosarcoma and 100% of Ewing's sarcoma survivors classified their health as good or excellent. Similar findings of apparently good health when compared to siblings were reported by Novakovic et al. [30], who studied 89 survivors of Ewing's sarcoma family tumours. However, the osteosarcoma survivors in the study by Nicholson et al. [29] were more likely than their siblings to perceive their health as fair or poor; this was neither explained by an excess of chronic health conditions nor related to amputation status. When Dolgin et al. [3] asked participants to rate their current health status on a five-point scale, survivors rated their health as poorer than controls.

However, the QL of the survivors and their controls was explored by use of the SF-12 in the study by Moe et al. [27] and with the Rand Health Insurance study General Well-being Measure by Tebbi et al. [38]. Neither of these studies found any statistical differences between the groups with respect to physical health and QL. However, Moe et al. [27] found that the somatisation score on the General Health Questionnaire with items closely related to fatigue demonstrated a significantly higher score for acute lymphoblastic leukaemia (ALL) survivors than for controls. Fatigue was also mentioned in Wasserman et al.'s study [42]. One of the physical residual effects, as reported by 5% of the Hodgkin's disease survivors, was easy fatigability. Nevertheless, Zeltzer et al.'s study [45] showed no difference between the Profile of Mood States (POMS) Fatigue subscale scores of 552 ALL survivors and 394 sibling controls.

Apajasalo et al. [1] used the 15D (a 15-dimensional questionnaire) to examine the health-related QL of 168 survivors with a range of different malignancies and 129 controls. They found that the QL score of the survivors was significantly better than that of the controls; survivors reported better levels of vitality, distress, depression, discomfort, elimination and sleeping dimensions. There were no differences in QL between survivors with different malignancies, but it should be noted that the numbers in each diagnostic group were small.

Three studies attempted to measure physical functioning in bone tumour survivors. Two studies used a study-specific questionnaire [29, 41], and the Karnofsky performance scale was used in the other study [30]. In all studies there is evidence that the bone tumour group had poorer physical functioning than their controls. These included specific difficulties with climbing stairs [29] and "general physical functioning" [30, 41].

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[1] As mentioned in the methods section, a number of studies included survivors both under and over the age of 18 years

Table 2 Standardised instruments used in quality of life studies of survivors of childhood cancer

Instrument	Studies using instrument
Physical functioning	
15 D (15-dimensional questionnaire)[a]	[1]
Items EORTC QLQ-BR23	[41]
Items EORTC QLQ-C30	[41]
General Health Questionnaire[a]	[27]
Karnofsky performance scale	[30]
Physical Abilities Battery (PAB)	[38]
Profile of Mood States (POMS) fatigue subscale[a]	[45]
SF-12[a]	[27]
SF-36	[41]
The Rand Health Insurance Study Functional Limitations Battery (FLB)	[38]
The Rand Health Insurance Study General Well-Being measure[a]	[38]
Psychological functioning	
Overall emotional functioning	
15 D (15-dimensional questionnaire)[a]	[1]
General Health Questionnaire[a]	[27]
Mental Health Inventory	[3]
Multi-dimensional Personality Questionnaire(MPQ) Well-Being and Stress Reaction Scales	[46]
Profile of Mood States (POMS)[a]	[8, 9, 45]
Questionnaire on Subjective Well-Being	[7]
SF-12[a]	[27]
Symptom Checklist-90 Revised	[5]
The Rand Health Insurance Study General Well-Being measure[a]	[38]
Depression and anxiety	
Diagnostic and Statistical Manual of Mental Disorders (DSM)	[42]
General Health Questionnaire[a]	[27]
Mental Health Inventory[a]	[3]
Profile of Mood States (POMS)[a]	[45]
Schedule for Affective Disorder and Schizophrenia lifetime (SADS-L)	[23, 39]
State-Trait-Anxiety Inventory	[7]
Symptom Checklist-90 Revised	[5]
Self-esteem	
Frankfurt Self-Concept Scales	[7]
Rosenberg Self-Esteem Scale	[8, 9]
Oxford Psychologists Press Adult Self-esteem Questionnaire	[6]
Other	
Control Belief Scale	[8, 9]
Desirability of Control Scale	[8, 9]
Eysenck's Short Scale of the EPQ-R	[27]
Impact of Event Scale	[8, 9]
Locus of Control Scale	[8, 9]
Minnesota Satisfaction Questionnaire-Short Form (MSQ)	[46]
Questionnaire on Life Goals and Satisfaction	[7]
Raven's standards progressive matrices with Life	[23]
Social functioning	
Adult Personality Functioning	[23]
Long-term Follow-up Questionnaire (LFQ)	[46]
Social Support List-Interactions and Social Support List-Discrepancies	[41]
Sexual functioning	
No instruments	

[a] Questionnaire consisting of both physical and psychological items

Psychological functioning

With respect to psychological functioning, we found that most studies focused on emotional aspects, using many different instruments. Most authors employed standardised measures with the availability of norms and comparison groups. In this section, emotional functioning is described in terms of overall emotional functioning, depression and anxiety, and self-esteem.

Overall emotional functioning

All investigations assessing the overall emotional or mental functioning of the survivors used standardised measures containing various dimensions of emotional well-being. In general, survivors seemed to be well adjusted. Most researchers found no difference in functioning between survivors and healthy peers and/or normative samples, based on the scores on the Rand Health Insurance Study General Well-Being measure [38], Multi-dimensional Personality Questionnaire Well-Being and Stress Reaction Scales [46], Profile of Mood States [8], SF-12 and General Health Questionnaire [27], Symptom Checklist-90-Revised (SCL-90-R) [5], Questionnaire on Subjective Well-Being [7], and Mental Health Inventory [3]. For the small percentage of survivors who did display one or more clinical elevations on the SCL-90-R, three factors were identified which were associated with increased risk of maladjustment: older age at follow-up, greater number of relapses, and presence of severe functional impairment [5]. Survivors of bone tumours diagnosed in adolescence had more problems than survivors who became ill during childhood or early adulthood [7].

In two studies survivors appeared to be less well adjusted emotionally than their healthy peers or the general population. Lansky et al. [21], who used a structured interview to assess overall psychological adjustment, reported a higher prevalence rate of episodes of treated depression, alcoholism and/or suicide attempts in survivors than in the general population. Both Gray et al. [8] and Zeltzer et al. [45] measured overall psychological adaptation with the Profile of Mood States. While the first authors reported that 62 survivors with a range of diagnoses were similar to their 51 healthy age-matched peers, the 580 ALL survivors in Zeltzer et al.'s study had a greater negative mood, more tension, depression, anger and confusion than their 396 sex-matched siblings. The female survivors reported the highest mood disturbance. However, their scores were not as high as were found in a psychiatric sample. Finally, Elkin et al. [5] found that survivors' scores on the SCL-90-R subscales Anxiety, Psychoticism, Global Severity Index, and Total Positive Symptoms were below normative values, suggesting that this group of survivors must be healthier than would be expected according to normative data.

Depression and anxiety

In some studies depression and anxiety were measured with a subscale of a standardised instrument measuring overall emotional adjustment. In most studies [3, 5, 8, 27, 39] no increased rates of depression and/or anxiety were reported. Zeltzer et al. [45], however, reported more depression among ALL survivors than among their siblings, and Lansky et al. [21] found that the prevalence of treated depression was higher in survivors than in the general population. Moreover, female survivors of ALL experienced more anxiety in stressful situations than the sex-appropriate norms, in contrast to males, who scored below the norms [46]. Felder-Puig et al. [7] used the scale "trait-anxiety" from the State-Trait-Anxiety Inventory in their study. No increased anxiety was found for the 26 survivors of bone tumours relative to the norm group.

In three studies, the Diagnostic and Statistical Manual of Mental Disorder (DSM) criteria were used to assess the frequency of affective disorders in survivors. Teta et al. [39] used the Schedule for Affective Disorder and Schizophrenia (SADS-L) and found that the prevalence of lifetime major depression in 450 survivors (with a variety of cancers) did not differ from that of their 587 sex-matched siblings. It was also similar to those reported in the literature for the general population. More recently, similar findings were reported by Mackie et al. [23], who found no increased rates of minor depression in 169 survivors of ALL or Wilms' tumours relative to 102 healthy age- and sex-matched controls. Finally, Wasserman et al. [42], who included a DSM psychiatric assessment in the interviews with 40 survivors of Hodgkin's disease, reported that the frequency of psychiatric diagnoses in the sample was basically no different from that found in community studies.

Self-esteem

In three studies assessing self-esteem with (a part of) a standardised instrument, no differences between survivors and control groups and/or normative groups were found. More specifically, the 60 bone tumour survivors in Felder-Puig et al.'s study [7] scored within normal ranges on the Frankfurt Self-Concept Scales, as did the 62 survivors on the Rosenberg Self-Esteem Scale [8]. The survivors in the latter study did not differ from their healthy peers. Finally, overall self-esteem of 48 survivors with a range of diagnoses was as high as that of their healthy siblings, as measured with the Oxford Psychologists Press Adult Self-esteem Questionnaire [6].

Social functioning

Across studies, social functioning has been operationalised in a variety of ways, covering such issues as education, employment, insurance cover, living situation, marital status, and fertility, including reproductive capacity and family planning. Most investigations used (semi-) structured interviews with author-developed questionnaires.

Education

With respect to education, many research studies have demonstrated that survivors of childhood cancer, as a whole, did not differ much from controls or from the general population [3, 6, 7, 14, 18, 21, 24, 25, 27, 30, 42], although there were exceptions in certain subgroups of survivors. Kelaghan et al. [18] investigated the level of education in 2,283 survivors and compared the results with those of 3,261 sibling controls. The survivors of CNS tumours diagnosed before age 15 were significantly less likely than their controls to complete the eighth grade of school. CNS tumour survivors who did complete secondary school were also less likely to enter college. The deficit was more severe in survivors who were treated with radiation therapy than those who underwent surgery alone. They also found that an early age at diagnosis was associated with a larger educational deficit than late age at diagnosis. Another study [14] reported that although 91% of the CNS tumour survivors had completed high school, only 10% had received a bachelor's or equivalent degree, as against 98% and 25%, respectively, in the non-CNS tumour group. Two studies evaluated the impact of treatment on scholastic performance in survivors of ALL [12, 20]. Significantly more survivors than controls were placed in a special educational programme [12, 20] or a learning-disabled programme [12]. In Kingma et al.'s study [20] in ALL survivors with cranial radiotherapy (CRT) a significant difference in the level of secondary education was found for all survivor/sibling comparisons except in the case of survivors aged over 7 years at the time of diagnosis, whose mean level of education no longer differed from that of their siblings. Younger age at diagnosis was also associated with referrals. The researchers found no effect of gender or irradiation dose on referral to special schools or on level of secondary education. In contrast, Haupt et al. [12] reported that the risk associated with special education and learning-disabled programmes increased with increasing dose of CRT. Survivors treated with 24 Gy and those diagnosed before 6 years of age were less likely to enter college.

Finally, Evans and Radford [6] concluded from their study of 48 survivors with various tumours that there was no significant difference between survivors and siblings in qualifications at 16 years. However, survivors were significantly less likely to go on to higher education (16 years onwards) than their siblings. Many survivors (67%) felt that their education had suffered as a result of their disease. This percentage was higher than that found in Dolgin et al.'s study [3], in which 45% of the survivors reported that their illness had impacted on their educational achievement to a (very) great extent. In contrast, 77% of survivors in another study said that their cancer had had no effect on their educational achievements [25].

Employment

The employment problems of cancer survivors have been of increasing interest during the last decades. Zeltzer et al. [45] studied 580 young adult survivors of ALL and found that significantly more survivors than sibling controls who had not enjoyed higher education were unemployed or were working less than half-time. This finding agrees partly with the study by Green et al. [11], who compared 227 former paediatric cancer patients with population norms. They found that the percentage of unemployed male survivors did not differ from the population norms. The percentage of unemployed female survivors, however, was slightly higher than that in the U.S. population in general. Other studies found that survivors and controls did not differ with respect to employment status [3, 6, 14, 21, 27, 38, 46] and that the majority of long-term survivors old enough to be in the work force were employed in a range of professional, clerical, and skilled labour positions [7, 38]. Two studies looked specifically at survivors of bone tumour survivors. Nicholson et al. [29] studied 111 survivors treated for Ewing's sarcoma and osteosarcoma and found that, in spite of a greater likelihood of having ever been disabled, their employment status did not differ from that of their siblings. Felder-Puig and colleagues [7], however, noted that many survivors treated for a bone tumour reported major difficulties in obtaining work.

In 1987, Mellette and Franco [26] reviewed the literature relating to employment of survivors of childhood cancer. They noted that, whereas in studies of a decade ago various forms of discrimination were reported, recent studies had been unable to document many such problems. Nevertheless, Green et al. [11] found evidence of employment-related discrimination in 11% of 227 childhood cancer survivors who were treated between 1960 and 1985. Almost 30% of the male survivors were rejected for military service. However, these frequencies were lower than those reported by Teta et al. [39] and Wasserman et al. [42] in 1986 and 1987, respectively. Teta et al. reported in their study of 450 survivors and their 587 siblings that there was significantly more rejection of survivors (85%) than of their siblings (18%) by the military and other prospective employers (survivors 32%, siblings 21%). In Wasserman et al.'s study of 40 survivors of childhood and adolescent Hodgkin's disease, 20% reported that they had experienced job discrimination. In a recent study by Dolgin et al. [3], 46% of the Israeli survivors reported that their illness had impacted on their employment histories "to a great extent" or "to a very great extent". Forty-five percent of the survivors had been rejected from a workplace, compared with 19% of the controls. Approximately half of these survivors felt that their workplace rejection was due to their cancer history. They also found that 55% of the survivors had difficulty being accepted into the military service. Rejection for the military has also been reported in another investigation [14].

Six studies have assessed the level of income. Dolgin et al. [3] and Hays [14] found that survivors reported lower annual income than the controls; however, in the latter study this difference was not significant. Interestingly, the survivors in Tebbi et al's [38] study reported a higher mean income than controls. The other studies found no differences [6, 7, 29].

Insurance

Obtaining adequate health and life insurance has been a recurring problem for survivors of cancer. Although the differences were not significant, male and female survivors reported they were turned down for life and health insurance more frequently than their siblings [39]. A report of insurance problems among 100 survivors who were treated during the years 1945–1975 showed that 24% had difficulty in securing health insurance and 15% had no health insurance at the time of the survey, versus 0% and 7%, respectively, in these categories among controls [16]. Difficulty in obtaining life insurance was noted by 44% of survivors and by only 2% of matched controls. Tebbi et al. [38] found that many survivors had difficulty in obtaining health, life, or disability insurance. Green et al. [11] found that the percentages of survivors who had life insurance and company-offered health insurance were lower than those reported for the general U.S. population. Twenty-four percent of those with life insurance had had difficulty in obtaining it. Although a small percentage (7%) of survivors in the study by Hays et al. [14] had been denied employment-related health insurance at some time and another 8% had at some time had health insurance cover that excluded cancer, most survivors were covered by health insurance policies without cancer-related restrictions. There were no differences from the controls. Evidence of both past and current discrimination in obtaining affordable life insurance on the basis of a cancer history was clearly recognisable. However, the majority of survivors who desired life insurance were insured and at standard rates. Novakovic et al. [30] found no difference in health care insurance status, but more problems in getting job-related health insurance. Finally, Jacobson Vann et al. [17] assessed the effects of having a cancer diagnosis on the subsequent acquisition of health insurance cover for young adults diagnosed as children in North Carolina. They found that survivors were turned down for health insurance cover more often than their siblings, which was due, according to the survivors, to their cancer history and related medical history. Survivors were also more likely than their siblings to have health insurance policies with clauses excluding cover for pre-existing health conditions. When participants were asked whether they had had problems in obtaining health insurance coverage, 24% survivors answered “yes”, as opposed to 2% of the responding siblings. Furthermore, survivors were 4.3 times as likely to be covered by their parents’ health insurance policies.

Living situation, marital status and family

Only two investigations have specifically addressed the living situation of young adult survivors. In a pilot study of 39 survivors Lansky et al. [21] found that survivors did not significantly differ from the sibling group in living arrangements (with parents versus other); however, the survivors left home at a slightly older age (21 versus 19 years). The survivors in Felder-Puig’s study [7] also seemed to stay at home longer after reaching adulthood than controls of a similar age.

Two studies have focused solely on marriage issues among childhood cancer survivors, and several studies of the late effects on cancer treatment have included data on marital status as an indicator of social competence. The largest and most comprehensive study of marriage, which compared 10,425 survivors with a broad range of diagnoses with U.S. population norms, was published by Rauck et al. in 1999 [33]. They found that the percentage of survivors who had ever been married was lower than that in the general U.S. population within similar age groups. In particular, compared with their age-matched counterparts in the general population, women and whites were less likely to have married, whereas black survivors were more likely to have married. Comparison of childhood tumour types showed that survivors with a diagnosis of CNS tumours, particularly males, were less likely to have married than those with other diagnoses or the general population. In the second largest study of marriage, which compared 2,170 survivors with sibling controls, Byrne et al. [2] also found that, as a group, survivors were less likely to be married and that the differences were greatest among male survivors of CNS tumours. Similar findings were reported in some smaller studies. Zevon et al. [46] found a decreased frequency of marriage for both men and women relative to the U.S. population in a group of 46 survivors with ALL. These conclusions were supported in a study of 227 survivors, including a few with a diagnosis of CNS tumour, by Green et al. [11] and in two other studies with survivors of bone cancer [7, 30]. Green et al. [11] also found that marital status was not affected by age at diagnosis, gender, history of disease recurrence or diagnosis. Teeter et al. [41] reported data collected by the University of Kansas on marital status among 263 survivors and 369 controls. Twenty-five percent of the survivors and 16 percent of the controls had never married. Makipernaa [24] studied survivors diagnosed with solid tumours (excluding CNS tumours) and found that fewer of the women and as many of the men were married as in the general population. Finally, in a study of 95 survivors, Meadows et al. [25] found that survivors were less likely to be married than members of the sibling control group. However, the authors stated that this was probably a biased comparison, because the siblings as a group were older than the survivors.

In contrast, other studies have suggested that there are no significant differences among survivor/control comparisons with respect to marital status. For example, Nicholson et al. [29] found no marriage deficit relative to controls in a population of 111 survivors of bone cancer. Hays et al. [14] reported marriage statistics from two centres, which showed no difference between survivors with a variety of diagnoses and the general U.S. population when CNS tumours were excluded. Wasserman et al. [42] studied 40 survivors of childhood and adolescent Hodgkin's disease and also found that the overall proportions of marriage in the survivors were not different from the general population statistics. Four other studies yielded similar results [3, 6, 21, 45].

Some studies provide data on specific reasons for not marrying. All the participants in the Teeter et al. study [40], were asked whether they had refrained from marrying for medical or health reasons. Twenty-one survivors (31%) and one control (2%) said that they had not married for health reasons. Green et al. [11] found that among the survivors who had never married or lived as married (*n*=96), almost 16% reported that their history of childhood cancer had influenced their decisions on marriage. In Makipernaa's study [24] 5 survivors reported that it was expressly the cancer treatment that had made them decide to remain single. One woman emphasised that knowing she had had a hysterectomy had prevented her marriage. Four others felt that the cancer and its treatment had so impaired their appearance that it hampered their personal contacts. Most single survivors in Meadows et al.'s study [25] indicated that having had cancer had no impact on their desires or opportunities for marriage. However, 21% said that having had cancer sometimes affected their ability to meet others, and 38% reported that their history of cancer sometimes scared others.

There was no significant difference in the overall frequency of separation or divorce in the study by Green et al. [11]. However, a more detailed analysis of the separation and divorce data revealed that the percentage of divorced women aged 35–44 was significantly greater relative to that in the normative group. Zevon et al. [46] also reported an elevated frequency of divorce in women compared with the rates for the general population. In contrast, separate analysis of the men in the study of Wasserman et al. [42] showed a significantly higher rate of divorce than in age- and race-specific statistics. Survivors of bone tumours were also found to be more likely to have divorced in the study by Novakovic et al. [30]. One study found that, in general, the proportion of survivors who were divorced or separated was lower than that in the U.S. population [33]. Men, however, were more likely to have divorced or separated than their age-matched counterparts in the general population, and women less likely. Survivors with the diagnosis of CNS tumour were also more often divorced or separated than those with other diagnoses or the general population. The latter finding was confirmed by Hays et al. [14], who found that in the CNS group 23% of survivors had been divorced, versus 8% in the non-CNS tumour category. Byrne et al. [2] also reported that first marriages of male survivors of CNS tumours who were diagnosed before age 10 years were three times as likely to end than those of controls. They also found that male survivors of retinoblastoma had higher divorce rates than male controls.

The effect of a history of childhood cancer on divorce was addressed in one study [11]. For those survivors who were separated or divorced, 20% (*n*=5) reported that their history of childhood cancer had been a contributing factor to the dissolution of their relationships.

The issue of fertility has been investigated by several investigators. Nicholson et al. [28] found that although deficits in crude fertility rates were significant when all former bone cancer survivors were compared against all controls, these differences were nonsignificant after controlling for sex. According to Moe et al. [27] men once diagnosed with ALL had significantly fewer offspring than the men in the control group, whereas the women in the ALL group had slightly more children than their controls. Three other studies reported that the percentage of survivors with children was lower than the percentage of controls [14, 30, 40]. Among the survivors who had ever been married or lived as married in Green et al.'s [11] study, 10% indicated that their history of childhood cancer influenced their decision to limit the number of children they had to a moderate or greater degree. For an additional 10%, their medical history was a factor that contributed to their decision to have no children. Worries about reproductive capacity were reported in three studies. Gray et al. [8] found that survivors were more likely than a matched control group of peers to report worrying about being able to conceive a child. When Wasserman et al. [42] conducted open-ended interviews in 40 adult survivors of Hodgkin's disease, they found that female survivors often reported concerns about fertility, whereas male survivors did so much less often. Forty-six percent of the female ALL survivors and 29% of the male ALL survivors in Zevon et al.'s study [46] reported being concerned about possible future health problems their children might experience as a result of their cancer history.

Sexual function

So far, not many studies provide data on sexual function. Veenstra et al. [41] assessed body image and sexual function in 33 bone tumour survivors with a rotation plasty. Almost half of the survivors felt slightly to very limited in initiating intimate relationships as a result of the rotation plasty. While 19 survivors reported that they did not feel physically unattractive as a result of the rotation plasty during the week prior to the assessment, 10 reported feeling a little unattractive and 4 reported feeling quite a bit to very unattractive. Of the survivors who were sexually active (n=21), 10 survivors reported that they were limited in their sexual activities to a small (n=8) or moderate (n=2) degree as a result of the surgery.

Puukko et al. [32] investigated possible changes in sexual identity, sexual attitudes, and sexual behaviour of 30 female survivors diagnosed with acute leukaemia as compared with healthy age-matched controls. They found that survivors did not differ from controls with respect to the following aspects of sexual behaviour: age at which dating began, onset and frequency of sexual intercourse, and opinions on sexual behaviour. They also found that there were significant differences in behaviour: survivors were less likely to have experienced sexual intercourse, less likely to have initiated intercourse, less likely to masturbate, and less likely to have talked with friends about sexual topics. With regard to inner sexuality, survivors also differed from controls. Their images of sexuality were more restrictive, and their attitudes, especially those concerning sexual pleasure, were more negative than those of the controls. Finally, sexual identity among the survivors was less often feminine and more often infantile than among controls.

Factors related to survivors' functioning

Fortunately, not all young adult survivors of childhood cancer seem to suffer from the late sequelae of their disease and/or treatment. So it is very important to identify factors that predict good QL and to trace risk factors. In most studies factors related to survivors' function have been discussed to some extent. Predictors can be divided into demographics and illness- and treatment-related factors.

Demographics

In several studies gender has been investigated in relation to survivors' functioning. Especially female survivors seemed to be at risk for psychological problems. According to Zevon et al. [46], female ALL survivors had an increased tendency to experience anxiety in stressful situations, and in the Zeltzer et al. study [45] female ALL survivors reported the greatest total mood disturbance. With respect to marriage, the percentage of married female survivors was lower [11, 33], but according to Rauck et al. [33] female survivors were less likely to divorce/separate. However, Green et al. [11] found that a subgroup of female survivors (aged 35–44) had a significantly higher frequency of divorce than age-specific group norms. Male gender was positively related to employment [11]. In contrast with these findings, Apajasalo et al. [1], Elkin et al. [5] and Kingma et al. [20] reported that gender was not associated with survivors' functioning respectively with QL, maladjustment according to the SCL-90-R, and educational status.

In five studies, age at study has been analysed in relation to outcome. Age was found to be negatively related to psychological functioning. Younger survivors reported a better QL [1], and older survivors scored higher on the Symptom Checklist [5]. Older survivors were also more likely never to have married than younger survivors [45], but they were more likely to be employed [11]. The sexual identity of the survivors seemed not to be associated with age according to Puukko et al. [32].

Two studies reported results relating to minority survivors. Minority survivors of ALL showed the highest mood disturbance [45]. Black survivors were generally found to be more likely to have married, but also more likely to have divorced/separated once married than the general US population [33].

Illness and treatment related factors

Age at diagnosis is one of the factors that has been most frequently investigated in relation to survivors' functioning. Survivors diagnosed at a younger age were at higher risk of poor educational performance [12, 18, 19]. Felder-Puig [7] concluded that survivors of bone tumours diagnosed in adolescence had more problems (especially less social well-being) than those diagnosed in childhood or early adulthood. In contrast, in seven other studies age at diagnosis appeared not to be associated with outcome, and/or not to be related to emotional functioning [8], depression [39], maladjustment in terms of the SCL-90 [5], poor close relationships [23], sexual identity [32], educational level [25], or marriage, divorce, employment and insurance [11].

With respect to the diagnosis (type of cancer), CNS tumours versus other diagnoses is the comparison that has been most intensively investigated. It was found that survivors of CNS tumours were more seriously affected. Their educational level was lower [8, 14, 18], and they were less likely to be married [2, 14]. Moreover, they were more likely to have divorced and their rates of parenthood were also lower [14]. Elkin et al. [5], who studied survivors with a range of diagnoses, found no relation between type of cancer and QL. Similar findings were reported by Apajasalo et al. [1], who excluded survivors with CNS tumours.

With respect to type of treatment, radiation therapy appeared to be a risk factor. First, survivors who were treated with cranial irradiation showed less well-being than the other ALL survivors [46]. Second, treatment with radiation therapy versus surgery alone [18] and a higher dose of cranial irradiation [12] seemed to be risk factors for poor educational performance. However, among the ALL survivors in Kingma et al.'s study [20], the cranial irradiation was not associated with educational level.

In a sample of survivors with a range of diagnoses (except CNS tumours) survivors of bone marrow transplantation has a slightly lower QL than the other survivors [1]. In three other samples with a variety of diagnoses no association was found between the type of treatment and outcome: emotional functioning according to the SCL-90 [5], depression [39], or educational level [25]. Moreover, Puukko et al. [32] concluded that the sexual identity of ALL survivors was not predicted by the type of treatment and Novakovic et al. [30] found that the treatment protocol of bone tumour survivors was not related to marriage and having children.

According to Mackie et al. [23], longer duration of treatment in survivors of ALL and Wilms' tumour was related to poor close relationships. In the same study this was also found in survivors whose illness was more recent. In three studies in which time since diagnosis or time since end of treatment was investigated no association with outcome was found [1, 8, 32].

Only three studies looked at the effect of recurrence of the disease. While Elkin et al. [5] concluded that disease relapse was a risk factor for emotional maladjustment, the opposite was found in the study by Gray et al. [8]. Green et al. [11] also found no evidence that recurrence of cancer was related to survivors' functioning; specifically it was not related to marriage, divorce, employment and insurance.

Medical and functional late effects were investigated in two samples of survivors of bone tumours. Nicholson et al. [29] reported that amputation status was not associated with health perception and Felder-Puig et al. [7] found no correlation between emotional functioning and physical or functional sequelae. In line with these results, disability, which was reported by survivors with different tumours, was not related to emotional functioning [8]. In contrast, Elkin et al. [5] concluded that severe functional impairment was a risk factor for maladjustment, while cosmetic status was not.

Conclusions and future directions

The purpose of this review was to give an overview of the research about QL in young adult survivors of childhood cancer populations during the last two decades. This review identified a wide variety of studies. Studies are characterised by a high degree of heterogeneity with respect to: the patient samples investigated (e.g. survivors with different cancers who had undergone a variety of treatments), the comparison groups selected, the QL dimensions assessed and the instruments employed. Additionally, age at time of evaluation, age at diagnosis, and time elapsed since completion of therapy varied widely. Moreover, the majority of the studies reviewed suffered from at least one of the following methodological weaknesses: small samples, nonstandardised, study-specific instruments, and cross-sectional rather than prospective designs. Given all these differences between studies, perhaps it is not surprising that outcomes of studies differ and that the QL reported by survivors also varies, making it impossible at this time to come to firm conclusions about the magnitude and nature of long-term consequences for childhood cancer survivors.

However, despite the heterogeneity in study procedures and the methodological shortcomings, some clear trends emerge from this review. Although some inconsistent data have been reported across studies, the results suggest the following.

- Physical functioning

1. The majority of survivors reported they were in apparently good health, with the exception of bone tumour survivors, who were more likely to perceive their health as fair or poor. Bone tumour survivors also had poorer physical functioning than their controls. Difficulties in climbing stairs and poor "general physical functioning" were reported.
2. Some studies mentioned fatigue as a residual effect of treatment.

- Psychological functioning

1. Most long-term survivors functioned well psychologically and did not have significantly more emotional problems than controls. The subgroup of survivors who reported problems mentioned depression, mood disturbances, tension, anger, confusion and anxiety. Female gender, older age at follow-up, greater number of relapses, presence of severe functional impairment, cranial irradiation and minority survivors were associated with an increased risk for emotional problems in some studies.

- Social functioning

1. Survivors of CNS tumours and survivors of ALL seemed to be at risk for educational deficits. Cranial irradiation and an early age at diagnosis was associated with educational deficits. Many survivors reported that their education had suffered as a result of their disease.
2. The majority of survivors old enough to be in the workforce were employed. Although in almost all research survivors did not differ from controls with respect to employment status, some survivors experienced some form of job discrimination and difficul-

ties in obtaining work. Problems in obtaining health and life insurance were also reported.

3. Survivors seem to stay at home longer after reaching adulthood and leave home at an older age than their controls.
4. There is a lower prevalence of marriage among survivors, particularly in male survivors with a diagnosis of CNS tumours. The survivors reported that the history of childhood cancer, the consequences of treatment and problems with health as specific reasons for not marrying.
5. The percentage of survivors with children seems lower. The survivors indicated that the medical history is a factor that contributes to the decision to have no children. Many survivors reported worrying about their reproductive capacity and/or about possible future health problems their children might experience as a result of their cancer history.

Childhood cancer was almost always a fatal disease in the not-too-distant past. Over the last decades significant treatment advances have been made, and long-term survival is now a reality. With the increasing number of long-term childhood cancer survivors, the need to assess their QL is becoming more important and meaningful. This article has summarised what is known about the long-term effects of disease and treatment on the QL of survivors. Where do we go from here?

It is evident that additional research is needed. Although the low incidence of childhood cancer, the variety of diseases and treatments and the wide range in ages pose methodological problems in QL assessment, we need well-designed studies. Since not many institutions have a sufficient number of patients to control for the numerous patient-specific and therapy-specific variables involved, multi-institutional collaboration is recommended. At the least, account must be taken of the age of the child at diagnosis and treatment, the length of time since completion of therapy, and the differences in severity of the cancer and its treatment, and thus the treatment era. The QL dimensions of interest, and therefore the outcome measures of the study, must be clearly defined. This will enhance the possibility of comparing international studies and conducting systematic reviews. Researchers should attempt to use prospective study designs with sufficiently large sample sizes, choose instruments appropriate to their goals, and establish the methodological properties of the instruments they use in keeping with that goal. However, in this still-evolving area of research, it is wise for investigators to include an opportunity for survivors to report additional concerns not covered in standardised QL scales wherever possible. Naturally, one or another is dependent on the question of whether the main objective is measurement of differences between patients at one particular point in time or of longitudinal change within patients over time.

As Gotay and Muraoka [10] stated in their review on QL in adult-onset cancer survivors, there is a need to understand the long-term impact of different treatments on QL. It is important to document how varying therapeutic modalities can give rise to different long-term effects. Such information can establish whether there are any residual effects of one treatment but not another and whether there are treatment-related decrements in QL that vary in the short term and long term. Further, little is known about the impact of persistent effects of cancer treatment on survivors' QL. Survivors may learn to live with and adjust to their possible limitations, they may continue to experience problems to the same degree as during short-term survival, or their tolerance of disability may decline with the passage of time (i.e., an enhanced QL, an unchanged QL, or a worsened QL, respectively) [10]. It is also important to identify the subgroups of survivors who have problems rather than evaluating only differences between survivors as a whole and their controls.

Many of the studies reported to date are based on North American samples; this seems to be an area of research in which North American researchers have taken a lead. However, there are many cultural differences between the United States and European countries, in addition to dissimilarities in their health care systems, particularly with respect to health care insurance. No studies were found for this review from anywhere outside the United States and Europe, and this raises questions about the functioning of childhood cancer survivors in other countries. The increasing cultural/ethnic diversity of people within the borders of all countries and the growing communication network around the globe underscore the relevance of cross-cultural comparisons [31]. It is known that there are many differences in adjustment to cancer across cultures. The cultural distinctions between and within national boundaries provide a unique opportunity to examine differences in the meaning of survivorship, as well as values and behaviours, in different groups.

Future research efforts should also be directed at the intermediate factors of QL that have received relatively little attention in previous studies, including the role of coping and adaptation, social relationships and family variables. Considering that many survivors are functioning reasonably well and that not much difference is found between results in survivors and in their peers, it would be interesting and advisable to investigate the role of denial and response-shift. It would also be interesting to know whether survivors meet developmental tasks in growing up. More insight is therefore needed into the relation between the survivors' course of life and their functioning in later life. The need for future studies applies for other aspects as well, such as posttraumatic stress, body image and spiritual dimensions. Although these concepts are investigated in younger survivors, we did not find any studies in which these topics had been measured with standardised questionnaires and compared with norms in young adults. It is also remarkable that no studies about cognitive functioning in (young) adult survivors of childhood cancer were found, in contrast with the large number of studies done in children. As Kingma [19] has mentioned, it is not yet known what may happen to maturing brains long after exposure to CRT and/or chemotherapy in childhood. Furthermore, in the adult cancer literature it is suggested that more research is needed because neuropsychological symptoms, particularly problems with memory and concentration, are frequently reported by cancer patients treated with chemotherapy, even years after completion of treatment [35].

As we learn more about the challenges associated with long-term childhood cancer survival, interventions will be needed to address the problems identified. It is possible that some problems can be prevented and others remedied if appropriate care is provided. However, it is critical to determine the kind of support desired by long-term survivors and to identify who is most in need of and likely to benefit from such interventions [34, 43]. Therefore, it is critical to ask survivors what they need and what they want, for example by means of focus groups. Interventions to reduce psychological morbidity or improve QL, such as patient education, coping skills management, and support groups deserve continued attention. Studies are needed to identify the extent to which these interventions improve QL.

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