



## Review article

## Cancer-related fatigue in adolescents and young adults: A systematic review of the literature

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## ABSTRACT

Adolescents and young adults with cancer (AYA) represent a specific age cohort dealing with the disease in a stage of life characterized by development, upheavals, and establishment. The aim of this study was to point out the state of research on how AYA are affected by cancer-related fatigue (CRF).

**Results:** Twelve articles were included. CRF was found to be higher in AYA than in either of the comparison groups, healthy peers and older cancer patients. Most included studies did not measure CRF with multidimensional, fatigue-specific instruments.

**Conclusion:** We found a gap in research concerning CRF in AYA. The existing findings suggest that CRF is a significant issue for AYA cancer patients. However, less is known about the prevalence, severity, and impact of CRF in AYA, and their treatment. This should be considered in future research, and risk and prevention factors should be ascertained. Multidimensional and fatigue-specific measuring tools should be used to do this.

## 1. Introduction

The cohort of Adolescents and Young Adults with cancer (AYA) is strongly underrepresented in cancer research (Reuben, 2017; National Cancer Institute, 2006) although the incidence of cancer in AYA in Europe, the USA, and Canada has increased over the last decades (Midtgaard and Quist, 2008). As the overall-survival rate in this cohort is about 80% (Borchmann et al., 2017), the number of cancer survivors who were first diagnosed during their adolescence or young adulthood is continually increasing. While the age definition of AYA is not consistent in research, the National Cancer Institute (NCI) has adopted the age range of 15–39 years (National Cancer Institute, 2006). Even though AYA are an inhomogeneous cohort with many different cancer entities, stages, and treatment protocols, they must cope with the same twofold burden: Adolescence and young adulthood are characterized by developmental challenges such as becoming financially and socially independent, moving out of the parental home, establishing a partnership, and starting a family and career (Warner et al., 2016; Ramphal et al., 2011; Zebrack, 2011). In addition to these tasks, AYA must deal with their illness, diagnostics, cancer treatment, follow up visits, and survivorship concerns as well as body image disruptions, sexual problems, obesity, and secondary malignancies (Cooke et al., 2011; Eiser et al., 2007; Thomas et al., 2006).

One of the most common symptoms reported by both adults and

children with cancer is cancer-related fatigue (CRF) (Barsevick et al., 2013). CRF affects almost all cancer patients, regardless of the specifics of their diagnosis (Bower et al., 2014; Brown and Kroenke, 2009). The National Comprehensive Cancer Network (NCCN) defined CRF as ‘a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning’ (Berger et al., 2010). Nowadays CRF is regarded as a multidimensional construct that encompasses physical, emotional, and cognitive fatigue (deRaaf et al., 2013; Scott et al., 2011). Both cancer and cancer treatment seem to influence fatigue (Brown and Kroenke, 2009; Bower et al., 2000). CRF has been found in patients before, during, and after treatment as well as years after complete remission (Bower et al., 2000). However, the state of knowledge about the prevalence of CRF specifically in the AYA cohort lags behind that for other groups (Barsevick et al., 2013; Curt et al., 2000).

Many studies have focused on cancer-related fatigue in older patients (> 39 years) as several previous reviews have pointed out (Campos et al., 2011; Oh and Seo, 2011). Other reviews have shown that research on cancer-related fatigue is also more comprehensive in younger adolescents (< 18 years) (Erickson, 2004; Spathis et al., 2015). As early as 2004, Erickson found 15 studies dealing with CRF in younger adolescents (12–19 years) (Erickson, 2004), and Spathis et al. included 27 studies in their 2015 review that investigated CRF in young

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adolescent cancer patients and long-term cancer survivors (13–24 years) (Spathis et al., 2015). However, to our knowledge, so far, no reviews have been done on CRF in AYA specifically in the age-range defined by the National Cancer Institute (National Cancer Institute, 2006). This is the case in spite of the fact that former research has recognized cancer patients 15–39 years old as a specific age cohort deeming investigation independent of other age groups (National Cancer Institute, 2006).

The aims of this review were to show the current state of research on cancer-related fatigue in adolescents and young adults diagnosed with cancer. The analysis was based on the following questions:

- What is the prevalence and severity of CRF in AYA?
- Which factors are associated with CRF in AYA?
- Which interventions exist to effectively alleviate CRF symptoms in AYA?

## 2. Methods

The databases PubMed, Web of Science, CINAHL, and PsychInfo were searched for articles in English or German published between January 1990 and September 2015. The publishing date filter was chosen based on the fact that most of the research that has been done on AYA has taken place in that time frame (National Cancer Institute, 2006). Thus, that parameter seemed most likely to yield appraisable results. The search string was applied to titles and abstracts. In addition to the word-for-word search, the Medical Subject Headings (MeSH) “fatigue”, “adolescent”, “young adult”, “medical oncology”, and “neoplasms” were integrated in the PubMed search.

The terms used are shown in detail in Table 1.

After removing duplicates, the titles and abstracts of the identified literature were first screened independently by two reviewers. Articles were then included if the studies they described:

- used quantitative methods,
- focused on cancer patients diagnosed between 15 and 39 years of age, and
- measured cancer-related fatigue.

In the second screening, the full-text articles were assessed by two authors working together. The inclusion criteria were as stated above. Additionally, hand searches were carried out for the references of the assessed full-text articles ( $n = 102$  screened; one article included (Singer et al., 2011)).

To assess the quality of the included studies, we used a quality score computed as follows:

- |                           |   |
|---------------------------|---|
| • Used scale:             | 1-Item-Scale (0 points)<br>Scale with more than 1 item (2 points)<br>Multidimensional fatigue instrument (4 points) |
| • Number of participants: | $n < 50$ (0 points)<br>$50 < n < 100$ (1 point)<br>$n > 100$ (2 points)   |

**Table 1**  
Search terms.

#1	fatigue OR CRF OR weariness OR weary OR tired*
AND	
#2	adoles* OR young adult OR young adults OR youth OR AYA OR teen* OR child* OR paediatric OR CCS
AND	
#3	oncolog* OR cancer OR neoplasm* OR tumour OR tumour OR malign*

Thus, the highest possible quality score of an included study was 6 points and the lowest was 0 points.

## 3. Results

Out of 2128 search results, 102 articles were preselected based on their title and abstract for full-text screening. In total, 12 studies were included in this review. Fig. 1 illustrates the selection strategy.

### 3.1. Characteristics of the 12 included studies

Table 3 gives an overview of the characteristics of the articles included in the review: Seven studies were conducted in the USA (Erickson et al., 2014; Rabin et al., 2011; Rosenberg et al., 2013; Sanford et al., 2014; Smith et al., 2013a,b) while the other included studies were executed in Europe (Bifulco et al., 2012; Geue et al., 2014; Hauken et al., 2015; Heutte et al., 2009; Singer et al., 2011; Weiss et al., 2013) (Table 3). Six articles reported on AYA with all cancer entities (Erickson et al., 2014; Rabin et al., 2011; Geue et al., 2014; Hauken et al., 2015; Singer et al., 2011; Weiss et al., 2013). Regarding to the different cancer sites, the included studies reported on patients treated with different types of cancer therapy (e.g. surgery, chemotherapy, radiotherapy) (Table 3). Two studies (Smith et al., 2013a,b) used the same raw data derived from the *AYA Hope Study* (Harlan et al., 2011). The sample size of the included studies ranged from  $n = 14$  to  $n = 484$ . Two of the selected studies only investigated cancer-related fatigue in women (Rosenberg et al., 2013; Bifulco et al., 2012). Seven studies had longitudinal designs (Erickson et al., 2014; Rabin et al., 2011; Sanford et al., 2014; Hauken et al., 2015; Heutte et al., 2009; Singer et al., 2011; Weiss et al., 2013) and three of those were interventional studies (Rabin et al., 2011; Hauken et al., 2015; Weiss et al., 2013). The time of enrolment differed greatly between the reviewed studies (Table 3). Four studies compared AYA to older cancer patients (Sanford et al., 2014; Bifulco et al., 2012; Heutte et al., 2009; Singer et al., 2011), and another three used comparisons with age-matched reference samples from the general population (Smith et al., 2013a; Geue et al., 2014; Hauken et al., 2015). Six of the 12 included studies got a quality score  $\geq 4$ . The other 6 included studies used 1-Item-Scales to assess CRF ( $n = 2$ ) or included too few participants ( $n = 4$ ) (Table 3).

The most commonly used instrument for measuring fatigue was the *European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30* (EORTC-QLQ 30) (Bifulco et al., 2012; Geue et al., 2014; Hauken et al., 2015; Heutte et al., 2009; Singer et al., 2011; Weiss et al., 2013). Two studies used 1-item fatigue scales (Rosenberg et al., 2013; Sanford et al., 2014) and two studies used the *Multidimensional Fatigue Inventory* (MFI-20) (Heutte et al., 2009; Singer et al., 2011). All of the instruments used are described in Table 2.

### 3.2. Prevalence of CRF in AYA

Of the 12 included studies, one reported on the prevalence of CRF in all AYA cancer patients aged 20–39 years old, regardless of cancer site (Singer et al., 2011). Singer et al. (Singer et al., 2011) used the MFI to assess CRF. At the beginning of treatment (t1), the authors found a prevalence of CRF of 53.1% (95% CI: 43.1–63.1%) for the participants. This rate was seen to have increased at hospital discharge (t2) (Prevalence of CRF = 55.1%;  $p < 0.05$ ) (Singer et al., 2011).

### 3.3. CRF in AYA compared to healthy peers and older cancer patients

AYA reported significantly higher fatigue scores compared with age matched healthy reference samples in two studies, one that reported on all cancer sites in patients having completed acute treatment (Geue et al., 2014), and another that only included patients with haematological cancer and sarcoma 6–14 months after their diagnoses (Smith et al., 2013a). Although the Hauken et al. (Hauken et al., 2015) results

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