

# Fear of cancer recurrence in adolescent and young adult cancer survivors: a systematic review of the literature

Running title: FCR in AYAs

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## **Abstract**

**Objective:** The current systematic review aims to provide an overview of fear of cancer recurrence (FCR) in adolescent and young adult cancer survivors (15-39 yrs at cancer diagnosis, AYAs).

**Methods:** MEDLINE, PubMed, PsycINFO and Embase databases were independently searched to identify relevant quantitative articles. PRISMA systematic review procedures were followed with quality assessment.

**Results:** Seventeen studies were included in the current review. All were quantitative studies that utilized a cross-sectional study design. Seven articles reported results of FCR prevalence, six studied determinants related to FCR and eleven articles provided information about consequences of FCR. Prevalence of FCR ranged from 31% to 85.2% among AYA survivors. Associations between sociodemographic/clinical variables and FCR were inconsistent. Psychological distress, and higher treatment intensity were positively associated with higher FCR levels. Lower scores on levels of physical, psychological functioning and overall health-related Quality of Life (QoL) were identified as consequences of increased FCR.

**Conclusion:** FCR appears to be a prevalent concern among adolescent and young adult cancer populations. Adequate assessment to determine need for support and intervention is still required. Longitudinal studies in AYAs are warranted to understand the development and potential influence of FCR. Age-appropriate and flexible psychological care would be more successful potentially with this crucial background information.

## **Keywords:**

Adolescent, Cancer, Fear of recurrence, Oncology, Review, Survivor, Young adult

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## 1. Introduction

Many different labels have been utilized to describe fears about the spread or relapse of cancer, such as fear of recurrence/fear of cancer recurrence (FoR or FCR) [1], fear of progression (FoP) [2], or worry/concern about disease return [3] etc. However, researchers tend to believe that these descriptions are virtually comparable on a conceptual level [2, 4, 5], and for practical purposes, there is indeed very strong overlap among them. In this review, the term FCR was used. FCR is commonly defined as: *fear, worry, or concern relating to the possibility that cancer will come back or progress* [6]. Patients with high FCR often report significant psychological distress (i.e. depression, anxiety), increased health service use [7, 8], as well as negative behavior changes (i.e. avoidance, excessive personal self-examination behaviors) [9-12]. This concern may appear immediately after cancer diagnosis or treatment and has been shown to remain stable for years [13].

Recent studies have shown that about 24-40% of the survivors reported moderate to high levels of need for help dealing with their FCR [14-16]. Studies consistently reported that survivors diagnosed at a young age, female gender, and patients with more physical symptoms were more likely to experience higher FCR [14, 17]. Meta-analysis showed that having had a mastectomy [4], radiotherapy [18] or chemotherapy [19] were significantly related to elevated fear level. A recent study indicated that psychological factors play a stronger role in FCR than demographic or clinical factors [20]. Lebel *et al.*, found that a patient's FCR was significantly predicted by the individual's perceived risk of recurrence, illness uncertainty, and triggers [7]. Smith and colleagues indicated that negative metacognitive beliefs, as well as intrusive post-traumatic stress symptoms were independent correlates of FCR, which accounted for 26% and 28% of the total observed variance, respectively [21]. Another large sample study in Chinese cancer patients revealed that higher stress, anxiety, depressive symptom and personality (pessimism) were significant predictors of FCR, and hierarchical regression analysis showed that sociodemographic and clinical factors only accounted for 6.9% of the variance of FCR while psychological variables explained 33.1% of the total variance [22].

Many reviews have been conducted to provide overall knowledge about FCR in adult survivors. The first literature review on FCR was published in 1997 by Lee-Jones and

colleagues [1]. Since the publication of the first review, FCR research has expanded considerably. In recent years, Crist *et al.* [23] performed a systematic review to identify key variables associated with FCR and eventually included 43 studies in the article. They reported the most consistent predictor of elevated FCR was younger age, and revealed that low optimism, family stressors as well as fewer significant others were additional important factors moderately associated with higher FCR. Simard and his colleagues [17] performed the most recent and robust review of quantitative studies in 2013 by searching more databases and identified 130 eligible articles. They concluded that younger age, psychological distress, and lower quality of life (QoL) were consistently associated with increased FCR, and family caregivers tended to report higher FCR than the patients. In the same year, Koch *et al.* [4] completed a systematic review in long-term cancer survivors (above 5 years since diagnosis). They reported that survivors suffered from FCR even years after initial cancer diagnosis, and studies including long-term and short-term survivors showed no significant change of FCR over time. In addition, reviews concentrating on specific cancer populations were also conducted. In 2015, a review by Ozga *et al.* [24] was published and it concluded that hopelessness, anxiety about death, uncertainty of the future, faith and more PTSD symptoms were significantly related to FCR in ovarian cancer survivors.

Even though these FCR literature reviews have been published since 1997, and previous research has consistently showed that young age was significantly associated with increased FCR, this relationship has only been observed in adult samples, and no review has focused specifically on how FCR manifests itself in adolescent and young adult (AYA) cancer survivors. However, cancer is the leading cause of disease-related death among AYAs [25], and recently national AYA programs have been attempted to fill the gap between the pediatric and adult oncology services and to provide better support for AYAs cancer patients [26]. We believe these features indicate an important need to conduct a specifically targeted systematic overview of FCR in adolescent and young adults.

There are different definitions of the AYAs among countries [26]. In a recent report WHO summarizes that adolescents and youth are referred to as young people, encompassing the ages of 10 to 19 years [27]. In the United States, adolescent and young adults are patients

aged between 15 to 39 years at cancer diagnosis. However, in the UK, the spectrum of AYAs are patients aged between 13 to 24 years. Other countries, such as Netherlands, consider patients aged of 18 to 35 years at diagnosis as AYAs, while some other countries have not yet set a clear definition of it.

In the current review, we use the US definition of AYAs in order to include more eligible studies. It has been reported that around 70,000 AYAs are diagnosed with cancer every year in the US, which accounts for nearly 5% of the total cancer diagnoses in the country [28]. Research also reported that AYAs are more likely than either younger persons or older adults to be diagnosed with certain types of cancer, such as leukemia, testicular cancer, thyroid cancer and Hodgkin lymphoma, and the most common cancers in AYAs are: brain, breast, cervical and colorectal cancer [28]. However, the unique genetic and biological features of adolescent and young adult cancer patients were still unclear.

In all, the majority of existing studies on FCR has been performed with mixed-age samples or adult samples of breast cancer patients. It is still unclear how FCR behaves among AYA cancer survivors. This current review focuses on this special group of people aged between 15 to 39 years old at cancer diagnosis and aims to assess the prevalence, potential determinants (i.e. correlates or predictors) and consequences/outcomes of FCR among AYAs.

## **2. Methods**

### **Literature search**

MEDLINE, PubMed, PsycINFO and Embase databases were systematically and independently searched by two authors (HMW and WJL), from their inception until 1<sup>st</sup> September 2018, to identify relevant articles. No restrictions were placed on publication date. PRISMA systematic review procedures were followed including a quality assessment (the PRISMA checklist is presented in supplementary file 1) [29]. The systematic review was registered on PROSPERO on 11<sup>th</sup> Oct 2018, and the registration number is: CRD42018112306.

The key search terms were: (“fear” [Mesh] or worry or concern), (“neoplasm” [Mesh] or cancer or carcinoma), (“recurrence” [Mesh] or progression or return or relapse), and (“adolescent” [Mesh] or teenager or teens or “young adult” [Mesh] or youngster or young or

AYA). Searching was conducted using the 'OR' and 'AND' functions. The detailed strategy and search result of each database is outlined in supplementary file 2. The references in identified articles were also screened manually for any additional relevant studies.

### **Inclusion and exclusion criteria**

Studies were screened for eligibility before inclusion. According to the PICOS acronym, to be included in this review, references had to meet the following criteria: Participants (*P*): AYAs aged between 15 to 39 years at cancer diagnosis; Interventions (*I*): NA; Comparisons (*C*): NA; Outcomes (*O*): quantitative FCR results on prevalence, influencing factor, and consequence; Study Design (*S*): cross-sectional, longitudinal or RCT studies. Papers needed to be written in English and published in peer-reviewed journal. References were excluded if they were conference abstracts, editorials, commentaries, dissertations, review articles, or case studies. Studies using similar, however not accurate keywords such as 'fear of dying', 'fear of the future' or 'fear of the worst happening' were also excluded. Studies that compared FCR outcomes between AYA group and older adult group were included in the review, but only when FCR results of AYAs were reported. References were screened for eligibility by two authors (YY and YHW).

### **Data extraction**

Titles and abstracts of potential eligible records were reviewed after removing duplicate studies, then unsuitable articles were excluded. Full papers were subsequently obtained and examined. Only papers that fulfilled the full inclusion criteria for the review were kept. For each study, the following data were extracted: 1) first author's name, 2) year of publication, 3) country of study, 4) study design, 5) basic sociodemographic and clinical/treatment information of the study sample (such as age at diagnosis and at survey, gender percentage, time since diagnosis), 6) FCR measurement, and 7) main findings of the study (i.e. FCR prevalence, potential determinants and outcomes). The independent variables of the original article were classified as the 'potential determinants', while the dependent variables were considered as the 'outcomes/consequences'.

## **Quality assessment**

The quality of each included article was assessed using the Standard Quality Assessment Criteria for quantitative studies (QualSyst criteria) [29]. Items were scored on the specific criteria (Yes = 2, Partial = 1, or No = 0). Items not applicable to a particular study design were marked 'N/A' and were excluded from the calculation of the total quality score. A summary quality score was calculated for each study by summing the total score obtained across relevant items and dividing by the total possible score (i.e.: 28-(number of 'N/A' x 2)). Strong quality was defined as (> 0.80), good quality (0.70 - 0.80), adequate quality (0.50 - 0.70), or limited quality (<0.50) [29]. The quality assessment was conducted by two researchers independently (YY and YHW). In situations of disagreement of a study, another researcher (LW) repeated the assessment and in discussion reached consensus. Senior author (HWS) overviewed the procedures.

## **3. Results**

### **Study selection**

The search process is presented in Figure 1. The literature search of Pubmed, Embase, PsycINFO and MEDLINE databases identified 1004 references. After duplicates were excluded, 835 records remained. Examination of titles and abstracts for appropriateness left 58 articles. After retrieving full texts and further evaluation, 17 studies were included in the systematic review. All the included studies were assessed by the QualSyst criteria, and none were scored as limited quality. Detailed scores of quality assessment are showed in supplementary file 3.

### **Characteristics of included studies**

The publication dates of the studies ranged from 1997 to 2018 (two articles were published in the 1990s [30, 31], three in the 2000s [32-34], and the remaining articles were all published since 2010). Nine studies were conducted in the US, two each in Canada, Netherlands, and Germany, and one each in Sweden and Finland. Sample size varied from 20 to 1395. Three studies concentrated specifically on AYA breast cancer survivors [32, 35, 36], one focused on gynecological cancer [37], one on leukemia [30], eleven articles studied mixed AYA cancer populations, and one did not report cancer type [38].

Eleven studies reported both age at cancer diagnosis and age at survey, two studies only reported age at diagnosis [26, 36] and 4 only reported age at survey [31, 32, 35, 39]. As for FCR measurement, questionnaire(s) were frequently utilized (as opposed to standardized clinical interview). The number of scale items ranged from 1 to 30, and only eight studies utilized a validated instrument, such as Cancer Worry Scale (CWS), Concerns About Recurrence Scale (CARS) and Fear of Progression Questionnaire-short form (FoP-SF). Four studies used a single FCR question [25, 31, 32, 40] and five used study-specific questions. In all, seven articles reported results of FCR prevalence, six of them studied determinants related to FCR and 11 articles provided information about consequences of FCR. Main characteristics and findings of the included articles are presented in Table 1.

### **Prevalence of FCR**

Seven articles reported prevalence data on FCR [25, 26, 30, 32, 37, 41, 42]. Thewes [26] and colleagues investigated 73 adolescents and young adults (aged 18-35) and found 45 of them (62%) reported high levels of FCR (CWS total score  $\geq 14$ ). This finding is similar to Mattsson's study which reported 185 out of 286 (61%) of young gynecological cancer survivors experienced FCR [37], but it is inconsistent with Wang's study which found that only 7% of the AYAs reported strong worry about recurrence (rated as 'strongly agree') [42]. Another study with 292 survivors showed that about half of the participants experienced moderate-to-high recurrence fear ( $2 \leq \text{FCR mean score} < 3$ ), but only 13% of them reported high level of FCR (mean score=3) [41]. Puukko *et al.* also suggested that around 52% of survivors experience FCR. However, a much higher figure (85.2%) was reported in a large sample study of 1395 AYAs using a single FCR question derived from the Quality of Life in Adult Cancer Survivors Scale [25]. Only one study reported longitudinal outcomes of FCR prevalence, this study revealed that about 29% of AYA survivors reported FCR at study baseline, and the percentage slightly increased at one-year follow up (31%), which indicated that FCR tended to remain stable in AYAs. Overall, across different cancer types and evaluation strategies, 29% to 85.2% of AYA survivors reported some degree of FCR [25, 30, 32, 37], 31% to 49.1% reported moderate to high level of FCR [41, 42] and 13% to 62% reported high level of FCR [26, 42].



## **Determinants of FCR**

Potential determinants of FCR were classified into three groups (demographic, clinical/treatment, and psychological) according to conceptual similarity. In those studies where both univariate and multivariate analyses were employed, multivariate results were presented preferentially. In all, six studies investigated determinants related to FCR [25, 26, 35, 37, 42, 43].

Detailed factors associated with FCR in AYA cancer survivors were presented in Table 2.

Thewes *et al.* [26] examined the relationship between a number of sociodemographic and clinical variables with levels of FCR. Results show that participant's age, gender, education, living situation, occupational status, cancer type, phase of treatment, and cancer stage were not significantly related to recurrence fears [26]. Mattsson *et al.* [37] investigated 337 gynecological cancer survivors and found that age at diagnosis, previous serious life events and have children or not did not have significant associations with FCR levels. However, multimodal treatment (such as surgery, and/or chemotherapy and/or radiotherapy) and a history of psychological distress significantly predicted cancer related distress, such as FCR. Inconsistent findings were reported by Shay and her colleagues. They found that FCR was associated with gender, employment and type of cancer. Survivors who were employed and less than 5 years from treatment were positively related to FCR, while thyroid cancer survivors, and those in clinical trial were less likely to report FCR [25].

Additionally, Lebel [35] concluded that younger age at diagnosis (less than 35) was associated with greater FCR than survivors in the other age categories. Wang *et al.* [42] revealed that female and higher treatment intensity were significantly associated with increased FCR. One study examined the relationship between spiritual distress and FCR in 120 mixed AYA cancer survivors and found that spiritual struggle was significant positively related to FCR in a bivariate correlation analysis. However, this association disappeared when having undergone chemotherapy was controlled [43].

## **Consequences of FCR**

Eleven articles reported information about consequences of FCR [26, 30, 32-34, 36, 38-41, 44]. A study [31] found that FCR was the foremost intense life change the AYA survivors had

experienced. Strong evidence has been found to support the relationship between high FCR and low Quality of Life [26, 33, 41]. Thewes *et al.* [26] found that adolescent and young adult cancer survivors who reported high FCR tended to report worse functioning in both psychological and social domains. Compared with survivors with low FCR, those who experienced higher FCR were also more likely to report higher anxiety levels, total psychological distress and lower overall health-related quality of life. However, no difference was found for depression, physical or religious functioning. Cho *et al.* [41] found that FCR was significant negatively associated with both mental and physical health related QoL. Additionally, the negative relationship between FCR and mental health-related QoL was moderated by perceived growth.

Poort and colleagues [44] examined the association between FCR and fatigue severity by the Cancer Worry Scale and Checklist Individual Strength (CIS-fatigue). Findings revealed that higher FCR was moderately correlated to fatigue severity [44]. Studies also found that FCR may lead to decreased breast self-examination frequency [32] and less nicotine dependence [40]. Compared to younger adolescents (aged 12-15), older adolescents (aged 16-18) are less likely to perform breast self-examination because of general fear about cancer and FCR.

In addition, FCR may also influence AYA survivor's attitude towards future pregnancy and parenting, one study showed that more than one third of the participants did not want to have additional children because of FCR [36]. However, other studies indicated that FCR did not significantly affect an individual's attitude towards self-image or life outlook, and Puukko *et al.* [30] indicated that FCR was not related to the frequency of somatic symptoms in AYA cancer survivors. Consequences of FCR in AYA cancer survivors are summarized in Table 3.

#### **4. Discussion**

Even though FCR study has expanded progressively over the last decade, there are only a few studies that focus specifically on FCR in AYA cancer survivors. To our best knowledge, at least three reviews of the literature have been conducted in AYAs to investigate their post-treatment outcomes, Quality of Life, as well as the influence of psychosocial interventions [45-47]. However, this is the first review to explore FCR in AYAs. It has been frequently reported that younger age is significantly associated with higher levels of FCR [17].

Therefore, we believe it is of importance to systematically explore the prevalence, correlates and potential consequences of FCR in this special population group.

Of the 17 included articles, of which all, but one, received a strong overall quality rating, three concentrated specifically on breast cancer survivors, and one on leukemia. It has been found that the incidence of specific cancer types varies according to age [28]. For example, leukemia, lymphoma, testicular cancer, and thyroid cancer are the most common cancers among 15-24-year-olds, and among 25-39-year-olds, breast cancer and melanoma are the most common. Our review also found that all of the included studies were conducted in North America or European countries, which indicated that Asian countries have not provided sufficient attention on FCR in AYA survivors.

### **Prevalence of FCR**

The prevalence data on FCR is inconsistent. Simard *et al.* [17] reported that around 39% to 97% (on average 73%) of adult cancer survivors reported some degree of FCR and 0% to 15% (on average 7%) reported high degree. In the current review, we found 29% to 85.2% of AYA survivors reported some level of FCR, and 13% to 62% reported high level. The interpretation of the prevalence across studies is challenging as many studies utilized single question/unvalidated study-designed scales which provided limited psychometric evidence. In addition, no consensus is available about the definition of AYA or what constitutes clinical levels of FCR.

One study found that there was a slight increase in FCR over time in AYA cancer population. A recent study followed adult breast cancer patients soon after primary surgery and assessed FCR at baseline, 6 and 18 months follow up [48]. They reported that FCR was stable for the first 6 months but at 1.5 years increased in younger compared to older patients. Another study by Manne and colleagues [49] found that nearly 50% of the adult patients diagnosed with gynecological cancer continued to experience a high level of FCR (high-stable) 6 months after cancer diagnosis, and about 25% of them reported decreasing FCR over time (high-decreasing) while the remaining 25% reported consistently low FCR (low-stable).

## **Determinants of FCR**

Most the demographic and clinical factors were found to be not significantly associated with levels of FCR in AYAs, but weak evidence emerged for gender, treatment intensity and psychological distress. Even though only two studies suggested that female experienced greater fear than male AYAs, this finding is consistent with several studies in adult cancer patients [13, 50-52]. However, many contrary findings were also reported. In Simard's review [17], a total of 12 studies found no relationship between gender and FCR in adults. In our current review, one study also reported a nonsignificant association [26]. Further research is needed to better understand the association between gender and FCR.

Our finding showed that different treatment type (i.e. surgery) was unrelated to FCR, but higher treatment intensity was significantly associated with increased FCR. Some previous studies identified radiotherapy/chemotherapy as predictors of higher FCR, however, this relationship tended to disappear in multivariate analyses [53, 54]. One possible reason is that those who were more intensively treated may have greater awareness and more knowledge about risks for chronic health complications. Another reason may be the treatment-related symptoms/side effects, such as tiredness, nausea, and skin reaction caused by radiotherapy and chemotherapy. It has been found that physical and cognitive impairments through treatment side effects could greatly contribute to elevated FCR [55]. Higher treatment intensity and longer treatment duration might cause more side effects. Those symptoms might be viewed by the patients as a constant reminder of their disease, which further leads to increased FCR [18].

Regarding psychological factors, there are a number of existing studies [56-59] that have demonstrated a moderate positive correlation between FCR and generalized anxiety, hypochondriasis, as well as depression. In particular, a strong association between depression, symptom distress and elevated FCR in adult cancer survivors has been consistently identified [23, 60].

## **Consequences of FCR**

Our review found that AYA cancer survivors with FCR were more likely to have impaired psychological functioning and overall health-related Quality of Life. As a common and

persistent concern, FCR was consistently found to have a detrimental effect on patient's QoL [61, 62]. Simard *et al.* also reported a strong negative association between FCR and QoL or functional domains (i.e. mental, role, social and cognitive functioning etc.) in adult cancer populations [17]. It is reasonable to assume that unexpected cancer diagnosis and treatment may present great challenges to AYAs and may also influence their choices in education, marriage, and occupational pursuits in the future, which further worsen their psychological distress and impair their QoL [45-47]. Researchers believe that alleviating this concern could considerably help to improve patient's life outcomes [62].

### **Clinical Implications**

It is of importance to ensure AYAs receive sufficient information and help on dealing with FCR. To date, several organizations have developed detailed guidelines for AYA cancer populations to provide better psychological service [46]. However, specific FCR interventions for AYAs are still lacking. Therefore, providing more attention to AYA populations and developing more specific psychological programs for them is necessary. Researchers suggested that AYA-specific programs should consist of a multidisciplinary group with professional knowledge and skills [63]. Besides traditional counsellors, religious peers, support groups and clinical psychologists, in particular, the team should include a highly motivated person with a professional interest in AYA oncology/survivorship (an 'AYA champion') [63]. It is believed that with this 'champion' the multidisciplinary team would identify better the unique needs of AYAs. In addition, routines assessment for FCR during clinical follow-up appointments could also greatly help to identify the problem. Early identification could lead to early intervention and management, and consequently improve the patient's life outcomes.

This review also highlighted significant implications in the clinical research of FCR in AYAs. First, the instruments to adequately measure FCR in AYA cancer survivors are not satisfactory. All the existing FCR measurements were developed based on adult cancer populations. Hence some reassurance that these measures have good psychometric properties for AYAs would be beneficial. Second, there is a need for further investigation on FCR in more diverse samples, particularly in Asian AYA populations. Third, longitudinal studies that can monitor the change of FCR over time and to further identify causal

associations are warranted. The majority of the FCR studies used cross-sectional designs, therefore, limited the examination of the development of FCR, and the dynamics of the relationship between FCR and psychosocial consequences. Better understanding of FCR in AYAs would be beneficial for developing AYA-specific programs in health care institutions.

### **Study Limitations**

There are several limitations in this review that require consideration. First, the overall target sample is homogenous (all white, from north America or European countries). This may preclude generalization to other populations. Also, most of the included studies were cross-sectional and the sample size varied significantly (ranged from 20 to 1395). Out of the seventeen included studies, ten of them were published after Simard's robust review in 2013 and seven were published recently within three years. However, there is still an overlap between the studies included in the current review and those in previous reviews. The number of scale items also varied widely and FCR was assessed using a range of measurements among the included studies, additionally, insufficient efforts have been made to establish standard clinical cut-offs of FCR. Finally, no attempt was made to search for non-English articles or unpublished articles, and qualitative studies were excluded in the current review. Therefore, we suggest that these results should be interpreted with caution.

### **5. Conclusion**

FCR is a prevalent concern among AYA population but it has not been adequately assessed or research advanced enough to establish design criteria for development of targeted interventions to manage FCR for this specialist group of patients. Longitudinal studies in AYAs are needed to examine further the long-term development and influence of FCR. Age-appropriate and flexible psychological care services are likely to be indicated from this more advanced information base, if initial speculation from this review is confirmed. Decreasing FCR may lead to improved Quality of Life and better adherence to cancer surveillance, therefore, increased attention should be targeted at AYA cancer survivors.

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## **Compliance with Ethical Standards**

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### **Conflict of interest**

Authors declare that they have no conflict of interest.

### **Ethics Approval**

The Southern Medical University Nanfang Hospital Research Ethics Committee examined and approved the study (ref No: NFEC-2018-038)

Accepted Article

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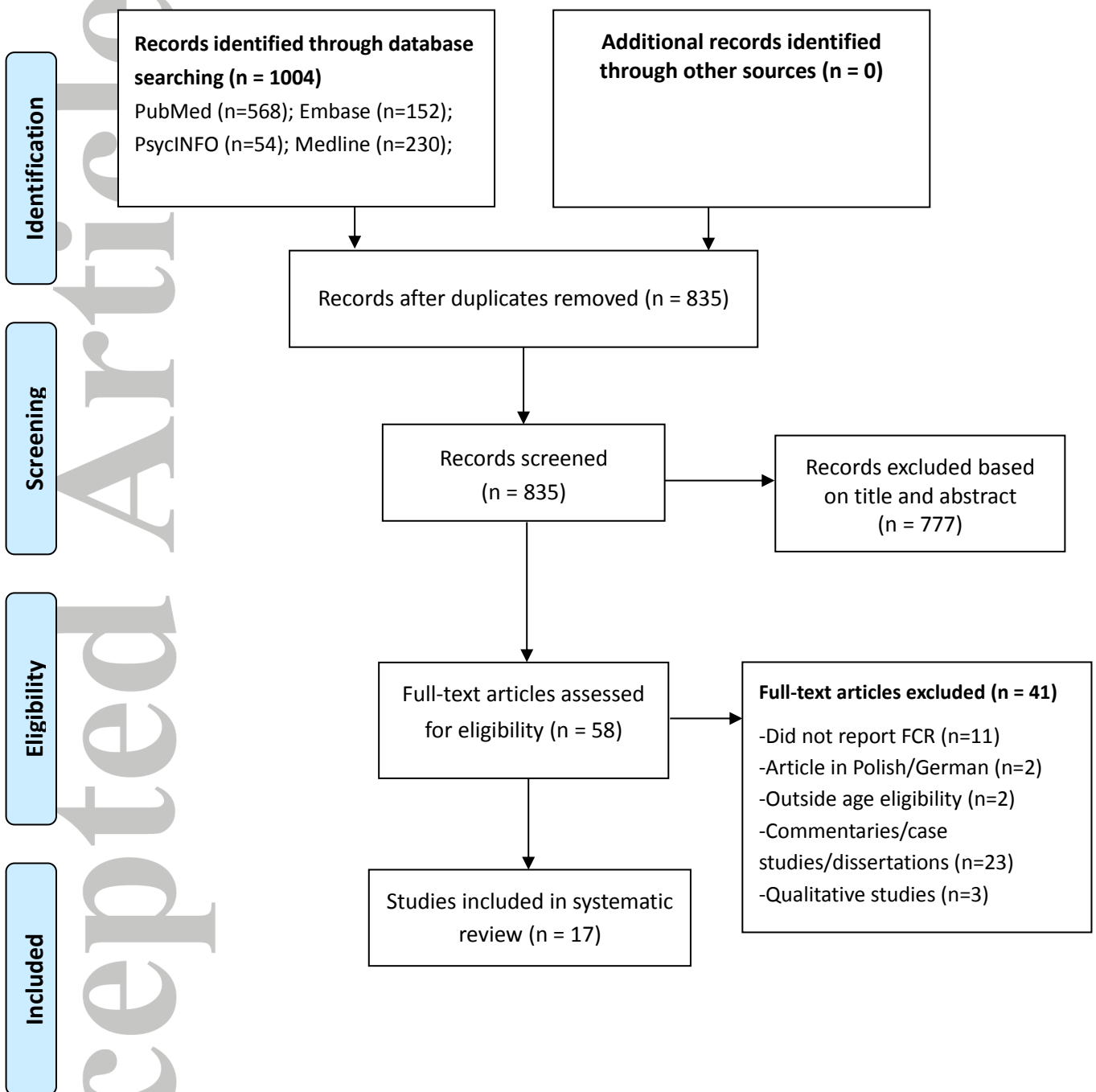


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Figure 1. PRISMA flowchart



**Table 1 Characteristics of included studies**

-Author -Year	Country	Study Design	Cancer Type	N (female %)	-Age at Diagnosis -Age at Survey Mean (SD) <sup>a</sup>	Time since Diagnosis Mean (SD) <sup>a</sup>	Instrument	Main finding (FCR Prevalence, Determinants, and consequence)
-Thewes [26] -2018	Netherlands	Cross-sectional	Mix	73 (51%)	-27.4 (4.6), range from 18 to 35 -NR	1.9 (2.6)	CWS	- <b>Prevalence:</b> 62% reported high FCR - <b>Determinants:</b> sociodemographic and clinical variables were not significantly associated with levels of FCR - <b>Consequence:</b> High FCR was associated with lower psychological, social functioning and overall QoL ( $P<0.01$ )
-Mattsson -2018 [37]	Sweden	Cross-sectional	gynecological	337 (100%)	-32.6 (4.9), range from 19 to 39 -36.9 (5.1)	2.9 (1.9)	Study-specific questionnaire	- <b>Prevalence:</b> 61% reported FCR - <b>Determinants:</b> multimodal treatment (OR=2.25) and a history of psychological distress (OR=3.44) predicted cancer related distress (including FCR)
-Poort -2017 [44]	Netherlands	Cross-sectional	Mix	83 (48%)	-27.3 (4.4), range from 18 to 35 -29.4 (4.7)	2.1 (2.6)	CWS	- <b>Consequence:</b> higher FCR was moderate correlated with severe fatigue ( $r$ 's: 0.30-0.50, $P<0.01$ )
-Park [43] -2017	US	Cross-sectional + follow up	Mix	120 (77.9%)	-28.9 (6.8), range from 15 to 39 -32.6 (7.4)	3.8 (3.0)	CARS	- <b>Determinants:</b> spiritual struggle was positively associated with FCR ( $r=0.24$ , $P=0.04$ )
-Cho [41] -2017	US	Cross-sectional	Mix	292 (80.5%)	-range 15-34 -33.3 (7.1)	3.8 (2.5)	ASC	- <b>Prevalence:</b> 49.1% reported moderate-to- high FCR, 13% reported high FCR - <b>Consequence:</b> FCR was negatively related to both physical ( $P=0.01$ ) and mental health-related QoL ( $P<0.001$ )
-Shay [25] -2016	US	Cross-sectional	Mix	1395 (59.7%)	-30.0 (6.6), range from 15 to 39	NR	Single item from the QoL in Adult	- <b>Prevalence:</b> 85.2% reported FCR - <b>Determinants:</b> being employed, less than 5yrs off treatment were positively

					-38 (range 18-73)		Cancer Survivors Scale	related to FCR; thyroid cancer patients, and those in clinical trial were less likely to report FCR
-Kremer [38] -2016	Germany	Cross-sectional	NR	33 (45.5%)	-8.1 (5.1), range from 0 to 18 -23.8 (3.8), range from 18 to 34	NR	Fear of disease Progression questionnaire-short form	- <b>Consequence:</b> posttraumatic growth was experienced by AYAs, FCR reported by Childhood cancer survivors was lower than AYA patients with type 1 diabetics ( $P<0.001$ )
-Wang [42] -2015	Canada	Cross-sectional	Mix	250 (46%)	-range 0-17 -range 15-26	NR	6-item CWS	- <b>Prevalence:</b> 7% strongly worry about relapse and 31% reported moderate FCR - <b>Determinants:</b> female and higher treatment intensity were associated with higher cancer worry
-Senkus [36] -2014	US	Cross-sectional	Breast	389 (100%)	-aged < 36 -NR	0.5 (NR)	Interview question	- <b>Consequence:</b> 36% survivors who did not want additional children because of FCR
-Seitz [39] -2014	Germany	Cross-sectional + follow up	Mix	20 (70%)	-NR -27.3 (4.8), range from 20 to 36	13.8 (4.7)	FoP-SF	- <b>Consequence:</b> 45% of the survivors showed an improvement on FCR after an internet-based CBT intervention ( $P=0.031$ )
-Lebel [35] -2013	Canada	Cross-sectional	Breast	100 (100%)	-NR -aged < 35	2.87 (3.94)	CARS	- <b>Determinants:</b> younger age at diagnosis (< 35) was associated with increased FCR than women in the other age categories
-de Moor [40] -2011	US	Cross-sectional	Mix	374 (49%)	-aged < 35 -32.4 (7.94) range from 18 to 55	20 (9.61)	Single question from IES	- <b>Consequence:</b> survivors who did not have FCR were more likely to be nicotine dependent (OR=2.08, 95%CI: 0.81, 5.32)
-Cox [32] -2008	US	Cross-sectional + follow up	Breast	149 (100%)	-NR -median=15, range from 12-19	Median=11.72, range 2.23-16.89	Single item	- <b>Prevalence:</b> 29% reported FCR at baseline, and 31% reported FCR one year later - <b>Consequence:</b> FCR predicted decreased breast self-examination

								frequency
-Zebrack -2002 [34]	US	Cross-sectional	Mix	176 (57.4%)	-8.5 (5.1), range from 0 to 22 -21.8 (3.3), range from 16 to 28	13.3 (5.7)	Items from Quality of life-cancer survivors	<b>-Consequence:</b> FCR was associated with low overall quality of life in AYAs ( $r=0.745$ )
-Zebrack -2001 [33]	US	Cross-sectional	Mix	303 (53%)	-8.6 (5.18), range from 0 to 22 -20.0 (3.39), range from 14 to 29	11.3 (5.76)	Self-designed items	<b>-Consequence:</b> cancer specific worry (including FCR) did not significantly predict survivors' self-image or life outlook.
-Puukko -1998 [30]	Finland	Cross-sectional	leukemia	42 (100%)	-7.4 (3.4) -18.6 (3.9)	NR	Two questions	<b>-Prevalence:</b> 52% reported FCR <b>-Consequence:</b> FCR was unrelated to frequency of somatic symptoms
-Roberts -1997 [31]	US	Cross-sectional	Mix	46 (NR)	-NR -31.4 (4.0), range from 22 to 35	4.3 (2.7)	Single item	<b>-Consequence:</b> FCR was the most intense life changes the survivors had experienced (degree of change=6.78)

<sup>a</sup> mean (SD) in years; Abbreviation: NR: Not Report; FCR: Fear of Cancer Recurrence; QoL: Quality of Life; CWS: Cancer Worry Scale; CARS: Concerns About Recurrence Scale; ASC: Assessment of Survivor Concerns; FoP-SF: Fear of Progression Questionnaire-short form; IES: Impact of Event Scale

**Table 2 Factors associated with FCR in AYA cancer survivors**

<b>Factors</b>	<b>Nil</b>	<b>Positive association</b>	<b>Negative association</b>
<b>Demographic</b>			
Gender (Female)	[26] <sup>a</sup>	[25] <sup>b</sup> , [42] <sup>b</sup>	
Age at survey (years)			[25] <sup>b</sup>
Race (white/other)	[25] <sup>a</sup> , [42] <sup>a</sup>		
Employment (Yes/No)	[26] <sup>a</sup>	[25] <sup>b</sup>	
Education level	[25] <sup>a</sup> , [26] <sup>a</sup> , [42] <sup>a</sup>		
Married/Partnered	[25] <sup>b</sup> , [26] <sup>a</sup>		
Have children (Yes/No)	[26] <sup>a</sup> , [37] <sup>b</sup>		
Living situation	[26] <sup>a</sup>		
Total household income	[25] <sup>a</sup>		
Insurance status	[25] <sup>a</sup>		
<b>Clinical/Treatment</b>			
Age at diagnosis (Years)	[26] <sup>a</sup>		[35] <sup>a</sup> , [37] <sup>b</sup>
Time since diagnosis (Years)	[26] <sup>a</sup> , [42] <sup>a</sup>		
Cancer type	[26] <sup>a</sup> , [42] <sup>b</sup>		
Cancer stage	[26] <sup>a</sup>		
Treatment status (On/off)	[26] <sup>a</sup>		
Surgery (Yes/No)	[25] <sup>b</sup> , [26] <sup>a</sup>		
Radiotherapy (Yes/No)	[25] <sup>b</sup> , [26] <sup>a</sup>		
Chemotherapy (Yes/No)	[26] <sup>a</sup>	[43] <sup>b</sup>	
Hormonal therapy (Yes/No)	[26] <sup>a</sup>		
Immunotherapy (Yes/No)		[26] <sup>a</sup>	
Number of treatment(s)		[37] <sup>b</sup> , [42] <sup>b</sup>	
Less than 5 yrs off treatment		[25] <sup>b</sup>	
Thyroid cancer			[25] <sup>b</sup>
In clinical trial			[25] <sup>b</sup>
Currently seeing a doctor	[25] <sup>b</sup>		
Relapse status (Yes/No)	[42] <sup>a</sup>		
<b>Psychological</b>			
Anxiety		[26] <sup>ac</sup>	
Depression	[26] <sup>ac</sup>		
Psychological distress		[26] <sup>ac</sup>	
Past psychological distress		[37] <sup>b</sup>	
Previous serious life events	[37] <sup>b</sup>		
Spiritual struggle		[43] <sup>d</sup>	

<sup>a</sup> Mean or frequency comparison analysis, <sup>b</sup> Multivariate regression model analysis, <sup>c</sup> Clinically relevant difference, <sup>d</sup> Correlations, AYA: adolescent and young adult



**Table 3 Consequences of FCR in AYA cancer survivors**

<b>Consequences</b>	<b>Nil</b>	<b>Positive association</b>	<b>Negative association</b>
<b>Quality of Life</b>			
Physical functioning	[26] <sup>ac</sup>		[41] <sup>d</sup>
Psychological functioning			[26] <sup>ac</sup> , [41] <sup>d</sup>
Social functioning			[26] <sup>ac</sup>
Religious functioning	[26] <sup>ac</sup>		
Overall health-related QoL			[26] <sup>ac</sup> , [34] <sup>d</sup>
<b>Other outcomes</b>			
Nicotine dependent (Yes/No)			[40] <sup>b</sup>
Breast self-examination			[32] <sup>a</sup>
Somatic symptoms frequency	[30] <sup>d</sup>		
Have additional children			[36]
Fatigue severity		[44] <sup>d</sup>	
Self-image	[33] <sup>b</sup>		
Life outlook	[33] <sup>b</sup>		

<sup>a</sup> Mean or frequency comparison analysis, <sup>b</sup> Multivariate regression model analysis, <sup>c</sup> Clinically relevant difference, <sup>d</sup> Correlations, AYA: adolescent and young adult, QoL: Quality of Life

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