Risk factors, prevalence, and course of severe fatigue after breast cancer treatment: a meta-analysis involving 12 327 breast cancer survivors

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Background: This meta-analysis aimed to (i) examine demographic, disease-related, and treatment-related risk factors, (ii) estimate the prevalence, and (iii) describe the course of severe fatigue following breast cancer (BC) treatment.

Methods: PubMed, PsycINFO, Cochrane, CINAHL, and Web of Science were systematically searched from inception up to 23 November 2015. Risk factors and prevalence rates were analyzed with inverse variance random-effects analyses. Heterogeneity was studied with sensitivity analyses.

Results: Twenty-seven studies were included (N = 12 327). Breast cancer survivors (BCS) with a partner were at lower risk for severe fatigue than survivors without a partner [risk ratio (RR) 0.96, 95% confidence interval (CI) 0.93–0.98]. Survivors with stage II or III cancer, and survivors treated with chemotherapy were at higher risk for severe fatigue than survivors with stage 0 or I cancer and without chemotherapy (RR respectively 1.18, 95% CI 1.08–1.28; 1.12, 95% CI 1.06–1.19). Survivors treated with surgery, radiotherapy, and chemotherapy, and survivors with this combination plus hormone therapy were at higher risk than survivors with other treatment combinations (RR respectively 1.18, 95% CI 1.05–1.33; 1.38, 95% CI 1.15–1.66). Survivors treated with surgery and surgery plus radiotherapy were at lower risk than survivors with additional treatments (RR respectively 0.83, 95% CI 0.70–0.98; 0.87, 95% CI 0.78–0.96). Hormone and targeted therapy were no significant risk factors. The pooled prevalence of severe fatigue was 26.9% (95% CI 23.2–31.0), but this should be interpreted with caution because of high heterogeneity. A relatively large decrease in the prevalence of severe fatigue seemed to occur in the first half year after treatment completion.

Conclusions: Approximately one in four BCS suffer from severe fatigue. Risk factors of severe fatigue were higher disease stages, chemotherapy and receiving the combination of surgery, radiotherapy, and chemotherapy, both with and without hormone therapy. Having a partner, receiving only surgery, and surgery plus radiotherapy decreased the risk.

Key words: meta-analysis, breast cancer, fatigue, risk factors, prevalence, course

introduction

Breast cancer (BC) represents one-fourth of all cancer cases and is the most common tumor type in women worldwide [1]. As survival rates have improved due to the advances in BC treatment, an increased number of women are faced with persistent symptoms that are related to the diagnosis and treatment [2, 3]. Cancer-related fatigue is among the most troublesome symptoms, defined by the National Comprehensive Cancer Network (NCCN) as ‘a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness, related to cancer or cancer treatment, that is not proportional to recent activity and interferes with usual functioning [4].’

The prevalence of fatigue in breast cancer survivors (BCS) was examined in two reviews [5, 6]. Minton et al. reported in a systematic review of 18 studies that fatigue is a problem for a significant percentage of BCS (up to 50% in some studies) [5]. The overall prevalence in this review was not estimated with a meta-analysis. Ganz et al. reported in a narrative review that, based on three studies, approximately one in three BCS experience fatigue symptoms [6]. This prevalence rate was not based on a systematic search of the literature. Both reviews did not describe how the prevalence rates of fatigue after treatment develop over time. Therefore, the prevalence rate and course of fatigue in BCS are still unclear.
To identify which BCS are more likely to develop severe fatigue following treatment, it is important to know which demographic, disease, and treatment characteristics are risk factors. Previous reviews on risk factors for fatigue in cancer survivors did not specifically examine these risk factors in BCS. Prue et al. and Servaes et al. performed a systematic review in survivors with various tumor types and included respectively 24 and 22 studies [7, 8]. Findings regarding demographic variables and fatigue were mixed. About half of studies found no association between the age of BCS and fatigue, whereas the other half reported that being younger was associated with fatigue. A few studies found that fatigue was associated with marital status and education [7, 8]. Almost all disease characteristics, including stage of disease and lymph node status, were not found to be related to fatigue after the treatment of various tumor types. In addition, almost all treatment characteristics, including type of cancer treatment and time since cancer treatment, were not significantly related to fatigue [7, 8].

It is uncertain if these findings can be generalized to BCS, because at least half of the study populations in both reviews were survivors with other tumor types [7, 8]. Besides, the literature was searched up to September 2005, whereas BC treatment has evolved during the past decade. The understanding of tumor biology has rapidly developed, generating a range of molecularly targeted drugs of which fatigue is a well-known side-effect [9, 10]. These kinds of changes in BC treatment over time should be considered when examining treatment-related risk factors for fatigue. Moreover, no meta-analysis was performed before, and sample sizes of individual studies were possibly too small to detect significant associations between the mentioned characteristics and fatigue.

Our meta-analysis focused on clinically relevant severe fatigue, because this level of fatigue often has profound negative effects on patients’ daily life, work ability, and quality of life [11]. The aims of this meta-analysis were to (i) determine which demographic characteristics (i.e. age, ethnicity, partner status, and education level), disease characteristics (i.e. lymph node status, stage of disease, and menopausal status), and treatment characteristics (i.e. type of cancer treatment, type of surgery, breast reconstruction, treatment combinations, and time since cancer treatment) were risk factors, (ii) to estimate the prevalence rate and (iii) to describe the course of severe fatigue following BC treatment.

Methods

Protocol and registration

This section is written in accordance with the PRISMA statement for systematic reviews and meta-analyses [12]. A detailed protocol is published in the International Prospective Register of Systemic Reviews (PROSPERO, reference no. CRD42015015768) [13].

Search strategy

PubMed, PsycINFO, Cochrane, CINAHL, and Web of Science were systematically searched from inception up to 23 November 2015 for studies on fatigue in disease-free BCS. The search strategy existed of three components, used as MeSH-headings and free text words: BC, fatigue, and survivors (complete search strategy: supplementary Appendix, available at Annals of Oncology online).

Study selection

Two reviewers (HA and IS) independently assessed the eligibility of articles based on title and abstract. If necessary, full text versions were retrieved. In case of disagreement about eligibility, consensus was reached by consulting a third reviewer (MG). The eligibility criteria were: (i) quantitative data were reported on the prevalence, course, or related factors of fatigue in BCS; (ii) only disease-free BCS were examined, defined as patients who had completed curative cancer treatment, except for ongoing adjuvant hormone therapy; (iii) sample size was ≥50; (iv) a full-report in English, Dutch, or German was provided.

Data extraction and quality assessment

All corresponding authors who used a fatigue instrument with published cutoff score for severe fatigue were contacted for primary data by e-mail. We asked the authors to distinguish between severely fatigued and nonseverely fatigued survivors in their study. All cutoff scores including its references are reported in Tables 1 and 2. We asked the authors to provide us with information on age (continuous), partner status (having a partner: yes/no), ethnicity (Caucasian/not Caucasian), and education level (≤primary school/>primary school). Three disease characteristics were included: lymph node status (positive/negative), menopausal status (premenopausal/postmenopausal), and stage of disease (0 or I/ II or III). Guidelines differ with regard to the latter variable [14, 15]. We followed the NCCN guidelines, in which stage 0 was described as early-stage BC [15]. Eight treatment characteristics were included: treated with chemotherapy (yes/no), radiotherapy (yes/no), hormone therapy (yes/no), targeted therapy (yes/no), type of surgery (lumpectomy/mastectomy), having had breast reconstruction (yes/no), time since cancer treatment (continuous), and treatment modalities (combinations of surgery, chemotherapy, radiotherapy, hormone therapy, and/or targeted therapy). If the corresponding author did not respond within 2 weeks, one reminder was e-mailed to the corresponding author and all co-authors.

Two reviewers (HA, MG) assessed the methodological quality of the included studies using a checklist [16, 17], especially designed for studies in psychosocial oncology (Table 3). One point was assigned for each criterion that was fulfilled, with a maximum score of 14 points. Studies attaining ≥75% of the maximum score (≥11 points) were considered high-quality studies. Studies with a score of 50%–75% (7–11 points) were considered moderate-quality studies, and studies with a score of <50% (<7 points) low-quality studies [16, 17].

Data synthesis and analyses

Data of both cross-sectional and longitudinal studies were used to plot individual study estimates of incidences and proportions. From longitudinal studies, the first reported prevalence rate after the period of early survivorship (≥6 months after BC treatment [18]) was used to prevent a confounding influence of direct consequences of cancer treatment. We used the inverse variance method for pooling the incidences and to calculate the corresponding 95% confidence intervals (CIs). As recommended in the Cochrane handbook, we used I² tests to measure heterogeneity. We defined an I² value of 50%–75% as substantial heterogeneity and an I² value of ≥75% as considerable heterogeneity.
Table 1. Cross-sectional studies on prevalence and/or determinants of severe fatigue in breast cancer survivors

<table>
<thead>
<tr>
<th>Study</th>
<th>Fatigue primary outcome</th>
<th>Sample size (N)</th>
<th>Fatigue measure</th>
<th>Prevalence severe fatigue</th>
<th>Time since BC treatment* (months)</th>
<th>Population Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexander [26]</td>
<td>Yes</td>
<td>200</td>
<td>Diagnostic interview –</td>
<td>30%</td>
<td>10 (6)</td>
<td>3</td>
</tr>
<tr>
<td>Berger [27]</td>
<td>No</td>
<td>162</td>
<td>Single item BCSSS, item fatigue worst ≥7 [27]</td>
<td>24%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Crosswell [28]</td>
<td>Yes</td>
<td>84</td>
<td>Single item FSI, item average fatigue ≥5 [29]</td>
<td>46%b</td>
<td>44 (26)c</td>
<td>–</td>
</tr>
<tr>
<td>Dupont [30]</td>
<td>No</td>
<td>558</td>
<td>Single item FSI, item average fatigue ≥5 [29]</td>
<td>35%b</td>
<td>6 (3)c</td>
<td>–</td>
</tr>
<tr>
<td>Fu [31]</td>
<td>No</td>
<td>139</td>
<td>Single item MSAS-SF item fatigue ≥4 [31]</td>
<td>22%</td>
<td>–</td>
<td>≥3</td>
</tr>
<tr>
<td>Goldstein [32]</td>
<td>Yes</td>
<td>176</td>
<td>Multi-item SPHERE, subscale SOMA Not reported</td>
<td>49%</td>
<td>10d</td>
<td>–</td>
</tr>
<tr>
<td>Hall [33]</td>
<td>Yes</td>
<td>313</td>
<td>Multi-item PFS-R ≥7 [34]</td>
<td>13%b</td>
<td>36</td>
<td>24</td>
</tr>
<tr>
<td>Hall [35]</td>
<td>Yes</td>
<td>67</td>
<td>Single item FSI, item average fatigue ≥5 [29]</td>
<td>21%b</td>
<td>63 (1)c</td>
<td>–</td>
</tr>
<tr>
<td>Hong [36]</td>
<td>No</td>
<td>3088</td>
<td>Multi-item RAND SF-36, subscale vitality ≤50 [37]</td>
<td>36%b</td>
<td>23 (12)c</td>
<td>–</td>
</tr>
<tr>
<td>Jones [38]</td>
<td>Yes</td>
<td>1294</td>
<td>Single item FACT-F ≤36 [39]</td>
<td>43%b</td>
<td>–</td>
<td>6</td>
</tr>
<tr>
<td>Karakoyun-Celik [40]</td>
<td>No</td>
<td>120</td>
<td>Multi-item EORTC-QLQ-C30 subscale fatigue ≥40 [41]</td>
<td>30%b</td>
<td>49</td>
<td>12</td>
</tr>
<tr>
<td>Kim [42]</td>
<td>Yes</td>
<td>1884</td>
<td>Single item BFI, item fatigue worst Not reported</td>
<td>32%</td>
<td>55 (29)c</td>
<td>–</td>
</tr>
<tr>
<td>Klubovskov [43]</td>
<td>Yes</td>
<td>202</td>
<td>Multi-item PFS-R ≥4 [43]</td>
<td>38%f</td>
<td>59 (56)c</td>
<td>–</td>
</tr>
<tr>
<td>Meeske [44]</td>
<td>Yes</td>
<td>800</td>
<td>Multi-item PFS-R ≥4 [44]</td>
<td>7%</td>
<td>35</td>
<td>24</td>
</tr>
<tr>
<td>Minton [45]</td>
<td>Yes</td>
<td>114</td>
<td>Diagnostic interview –</td>
<td>39%</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Reinusdatter [46]</td>
<td>Yes</td>
<td>221</td>
<td>Multi-item EORTC-QLQ-C30 subscale fatigue ≥40 [41]</td>
<td>30%b</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>Ventura [47]</td>
<td>No</td>
<td>163</td>
<td>Single item FSI, item average fatigue ≥5 [29]</td>
<td>55%b</td>
<td>41 (18)c</td>
<td>–</td>
</tr>
<tr>
<td>Versmessen [48]</td>
<td>No</td>
<td>121</td>
<td>Multi-item EORTC-QLQ-C30 subscale fatigue ≥40 [41]</td>
<td>31%b</td>
<td>3d</td>
<td>–</td>
</tr>
<tr>
<td>Young [49]</td>
<td>Yes</td>
<td>69</td>
<td>Diagnostic interview –</td>
<td>19%</td>
<td>–</td>
<td>≥6</td>
</tr>
</tbody>
</table>

*Time since completion of BC treatment (surgery, chemotherapy, and/or radiotherapy), unless stated otherwise.

bPrevalence rate was obtained through a data request.

cTime since diagnosis.

dThis concerns a fixed measurement point.

eTime since surgery.

fThis concerns the prevalence of moderate instead of severe fatigue after BC treatment.

gMean time since the diagnosis of fatigued BCS only.

BCS, breast cancer survivor; BCSSS, BC Survivor Symptom Survey; BFI, Brief Fatigue Inventory; CFS, Chronic Fatigue Syndrome; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer—Quality-of-Life Questionnaire-C30; FSI, Fatigue Symptom Inventory; MSAS-SF, Memorial Symptoms Assessment Scale Short Form; PA, physical activity; PFS-R, Piper Fatigue Scale-revised; SPHERE, Somatic and Psychological Health Report.
Table 2. Longitudinal studies on course and/or determinants of severe fatigue in breast cancer survivors

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Time since BC treatment</th>
<th>Prevalence severe fatigue (%)</th>
<th>Fatigue measure</th>
<th>Fatigue measure Category</th>
<th>Quality rating</th>
<th>Study population</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrykowski (2010) [50]</td>
<td>Yes</td>
<td>T1</td>
<td>304 (months)</td>
<td>22</td>
<td>Diagnostic interview</td>
<td>–</td>
<td>Selected</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2</td>
<td>282</td>
<td>9</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3</td>
<td>222</td>
<td>13</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Bower (2006) [51]</td>
<td>Yes</td>
<td>T1</td>
<td>1953 (months)</td>
<td>35</td>
<td>Multi-item RAND SF-36, subscale vitality</td>
<td>≤50 [37]</td>
<td>Selected</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2</td>
<td>763</td>
<td>34</td>
<td>Multi-item SPHERE, subscale SOMA</td>
<td>Not reported</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Goldstein (2012) [52]</td>
<td>Yes</td>
<td>T1</td>
<td>218 (months)</td>
<td>41</td>
<td>Multi-item POMS, subscale fatigue</td>
<td>–</td>
<td>Selected</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2</td>
<td>218</td>
<td>28</td>
<td>Multi-item POMS, subscale fatigue</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3</td>
<td>218</td>
<td>23</td>
<td>Single item FSI, item average fatigue</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td></td>
<td></td>
<td>T4</td>
<td>218</td>
<td>18</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T5</td>
<td>218</td>
<td>15</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T6</td>
<td>218</td>
<td>14</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T7</td>
<td>218</td>
<td>21</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Jacobsen (2007) [29]</td>
<td>Yes</td>
<td>T1</td>
<td>221 (months)</td>
<td>28</td>
<td>Multi-item POMS, subscale fatigue</td>
<td>–</td>
<td>Selected</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2</td>
<td>221</td>
<td>18</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3</td>
<td>221</td>
<td>17</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T4</td>
<td>221</td>
<td>16</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T1</td>
<td>221 (months)</td>
<td>28</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
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<td></td>
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<td>221</td>
<td>18</td>
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<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3</td>
<td>221</td>
<td>19</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
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<td>T4</td>
<td>221</td>
<td>18</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Nieboer (2005) [53]</td>
<td>Yes</td>
<td>High-dose CT:T1</td>
<td>186 (months)</td>
<td>19</td>
<td>Multi-item RAND SF-36, subscale vitality</td>
<td>≤46 [53]</td>
<td>Selected</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2</td>
<td>181</td>
<td>17</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3</td>
<td>170</td>
<td>19</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Standard CT: T1</td>
<td>206 (months)</td>
<td>21</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
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<td>T2</td>
<td>207</td>
<td>21</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3</td>
<td>195</td>
<td>22</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Reinertsen (2010) [54]</td>
<td>Yes</td>
<td>T1</td>
<td>249 (months)</td>
<td>33</td>
<td>Multi-item CFS</td>
<td>≥4 [54]</td>
<td>Selected</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2</td>
<td>249 (months)</td>
<td>30–84</td>
<td>Multi-item CFS</td>
<td>≥4 [54]</td>
<td>Selected</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3</td>
<td>249 (months)</td>
<td>30–36 thereafter</td>
<td>Multi-item CFS</td>
<td>≥4 [54]</td>
<td>Selected</td>
<td>High</td>
</tr>
<tr>
<td>Schmitz (2012) [55]</td>
<td>No</td>
<td>T1</td>
<td>275 (months)</td>
<td>16</td>
<td>Single item FACT-B fatigue item</td>
<td>≥4 [55]</td>
<td>Selected</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2</td>
<td>272 (months)</td>
<td>12</td>
<td>Single item FACT-B fatigue item</td>
<td>≥4 [55]</td>
<td>Selected</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3</td>
<td>182 (months)</td>
<td>16</td>
<td>Single item FACT-B fatigue item</td>
<td>≥4 [55]</td>
<td>Selected</td>
<td>High</td>
</tr>
<tr>
<td>Servaes (2007) [56]</td>
<td>Yes</td>
<td>T1</td>
<td>150 (mean)</td>
<td>38</td>
<td>Multi-item CIS, subscale fatigue severity</td>
<td>≥35 [56]</td>
<td>Selected</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2</td>
<td>121 (mean)</td>
<td>23</td>
<td>Multi-item CIS, subscale fatigue severity</td>
<td>≥35 [56]</td>
<td>Selected</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

*a*Time since completion of BC treatment (surgery, chemotherapy, and/or radiotherapy), unless stated otherwise.

*b*Time since diagnosis.

*c*After standard dose chemotherapy.

*d*After high-dose chemotherapy.

*e*This concerns the prevalence of moderate instead of severe fatigue after BC treatment.

BCS, breast cancer survivor; CT, chemotherapy; RAND SF-36, RAND Short Form-36; CIS, checklist individual strength; CFS, Chalder Fatigue Scale; FACT-B + 4, Functional Assessment of Cancer Therapy-Breast.
As we expected heterogeneity between studies, we used random-effects meta-analyses for the primary analyses. Random-effects meta-analysis models assume that the estimated effects of the different studies are not identical, but follow some distribution. In case of heterogeneity, sensitivity analyses were carried out to study whether specific groups of patients would provide more homogeneous results. Specific groups of patients were composed based on type of study (cross-sectional/longitudinal), primary study outcome (fatigue/other outcomes), type of fatigue measure (clinical interview/questionnaire/single item), study population (selected with eligibility criteria/consecutively screened patient samples), study quality (high/moderate/low), and study period (before/after 2007). The latter division was applied, because we know from clinical practice that treatment regimens have become more intensive since ∼2007.

The associations of demographic, disease, and treatment characteristics with severe fatigue were analyzed with inverse variance analyses, using Review Manager 5 statistical software (version 5.3). Risk ratios and their corresponding 95% CIs were calculated for dichotomous variables and standardized mean differences for continuous variables. A separate meta-analysis was carried out for each risk factor.

### results

#### study selection and data request

The literature search resulted in 5003 hits (flow chart: Figure 1). Duplicates were removed (N = 1611) and titles were screened (2145 records excluded). The abstracts and/or full-texts of the remaining 1247 studies were reviewed for eligibility. Studies were excluded because: (i) no quantitative data were provided on prevalence, course and/or related characteristics of fatigue (N = 777); (ii) disease-free BCS were not examined (N = 248); (iii) no full report in English, Dutch, or German was provided (N = 96); and (iv) sample size was <50 (N = 58).

Altogether, 68 studies were eligible. Useful data for the meta-analysis were reported in 15 eligible studies. The other 53 studies were considered for a data request. Twenty studies were excluded

### Table 3. Risk factors of severe fatigue in breast cancer survivors

<table>
<thead>
<tr>
<th>Variables</th>
<th>References</th>
<th>Number of studies</th>
<th>Sample size (N)</th>
<th>Risk ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>[28, 30, 32, 33, 35, 36, 38, 40, 43, 45–48, 50, 54–57]</td>
<td>19</td>
<td>8678</td>
<td>−0.06 (−0.14 to 0.03)*</td>
</tr>
<tr>
<td>Having a partner</td>
<td>[28, 30, 33, 35, 36, 40, 42, 43, 46, 47, 50, 54–57]</td>
<td>16</td>
<td>9991</td>
<td>0.96 (0.93 to 0.98)*</td>
</tr>
<tr>
<td>Ethnicity (Caucasian)</td>
<td>[26, 28, 30, 33, 35, 36, 43, 45, 47, 50]</td>
<td>10</td>
<td>4877</td>
<td>1.00 (0.97 to 1.04)</td>
</tr>
<tr>
<td>Education level (≥primary school)</td>
<td>[36, 38, 40, 42, 46, 47, 50, 54, 55]</td>
<td>8</td>
<td>6456</td>
<td>1.09 (0.99 to 1.20)</td>
</tr>
<tr>
<td>Disease characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage of disease (II or III)</td>
<td>[26, 35, 38, 42, 43, 45–48, 50, 54, 55]</td>
<td>11</td>
<td>4093</td>
<td>1.18 (1.08 to 1.28)*</td>
</tr>
<tr>
<td>Negative lymph node status</td>
<td>[26, 43, 45, 46, 48, 54]</td>
<td>6</td>
<td>1068</td>
<td>0.89 (0.77 to 1.03)</td>
</tr>
<tr>
<td>Menopausal status (pre-/perimenopausal)</td>
<td>[26, 33, 36, 43, 45, 47, 50]</td>
<td>9</td>
<td>6269</td>
<td>0.98 (0.94 to 1.02)</td>
</tr>
<tr>
<td>Treatment characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>[26, 28, 30, 32, 36, 38, 42, 43, 45–48, 50, 54–57]</td>
<td>17</td>
<td>10 100</td>
<td>1.12 (1.06 to 1.19)*</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>[26, 28, 30, 32, 36, 38, 43, 45, 47, 55–57]</td>
<td>12</td>
<td>7342</td>
<td>1.01 (0.98 to 1.05)</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>[26, 30, 36, 38, 42, 43, 45–48, 51, 54, 55]</td>
<td>13</td>
<td>9412</td>
<td>0.98 (0.93 to 1.03)</td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>[46–48]</td>
<td>4</td>
<td>611</td>
<td>0.66 (0.43 to 1.00)</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>[26, 28, 30, 32, 35, 36, 42, 43, 45–48, 50, 54–56]</td>
<td>16</td>
<td>7784</td>
<td>1.01 (0.96 to 1.07)</td>
</tr>
<tr>
<td>Breast reconstruction</td>
<td>[30, 43, 45, 47, 54, 56]</td>
<td>7</td>
<td>1587</td>
<td>1.02 (0.94 to 1.12)</td>
</tr>
<tr>
<td>Time since cancer treatment</td>
<td>[26, 35, 45, 50, 54, 56]</td>
<td>7</td>
<td>1260</td>
<td>−0.01 (−0.14 to 0.11)</td>
</tr>
<tr>
<td>SMD (CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment combinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SU</td>
<td>[26, 38, 42, 45, 47, 56, 57]</td>
<td>6</td>
<td>3028</td>
<td>0.83 (0.70 to 0.98)*</td>
</tr>
<tr>
<td>SU + CT</td>
<td>[32, 38, 42, 47, 55–57]</td>
<td>7</td>
<td>3379</td>
<td>1.33 (0.97 to 1.82)</td>
</tr>
<tr>
<td>SU + RT</td>
<td>[26, 32, 38, 45–48, 50, 55–57]</td>
<td>11</td>
<td>4164</td>
<td>0.87 (0.78 to 0.96)*</td>
</tr>
<tr>
<td>SU + HT</td>
<td>[38, 42, 45–47]</td>
<td>4</td>
<td>981</td>
<td>0.83 (0.57 to 1.20)</td>
</tr>
<tr>
<td>SU + CT + RT</td>
<td>[26, 32, 38, 45–48, 55–57]</td>
<td>10</td>
<td>3882</td>
<td>1.18 (1.05 to 1.33)*</td>
</tr>
<tr>
<td>SU + CT + HT</td>
<td>[38, 42, 45–47]</td>
<td>4</td>
<td>981</td>
<td>0.99 (0.66 to 1.49)</td>
</tr>
<tr>
<td>SU + RT + HT</td>
<td>[26, 38, 45–48]</td>
<td>6</td>
<td>1264</td>
<td>0.89 (0.74 to 1.07)</td>
</tr>
<tr>
<td>SU + CT + RT + HT</td>
<td>[26, 38, 45–48]</td>
<td>6</td>
<td>1264</td>
<td>1.38 (1.15 to 1.66)*</td>
</tr>
</tbody>
</table>

$I^2$ was <50% in all analyses, unless indicated otherwise. Results are reported as risk ratio (CI), unless indicated otherwise.

*P < 0.05.

$I^2$ = 55%.

SU, surgery; CT, chemotherapy; RT, radiotherapy; HT, hormone therapy; SMD, standardized mean difference; SD, standard deviation.
because: (i) a measure without cutoff point for severe fatigue was used ($N = 16$); (ii) study populations were duplicate ($N = 4$); and (iii) authors could not be located ($N = 3$) (see also Figure 1). A data request was sent to authors of the remaining 30 studies. Authors of 21 studies were willing to provide data (70%). However, the authors of nine studies had no access to the raw data. Data were provided for the remaining 12 studies. Finally, 27 studies (12,327 patients) were included in the meta-analysis.

**study characteristics**

Sample sizes ranged from 67 to 3088 patients per study. Fourteen different fatigue instruments were used. A multi-item questionnaire was used in 14 studies, a diagnostic interview in four studies and a single item in nine studies. An unselected population (i.e. consecutive patients screened for fatigue) was included in five studies. The other 22 studies used eligibility criteria to select their study population. Eight studies had a longitudinal design (Tables 1 and 2).

**methodological quality**

Ten studies were of high quality, 13 of moderate quality, and 4 of low quality. The mean quality score was 9.2 of 14 (range 4–13; standard deviation = 2.33). The most common methodological shortcomings were not explaining how the sample size was determined (78%) and a lack of a validated questionnaire to...
measure fatigue (63%) (supplementary Table S1, available at Annals of Oncology online).

risk factors

BCS with a partner had a lower risk of severe fatigue than BCS without a partner (RR 0.96, 95% CI 0.93–0.98; supplementary Figure S1a, available at Annals of Oncology online). BCS with stage II or III cancer had a higher risk than BCS with stage 0 or I cancer (RR 1.18, 95% CI 1.08–1.28; supplementary Figure S1b, available at Annals of Oncology online). The risk was higher in BCS treated with chemotherapy than BCS without chemotherapy (RR 1.12, 95% CI 1.06–1.19; supplementary Figure S1c, available at Annals of Oncology online). Radiotherapy, hormone therapy, and targeted therapy were no significant risk factors.

Survivors treated with the combination surgery, chemotherapy, and radiotherapy were at higher risk than other treatment combinations (RR 1.18, 95% CI 1.05–1.33; supplementary Figure S1d, available at Annals of Oncology online). If hormone therapy was added to these three treatment modalities, the risk was 38% higher than in other treatment combinations (RR 1.38, 95% CI 1.15–1.66; supplementary Figure S1e, available at Annals of Oncology online). The risk was decreased in survivors who only had received surgery and surgery plus radiotherapy compared with survivors who had received additional treatment modalities (RR respectively 0.83, 95% CI 0.70–0.98 and 0.87, 95% CI 0.78–0.96; supplementary Figures S1f and S1g, available at Annals of Oncology online). All other examined risk factors were not significant (Table 3).

prevalence of severe fatigue

Prevalence rates of severe fatigue in cross-sectional studies ranged from 7% to 52%. The pooled prevalence was 26.9% (95% CI 23.2–31.0; Figure 2) in a sample of 12125 BCS. The heterogeneity in prevalence rates was high ($I^2 = 95$). Sensitivity analyses on study selection showed a fatigue prevalence of 27.7% (95% CI 22.8–33.2) in studies examining consecutively screened patient samples, with a lower level of heterogeneity ($I^2 = 67$). Sensitivity analyses on type of study (longitudinal/cross-sectional), primary study outcome (fatigue/other outcomes), type of fatigue measure (diagnostic interviews/multi-item questionnaires/single items), and study quality (high/moderate/low) did not reduce heterogeneity (supplementary Table S2, available at Annals of Oncology online).

course of severe fatigue

Given the high heterogeneity in prevalence rates, a meta-analysis on the course of severe fatigue after treatment could not be carried out. Visual inspection suggested a relatively large decrease in the prevalence of severe fatigue in the first half year after treatment completion (Figure 3). Afterward, findings on

![Table](https://example.com/table.png)

Notes. statistics are reported as risk (CI), unless indicated otherwise. $I^2 = 95.13$

Figure 2. Prevalence of severe fatigue in breast cancer survivors.
prevalence rates were inconsistent and seemed relatively high when assessed approximately 5 years after cancer treatment.

**Discussion**

In this meta-analysis on severe fatigue in BCS, data of 12,327 BCS were analyzed. Results demonstrated that BCS with a partner were at lower risk for severe fatigue. In addition, higher stages of BC and chemotherapy increased the risk for severe fatigue following cancer treatment. The risk was also increased in BCS treated with the combination surgery, chemotherapy, and radiotherapy, and in survivors treated with this combination plus hormone therapy. The risk was lower in survivors treated with surgery and surgery plus radiotherapy. Reported prevalence rates of severe fatigue ranged from 7% to 52%. The pooled prevalence was 27%, but this should be interpreted with caution because of high heterogeneity. A relatively large decrease in the prevalence of severe fatigue occurred in the first half year after BC treatment. Afterward, findings on prevalence rates were inconsistent.

In contrast to our findings, the majority of included studies in previous reviews on cancer survivors did not find a significant association between fatigue, and having a partner, stage of disease, chemotherapy, and cancer treatment modalities. It is likely that sample sizes of individual studies in these reviews were too small to detect a significant association. However, our finding on having a partner is in line with several community-based studies, in which having a partner was also significantly associated with being less fatigued [19–21]. Notably, hormone therapy only was a significant risk factor if received in addition to surgery, radiotherapy, and chemotherapy, in spite of the fact that fatigue is often seen as a side-effect of hormone therapy [22]. Limited data were available on targeted therapy. More studies are needed to determine whether targeted therapy is associated with severe fatigue after cancer treatment. Clear conclusions on the prevalence rate and course of severe fatigue in BCS were not drawn in previous reviews. However, our finding that the prevalence of severe fatigue especially decreased in the first half year after cancer treatment corresponds with the current literature on early survivorship. This time period is known as the re-entry phase, in which patients need to adapt to multiple adaptive challenges [18]. After this phase, only a subgroup of patients experience persistent symptoms like severe fatigue [23].

The major strengths of our study are the large sample size of over 12,000 BCS, the wide range of examined risk factors and the specification of our target population (i.e. preventing any confounding influence of active, noncurative cancer treatment, and tumor type on the results). Some potential limitations should also be discussed. To start with, cutoff scores of fatigue questionnaires were used to divide BCS in severely fatigued and nonseverely fatigued groups. The criteria for severe fatigue differ between questionnaires, which probably led to variability between studies and could have distorted our results. Second, data of 18 eligible studies could not be included in our meta-analysis, mostly because the authors had no access to the raw data. Especially, our results on risk factors with small subsets of studies, like targeted therapy and time since cancer treatment, might have been different if more eligible studies were included. Third, our meta-analysis on the prevalence of severe fatigue was limited because of high heterogeneity. Sensitivity analyses showed that the level of heterogeneity was only reduced, though still substantial, in studies that screened patients consecutively in clinical practice. It is disappointing that no firm conclusions can be drawn about the prevalence of severe fatigue in BCS after more than 20 years of research. Not knowing the scope of the problem makes it unclear what sources have to be allocated to follow guidelines for screening and management of severe fatigue [24]. Fourth, fatigue was described as one unified concept, whereas fatigue actually consists of multiple dimensions like mental fatigue, physical fatigue, and the impact of fatigue [25]. We had access only to the total scores of questionnaires and were not able to select specific items that distinguish different dimensions of fatigue. Finally, the patients in the included studies were recruited over a period of more than 20 years. It is important to note that treatments and diagnostic
criteria of cancer have changed in this time period. However, a sensitivity analysis on study period (before and after 2007) did not show substantial differences in prevalence rates of severe fatigue between both study periods.

This meta-analysis involves several implications for future research and clinical practice. To start with, extra attention should be paid to BCS at increased risk for severe fatigue. Our results showed that the risk for severe fatigue is relatively highest in BCS treated with a combination of surgery, chemotherapy, radiotherapy, and hormone therapy. These patients should especially be monitored closely during follow-up examinations. Second, the included studies in our meta-analysis used 14 different instruments to measure fatigue, which reflects that a generally accepted definition for fatigue in cancer survivors is lacking. Future studies should agree on one definition or at least describe which definition is used in their assessment. Besides, future studies should acknowledge that fatigue is a multidimensional concept; distinguish different domains of fatigue in their assessment, and make more explicit which dimensions are studied. This might also help to reduce heterogeneity when estimating the prevalence of severe fatigue. Third, insight should be gained in the course of severe fatigue after BC treatment. More longitudinal studies that measure severe fatigue frequently over longer time periods are needed. This would clarify which patients recover spontaneously from fatigue, and which patients remain fatigued and may need fatigue-oriented interventions. According to a recent practice guideline of the American Society of Clinical Oncology, available evidence-based interventions for fatigue in cancer survivors are exercise and psycho-social interventions (i.e. cognitive behavioral therapy and psycho-educational therapies). Evidence for the efficacy of mind–body interventions (i.e. mindfulness-based approaches, yoga, and acupuncture) is limited, and evidence for pharmacologic interventions (i.e. psychostimulants and supplements like vitamin D) is lacking [11]. Finally, next to demographic, disease, and treatment characteristics, other categories of risk factors for severe fatigue in BCS should be examined in future studies. For instance, behavioral risk factors should be further examined as there is evidence for behavioral characteristics that maintain severe fatigue in cancer survivors (e.g. physical inactivity and deregulated sleep patterns) [8, 11].

In conclusion, approximately one in four BCS suffer from severe fatigue. Risk factors of severe fatigue were higher disease stages, chemotherapy and receiving the combination of surgery, radiotherapy, and chemotherapy, both with and without hormone therapy. Having a partner, receiving only surgery, and surgery plus radiotherapy decreased the risk.

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disclosure

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references


