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REVIEW

How common is fatigue in disease-free breast cancer survivors? A systematic review of the literature

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Abstract *Background* There is some debate in the literature as to whether fatigue persists in the long term in women who have completed adjuvant breast cancer treatment. *Methods* A systematic review was conducted in order to characterise and quantify the phenomenon of post treatment fatigue (PTF). *Results* There was a wide variation in the measures of fatigue used, duration of follow-up and type of comparison made. Overall 18 studies were identified with a follow-up period of between 4 months and 10 years. Fourteen studies demonstrated the presence of continued PTF and/or differences in fatigue levels compared to a reference population up to 5 years after treatment. One short-term study reported no increase in fatigue at 4 months. Three studies (with an average follow up period of longer than 5 years) did not identify overall quality of life differences in breast cancer survivors when compared with a reference population. However there were significant differences in measures of physical functioning and mental fatigue. *Conclusion* The authors conclude that there is good evidence of PTF occurring up to 5 years after completion of adjuvant therapy.

Keywords Cancer related fatigue · Breast cancer survivors

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Introduction

Numerous studies have reported that fatigue can be a major problem during primary breast cancer treatment [1, 2]. Fatigue has been reported post-mastectomy [3] and during adjuvant chemotherapy [4], radiotherapy [5] or hormone therapy [6]. Fatigue during treatment can have a major impact on quality of life [7]. Anti-cancer therapy can have a number of other side-effects including nausea, vomiting, anorexia and alopecia. However, most of these acute side-effects do not persist after the end of treatment and women are generally willing to tolerate them in order to maximise their chances of a successful outcome.

Is fatigue simply another acute side-effect of treatment? Or might it persist for months or years after the completion of therapy? Increasing efforts and resources are being directed to investigating the causes and management of persistent fatigue in cancer survivors [8–10]. However, there is some uncertainty as to whether fatigue really is a persistent problem. At least one recent study suggested that disease-free breast cancer survivors are no more fatigued than age-matched women with no history of cancer [11]. We therefore decided to undertake a systematic review of the literature in order to determine whether or not fatigue is a genuine problem for breast cancer survivors and if so, for how long the fatigue persists.

Methods

A systematic review of the literature was undertaken. The following terms were used to search Medline, Embase, CINAHL (1950-week 1 August 2007).

#1 Exp breast neoplasms #2 breast adj (neoplasm* or cancer* or carcinoma* or tumour* or adenocarcinoma*

or tumor* or malignan*) (title, abstract & keywords) #3 (#1 or #2) #4 exp fatigue #5 fatigue* (title, abstract & keywords) #6 tired* or weary or weariness or exhaustion or exhausted or lacklustre or astheni* or asthenia* #7 (lack* or loss or lost) adj2 (energy or vigour or vigor).

#8 apathy or apathetic or lassitude or letharg* (title, abstract & keywords) #9 (feeling adj3 (drained or sleepy or sluggish or weak*(title, abstract & keywords). #10 (#4 or #5 or #6 or #7 or #8 or #9) #11 #10 AND #3.

The titles and abstracts of the papers identified using this search strategy were screened by one of the authors (OM) and where necessary the full text articles were retrieved. The reference lists of included articles were also examined. OM was responsible for the search strategy and retrieving studies. The final list of included studies was agreed by both authors.

Studies were included in this review if they fulfilled two inclusion criteria:

(1) The study had to include a multi-item fatigue measure. It was decided to exclude studies that only used a single-item (or single visual analogue scale) to measure fatigue as this was considered to be an insufficiently robust outcome measure. Studies that did not use a specific fatigue scale, but which did include a general quality of life measure that contained a multi-item fatigue sub-scale (such as the EORTC QLQc30 [12]) were considered to have fulfilled this inclusion criterion, and were included in the review.
(2) The study had to involve a comparison group. This could either be a within patient (before and after treatment) comparison, or a between groups (e.g., patients versus controls) comparison.

Results

The initial search strategy yielded 941 titles. Only 18 studies fulfilled both inclusion criteria and were considered eligible for inclusion in this review. The studies are described in detail in Tables 1 and 2.

The 18 studies included women between 4 months and 10 years after completion of breast cancer treatment. The total number of breast cancer survivors included in the 18 studies was 7861. Some studies ($n = 9$) reported fatigue severity in survivors with reference to baseline fatigue values before, during or immediately after treatment (longitudinal studies). Other studies ($n = 9$) reported fatigue severity in comparison with general population norms or with reference to a control population with no history of breast cancer (cross-sectional studies). Over all 14/18 studies reported either that fatigue persisted after treatment or was higher in survivors than in control groups. For the purposes of discussion the studies were considered as either "short-term" or "long-term" (greater than 2 years post-treatment).

Short-term studies

Nine short-term (1 month to 2 years post-treatment) studies were identified: Ahn 2007 [13], Andrykowski 2005 [14], Bower 2000 [15], Broeckel 1998 [16], Curran 2004 [17], De Jong 2005 [18], Fan 2005 [19], Hann 1997 [20] and Servaes 2002 [21].

Longitudinal studies

Three of the short-term studies were longitudinal in nature. Andrykowski [14] used Cella's diagnostic criteria [22] to determine the prevalence of "cancer related fatigue syndrome" (CRFS) in 288 women before and after 4 months of adjuvant chemotherapy. In order to fulfil the diagnostic criteria for CRFS women had to have experienced severe fatigue on most days or every day for two weeks in the previous month, to have experienced five out of eleven other fatigue-related symptoms and had to have had no evidence of co-morbid psychiatric disorders that may have explained the fatigue (e.g., depression). Using these criteria, the baseline prevalence of CRFS was found to be 10% rising to 26% after completion of treatment.

De Jong and co-workers [18] examined the course of mental fatigue and motivation in 157 women during, and up to 12 weeks after completion of, adjuvant treatment. Fatigue was assessed at five time points using the Multidimensional Fatigue Inventory [23]. The authors reported no clear pattern of fatigue following treatment and found that fatigue levels had returned to baseline by the end of the study. There was an association between fatigue and depressive symptoms at all assessment times.

Fan and co-workers [19] evaluated fatigue and cognitive symptoms in 104 women undergoing adjuvant chemotherapy and hormone therapy at baseline and followed them up at one and 2 years. They were compared to a patient-nominated, age-matched control group ($n = 102$). Fatigue was assessed using the Functional Assessment of Cancer Therapy Fatigue subscale (FACT F [24]). The treatment population was initially compared to the control group during chemotherapy [25]. These initial results demonstrated a significant difference in FACT F scores between the two groups during and immediately after chemotherapy. A subsequent paper [19] reported on the ongoing course of fatigue in this group at both one and

Table 1 Short-term studies

Type of Study	Study ID	Mean time since treatment	Comparison group (if any)	Numbers of participants	Outcome measures	Results
Cross sectional	Ahn 2007	1 year	General population	1933	EORTC QLQ 30 fatigue subscale	Mean score 36.3 (breast cancer) vs 25.3 (controls) $P < 0.01$
Cross sectional	Bower 2000	1 year	General population	1957	Short form 36	Subset $n = 684$ (30% of total) of fatigued women (scoring less than 50% cut off on SF36 energy/fatigue subscale)
Cross sectional	Broeckel 1998	1 year	General population	110	POMS F Fatigue symptom inventory	Mean score 8.15 (breast cancer) vs 5.32 (controls) $P < 0.01$
Cross sectional	Curran 2004	15 months	General population	49	Diary for 4 days and pedometer recording	Mean diary score 3.0 (breast cancer) vs 2.5 (control) ANOVA $P < 0.01$
Cross sectional	Hann 1996	20 months	General population control	77	POMS F	Mean scores POMS 9.6 (breast cancer) vs 6.3 (control) $P < 0.05$
Cross sectional	Servaes 2002	29 months	General population control	150	Checklist individual strength—CIS (fatigue subscale)	Mean score 28.5 (breast cancer) vs 19.4 (controls) $P < 0.001$
Longitudinal	Andrykowski 2005	4 months	N/A	288	Diagnostic interview for cancer related fatigue	10% pre treatment leading to 26% prevalence PTF
Longitudinal	Andrykowski 1998	28 months	Benign breast disease (BBD)	88	Piper fatigue inventory	Mean score 32.5 (breast cancer) vs 25.9 (BBD) $P < 0.05$
Longitudinal	De Jong 2005	12 weeks (followed through treatment)	N/A	157	Multidimensional fatigue inventory	No significant change from baseline at 12 weeks (MFI score unchanged +−1) Increased fatigue during treatment and at 5 weeks.
Longitudinal	Fan 2005	1 & 2 years	General population control	278	FACT F	Mean score at 1 year 43 (breast cancer)vs 47 (control) at 2 years 45(breast cancer) vs 48 (control) $P < 0.01$

Table 2 Long-term studies

Type of Study	Study ID	Mean time since treatment	Comparison group (if any)	Numbers of participants	Outcome measures	Results
Longitudinal	Bower 2006	2 groups 1–5 years and 5 –10 years	N/A	863	Short form 36	Both groups reported 34% prevalence of fatigue (<50% cut off score on SF 36 energy/fatigue) 21% had persistent fatigue at both time points
Longitudinal	Ganz 2002	6.3 years	N/A	817	Short form 36	Decline in physical functioning (81.9 (1–5 years) vs 79.4 (5–10 years)$P<.0.01$ Improvement in mental health 76.5 (1–5 yrs) vs 78 (5–10 yrs) $P < 0.05$
Longitudinal	Goldstein 2006	48 month follow up	N/A	176	Brief Disability Questionnaire (BDQ) Somatic and Psychological Health Report (SPHERE) questionnaire	Prevalence of fatigue 18% 10 months, 15% 24 months, 12% 36 months, 5% at 48 months. With mood disorder – prevalence 48% at 10 months falling to 18% at 48 months
Longitudinal	Nieboer 2005	3 years	N/A	430	Short form 36 Rotterdam symptom control checklist	Prevalence fatigue (SF 36 vitality score < 46) baseline 19% , 2 years 17% , 3 years 19%.
Longitudinal	Servaes 2007 (online access) Follow up 2002 study	4 years	N/A	121	Checklist individual strength –CIS (fatigue subscale)	Reduction form 39% at baseline to 23% prevalence of severe fatigue at 2 years.
Cross sectional	Helgeson 2005 (complete report of 2002 study)	5 years	General population	267	Short form 36	Physical functioning 83.55 (breast cancer) vs 87.5 (control) $P < 0.05$ Mental fatigue 1.82 (breast cancer) vs 1.65 (controls) $P < 0.05$ Other QOL indices non significant changes.
Cross sectional	Neyt 2006	1–10 years (3 groups post treatment-short < 1 year; medium 1–5 years; long-term 5–10 years.)	3 separate groups at different times post treatment compared with pre-treatment baseline.	184 in total	Combination of SF 36 & EORTC QLQ30	No significant difference between short and long-term feeling weak 0.10 difference $P = 0.31$ Being tired improved long-term 0.25 mean difference $P < 0.01$. Long-term improved to pre-treatment levels
Cross sectional	Robb 2007	Average 5 years	General population control	214	SF 36	Mean scores SF36 69(breast cancer) vs 82 (control) $P < 0.001$

GP – general age matched population; PT – post treatment group; SF 36 – short form 36 quality of life questionnaire; POMS –profile of mood states questionnaire; FACT F – functional assessment of cancer therapy fatigue subscale; EORTC QLQ 30 – European oncology research 30 item quality of life questionnaire

2 years after the completion of treatment. The follow-up results showed that cognitive symptoms and overall quality of life scores had improved and were no longer different between groups. However despite an improvement in fatigue there were still statistically significant differences in FACT F scores at one and 2 years when compared to the controls.

Cross sectional studies

Six of the short-term studies were cross-sectional in nature. Ahn and co-workers [13] studied 1933 disease-free women 1 year after completion of adjuvant therapy (surgery, radiotherapy and/or chemotherapy) and 500 women in the general population (selected by a random sample). Quality of life was assessed using the EORTC QLQ 30 [12] questionnaire. This is a 30-item cancer-specific quality of life questionnaire that contains a three-item fatigue subscale. The authors found no significant differences in over all quality of life between the groups but did find significant differences in a number of subscales including physical functioning and fatigue.

Bower and co-workers [15] examined fatigue and quality of life in 1957 disease-free women up to 2 years after completion of cancer therapy. Fatigue and quality of life were assessed using the Short Form-36 [26]. Women scoring less than 50% on the energy/fatigue subscale were classified as "fatigued". Scores were then compared with population norms (for age-matched women) in order to interpret the significance of the findings. The overall comparison demonstrated no significant differences between the study populations and published normal values. However the post-treatment group contained a substantial minority (approximately 30%) who had persistent fatigue.

Broeckel and co-workers [16] examined 61 women 1 year post-treatment. The purpose was to examine the characteristics of fatigue after therapy compared to a control population. This group was obtained by participant nomination of age-matched women The authors used the Fatigue Symptom Inventory [27]. This is an 11-item questionnaire which assesses the frequency and severity of fatigue as well as its perceived interference with quality of life. The results demonstrated a significant difference in the level of fatigue and a worse quality of life as a result of fatigue.

Curran and co-workers [17] studied 25 women on average 2 years post-treatment compared with 25 controls in order to examine the diurnal variation in fatigue. The authors used "ecological momentary assessment" which involves sampling multiple measures throughout the course of a day. This study used pedometer measurements as well as fatigue diaries. There was a significant difference on diary measures of fatigue between the two groups but no differences in objective measures.

Hann and co-workers [20] examined 43 women 20 months after autologous bone marrow transplant for breast cancer in order to determine the severity and impact of fatigue. They compared the treatment group to 44 participant-nominated, age-matched controls. The authors assessed quality of life using the Profile Of Mood States Fatigue subscale (POMS F [28]). This is a seven-item measure of fatigue severity assessing symptoms over the last week. The authors reported that patients experienced significantly more severe fatigue and more frequent episodes of fatigue than the control group.

Servaes and co-workers [21] examined 150 disease-free women who had undergone primary curative treatment. They were compared with 78 peer-nominated, age-matched controls using the Checklist of Individual Strength (CIS) fatigue subscale [29]. The authors found significant differences in CIS scores between the two populations. There was also a difference in the prevalence of severe fatigue (CIS cut-off score >35) between the groups (38% post treatment vs 11% controls).

Long-term studies

Nine long-term studies were identified: Bower 2006 [30], Ganz 2002 [31], Goldstein 2006 [32], Helgeson 2005 [11], Neyt 2006 [33], Nieboer 2005 [34], Robb 2007 [35], Servaes 2007 [36], Andrykowski 1998 [37].

Longitudinal studies

Seven of the nine long-term studies were longitudinal in nature. Andrykowski and co-workers [37] undertook a controlled comparison to determine the impact of off-treatment fatigue. The authors studied 88 women, an average of 28 months post treatment, and compared them to 88 women with benign breast disease. Women were studied at two time points, 4 months apart. Eligible disease-free women (between 6 and 57 months post primary treatment) completed the first assessment after being identified at the follow up clinic. The second assessment was completed 4 months later. Fatigue was assessed using the 35-item Piper Fatigue Scale [38] and quality of life was measured using the Short Form 36 [26]. The authors reported that the breast cancer group had significantly worse fatigue and lower quality of life scores at the initial comparison with the benign breast disease group. This difference was unaltered at the repeat assessment 4 months later.

Bower and co-workers [30] examined a group 763 women up to 10 years post-treatment. They used the Short

Form 36 and applied the same cut off value of 50% on the energy/fatigue subscale to identify a case of PTF. This study followed-up the same population surveyed in the earlier study [15]. There was a point prevalence of 34% 5 to 10 years post-treatment. This value is similar to earlier results demonstrating a 35% prevalence between 1 and 5 years after treatment [15].

Ganz and co-workers [31] examined 817 women up to 10-years post treatment. This group was examined 5 years after participating in a previous study [39] which examined sexual function and QOL after treatment. These women were initially examined 1–5 years after completion of primary treatment. This follow-up study examined the same cohort 5 years after initial recruitment. It examined women up to 10 years after treatment. The follow-up study primarily assessed over all QOL but used the SF 36 and so measures of physical functioning and mental fatigue could be derived. The over all results showed a decline in physical functioning but this was felt to be an age-related change and not clinically significant.

Goldstein and co-workers [32] examined 176 women with fatigue and/or mood disorders at multiple time points up to 4 years post-treatment. The first assessment was conducted on women less than 12 months after completion of adjuvant therapy. Repeat measures were recorded at 24, 36 and finally at 48 months .The authors used a combination of the somatic and psychological health report [40] and brief disability questionnaire [41]. Fatigue and mood disturbance were defined using cut-off scores on each measure. The results demonstrated persistent PTF with and without associated mood disorder. The prevalence declined over 4 years. The fatigue prevalence was 20% up to 2 years post treatment (35% when associated with mood disorder). This figure fell between 24 and 48 months after completion of treatment. The prevalence at 48 months was 5% for isolated fatigue and 15% when associated with mood disturbance.

Nieboer and co-workers [34] examined 430 women who had received high dose or standard chemotherapy. Participants had quality of life assessments undertaken at pre-treatment baseline, on completion of treatment and annually thereafter for 3 years. The purpose was to examine the relationship between treatment regimen and fatigue. The authors used a cut-off value on the Short Form 36 to identify fatigue. The results demonstrated a 20% prevalence of fatigue at 3 years independent of treatment. This remained unchanged from a 19% baseline pre-treatment level. There was an association between lower mental health scores and increased fatigue.

Servaes and co-workers [36] examined a follow up population of 121 women from their original study (see above) [21]. Their purpose was to investigate whether fatigue was a persistent problem. They observed levels of fatigue over a 2-year period after completion of adjuvant therapy. The results demonstrated a prevalence of 23% of severe fatigue compared with 39% at baseline. This was associated with high levels of measured anxiety and impairment of physical functioning at baseline assessment.

Cross sectional studies

Three of the nine long-term studies were cross-sectional in nature. Helgeson and co-workers [11] examined a group of disease-free women who had undergone adjuvant curative treatment ($n = 267$) with age-matched controls from the local population [42] comparing a number of QOL variables. The purpose was to examine the long-term impact of breast cancer treatment. Some of the women included in this study had also participated in an earlier study to assess the impact of an educational intervention [43] on outcomes in women with breast cancer. The participants were re-surveyed 5 years after treatment and intervention and so the results must be interpreted with caution. Overall QOL differences were non-significant. However there were significant differences in mental fatigue and physical functioning between the two groups.

Neyt and co-workers [33] examined women ($n = 184$ total) in three separate groups up to 10 years after treatment. The three groups were defined by time after adjuvant treatment (<1 year; 1 to 5 years and 5 to 10 years) Their purpose was to compare between-group characteristics of disease free women at different times after treatment. The results were compared to pre-treatment baseline responses. They used a combination of SF 36 and EORTC QLQ 30. The results demonstrated persistent fatigue in the short and medium term (up to 5 years). The fatigue scores in the long-term treatment group (over 5 years) were not significantly different from baseline.

Robb and co-workers [35] examined older women (over 70) up to 15 years (mean 5.1 years) post treatment ($n = 127$) with age-matched controls ($n = 87$) sampled from an epidemiological study examining healthy aging in order to examine overall QOL. Fatigue was measured using the Multidimensional Fatigue Inventory [44]. The study demonstrated significant differences in the level of physical functioning and the degree to which fatigue interfered with daily activities.

Discussion

This systematic review has identified a number of studies reporting on the prevalence of PTF in breast cancer survivors. However, there were limitations to most of these

studies that need to be taken into account when interpreting the significance of their findings.

Fatigue has a baseline prevalence within the general population which increases with age or other co-morbidities [45]. As a result of this, some degree of fatigue is a near-universal phenomenon. It is therefore vital to define what constitutes significant PTF. It is apparent on reviewing the literature that there is no agreed consensus on a definition for significant fatigue. We suggest that significant PTF should be at a greater level than fatigue experienced by age-matched controls and ideally should meet the criteria for a case of cancer related fatigue syndrome [22]. This then distinguishes PTF from other types of fatigue. There were a wide variety of measures used to assess the symptoms associated with PTF. Some authors used tools to compare group scores while others used a cut-off score to define the fatigued group. The different methods used may have influenced the level of reported PTF depending on the study design and population studied. This is especially important for the longitudinal studies where the lack of a control population comparison may have resulted in an artificially high prevalence of PTF.

This review has focused on PTF only and has not sought to examine over all QOL changes after breast cancer treatment. These are two separate constructs and while there is likely to be a strong correlation this review cannot make comment on overall QOL. The search strategy was designed to look for studies where fatigue was a primary outcome of interest. Studies which examined quality of life without measuring fatigue have not been included.

The variety of measures used and the methods by which data was collected has meant it was not possible to combine the prevalence data in a meta-analysis.

The short-term studies seem to provide consistent evidence that PTF is an ongoing problem. There is a significant difference between treated women and control populations for fatigue measures in all but one of the studies [18]. The results of Bower et al. [15] demonstrated no over all differences in fatigue between the two populations studied. However the prevalence of severe PTF was approximately 30% at up to 2 years in the adjuvant treatment group. It is important to note that this level of fatigue is significantly different from the level seen in the age-matched comparison population. PTF is comparable to fatigue experienced during adjuvant therapy. Women are affected to different degrees by fatigue and some experience no fatigue at all. Despite PTF only occurring in the minority of women there is a still a significant level of PTF (20–30%) at up to 2 years. The consistent level of evidence must imply that PTF is not artefactual and strategies need to be in place to identify and treat this group.

The longitudinal studies suggest the existence of ongoing PTF but with an improvement in fatigue symptoms over time. The studies with longer follow up (over 5 years) show a trend towards improvement in fatigue, however the numbers become too small to definitively state if and/or when PTF resolves entirely. These results demonstrate a significant minority of women still experience PTF up to 5 years after completion of treatment. There is a wide variation around this figure from 5 to 34% prevalence with a mean figure of approximately 20%. There is some difficulty in interpreting the results as all baseline measures are taken following completion of primary treatment.

The longer-term studies demonstrate some important negative results. While Ganz et al. [31] found statistically significant differences in physical functioning this was likely due to sample size and not clinically important factors. A similar interpretation can be made for the results seen in Helgeson et al. [11]. The authors demonstrated statistically significant differences in physical functioning and mental fatigue. This may again be artefactual as a result of sample size and not clinically meaningful. However these studies were primarily examining over all quality of life which was not significantly different in the two populations. Both studies used the Short Form 36. This is a useful scale for examining a healthy population but may not be discriminating enough to examine the multi-dimensional nature of PTF. Even with this interpretation these studies do highlight important differences in the treated group compared with the general population. This is most notable in respect to physical functioning and mental fatigue. This discrepancy between populations is seen up to 5 years after treatment. It has been argued that PTF is a short-term problem and resolves quickly. The evidence currently available does not support this contention. The data strongly suggests that in affected women any improvement is seen only after 2 years and that fatigue may continue up to 5 years following treatment.

There is no clear temporal relationship between study publication and results. It has been argued that earlier poorly designed studies were positive and more robust later studies had negative findings. This does not appear to be the case.

The data suggests that PTF is a problem for a significant percentage of women (up to 50% in some studies). This is not a phenomenon that occurs solely during treatment and given the increasing number of breast cancer survivors [46] it is something not to be dismissed lightly.

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