# Fatigue during and after breast cancer therapy –

# A prospective study

**Running head: Fatigue predictors in breast cancer survivors**

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**Abstract**

*Context:* Chronic fatigue (CF) in breast cancer (BC) survivors is multifactorial and may be caused by immune activation triggered by BC or its treatment. In the NeoAva study, BC patients received neoadjuvant chemotherapy (FEC100→taxane) +/- bevacizumab, a monoclonal antibody with fatigue as a potential side effect.

*Objectives:* To examine fatigue levels and prevalence of CF before and during chemotherapy and at follow-up (FU), and their associations with C-reactive protein (CRP) and clinical variables.

*Methods:* 84 HER2 negative patients with cT2-4N0-3M0 BC responded to questionnaires, and had CRP measured before treatment (T0), after FEC100 (T1), after taxanes prior to surgery (T2), and at 2 years FU (T3).

*Results:* The prevalence of CF increased from 8% at T0 to 36% at T3, $p<0.0001$. Fatigue levels peaked during chemotherapy from 12.0 at T0 to 20.0 at T2, and declined to 16.7 at T3, $p<0.001$. Women with CF at T3 had higher fatigue levels at T0, T2 and T3 than those without CF ($p\leq 0.01$). Psychological distress ($p=0.03$) and pain ($p=0.04$) at T3 were associated with CF at T3. Only psychological distress remained a significant predictor in multivariate analysis. CRP increased from T0 to T1 ($p<0.01$), and declined to baseline values at T3, but changes were not associated with bevacizumab- treatment. No association was found between bevacizumab or CRP, and fatigue levels or CF.

*Conclusions:* Neither bevacizumab-treatment nor low-grade systemic inflammation as measured by CRP was associated with the increased fatigue levels and raised prevalence of CF, observed during and after BC therapy. Increased fatigue levels at baseline and psychological distress at T3 were associated with CF at T3.

## 1. Introduction

Fatigue is a subjective feeling of tiredness, weakness and lack of energy [1]. Fatigue is the most common and distressing symptom during breast cancer (BC) treatment, with prevalence estimates ranging from 25-99%, and with the highest prevalence during chemotherapy [2,3]. Even though fatigue generally improves after BC treatment cessation [3], a substantial number of individuals experience more enduring complaints. Chronic fatigue (CF) is defined as elevated levels of fatigue for ≥ 6 months [4]. CF affects approximately 30% of BC survivors more than 5 years into survivorship, significantly reducing daily function and quality of life in affected individuals [5-7].

Both somatic and psychosocial factors are associated with fatigue in BC survivors [3,8,9]. Our group demonstrated that psychological distress, discomfort in the BC-treated area and high body mass index (BMI) were associated with CF in women up to 7 years after their BC treatment, and that these factors also predicted persistence of fatigue symptoms three years later [6]. Neuroticism is a personality trait characterized by anxiety and worry, that has been associated with fatigue in survivors of testicular cancer [10]. To our knowledge, neuroticism has not been studied in relation to fatigue in BC survivors.

The mechanisms underlying CF after end of BC treatment are not yet clear. From a biological perspective, evidence suggests that immune activation play a role in the development of fatigue in both BC patients and survivors [3,11]. C-reactive protein (CRP) is a sensitive and reliable biomarker of systemic inflammation, easily measured in clinical practice[12]. Increased CRP- levels were associated with fatigue in BC patients prior to radiotherapy [13] and chemotherapy [14] and in BC survivors [6,15-17], but findings are inconsistent [18,19]. Moreover, of the few studies showing a positive association between CRP and fatigue in BC survivors most are cross-sectional [15-17]. Further, few of the prospective studies assessing predictors of fatigue prior to- and during treatment have evaluated fatigue into survivorship [20].

Therefore, at present, we have limited knowledge on the course of fatigue in BC survivors, on factors associated with CF, and on factors that put individuals starting BC therapy at risk of developing CF. A recent review addressing these questions concluded that "longitudinal studies are required that track patients before, during and after cancer therapy and include comprehensive assessment of biobehavioural risk factors"[3]. Also, little data exists on fatigue during and after modern BC treatment, including targeted therapy.

Bevacizumab is a monoclonal antibody targeting human vascular endothelial growth factor [21] and improves progression free survival in metastatic BC patients when combined with standard chemotherapy [22,23]. The BC patients receiving bevacizumab combined with chemotherapy were significantly more fatigued than those treated with chemotherapy alone [22]. In studies addressing the effect of combining bevacizumab with chemotherapy as a neoadjuvant regimen, the prevalence of fatigue was not reported [24] or was similar in the treatment arms [25].

The **Neo**adjuvant **Ava**stin in Breast Cancer (NeoAva) study compared neoadjuvant treatment with chemo- or endocrine therapy +/- bevacizumab in patients with HER2-negative BC. The primary aim of the NeoAva study was to explore molecular and metabolic determinants of pathological complete response in breast and lymph nodes in the different treatment arms. A substudy of the NeoAva study was designed to prospectively assess the levels of fatigue and its course in the different treatment arms from baseline and into survivorship.

On this background, aims of the present study were two-fold. Firstly, we examined possible differences between treatment-groups (+/- bevacizumab) regarding fatigue and CF at at the time of BC diagnosis, end of chemotherapy and at 2 years of follow-up (T3). Secondly, we wanted to identify if neuroticism, CRP-levels, psychological distress, BMI, sleep problems or pain, measured as early as possible after BC diagnosis were associated with CF at T3.

We hypothesized that fatigue levels would increase during the course of therapy, and that targeted therapy with bevacizumab, added to modern regular chemotherapy would promote fatigue in treated individuals. Further, we hypothesized that low grade systemic inflammation as measured by CRP, would correlate with increased fatigue levels and higher prevalence of CF in BC patients.

## 2. Methods

### *2.1. Patients*

Inclusion criteria were: patients ≥ 18 years of age, diagnosed with (≥ 2.5 cm) HER2 negative breast adenocarcinomas (cT2- cT4) with no clinical or radiological signs of metastatic disease, ECOG/WHO performance status ≤ 2, adequate haematological, liver and renal function and normal baseline cardiac function measured by MUGA or ECHO.

Exclusion criteria were: any carcinoma diagnosed less than 5 years and BC less than 2 years prior to the current disease, except for basal cell or in situ cervical carcinoma, major surgery during the past 4 weeks, clinically significant cardiovascular disease (*i.e.* myocardial infarction past months, unstable angina, congestive heart failure NYHA Class ≥II, serious cardiac arrhythmia), neurological or metabolic dysfunction, any other disease or clinical or laboratory finding giving reasonable suspicion of a condition that contraindicated the use of bevacizumab or put the patient at high risk for treatment-related complications.

In total, 150 patients were included in the NeoAva study. Due to delayed initiation of the substudy, only the last 106 of these patients were included in the present NeoAva substudy.

*2.2. Treatment*

The NeoAva study was a multicenter, randomized phase II clinical trial with two study cohorts. All subjects were randomized using a 1:1 ratio +/- bevacizumab stratified by tumor- and hormone receptor status. Patients treated with *chemotherapy* received 4 three-weekly cycles of FEC100 (fluoruracil 600mg/$m^2$, epirubicin 100mg/$m^2$, cyclophosphamide 600mg/$m^2$), followed by 4 three-weekly docetaxel (100mg/ $m^2$) or 12 weekly paclitaxel (80mg/ $m^2$) cycles. Patients ≥ 55 years of age with hormone-receptor positive tumors received *endocrine therapy* if this treatment was considered more favorable than chemotherapy. Bevacizumab was administered intravenously for a total of 8 courses at a dose of 15 mg/kg every three weeks, or, for those receiving paclitaxel, 10 mg/kg every other week.

The study treatment period was 24 weeks, followed by surgery (mastectomy or breast conserving surgery and axillary clearance) and eventual radiotherapy and endocrine therapy according to national treatment guidelines (www.nbcg.no).

*2.3. Patient-reported assessments*

Information on fatigue, socio-demographics, sleep, somatic and mental health was obtained by a questionnaire including standardized patient-reported outcome measures and selected single items. The first questionnaire was filled in before randomization and treatment (T0). Further assessments were performed 12 (at change from FEC100 to taxane-based therapy, T1) and 25 weeks (before surgery, T2) and 2 years after T0 (T3) (Figure 1).

The main outcomes in this study are *levels of fatigue* and *chronic fatigue* assessed by the Fatigue Questionnaire (FQ) [4]. The FQ consists of 11 items with four response alternatives (0,1,2,3) and inquires about fatigue symptoms during the past month compared to when the subject last felt well. Responses are scored in two ways. Physical (PF, 7 items), mental (MF, 4 items) and total fatigue (TF, all 11 items) are constructed by simply adding the response-scores. Higher scores imply higher levels of fatigue. An additional item assesses the duration of the fatigue symptoms. A

dichotomized score (0,0,1,1) of the raw response-scores are used for definition of C*hronic fatigue* (CF) which is defined by a sum of dichotomized scores ≥4 and symptom duration for 6 months or longer [4,26]. The FQ has been recommended for assessment of cancer-related fatigue, and has been used in numerous studies involving cancer patients with internal consistencies ≥ 0.85 and a stable factor structure supporting its construct validity [4,27,28]. Internal consistency (Cronbach's α's) in the present sample were 0.86 (PF), 0.76 (MF) and 0.86 (TF).

*Neuroticism* is a personality trait representing an individual's tendency to worry and feeling insecure, and has been associated with CF in testicular cancer survivors [10]. Neuroticism was measured at baseline by 6 items originally included in the broader Eysenck Personality Questionnaire [29]. Each item was scored as "present" (1) or "absent" (0). Higher scores imply higher levels of neuroticism. In line with prior research "high neuroticism" was defined by a sum score ≥5 [30]. Internal consistency in the present sample was 0.79.

A single item assessed *Consultation for mental problems prior to* BC which included consultations with a psychiatrist or a clinical psychologist before BC diagnosis [6].

*Pain* intensity last 24 hours was assessed on a 0-10 numerical rating scale from the Brief Pain Inventory [31].

*Psychological distress (i.e. Emotional functioning)* was measured by the four items in the emotional functioning scale of the European Organization for Research and Treatment of Cancer Quality-of Life Questionnaire (EORTC QLQ C30) asking for levels of anxiety, depression, tenseness and irritability[32]. The raw score was linearly transformed to a 0-100 scale [33]. According to the construction of the EORTC scale, higher scores implicate better functioning, lower scores indicate *psychological distress.*

*Sleep* was assessed by two items previously used in the Nord-Trøndelag Health Study II (HUNT II) (www.hunt.no) asking about "sleep onset insomnia" and "too early awakening" during the past month, and by one item from the EORTC QLQ C30 asking about "trouble

sleeping" during the past week. Each item has four response alternatives, which were dichotomized into "present" (often/almost every night [HUNT II], very much/quite a bit [QLQ C30]) or "absent" (never/occasionally [HUNT II], some/not at all [QLQ C30]) based on previous studies [34]. *Sleep problems* was defined as present if the patient answered "yes" on at least one of the three dichotomized items. S*leep duration;* hours of sleep during the past 24 hours.

The following demographic information was dichotomized: Marital status as paired (married/cohabiting) versus non-paired (never married/separated/divorced/widows), level of education as ≤12 years or >12 years of education.

*2.4. Clinical and disease-related data*

Clinical data were collected from the women's medical records. *Body mass index (BMI)* was calculated from height and weight measured before chemotherapy and at T1, T2 and T3 using the formula BMI=weight (kg)/height $(m)^2$ [35]. Based on the calculated BMIs, patients were dichotomized as 1: obese (≥30) or 0: not obese (<30).

*2.5. CRP measurements*

Blood samples were drawn at T0, T1, T2 and T3 at similar time points as the subjects responded to the questionnaires. Aliquots of serum were collected and immediately stored at -80ºC until analyzed. Serum CRP-levels were measured using a particle-enhanced immunoturbidimetric assay (Tina-Quant CRP Gen.3, Roche Diagnostics, Basel, Switzerland). The detection limit for CRP was 0.6 mg/L. For calculations, samples with CRP-values registered as < 0.6 mg/L, were coded as 0.5.

*2.6. Statistics*

Continuous variables were described using median and [range], categorical variables as proportions. Unadjusted associations were assessed using Mann-Whitney-Wilcoxon and Chi-square tests for continuous and categorical variables, respectively.

Selected variables (total fatigue score, CRP-levels, BMI, pain, emotional function and sleep duration) were analyzed using mixed models for repeated measures with random intercept and unstructured covariance matrix (measurement points were not distributed evenly in time) adjusted for marital status, education, age, neuroticism and prior mental problems. The results were expressed as overall p-values (all measurements considered) and as estimated means with 95% confidence intervals (CI).

Univariate and multiple logistic regression analyses were performed with CF at T3 as the dependent variable. Clinically relevant explanatory variables with a p-value <0.1 in the univariate analyses were entered into the multiple logistic regression model, and odds ratio (OR), 95% CI and p-values are presented.

Two-sided p-values <0.05 were considered statistically significant. All analyses were considered explorative, so no correction for multiple testing was performed. All analyses were performed using SPSS version 21.0 (SPSS Inc, Chicago IL).

*Ethics*

The Regional Committee for Medical and Research Ethics, Health Region South, Norway and the Norwegian Medical Agency approved the study. A signed informed consent was required for study participation.

**3. Results**

Of the 106 women who received the baseline FQ, 17 were excluded ; 2 because they were unable to read Norwegian, 4 because they did not respond to the questionnaires and 11

because they died/developed recurrent disease during the study period. Five individuals received only endocrine treatment and were excluded from further analyzes due to their limited number. Thus, our sample consisted of 84 women (Figure 1).

### *3.1. Patients' characteristics at BC diagnosis*

Median age at BC diagnosis was 50 [25-68] years. Half of the participants received bevacizumab in addition to chemotherapy. At baseline, more women in the non-bevacizumab than in the bevacizumab group reported CF (p=0.05) and previous consultation for mental problems (p= 0.03). Further baseline patient characteristics are listed in Table 1.

### *3.2. Effects of bevacizumab*

In univariate analyses, there was no difference in fatigue level or CF between the women treated with or without bevacizumab (Table 2, Figures 2 and 3). Furthermore, there was no difference in the time trajectories with respect to fatigue levels or CF between the treatment arms, nor were there any association between bevacizumab-treatment and CRP-levels (data not shown). Therefore the study cohort is presented as a whole with respect to the other predictors.

### *3.3. Fatigue and associated factors during longitudinal follow-up*

TF steadily increased from baseline throughout chemotherapy (median 12.0 [3-25] at T0, 17.5 [10-29] at T1 and 20.0 [5-30] at T2, p<0.001), and then declined at T3 (16.7 [2-31], p<0.001) (Tables 2 and 3, Figure 2). Women with CF at T3 had higher fatigue levels

compared to those without CF at T3 at T0 (15.0 vs 11.5, p=0.004), T2 (22.0 vs 19.0, p=0.01) and T3 (23.0 vs 12.0 p<0.0001).

CF afflicted 8% (N=7) at T0 and 36% (N=27) of the women at T3, representing a significant increase in CF compared to the prior time points (p<0.0001) (Table 3, Figure 3). Two patients with CF at baseline dropped out of the study at T3. These individuals were not treated with bevacizumab, and none of them had CF at T2. The longitudinal data showed that the course of CF was dynamic – no individual had CF at all time points. Of the 27 with CF at T3, only 6 had CF at T2, and among those only 2 had CF at T1.

The estimated course of fatigue, CRP, BMI, pain, psychological distress and sleep during follow-up is listed in Table 3.

CRP-levels increased from baseline to T1 (p<0.01) and then declined to baseline values at T3 (Table 3), but there was no association between CRP and fatigue levels or CF at any time point (data not shown).

Among the variables at baseline and at T2, only TF was associated with CF at T3 in the univariate analyses (Table 4). At T3, high emotional function *i.e.* less psychological distress (OR 0.96, 95%CI 0.94-0.99, p= 0.003) and pain (OR 1.3, 95%CI 1.02-1.67, p=0.04) were associated with increased risk of having CF at T3 in univariate analyses, and were included in the multivariate model together with baseline TF score. In the multivariate analysis, only high emotional function, *i.*e. less psychological distress at T3 was associated with a decreased risk of having CF at T3 (OR 0.97, 95%CI 0.94-0.99, p=0.03) (Table 4).

## 4. Discussion

This study demonstrates a strong increase in the prevalence of CF in BC survivors from 8% at BC diagnosis to 36% at 2 year follow-up. The highest fatigue levels were reported at the end of chemotherapy, and even though fatigue levels declined after chemotherapy cessation, TF was still significantly higher at 2 year follow-up than at BC diagnosis (16.7 and

12.0, respectively). Further, neither bevacizumab-treatment nor low-grade systemic inflammation as measured by CRP were associated with the increased fatigue levels and raised prevalence of CF, observed during and after BC therapy.

Our results are in line with prior findings that about one third of BC survivors have chronic fatigue up to 10 years after diagnosis [1,5,6]. In further support of our results are findings by Pertl *et al* indicating that fatigue levels increased during BC chemotherapy and subsequently decreased after treatment termination in 61 women assessed at three time points from BC diagnosis into BC survivorship [14].

In a study by Loge *et al*, women in the general Norwegian population with an age-span relevant for the current study had an average fatigue level of 13.0 and a prevalence of CF ranging from 12% to 22% [36]. These numbers were higher than the fatigue level and prevalence of CF observed in our study prior to BC treatment. Thus, our data strongly suggest that the high prevalence of CF observed among the BC survivors at 2 years follow-up is BC-related.

Higher fatigue levels at baseline or at end of chemotherapy predicted CF in BC survivors at 2 year follow-up. Also, pain and psychological distress at 2 year follow-up were significantly related to CF at that time point. Current psychological distress was the only factor remaining significantly associated with CF at 2 year follow-up in multivariate analyses. Interestingly, a recent randomized trial demonstrated that mindfulness-based stress reduction improved both psychological distress and fatigue among 322 BC survivors [37]. Thus, a prospective study offering stress reduction techniques to BC survivors experiencing psychological distress, and to those who had high fatigue levels during BC therapy, should be pursued.

Bevacizumab-treatment, sleep problems or CRP-level measured at any of the assessment points were not associated with CF at 2 year follow-up. Even though prior studies

found increased CRP-levels associated with fatigue in BC survivors [6,15], results are conflicting. Zick *et al* did not find different CRP-levels between 16 fatigued and 13 non-fatigued women examined at least 3 months after end of BC therapy [38]. Further, there was no link between increasing fatigue in BC survivors and CRP-levels in the studies by Wratten *et al* and Pertl *et al* [13,14]. However, both these studies found that higher CRP-levels were associated with fatigue in BC patients *prior to* radio- and chemotherapy. The majority of patients in these two studies had completed BC surgery prior to study inclusion. Therefore, we cannot rule out that the association between higher CRP-levels and baseline fatigue observed in these studies was related to the surgical procedure. The women included in the present study had undergone a breast core biopsy for confirmation of their BC diagnosis, but no definite surgery. Therefore, any CRP-elevation at baseline due to surgical intervention is unlikely. CRP-levels increased transiently during BC-treatment in our study, but we did not find any association between CRP and fatigue levels or CF at any time point. Specifically, we found no evidence that persisting low-grade inflammation at 2 year follow-up was associated with the high number of women with CF at T3.

In line with the study by Bear *et al*, the current study did not demonstrate any association between neoadjuvant bevacizumab-treatment and fatigue [25]. In contrast, Miller *et al* reported an increased prevalence of fatigue in BC patients receiving bevacizumab in combination with paclitaxel compared to paclitaxel alone [22]. However, they included metastatic BC patients who continued therapy until disease progression. Thus, that study is not directly comparable to our study.

The primary strength of our study is the longitudinal study design and long follow-up time including examination of fatigue and multiple putatively associated factors at BC diagnosis, during modern BC chemotherapy, +/- targeted therapy with bevacizumab, and at 2 years follow-up. In June 2016, Abrahams et al published a combined review and meta-

analysis on severe fatigue after BC therapy including more than 12000 individuals [39]. The authors stated that more longitudinal studies are needed to gain insight in the course of fatigue after BC treatment. Further, they asked for studies including novel therapy with targeted drugs as so far, data are too limited to determine whether such treatment is associated with severe fatigue after BC treatment or not. Our study specifically addresses these issues and therefore adds new information and valuable knowledge about the course of fatigue after modern BC therapy.

Another strength is the homogeneity of the patient population with a uniform disease burden and treatment. Due to strict inclusion criteria, women with serious co-morbidities (including those who relapsed with BC during the study period) were excluded, thus minimizing the risk for having fatigue due to comorbid conditions. Further, well-established questionnaires were used to assess patient-reported variables.

A limitation of the current study is that CRP was the only immune marker measured. Our rationale for assaying only CRP was that it is a general and reliable indicator of systemic inflammation, and it is easily measured in daily clinical practice. CRP is synthesized in response to interleukin (IL)1 and IL6 stimulation [40], cytokines that have been linked to the development of fatigue [7]. CRP may thus be regarded as an indicator for IL1 and IL6 activity. However, after the initiation of our study, Zick *et al* presented data showing increased serum-levels of IL6 in fatigued as compared to non-fatigued BC survivors, but no difference in CRP between the groups [38]. Thus, other biomarkers could have been assessed for a more comprehensive study of the inflammatory response to BC treatment and its possible association with fatigue. A further limitation of the study is that we did not record intercurrent co-morbidities or medications, which might have influenced CRP levels.

The current study sought to assess if factors present prior to or at end of BC therapy would predict CF in women at follow-up 2 years after their diagnosis. However, the moderate

number of individuals included in the current study, limited the number of explanatory variables that could be included in our analyses. Thus, we cannot rule out that putatively causative variables for development of fatigue in BC survivorship, present at BC diagnosis or at end of chemotherapy, have been omitted and not explored in our analyses. However, prior studies on inflammation and fatigue in BC survivors have been carried out on even smaller samples [38];Pertl, 2013 #471}. The questionnaires used in this study were comprehensive. To limit the respondent's burden, some variables are measured using only a couple of items of multi-items scales, which may be considered a limitation of our study. Also, the moderate number of included individuals might cause the study to be underpowered with respect to detecting a clinically relevant difference in fatigue levels or CF between women treated with or without bevacizumab. However, as shown in Figures 2 and 3 there was a trend for reduced fatigue levels and prevalence of CF with bevacizumab at T3, making it unlikely that bevacizumab should cause increased fatigue in BC survivors.

## 6. Conclusions

Our data revealed that while fatigue levels peaked during BC therapy, the prevalence of CF increased the most after treatment cessation into survivorship. Targeted therapy with bevacizumab was not associated with increased fatigue levels nor with the raising prevalence of CF, observed during and after BC therapy. Low-grade systemic inflammation as measured by CRP transiently increased during BC therapy, but did not correlate with fatigue levels or the onset of CF. Increased fatigue levels at baseline and psychological distress at 2 year follow-up were associated with CF at T3. In light of recent research demonstrating that stress reduction techniques can improve psychological distress and fatigue in BC survivors [37], we propose a prospective study offering such stress reduction techniques targeting BC survivors experiencing psychological distress and to those who had high fatigue levels during BC therapy.

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**Conflict of interest**

The authors have declared that there is no conflict of interest for this manuscript.

Figure legends

Figure 1. Cohort and treatment overview and assessments

Figure 2. Course of total fatigue (TF) score, in the whole cohort and in women treated with- and without bevacizumab. Median fatigue level on the y-axis, assessment points on the x-axis.

Figure 3. Prevalence (%) of chronic fatigue (CF) in the whole cohort and in women treated with- and without bevacizumab at T0, T1, T2 and T3. % CF on the y-axis, assessment points on the x-axis.

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