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Light Treatment Prevents Fatigue in Women Undergoing Chemotherapy for Breast Cancer

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Abstract

Purpose—Fatigue is one of the most disturbing complaints of cancer patients and often is the reason for discontinuing treatment. This randomized controlled study tested the hypothesis that increased morning bright light, compared to dim light, would result in less fatigue in women with breast cancer undergoing chemotherapy.

Methods—39 women newly diagnosed with Stage I-III breast cancer were randomized to either bright white light (BWL) or dim red light (DRL) treatment and were instructed to use the light box for 30 minutes every morning throughout the first 4 cycles of chemotherapy. The Multidimensional Fatigue Symptom Inventory was administered prior to the start of chemotherapy (baseline), during the chemotherapy treatment week of cycle 1 (C1TW), the last week (recovery week) of cycle 1 (C1RW), chemotherapy treatment week of cycle 4 (C4TW), the last week (recovery week) of cycle 4 (C4RW).

Results—The DRL group reported increased fatigue at C1TW ($p=0.003$) and C4TW ($p<0.001$) compared to baseline while there was no significant change from baseline in the BWL group. A secondary analysis showed that the increases in fatigue levels in the DRL group were not mediated through associated with changes in sleep or in circadian rhythms as measured with wrist actigraphy.

Conclusions—The results of this study suggest that morning bright light treatment may prevent overall fatigue from worsening during chemotherapy. Although our hypothesis that overall fatigue would improve with bright light treatment was not supported, the lack of deterioration in total fatigue scores suggests that bright morning light may be a useful intervention during chemotherapy for breast cancer.

Keywords

fatigue; breast cancer; chemotherapy; light treatment

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Fatigue is one of the most frequent and most disturbing complaints of cancer patients.[1] Studies have shown that over 75% of patients undergoing radiation or chemotherapy report feeling tired or weak.[2] Fatigue interferes with daily activities, reduces quality of life,[1] and often is the reason for discontinuing treatment.[2] The fatigue of cancer is different from general fatigue. Cancer related fatigue (CRF) has been defined as a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.[3] CRF is characterized by feeling tired even after rest, a reduced capacity to carry out normal daily activities, slow physical recovery from tasks, diminished concentration, and is more severe and distressing than typical fatigue.[4, 5]

Factors contributing to fatigue include post-operative pain, emotional distress (depression, anxiety), anemia, sleep disturbance, nutritional deficits, decreased physical fitness and activity levels, endocrine dysfunction, inflammatory cytokines and/or disrupted circadian rhythms.[6, 7, 8, 9] There is some evidence that the amount of fatigue might be affected by chemotherapy.[10] In our previous work however, we found that patients are already fatigued even before they began chemotherapy, and that fatigue worsened during treatment.[8] Other clinical studies have indicated that a large proportion of breast cancer patients continue to experience fatigue for months after therapy is completed.[11], [12]

On the other hand, fatigue is also a common complaint in patients with other disorders, such as depression, jet lag, shift work disorder, circadian rhythm disturbances (e.g., delayed or advanced sleep phase) and sleep disorders. These disorders are commonly treated with bright light therapy.[13, 14] In addition to improving depression, sleep and shifting circadian rhythms,[15, 16, 17, 13, 18, 19] light is known to have an alerting effect. Phipps-Nelson et al. found that increasing bright light exposure as compared to dim light, decreased subjective sleepiness and improved performance.[20] Other investigators found similar results.[21, 22, 23] Reviews and meta-analyses have confirmed the efficacy of light treatment for these disorders.[24] Although fatigue among breast cancer patients has been found to be related to disrupted circadian rhythms;[25, 26] and it is known that bright light improves circadian rhythms, the effect of light treatment on fatigue has not been investigated.

Liu et al. examined the relationship between ambient light exposure and fatigue in women with breast cancer prior to and during chemotherapy.[27, 28] Prior to chemotherapy, women were exposed to 54 minutes of bright light with a mean of 468 lux exposure per day. (As a point of references, social lighting is <200 lux, a bright office <500 lux, outdoors on a cloudy day 1500-5000 lux, and outdoors on a sunny day 10,000 to 50,000 lux or more.) During chemotherapy, particularly during week 1 of cycle 1 and week 1 of cycle 4, the amount of time exposed to bright light was reduced to about 35 minutes with a mean of only 300 lux. In addition, greater fatigue was associated with lower light intensity and less time exposed to bright light.[28] This association between fatigue and light exposure may suggest the existence of a vicious cycle, with side-effects of chemotherapy causing more severe fatigue, more severe fatigue causing less outdoor activity, less time spent outdoors causing lower bright light exposure, and lower light exposure then further exacerbating the fatigue (see Fig 1a). Increased light exposure may break this vicious cycle and mitigate the fatigue (see Fig 1b). As many studies have shown that light treatment is more effective when administered in the morning than in the evening,[29, 30] this randomized controlled study tested the hypothesis that increased morning bright light, compared to dim light exposure, would result in less fatigue during chemotherapy.

Methods

Subjects

Fifty-eight women were referred by medical oncologists in the San Diego community or from the Moores UCSD Cancer Center. All women were newly diagnosed with State I-III breast cancer, as determined by their oncologist using the American Joint Committee on Cancer Staging Manual 6th Edition,[31] and each was scheduled to receive at least 4 cycles of chemotherapy. As shown in Fig 2, of the 58 women screened, 41 (71%) were consented and randomized, and two dropped out after randomization but before the start of light treatment. The mean age of the remaining 39 women (67% of the original sample) was 53.95 yrs (SD=9.1, range=32-70 years).

Exclusion criteria included being pregnant, having metastatic or stage IIIB (including inflammatory) breast cancer, significant pre-existing anemia or confounding underlying medical illnesses or any other physiological or psychological impairments that would have limited participation.

The study was approved by the University of California Committee on the Protection of Human Subjects.

Procedure

Once informed consent was signed, the women were randomized based on a randomization table, to either the bright white light group (BWL; n=23) or the dim red light group (DRL; n=16) with a larger proportion randomized to BWL to provide a larger sample treated with this noninvasive, potentially beneficial treatment. Rather than being told that the DRL was a placebo, participants were told that “It is unclear if certain frequencies of light are better than others and so both white and red lights are being tested.”

Participants met with research staff either at their homes or at the UCSD General Clinical Research Center where questionnaires were administered prior to the start of chemotherapy (baseline, BL), during the chemotherapy treatment week of cycle 1 (C1TW), the last week (recovery week) of cycle 1 (C1RW), chemotherapy treatment week of cycle 4 (C4TW), and the last week (recovery week) of cycle 4 (C4RW). All but two women received 3-week cycles of chemotherapy while the two receiving two-week cycles. Only data from the primary outcome of fatigue are presented.

Actigraphy

Wrist actigraphs were used to estimate sleep/wake activity and circadian rhythm data. Activity was recorded with the Actiwatch-Light® (Mini Mitter/Phillips/Respironics) for three consecutive days (i.e., 72 hours) at each time point: pre-chemotherapy and during the treatment and recovery weeks of cycle 1 and cycle 4. The Actiwatch-Light® uses a piezoelectric linear accelerometer (sensitivity <.01 g-force) with a sampling rate of 32Hz to measure and record wrist movement. Calculating wrist activity over time allowed for an objective measure of duration and disruption of sleep and circadian activity rhythms. The recorded actigraphy data were analyzed using Actiware® sleep and activity monitoring software program (version 5, by Mini Mitter|Respironics/Philips). Women kept a sleep log with bed time and up time for each of the three days at each time point and the sleep log was used to edit the actigraphy data.

Light Treatment

Light Treatment: Light was administered via a Litebook 1.2 (Litebook®, Ltd. Medicine Hat, Canada). The Litebook® is a small (6” ×5” ×1”) and lightweight (8 oz.) box designed to be

placed on a table about 18” from the patient’s head and within 45° of the midline of the visual field. The Litebook® utilizes 60 white light emitting diode (LED) lights with a distribution of energy particularly concentrated in the middle and long wavelengths.[32] For purposes of safety, the Litebook® emits no ultraviolet (UV) light. An identical-appearing device utilizing red LEDs emitting dim red light at less than 50 lux was used for the placebo group.

The appropriate light box was given to each woman. All women were instructed to place the light box on a table or countertop while seated with the distance between the eyes and the device of approximately 18” and to self-administer the light treatment for 30 minutes every morning upon awakening throughout the first 4 cycles of chemotherapy.

The Litebooks® used for this study were modified to include an integrated meter which allowed for compliance monitoring by recording time and duration the light box was on each day. Partial compliance data were available for 30 patients (BWL n=17; DRL n=13), with some data missing for some weeks. The compliance meter failed to record usage for the remainder of the patients.

Fatigue

The Short Form of the Multidimensional Fatigue Symptom Inventory (MFSI-sf) was used to measure fatigue. The MFSI-sf is a 30-item scale with five subscales: General, Physical, Emotional, and Mental Fatigue, and Vigor. Each subscale includes 6 items and each item is rated on a 5-point scale indicating how true the statement was during the last week (0=not at all, 4=extremely). The sum of General, Physical, Emotional, and Mental subscale scores minus the Vigor subscale score generates a total score. Range of possible score for each subscale is 0 to 24, and the range for total score is −24 to 96, with higher score indicating more severe fatigue, except for the Vigor subscale, where larger score indicates less fatigue. The mean of the normal controls in the original validation study was 0.85.[33, 34]

Data Analysis

Descriptive statistics were calculated both for the entire group and separately for each treatment group. T-tests and Fisher’s exact tests were used to assess group differences at baseline for possible confounders (i.e., demographic variables, clinical characteristics, and chemotherapy regimen). Variables that significantly differed between the treatment groups were to be controlled for in the inferential analysis, however there were no significant differences between groups so no confounders were controlled for.

Linear mixed-effects models and restricted maximum likelihood methods were used for comparing the progression of fatigue during chemotherapy for each group.[35] Contrasts were included in the models to compare fatigue levels during chemotherapy regimen (i.e., C1TW, C1RW, C4TW, and C4RW) to pre-treatment baseline values for each treatment group.

Mixed models allow for partial data where the number of measures per person could vary and therefore women with missing data at some time-points could be included in the analysis.[35] Mixed models rely on the “missing at random” assumption. Furthermore, mixed models decrease the chance of bias from analyzing only completing subjects.

Results

Demographics

The women were primarily Caucasian, married with high school or some college education and a yearly family income of less than $100,000 (Table 1). Their cancer history is presented in Table 2 which shows the percent of women in each stage of breast cancer, menopausal status at study entry, surgery status and chemotherapy regimen. All but two women had chemotherapy regimens that lasted three weeks per cycle. There were no significant differences between randomized groups in any of these variables.

Compliance with Treatment

In the BWL group, the 17 patients for whom compliance data were available used their light boxes for a mean of 32 days (mean of 46.7% of the days) for an average of 31.5 (SD=9.89) minutes per day. In the DRL group, the 13 patients for which compliance data were available used their light boxes for a mean of 36 days (mean of 48.7% of the days) for an average of 33.92 (SD=10.93) minutes per day. There were no significant differences in compliance between the two groups.

Fatigue – MFSI-sf Total Score

Fig 3 shows the levels of the total MFSI-sf scores for each group for each time point. There was no statistical difference between groups at baseline prior to the start of chemotherapy. There was a group × time interaction at C4TW ($p=0.022$) suggesting that the change from baseline in the DRL group was significantly different than the change in the BWL group. The DRL group fatigue scores significantly increased 11.7 points from baseline to C1TW ($p=0.003$), and 22.2 points from baseline to C4TW ($p<0.001$). There were no significant changes from baseline to recovery weeks in cycle 1 or cycle 4 in the DRL group. On the other hand, the fatigue scores for the BWL group did not significantly change at any time point compared to baseline.

A secondary mixed-model analysis was conducted to examine whether these changes in fatigue levels were associated with concomitant changes in sleep or circadian activity rhythms. The results indicated that the changes in fatigue were not significantly associated with changes in sleep or in circadian rhythms, and hence the effect of light treatment on fatigue was not mediated through either of these other variables.

Fatigue – MFSI-sf Subscales

Analyses were conducted on the MFSI-sf subscales showing different results for the different subscales. Table 3 shows the means and standard errors for each group for each subscale.

There were no group × time interactions for the general or physical, or mental sub-scales. On the general MFSI-sf subscale, both groups had worse scores compared to baseline during C1TW (BWL $p=0.033$; DRL $p=0.0006$) and during C4TW (BWL $p=0.002$; DRL $p<0.0001$). There was a similar pattern on the physical subscale, with both groups again having worse scores compared to baseline during C1TW (BWL $p=0.035$; DRL $p=0.026$) and C4TW (BWL $p=0.048$; DRL $p=0.0008$). On the mental subscale, the two groups showed a decrement compared to baseline but at different time points, with the BWL group showing a decrement during C4RW ($p=0.0019$) and the DRL showing a decrement during C4TW ($p=0.022$).

However, on the emotional subscale, there was a group effect ($p=0.014$) indicating that the groups differed at baseline, and a group × time effect ($p=0.03$) suggesting that the change in

emotional subscale scores from baseline in the BWL group was significantly different than the change in the DRL group. The BWL showed an improvement compared to baseline during C1RW (p=0.006), C4TW (p=0.053) and C4RW (p=0.058) while there were no significant changes in the DRL group.

There were no significant changes in the BWL group and no group × time interaction on the vigor subscale, however, the DRL group showed decreased vigor compared to baseline during C1TW (p=0.0092) and C4TW (p=0.0135).

Adverse Effects

There were no adverse effects reported in either the BWL or DRL group. Three women, all in the BWL group, dropped out of the study (one during C1TW and two at the end of C1TW) because they found the light uncomfortable.

Discussion

The results of this study suggest that morning bright light treatment may prevent overall fatigue from worsening during chemotherapy. Although our hypothesis that overall fatigue would improve with bright light treatment was not supported, the lack of deterioration in total fatigue scores is very encouraging. Women with breast cancer experience increasing fatigue during chemotherapy. Minimizing an increase in fatigue could have a substantial positive impact on these women.

Analyses of the subscales showed that the group receiving bright white light showed improvement on the emotional subscale while the dim red light group showed no change, and the dim red light group had less vigor while the bright white light group reported no change compared to baseline. Both groups showed deterioration on the general, physical and mental subscales.

The mechanism by which light is related to fatigue is not clear. Analyses examining whether changes in fatigue were related to changes in sleep or in circadian rhythms, as measured by wrist actigraphy, showed no such association so it is likely that changes in fatigue were not mediated through these other factors. However, it is also possible that statistical power was insufficient to demonstrate any relationship. It is also possible that the addition of morning bright light broke the cycle of low light levels contributing to increased fatigue (Fig 1a and 1b). But whether it was the alerting effect of light or some other mechanism that led to the lack of deterioration of fatigue can not be determined from this study.

Although the mechanism is unclear, other investigators have also found light therapy to be alerting and alertness could be construed to be the opposite of fatigue. Daurat et al.[23] found that bright light vs. dim light counteracted the effects of sleep deprivation on alertness and performance. In a study of simulated shift work, increased bright light exposure was associated with an amelioration of sleepiness and increased alertness.[36] Campbell et al., [37] in a consensus report on the alerting and activating effects of bright light, concluded that data from studies of bright light support the notion that bright light is associated with reports of alertness as well as with objective physiological measures.

To date, few behavioral treatments have been tested in cancer. One small study found that progressive muscle relaxation training improved sleep quality (measured with questionnaire) and CRF in women with breast cancer undergoing adjuvant chemotherapy compared to no treatment.[38] The one behavioral treatment most studied however, has been exercise.[39, 40, 41, 42] In one meta-analysis of 44 studies of survivors of various cancers, exercise was effective in reducing CRF, particularly when the exercise was of moderate-intensity and in

older cancer survivors.[40] In another meta-analysis of 18 studies (12 in breast cancer), Velthuis et al.[42] found that during breast cancer treatment, home-based exercise programs showed no significant reductions in fatigue while supervised aerobic programs resulted in a medium and significant reduction compared to no exercise. Adherence ranged from 39% of the patients in the supervised programs and 100% completion of a home-based walking program. Adverse events were reported in 67% of the studies. While the adherence rate was better in the home based exercise program than in our light study, there was no effect on CRF and there were more adverse events reported. In addition, none of the exercise studies controlled for the amount of light exposure, although many took place outdoors and so the amount of contribution of light vs. exercise is yet to be determined. Studies are needed to determine if increased light combined with increased exercise might lead to the most effective treatment of CRF.

There were some limitations to this study. The sample size was small, yet even with the small sample size our data support lack of worsening of fatigue and a protective effect of bright light therapy. While the compliance with treatment did not differ between groups and most women used their light box for the full 30 minutes, use was only for about half of the days. We know of no other study that measured compliance to light treatment, so we can not estimate if this compliance was better or worse than studies in other disorders. Nevertheless, even with partial compliance, BWL helped protect these women from increased fatigue. In this study, light was administered in the morning as for most other conditions, morning light is most effective. Future studies might compare the effect or morning vs. evening light on fatigue. Future studies should also examine the effect of bright light on fatigue in other cancer patients.

In summary, fatigue is a major complaint in women with breast cancer undergoing chemotherapy. There is no standard treatment for fatigue and so women suffer from this debilitating symptom, often discontinuing their chemotherapy treatment. Oncologists may want to council their breast cancer patients to increase their light exposure by either spending more time outdoors in the morning hours or buy using a bright light box. Morning bright light is an easy, non-invasive, non-harmful behavioral treatment that may prevent worsening of fatigue in the women with breast cancer.

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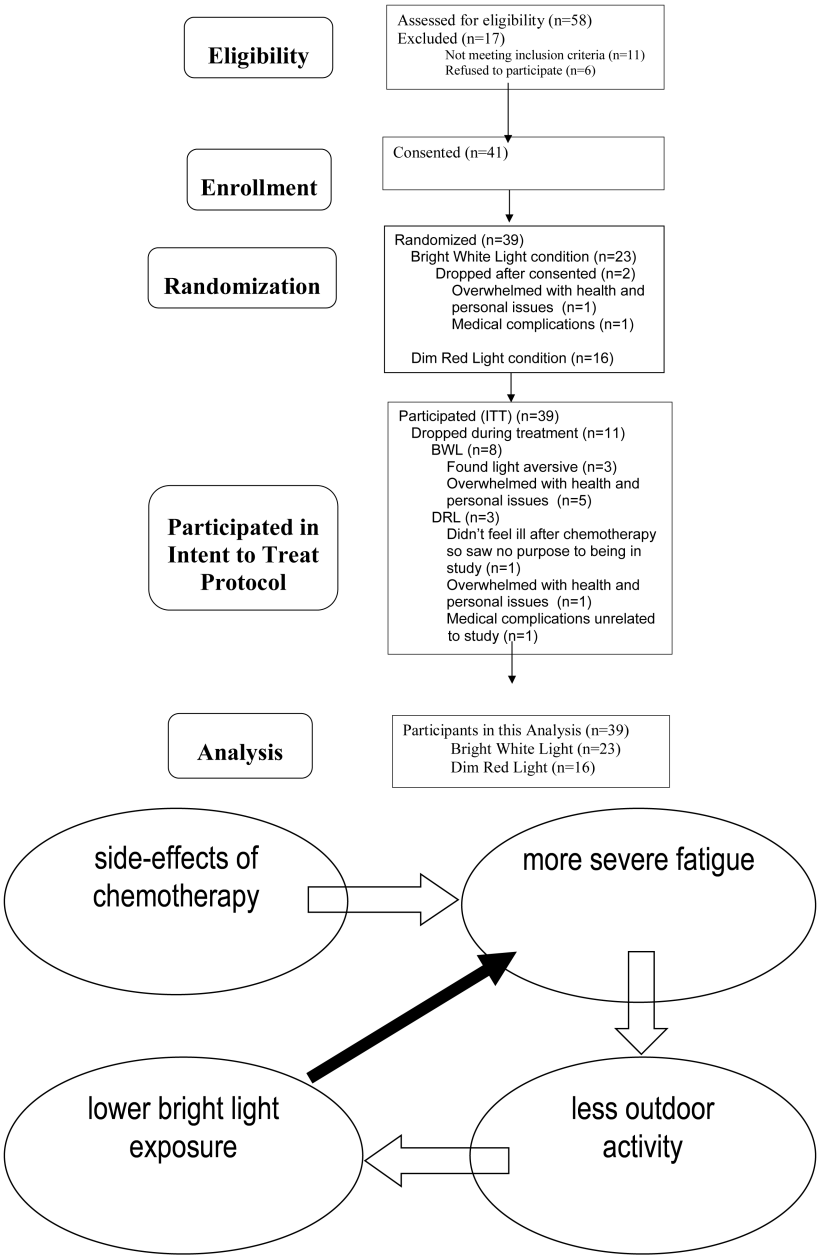

Figure 1a and b.

Model of a negative feedback loop of chemotherapy leading to fatigue, which leads to less time spent outdoors, which leads to less bright light exposure, which could lead to increased fatigue (Fig 1a). We hypothesized that the addition of morning bright light would break this cycle (Fig. 1b).

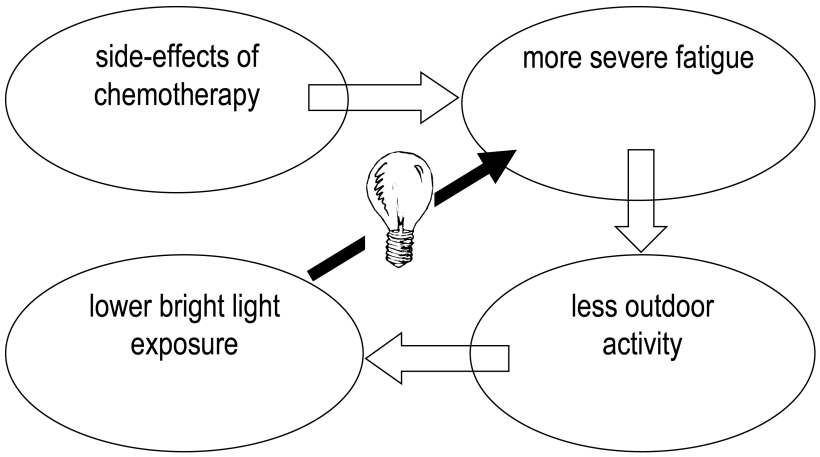

Figure 2.
Consort table of participant recruitment and retention

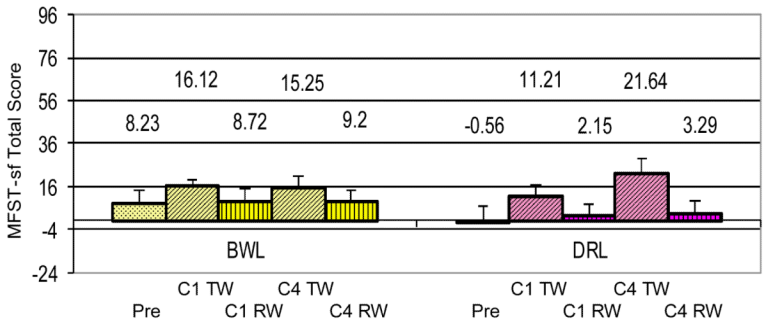

Figure 3.

MFSI-sf total fatigue scores for the BWL treatment group and the DRL treatment group at five time points (BL = pre-chemotherapy baseline; C1TW = cycle 1 chemotherapy treatment week; C1RW = cycle 1 recovery week; C4TW = cycle 4 chemotherapy treatment week; C4RW = cycle 4 recovery week). There was a group × time interaction at C4TW ($p=0.022$) suggesting that the change from baseline in the DRL group was significantly different than the change in the BWL group. The DRL group reported increased fatigue at C1 TW ($p=0.003$) and C4 TW ($p<0.001$) compared to baseline while there was no significant change from baseline in the BWL group.

Table 1

Demographic and medical characteristics at baseline for the two randomized groups

	Bright White Light (n=23)	Dim Red Light (n=16)
Age (mean years [SD])	54.3 (9.3)	53.5 (9.0)
Marital Status (n [%])		
Never Married	1 (4.4)	1 (6.3)
Divorced	7 (30.3)	3 (18.7)
Widowed	2 (8.7)	1 (6.3)
Married	13 (56.6)	11 (68.7)
Ethnicity/Race (n [%])		
Caucasian	15 (65.2)	13 (81.3)
African American Black	4 (17.4)	2 (12.4)
Asian	2 (8.7)	1 (6.3)
Other	2 (8.7)	
Education (n [%])		
Some High School or Less	1 (4.4)	0
Completed High School	1 (4.4)	0
Some College	6 (26.1)	6 (37.5)
College Degree	8 (34.7)	4 (25)
Graduate Degree	7 (30.4)	6 (37.5)
Annual Family Income (n [%])		
≤ $15,000	5 (21.7)	3 (18.8)
≤ $30,000	6 (26.1)	0
≤ $50,000	1 (4.4)	2 (12.5)
≤ $100,000	4 (17.4)	2 (12.5)
> $100,000	5 (21.7)	6 (37.4)
Did not Answer	2 (8.7)	3 (18.8)

Table 2

Cancer History at baseline for the two randomized groups, n (%)

	Bright White Light (n=23)	Dim Red Light (n=16)
Menopausal Status Pre-chemotherapy		
Premenopausal	5 (21.7)	4 (25.0)
Perimenopausal	3 (13.0)	2 (12.5)
Postmenopausal	8 (34.8)	7 (43.8)
Post-Hysterectomy	6 (26.1)	3 (18.8)
Unknown	1 (4.4)	0
Cancer Stage		
Stage I	4 (17.4)	5 (31.3)
Stage II	10 (43.5)	6 (37.5)
Stage III	4 (17.4)	2 (12.5)
Unknown	5 (21.7)	3 (18.7)
Surgery per chemotherapy		
Lumpectomy	7 (30.4)	8 (50.0)
Mastectomy	9 (39.1)	6 (37.5)
Double Mastectomy	4 (17.4)	1 (6.3)
Pre-op Chemotherapy	2 (8.7)	1 (6.3)
Unknown	1 (4.4)	0
Chemotherapy Regimen		
Exactly 4 cycles of AC	3 (13.0)	3 (18.8)
Exactly 4 cycles of AC + Taxotere	5 (21.7)	0
Exactly 4 cycles of AC + Taxol	6 (26.1)	2 (12.5)
6 cycles of TAC	2 (8.7)	4 (25.0)
Other regimen	7 (30.4)	7 (43.7)
Prior Use of Hormone Replacement Therapy		
Yes	2 (8.7)	4 (25.0)
No	13 (56.5)	10 (62.5)
Unknown	8 (34.8)	2 (12.5)

Table 3

Means (standard error) for MFSI-sf subscales

	Baseline	Cycle 1 Treatment Week	Cycle 1 Recovery Week	Cycle 4 Treatment Week	Cycle 4 Recovery Week
General					
Bright white light	6.59 (1.67)	9.59 (2.00)	8.06 (1.52)	10.69 (1.66)	7.6 (1.26)
Dim red light	4.44 (1.12)	9.50 (1.94)	7.46 (1.73)	13.71 (1.94)	6.64 (1.79)
Physical					
BWL	3.09 (0.83)	5.59 (1.54)	4.61(1.34)	5.13 (1.15)	3.33 (1.12)
DRL	2.25 (0.78)	4.93 (1.35)	2.15 (0.82)	6.43 (1.75)	3.21 (1.03)
Mental					
BWL	4.68 (1.23)	5.76 (1.75)	5.28 (1.53)	6.31 (1.11)	7.20 (1.49)
DRL	2.75 (0.65)	3.57 (1.12)	3.00 (1.06)	6.14 (1.61)	4.07 (1.28)
Emotional					
BWL	6.59 (1.48)	5.47 (1.26)	4.06 (1.37)	4.56 (1.19)	3.80 (0.86)
DRL	3.06 (0.75)	3.42 (1.33)	2.47 (0.81)	5.00 (1.50)	2.43 (0.77)
Vigor					
BWL	12.73 (1.16)	10.29 (1.38)	13.28 (1.12)	11.44 (1.54)	12.73 (1.36)
DRL	13.06 (1.15)	10.21 (1.70)	12.92 (1.85)	9.64 (1.95)	13.07 (2.03)

Note: Lower scores are better except for vigor, where higher scores are better.

See text for significance levels