HHS Public Access

Author manuscript

Eur J Cancer. Author manuscript; available in PMC 2019 September 01.

Published in final edited form as:

Eur J Cancer. 2018 September ; 101: 47–54. doi:10.1016/j.ejca.2018.06.009.

Prevalence and Risk Factors for Fatigue Among Breast Cancer Survivors on Aromatase Inhibitors

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Abstract

Purpose: Fatigue is the most common and distressing symptom experienced by cancer survivors. This study sought to determine the prevalence and risk factors for fatigue among breast cancer (BC) survivors receiving aromatase inhibitors (AIs).

Material and Methods: We conducted a cross-sectional survey study among postmenopausal women with stage 0 to III BC receiving adjuvant AI therapy at the outpatient breast oncology clinic of a large university hospital. Participants with a score ≥4 on the "worst fatigue" item of the Brief Fatigue Inventory (BFI) were classified as having moderate or severe fatigue. Multivariate logistic regression analyses were performed to evaluate risk factors.

Results: Among 1,103 participants, 616 (55.8%) had moderate or severe fatigue. In the multivariate logistic regression model, women younger than 55 years were significantly more likely to report moderate-severe fatigue than women older than 65 years (adjusted odds ratio (AOR), 1.58, 95% confidence interval (CI) 1.07–2.35; p=0.023). Compared to women with high school or less education, women with college or more education were significantly more likely to report moderate-severe fatigue (AOR, 1.40, 95% CI 1.02–1.91; p=0.037). Increasing body mass index (BMI) was significantly associated with increased risk of experiencing moderate-severe fatigue (overweight: AOR, 1.37, 95% CI 1.01–1.84; p=0.042; obesity: AOR, 2.08, 95% CI 1.53–2.81; p<0.001). Fatigue was significantly correlated with pain severity (r=0.48, p<0.001) and insomnia (r=0.62, p<0.001).

Conclusion: Moderate-severe fatigue complaints exceed 50% among AI users. Fatigue is highly related to younger age, higher education level, higher BMI, pain severity, and insomnia.

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Conflict of Interest Statement: None declared.

Keywords

Breast cancer; fatigue; aromatase inhibitor

INTRODUCTION

Cancer-related fatigue (CRF) is the most common and distressing symptom experienced by cancer patients. It is widely prevalent among breast cancer (BC) survivors, with a range of 27% to 96% depending on the stage or type of treatment received and method of assessment (1, 2). Fatigue is also the most uncomfortable symptom for BC survivors (3), impairing function and overall quality of life among this population(4, 5).

In the past decade, aromatase inhibitors (AIs) have been the recommended first-line adjuvant endocrine therapy in postmenopausal women with hormone-receptor-positive breast cancer (6); they are associated with improved disease free survival and overall survival (7). With an increase in AI use, BC survivors taking this class of medication are suffering from several troublesome AI-associated symptoms, including arthralgia, hot flashes, and mood disorders (8). Recent data indicates that arthralgia and insomnia related to AIs have a high prevalence and impact on BC survivors (9, 10). Research studies have shown a significant link between these AI-related symptoms and fatigue in BC survivors (11–13). Despite the wide use of AIs and evidence to indicate that their associated side effects may increase the risk of fatigue in BC survivors, to our knowledge, no data has been published to determinate the prevalence and risk factors for fatigue among this population.

Because fatigue may be particularly impacted by arthralgia and insomnia among postmenopausal breast cancer survivors receiving AIs, in the present study, we sought to determine its prevalence and risk factors. This information will help develop targeted interventions for addressing the overall fatigue burden in this population. Thus, the specific aims of this study were to: 1) define the prevalence of fatigue among postmenopausal breast cancer survivors on AIs, 2) identify socio-demographic and clinical risk factors for fatigue, and 3) evaluate the relationship between fatigue and comorbid symptoms (i.e. pain, insomnia) in this population.

MATERIAL AND METHODS

Study Design and Patient Population

Between November 2011 and April 2015, we conducted a cross-sectional survey study among BC survivors receiving care at the Rowan Breast Cancer Center at the Abramson Cancer Center of the University of the Pennsylvania (Philadelphia, PA). Potential participants were postmenopausal women with histologically confirmed stage 0 to III hormone receptor-positive breast cancer who were currently taking a third generation AI; had completed chemotherapy, radiotherapy, or surgery at least one month prior to enrollment; and had the ability to understand and provide informed consent in English. Research assistants obtained permission from the treating oncologist, screened medical records, and approached potential participants for recruitment at their regular follow-up

appointments. All participants provided written informed consent. They were then given a self-administered survey to complete. For those participants who could not complete the survey in time, we gave them a stamped envelope with our return address to mail the survey back to us. The Institutional Review Board of the University of Pennsylvania approved the study.

Outcome Measurement

The primary outcome was participants' self-reported fatigue as measured by the Brief Fatigue Inventory (BFI). This 9-item instrument was designed to assess fatigue severity in cancer and non-cancer populations on a numerical rating scale ranging from 0 to 10. Among these nine items, the "worst fatigue" item has been validated as a single-item dichotomous variable, with a cut point ≥4 indicating moderate-severe fatigue (14). The scale score has excellent internal consistency of 0.96 (14).

Participants completed questionnaires to assess the severity of comorbid symptoms (i.e. pain, insomnia). We assessed pain severity by using the pain severity score, which is the average of the first four items of the Brief Pain Inventory (BPI) (15). A cutoff point of ≥4 has been validated as clinically significant pain. We assessed participants' sleep disturbance using the Insomnia Severity Index (ISI). The ISI is a 7-item instrument with scores ranging from 0 to 28. The validated cutoff scores are 0–6 (no clinically significant sleep difficulties), 7–14 (mild insomnia), and 15+ (presence of clinically significant insomnia) (16). For the purpose of analysis, we used a cutoff point of ≥15 to indicate clinically significant insomnia.

We collected information on covariates including age, race, education, and employment status. Clinical and treatment variables including body mass index (BMI), stage of cancer, time since cancer diagnosis, and previous and current cancer treatments were assessed by self-report and medical chart abstraction.

Statistical Analysis

Data analysis was performed using STATA 12 for Windows (STATA Corporation, College Station, TX). Descriptive statistics were used to report the demographic variables of the study participants. Bivariate analyses using chi-square tests were then conducted to identify the factors associated with fatigue among breast cancer survivors on AIs. We then developed a multivariate logistic regression model to identify independent risk factors associated with the presence of moderate-severe fatigue. Variables with p-values of <0.1 in the bivariate analyses were included in the multivariate analysis. To evaluate the relationship between fatigue and comorbid pain and insomnia, we first used a Venn diagram to describe the overlap of symptoms by proportion. We then calculated Pearson's correlation coefficients among fatigue, pain, and insomnia. Statistical tests were 2-sided, and p values of <0.05 indicated statistical significance.

RESULTS

Participant Characteristics

Of the 1,518 consecutive BC survivors we screened, 1,321 (87.0%) agreed to participate and provided consent. Among the 197 who declined (13.0%), the main reasons were: lack of time to complete the survey (n=62, 31.5%), did not want to participate in research (n=85, 43.1%), and ineligible (n=50, 25.4%). Additionally, 15 (1.1%) subjects withdrew consent from the study and 26 (2.0%) subjects did not return their survey, resulting in the final sample of 1,280. This population reflects an 87.0% response rate among all initially approached subjects. Additionally, 177 subjects discontinued AIs due to various reasons. For this study, we restricted analysis to the 1,103 subjects who were on AIs at the time of enrollment.

Among these 1,103 participants, the mean age was 63.2 years (SD=9.8; range=20.0–92.0 years). Although the majority (82.7%) were non-Hispanic white, a substantial proportion (15.3%) were non-Hispanic black. For the purpose of analysis, we combined the race categories into white and nonwhite. Characteristics of the study population are listed in Table 1.

Prevalence and Severity of Fatigue Among Women on AIs

Among the 1,103 participants, 151 (13.7%) reported no fatigue, 336 (30.5%) had mild fatigue (“worst fatigue” score=1–3), 278 (25.2%) had moderate fatigue (“worst fatigue” score=4–6), and 338 (30.6 %) had severe fatigue (“worst fatigue” score=7–10). For the purpose of further analysis, we merged those four groups into two groups: no-mild fatigue (n=487, 44.2%) and moderate-severe fatigue (n=616, 55.8%).

Socio-demographic and Clinical Factors Associated with Fatigue Among Women on AIs

In bivariate analyses, we found statistically significant differences between BC survivors with moderate-severe fatigue and no-mild fatigue by age, race/ethnicity, education level, BMI, stage of cancer, time since breast cancer diagnosis, chemotherapy, surgery type, and duration of AIs (Table 1). Non-white participants, age younger than 55 years, and those with a college degree or more were more likely to report moderate-severe fatigue. Clinical risk factors for reporting moderate-severe fatigue included being overweight /obese, having stage III disease, being less than two years from diagnosis, having received chemotherapy with Taxane or having had mastectomy surgery, and having been on an AI for less than one year (Table 2).

In the multivariate logistic regression model (see Table 2), women younger than 55 years were significantly more likely to report moderate-severe fatigue than women older than 65 years (AOR, 1.58, 95% CI 1.07–2.35; p=0.023). Compared to women with high school or less education, women with college or more education were significantly more likely to report moderate-severe fatigue (AOR, 1.40, 95% CI 1.02–1.91; p=0.037). Also, higher BMIs were significantly associated with increased risk (up to a two-fold higher odds) of experiencing moderate-severe fatigue (overweight: AOR, 1.37, 95%1.01–1.84; p=0.042; obesity: AOR, 2.08, 95% CI 1.53–2.81; p<0.001). Clinical risk factors such as prior

chemotherapy and mastectomy were no longer significant when we adjusted for other co-variates.

Relationship Between the Comorbid Symptoms and Fatigue Among Women on AIs

Of the 605 subjects who experienced moderate-severe fatigue and also provided data on insomnia and pain, 340 (52.6%) had clinically significant insomnia and/or pain. Among the 289 subjects who experienced clinically significant pain, the majority (83.0%) had moderate to severe fatigue. Similarly, among the 213 subjects who experienced clinically significant insomnia, the majority (93.4%) had moderate to severe fatigue. Furthermore, among the 102 participants who had both clinically significant pain and insomnia, almost all (97.1%) experienced moderate-severe fatigue (Figure 1). The fatigue score was significantly correlated with pain severity ($r=0.48$, $p<0.001$) and insomnia ($r=0.62$, $p<0.001$). There was also a significant correlation between pain severity and insomnia ($r=0.39$, $p<0.001$) (Figure 2).

DISCUSSION

Fatigue is one of the most common and distressing symptoms affecting cancer survivors. In this study, we found that among breast cancer survivors receiving adjuvant AI therapy, more than four in five AIs users (86.3%) reported current fatigue and more than one in two (55.8%) experienced moderate to severe fatigue. Younger age, high education level, and obesity were also associated with increased risk for patient-reported moderate to severe fatigue. As expected, we found that fatigue, pain, and insomnia had substantial overlaps and were significantly correlated. These findings advance the current understanding of fatigue symptoms as experienced by breast cancer survivors on AIs and also highlight the need for targeted and effective treatments to manage fatigue in this population.

Among breast cancer patients, estimates of the prevalence of fatigue from prior data range from 27% to 96% (1, 2). Fatigue generally increases during chemotherapy (80% to 96%) (17) and radiotherapy (60% to 93%) (18). Studies indicate that at least 25% of cancer survivors continue to experience fatigue after completion of active treatment (19). Data about the prevalence of fatigue among BC survivors undergoing hormonal therapies is scarce; however, Schmidt et al. found that aromatase inhibitors were associated with long-term fatigue (20) and Haghighat et al. found that using Tamoxifen predicted fatigue (21). In our study, using a validated instrument, we found a high prevalence of fatigue among BC survivors on AIs, highlighting the magnitude of this clinical challenge for this population.

The etiology and pathogenesis of cancer-related fatigue in BC survivors is complex and multi-causal. Many prior studies have determined that fatigue often co-occurs with other symptom clusters such as sleeping disturbances, mood disorders, and pain (22). Accumulated evidence indicates that inflammation appears to be a key biological mechanism underlying this symptom cluster (23–26). The AI-induced decrease in estrogen levels may impact inflammation (27). Our prior study found that the coexistence of arthralgia, fatigue, and insomnia was associated with increased levels of inflammatory biomarkers among women on AIs (11). In this study, we found that for the majority of participants, clinically significant pain (83%) or insomnia (94%) was associated with

moderate-severe fatigue. But approximately half (47.4%) of the participants who experienced moderate-severe fatigue did not have clinically significant pain or insomnia. Therefore our findings support the idea that pain and insomnia contribute to fatigue. Of note, our data is cross-sectional in nature and will require a prospective data set and experimental design to enhance our understanding of the interplays of fatigue and comorbid symptoms.

Apart from comorbid symptoms, obesity is the only clinical variable that was related to an increased risk for moderate-severe fatigue. Our findings are consistent with prior data suggesting that BMI and fatigue are positively correlated (20). To date, in studies of female sex hormone concentration in postmenopausal women, BMI has been shown to be a meaningful proxy for directly measuring obesity (28). Excess android (abdominal and upper-body) adipose accumulation is associated with increased levels of inflammatory activity driven by macrophages resident in adipose tissue (29–31). Among breast cancer patients, obesity has been independently associated with inflammation in adjacent normal tissue (32). Indeed, a recent study found that anti-inflammatory foods should be promoted for prevention of obesity and related diseases (33). Therefore, inflammation may be a key biological mechanism underlying fatigue among obese postmenopausal BC survivors on AIs.

We also found that younger age (<55 years) and higher education level were significantly associated with fatigue. Some prior data has shown that younger age (34–36) and higher education level (37) are significantly correlated with fatigue. Conversely, others have shown a significant link between older age (37), lower education level (20), and fatigue. There are a number of reasons that may account for greater fatigue among younger postmenopausal BC survivors: First, when treated with AIs, younger survivors have a more absolute drop in their estrogen levels. Biologically, this can result in greater symptoms related to estrogen withdrawal. Second, previous literature has shown that younger survivors are more likely to report psychosocial problems (38) compared with older survivors, which are linked to greater fatigue (39). Third, younger people are often struck by a cancer diagnosis when they are in a state of “perfect health.” Their own interpretation of their energy level is related to their recall prior to the cancer diagnosis and in reference to people around their age. In contrast, older people may have experienced other chronic illnesses or seen their peers dealing with illness or death, and therefore, have likely developed coping strategies to better mitigate the impact of a cancer diagnosis and treatment (40). Lastly, younger BC survivors may experience higher demands from raising a family or from professional challenges such as work and school. To help younger survivors manage CRF likely requires a multi-disciplinary approach targeting both physical and psychological causes of fatigue.

We need to acknowledge several limitations. First, because our study relied on patient self-report, some degree of recall bias exists; however, for subjective symptoms like fatigue, patient-reported outcomes are considered to be the gold standard. Second, our study focused on the prevalence of fatigue among breast cancer survivors taking AIs, so we cannot compare our findings to breast cancer survivors who were not taking AIs. Finally, as the study is cross-sectional in nature, it is challenging to dissect the causal relationship between fatigue and comorbid symptoms.

To our knowledge, this study is the first and largest (n=1,103) cross-sectional survey study to focus on evaluating the prevalence of and risk factors for fatigue among breast cancer survivors taking AIs. We found more than half of BC survivors experienced moderate to severe fatigue, which relates to comorbid symptoms like insomnia and pain. Obesity, younger age, and higher education were associated with increased rates of fatigue. Developing and testing effective interventions for fatigue in this population represents an important unmet need. It is likely that one size does not fit all. Interventions targeting multiple symptoms and obesity are needed to improve fatigue management for this population.

Acknowledgments:

This research is funded in part by grants from the National Cancer Institute / National Institutes of Health (R01 CA158243, P30-CA008748), the Byrne Fund, and the Translational Research and Integrative Medicine Fund at the Memorial Sloan Kettering Cancer Center. Dr. H. Mao is supported by the National Natural Science Foundation of China (81603703). The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

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Highlights for "Prevalence and Risk Factors Among Breast Cancer Survivors on Aromatase Inhibitors"

- Moderate-severe fatigue complaints exceed 50% among AI users.
- Obesity, younger age, and higher education level were significantly associated with fatigue.
- The majority who experienced either pain or insomnia reported moderate to severe fatigue.

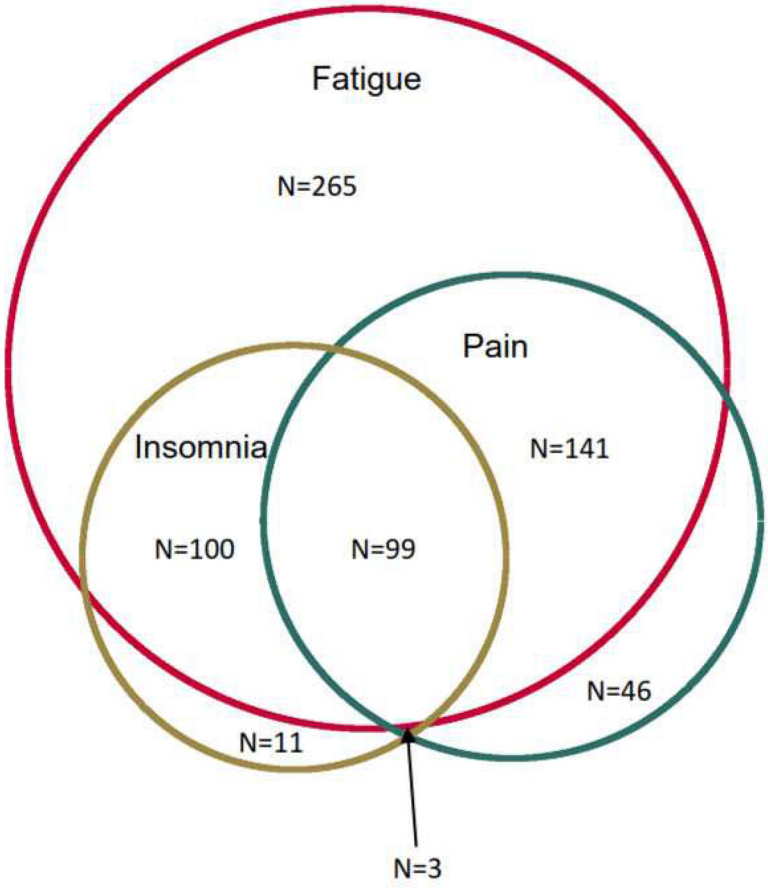

Figure 1.
Venn Diagram of Fatigue, Pain Severity, and Insomnia

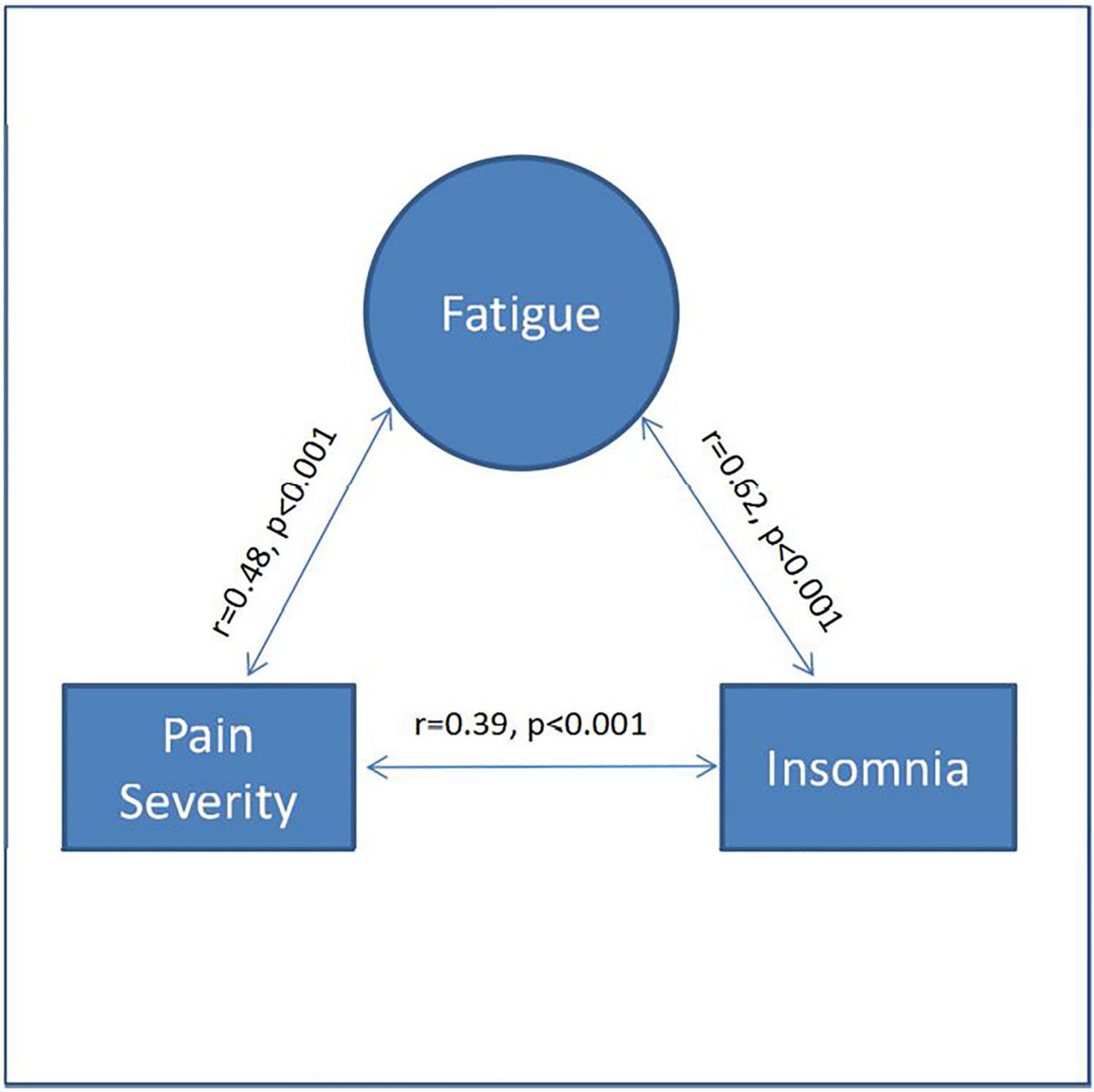

Figure 2.
Correlation of Fatigue, Pain Severity, and Insomnia

Table 1.

Demographic and Clinical Characteristic of Participants

Variables	N (%)	No-Mild Fatigue	Mod-Severe Fatigue	P-value
Total	1,103	487 (44.15)	616 (55.85)	
Age, years				**0.021**
<55	212 (19.22)	76 (35.85)	136 (64.15)	
55–65	515 (46.69)	233 (45.24)	282 (54.76)	
>65	376 (34.09)	178 (47.34)	198 (52.66)	
Race/Ethnicity				**0.033**
White	912 (82.68)	416 (45.61)	496 (54.39)	
Non-white	191 (17.32)	71 (37.17)	120 (62.83)	
Employment (n=1 missing data)				0.120
Full-time	423 (38.38)	189 (44.68)	234 (55.32)	
Part-time	151 (13.70)	77 (50.99)	74 (49.01)	
Not employed	528 (47.91)	220 (41.67)	308 (58.33)	
Education (n=1 missing data)				**0.059**
High school or less	225 (20.42)	112 (49.78)	113 (50.22)	
College or more	877 (79.58)	375 (42.76)	502 (57.24)	
Body Mass Index (Kg/m2)				**<0.001**
<25	426 (38.62)	222 (52.11)	204 (47.89)	
25–30	325 (29.47)	143 (44.00)	182 (56.00)	
>30	352 (31.91)	122 (34.66)	230 (65.34)	
Cancer Stage (n=12 missing data)				**0.085**
0 & I	568 (52.06)	260 (45.77)	308 (54.23)	
II	382 (35.01)	170 (44.50)	212 (55.50)	
III	141 (12.92)	50 (35.46)	91 (64.54)	
Years since breast cancer diagnosis				**0.045**
>5	190 (17.23)	91 (47.89)	99 (52.11)	
2–5	423 (38.35)	200 (47.28)	223 (52.72)	
<2	490 (44.42)	196 (40.00)	294 (60.00)	
Chemotherapy				**0.045**
None	534 (48.41)	250 (46.82)	284 (53.18)	
Chemo without Taxane	105 (9.52)	52 (49.52)	53 (50.48)	
Chemo with Taxane	464 (42.07)	185 (39.87)	279 (60.13)	
Radiotherapy				0.474
None	311 (28.20)	132 (42.44)	179 (57.56)	
Yes	792 (71.80)	355 (44.82)	437 (55.18)	
Surgery (n=1 missing data)				**0.011**
Lumpectomy	638 (57.89)	302 (47.34)	336 (52.66)	
Mastectomy	464 (42.11)	184 (39.66)	280 (60.34)	
Aromatase Inhibitors, current (n=6 missing data)				0.721
Anastrozole (Arimidex)	884 (80.58)	384 (43.44)	500 (56.56)	

Variables	N (%)	No-Mild Fatigue	Mod-Severe Fatigue	P-value
Exemestane (Aromasin)	61 (5.56)	28 (45.90)	33 (54.10)	
Letrozole (Femara)	152 (13.86)	71 (46.71)	81 (53.29)	
Duration of AI use, years				**0.059**
>3	272 (24.66)	136 (50.00)	136 (50.00)	
1–3	565 (51.22)	244 (43.19)	321 (56.81)	
<1	266 (24.12)	107 (40.23)	159 (59.77)	

Table 2.

Multivariate Logistic Regression Model

Variables	Bivariable Analysis OR (95% CI)	P-value	Multivariate Analysis AOR (95% CI)	P-value
Age, years				
>65	1		1	
55–65	1.09 (0.83–1.42)	0.535	1.03 (0.77–1.37)	0.839
<55	1.61 (1.14–2.27)	**0.007**	1.58 (1.07–2.35)	**0.023**
Race/Ethnicity				
White	1		1	
Non-white	1.42 (1.03–1.95)	**0.033**	1.32 (0.93–1.86)	0.116
Education				
High school or less	1		1	
College or more	1.33 (0.99–1.78)	**0.059**	1.40 (1.02–1.91)	**0.037**
Body Mass Index (Kg/m2)				
<25	1		1	
25–30	1.39 (1.04–1.85)	**0.028**	1.37 (1.01–1.84)	**0.042**
>30	2.05 (1.53–2.74)	**<0.001**	2.08 (1.53–2.81)	**<0.001**
Stage				
0 & I	1		1	
II	1.05 (0.81–1.37)	0.699	0.95 (0.70–1.28)	0.720
III	1.54 (1.05–2.25)	**0.028**	1.21 (0.77–1.89)	0.411
Years since breast cancer diagnosis				
>5	1		1	
2–5	1.02 (0.73–1.44)	0.888	0.96 (0.66–1.39)	0.818
<2	1.38 (0.98–1.93)	**0.062**	1.27 (0.83–1.94)	0.275
Chemotherapy				
None	1		1	
Chemo without				
Taxane	0.90 (0.59–1.36)	0.612	0.88 (0.54–1.41)	0.582
Chemo with Taxane	1.33 (1.03–1.71)	**0.027**	1.18 (0.86–1.63)	0.300
Surgery				
Lumpectomy	1		1	
Mastectomy	1.37 (1.07–1.74)	**0.011**	1.25 (0.96–1.63)	0.093
Duration of AI use, years				
>3	1		1	
1–3	1.32 (0.98–1.76)	**0.064**	1.10 (0.78–1.54)	0.588
<1	1.49 (1.06–2.09)	**0.023**	1.06 (0.68–1.65)	0.786