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Tamoxifen Therapy in Postmenopausal Iraqi Women with Breast Cancer: Evaluating Side Effects and Hot Flash Incidence

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1. Abstract

1.1. Background: Breast cancer stands as the most prevalent cancer among women worldwide and remains a significant cause of female cancer-related mortality. Tamoxifen plays a crucial role in reducing the risk of recurrence and metastasis in hormone-positive breast cancer cases. Hot flashes are the most common side effects of tamoxifen therapy that can affect patients adherence to treatment and patient's quality of life. The aim of this study to evaluate the incidence of hot flashes and other side effects associated with tamoxifen therapy in breast cancer women.

1.2. Patients and Methods: Across sectional study of 100 post-menopausal women with hormone receptor positive aged 45 years and above were included in this study. This study was conducted to detect hot flashes and other side effects in women with breast cancer who are receiving tamoxifen treatment. Estradiol level was measured of each patient may serve as predictive indicators for hot flash incidence and severity.

1.3. Results: The majority of participants (82%) experienced hot flashes, with 45% experiencing joint pain and 15 % had mood changes. The obtained results reflects that R Square value of 0.612 suggests that around 61.2% of the variation in hot flash scores can be explained by changes in the mean level of estradiol. The associated P-value of 0.05 indicates that this relationship is statistically significant.

1.4. Conclusion: Examining tamoxifen side effects, particularly hot flashes, revealed varying severity levels, with age influencing the outcomes. The regression analysis highlighted a potential correlation between estradiol levels and hot flash severity, challenging some prior research findings.

2. Introduction

Breast cancer stands as the most prevalent cancer among women worldwide and remains a significant cause of female cancer-related mortality [21]. In Iraq, it constitutes 22.3% of malignant tumors, with a notable rise in incidence among younger age groups, comprising 5% of cases in those under 30 and peaking at 75% in individuals over 40, predominantly within the 40-50 age brackets [2, 11].

Breast cancer treatment, particularly for hormone-positive cases, relies significantly on endocrine therapies, with Tamoxifen as a cornerstone medication. As a selective estrogen receptor modulator (SERM), Tamoxifen plays a crucial role in reducing the risk of recurrence and metastasis in hormone-positive (ER+) breast cancer cases [3, 20]. Its therapeutic significance is substantial, necessitating prolonged administration—often 5 to 10 years—for optimal risk reduction [6].

The diagnosis of breast cancer triggers a multifaceted crisis affecting diverse facets of a patient's life, encompassing physical, psychological, spiritual, and social dimensions [15]. To address estrogen's role in carcinogenesis, endocrine therapies, such as Tamoxifen, have been pivotal in managing hormone-positive (ER+) breast cancer, significantly reducing recurrence and metastasis risk. However, Tamoxifen usage comes with a spectrum of side

effects, including hot flashes, vaginal dryness, irregular menstrual periods, and musculoskeletal symptoms, impacting patient compliance and quality of life [23]. The struggle with these side effects often leads to non-compliance, diminishing the treatment's efficacy [14].

This study specifically aims to investigate the incidence of hot flashes and other side effects experienced by Iraqi women undergoing Tamoxifen therapy for breast cancer. Understanding these side effects is pivotal to enhancing patient care and treatment adherence in this demographic, ultimately improving the overall quality of life during breast cancer treatment.

2. Patients and Methods

Our study is conducted from the period of November 2022 until the end of April 2023. With the participation of 100 patients who were attended oncology center for follow-up after they have already been diagnosed with breast cancer. The Scientific and Ethical Committee of College of Pharmacy / University of Kerbala gave its approval to the study's protocol, and after describing the nature and goal of the study, each patient signed an informed consent form.

The inclusion criteria of the study are being breast cancer female with hormone receptor positive estrogen receptor and/or progesterone receptor (ER and/or PR), aged 45years and above being on tamoxifen 20mg/ day for at least 4 months as standard adjuvant therapy. All Patients had previously been completed all primary surgery, radiation, and adjuvant chemotherapy prior to tamoxifen treatment. Exclusion criteria included patients had started taking tamoxifen concurrently with either adjuvant chemotherapy or adjuvant radiotherapy (or both) or if they were undergoing other adjuvant endocrine therapies.

This study is a cross-sectional study conducted to detect hot flashes and other side effects in women with breast cancer who are receiving endocrine treatment. The questionnaires were administered in a single interview by interviewing the patients one-on-one and taking verbal consent from the patient, paying attention to the principle of voluntary participation. Other data such as cancer type and stage, chemotherapy, radiotherapy information is obtained from the patient file.

3. Estimation of Serum Estradiol (E2)

Intravenous blood collected from each of the patients, which included affected women with breast cancer. After allowing the samples to coagulate at room temperature, the serum was extracted from them by centrifuging them for 10 minutes at a speed of 5000 revolutions per minute. After that, the serum was kept in a freezer at a temperature of -20 C until it was required.

The chemiluminescence immunoassay (CLIA) was used to assess E2 level in human serum, with all procedures carried out in accordance with the manufacturer's guidelines (DIRUI / China) [27].

4. Healthy Control Group

Healthy controls were female that present about the same characteristics of the patients group, except were free from breast cancer. This group consists of 100 healthy women provides a critical comparison group for biochemical analysis (Estradiol level).

5. Hot flash surveys

The hot flash severity survey was adapted from Sloan et al., [26]. In-person surveys were conducted during clinic visits where blood samples were obtained. Data gathered from surveys included the average number of mild, moderate, severe, and very severe hot flashes experienced per day in the prior 7-day period using grade definitions as previously described [26]. The average number of mild, moderate, severe, and very severe hot flashes experienced each day were multiplied by a severity factor (mild = 1, moderate = 2, severe = 3, and very severe = 4) and values were cumulated to determine the hot flash severity score (HFSS). Participants indicated whether they had experienced additional side effects including loss of appetite, sleepiness, nausea, dizziness, fatigue, dry mouth, constipation, trouble sleeping, nervousness, or mood changes in the prior 7-day period.

5.1. Statistical analysis

We conducted all statistical analyses using the software tools GraphPad Prism. Baseline observational characteristics were summarized using percentages, means, and standard deviations. To compare Hot Flash Severity Scores (HFSS) between groups, we employed non-parametric Mann–Whitney U-tests at a significance level of 0.05. Given the prevalence of zero (0) HFSS scores, we further applied a zero-inflated negative binomial regression model to assess the association of estradiol concentrations and HFSS after adjusting for relevant factors.

6. Results

6.1. Demographic and Clinical Characteristics of the Study Population

The participants (n=100) characteristics are summarized as following: Our study population exhibit an average age of (49.17 ±4.77 years), (mean ± SD). with a mean BMI of (31.19 ±4.935 kg/m²), (mean ± SD), indicating relatively consistent age and BMI averages but considerable variability in the duration of tamoxifen use and disease duration, averaging 10 months (±11.86) and 8.333 years (±8.917), respectively. This broad variability implies substantial heterogeneity within the study group. Additionally, various demographic and clinical profiles are noted, such as a significant portion having a family history of breast cancer (47%), contraceptive usage (42%), 1-5 children (73%), tumors predominantly on the left (51%) or right side (46%), breastfeeding (54%), mastectomy (53%), chemotherapy (94%), and radiotherapy (80%). Immunohistochemical testing indicates diverse ER/PR statuses and 30% HER2-positive cases. Most individuals are at Stage II (67%)

of breast cancer, commonly experiencing hot flashes (82%) and showing a 5% recurrence rate, offering crucial context for understanding the population and its implications in breast cancer research and treatment.

6.2. Significant Disparities in Estradiol and Calcium Levels: Healthy Individuals vs. Breast Cancer Patients

Figure 1 (A and B) compare biomarker profiles between healthy individuals and breast cancer patients. Estradiol demonstrates a substantial reduction in patients (15.36 ± 10.66) compared to healthy individuals (19.62 ± 7.521) with a significant P value of 0.0158, suggesting its potential as a diagnostic marker for breast cancer. Conversely, calcium levels in patients (9.355 ± 1.190) are significantly elevated compared to healthy individuals (8.700 ± 0.6643) with a P value of 0.0005, indicating an unexpected association potentially linked to the disease or its treatment.

6.3. Incidence of Hot Flash in and Other Side Effects in Breast Cancer Women on Tamoxifen

Self-reported hot flash surveys were administered to patients during oncology center visits. Table 1 outlines the prevalence and severity of side effects experienced by breast cancer patients undergoing treatment, presenting the distribution of hot flash degrees and other associated symptoms in percentages. Regarding hot flashes, the data illustrates a spectrum of severity: 18% reported no significant signs, while nearly equal percentages experienced mild (18%) and moderate (19%) episodes. A substantial portion experienced severe (24%) and very severe (21%) hot flashes, indicating the varying degrees of this symptom among patients. Additionally, other undesirable side effects were reported but with lower frequencies as described in Table 1.
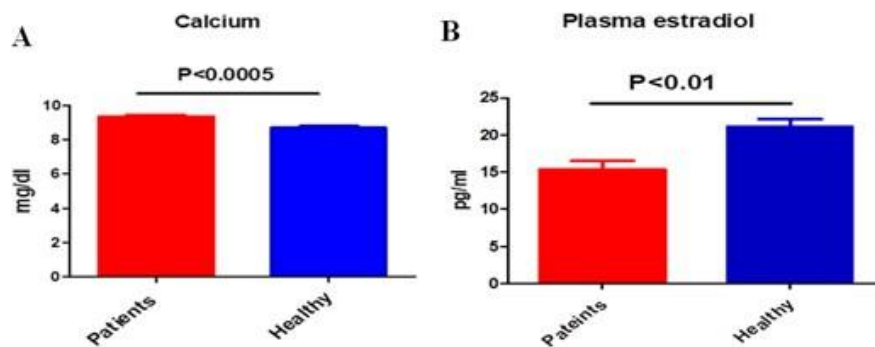

Figure 1: Estradiol and Calcium Discrepancies in Healthy vs. Breast Cancer Patients: A) Estradiol levels are notably reduced in patients, indicating a potential diagnostic relevance. B) calcium levels are significantly increased in the patients comparing to the healthy individuals. The data are shown in mean±SD.

Table 1: Hot flash severity spectrum among breast cancer patients

Side effects		Percentage %
Hot flash degree%	No sign	18
	Mild	18
	Moderate	19
	Severe	24
	Very severe	21
Other symptoms%	Joint pain	45
	Mood changes	15
	Fatigue	3
	Headache. Anorexia.	2
	Ocular toxicity	2
	Nausea	2
	Vitiligo	1
	Elevated liver enzyme	1
Results are presented as percentages of total		

6.4. Significant Variances in Hot Flash Severity across Age Groups of Breast Cancer Patients Exposed to Tamoxifen

The analysis of our data as described in the (Figure 2) reveals that substantial variations in hot flash severity across age brackets: comparisons between age groups such as 45-49 vs 50-54, 45-49 vs 55-59, and 45-49 vs >60 reveal statistically significant differences ($P < 0.05$), with notably higher mean differences in the latter age categories compared to the youngest group. Notably, the 55-59 vs >60 comparison shows no significant difference ($P > 0.05$) in hot flash severity. Overall, substantial variation exists among most age groups, particularly between the youngest (45-49) and older age categories (55-59 and >60), while non-significant difference is observed between patients aged 55-59 and those older than 60 concerning hot flash severity.

6.5. Relationship between Hot Flash Severity and Estradiol Levels in Breast Cancer Patients: A Regression Analysis

Analyzing the regression between hot flash scores and estradiol levels is elucidates whether estradiol levels may serve as predictive indicators for hot flash severity, potentially influencing treatment strategies and personalized care approaches. Not surprisingly, our data (Table 2) reflects that R Square value of 0.612 suggests that around 61.2% of the variation in hot flash scores can be explained by changes in the mean level of estradiol. The associated P-value of 0.05 indicates that this relationship is statistically significant. The Confidence Interval (CI) for the regression coefficient ranges from -1.45014 to 241.88005. Furthermore, the table breaks down the number of patients within each hot flash severity category (from 'No signs' to 'Very severe') and provides the mean level of estradiol for each severity group. For instance, the 'Mild' hot flash category (with 18 patients) displays a mean estradiol level of 143.945, suggesting a potential correlation between higher estradiol levels and milder hot flashes.
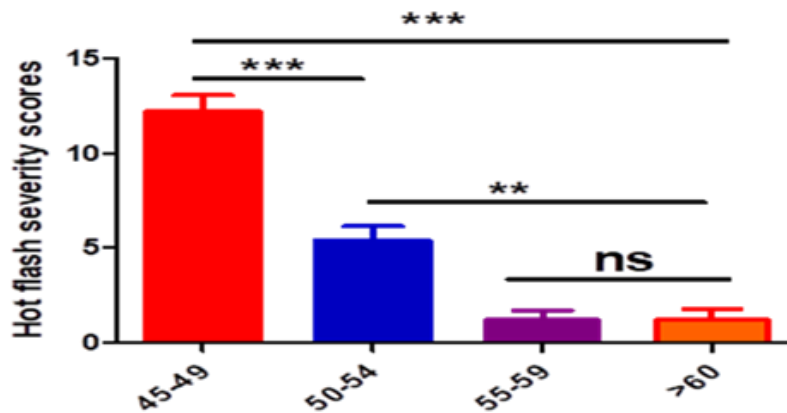

Figure 2: illustrates the comparative severity of hot flashes across distinct age groups within a cohort of breast cancer patients. Each age category, ranging from 45-49, 50-54, 55-59, to over 60. Data presented as mean±sd, *P<0.05, **P<0.01, ***P<0.001.

Table 2: Correlation of hot flashes and estradiol level in cancer patient on tamoxifen

Parameter			Patients, N=100	R Square	P-value	Lower 95%	Upper 95%
Hot flashes scores	**Score**	**# of patients**	**Mean of Estradiol**				
No signs	0	18	52.204				
Mild	1	18	143.945	0.612	**0.05**	-1.45014	241.88005
moderate	2	19	20.794				
severe	3	24	23.228				
very severe	4	21	21.472				
Total		100					

7. Discussion

Tamoxifen has remained an important therapeutic for reducing the risk of breast cancer recurrence and death when taken for 5–10 years among patients with hormone receptor-positive breast cancer [6, 10].

Tamoxifen use can be limited by undesirable side effects such as

hot flashes with approximately 80 % of patients reporting these adverse symptoms as consistent with other reports [4, 8, 9, 18, 22]. It is commonly believed that efficient metabolism of tamoxifen to its end metabolite will result in more hot flashes and other side effects; therefore, it is assumed as a biomarker for efficacy. However, the data surrounding such a hypothesis remains controversial.

The characteristics of the participants in a cohort of 100-breast cancer patients provide insights into the heterogeneity within the study group. The average age and BMI reflect a relatively consistent demographic profile, but the wide variations in tamoxifen use duration and disease duration underscore the complexity of breast cancer cases within our cohort.

Several demographic and clinical profiles, such as family history, contraceptive use, and tumor characteristics are described in this study. These factors may play crucial roles in influencing treatment outcomes and response to tamoxifen [13]. The majority of individuals are at Stage II of breast cancer, reinforcing the need for personalized treatment plans and long-term surveillance. Additionally, the prevalence of hot flashes and a 5% recurrence rate highlights the multifaceted nature of breast cancer and its impact on the quality of life for patients.

The significant reduction in estradiol levels in patients (15.36 ± 10.66) compared to healthy individuals (19.62 ± 7.521) is interesting. This finding suggests the promising using of estradiol as a diagnostic marker for breast cancer on TAM treatment. The observed disparity prompts further exploration into the mechanisms behind this reduction and its implications for disease detection and monitoring. Surprisingly, our analysis also reveals a significant elevation in calcium levels among breast cancer patients (9.355 ± 1.190) compared to healthy individuals (8.700 ± 0.6643). This unexpected association raises intriguing questions about the relationship between calcium metabolism and breast cancer.

In our investigation of breast cancer patients undergoing Tamoxifen treatment, the prevalence and severity of hot flashes, a significant concern in oncology, were assessed alongside other associated side effects. Survey data, captured the self-reported experiences of patients during oncology center visits. Hot flash symptoms were commonly observed by the majority of the patients (82%) consistent with other reports [9, 18, 19]. Additionally, joint pain was notably prevalent at 45%, followed by mood changes (15%), and elevated liver enzymes (1%), while other symptoms, such as fatigue, headaches, anorexia, ocular toxicity, nausea, and vitiligo, were reported but with lower frequencies as in other studies [1, 24].

Regarding the impact of age on hot flash severity among breast cancer patients exposed to tamoxifen, a study published in the Journal of Women's Health found that statistically significant differences (P < 0.05) were observed in comparisons between age groups, such as 45-49 vs 50-54, 45-49 vs 55-59, and 45-49 vs >60, with notably higher mean differences in the latter age categories compared to the youngest group. Interestingly, the 55-59 vs >60 comparison showed no significant difference (P > 0.05) in hot flash severity. Overall, substantial variation exists among most age groups, particularly between the youngest (45-49) and older age categories (55-59 and >60), while no significant difference is observed between patients aged 55-59 and those older than 60 concerning hot flash severity [7,16,17].

The examination of the relationship between hot flash severity and estradiol levels in breast cancer patients through regression analysis is a critical step in understanding the potential correlation between these factors and its implications for patient care. Our analysis reveals a substantial R Square value of 0.612, indicating that approximately 61.2% of the variation in hot flash scores can be explained by changes in the mean level of estradiol. The associated P-value of 0.05 attests to the statistical significance of this relationship. The Confidence Interval (CI) for the regression coefficient, ranging from -1.45014 to 241.88005, reinforces the reliability of our findings. Moreover, the table breaks down the number of patients within each hot flash severity category, from 'No signs' to 'Very severe,' and provides the mean level of estradiol for each severity group. For instance, the 'Mild' hot flash category, comprising 18 patients, displays a mean estradiol level of 143.945. This observation suggests a potential correlation between higher estradiol levels and milder hot flashes. The observed findings conflict with previous scientists finding that suggest the frequency and severity of hot flashes with plasma or serum estrogen levels are poor, or noteworthy [5,12,16,17]. The possible explanation for our findings is hot flashes are a common symptom in women, especially during menopause. The pathophysiology of hot flashes is not entirely understood, but several theories have been proposed. One theory suggests that a decline in estrogen levels causes a change in the thermoregulatory set point in the anterior portion of the hypothalamus. The thermoregulatory nucleus initiates perspiration and vasodilation to keep core body temperature within a well-regulated range called the thermoregulatory zone. Researchers have demonstrated a narrowing of the zone between sweating and shivering in symptomatic women, so that small elevations within the zone cause a change in hormones or neurotransmitters, producing a hot flash [12,25].

In conclusion, the unexpected findings of reduced estradiol levels and elevated calcium levels suggest potential diagnostic markers and highlight an intriguing link between calcium metabolism and breast cancer.

Examining tamoxifen side effects, particularly hot flashes, revealed varying severity levels, with age influencing the outcomes. The regression analysis showcased a potential correlation between estradiol levels and hot flash severity, challenging some prior research findings. Despite conflicting results, our study adds nuance to the understanding of hot flashes in breast cancer patients undergoing tamoxifen treatment.

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