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Original article

Prevalence of symptomatic dry eye in breast cancer patients undergoing systemic adjuvant treatment: A cross-sectional study

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ABSTRACT

Objectives: To investigate the prevalence of symptomatic dry eye (SDE) on women undergoing systemic adjuvant therapy for breast cancer and its association with treatment settings.
Methods: Woman undergoing breast cancer systemic adjuvant therapy were included in exposure group. An age-matched non-treatment control group was recruited. This cross-sectional questionnaire-based study utilised validated Ocular Surface Disease Index (OSDI) and NCCN-FACT-Breast Cancer Symptom Index (NFBSI-16) questionnaires to determine the presence of SDE and investigate other breast cancer treatment complications. Additionally, demographic data and medical histories were collected.
Results: Of 423 eligible participants, 200 in each of the control group and the exposure group were included in the final analysis. The prevalence of SDE was 59.0% in breast cancer patients with adjuvant treatment, statistically significantly higher than 25.5% in the control group ($P < 0.01$). Additionally, exposure group experienced higher prevalence of moderate and severe SDE, which were 20.0% and 19.5% respectively compared with 9.0% and 4.0% in the control group ($P = 0.002$, $P < 0.001$). There was a significantly high prevalence of SDE among patients who had received over four cycles of systemic therapy (71.0%, $P < 0.001$) and the application of targeted therapy (71.2%, $P = 0.014$). The severity of SDE positively correlated with the cycles of treatment administered.
Conclusion: SDE was significantly predominant in women with breast cancer undergoing systemic adjuvant treatment. Our findings suggest dry eye assessments among patients receiving more than four cycles of chemotherapy or targeted therapy, thus early revealing possible dry eye conditions to both patients and clinicians for further specialized examination and treatment.
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1. Introduction

According to the International Agency for Research on Cancer (IARC) report, the worldwide burden for breast cancer based on the GLOBOCAN 2018 report [1] was 2.1 million, accounting for 1 in 4 cancer cases among women. In China, an estimated 367,900 breast cancer cases were reported in 2018, accounting for 19.2% of total cancer cases in females [2,3]. Advancements in breast cancer screening, detection and treatment in the last few decades have led to an increased chance of cure for early-stage breast cancer patients, while advanced (metastatic) disease patients now have prolonged survival and varying degrees of controlled symptoms [4–6]. Apart from surgical intervention which remains the primary treatment for local and regional breast cancer, systemic adjuvant treatment is critical for almost all stages of patients. For early stage breast cancer, clinical features like estrogen receptor (ER), progesterone receptor (PR), and Her-2/neu (HER2) status, lymph node involvement and tumor size are key factors in determining systemic treatment settings. For stage IV disease, the receptor status and the locations of metastatic sites are crucial indications. Adjuvant chemotherapy is generally recommended for patients with disease at certain risk of recurrence. For patients with high-risk disease, additional cycles of paclitaxel should be included after standard course of cyclophosphamide plus doxorubicin [7]. Targeted therapy has been proven to be effective in HER2-positive patients. One year of adjuvant trastuzumab after standard chemotherapy for patients with HER2-positive early breast cancer has shown to improve long-term disease-free survival [8]. Adjuvant

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pertuzumab added to chemotherapy with trastuzumab is recommended for HER2-positive patients with high risk of recurrence [9]. Neoadjuvant therapy is considered the prior strategy in women with stage 2 or 3, HER2-overexpressing or triple-negative breast cancer [10], and dose-dense regimens are commonly preferred as preoperative treatment [11]. Continued evolution of breast cancer diagnosis and management has changed standardized treatment regimens into personalised medication targeting the unique genetic compositions of patients and tumors. However, dose-escalation treatments and multi-approach therapy may raise concerns on accumulated toxicity and increased risk of complications including emesis, myelosuppression, and cardiotoxicity. Additionally, ocular side effects of breast cancer systemic adjuvant therapy should be considered. Negative alterations to the tear film layer due to anti-cancer chemotherapy and targeted therapy have been reported to cause symptomatic and clinical presentation of ocular surface disease[1,2] [[,13].

The prevalence of dry eye disease, which is estimated to range from 5 to 50% globally, can lead to ocular discomfort and reduce visual acuity, affecting work productivity and lowering the quality of vision and quality of and life [14]. It is considered as one of the most prevalent ocular disease in China and globally [15,16]. The typical spectrum of symptoms in symptomatic dry eye (SDE) includes burning or stinging, tearing, foreign-body sensation, photophobia, and blurred vision [17]. Dry Eye Workshop Committee (DEWS) defined dry eye as a multifactorial disease of the ocular surface, characterised by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles. Dry eye disease is considered to be a dysfunction of the integrated functional unit comprising of the lacrimal glands, ocular surface, eyelids, and sensory and motor nerves [17,18], leading to increased osmolarity and ocular surface inflammation [17,19]. The loss of homeostasis of the tear film due to hormonal and neuronal regulatory mechanisms have also been reported [20]. Due to the variability of findings on clinical evaluation of dry eye disease, some clinicians base their assessment of dry eye disease on the results of validated questionnaires as there is no single definitive test or consensus of criteria to diagnose dry eye disease [17].

There are insufficient studies on the mechanism of anti-cancer drug's effect on ocular tissues, but it is known that cytotoxic drugs can interfere with normal cellular processes, expressing their efficacy by activating DNA cross-linking, strand breakage, interfering with DNA/RNA synthesis, competing with normal metabolites for the catalytic or regulatory site of enzymes, or substitution of metabolites that are generally incorporated into the DNA and RNA [21]. Rapidly proliferating cells such as epithelial cells on the cornea are therefore susceptible to the effects of chemotherapy [12,22]. Breast cancer patients under medication have been documented to have ocular side effects [23], however, research regarding the relation between breast cancer treatment cycle and potential dose dependent severity of SDE has not been explored before. The term 'dry eye' can also be a misnomer since people with SDE can exhibit watery eyes, typically more tears are produced to counteract the ocular surface discomfort in these patients [24]. The presence of dry eye due to chemotherapeutic agents in general is not preventable. While, to our knowledge, there is no definitive guidelines for the management of dry eye in cancer care, most of dry eye cases respond well to preservative free artificial tear drops [17,25]. Omega-3 fatty acid supplementation, topical cyclosporine, serum tears, topical azithromycin, oral doxycycline, cholinergics, lacrimal plug, lid massage and expression, warm compresses and amniotic membrane biologic corneal bandage lens have shown to improve the signs and symptoms of dry eye [19,26,27]. It is important to diagnose and treat it early, before it develops into severe ocular condition, then discontinuing or reducing the anti-cancer medication.

We designed a cross sectional study to assess the prevalence of SDE in breast cancer women undergoing anti-cancer chemotherapy and targeted therapy compared to controls. To the best of our knowledge, this is the first study to use validated questionnaires to assess the prevalence and severity of SDE in this patient group, as well as investigate the potential association between SDE and other breast cancer treatment associated symptoms.

2. Materials and methods

2.1. Study design and sampling methods

We conducted a cross-sectional, patient-reported questionnaire study and recruited patients who were clinically diagnosed with breast cancer undergoing two or more cycles of adjuvant, neo-adjuvant, chemotherapy or targeted therapy as exposures. The control group was comprised of women who visited breast clinic with no history of chemotherapy or targeted therapy over the same time period (Fig. 1). Participants were recruited from October to December 2019 from the Breast Surgery Department of The First Affiliated Hospital of China Medical University, Shenyang, China.

The primary outcome was to assess the prevalence of SDE on women undergoing breast cancer systemic adjuvant therapy. Since the prevalence and incidence SDE on women undergoing breast cancer systemic adjuvant therapy has not been reported before, a pre-study analysis was conducted to determine the sample size, which was based on the prevalence of SDE using the validated Ocular surface disease index (OSDI) questionnaire score (i.e. >12 score indicates presence of dry eye) of 30 women undergoing breast cancer systemic adjuvant therapy and 30 control participants (1:1 enrollment ratio). The primary endpoint was selected as presence of SDE (OSDI score >12) or no SDE (OSDI score <12). The pre-study analysis revealed a target sample size of 86 patients per group was needed to obtain a power of 0.9, with a 2-sided significance level of $\alpha = 0.05$ and type II error of $\beta = 0.1$. This number was adjusted to 200 in each group to improve the validity of this study.

Participants were excluded from either group if they had a history of endocrine therapy, Sjogren's syndrome, recent eye infection (previous month), previous ocular surgery or trauma, including chalazion section, blepharal dysraphism, history of blepharal and periorbital skin disease or allergies in the past 1 month, acute inflammation, rheumatic immune systemic diseases, herpes zoster infection, or were breastfeeding since these factors can influence dry eye symptoms. Demographic information (date of birth, marital status, education levels and living districts), and medical histories, including all previous cancer diagnosis, cancer medication, previous dry eye symptoms and treatment, recent eye infection and other systemic diseases, were collected from both groups. To minimize selection bias, participants for the exposure group were randomly chosen from the hospital's central registry.

The study protocol was approved by The First Affiliated Hospital of China Medical University, Shenyang, China ethics committee. All data collected from participants was anonymised and coded with serial numbers. Informed consent was obtained from all participants after careful explanation of the nature and possible consequences of the study.

2.2. Questionnaires

In this study, two validated questionnaires were used; the OSDI and the National Comprehensive Cancer Network – Functional Assessment of Cancer Therapy – Breast Cancer Symptom Index

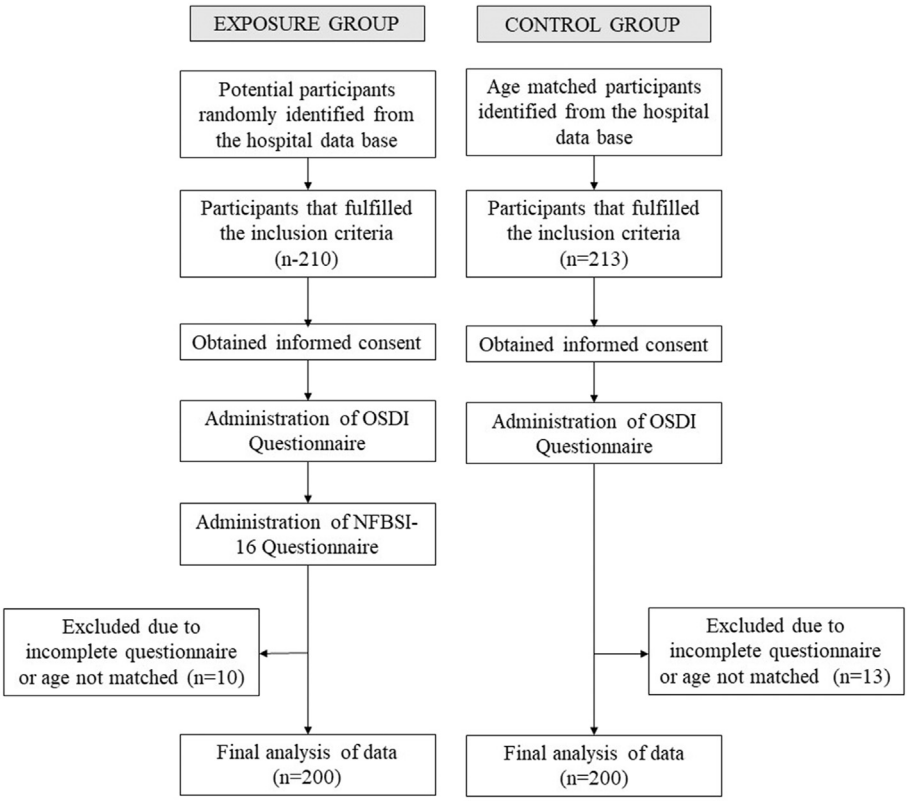

Fig. 1. Study profile.

(NFBSI-16).

The OSDI questionnaire (Fig. 2) was administered to all participants in this study. The OSDI is a validated questionnaire developed by the Outcomes Research Group (Allergan Inc, Irvine, CA) and is one of the most widely used survey instrument following its introduction in 1997 [28] for assessing ocular surface disease severity in dry eye for ophthalmology clinic and research. It consists of 12 items that assess symptoms, functional limitations, and environmental factors related to dry eye. Each item has the same five-category Likert-type response options, and each of the three subscales has its own question type. It provides quantifiable assessment of dry eye symptom frequency and the impact of these symptoms on vision-related function. SDE was defined as any symptom on the OSDI, reported as: "all of the time", "most of the time", "half of the time", "some of the time", or "none of the time". Those with SDE were classified into normal (scores 0–12), mild SDE (scores 13–22), moderate SDE (scores 23–32), and severe SDE (scores 33–100) according to their OSDI total scores based on validated OSDI guidelines [28].

The National Comprehensive Cancer Network – Functional Assessment of Cancer Therapy – Breast Cancer Symptom Index (NFBSI-16) questionnaire was administered to the exposure group only, in order to assess the presence of cancer therapy-related symptoms. NFBSI-16 is a 16-item patient-reported outcome (PRO) questionnaire that assesses disease related symptoms, treatment side effects, and general function and well-being [29]. PRO measures can provide important insight into the patient experience and treatment evaluation in oncology, it has rapidly gained popularity over the last several years [30]. The instrument has three subscales: Disease-Related Symptom (DRS), Treatment Side-Effect (TSE), and General Function and Well-Being (F/WB). All these items have a seven-day recall period and a five-point verbal descriptive response scale. NFBSI-16 allows clinicians to evaluate the priority breast cancer-specific symptoms and concerns of integrative therapies in clinical practice and research [29].

Patients in the exposure group had completed more than two cycles of either neoadjuvant or adjuvant chemotherapy or targeted therapy. The OSDI and NFBSI-16 questionnaires were administered to the exposure group on their day of next hospitalized treatment before receiving intravenous anti-cancer drugs. While the control group participants were only given the OSDI questionnaire after their outpatient visit. Both questionnaires interrogated the participant's symptoms for the previous week.

2.3. Statistical analysis

All statistical analyses were conducted using SPSS 25.0 (Chicago, IL, USA). Questionnaires that had missing values (items not answered) were not included in the statistical analysis. The quantitative variables are expressed through the average, the standard deviation, and its confidence interval; and the qualitative variables through their frequency. Frequency analysis and Wilcoxon signed ranks test was performed to determine the descriptive socio-demographic characteristics of patients. Pearson's chi-square and univariate logistic regression were used to investigate relations between categorical variables. Risk ratio (RR) was used to measures of effect size for categorical outcomes. A RR of 1.00 indicates that the risk is comparable in the two groups. A value greater than 1.00 indicates increased risk; a value lower than 1.00 indicates decreased risk (95% confidence interval). In all analysis, $P < 0.05$ was considered indicative of statistically significant differences. Fig. 3 (scatter plot) was generated in GraphPad Prism 7 (La Jolla, CA, USA).

Ocular Surface Disease Index© (OSDI©)[2]

Ask your patients the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

Have you experienced any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

Have problems with your eyes limited you in performing any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

Have your eyes felt uncomfortable in any of the following situations *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

Add subtotals A, B, and C to obtain D (D = sum of scores for all questions answered) (D)

Total number of questions answered (do not include questions answered N/A) (E)

Please turn over the questionnaire to calculate the patient's final OSDI© score.

Evaluating the OSDI© Score[1]

The OSDI© is assessed on a scale of 0 to 100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. The OSDI© is a valid and reliable instrument for measuring dry eye disease (normal, mild to moderate, and severe) and effect on vision-related function.

Assessing Your Patient's Dry Eye Disease[1, 2]

Use your answers D and E from side 1 to compare the sum of scores for all questions answered (D) and the number of questions answered (E) with the chart below.* Find where your patient's score would fall. Match the corresponding shade of red to the key below to determine whether your patient's score indicates normal, mild, moderate, or severe dry eye disease.

Number of Questions Answered (E from Side 1)	Sum of Scores for All Questions Answered (D from Side 1)									
	5	10	15	20	25	30	35	40	45	48
12	10.4	20.8	31.3	41.7	52.1	62.5	72.9	83.3	93.8	100.0
11	11.4	22.7	34.1	45.5	56.8	68.2	79.5	90.9	100.0	
10	12.5	25.0	37.5	50.0	62.5	75.0	87.5	100.0		
9	13.9	27.8	41.7	55.6	69.4	83.3	97.2			
8	15.6	31.3	46.9	62.5	78.1	93.8	100.0			
7	17.9	35.7	53.6	71.4	89.3	100.0				
6	20.8	41.7	62.5	83.3	100.0					
5	25.0	50.0	75.0	100.0						
4	31.3	62.5	93.8							
3	41.7	83.3								
2	62.5									
1										

*Values to determine dry eye severity calculated using the OSDI© formula. OSDI© = (sum of scores) x 25 / (# of questions answered)

Normal Mild Moderate Severe

Patient's Name: _____ Date: _____

How long has the patient experienced dry eye disease? _____

Eye Care Professional's Comments: _____

1. Data on file, Allergan, Inc.
2. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol.* 2000;118:615-621

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Fig. 2. The Ocular Surface Disease Index (OSDI) questions and disease severity scale.

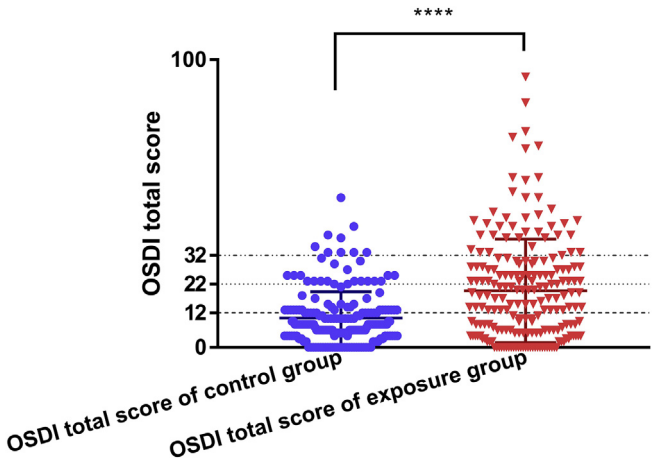

Fig. 3. Ocular surface disease index scores severity analysis. Scatter plot representation of the total ocular surface disease index scores in control and exposure group. ****Unpaired *t*-test with Welch's correction, P < 0.0001.

3. Results

The final analysis included 200 patients in the exposure group and 200 patients in the control group. In total, 423 participants were eligible for the study, however 23 were excluded from the final analysis, 10 in the exposure group and 13 in the control group as they could not complete the questionnaires entirely. There is demographic consistency between exposure and control group, as shown in Table 1. The mean age was 49.7 years (SD = 10.7) for exposure group and 49.5 years (SD = 11.1) for control group. No significant difference in terms of marital status, education level or living condition was found between two groups (Wilcoxon signed ranks test, $P > 0.05$).

The presence and severity of symptomatic dry eye was categorized according to the OSDI scale mentioned above (Fig. 2). The prevalence of SDE among the breast cancer patients receiving chemotherapy or targeted therapy was 59.0% (n = 118) which was statistically significantly higher than the control group (25.5%; n = 51, $P < 0.01$) (Table 2). The proportion of exposure group participants with mild SDE (total OSDI score: 13 to 22) was higher than that in the control group, but there was no statistically significant difference ($P = 0.056$). More importantly, the exposure group had significantly higher numbers of both moderate (total OSDI score: 23 to 32) and severe (total OSDI score: >32) SDE than the control group, with 20.0% and 19.5% compared to 9.0% and 4.0% respectively ($P = 0.002$ and $P < 0.001$). Fig. 3 depicts the distribution of OSDI total score for both groups, from which we can find an outstanding colony in exposure group with severe and moderate SDE while majority of the participants in the control group spread over non-symptomatic dry eye or mild dry eye.

Breast cancer patients' clinical pathological condition and their association with the prevalence of SDE is described in Table 3. Ki-67 status ($X^2 = 5.052$, $P = 0.025$) and molecular typing ($X^2 = 9.581$, $P = 0.022$) were significantly different among patients with or without SDE. Both Ki-67 and molecular typing are key indicators to determine medication settings, which suggests the association between SDE with anti-cancer treatment.

Univariate analysis of SDE and treatment settings showed that cycles of treatment received, and targeted therapy applied were significantly related to SDE (Pearson Chi-square test and logistic

Table 1
Demographic information of study participants.

Demographic features	Control group (n = 200)	Exposure group (n = 200)	All patients	*P* value
Age (years)				0.302
Mean (SD)	49.5 (11.1)	49.7 (10.7)	49.6 (10.9)	
IQR	41.0–56.0	41.3–56.0	41.0–56.0	
Marital Status				0.481
Single, n (%)	7 (3.5)	5 (2.5)	12 (3.0)	
Married, n (%)	193 (96.5)	193 (96.5)	387 (96.5)	
Education Level				0.053
Primary	26 (13.0)	35 (17.5)	61 (15.3)	
Secondary	79 (39.5)	76 (38.0)	155 (38.8)	
Tertiary	95 (47.5)	89 (44.5)	184 (46.0)	
Rural or Urban				0.386
Rural, n (%)	80 (40.0)	74 (37.0)	154 (38.5)	
Urban, n (%)	120 (60.0)	126 (63.0)	246 (61.5)	

Table 2
Prevalence of SDE in control and exposure groups, defined by the Ocular Surface Disease Index (OSDI) Score.

OSDI score	Classification	Control group (n = 200)	Exposure group (n = 200)	*P* value
≤12	Normal	149 (74.5%)	82 (41%)	**<0.001**
>12	SDE (total)	51 (25.5%)	118 (59%)	**<0.001**
12.1–22.0	Mild dry eye	25 (12.5%)	39 (19.5%)	0.056
22.1–32.0	Moderate dry eye	18 (9%)	40 (20%)	**0.002**
>32	Severe dry eye	8 (4%)	39 (19.5%)	**<0.001**

Bold values indicate significant difference ($P < 0.05$).

Table 3
Association analysis between SDE and breast cancer patients' clinical pathological factors.

Factors	Number (%)	SDE		χ^2	*P* value
		with (%)	without (%)		
Age (years)				3.97	0.265
<40	45 (22.5)	22 (48.9)	23 (51.1)		
41–50	59 (29.5)	38 (64.4)	21 (35.6)		
51–60	59 (29.5)	33 (55.9)	26 (44.1)		
>60	37 (18.5)	25 (67.6)	12 (32.4)		
Menstrual status				4.41	0.110
premenopausal	80 (40)	41 (51.2)	39 (48.8)		
artificial menopause	58 (29)	35 (60.3)	23 (39.7)		
menopausal	58 (29)	40 (69.0)	18 (31.0)		
Tumor sizes (cm)				1.34	0.512
≤2.0	48 (24)	29 (60.4)	19 (39.6)		
2.1–5.0	114 (57)	69 (60.5)	45 (39.5)		
>5.0	36 (18)	18 (50.0)	18 (50.0)		
Lymph node metastasis				1.67	0.196
negative	126 (63)	70 (55.6)	56 (44.4)		
positive	74 (37)	48 (64.9)	26 (35.1)		
ER/PR				2.34	0.126
positive	124 (62)	68 (54.8)	56 (45.2)		
negative	76 (38)	50 (65.8)	26 (34.2)		
Her2				3.75	0.053
positive	82 (41)	57 (69.5)	25 (30.5)		
negative	106 (53)	59 (55.7)	47 (44.3)		
Ki-67				5.05	**0.025**
≤30	86 (43)	43 (50.0)	43 (50.0)		
>30	114 (57)	75 (65.8)	39 (34.2)		
Molecular typing				9.58	**0.022**
luminal A	46 (23)	20 (43.5)	26 (56.5)		
luminal B	70 (35)	46 (65.7)	24 (34.3)		
HER-2	42 (21)	31 (73.8)	11 (26.2)		
basal-like	30 (15)	19 (63.3)	11 (36.7)		
TNM staging				1.29	0.524
I	36 (18)	20 (55.6)	16 (44.4)		
II	104 (52)	59 (56.7)	45 (43.3)		
III	60 (30)	39 (65.0)	21 (35.0)		

Bold values indicate significant difference ($P < 0.05$).
SDE = symptomatic dry eye.

regression analysis, $P < 0.05$, Table 4), indicating that those who received more than four cycles of systemic adjuvant treatment had higher rate of SDE (n = 66, 71.0%) and that was more prevalent in patients under targeted therapy (n = 47, 71.2%). The severity of SDE was related to cycles of treatment administered in both chemotherapy only group ($P < 0.01$) and chemotherapy plus targeted therapy group ($P = 0.01$). Among all exposure group participants, 74.5% (n = 149) underwent different surgery settings which had no impact on their dry eye (Table 4). There were 25.5% (n = 51) participants undergoing neoadjuvant systemic treatment and 74.5% (n = 149) administrating adjuvant therapy with similar prevalence of SDE. No negative effect on ocular surface were found in 14.0% (n = 28) patients that received dose-dense chemotherapy.

The risk ratio of SDE was calculated for the presence of breast cancer therapy related symptoms from NFBSI-16 and medical history. Patients with SDE had higher risk of breathlessness (RR 1.44; 95% CI, 1.14–1.81; $P < 0.001$), bone pain (RR 1.50; 95% CI, 1.15–1.95; $P = 0.001$), sleep disorder (RR 1.58; 95% CI, 1.05–1.28; $P = 0.002$), mouth sores (RR 1.80; 95% CI, 1.30–2.48; $P < 0.001$) and hair loss (RR 1.15; 95% CI, 1.01–1.31; $P = 0.017$). Our findings indicate the occurrence of SDE had no risk to systemic therapy related symptoms such as: agranulocytosis, achiness, fatigue, or nausea (Table 5).

4. Discussion

Our cross-sectional study suggests that the prevalence of SDE in women with breast cancer undergoing systemic adjuvant treatment is significantly higher at 59.0% compared with 25.5% in women with same demographic features. The meta-analysis conducted by Song et al. [16] reports that prevalence of symptomatic dry eye is 31.40% among the Chinese population, which was higher than our control group (25.5%). This difference is expected since we excluded participants with preexisting factors that might exacerbate dry eye symptoms, including: Sjogren's syndrome, recent eye infection (previous month), previous ocular surgery or trauma, including chalazion section, blepharal dysraphism, history of blepharal and periorbital skin disease or allergies in the past 1 month,

Table 4
Univariate analysis of SDE and treatment settings.

Factors	Numbers (%)	SDE		χ^2	*P* value	OR (95% CI)
		with (%)	without (%)			
Surgery settings				4.26	0.235	
mastectomy	123 (61.5)	72 (58.5)	51 (41.5)		*0.929*	*0.90 (0.08-9.71)*
conserving	18 (9.0)	14 (77.8)	4 (22.2)		*0.574*	*2.17 (0.15-32.19)*
mastectomy plus reconstruction	8 (4.0)	3 (37.5)	5 (62.5)		*0.367*	*0.33 (0.03-3.61)*
no surgery	51 (25.5)	29 (56.9)	22 (43.1)			*Reference*
Therapy settings				0.13	0.719	
adjuvant systemic treatment	149 (74.5)	89 (59.7)	60 (40.3)		*0.719*	*1.06 (0.77-1.46)*
neoadjuvant systemic treatment	51 (25.5)	29 (56.9)	22 (43.1)			*Reference*
Regime intensity				0.40	0.529	
conventional dose	172 (86.0)	103 (59.9)	69 (40.1)		*0.877*	*0.91 (0.28-3.0)*
dose-dense	28 (14.0)	15 (53.6)	13 (46.4)			*Reference*
Cycles				10.30	**0.001**	
≤4	107 (53.5)	52 (48.6)	55 (51.4)		***0.002***	*2.95 (1.49-5.83)*
>4	93 (46.5)	66 (71.0)	27 (29.0)			*Reference*
Targeted therapy				6.10	**0.014**	
no	134 (67)	71 (53.0)	63 (47.0)		*0.125*	*1.83 (0.85-3.98)*
yes	66 (33)	47 (71.2)	19 (28.8)			*Reference*

Italic values are logistic regression analysis.
Bold values indicate significant difference ($P < 0.05$).
SDE = symptomatic dry eye.

Table 5
Risk ratio of SDE and treatment-related symptoms in exposure group.

Chemotherapy-related symptom	Participants with SDE and symptom, n (% = n/118)	Participants without SDE but with symptom, n (% = n/82)	Risk ratio (95% CI)	P value	Z score
Agranulocytosis	17 (14.4)	9 (11)	1.31 (0.62, 2.80)	0.241	0.70
General achiness	95 (80.5)	67 (81.7)	0.96 (0.84, 1.10)	0.278	0.59
Breathless	89 (75.4)	43 (52.4)	1.44 (1.14, 1.81)	**<0.001**	3.09
Fatigue	111 (94.1)	73 (89.0)	1.06 (0.97, 1.15)	0.111	1.22
Bone pain	82 (69.5)	38 (46.3)	1.50 (1.15, 1.95)	**0.001**	3.03
Sleep disorder	115 (97.5)	69 (84.1)	1.16 (1.05, 1.28)	**0.002**	2.93
Nausea	90 (76.3)	62 (75.6)	1.01 (0.86, 1.18)	0.457	0.11
Mouth sores	75 (63.6)	29 (35.4)	1.80 (1.30, 2.48)	**<0.001**	3.56
Hair loss	106 (89.8)	64 (78.1)	1.15 (1.01, 1.31)	**0.017**	2.12

Bold values indicate significant difference ($P < 0.05$).
SDE = symptomatic dry eye.

acute inflammation, rheumatic immune systemic diseases, herpes zoster infection, or were breastfeeding. In addition, the balance between estrogens and androgens is important for healthy ocular surface and preventing dry eye disease [31,32]. The selective-estrogen-receptor-modulator (SERM) tamoxifen, long served as a standard endocrine-therapy for hormone-receptor-positive breast cancer, increases the risk of posterior subcapsular cataract [33] and leads to optic nerve head swelling [34]. Aromatase inhibitors have also been reported as a potential factors to dry eye [35], therefore we excluded any participants who had a history of endocrine therapy.

A case report by Kalra et al. [36], reported epiphora due to combination regimen of cyclophosphamide and anthracyclines. And cyclophosphamide was the suspected agent for causing reflex epiphora. Taxanes act against breast cancer by stabilizing microtubules, thereby inhibiting mitosis [37] and have been reported to increase the occurrence of ocular side effects, epiphora and canalicular stenosis [38]. Breast cancer patients undergoing docetaxel treatment have been found to have it in their tears, which is suggested to be the mechanism of canalicular inflammation and tear drainage obstruction [39]. As a member drug of the first standard chemotherapeutic regime "CMF" in early stage breast cancer [40], 5- fluorouracil was reported to cause epiphora in 25% or more of patients, suggesting an inherent vulnerability of the ocular drainage apparatus [41]. These studies might imply that the presence of SDE increasing by the accumulation of cytotoxic chemotherapy was due to the obstruction of the lacrimal apparatus, leading to the toxic agents remaining in contact longer with the cornea.

Concerns on ocular toxicities of targeted agents used in solid tumor has been raised. SDE occurred in 71.2% of patients who received anti-HER2 targeted therapy (with or without cytotoxic chemotherapy), significantly higher than that among chemotherapy only participants (Spearman's chi-square, $X^2 = 6.073$, $P = 0.014$) in our study. Clinical trials involving trastuzumab combined with docetaxel (DH) found increased lacrimation. In addition, 2.4% of the participants reported severe conjunctivitis with DH regime [42–44]. Trastuzumab's label issued by U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) mentions its ocular side effects including common dry eye and lacrimation increased, and unknown papilloedema and retinal haemorrhage. Pertuzumab and bevacizumab are both informed with common lacrimation disorder in FDA/EMA issued labels. No ocular adverse events were reported in lapatinib. These reports suggest that targeted agents are associated with increased lacrimation and tear film disorder, but the physiopathologic mechanism responsible and dose dependent relationship has not been investigated. Our findings indicate that there is a significant correlation between the severity of SDE and the cycle duration of anti-HER2 targeted therapy (Spearman's rho, Correlation Coefficient 0.315, $P = 0.01$).

One of the limitations of this study is that dry eye disease is

diagnosed largely according to the presence of subjective symptoms of discomfort of the ocular surface such as a “gritty” or “dryness” sensation, and is prevalent among post-menopausal women [45], which coincidently are the people that can also develop breast cancer [46]. Our age matched control group concurs with previous findings that the prevalence SDE is high among post-menopausal women [47] and suggest that its exacerbated by systemic chemotherapy treatment cycles. In addition, recollective data gathered by OSDI and NFBSI-16 questionnaires have the likelihood of recall bias. It is also possible that our findings could be the result of patients learning to cope with their symptoms and therefore under-reporting dry eye symptoms. Additionally, dry eye symptoms are thought to wax and wane, and it is reasonable to speculate that patients are less able to accurately estimate their condition and therefore in future studies we aim to include clinical dry eye tests and verify our current findings.

In summary, the prevalence of SDE appears to be higher in women undergoing breast cancer systemic adjuvant treatment than age-matched females, which also showed cycle dependency. Currently, ocular toxicities such as SDE induced by anti-cancer agents are not preventable in breast cancer patients; therefore, clinicians must be aware of the potential of such complications. Timely intervention and addressing the dry eye symptoms can lead to better quality of life in patients undergoing systemic adjuvant treatment and thereby ensuring patients’ compliance of anti-cancer treatment. Therefore, we recommend administration of OSDI questionnaire and clinical evaluation of dry eye disease, possibly an ophthalmological examination among patients receiving more than four cycles of chemotherapy or targeted therapy. A larger scale prospective study is warranted to evaluate the association between dry eye disease and breast cancer treatment regimens.

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Declaration of competing interest

No conflicts of interest.

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