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EPIDEMIOLOGY

Quantitative changes in skin composition parameters due to chemotherapy in breast cancer patients: a cohort study

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Abstract The objective of this study is to evaluate objective changes in water content, sebum content, transepidermal water loss (TEWL), and melanin due to breast cancer chemotherapy, and their association with subjective symptoms. Prospective cohort study of 61 patients 18 years of age or older with a postoperative diagnosis of stage I–III breast cancer, who received adjuvant chemotherapy between February and September 2012 at an outpatient breast cancer clinic in Korea. Objective skin parameters, measured using a noninvasive bioengineering device, and patient-reported dryness and dullness were assessed before chemotherapy, after two cycles of chemotherapy, and 1, 3, and 6 months after completion of chemotherapy. Water content (−6.5 %), sebum (−75.5 %), and TEWL (−22.4 %) significantly decreased during chemotherapy compared to pre-chemotherapy levels (all p values <0.001). These parameters were lowest at 1 month after completion of chemotherapy and recovered thereafter but did not return to baseline levels after 6 months of follow-up. Melanin increased during chemotherapy with respect to pre-chemotherapy levels (8.4 %; $p < 0.001$) but decreased from the first month after completion of chemotherapy through the end of follow-up (−17.1 %; $p < 0.001$). The patterns of skin changes were similar in patients with or without hormone therapy. Most of patients reported dryness (57.9 %) and dullness (49.1 %) after chemotherapy, and patient-reported dryness was significantly associated with decreased sebum content. Chemotherapy-induced substantial changes in objective skin composition parameters. These changes persisted after 6 months from completion of chemotherapy and were associated with patient-reported symptoms. Additional research is needed to translate these findings into interventions for improving the dermatologic quality of life of breast cancer patients undergoing chemotherapy.

Dong-Youn Lee and Juhee Cho contributed equally to this study.

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Keywords Breast cancer · Chemotherapy-induced skin change · Dryness · Dullness · Objective measured · Patient-reported outcome (PRO)

Abbreviations

T1	Before chemotherapy
T2	After two cycles of chemotherapy
T3	1 Month after completion of chemotherapy
T4	3 Months after completion of chemotherapy
T5	6 Months after completion of chemotherapy
CG	Received chemotherapy only group
CHG	Received chemotherapy and hormone therapy
AC	Doxorubicin, cyclophosphamide
FAC	Cyclophosphamide, doxorubicin, fluorouracil
T	Docetaxel
TEWL	Transepidermal water loss

Introduction

Between 75 and 92 % of breast cancer patients receive standard adjuvant chemotherapy, including doxorubicin, cyclophosphamide, fluorouracil, or taxotere (docetaxel) [1, 2]. These drugs target rapidly dividing cells and affect all proliferating cells [3], causing multiple cutaneous side effects such as alopecia, erythema, pruritus, and desquamation [4–10]. Indeed, dermatologic reactions are the most common side effect reported by cancer patients receiving chemotherapy [11].

The impact of dermatologic side effects from chemotherapy is substantial. The majority of breast cancer patients reported that chemotherapy-related skin irritation and dryness was worse than they anticipated, affecting their daily activities, personal relationships, and quality of life [12, 13]. Furthermore, some patients discontinued or reduced treatment as a consequence of dermatologic side effects, which could potentially affect clinical outcomes [14]. In contrast, oncologists often consider the dermatologic side effects of chemotherapy as minor problems and do not manage them well [15].

A major limitation in advancing management and care of chemotherapy-related dermatologic side effects is the paucity of studies evaluating the mechanisms underlying the skin changes, and available studies were restricted to case reports with limited samples [11, 13]. As a consequence, we conducted a cohort study to evaluate objective changes in skin composition and associated patient-reported symptoms among breast cancer patients undergoing chemotherapy. Objective parameters included quantitative evaluations of changes in water content, sebum content, transepidermal water loss (TEWL), and melanin. Patient-reported outcomes included dryness, dullness, blemishes, wrinkles, and loss of elasticity.

Methods

Study population

We conducted a prospective cohort study of consecutive breast cancer patients attending the outpatient breast cancer clinics at the Samsung Medical Center in Seoul, Korea, between February and September, 2012. Patients were eligible if they were 18 years of age or older, had a post-operative diagnosis of stage I to III breast cancer, and were expected to receive doxorubicin plus cyclophosphamide (AC), fluorouracil plus cyclophosphamide, and doxorubicin (FAC), or AC plus docetaxel (T) as adjuvant chemotherapy. We excluded patients with atopic dermatitis, psoriasis, or infectious skin diseases, as well as patients who were taking steroids, antihistamines, anti-depressants, or anticonvulsants. The study was approved by the Institutional Review Board of the Samsung Medical Center (IRB number: 2011-07-019). All patients provided written informed consent.

Measurements

Patients were initially evaluated prior to chemotherapy on the first day of chemotherapy (T1). Follow-up assessments were conducted after two cycles of chemotherapy (T2), and 1 (T3), 3 (T4), and 6 (T5) months after completion of chemotherapy. At each visit, patients were asked to wash their face and allow it to dry for 15–20 minutes before skin assessments. During the exam, patients laid face up on a bed keeping a straight body position. Room temperature was maintained between 20 and 22 °C and relative humidity between 30 and 40 % during the duration of the skin assessment [16, 17]. Skin parameters were measured according to a standard protocol on the front of the right cheek by trained researchers using a Multi-Probe Adapter System (Courage-Khazaka, Germany) which included a Corneometer CM 825 to measure water content (in arbitrary units, AU); a Sebumeter SM 815 to measure surface sebum content ($\mu g/cm^2$), and a Mexameter MX 18 to measure melanin content (AU). TEWL (g/m^2 h) was measured with a VapoMeter® (Delfin Technologies Ltd, Kuopio, Finland) which is a portable, battery-operated, closed, unventilated chamber evaporimeter. Each measurement was repeated three times and averaged except for sebum content which was measured only once.

Patient-reported dryness, dullness, blemishes, wrinkles, and loss of elasticity were assessed at each time point. Patients were asked to check any skin problem (yes or no)

due to cancer treatment from the list of symptoms. This list was selected based on extensive literature review and discussion by an expert group consisting of two oncologists, three oncology nurses, one dermatologist, and one behavior scientist.

Information regarding marital status, employment status, education, income, smoking, and drinking were collected using standardized questionnaires. Clinical data including age, body mass index (BMI), disease stage at diagnosis, treatment received, and co-morbidities were obtained from electronic medical records.

Statistical analysis

We used mixed effect models for longitudinal data analysis to model changes in water content, sebum content, TEWL, melanin, and patient-reported skin changes over time. For objective skin parameters, we modeled the trajectory of each parameter as a continuous variable and calculated the percent change in skin parameters at each time points with respect to T1 and the corresponding 95 % confidence intervals (CI). For patient-reported outcomes, we modeled the proportion of participants with each symptom over time and calculated the odds ratios and 95 % CI for symptoms at each time point compared to T1.

In our study, 70 % of the participants received additional hormone therapy after chemotherapy. Since anti-estrogen drugs can have multiple effects on the skin [18, 19], we compared the patients who received chemotherapy only to those who received chemotherapy and hormone therapy. Differences of outcomes between the groups were compared using χ^2 tests for categorical variables and t tests for continuous variables. In addition, we also compared the patterns of skin changes by different chemotherapy drugs.

To evaluate the association between objective skin parameters and the development of patient-reported dryness and dullness, we selected patients who did not report dryness or dullness at baseline (T1) and compared the percent change in objective skin parameters in patients with and without skin problems at T3 in multivariable linear models adjusted for age and stage. All analyses were conducted using Stata 12.0 (Stata Corp, College Station, TX). $p < 0.05$ was considered statistically significant.

Results

Study population

Among 312 eligible patients, 82 patients (26.3 %) agreed to participate. We further excluded 20 patients who did not receive chemotherapy and one patient diagnosed with thyroid cancer. The final number of patients included was 61. All participants completed the baseline measurements, and 59 (96.7 %), 57 (93.4 %), 57 (93.4 %), and 46 (75.4 %) patients completed clinic visits T2, T3, T4, and T5, respectively. The total number of patient-visits was 280.

The baseline clinical and socio-demographic characteristics of the participants are presented in Table 1. The average (SD) levels of water content, sebum content, TEWL, and melanin were 69.2 AU, 8.7 μg/cm^2, 18.6 g/m^2 h, and 141.0 AU, respectively. Prior to chemotherapy, 11.5 and 6.6 % of patients reported skin dryness and dullness, respectively. Forty-three patients (70.5 %) received additional hormone therapy after completion of chemotherapy. Patients in the chemotherapy plus hormone therapy group (CHG) were older (46.4 vs. 48.8 years), diagnosed at higher stage (stage III, 48.8 vs. 27.8 %), and more likely to receive a mastectomy (51.2 vs. 16.7 %) compared to the chemotherapy group (CG). The levels of objective skin parameters were similar in CHG and CG patients at baseline.

Changes in objective skin parameters

Water content decreased until T4 and increased slightly at T5 (69.2 AU at T1, 59.5 AU at T4, and 60.7 AU at T5; Fig. 1a; Table 2). In contrast, sebum content decreased by 75.5 % at T2 compared to baseline (8.67 vs. 2.28 μg/cm^2, respectively $p < 0.001$), reached the minimum at T3 (1.65 μg/cm^2) and increased thereafter but did not return to baseline levels (Fig. 1b; Table 2). TEWL showed trends similar to sebum content (Fig. 1c). The melanin index increased by 8 % between T1 and T2 (140.98 vs. 153.16 AU, respectively), but decreased thereafter, so that by the end of the study, participants had a lower melanin index by 17.1 % compared to T1 (117.09 AU at T5) (Fig. 1d; Table 2). All these changes were statistically significant with respect to baseline levels ($p < 0.001$)

When changes in objective skin parameters were evaluated by hormone treatment group, water content decreased in both groups until T4, but kept decreasing until T5 in CG while it began to increase at T4 in CHG (Fig. 1a). The patterns of changes of sebum content, TEWL, and melanin index were similar between CHG and CG patients. The patterns of changes in objective skin parameters were also similar for different chemotherapy agents (Fig. S1 in ESM).

Patient-reported skin problems and discomfort

The proportion of patients who reported skin dryness and dullness significantly increased from T1 to T3 (Table 3). At T3, 49.2 and 47.5 % of patient-reported skin dryness and dullness, respectively. A high proportion of patients

Table 1 Characteristics of study participants ($n = 61$) at pre-chemotherapy baseline (T1)

	Overall ($n = 61$)	CG ($n = 18$)	CHG ($n = 43$)	p value
Age (years)	47.1 ± 9.5	48.8 ± 10.7	46.4 ± 9.0	0.38
Marital status (married)	48 (78.7)	15 (83.3)	33 (76.7)	0.56
Education (≥college)	28 (45.9)	10 (55.6)	18 (41.9)	0.33
Working status (employed)	17 (27.9)	4 (22.2)	13 (30.2)	0.53
Monthly family income (≥4000$)	36 (60.0)	10 (55.6)	26 (61.9)	0.64
Alcohol drinking	16 (26.2)	4 (22.2)	12 (27.9)	0.64
BMI (kg/m^2)	23.0 ± 2.9	22.7 ± 3.6	23.1 ± 2.6	0.65
Disease stage at diagnosis				0.66
Stage 1	19 (31.2)	7 (38.9)	12 (27.9)	
Stage 2	21 (34.4)	6 (33.3)	15 (34.9)	
Stage 3	21 (34.4)	5 (27.8)	16 (37.2)	
Type of chemotherapy				0.06
AC	16 (26.2)	2 (11.1)	14 (32.6)	
FAC	16 (26.2)	8 (44.4)	8 (18.6)	
AC + T	29 (47.5)	8 (44.4)	21 (48.8)	
Hormone therapy	43 (70.5)	0	43 (100)	
Tamoxifen	31 (50.8)	0	31 (72.1)	
Others	12(19.7)	0	12 (27.9)	
Breast surgery (mastectomy)	25 (41.0)	3 (16.7)	22 (51.2)	0.01
Menopause	22 (36.1)	8 (44.4)	14 (32.6)	0.38
Co-morbidities[†]	11 (18.0)	4 (22.2)	7 (16.3)	0.45
Water content on cheek (AU)	69.2 ± 12.1	71.5 ± 13.4	68.3 ± 11.5	0.35
Sebum content on cheek (μg/cm^2)	8.7 ± 8.4	6.7 ± 7.7	9.5 ± 8.6	0.24
TEWL on cheek (g/m^2 h)	18.6 ± 7.1	18.5 ± 7.3	18.7 ± 7.1	0.91
Melanin on cheek (AU)	141.0 ± 30.2	142.7 ± 35.4	140.3 ± 28.2	0.77
Dryness	7 (11.5)	2 (11.1)	5 (11.6)	0.95
Dullness	4 (6.6)	1 (5.6)	3 (7.0)	0.84
Blemishes	4 (6.6)	2 (11.1)	2 (4.7)	0.35
Wrinkles	2 (3.3)	0	2 (4.7)	0.35
Loss of elasticity	5 (8.2)	2 (11.1)	3 (7.0)	0.59

Values are mean ± SD or numbers (%)

CG received chemotherapy only group; *CHG* received chemotherapy and hormone therapy; *AC* doxorubicin, cyclophosphamide; *FAC* cyclophosphamide, doxorubicin, fluorouracil; *T* docetaxel

[†] Having hypertension, hyperlipidemia, or diabetes

kept reporting dryness (45.7 %) and dullness (34.8 %) at T5.

Quantitative dermatologic parameters and patient-reported dryness and dullness

Among patients who did not experience dryness at T1 ($n = 50$), 29 (58 %) reported dryness at T3. Patients with new onset dryness after chemotherapy showed a greater decrease in water content (−7.9 vs. −0.4 %, $p = 0.11$), sebum content (−78.9 vs. −35.4 %, $p = 0.03$), and TEWL (−26.2 vs. −17.8 %, $p = 0.62$) between T1 and T3 compared to patients who did not experience dryness at T3 (Fig. 2a). Among patients who did not report dullness at T1 ($n = 53$), 24 (54 %) reported dullness at T3. Patients with new onset dullness after chemotherapy showed greater decrease in water content (−8.3 vs. 0.6 %, $p = 0.53$) and TEWL (−31.3 vs. −20.8 %, $p = 0.29$), and greater increase in melanin (6.6 vs. −5.1 %, $p = 0.19$) compared to patients who did not experience dullness at T3 (Fig. 2b), but none of these differences were statistically significant.

Discussion

To our knowledge, this is the first study that prospectively evaluated both objective and subjective dermatologic changes due to breast cancer chemotherapy. Water content,

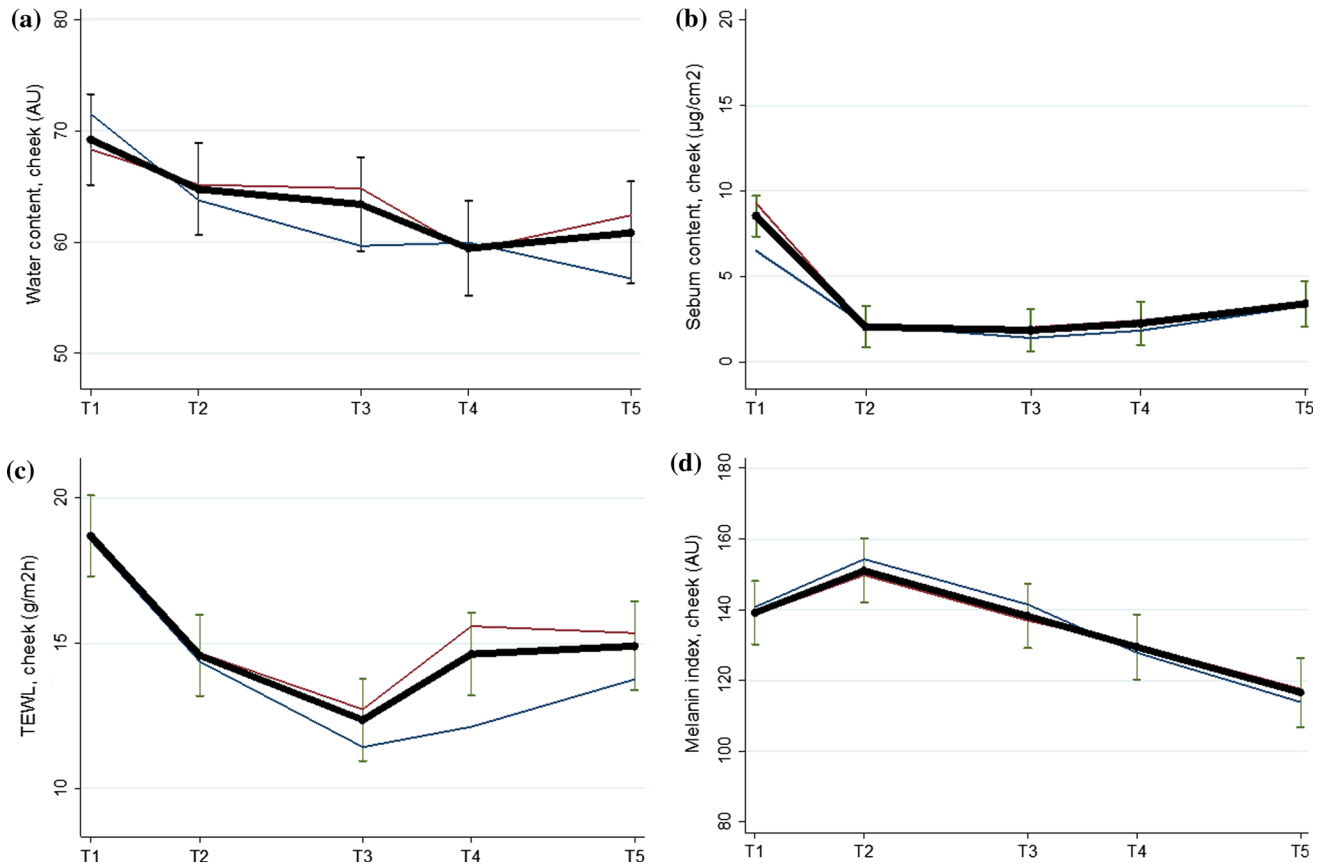

Fig. 1 Quantitative changes in water content (*AU*), sebum content (μg/cm^2), transepidermal water loss (*TEWL*, g/m^2 h), and melanin index (*AU*) before, after two cycles of chemotherapy, and after completion of chemotherapy. A *black bold line* combined, a *red line* received chemotherapy only group (*CG*), a *blue line* received chemotherapy and hormone therapy (*CHG*). For the combined group, the *vertical bars* represent the 95 % CI at time each point. *T1* before chemotherapy, *T2* after two cycles of chemotherapy, *T3* 1 month after completion of chemotherapy, *T4* 3 months after completion of chemotherapy, *T5* 6 months after completion of chemotherapy

Table 2 Percent change in water content, sebum content, TEWL, and melanin from pre-chemotherapy baseline (T1)

	Percent change (%) from T1					
	T1	T2	T3	T4	T5	*p* for trend
Water content on cheek (AU)	Reference	−6.5 (−6.5, −6.4)	−8.2 (−8.3, −8.1)	−14.0 (−14.2, −13.9)	−12.2 (−12.4, −12.1)	<0.01
Sebum content on cheek (μg/cm^2)	Reference	−75.5 (−78.3, −72.7)	−82.9 (−86.0, −79.8)	−78.3 (−81.3, −75.4)	−62.0 (−64.8, −59.2)	<0.01
TEWL on cheek (g/m^2 h)	Reference	−22.4 (−22.8, −22.1)	−33.7 (−34.2, −33.2)	−21.6 (−22.0, −21.3)	−20.3 (−20.6, −19.9)	<0.01
Melanin on cheek (AU)	Reference	8.4 (8.3, 8.5)	−3.3 (−3.4, −3.3)	−9.8 (−9.9, −9.7)	−17.1 (−17.3, −16.8)	<0.01

Percent changes and 95 % CI adjusted for age, baseline menopause status, type of regimen and hormone therapy

T1 before chemotherapy; *T2* after two cycles of chemotherapy; *T3* 1 month after completion of chemotherapy; *T4* 3 months after completion of chemotherapy; *T5* 6 months after completion of chemotherapy

sebum, TEWL, and melanin rapidly and significantly deteriorated after completion of chemotherapy. While these skin changes improved over time, they did not return to baseline levels even 6 months after completion of chemotherapy. Patients who received additional hormone therapy after chemotherapy showed different patterns of

Table 3 The number and percentage of participants with the symptom in each time and odds ratios (95 % CI) for patient-reported outcomes (PROs) compared to pre-chemotherapy baseline (T1)

PROs	Time				
	T1	T2	T3	T4	T5
Dryness, *n* (%)	7 (11.5)	29 (49.2)	53 (92.9)	53 (93.0)	39 (86.7)
OR (95 % CI)	Reference	10.1 (3.6, 28.3)	15.3 (5.3, 44.2)	14.0 (4.9, 40.0)	8.9 (3.0, 26.2)
Dullness, *n* (%)	4 (6.6)	28 (47.5)	28 (49.1)	21 (36.8)	16 (34.8)
OR (95 % CI)	Reference	28.9 (7.2, 116.5)	32.6 (8.0, 133.4)	16.3 (4.1, 64.7)	12.4 (3.1, 49.9)
Blemishes, *n* (%)	4 (6.6)	18 (30.5)	17 (29.8)	16 (28.1)	10 (21.7)
OR (95 % CI)	Reference	10.7 (2.8, 41.3)	10.3 (2.7, 40.0)	9.2 (2.4, 35.5)	5.8 (1.4, 23.9)
Wrinkles, *n* (%)	2 (3.3)	4 (6.7)	16 (28.1)	13 (22.8)	12 (26.1)
OR (95 % CI)	Reference	2.2 (0.4, 12.8)	13.7 (2.8, 67.2)	9.9 (2.0, 48.5)	12.6 (2.5, 63.2)
Loss of elasticity, *n* (%)	5 (8.2)	16 (27.1)	14 (24.6)	21 (36.8)	13 (28.3)
OR (95 % CI)	Reference	5.2 (1.6, 17.0)	4.5 (1.4, 14.8)	9.3 (2.9, 30.4)	5.8 (1.7, 19.8)

Odds ratios (OR) and 95 % CI were obtained from mixed models adjusted for age, baseline menopause status, type of regimen and hormone therapy

T1 before chemotherapy; *T2* after two cycles of chemotherapy; *T3* 1 month after completion of chemotherapy; *T4* 3 months after completion of chemotherapy; *T5* 6 months after completion of chemotherapy

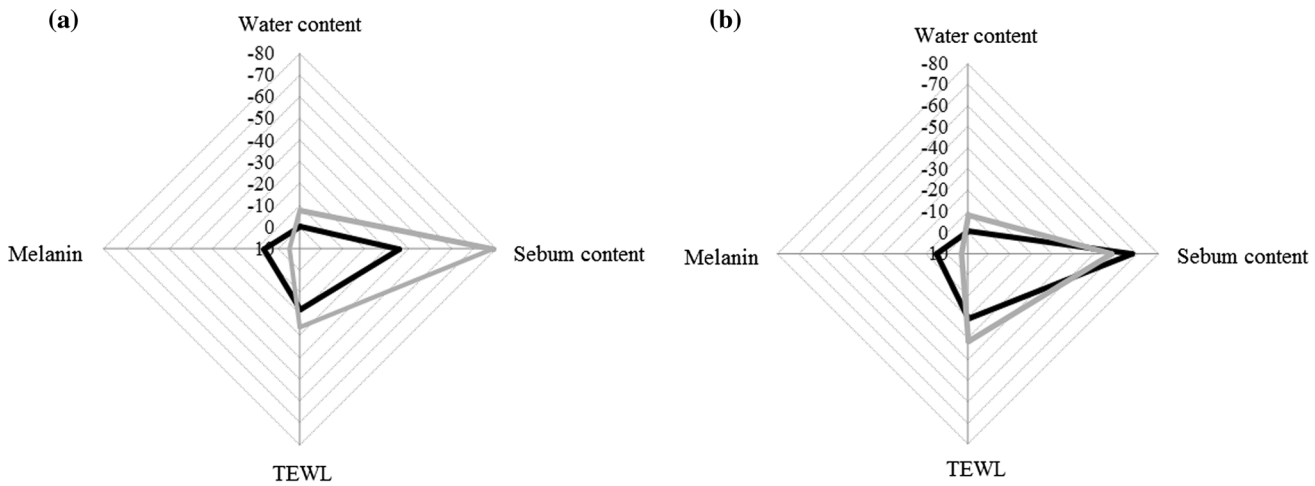

Fig. 2 Percent change in water content, sebum content, transepidermal water loss (*TEWL*), and melanin among patients with **a** dryness arisen or **b** dullness arisen compared to patients who did not experience dryness or dullness. **a** *Black bold line* did not experience dryness ($n = 21$), *gray bold line* dryness arisen ($n = 29$); **b** *Black bold line* did not experience dullness ($n = 29$), *gray bold line* dullness arisen ($n = 24$)

water content and TEWL compared to the patients with chemotherapy. Finally, we found an association between objective skin parameters and patient-reported symptoms.

Sebum content significantly decreased after chemotherapy. The rate of triglyceride turnover in sebaceous glands is high [20, 21] and triglycerides are hydrolyzed to glycerol prior to delivery to the skin surface [22]. Indeed, doxorubicin killed SZ95 sebaceous gland line cells in vitro and in vivo 7-day-old rat and adult mouse models [23]. Chemotherapy may damage or destroy sebaceous glands resulting in decreased sebum [24].

Water content continuously decreased after chemotherapy. Lipids have a water-holding function in the stratum corneum [25] and animal studies found a much lower water content in the stratum corneum of sebaceous gland-deficient mice compared to wild-type mice [21]. Decreased sebum content in our study might be linked with decreased water content, but further research is needed to establish

the connection between sebum and water content after chemotherapy.

In our study, patient-reported dryness was significantly associated with decreased sebum level, providing an objective validation of patient-reported outcomes and confirming that dryness was likely due to dermatologic changes. Patient-reported outcomes could thus be a useful tool that multi-disciplinary cancer care teams could use to provide appropriate interventions and treatment [26].

Some studies have reported increased TEWL with chemotherapy [27], a phenomenon that was ascribed to chemotherapy-related damage to the skin barrier [28]. In contrast, we found decreased TEWL with chemotherapy, similar to the association between aging and TEWL [29, 30]. In the normal epidermal turnover process, dead skin cells are continually shed from the skin surface and replaced by dividing cells in the basal cell layer to produce a state of constant renewal [31]. With aging, the epidermal turnover rate slows down and TEWL decreases [32]. Chemotherapy may also disrupt degradation cycles [33] resulting in decreased TEWL due to the accumulation of corneocytes in the surface of the stratum corneum [28].

In our study, melanin increased during chemotherapy but significantly decreased after completion of chemotherapy and kept decreasing up to 6 months after completion of chemotherapy. It is well known that melanin increases in the basal skin layers during chemotherapy [34], but no study has evaluated the melanin content of the skin after chemotherapy. Decreased melanin may be associated with defective maintenance of melanocyte stem cells [35]. Chemotherapy, which affects rapid differentiating cells [3], might cause loss or failure of differentiation from melanocyte stem cells to melanocytes, resulting in decreased melanin. While melanin decreased beyond completion of chemotherapy, more than 50 % of the patients in our study reported dullness arisen after completion of chemotherapy. Patient-reported dullness might be associated with decreased TEWL. Rough and dry skin due to accumulation of corneocytes with chemotherapy (decreased TEWL) may lead to a reduction of skin shininess and a feeling of "ashiness" or "ashy" skin [36].

Patients with and without hormone therapy showed similar patterns of skin changes overall but water content and TEWL increased more in the CHG than in the CG group from T3. Breast cancer patients in our study received anti-estrogen drugs, but our findings are different from the skin changes reported with lack of estrogen [37]. Little is known about the effects of selective estrogen-receptor modulators (SERMs), such as tamoxifen or raloxifene, on the skin. SERMs have mixed estrogenic and anti-estrogenic effects depending on the tissue [38]. In in vitro and animal studies, SERMs act an estrogen agonists in the skin [39, 40]. Furthermore, a recent case report described a woman that developed pigmented macules on the face 1 month after tamoxifen administration related to increased estrogen [41]. In sum, increased water content and TEWL in the CHG of our study may be due to the estrogenic effect of SERM in the skin.

There are several limitations to our study. The study was conducted at a single institution, and the results of our study might not be generalizable to patients in other institutions or other countries. In addition, patients who were more interested in skin conditions may have been more likely to participate in this study, and our participants may have been more likely to have skin problems at baseline compared to other breast cancer patients. However, we evaluated objective and subjective skin variables with valid measurements and obtained baseline pre-chemotherapy levels of skin parameters in all patients.

In conclusion, sebum content, water content, TEWL, and melanin in the skin decreased after chemotherapy, and they did not regain pre-chemotherapy levels even 6 months after completion of treatment. In addition, these objective changes were associated with patient-reported symptoms. Further investigation is necessary to determine the specific mechanisms underlying these changes. Moreover, additional translational research is necessary to develop interventions for improving the dermatologic quality of life among cancer patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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