Original Research Papers

# Effects of a holistic, patient-centered approach on breast cancer relative dose intensity

Rebecca Louison[a], Jennifer Lee[a,b,*], Victoria Roe[a], Chirantan Ghosh[c]

[a] Department of Psychology, Mount Mercy University, Cedar Rapids, Iowa, United States
[b] College of Nursing, University of Iowa, Iowa City, Iowa, United States
[c] Ghosh Cancer Center, Cedar Rapids, Iowa, United States

ABSTRACT

*Purpose:* A critical component of breast cancer (BC) chemotherapy effectiveness is relative dose intensity (RDI), as <85% RDI lessens treatment efficacy. Over half of BC patients have an RDI < 85% due to dose-limiting treatment side effects. Evidence suggests nonpharmacologic approaches (e.g., yoga, nutrition) improve cancer symptoms (e.g., pain, fatigue), yet no studies examined them for RDI. This descriptive, preliminary study will investigate the effects of a patient-centered, holistic approach on RDI, and associations among RDI and patient characteristics (age, race, ethnicity, body mass index, body surface area, hormone status [estrogen- or progesterone-receptor positive, HER2, menopause], marital status, employment status, cancer stage, treatment type, insurance type).
*Methods:* The medical records of 161 BC patients (*M* = 61.5 years, *SD* = 12.7) from a holistic cancer clinic were collected and analyzed. This clinic offers a patient-centered approach (i.e., patients actively make decisions, treatment education, chair yoga, reiki, and nutritional counseling). RDI was determined by calculating the ratio of the received dose versus the intended dose intensity.
*Results:* 92% of patients had an RDI $\geq$ 85% (Mean = 96%) and 8 of the 9 treatment regimens' RDI exceeded 85%. RDI had a significant positive association with BMI (p = .06), and being ER+ and/or HER2+ (*p's* = .08). None of the remaining demographic or clinical characteristics were associated.
*Conclusions:* This non-pharmacologic approach led to a higher RDI than recommended, potentially improving BC patients' prognosis. Higher RDI was related to BMI, and ER+ and HER2 status. Additional research is needed; however, these results provide promising evidence regarding the benefits of a patient-centered, holistic approach.

© 2018 Elsevier Ltd. All rights reserved.

## 1. Introduction

With over 246,000 new breast cancer (BC) cases in the United States during the year 2016, the number of women affected is second only to skin cancer [1]. Thankfully, there are increased survival rates [2,3], including American Cancer Society-reported 5-year survival changing from 63% in the 1960's to 90% in 2012 [2]. Improved outcomes are generally attributed to improved early detection and treatment [2,3]. To be effective, chemotherapy must achieve >85% relative dose intensity (RDI; intended versus received dose) [2–5]; an RDI < 85% may have limited or nonexistent efficacy [2–5]. For example, 80% RDI compromises remission/cure by ~50%, and patients with <65% RDI have a survival expectancy similar to no treatment [2–5].

Although RDI's importance is documented, up to half of BC patients have <85% RDI [2,6]. Receiving less than the intended dose and/or having treatment delays is problematic because every chemotherapy dose kills cancer cells [3]; treatment delays allow

cell growth, increasing the chance of negative outcomes. In many cases, delayed appointments are not rescheduled quickly, or the oncologist is unaware and does not adjust the treatment plan [3,5]. Treatment reductions and delays occur for many reasons, withnon-treatment-related delays possibly due to: lacking transportation, patient/family illness, fear, and/or caring for family member [3,5]. Treatment-related delay reasons include: (1) lower socioeconomic status (e.g., inflexible work schedules); (2) body mass (i.e., surface area >2m$^2$); (3) therapy toxicity; (4) treatment length (≥28 days); (5) neutropenia (low white blood cell count); (6) side effects (e.g., fatigue,); and/or (7) age (i.e., >65 years) [2–5].

There is no current standard of care for improving RDI for BC, but strategies may include: patient and caregiver education, assessing neutropenia risk pre-treatment, using G-CSF (granulo-cyte-colony-stimulating factor, a supportive care agent), and/or strict cancellation protocols [5]. Additionally, nutritional counsel-ing may help [7], especially people with a high body mass index (BMI) or body surface area (BSA) since chemotherapy maximums may restrict heavier individuals from receiving a full dose [6]. Finally, non-pharmacologic, holistic approaches are used with increasing frequency to decrease treatment-limiting side effects (e.g., fatigue) and improve quality of life [1–3,8]. Yoga improves quality of life and psychological well-being, thus is recommended during and after treatment [9,10]. Reiki (light touch to stimulate healing) also improves physical and psychological cancer symp-toms [11]. Indeed, according to Maslow's Humanistic Hierarchy of Needs Theory [12], humans have a myriad of needs (e.g., physical, emotional, social, spiritual), and benefit from holistic approaches. Maslow's theory is consistent with the concerns and needs of women with BC, as indicated by the Institute of Medicine and NCCS Breast Cancer Survivorship Program [13–15]. Ng et al. [16] eloquently applied Maslow's Theory to BC, arguing that cancer care should be individualized, comprehensive, and address patients' holistic needs to promote healing (Fig. 1).

Despite evidence supporting holistic cancer approaches, no known studies examined whether a patient-centered, non-pharmacologic approach improves RDI. To address this gap, this descriptive study's objective is to examine RDI rates in a BC sample from a clinic emphasizing the patient experience and high quality, individualized, compassionate care. Given the lack of research on patient-specific variables and RDI, secondary analyses will include patient/clinical factors (e.g., age, hormone status, cancer stage). This clinic was chosen because it offers a unique, holistic approach, including continuous communication and education, and allowing patients to be active decision-makers. Also included at no cost to the patient are: chair yoga, Reiki, and nutritional counseling. If this patient-centered, holistic approach improves RDI rates for BC, other clinics may benefit from similar practices.

## 2. Materials and methods

### 2.1. Study design

After obtaining approval from the Mount Mercy University Institutional Review Board (IRB), medical records from the Ghosh Center (Cedar Rapids, IA) were retrospectively evaluated and de-identified before coding and analysis.

Participants were 161 consecutive BC patients between 1/15/1998 and 7/18/2013. This cohort was selected at random, and included every single adult (18 + years) BC patient diagnosed at the Ghosh Clinic over this 5-year-period. Inclusion criteria consisted of: (1) BC diagnosis; (2) stages I to IV; and (3) prescribed adjuvant chemotherapy at the Ghosh Clinic. Exclusion criteria included: (1) recurrence; and/or (2) receiving palliative care.
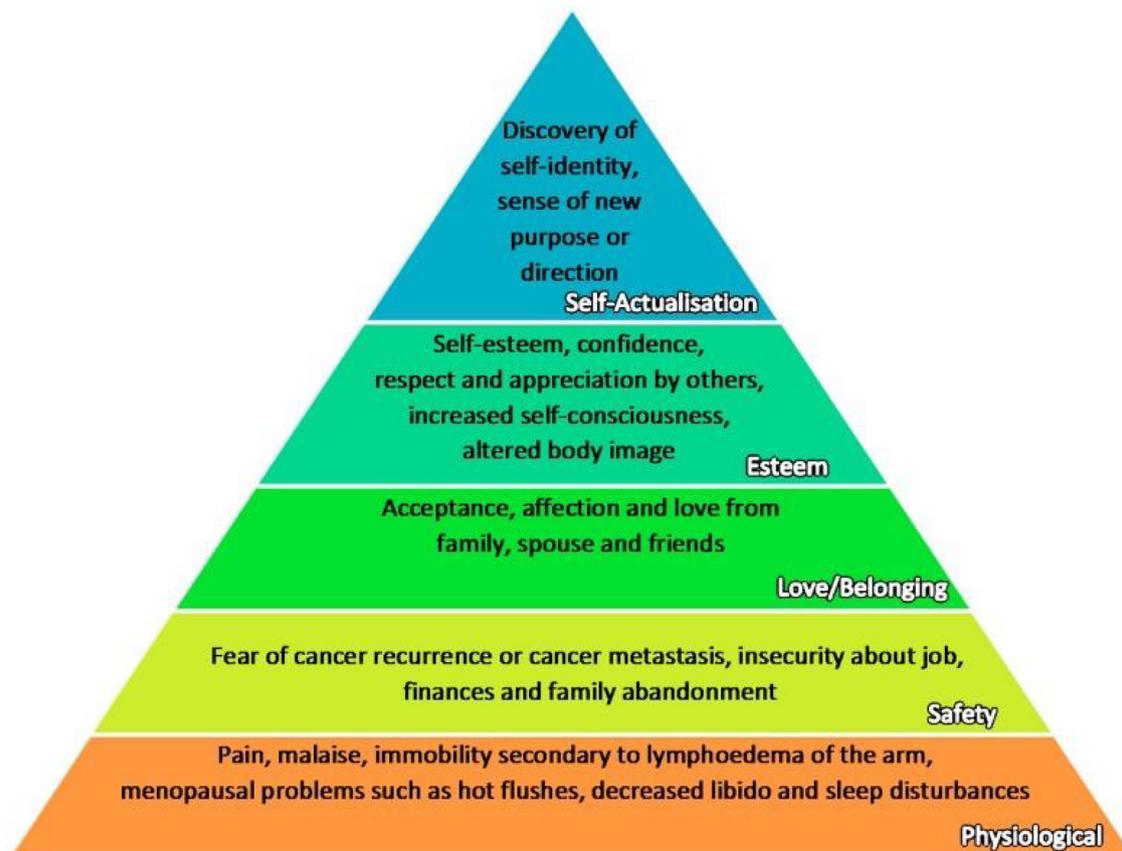


**Fig. 1.** Maslow Hierarchy of Needs applied to breast cancer (reprinted with permission from Ng et al., 2017) [15].

## 2.2. Independent measures

### 2.2.1. Demographics and clinical characteristics

Data was extracted at the time of diagnosis, including: age, race (Asian, Black/African American, Caucasian), ethnicity (Hispanic/ Latino; not Hispanic/Latino), body mass index (BMI), body surface area (BSA), hormone status ([estrogen receptor- or progesterone receptor positive; ER+, PR+]; human epidermal growth factor receptor 2 overexpression; HER2+], menopause [pre or post]), marital status (single, married, widowed, other), employment status (full-time, part-time, retired, unemployed), cancer stage, treatment (nine regimens, see Table 2), and insurance type (private or public). Due to prior research analyzing BMI and BSA continuously and categorically) [6], they were recorded both ways for study comparison. BMI was grouped into: (1) <25; (2) 25–30; or (3) >30. BSA was grouped into: (1) <2.0 m$^2$; or (2) >2.0 m$^2$. To allow comparison with a recent, similar BC study, we grouped cancer stages into two categories (I to IIa; IIb to IV) [6]. Data was also collected on treatment delays, and categorized as: (1) zero delays; (2) 1+ delays.

## 2.3. Dependent measure

### 2.3.1. Relative dose intensity

RDI is the ratio (%) of actual/received chemotherapy dose (ADI) versus intended/prescribed dose (IDI). To obtain ADI, the total chemotherapy (mg) received is divided the number of chemotherapy weeks, providing a mean mg/week of chemotherapy:

$$IDI(mg/week) = \frac{Intended\ Dose\ (mg)}{Intended\ duration\ of\ therapy\ (weeks)}$$

$$ADI(mg/week) = \frac{Actual\ Dose\ (mg)}{Actual\ duration\ of\ therapy\ (weeks)}$$

$$RDI(\%) = \frac{ADI}{IDI}\ x\ 100$$

## 2.4. Holistic approach

The study's community oncology clinic (http://www.theghosh-center.org/) has this aim: "The Ghosh Center lives the philosophy of putting patients first, providing the highest quality of care with respect and compassion." The Center uses a six-step, individualized approach to decrease delayed, missed, or reduced chemotherapy. An overarching theme is getting to know every patient and family through regular communication and active listening, creating compassionate provider-patient relationships. First, information about cancer types (i.e., ductal, lobular) and the biological properties, processes, and stages of cancer is presented in a clear way using simple breast diagrams (Fig. 2).

Second, a commonly used online program (Adjuvant!; http://www.newadjuvant.com) [17], provides each patient's specific anticipated survival vs. relapse timeline if they accept or decline treatment, respectively (based on SEER data). Research suggests that an online, symptom monitoring program for BC patients led to longer survival than usual care [18]. Third, clinicians thoroughly review potential side effects before treatment, including a detailed consent form (Figs. 3 and 4); side effects are also reviewed before every treatment.

These strategies allow patients to actively participate in the decision-making process of treatment. Fourth, patients receive the detailed treatment plan, including: drug, dosages, schedule, and
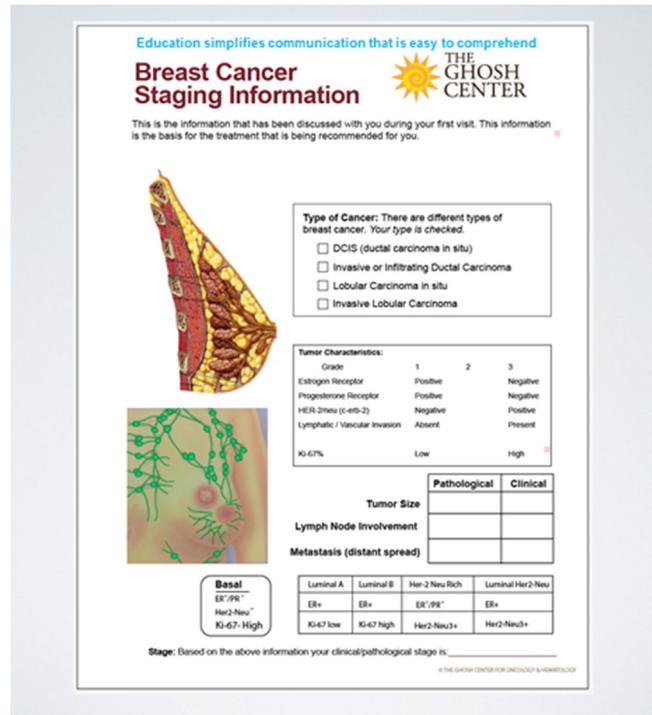


**Fig. 2.** Information about the difference between types of cancer (i.e., ductal, lobular), as well as the biological properties, processes, and stages of cancer is presented in a clear way using simple diagrams of the breasts.

costs (i.e., insurance plan, expected treatment costs, financial assistance resources) (Fig. 5).

Fifth, patients are regularly encouraged to contact the staff immediately about complications any time of day (phones answered 7 days/week). All calls are answered by oncology nurses, and the entire staff is continually trained on the importance of timely and thorough evaluation of all complications, and ways to ensure a prompt response. Finally, patients are strongly encouraged to participate in the free chair yoga, Reiki, and nutritional counseling at the Ghosh Clinic.
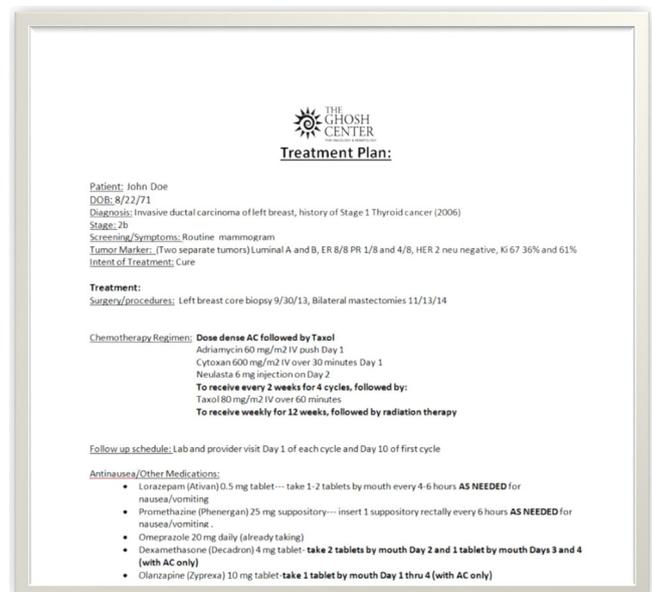


**Fig. 3.** Sample treatment plan discussed before initiating treatment covers all potential chemotherapy side effects.

Fig. 4. Individualized consent form allows the patient to be an active decision-maker in their treatment.

### 2.4.1. Yoga and Reiki

Yoga and Reiki are included at no cost to all Ghosh Center patients as standard of care, and are facilitated by trained, local experts. Specifically, this clinic offers TriYoga, a chair yoga that coordinates rhythmic breathing and motion. This chair-based, hatha yoga (i.e., physical postures) method is a gentle form of exercise found to be safe and feasible for older and/or medically fragile individuals [19]. TriYoga emphases three components: (1) asana (posture); (2) pranayama (breath), and (3) mundra (focus); These three components are intended to calm the mind, spirt, and body to allow meditation. Yoga is 45 min per class, once a week, and is held at the Ghosh Center or at a community retreat space just outside of town (when the weather is warm enough). The Reiki used is called Usui Reiki, where hands are laid directly on or above the body in a specific pattern to allow energy to flow from the healer to the patient. This type of Reiki was founded by Japanese Buddhist Mikao Usui as an intervention to increase relaxation and decrease stress through the healer's hands. Indeed, Reiki activates the parasympathetic nervous system to produce calm and relaxation [20]. Usui Reiki is offered once per week for two hours in the clinic.

Due to a wealth of research highlighting yoga's positive impact on BC [21–23], yoga is a quickly becoming the most used complementary therapy in oncology [9,10]. A recent Cochrane Review [24], concluded that yoga improves BC-related health-related quality of life, fatigue, sleep disturbances, depression, and anxiety when compared to psychosocial/educational interventions or usual care. Importantly, yoga can be done at home for free by most patients; therefore, appealing and accessible to many patients [10]. Reiki has similar benefits, decreasing psychological and physical symptoms, and improving stress, anxiety, pain, sleep quality, and well-being (e.g., increased relaxation, inner peace) [25]. In one study, Reiki improved cancer pain ratings more than massage and yoga [11], as well as quality of life and perceived health [11]. As a result, Reiki is used increasingly for patient groups, but more research is needed to determine its specific benefits for BC compared to other complementary and alternative medicine (CAM) approaches (e.g., yoga, massage, healing touch, etc.).

### 2.4.2. Nutritionalcounseling

This clinic specifically offers a free health coach as standard of care; this coach is accessible during and following treatment to all patients/caregivers by phone or in person. Prior to initiating adjuvant chemotherapy, the health coach meets with the patient to determine their specific nutritional needs and cancer treatment



Fig. 5. Once an adjuvant treatment plan is decided, the patient receives a copy of the detailed treatment plan which includes vital information like drug type, dosages, schedule of administration, treatment, as well as financial information.

**Table 1**
Participant demographic and clinical characteristics.

| Continuous Variables | n | Mean | SD |
|---|---|---|---|
| Age (years; range 23 to 93) | 161 | 56.2 | 0.1 |
| Body mass index (BMI) (kg/m$^2$; range 17 to 47) | 144 | 29.3 | 6.1 |
| Body surface area (BSA) (kg/m$^2$; range 1.38 to 2.63) | 144 | 2.6 | 0.2 |

| Categorical Variables | n | | % |
|---|---|---|---|
| Sex, Female | 161 | | 100 |
| Racial heritage | | | |
|   White | 146 | | 96.7 |
|   Black/African American | 2 | | 1.3 |
|   Asian/Asian American | 2 | | 1.3 |
|   Declined to answer | 1 | | 0.6 |
| Ethnicity | | | |
|   Not Hispanic/Latino | 150 | | 99.3 |
|   Hispanic/Latino | 1 | | 0.6 |
| Employment status | | | |
|   Full-time | 69 | | 45.7 |
|   Part-time | 6 | | 4.0 |
|   Unemployed | 14 | | 9.3 |
|   Retired | 62 | | 41.1 |
| Marital status | | | |
|   Single | 22 | | 14.6 |
|   Married | 95 | | 62.9 |
|   Widowed | 2 | | 1.3 |
|   Other | 32 | | 21.2 |
| Insurance | | | |
|   Private | 76 | | 50.3 |
|   Public | 75 | | 49.7 |
| Age | | | |
|   Under 65 | 121 | | 75.2 |
|   Over 65 | 40 | | 24.8 |
| Cancer Stage | | | |
|   I-IIa | 101 | | 62.7 |
|   IIb + | 60 | | 37.3 |
| Body surface area (BSA) | | | |
|   1.38 m$^2$ to 1.99m$^2$ | 113 | | 78.5 |
|   2.00 m2 + | 31 | | 21.5 |
| Body mass index (BMI) | | | |
|   Under 25 | 36 | | 25.2 |
|   25-30 | 54 | | 37.8 |
|   Over 30 | 53 | | 37.0 |
| Hormone receptor positivity | | | |
|   Yes | 111 | | 68.9 |
|   No | 50 | | 31.1 |
| Hormone receptor status | | | |
|   ER+ | 42 | | 29.2 |
|   ER− | 102 | | 70.8 |
|   PR+ | 74 | | 51.3 |
|   PR− | 69 | | 48.0 |
|   PR unknown | 1 | | 0.7 |
|   HER2+ | 42 | | 29.2 |
|   HER2− | 95 | | 66.0 |
|   HER2 unknown | 7 | | 4.8 |
| Menopause status | | | |
|   Premenopausal | 51 | | 35.4 |
|   Postmenopausal | 86 | | 60.0 |
|   Menopause unknown | 7 | | 4.8 |

Note: Variables with less than n = 161 indicate missing data.

plan. The health coach then recommends patient-specific vitamins and supplements, as well as a detailed diet plan. The focus of the Ghosh Center nutritional counseling is "prehabilitation", a proactive health approach with the aim of limiting health issues starting prior to treatment.

Nutritional interventions for BC (e.g., less red meat, increased fish, fruits, vegetables), are implemented with increasing frequency to improve overall quality of life, and reduce the likelihood of: (1) nutrient deficiencies; (2) decreased lean body mass; and (3) nutrition side effects (e.g., diminished appetite, nausea, taste changes, or bowel changes) [26,27]. In addition to nutrition-specific benefits, dietary counseling for people with different types of cancer is related to improved nutritional intake, emotional and physical function, pain, fatigue, nausea, appetite, treatment response, recovery speed, recurrence risk, and quality of life [28,29]. Further, a meta-analysis of 65 BC studies found that nutritional interventions can enhancethe physical and psychological well-being of BC patients in particular [7]. As a result of this compilation of studies on BC and nutrition (and other cancers), the American Cancer Society now recommends nutritional screening and assessment for BC patients from the time of diagnosis, through the end of treatment and recovery [26]. Thus, in addition to the other non-pharmacologic, holistic approaches used at the Ghosh Center, nutritional counseling seems a logical addition to the CAM therapies offered.

**Table 2**
Relative dose intensity for each treatment regimen.

| Category | Mean RDI (%) | SD | n (%) |
|---|---|---|---|
| FEC | 99.8 | 0.002 | 3 (1.9) |
| TC | 99.6 | 0.008 | 27 (16.9) |
| T | 99.4 | 0.009 | 2 (1.3) |
| AC | 98.9 | 0.02 | 29 (18.1) |
| TAC | 95.6 | 0.10 | 17 (10.6) |
| AC-T | 95.0 | 0.16 | 71 (44.4) |
| TCH | 94.8 | 0.09 | 3 (1.9) |
| CMF | 91.2 | 0.003 | 2 (1.3) |
| FAC | 76.7 | 0.34 | 6 (3.8) |

NOTE: AC-T = Adriamycin (Doxorubicin) + Cytoxan (Cyclophosphamide) + Taxol (Paclitaxel); AC = Adriamycin (Doxorubicin) + Cytoxan (Cyclophosphamide); TC = Taxotere (Docetaxel) + Cytoxan (Cyclophosphamide); TAC = Taxotere (Docetaxel) + Adriamycin (Doxorubicin) + Cytoxan (Cyclophosphamide); FAC = Fluorouracil (5FU) + Adriamycin (Doxorubicin) + Cytoxan (Cyclophosphamide); T= Taxol (Paclitaxel); FEC = Fluorouracil (5FU) + Cytoxan (Cyclophosphamide) + Ellence (Epirubicin); TCH = Taxotere (docetaxel) + Carboplatin (Paraplatin) + trastuzumab (Herceptin); CMF = Cytoxan (Cyclophosphamide) + Methotrexate (Trexall) + Fluorouracil (5FU).

## 2.5. Statistical analyses

Descriptive statistics were calculated first (means, standard deviations [SD], frequencies). Outliers were verified for accuracy. Kolmogorov-Smirnov assessed normality of the continuous variables (e.g., age, RDI). If data was not normally distributed, more conservative analyses were used Table 1.

To determine whether RDI was associated with demographic or clinical characteristics univariate analyses were completed. RDI, our continuous dependent variable, was analyzed with: (1) *continuous variables* (age, BMI, BSA); and (2) *categorical variables*: age (≥65 or <65 years), race (Hispanic/Latino; not Hispanic/Latino), ethnicity (Asian, African American, Caucasian, declined), marital status (single, married, widowed, other), employment status (full-time, part-time, unemployed, retired), insurance (private or public), cancer stage (I, II, III, IV; and I-IIa, IIb-IV), treatment (nine regimens), BMI (i.e., <25, 25 to 30, or 30 < ), BSA (1.38 $m^2$ to 1.99 $m^2$ or 2.00 $m^2$+), hormone receptor status (ER + and/or PR+; yes or no), HER2 status (yes or no), menopausal status (pre or post menopause). If univariate analyses were significant, post hoc Tukey tests were completed. The data was analyzed (IBM SPSS Statistics for Windows, V24) [30], using two-tailed tests, alpha ≤ 0.10 due to the exploratory, pilot nature of this study (decreases Type II Error).

## 3. Results

### 3.1. Participants

A total of 180 medical records were initially reviewed. Fourteen were excluded due to missing/incomplete initial *prescribed* dose records, and five had missing/incomplete *received* dose records (started or completed treatment at a different clinic). The remaining 161 patients' data were included in the analyses (Table 1), with a mean age of 56.0 years (SD = 13.0; range 23 to 93). The majority of the sample was Caucasian (96.7%, n = 146), not Hispanic or Latino (99.3%, n = 150), married (62.9%; n = 95), employed full-time (45.7%; n = 69), and had Stage II BC (42.2%; n = 68). In total, the majority of patients (86%) used at least one of the complementary and alternative services (TriYoga, Usui Reiki, nutritional counseling) during the data collection period. Finally, Table 2 shows how many people received each of the nine possible chemotherapy regimens.

### 3.2. Relative dose intensity

The average RDI was 96% (range 11 to 136%), with 92% meeting or exceeding the recommended 85% RDI. It was possible for RDI to be >100% if: (1) more than the prescribed dose was administered during a cycle; (2) more cycles were administered than initially prescribed; or (3) the treatment duration was shortened to less than the typical duration [6]. The highest mean RDI was for Stage I (99%), followed by Stage IV (98%), Stage II (96%), and then Stage III (93%).

### 3.3. Dose delays and reductions

Across chemotherapy regimens, most patients received treatment on time (n = 135; 83.9%). Twenty-six (16.1%) had 1+ delay/reduction due to: (1) neutropenia (n = 8, 5.0%), neuropathy (n = 7, 4.3%), side effects (n = 9, 5.6%), patient schedule conflict; n = 1, 0.01%), and personal injury (n = 1, .01%). Twenty were hospitalized (12.4%), and 1 visited the emergency room (0.01%). Treatment delays/reductions per regimen happened in this order: AC-T (n = 18, 25.4%); TAC (n = 3; 17.6%); TC (n = 2; 7.4%); AC (n = 1; 3.4%); FEC (n = 1; 33.3%); and TCH (n = 1; 33.3%) (none for CMF, T or FAC).

### 3.4. Continuous variables

Tests for normalcy found RDI and BMI were not normally distributed (p's < 0.0001), so conservative analyses were done, when applicable. Associations among RDI and the demographic and clinical characteristics are in Table 3.

Age was examined first as a continuous variable, and it was not related to RDI (F [1,1] = .01, p = 0.91). Neither BMI (F [1,1] = .41, p = 0.52) nor BSA (F [1,1] = .39, p = 0.53) were related to RDI.

### 3.5. Categorical variables

RDI was not related to race (F [1,3] = .08, p = 0.97), ethnicity (F [1,1] = .03, p = 0.85), marital status (F [1,3] = .98, p = 0.40), employment (F [1,3] = 1.14, p = 0.34), or insurance (F [1,1] = 1.50, p = 0.22). When also examined categorically, age was not related (F [1,2] = .18, p = 0.84). The average RDI for patients younger and older than 65 years was 96% and 96%, respectively.

BMI and BSA were also analyzed categorically, and BMI was statistically significantly related to RDI (F [1,2] = 2.95, p = 0.06). Follow-up Tukey's found the RDI of patients with a BMI < 25 was statistically higher (RDI = 99.4, SD = 0.1) than those with a BMI 25 to 30 (RDI = 92.2, SD = 0.2, p = .09). BSA was not associated with RDI (F [1,1] = 1.67, p = 0.20).

RDI was significantly related to hormone status (i.e., ER+, PR+, HER2) (F [1,1] = 5.236, p = 0.02). Follow-up analyses found RDI was significantly higher in ER+ (F [1,1] = 3.06, p = 0.08) and HER2+ patients (F [1,1] = .06, p = 0.08). Specifically, ER + versus ER- women had an RDI of 97.1 and 92.6%, respectively. HER2+ versus HER2- women had an RDI of 98.9 and 94.3%, respectively. RDI was not related to PR status (F [1,1] = .000, p = 0.997) or menopausal status (F [1,1] = .84, p = 0.36).

RDI was not related to cancer stage (F [1,1] = 2.47, p = 0.12), but there were significant RDI differences between treatments (F [1,8] = 2.29, p = 0.02). Follow-up analyses found that patients receiving FAC had significantly lower RDI than: AC (p = .01), AC-T (p = .03), TC (p = .004), and TAC (p = 0.06). Five treatments had fewer than 10 patients (FEC, T, TCH, CMF, FAC), so we excluded these regimens in additional analyses and RDI was no longer related to treatment (F [1,3] = 1.42, p = 0.24).

**Table 3**
Associations among mean (SD) relative dose intensity (RDI), and demographic and clinical characteristics.

| Continuous variables | RDI (%) | SD | n | Overall p-value |
|---|---|---|---|---|
| Age (years; range 23 to 93) | 96.0 | 0.1 | 161 | 0.91 |
| Body mass index (BMI)(kg/m², range 17 to 47) | 95.8 | 0.1 | 144 | 0.52 |
| Body surface area (BSA)(kg/m², range 1.38 to 2.63) | 95.8 | 0.1 | 144 | 0.20 |

| Categorical variables | RDI (%) | SD | n | Overall p-value |
|---|---|---|---|---|
| Racial heritage | 95.8 | 0.1 | 161 | 0.97 |
|   Hispanic/Latino | n/a | n/a | 0 | |
|   Not Hispanic/Latino | 95.8 | 0.1 | 150 | |
|   Declined to answer | 98.2 | n/a | 1 | |
| Ethnicity | 95.8 | 0.1 | 161 | 0.85 |
|   Asian | 95.7 | 0.1 | 2 | |
|   Black/African American | 99.9 | 0.0 | 2 | |
|   Caucasian | 95.7 | 0.1 | 146 | |
|   Declined to answer | 98.2 | n/a | 1 | |
| Marital status | 95.8 | 0.1 | 161 | 0.40 |
|   Married | 94.9 | 0.2 | 95 | |
|   Widowed | 86.9 | 0.1 | 2 | |
|   Single | 96.6 | 0.1 | 22 | |
|   Other | 98.6 | 0.0 | 32 | |
| Employment status | 95.8 | 0.1 | 161 | 0.34 |
|   Full-time | 97.5 | 0.1 | 69 | |
|   Part-time | 99.2 | 0.0 | 6 | |
|   Retired | 94.4 | 0.1 | 14 | |
|   Unemployed | 92.2 | 0.2 | 62 | |
| Insurance status | 95.8 | 0.1 | 161 | 0.22 |
|   Private | 97.1 | 0.1 | 76 | |
|   Public | 94.5 | 0.1 | 75 | |
| Age | 96.0 | 0.1 | 161 | 0.84 |
|   <65 | 96.5 | 0.1 | 40 | |
|   >65 | 95.8 | 0.1 | 121 | |
| Cancer stage | 96.0 | 0.1 | 161 | 0.12 |
|   I-IIa | 97.3 | 0.1 | 101 | |
|   IIb to IV | 93.9 | 0.2 | 60 | |
| Body mass index (BMI) | 95.8 | 0.1 | 161 | **0.06*** |
|   <25 | 99.4 | 0.1 | 36 | |
|   25-30 | 92.2 | 0.2 | 54 | |
|   >30 | 97.5 | 0.1 | 54 | |
|   Unknown | 97.9 | 0.0 | 17 | |
| Body surface area (BSA) | 95.8 | 0.1 | 161 | 0.20 |
|   <1.99 | 95.0 | 0.2 | 113 | |
|   >2.00 | 98.7 | 0.0 | 31 | |
|   Unknown | 97.9 | 0.0 | 17 | |
| Hormone receptor status | 95.8 | 0.1 | 161 | **0.02**** |
|   ER+ | 97.1 | 0.1 | 102 | **0.08*** |
|   ER- | 92.6 | 0.2 | 42 | |
|   PR Status | 95.8 | 0.1 | 74 | 0.90 |
|   PR- | 95.8 | 0.2 | 69 | |
|   PR Unknown | 91.7 | n/a | 1 | |
|   HER2+ | 98.9 | 0.1 | 42 | **0.08*** |
|   HER2- | 94.3 | 0.2 | 95 | |
|   HER2 unknown | 97.7 | 0.0 | 7 | |
| Menopausal status | 95.8 | 0.1 | 161 | 0.36 |
|   Pre | 97.6 | 0.1 | 51 | |
|   Post | 95.5 | 0.2 | 86 | |
|   Unknown | 86.5 | 0.3 | 7 | |

NOTE: *p < .10; **p < .05;Variables with less than n = 161 indicate missing data; ER+ = Estrogen Receptor positive, ER- = Estrogen Receptor negative, PR+ = Progesterone receptor positive, PR- = Progesterone receptor negative, HER2+ = human epidermal growth factor receptor 2 overexpression, HER2- = no overexpression of human epidermal growth factor receptor 2.

## 4. Discussion

This patient-centered, holistic approach contributed to BC patients achieving an impressive, overall RDI of 96%, which is over 10% higher than the recommended 85% RDI for optimal BC treatment outcomes. In fact, 92% of patients met or exceeded 85% RDI. Every treatment regimen had an RDI above 91.5% (highest RDI = 99.8% for FEC), with the exception of FAC, which had an RDI of 76.7%. Relative dose intensity was significantly higher in women who: (1) had a low BMI (<25); (2) were ER+; and/or (3) HER2+. The majority of patients (83.9%) received treatments on time, and delays happened the most for AC-T and TAC (but RDI was 95 and 95.6% RDI respectively, suggesting delays did not impact treatment efficacy). There were only two patient-requested treatment delays (i.e., injury, no show), while other delays were clinically advised. Overall, these findingssuggest this patient-centered and individualized approach, including continual reminders about of avoiding delays, was effective in achieving an ideal RDI. The current results are consistent with Ng et al.'s (2017) conceptualization of BC patients as benefitting greatly when their physical, social, psychological, emotional, and spiritual needs are met, especially in terms of optimal health outcomes (in line with Maslow's Hierarchy of Needs Theory) [12,16].

### 4.1. Age

Traditionally, BC patients older than 65 years have a reduced RDI (<85%) due to limited clinical trials with older individuals, leading clinicians to prescribe a reduced dosage for frailty concerns [6]. This study did not find an age-RDI association, but as suggested [6], there is under-representation of older adults in oncology research. Indeed, recent research found limited age-RDI differences [6], providing support for the current findings. However, the current results do show slightly higher RDI in older adults than other research. Lyman and colleagues [6] indicated 81.2% of BC patients >65 years had an RDI > 85%, compared to 90% in this study; 84.6% of the Lyman patients <65 had an RDI > 85%, compared to 92.6% in this study. Another study reported a mean RDI of 86.7% among patients <65 and 85.5% for patients >65 [2], compared to 95.8% and 96.5%, respectively, in this study. Thus, the Ghosh Clinic had higher RDI for patients of any age; whether RDI differences translate to clinical outcomes merits further investigation.

### 4.2. Body mass index and body surface area

Patients with a relatively high BMI (i.e., obese) and BSA are more at-risk for RDI < 85% [6] due to possible under-treatment of obese patients. Chemotherapy dose is determined by a standardized, weight-based calculation, and some patients exceed the weight limits for standardized dosing, therefore receiving a lower dose than perhaps needed [6]. While previous research found that patients with a higher BSA (>2.00 $m^2$) had a lower RDI [2,6], BSA and BMI were not associated with RDI in the current study. However, when examined as a categorical variable, patients with a BMI < 25 had a significantly higher RDI (99.4%) than those with a BMI of 25 to 30 (92.2%). That said, these percentages both exceed the necessary 85% for treatment effectiveness, so they all likely experience the same clinical benefits, regardless of BMI category.

### 4.3. Hormone status

Relative dose intensity was significantly associated with being ER+ (97.1%) and/or HER2+ (98.9%), when compared to being ER- (92.6%) or HER- (94.3%). However, the mean RDI of ER- or HER2- patients was still higher than 85%, suggesting hormone status likely did not affect clinical outcomes. While hormone receptor status was explored previously, no significance was reported [6]. Hormone receptor status should be examined in future studies to ascertain whether these results are unique to this clinic, or generalizable to other BC patients.

Consistent with prior research [6], RDI was not associated with menopausal status. Adjuvant BC chemotherapy can reduce mortality in premenopausal patients by 30% and relapse by 37%; Adjuvant chemotherapy reduces mortality and relapse 12%, and 19%, respectively, in postmenopausal women [4]. Thus, the association between menopause and BC outcomes appears not to be a result of RDI, but future studies should explore this correlation.

### 4.4. Cancer stage

RDI and cancer stage were not significantly related, similar to some prior research [2,4]. However, Lyman and colleagues [6] reported stage IIb to IIIa disease was associated with RDI < 85%, but they did not include the specific data to allow between-study comparisons. The current study's RDI for each stage was 7 to 12% higher than the Lyman study, but Lyman et al. reported RDI >85% for all stages, suggesting similar treatment effectiveness for both studies.

### 4.5. Treatment regimen

The most prescribed treatment was AC-T (RDI = 95%), consistent with other clinics, as the use of AC-T has generally increased [6]. National Comprehensive Cancer Network (NCCN)-preferred therapies include AC and AC-T, followed by TC [6], each of which was commonly used in this study. This suggests the Ghosh Clinic chemotherapy regimens are used with similar frequency as other centers nationally, yet still exceed the recommended 85% RDI. Moreover, since FAC had an RDI of only 76.7%, future prescriptions of FAC might consider its reduced RDI when deciding whether to use it since this can limit treatment effectiveness. Indeed, FAC is no longer used at the Ghosh Clinic due to toxicity exceeding treatment benefits. In general, the mean RDI for each treatment in this study was higher than prior research: Whereas RDI per treatment regimen in the current study was 99.6% (TC), 98.9% (AC), 95% (AC-T), and 94.8% (TCH), previous research reported RDI rates of 93%, 96%, 94%, and 91%, respectively for each treatment regimen [6]. That said, the previous study also found RDI > 85% for all treatments, suggesting both studies reached adequate RDI for optimal outcomes.

## 5. Limitations

Contains missing data, limiting the ability to determine. The patient medical charts did not include detailed data on complementary therapy participation (e.g., exact minutes per sessoin, frequency per patient), disallowing assessment of dose-response relationships in patient outcomes. It was also challenging to analyze certain demographic and clinical characteristics due to small samples sizes within groups (e.g., $n = 6$ receiving FAC), limiting the ability to evaluate the effects of patient variables on RDI. Most of the BC patients (63%) had I-IIa stage cancers, so these results might only generalize to lower stages of BC. Finally, this was a Midwestern clinic, with little racial and ethnic diversity, limiting generalizability.

## 6. Conclusions

A non-pharmacologic, holistic BC approach led to an RDI 11% higher (i.e., 96%) than the recommended 85% RDI for optimal treatment outcomes (92% of patients' RDI exceeded 85%). RDI was significantly associated with BMI and being ER+ and HER2+. Additionally, this patient-centered approach led to 83.9% of patients receiving treatment on time. While a retrospective analysis disallows examination of the specific effects of each complementary approaches, this study provides preliminary evidence of its potential benefits for people with BC. Subsequent, prospective studies are needed to determine the role of each component (e.g., patient education, nutritional counseling, yoga) on RDI, including whether there is an optimal dose and/or timing of these CAM tools. Future research should examine this approach for other cancers to determine if similar benefits are observed.

## References

[1] S.B. Giordano, W. Gradishar, BC: updates and advances in 2016, Curr. Opin. Obstet. Gynecol. 29 (2017) 12–17, doi:http://dx.doi.org/10.1097/GCO.0000000000000343.

[2] D.A. Griffin, B. Penprase, J.F. Klamerus, Relative dose intensity–improving treatment and outcomes in early-stage BC: a retrospective study, Oncol. Nurs. Forum 39 (2012) E459–E467, doi:http://dx.doi.org/10.1188/12.ONF.E459-E467.

[3] Amgen: Increasing awareness of relative dose intensity in an evidence-based practice, 9/08 update. http://www.onsedge.com/pdf/amgenEBP.pdf.

[4] S. Raza, S. Welch, J. Younus, Relative dose intensity delivered to patients with early BC: Canadian experience, Curr. Oncol. 16 (2009) 8–12.

[5] C. Uptigrove, K. Vavra, C. Saadeh, G. Srkalovic, Relative dose intensity of systemic chemotherapy in an outpatient cancer center, Acta Medica Academica 39 (2010) 144–149.

[6] G.H. Lyman, D.C. Dale, D. Tomita, S. Whittaker, J. Crawford, A retrospective evaluation of chemotherapy dose intensity and supportive care for early-stage BC in a curative setting, BC Res. Treat. 139 (2013) 863–872.

[7] C. Brems, J. Barnett, V.C. Parret, J. Metzger, M.E. Johnson, Alternative and complementary treatment needs and experiences of women with breast cancer, J. Altern. Complement. Med. 19 (2013) 657–663, doi:http://dx.doi.org/10.1089/acm.2012.0161.

[8] H. Greenlee, M.J. DuPont-Reyes, L.G. Balneaves, L.E. Carlson, M.R. Cohen, G. Deng, et al., Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment, CA: Cancer J. Clin. (2017).

[9] H. Cramer, S. Lange, P. Klose, A. Paul, G. Dobos, Yoga for BC patients and survivors: a systematic review and meta-analysis, BMC Cancer 12 (2012) 412–424, doi:http://dx.doi.org/10.1186/1471-2407-12-412.

[10] J. Hart, Yoga as an adjunctive therapy in the clinical setting, Altern. Complement. Ther. 19 (2013) 89–93, doi:http://dx.doi.org/10.1089/act.2013.19204.

[11] M.S. Rosenbaum, J. Van de Velde, The effects of yoga, massage, and reiki on patient Well-being at a cancer resource center, Clin. J. Oncol. Nurs. 20 (2016) E77–E81, doi:http://dx.doi.org/10.1188/16.CJON.E77-E81.

[12] A.H. Maslow, Motivation and Personality, 3rd ed., Pearson Education, Delhi, India, 1987.

[13] N.E. Adler, A.E.K. Page, The Psychosocial Needs of Cancer Patients (Accessed on 14 November 2016)]. Committee on Psychosocial Services to Cancer Patients/Families in a Community Setting; Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs. Available online:, 1st ed., National Academies Press, Washington, DC, USA, 2008. https://www.ncbi.nlm.nih.gov/books/NBK4011/.

[14] S. Schmid-Büchi, R.J. Halfens, T. Dassen, B. Van Den Borne, A review of psychosocial needs of breast-cancer patients and their relatives, J. Clin. Nurs. 17 (2008) 2895–2909, doi:http://dx.doi.org/10.1111/j.1365-2702.2008.02490.x [PubMed] [Cross Ref].

[15] G.H. Ho, B.L. Tan, Implementing Breast Cancer Survivorship Programme; Proceedings of the 3rd Regional Oncology Nursing Conference; Singapore. 18 January 2013; Accessed on 18 December 2016)]. Available online: https://www.nccs.com.sg/documents/ronc/conference_slides/Con_17Jan_Breast_Care_Survivorship_Programme_NCCS.pdf.

[16] Z.X. Ng, M.S. Ong, T. Jegadeesan, S. Deng, C.T. Yap, Breast cancer: exploring the facts and holistic needs during and beyond treatment, Healthcare 5 (2) (2017) p. 26. Multidisciplinary Digital Publishing Institute.

[17] M. Rejali, M. Tazhibi, F. Mokarian, N. Gharanjik, R. Mokarian, The performance of the Nottingham prognosis index and the adjuvant online decision-making tool for prognosis in early-stage breast cancer patients, Int. J. Prevent. Med. 6 (2015) 93, doi:http://dx.doi.org/10.4103/2008-7802.166503 Published online 2015 Oct 1.

[18] A. Fisher, Web-based system for self-reporting symptoms helps patients live longer, ASCO: Am. Soc. Clin. Oncol. (2017). Retrieved from: https://www.asco.org/about-asco/press-center/news-releases/web-based-system-self-reporting-symptoms-helps-patients-live.

[19] M.L. Galantino, L. Green, J.A. DeCesari, N.A. MacKain, S.M. Rinaldi, M.E. Stevens, et al., Safety and feasibility of modified chair-yoga on functional outcome among elderly at risk for falls, Int. J. Yoga 5 (2) (2012) 146–150, doi:http://dx.doi.org/10.4103/0973-6131.98242.

[20] D.E. McManus, Reiki is better than placebo and has broad potential as a complementary health therapy, J. Evid.-Based Complement. Altern. Med. 22 (4) (2017) 1051–1057.

[21] X. Chen, Y. Zheng, W. Zheng, K. Gu, Z. Chen, W. Lu, X.O. Shu, The effect of regular exercise on quality of life among breast cancer survivors, Am. J. Epidemiol. 170 (7) (2009) 854–862.

[22] H.M. Fisher, J. Jacobs, C.J. Taub, S. Lechner, J.E. Lewis, C.S. Carver, et al., How changes in physical activity relate to fatigue interference, mood, and quality of life during treatment for non-metastatic breast cancer, Gen. Hosp. Psychiatry (2017).

[23] A.S. Levine, J. Balk, Yoga and quality-of-life improvement in patients with breast cancer: a literature review, Int. J. Yoga Ther. 22 (1) (2012) 95–100.

[24] H. Cramer, R. Lauche, P. Klose, S. Lange, J. Langhorst, G.J. Dobos, Yoga for improving health-related quality of life, mental health and cancer-related symptoms in women diagnosed with breast cancer, Cochrane Libr. (2017).

[25] M.N. Kirshbaum, M. Stead, S. Bartys, An exploratory study of reiki experiences in women who have cancer, Int. J. Palliat. Nurs. 22 (2016) 166–172.

[26] C. Doyle, L.H. Kushi, T. Byers, K.S. Courneya, W. DemarkWahnefried, B. Grant, et al., Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices, CA: Cancer J. Clin. 56 (6) (2006) 323–353.

[27] R.E. Rossi, M. Pericleous, D. Mandair, T. Whyand, M.E. Caplin, The role of dietary factors in prevention and progression of breast cancer, Anticancer Res. 34 (12) (2014) 6861–6875.

[28] J.H. Chelf, P. Agre, A. Axelrod, L. Cheney, D.D. Cole, K. Conrad, et al., Cancer-related patient education: an overview of the last decade of evaluation and research, Oncol. Nurs. Forum (7) (2001) 28.

[29] P. Ravasco, I. Monteiro-Grillo, P.M. Vidal, M.E. Camilo, Dietary counseling improves patient outcomes: a prospective, randomized, controlled trial in colorectal cancer patients undergoing radiotherapy, J. Clin. Oncol. 23 (7) (2005) 1431–1438.

[30] IBM Corp, IBM SPSS Statistics for Windows, Version 24.0, IBM Corp, Armonk, NY, 2016.