Critical Reviews in Oncology / Hematology 129 (2018) 54–66

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Clinical implication of changes in body composition and weight in patients with early-stage and metastatic breast cancer

Ilaria Trestini[a,1], Luisa Carbognin[a,1], Sara Monteverdi[a], Sara Zanelli[a], Alessandro De Toma[a], Clelia Bonaiuto[a], Rolando Nortilli[a], Elena Fiorio[a], Sara Pilotto[a], Massimo Di Maio[b], Antonio Gasbarrini[c], Giovanni Scambia[d], Giampaolo Tortora[a,2], Emilio Bria[e,*,2]

[a] U.O.C. Oncology, University of Verona, Azienda Ospedaliera Universitaria Integrata, Verona, Italy
[b] SCDU Medical Oncology, Ordine Mauriziano Hospital, Department of Oncology, University of Torino, Torino, Italy
[c] Gastroenterology and Hepatology Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Roma, Italy
[d] Division of Gynecologic Oncology, Department of Woman and Child Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Roma, Italy
[e] Medical Oncology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Roma, Italy

ARTICLE INFO

Keywords:
Breast cancer
Body mass index
BMI
Weight gain
Body composition
Prognosis
Toxicity

ABSTRACT

Breast cancer represents the most frequent cancer among women in Western countries. Although physicians and patients have witnessed a significant evolution in both treatment strategies and personalized medicine (the identification of featured patients' subsets such as HER2-driven disease), the identification of additional prognostic clinical predictors referring to patients' dietary habits represents a research area aiming to further improve the overall management of this disease. In this regard, body composition (i.e. the relative proportion of fat and muscles) and its changes have recently generated growing interest. A large body of evidence supports the relationship between overweight or weight gain and poor outcome in patients with early-stage breast cancer during adjuvant, and more recently, also neoadjuvant therapy. Nevertheless, available data on post-diagnosis weight variations and mortality report controversial results. Indeed, the limited data produced in the metastatic setting do not indicate an impact of body size on the outcome of these patients. With these perspectives, this review aims to elucidate the complex association between weight, body composition and breast cancer outcome, across the different settings of such disease. The more recent and important findings are highlighted, emphasizing the potential role of body composition assessment to predict individualize chemotherapy dosing, toxicity and efficacy, in order to improve the overall health status and prognosis of such still to date growing patients' population.

1. Introduction

Breast cancer (BC) represents the most common cancer and the second cause of cancer-related mortality among women in developed countries. The number of women living with a BC continues to grow, due to advances in early detection and targeted treatment strategies (Siegel et al., 2018).

The discovery of new clinical and biological predictors, in addition to the well-defined prognostic factors, as tumor size, lymph node status, histological type, and immunophenotypical characteristics, represents one of the main goals of ongoing research, in order to improve the overall management of BC. In this regard, overweight and obesity (identified by having a body mass index (BMI) of 25–30.0 kg/m^2 and a BMI ≥ 30.0 kg/m^2, respectively), weight gain and body composition measures have received increasing attention as potential prognostic and predictor factors of toxicity in BC (Kroenke et al., 2005; Chen et al., 2010; Shachar et al., 2016; Thivat et al., 2010; Bradshaw et al., 2012), besides the well-known role as risk factors for the development of BC, particularly in the postmenopausal setting (van den Brandt et al., 2000; Cotterchio et al., 2003; De Pergola and Silvestris, 2013).

The results of the National Health Interview Surveys, a cross-sectional survey in the United States from 1997 to 2014, highlighted a statistically significant annual trend in increasing obesity prevalence in BC survivors (3.0%) ($p < 0.001$) (Greenlee et al., 2016). Moreover, a

* Corresponding author at: Medical Oncology, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario A. Gemelli'IRCCS, Roma, Italy.
E-mail address: emilio.bria@unicatt.it (E. Bria).
[1] These authors share first co-authorship.
[2] These authors share last co-authorship.

https://doi.org/10.1016/j.critrevonc.2018.06.011
Received 6 May 2018; Received in revised form 28 May 2018; Accepted 15 June 2018

series of clinical trials have observed that the excess of weight in pre- and postmenopausal BC patients is associated with higher recurrence rate and poorer survival compared to normal weight (Ewertz et al., 2011; Cecchini et al., 2016; Kamineni et al., 2013). This negative prognostic effect of obesity was additionally supported by several meta-analyses (Niraula et al., 2012; Cheraghi et al., 2012; Protani et al., 2010).

The variation of weight represents a frequent condition during and after treatment for BC (Vance et al., 2011; Irwin et al., 2005; Demark-Wahnefried et al., 2001), due to changes in metabolism, food intake, decreased energy expenditure and physical activity (Champ et al., 2012). Particularly, the weight gain following a diagnosis of early-stage BC seems to predict poor survival (Chen et al., 2010; Bradshaw et al., 2012), despite the impact is not consistent in all studies (Caan et al., 2012; Cespedes Feliciano et al., 2017a). In addition, patients do not easily lose the extra weight after the end of treatment, with negative consequences on self-image, quality of life and overall health (Makari-Judson et al., 2007; Saquib et al., 2007).

Besides the weight gain, patients affected by BC reported unfavourable changes in body composition, with a significant increase in the percent of adipose tissue along with a decrease in lean body mass (Vance et al., 2011; Wang et al., 2010). In this regard, the body composition has emerged as an important prognostic factor in cancer patients (Shachar et al., 2016; Fearon et al., 2011). Particularly, a series of studies in BC have explored the association between loss of skeletal muscle and treatment outcomes in early-stage (Shachar et al., 2017a) and metastatic disease (Shachar et al., 2017b), raising the potential use of body composition assessment to predict toxicity, tailor dosing and improve treatment planning.

Given these perspectives, the aim of this review was to explore the complex association between weight, body composition and BC outcome, across the different settings of such disease. The more recent and relevant findings are highlighted, emphasizing the potential role of body composition assessment to predict outcome, toxicity and individualize chemotherapy dosing.

1.1. Weight changes following BC diagnosis

The majority of patients experience weight changes after BC diagnosis (Chlebowski et al., 2002). In this regard, the first reports suggested that 50–96% of women with early-stage disease experience significant weight gain during the treatment phase (Vance et al., 2011; Demark-Wahnefried et al., 2012). Furthermore, other studies showed that weight change continues progressively for some years after diagnosis, even in patients whose weight remains stable during treatment (Demark-Wahnefried et al., 2001). In this context, a retrospective study of 185 women diagnosed with BC in stage I-III found that the mean weight change across all women was +1.5 kg at year one from diagnosis, +2.7 kg at year two and +2.8 kg at year three, suggesting that weight gain is persistent after diagnosis (Makari-Judson et al., 2007). This aspect was also observed in a long-term follow-up study, in which the risk of weight gain was positively related to the time elapsed since diagnosis (adjusted Odds Ratio (OR) = 1.19/year, 95% Confidence Interval (CI) 1.04–1.36) (Sedjo et al., 2014).

Despite a large body of literature has reported weight gain in women after BC diagnosis, the causal factors underlying such change remain unclear (Raghavendra et al., 2018). A series of studies suggested that the weight gain may be attributable to the effect of some treatment regimens (Playdon et al., 2015). Moreover, this effect is highly related to the type and duration of therapies. Several investigations in this area suggested that the weight gain is greater among women who receive chemotherapy as part of their treatment, even if most analyses failed to specify the chemotherapy regimens (Sedjo et al., 2014; Basaran et al., 2011), compared with women who received hormonal treatment only, or no systemic treatment (Goodwin et al., 1999). Early evidence describing weight gain observed that adjuvant chemotherapy, included long duration treatments of non-anthracycline containing regimens such as cyclophosphamide, methotrexate, and fluorouracil (CMF), was associated with changes of up to median 8–10 kg (Makari-Judson et al., 2014). The Women's Healthy Eating and Living (WHEL) study, a prospective randomized clinical trial that included 3088 BC patients, reported an association of weight gain with chemotherapy (OR = 1.65, 95% CI 1.12–2.43, $p = 0.01$), for both anthracycline and non-anthracycline regimens (OR = 1.63, $p = 0.01$ and OR = 1.79, $p = 0.003$, respectively). In particular, all the chemotherapies (Adriamycin and Cyclophosphamide (AC): OR = 1.55, $p = 0.01$; Cyclophosphamide, Adriamycin and Fluorouracil: OR = 1.83, $p = 0.003$; CMF: OR = 1.76, $p = 0.004$) were related to weight gain, without a significant difference between one and the other (Saquib et al., 2007).

In more recent studies, including also taxanes, the weight gain is reported with a lower prevalence (35–85%) and a lesser degree than earlier studies, with a weight gain varying between median 1.4–5.0 kg (Makari-Judson et al., 2014).

The underlying mechanism contributing to the weight change during chemotherapy is unclear. It may be promoted by common treatment-related side effects such as fatigue, changes in dietary eating patterns, induced by alterations in taste and smell, and a significant reduction in physical activity and in basal metabolic rate, which may lead to an impairment in energy balance (van den Berg et al., 2017).

Furthermore, a series of evidence suggested that premenopausal status at BC diagnosis may be a strong predictor of weight gain (Thomson and Reeves, 2017; Gu et al., 2010). In this regard, a recent retrospective study, assessing a cohort of 1282 women with a diagnosis of stage I–III, hormone receptor-positive, HER2-negative BC, who had completed 5 years of adjuvant endocrine therapy (54.8% of patients received prior chemotherapy), identified that women who were premenopausal at diagnosis were 1.40 times more likely than women who were postmenopausal at diagnosis to have a > 5% weight gain (OR = 1.40, 95% CI 1.01–1.93, $p = 0.040$) (Raghavendra et al., 2018). This effect seems to be mediated by premature ovarian failure induced by treatment, which may produce adverse changes in fat distribution and a decrease in lean body mass, promoting weight gain (Thomson and Reeves, 2017).

Unlike chemotherapy, hormonal treatment seems to be less often associated with significant weight change, even if the evidence is uncertain (Sedjo et al., 2014; Mortimer and Behrendt, 2013; Sadim et al., 2017; Vagenas et al., 2015; Aiello Bowles et al., 2012). In this regard, tamoxifen or aromatase inhibitors treatment alone (without chemotherapy) do not appear to significantly impact on body weight (Saquib et al., 2007; Goodwin et al., 1999; Fisher et al., 1998; McTiernan, 2018). Moreover, the ATAC trial, a large randomized study of early-stage postmenopausal BC patients, showed no statistically significant differences in weight gain between anastrozole and tamoxifen after 12 months of follow-up (+1.4 kg vs. +1.5 kg, $p = 0.4$) (Sestak et al., 2012). Recently, the Italian FATA-GIM3 study, a randomized phase 3 trial, showed a prevalence of grade 1–2 and grade 3 weight gain of 4% and < 1%, respectively, in the upfront treatment strategy (5 years of aromatase inhibitors). In the switch schedule (aromatase inhibitors were administered after 2 years of Tamoxifen) the prevalence of grade 1–2 and grade 3 weight gain was 5% and < 1%, respectively. No differences in weight gain were observed according to the three aromatase inhibitors adopted (letrozole, exemestane or anastrozole) (De Placido et al., 2018).

1.2. Body composition variation following BC diagnosis and treatment

Several studies have identified a shift in body composition following BC diagnosis and treatment, with an increase in adipose tissue and a reduction of lean tissue, with the development of sarcopenic obesity, independent of the amount of weight gain and BMI (Thomson and Reeves, 2017; Deluche et al., 2018). The BMI, which can be easily determined, is used in most studies as a simple and reliable surrogate