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Title:

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

Authors:

Ilaria Trestini^{1#}, Luisa Carbognin^{1,2#}, Sara Monteverdi¹, Sara Zanelli¹, Alessandro De Toma¹, Clelia Bonaiuto¹, Rolando Nortilli¹, Elena Fiorio¹, Sara Pilotto¹, Roberto Iacovelli¹, Massimo Di Maio³, Giampaolo Tortora^{1*}, Emilio Bria^{1,4*}.

these authors share first co-authorship.

* these authors share last co-authorship.

Affiliations:

¹U.O.C. Oncology, University of Verona, Azienda Ospedaliera Universitaria Integrata, Verona, Italy.

²Ginecologia Oncologica, Università Cattolica del Sacro Cuore, Fondazione Policlinico 'A. Gemelli', Roma, Italy.

³

⁴ Oncologia Medica, Università Cattolica del Sacro Cuore, Fondazione Policlinico 'A. Gemelli', Roma, Italy.

Corresponding author:

Prof. Emilio Bria, Oncologia Medica, Università Cattolica del Sacro Cuore, Fondazione Policlinico 'A. Gemelli', Roma, Italy, ph.: +3906-30154953, fax: +3906-30154838, e-mail: emiliobria@yahoo.it.

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, a series of data on post-diagnosis weight variations and mortality reports controversial results. Indeed, the limited available data in the metastatic disease 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.

Key-words: Breast cancer; Body Mass Index; weight gain; body composition; prognosis.

2 **Introduction.**

3 Breast cancer (BC) represents the most common cancer and the second cause of cancer-related mortality
4 among women in developed countries. The number of women living with a BC continues to grow due to
5 advances in early detection and targeted treatment strategies [1].

6 The discovery of new clinical and biological predictors, in addition to the well-defined prognostic factors, as
7 tumor size, lymph node status, histological type, and immunophenotypical characteristics, represents one of
8 the main goals of ongoing research in order to improve the overall management of BC. In this regard,
9 overweight and obesity, (identified by having a body mass index (BMI) of 25 to 30.0 kg/m² and a BMI
10 ≥ 30.0 kg/m², respectively), weight gain and body composition measures have received increasing attention
11 as potential prognostic and predictor factors of toxicity in BC [2-6], besides the well-known role as risk
12 factors for the development of BC, particularly in the postmenopausal setting [7-9].

13 The results of the National Health Interview Surveys, a cross-sectional survey in the United States from 1997
14 to 2014, highlighted a statistically significant annual trend in increasing obesity prevalence in BC survivors
15 (3.0%) ($p < 0.001$) [10]. Moreover, a series of clinical trials have observed that the excess of weight in pre-
16 and postmenopausal BC patients is associated with higher recurrence rate and poorer survival compared to
17 normal weight [11-13]. This negative prognostic effect of obesity was additionally supported by several
18 meta-analyses [14-16].

19 The variation of weight represents a frequent condition during and after treatment for BC [17-19], due to
20 changes in metabolism, food intake, decreased energy expenditure and physical activity [20]. Particularly,
21 the weight gain following a diagnosis of early-stage BC seems to predict poor survival [3, 6], despite the
22 impact is not consistent in all studies [21, 22]. In addition, patients do not easily lose the extra weight after
23 the end treatment, with negative consequences on patient self-image, quality of life and overall health [23,
24 24].

25 Besides the weight gain, patients affected by BC reported unfavourable changes in body composition, with a
26 significant increase in the percent of adipose tissue and decreases of lean body mass [17, 25]. In this regard,
27 the body composition has emerged as an important prognostic factor in cancer patients [4, 26]. Particularly, a
28 series of studies in BC have explored the association between loss of skeletal muscle and treatment outcomes
29 in early-stage [27] and metastatic disease, raising the potential use of body composition assessment to predict
30 toxicity, tailor dosing and improve treatment planning [28].

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

35 **Weight changes following BC diagnosis.**

36 The majority of patients experience weight changes after BC diagnosis [29]. In this regard, the first reports
37 suggested that 50–96% of women with early-stage disease experience significant weight gain during the

38 treatment phase [17, 30]. Furthermore, other studies showed that weight change continues progressively for
39 some years after diagnosis, even in patients who remain weight stable during treatment [19]. In this context,
40 a retrospective study of 185 women diagnosed with stage I-III of BC found that the mean weight change
41 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,
42 suggesting that weight gain is persistent after diagnosis [23]. This aspect was also observed in a long-term
43 follow-up study in which the risk of weight gain was positively related to the time elapsed since diagnosis
44 (adjusted Odds Ratio (OR)=1.19/year, 95% Confidence Interval (CI) 1.04-1.36) [31].

45 Despite a large body of literature has reported weight gain in women after diagnosis of BC, the causal factors
46 underlying such change remain unclear [32]. A series of studies suggested that the weight gain may be
47 attributable to the effects of some treatment regimens [33]. Moreover, this effect is highly related to the type
48 and duration of therapies. Several investigations in this area suggested that the weight gain is greater among
49 women who receive chemotherapy as part of their treatment, even if most analyses failed to specify the
50 chemotherapy regimens [31, 34], compared with women who received hormonal treatment or no systemic
51 treatment [35]. Early evidence describing weight gain observed that adjuvant chemotherapy, included long
52 duration treatments of non-anthracycline containing regimens such as CMF, was associated with changes of
53 up to 8-10 kg [36]. The Women's Healthy Eating and Living (WHEL) study, a prospective randomized
54 clinical trial that included 3088 BC patients, reported an association of weight gain with chemotherapy
55 (OR=1.65, 95% CI 1.12-2.43, $p=0.01$), for both anthracycline and non-anthracycline regimens (OR=1.63,
56 $p=0.01$ and OR=1.79, $p=0.003$, respectively). In particular, all the chemotherapies (Adriamycin and
57 Cyclophosphamide (AC): OR=1.55, $p=0.01$; Cyclophosphamide, Adriamycin and Fluorouracil: OR=1.83,
58 $p=0.003$; cyclophosphamide, methotrexate, and fluorouracil (CMF): OR=1.76, $p=0.004$) were related to
59 weight gain, without a significant difference between one and the other [24].

60 In more recent studies, including also taxanes, the weight gain is reported with a lower prevalence (35-85%)
61 and lesser degree than earlier studies, with a weight gain varying between 1.4 to 5.0 kg [36].

62 The underlying mechanism contributing to the weight change during chemotherapy is unclear. It may be
63 promoted by common treatment-related side effects such as fatigue, changes in dietary eating patterns,
64 induced by alternations in taste and smell, and a significant reduction in physical activity and in basal
65 metabolic rate, which may lead to an impairment in energy balance [37].

66 Furthermore, a series of evidence suggested that premenopausal status at BC diagnosis may be a strong
67 predictor of weight gain [38, 39]. In this regard, a recent retrospective study, assessing a cohort of 1282
68 women with a diagnosis of stage I-III, hormone receptor-positive, HER2-negative BC, who had completed 5
69 years of adjuvant endocrine therapy, identified that women who were premenopausal at diagnosis were 1.40
70 times more likely than women who were postmenopausal at diagnosis to have a >5% weight gain (OR=1.40,
71 95% CI 1.01-1.93, $p=0.040$) [32]. This effect seems to be mediated by premature ovarian failure which may
72 produce adverse changes in fat distribution and a decrease in lean body mass, promoting weight gain [38].

73 Unlike chemotherapy, hormonal treatment seems to be less often associated with significant weight change,
74 even if the evidence is uncertain [31, 40-43]. In this regard, tamoxifen or aromatase inhibitors treatment

75 alone (without chemotherapy) do not appear to significantly impact on body weight [24, 35, 44, 45].
76 Moreover, the ATAC trial, a large randomized study of early-stage postmenopausal BC patients, showed no
77 statistically significant differences in weight gain between anastrozole and tamoxifen after 12 months of
78 follow-up (+1.4 kg vs. +1.5 kg, $p=0.4$) [46].

79 **Body composition variation following BC diagnosis.**

80 Several studies have identified a shift in body composition, with an increase in adipose tissue and a reduction
81 of lean tissue, with the development of sarcopenic obesity, independent of the amount of weight gain and
82 BMI [38, 47]. The BMI, which can be easily determined, is used in most studies as a simple and reliable
83 surrogate measure for obesity, even if it fails to discriminate between proportions of fat and lean tissues [48,
84 49].

85 To further underline this difference, more precise methodologies have been adopted in recent studies, such as
86 the development of image analysis methods (ex. dual X-ray absorptiometry (DXA) scans and computed
87 tomography (CT)), and the bioelectric impedance analyzer (BIA).

88 In this regard, an observational study, evaluating the body composition by DXA in women receiving
89 chemotherapy (AC or AC followed by paclitaxel), found that patients who were of normal weight at the time
90 of BC diagnosis were more likely to gain in body fat (besides in body weight) than overweight or obese
91 women. Indeed, baseline BMI was inversely related to gains in weight ($p=0.01$) and fat mass in the torso
92 ($p=0.006$) [50]. Moreover, *Freedman et al.*[51] analyzed data from a prospective study in 20 women with
93 Stage I-III BC receiving adjuvant chemotherapy. This small study did not report
94 significant changes in weight during the treatment. However, the investigators showed
95 unfavorable changes in body composition. Indeed, the percentage of body fat, assessed by DXA, increased
96 (+0.9 +/-1.6%; $p=0.02$) and the bone mineral content decreased (-0.02 +/- 0.04 kg; $p=0.02$). Furthermore,
97 using CT, an unfavorable change of decrease in the ratio of visceral adipose tissue to subcutaneous fat was
98 detected (-0.02 +/- 0.05 ml; $p=0.02$).

99 Besides the adiposity, the evaluation of the depletion of muscle mass (MM), implicated in the definition of
100 sarcopenia, represents a relevant aspect in the nutritional assessment of cancer patients, due to the high
101 prevalence in the oncology setting [52]. In this context, *Villaseñor et al.* [53] investigated the prevalence of
102 sarcopenia, assessed by DXA scans in a cohort of women diagnosed with invasive BC (stages I-III A).
103 Sarcopenia was defined as two standard deviations below the young healthy adult female mean of
104 appendicular lean mass divided by height squared ($< 5.45 \text{ kg/m}^2$). The authors showed that among the 471
105 women included in this study, 75 (16%) were sarcopenic, with 38% of these women classified as obese (total
106 body fat percentage, $\geq 38\%$) and 61% as not obese ($< 38\%$). In addition, a recent retrospective study,
107 conducted by *Deluche et al.* in patients with early BC, evaluated the prevalence of sarcopenia (defined as
108 skeletal muscle index at the third lumbar vertebra (L3) $< 41 \text{ cm}^2/\text{m}^2$) by CT used for disease staging. The
109 authors found that among the 119 evaluable patients, 58 (48.8%) were sarcopenic, whose 22 patients had a
110 BMI $\geq 25 \text{ kg/m}^2$ [47]. This study detected a greater prevalence of sarcopenia compared to the results of

111 Villaseñor *et al.* probably because DXA scans is less accurate than CT for the evaluation of sarcopenia,
112 although both methods were validated.

113 Overall, sarcopenia was more common in women who were older at diagnosis, generally in post-menopause
114 [47, 53]. Therefore, the menopause status seems to cause marked changes in body composition, thorough a
115 redistribution of the pattern of adiposity, with an increase in visceral fat mass [54, 55]. In this regard, a
116 retrospective analysis of 172 BC patients who underwent surgery after neoadjuvant chemotherapy, reported a
117 statistically significant reduction of skeletal muscle area and a gain of fat, particularly visceral fat, after
118 menopause and these changes are not reflected in the BMI measures [56]. Besides the menopausal status,
119 adjuvant treatment for BC, including hormone therapy and chemotherapy, are proposed to be the major
120 contributors to the alterations in body composition [57, 58].

121 In this regard, the majority of evidence in the literature is based mostly on data generated by retrospective
122 studies [59-61], few data are available from prospective analyses.

123 A recent prospective cohort study, investigating the change in weight and body composition using BIA after
124 current standard adjuvant treatment in 95 women with BC (stage I-III), found that after 18 months, there was
125 an increase in weight of 0.9 kg (95% CI, 0.3-1.5; $p=0.003$) and an average positive association of 0.35 kg/cm
126 increased waist circumference (95% CI, 0.29-0.42 kg; $p<0.0001$). Weight gains associated with increased
127 body fat were observed mainly in premenopausal women receiving chemotherapy (1.4 kg, 95% CI 0.4-2.4;
128 $p=0.007$) [62].

129 The majority of literature regarding the assessment of body composition in BC patients were conducted in
130 the early stage setting, while few analyses included the metastatic disease. In this regard, a recent analysis
131 compared body composition measures, through CT scans at L3 lumbar segments, between patients with early
132 BC receiving adjuvant chemotherapy and metastatic BC initiating first-line chemotherapy. This study
133 reported that, although mean BMI and body surface area were similar in both groups (29.0 vs. 28.8, $p=0.84$
134 and 1.87 vs. 1.86 m², $p=0.55$, respectively), skeletal muscle index (41.3 vs. 44.7 cm²/m², $p=0.009$), skeletal
135 muscle density (29.8 vs. 36.4 Hounsfield Units, $p<0.0001$) and lean body mass (LBM, 39.3 vs. 41.9 kg,
136 $p=0.024$) were significantly lower in the metastatic cancer patients. Moreover, patients with advanced BC
137 was associated with a higher proportion of sarcopenia (defined as skeletal muscle area/height² <41) than
138 early BC (58% vs. 31%, $p=0.0016$) [63]. In this regard, the loss of MM is a common condition in patients
139 with advanced cancer. In a meta-analysis, included 7843 patients with solid tumors from 38 studies, the
140 percentage of advanced cancer patients with sarcopenia varied from 19% to 74% [4].

141 **The impact of baseline BMI and weight change on clinical outcome according to the different stages of** 142 **BC.**

143 Recent evidence has shown that overweight, obesity or underweight are correlated to adverse survival
144 outcome in women with BC [16]. In this regard, *Chan et al.* conducted the most extensive meta-analysis on
145 BMI and BC survival. The authors included 213075 BC patients from 82 prospective cohort studies and
146 analyzed total mortality and BC-specific mortality according to BMI, defined as the World Health

147 Organization criteria, at baseline and after diagnosis. Compared with normal weight women, the summary
148 relative risk (RR) for total mortality and BC-specific mortality for obese versus normal-weight patients
149 before diagnosis were 1.41 (95% CI 1.29-1.53) and 1.35 (95% CI 1.24-1.47), respectively. Furthermore, the
150 RR for total mortality were 1.07 (95% CI, 1.02-1.12) for overweight women and 1.10 (95% CI 0.92-1.31) for
151 underweight women compared with normal weight patients [64].

152 A recent study, analyzing data from a prospective cohort of approximately 5000 women with early-BC,
153 reported that high BMI at either pre- or post-diagnosis was associated with a higher risk of BC-specific
154 mortality (pre-diagnosis, HR=1.27, 95% CI 1.14-1.41, $p=0.001$; post-diagnosis, HR=1.19, 95% CI 1.04-1.36,
155 $p=0.02$) only among patients aged 65 years or older [65].

156 • **The adjuvant setting.**

157 In patients with resected BC, a growing number of studies indicated that obese women had a poorer
158 prognosis than lean women [2, 13, 66, 67].

159 In this context, a large study of 18967 patients from Denmark, suggested that obesity is an independent
160 prognostic factor for developing distant metastasis and BC death. Particularly, the investigators found that
161 the increased risk of distant recurrence was significant only in years 5 to 10 after diagnosis, with an HR of
162 1.42 (95% CI 1.17-1.73, $p<0.001$) and 1.46 (95% CI 1.11-1.92, $p=0.007$) for overweight and obese patients,
163 respectively [68].

164 Of interest, several evidence suggested that an increase in weight after early BC diagnosis could potentially
165 affect the outcomes of BC survivors, despite this effect is not consistent in all studies [30]. In this regard, a
166 meta-analysis including 12 studies found that weight gain $\geq 5\%$ compared with maintenance ($\leq \pm 5.0\%$) was
167 associated with increased all-cause mortality (HR=1.12, 95% CI 1.03-1.22, $p=0.01$). In particular, higher
168 risk of mortality was apparent for weight gain $\geq 10\%$ after diagnosis (HR=1.23, 95% CI 1.09-1.39, $p<0.001$)
169 [33]. Similarly, the retrospective study of 520 early-stage BC patients by *Fedele et al.*, showed that BMI gain
170 was a significant determinant of recurrence (95% CI 0.163-0.323, $p=0.0008$) [69]. Conversely, the recent
171 study of *Raghavendra et al.* reported that patients with a weight gain of $>5\%$ after 5 years of endocrine
172 therapy did not have an increased risk of disease recurrence (HR=0.95, 95% CI 0.62-1.47, $p=0.829$) [32].
173 These results are consistent with those reported from a study that combined a cohort of the WHEL and the
174 LACE study, which evidenced no effect of weight gain on disease recurrence [70].

175 With regard to BC histotype, a high BMI and weight gain have been reported to negatively affect the
176 outcome particularly in early BC women with hormone receptor-positive, treated with endocrine therapy [71,
177 72]. Indeed, *Robison et al.* in a study of 1155 women with luminal, HER2-negative BC, (53.8% had Stage I
178 disease and 88.9% received adjuvant endocrine therapy) reported that obesity was significantly associated
179 with an increased risk of disease recurrence (HR=1.71, 95% CI 1.12-2.62, $p=0.014$) [73].

180 In a recent study exploring BC recurrence and survival across subtypes defined by PAM50 gene expression,
181 women with Luminal A tumors and class II/III obesity at BC diagnosis had worse outcomes with an HR of
182 2.24 (95% CI 1.22-4.11) for BC-specific death and 1.24 (95% CI 1.00-1.54) for recurrence [74]. A similar
183 effect has been identified in other previous studies [75, 76].

184 The analysis of 3385 with hormone receptor-positive BC included in the National Surgical Adjuvant Breast
185 and Bowel Project B-14, a randomised placebo-controlled trial of adjuvant tamoxifen, indicated that obese
186 women had greater all-cause mortality (HR=1.31, 95% CI 1.12-1.54, $p<0.001$) and non-BC mortality
187 (HR=1.49, 95% CI 1.15-1.92, $p<0.001$) compared with normal weight women, without difference in terms
188 of BC-mortality or recurrence. Furthermore, obese women benefited from tamoxifen therapy as much as
189 leaner women [77].

190 *Sparano et al* analyzed the relation between BMI and outcome in 3 adjuvant trials coordinated by the Eastern
191 Cooperative Oncology Group that included different anthracyclines-based chemotherapy regimens. They
192 highlighted that BMI ≥ 30 kg/m² was associated with inferior DFS (HR=1.24; 95% CI 1.06-1.46, $p=0.0008$)
193 and OS (HR=1.37; 95% CI 1.13-1.67, $p=0.002$) only in patients with hormone receptor-positive early BC
194 treated with both standard chemotherapy and hormonal therapy [76]. Several studies have also suggested that
195 obesity modulated response to endocrine therapy, in particular, it seems to reduce the response to aromatase
196 inhibitors [78-80].

197 The negative prognostic effect of obesity may be related to the decrease of sex hormone binding globulin,
198 which can bind and inhibit estradiol, with a consequent increased of circulating unbound estrogen levels
199 [81], that may promote tumor progression. Moreover, excess of adiposity may intensify estrogen production
200 by the conversion of androgens by aromatase in adipose fat [45, 82]. Another potential mechanism through
201 elevated BMI may influence prognosis in tumors includes prolonged hyperinsulinemia, reduced production
202 of insulin-like growth factor binding proteins 3, resulting in elevated circulating insulin-like growth factor
203 and alteration of synthesis of adipokines and cytokines [83].

204 Recently, *Schvartsman et al.* indicated that BMI increase during adjuvant chemotherapy (within one year
205 from starting chemotherapy) of >0.5 kg/m² compared to maintaining BMI was associated with increased
206 locoregional recurrence risk (HR=2.53, 95% CI 1.18-5.45, $p=0.017$), adjusting for grade, stage, and radiation
207 delivery [84].

208 As opposed to luminal disease, the impact of BMI and weight change on outcome is not well established for
209 triple-negative BC (TNBC) [85-90]. In a recent analysis, overweight was an independent prognostic factor
210 for OS (HR=2.903, 95% CI 1.551-5.432, $p=0.001$) and DFS (HR=1.899, 95% CI 1.05-3.433, $p=0.034$) at 5
211 years in patients with TNBC. Furthermore, the menopausal status may be a mitigating factor. Indeed,
212 overweight was related to a greater risk of death (HR=2.752, 95% CI 1.267-5.978, $p=0.011$) and recurrence
213 (HR=3.242, 95% CI 1.249-8.412, $p=0.016$) only among premenopausal women, but not in postmenopausal
214 women [91]. This results are consistent with data from another analysis by *Turkoz et al.* [92], which
215 evidenced that obesity at diagnosis was associated with worse survival (HR=1.7, 95% CI 1.1-2.5, $p=0.02$)
216 and recurrence (HR=1.4, 95% CI 1.0-2.0, $p=0.04$) among premenopausal TNBC patients. Similar results for
217 TNBC, especially for the premenopausal setting, have been found in other analyses [93, 94].

218 On the contrary, the largest retrospective study published, including 2311 women with early TNBC,
219 reported no difference in DFS in patients with BMI of 25-29.9 kg/m² (HR=1.04, 95% CI 0.87-1.25, $p=0.66$)
220 and those with BMI ≥ 30 kg/m² (HR=0.99, 95% CI 0.83-1.18; $p=0.89$) compared with patients with BMI <25

221 kg/m²[87]. Similarly, no impact of obesity on TNBC was also reported in two retrospective studies [86, 95].
222 Moreover, a randomized phase III trial of adjuvant chemotherapy with or without anthracyclines in 1066
223 patients affected by aggressive biological phenotypes (as defined by thymidine labeling index >3%, or
224 histological grade 3 or S-phase >10%, or Ki67/MIB1 >20%) suggested that BMI has not a significant impact
225 on DFS and OS [96].

226 Given the small size of these studies and the overall poor outcome of TNBC itself, larger studies or meta-
227 analyses are needed to assess whether BMI is linked to survival in women with TNBC or aggressive
228 biological phenotypes [90].

229 • **The neoadjuvant setting.**

230 In the BC neoadjuvant setting, current evidence suggested that obese patients treated with neoadjuvant
231 chemotherapy had a significantly lower pathologic complete response (pCR) [97] and worse OS [98-101], in
232 contrast with other previous studies which did not confirm this relationship [102, 103].

233 A large study of 1169 patients, who have received neoadjuvant chemotherapy, reported an association
234 between the rate of pCR and the BMI. Overweight and the combination of overweight and obese patients
235 were significantly less likely to have a pCR (OR=0.59, 95% CI 0.37-0.95, and OR=0.67, 95% CI 0.45-0.99,
236 respectively, $p=0.03$) [98]. A more recent analysis of 295 Turkish patients with stage II-III BC showed that
237 obesity was an independent adverse predictive factor of pCR compared with normal or underweight
238 patients (OR=0.34, 95% CI 0.13-0.85, $p=0.02$). Moreover, higher BMI was statistically significant related to
239 an increased recurrence rate and a decreased OS [97]. These data were consistent with a prior analysis
240 conducted in the neoadjuvant setting by *Fontanella et al.*, which reported a shorter median DFS and OS in
241 obese patients versus normal-weight patients (87.3 months vs. 91.5 months, $p=0.014$ and 94.9 months vs.
242 98.8 months, $p=0.001$, respectively) [100]. On the contrary, *Farr et al.*, in a retrospective study of women
243 who underwent neoadjuvant anthracycline-taxane-based chemotherapy, found that obesity had an
244 independent positive predictive impact on pCR (OR=4.29, 95% CI 1.42-13.91, $p=0.011$) and a high BMI
245 was associated with longer PFS (HR=0.1, 95% CI 8.448×10^{-4} -0.81, $p=0.025$) [104].

246 Recently, a retrospective analysis, exploring the impact of BMI on event-free survival (EFS) and OS,
247 according to tumor subtype suggested that, overall, obesity was related to worse EFS (HR=1.71, 95% CI
248 1.03-2.84, $p=0.04$) without a statically significant difference in OS. The negative impact of obesity in terms
249 of EFS was strongest in TNBC (HR=2.62, 95% CI 1.03-6.66, $p=0.04$), with only a trend in HER2-positive
250 disease (HR=3.37, 95% CI 0.97-11.72, $p=0.06$) [105]. Additionally, *Warner et al.* in a patient cohort of 1797
251 from 4 clinical trials including neoadjuvant systemic therapy for BC, suggested that the effect of BMI on
252 pCR rate seems to differ according to tumor subtype. In particular, the authors observed a statistically
253 significant inverse relationship between BMI and pCR in estrogen-receptor positive and HER2-positive
254 patients. No significant differences were found in pCR rates according to BMI among patients with estrogen-
255 receptor positive and HER2-negative patients or TNBC [103].

256 In the context of neoadjuvant setting, a series of studies explored the relationship between weight change and
257 variations in Ki67, a well-established proliferation marker in BC. Overall, weight change during neoadjuvant

258 chemotherapy seems to not have a significant impact on Ki67 reduction in both estrogen receptor-positive
259 and TNBC [106, 107].

260 • **The metastatic setting.**

261 Considering the metastatic setting of BC, limited data focusing on the impact of BMI on survival are
262 available. In a study of 557 patients with BC metastasis, a better prognosis was reported only in women with
263 a BMI<20 kg/m² compared with women with normal weight (HR=0.52, 95% CI 0.31-0.87, $p=0.013$), while
264 no difference was seen between normal weight, overweight, and obese patients [108].

265 A retrospective analysis, conducted by *Drygalski et al.* [109], in a small cohort of 96 metastatic BC patients
266 who had received high-dose chemotherapy with autologous stem cell support, indicated that BMI>30 kg/m²
267 was an independent negative predictor of time from initial diagnosis to metastatic disease (HR=1.14,
268 $p=0.04$) and survival at the time of metastasis (HR for progression=2.23, $p=0.005$; HR for death=1.82,
269 $p=0.04$).

270 Similarly, *Parolin et al.* found that higher BMI was related to poor prognosis in HER2-positive metastatic
271 BC treated with trastuzumab: median OS for normal weight, overweight and obese patients was 67, 54, and
272 39 months, respectively ($p=0.001$) [110]. The crosstalk between leptin and IGF-1 pathway can potentially
273 modulate the phosphorylation of HER2, reducing the activity of anti-HER2 treatments [111, 112]. However,
274 these findings are in contrast with the results of a recent multicenter retrospective cohort study, including
275 data of 329 women with HER2-positive metastatic BC treated with first-line trastuzumab-based regimens:
276 the BMI was not related with PFS (adjusted-HR=0.88; 95% CI 0.66-1.17; $p=0.387$) and OS (adjusted-
277 HR=0.88, 95% CI 0.59-1.31, $p=0.525$) [113].

278 Recently, *Pizzuti et al.* [114] analyzed data of 196 women with HER2-negative metastatic BC, a subgroup of
279 patients from the TOURANDOT trial, treated with paclitaxel and bevacizumab in first-line. In this analysis,
280 the BMI showed no impact on PFS, OS and clinical benefit rates, particularly in the luminal subgroup. On
281 the contrary, in TNBC patients with a BMI ≥ 25 kg/m², PFS and OS were significantly longer (6 vs. 14
282 months, $p=0.04$ and 25 vs. 19 months, $p=0.02$, respectively) and disease control rates were significantly
283 higher (60% vs. 91%, $p=0.03$). Similarly, the analysis conducted by *Gennari et al* in 489 women with
284 metastatic BC treated with first-line chemotherapy, indicated that the BMI has not a significant impact on
285 PFS and OS [115].

286 Moreover, a more recent prospective study suggested that being overweight could improve OS in patients
287 with metastatic BC receiving chemotherapy. Indeed, normal BMI was related to increased risk of death
288 compared with BMI ≥ 25 kg/m² (HR=0.51, 95% CI 0.26–0.99, $p=0.047$) [116].

289 Therefore, the majority of the most recent findings in the metastatic BC are in conflict with data from studies
290 in early-stage BC [2, 13, 66-68]. Indeed, the presence of obesity seems to be a paradoxical protective factor
291 in the metastatic setting of BC. This unexpected inverse association between obesity and cancer mortality,
292 called ‘obesity paradox’, represents a recently emerged phenomenon even in other cancer types [117, 118].
293 However, current evidence suggested that body composition phenotypes may disprove this protective effect

294 [119]. Additional investigations are needed to clarify the complex relationship between BMI and treatment
295 outcomes in metastatic BC.

296 **The prognostic role of body composition in BC.**

297 Although the obesity represents the main factor included in the majority of studies exploring the prognostic
298 impact of body weight in BC, emerging evidence examines the potential role of body composition
299 parameters such as the sarcopenia in all settings of BC. The results of studies exploring the prognostic role of
300 body composition in the adjuvant and neoadjuvant setting are summarized in Table 1.

301 • **The adjuvant setting.**

302 The impact of body composition on prognosis in patients treated in the adjuvant setting for operated BC was
303 mainly explored by DXA and CT scan. The first method was adopted in a study cohort of 471 women with a
304 diagnosis of in situ or stage I–IIIA primary BC enrolled in the Health, Eating, Activity, and Lifestyle
305 (HEAL) study. The prevalence of sarcopenia was 16%, with 38% of sarcopenic women classified as obese.
306 At a median follow-up of 9.2 years, the sarcopenia was an independent poor prognostic factor for OS
307 (HR=2.86, 95% CI 1.67–4.89, $p<0.001$), however not statistically significant for BC related death (HR=1.95,
308 95% CI, 0.89–4.35) [53]. The images from CT scan, performed for staging, was applied in a retrospective
309 study to evaluate the impact of body composition in 119 BC survivors. Sarcopenia and inter muscular
310 adipose tissue areas were independent poor prognostic factors for DFS (HR=0.3, 95% CI 0.1–0.8, $p=0.02$
311 and HR=2.8, 95% CI 1.0–7.8, $p=0.04$, respectively) and OS (HR=0.3, 95% CI 0.1–0.99, $p=0.05$ and HR=3.6,
312 95% CI 1.2–10.8, $p=0.02$, respectively) [47]. Recently, a study including 3241 patients with stage II–III,
313 evaluated muscle area, muscle radiodensity, and adiposity measured from CT scan within 6 months from
314 diagnosis. At a median follow up of 6 years, patients with sarcopenia presented a 41% greater RR for death
315 compared with patients without sarcopenia and patients in the highest tertile of adiposity had a 35% higher
316 RR for death compared with patients in the lowest tertile. Moreover, the mortality risk was highest among
317 patients with both sarcopenia and high levels of total adiposity, among whom the RR for mortality was 89%
318 higher than that in patients without sarcopenia and with low levels of total adipose tissue. In contrast, low
319 radiodensity and BMI was not significantly associated with survival risk [120].

320 With regard to body fat distribution and gain, two prospective observational studies explored its prognostic
321 role in the adjuvant setting. The first suggested that higher abdominal fat distribution, defined as elevated
322 waist-to-hip ratio (WHR), was associated with BC mortality for postmenopausal patients (for highest quartile
323 vs. lowest, RR=3.3, 95% CI 1.1–10.4), however not in premenopausal patients (RR=1.2, 95% CI 0.4–3.4)
324 [121]. The second evaluated the relationship between body-fat gain and disease recurrence in Taiwanese
325 women who underwent surgery for stage 0–III BC. Body fat was measured by BIA and its gain was defined
326 by the difference between measures at pre-surgery and 6 months post-surgery. Higher gain in body fat
327 percentage was associated with higher risk of disease metastasis (HR=1.3, 95% CI 1.02–1.72, $p=0.035$) and
328 marginally associated with higher risk of all-cause mortality (HR=1.5, 95% CI 0.94–2.25, $p=0.091$) for
329 postmenopausal patients, but not for premenopausal women [122].

330 • **The neoadjuvant setting.**

331 As BMI and obesity [98, 100], body composition seems to play a potential prognostic role in the BC
332 neoadjuvant setting, even if less studies are available. In 2016 *Iwase et al.* found that, in 172 patients who
333 underwent surgery after neoadjuvant chemotherapy, higher amounts of visceral fat (visceral fat area >100
334 cm²) correlated with shorter distant DFS (HR=2.36, 95% CI 1.27-4.38, $p<0.05$), especially in
335 postmenopausal women who are likely to accumulate more visceral fat than subcutaneous fat [56]. The
336 authors suggested that a possible explanation of this result relies in the key role of visceral fat in promoting
337 cancer progression through different pathways [123]. In this study just 5 patients had sarcopenia and this did
338 not correlate with the prognosis.

339 Overall, the role of sarcopenia in the neoadjuvant setting is actually still debated. A study published in 2012
340 by *Del Fabbro* and colleagues reported that, between patients with operable BC exposed to neoadjuvant
341 chemotherapy, those with lower Skeletal Mass Index (defined as Skeletal Muscle Area/height²) had longer
342 OS (HR=1.006, 95% CI 1.001-1.012, $p=0.0193$). Moreover, sarcopenia was associated with higher pCR rate
343 than normal weight population ($p=0.023$) [99]. On the other hand, a recent retrospective study found that
344 sarcopenia was associated with shorter DFS intervals (HR=0.3, 95% CI 0.1-0.8, $p=0.02$), even if none of
345 composition parameter correlated with pCR. This analysis included a remarkable number of patients who
346 received NAC (55/119), but also patients who underwent adjuvant chemotherapy (64/119) [47].

347 The different results of the impact of sarcopenia through the various researches may be conferred to different
348 definitions of this parameter and different cut-offs. However, although the impact of sarcopenia on the
349 prognosis has been evaluated in many cancer types [49, 124-128], just few analyses are focused on the
350 neoadjuvant setting in patients with BC, so more prospective studies are needed.

351 The inter-muscular adipose tissue areas (IMAT) index represents a newer body composition parameter that
352 showed an independent prognostic value in patients with early BC. Indeed, higher IMAX index (>3,5
353 cm²/m²) correlated with shorter DFS (HR 2.8, 95% CI 1.0-7.8, $p=0.04$) and shorter OS (HR 3.6, 95% CI 1.2-
354 10.8, $p=0.02$). A great IMAT was also associated with other body composition variables as sarcopenia, high
355 visceral adipose tissue index and high visceral/subcutaneous adipose tissue ratio, suggesting a potential
356 relative influence of these parameters on the BC outcome [47].

357 • **The metastatic setting.**

358 Even if several body composition parameters, like MM, muscle attenuation (MA), sarcopenia and adipose
359 tissue measurements, have been investigated in metastatic BC, their prognostic role remains unclear, as the
360 few available studies reported controversial findings (Table 2).

361 In 2016 *Rier* and colleagues suggested that, between patients with metastatic BC after first-line
362 chemotherapy, those with low MA had worse outcomes in terms of OS (median OS 15 vs. 23 months,
363 $p=0.005$) and time to the next treatment (HR=1.72, 95% CI 1.14-2.62, $p=0.01$) compared with patients with
364 normal MA [129]. No significant association was found between low MM or sarcopenic obesity and OS (for
365 low MM median OS 19 vs. 18 months, $p=0.845$; for sarcopenic obesity 20 vs. 18 months, $p=0.481$). These
366 findings are in contrast with the results of a previous study by *Prado et al.* in which sarcopenia adversely

367 influenced the time to progression (TTP) in women with metastatic BC who received capecitabine treatment
368 (62 days in sarcopenic patients vs. 105 days in non-sarcopenic patients; HR=2.6, 95% CI 1.2-5.6, $p=0.01$)
369 [130]. It is worth noting that this paper included patients with different characteristics from the previous one,
370 in particular patients who failed at least the first chemotherapeutic line; therefore, it is possible that low MM
371 had a prognostic impact in more advanced disease than in first-line chemotherapy.

372 Anyway, the negative prognostic impact of sarcopenia is sustained also by a meta-analysis, which included
373 patients with advanced solid tumors [4], and by a research investigating the effect of body composition in
374 patients with metastatic BC who received taxane-based chemotherapy [28]. In the last one low skeletal
375 muscle Gauge (a parameter obtained by multiplying skeletal muscle index x skeletal muscle density)
376 correlated with time to treatment failure (HR=0.91, 95% CI 0.84-0.99, $p=0.03$) and had borderline significant
377 association with short OS (HR 0.93, 95% CI 0.87-1, $p=0.07$) suggesting that the quality of the muscle
378 composition may be relevant too.

379 To our knowledge the more recently published study investigating the changes in body composition and
380 muscle quality was conducted in 98 patients with metastatic BC who received first-line chemotherapy with
381 anthracyclines or taxanes. This analysis reported that in patients who received paclitaxel the median MA
382 significantly decreased (-0.9 HU, $p=0.03$), otherwise in patients who received anthracyclines no significant
383 change in median MA was found. A possible explanation may be found in the specific nature of toxicities
384 related to taxanes, such as the development of neuropathy and myalgia and the effect of administration of co-
385 medication, such as corticosteroids. Furthermore, no significant association was described between decrease
386 in MA, loss of MM or loss of adipose tissue and OS. The authors suggested that maybe the entity of the MA
387 decrease was not enough to impact on the outcome [131].

388 With regard to fat distribution, a small study of 42 metastatic BC patients treated with aromatase inhibitors
389 suggested that high abdominal fat distribution was associated with better survival: median OS was 472 days
390 vs. unreached for patients with a WHR of <0.92 and ≥ 0.92 ($p=0.002$), respectively. Similarly, the
391 corresponding PFS for patients with a WHR of <0.92 and ≥ 0.92 were 423 vs. 1004 days ($p=0.012$),
392 respectively [132].

393 The relationship between body composition and prognosis in the metastatic setting still lacks adequate
394 studies. Further investigations are needed to assess in which way the body composition parameters may
395 influence the survival in metastatic BC patients.

396 **Body composition as a key predictor of chemotherapy toxicity.**

397 The obesity and the body composition may influence the development of chemotherapy toxicity, besides
398 their impact in terms of prognosis. A recent prospective observational study by *Greenlee et al.*, included
399 1237 patients who received taxane-based chemotherapy, observed that overweight and obesity were
400 associated with chemotherapy-induced peripheral neuropathy at 24 months (OR=2.37, 95% CI 1.19 - 4.88,
401 $p=0.02$ and OR=3.21, 95% CI 1.52-7.02, $p=0.003$, respectively) [133]. These findings are consistent with a
402 previous study which observed that obesity was related to increased risk of chemotherapy-induced peripheral

403 neuropathy (adjusted OR=1.94, 95% CI 1.03-3.65, $p=0.039$), compared with normal-weight women, among
404 postmenopausal women with a history of stage I-III hormone receptor-positive BC who received taxanes
405 [134].

406 In addition, overweight and obesity have recently been related to higher risk of cardiotoxicity after treatment
407 with anthracyclines or sequential anthracyclines and trastuzumab [135, 136]. The mechanisms by which
408 obesity may negatively influence cardiotoxicity are affected by numerous confounding factors, therefore,
409 further studies are needed to establish the independent predictive value of obesity on cardiotoxicity in BC
410 patients.

411 With regard to hematological toxicity, a systematic review suggested that obese women, receiving adjuvant
412 chemotherapy treatment for BC, tolerated chemotherapy better than lean patients, with lower febrile
413 neutropenia (OR=4.4, 95% CI 1.65–12.01), fewer hospital admissions (OR=0.61, 95% CI 0.38–0.97), and
414 fewer neutropenic events (OR=0.49, 95% CI 0.37–0.66) [137]. However, this effect may be confounded by
415 the use of hematopoietic growth factors and by poorly specified dose capping practices. Indeed, in the
416 clinical practice, chemotherapy doses are frequently capped at a body surface area (BSA) of 2.0 m² or
417 adjusted to an ideal weight for obese patients in order to avoid excessive toxicity, which may compromise
418 survival outcome in these patients. However, a retrospective cohort study of 537 women receiving adjuvant
419 chemotherapy, in which obese patients received chemotherapy with proportionally lower mean relative dose
420 intensity than non-obese patients (94 vs. 97% of reference dose, $p=0.03$), showed that there was no
421 significant evidence of increased toxicity among obese women with either full or adjusted chemotherapy
422 doses. Overall, obesity was not statistically related to chemotherapy-related admission risk (OR=1.27, 95%
423 CI 0.78–2.09) or febrile neutropenia risk (OR=0.56, 95% CI 0.28–1.21) [138]. Similarly, a more recent
424 retrospective analysis of 325 early BC patients treated with neoadjuvant or adjuvant chemotherapy,
425 observed that obese women receiving uncapped chemotherapy did not experience a significant difference in
426 febrile neutropenia rate when compared with overweight or normal bodyweight groups [139]. In this regard,
427 ASCO guidelines recommend that obese patients should receive full weight-based chemotherapy doses
428 determined using their actual body weight, particularly when the goal is the cure [140].

429 Nevertheless, *Furlanetto et al.* reported that a dose adjustment of intense dose-dense chemotherapy should
430 be made to avoid several complications in obese women with early BC. They analysed data of 555 obese
431 women, from patients enrolled in the GAIN study, a randomized phase III adjuvant trial, comparing two
432 types of dose-dense regimens. The obese patients receiving full dose-dense chemotherapy experienced
433 significantly more hematological toxicities, particularly febrile neutropenia and higher-grade thrombopenia,
434 thromboembolic events and higher-grade hot flushes compared with obese patients receiving chemotherapy
435 dose according to an adjusted BSA. Moreover, they observed no differences in DFS and OS between obese
436 patients receiving full-dose chemotherapy or according to an adjusted BSA [141].

437 The lack of the evaluation of the relationship between body composition parameters and treatment toxicity
438 represents a limit of these studies. Indeed, LBM and others parameters may be better parameters than BMI
439 and BSA for tailoring drug dosages in cancer patients [49, 124, 142].

440 For what concerns the correlation between body composition parameters and toxicity in BC, the studies
441 available include only chemotherapy regimens (especially anthracyclines and taxanes), while there are no
442 studies regarding tyrosine-kinase inhibitors or monoclonal antibodies (Table 3).

443 One of the most recent study in early BC showed that neutropenia, hematological grade 3-4 toxicities, dose
444 reductions and delays rates were statistically significant more frequent in patients with sarcopenic obesity.
445 Moreover, hospitalization rate was more frequent in patients with altered body composition, with almost
446 twice RR (RR=1.91, $p=0.05$) [27]. Another study explored the correlation between body composition and
447 taxanes toxicity in 40 advanced BC patients. In this study, the rate of grade 3-4 toxicities was higher in the
448 sarcopenic group than in the non-sarcopenic patients (57% vs 18%, $p=0.02$) and frequently since from the
449 first chemotherapy cycle ($p=0.04$). Moreover, other adverse events, like hospitalizations, delays or dose
450 reductions rates resulted higher in the sarcopenic patients (74% vs 35%, $p=0.02$) [28].

451 In an Asiatic analysis of 84 patients from 2 phase II studies, *Wong et al.* tried to demonstrate a link between
452 body composition and toxicity of taxanes and anthracyclines in patients with non-metastatic BC. This
453 analysis showed that that visceral fat was significantly associated with grade 4 leukopenia and also that a low
454 muscle volume was associated with grade 3-4 leukopenia and neutropenia [143]. Another study, evaluating
455 body composition and its association with epirubicin toxicity in a small cohort of 24 patients affected by
456 early BC, suggested that LBM was higher in the toxicity-absent group than in the toxicity-present group
457 ($p=0.002$). Moreover, the neutrophilic count resulted better in patients with higher LBM ($p=0.023$) [144].
458 These studies suggest that the pharmacokinetic profile of anthracyclines may be altered by body fat content
459 and, consequently, associated with a greater myelosuppression.

460 With regard to other chemotherapy drugs, a prospective study investigated the role of body composition in
461 55 patients with metastatic BC treated with capecitabine and previously treated with anthracyclines and
462 taxanes. In this study, sarcopenic patients presented a higher risk to have toxicity than non-sarcopenic
463 patients (50% vs. 20%, $p=0.03$), especially diarrhea and stomatitis. Moreover, the TTP resulted better in non-
464 sarcopenic patients, with a difference in over two months ($p=0.05$) [130].

465 The paucity of studies and the small number of patients included are not enough to draw precise conclusions
466 regarding the role of body composition parameters in terms of toxicities. Further studies are needed to
467 develop new strategies in dosing cancer therapy according to body composition to reduce toxicities.

468 **Conclusion and future directions.**

469 The obesity seems to be associated with poor disease outcome in the early stage of BC, even if a series of
470 evidence do not support this prognostic impact [145]. In the metastatic setting the prognostic relationship
471 between BMI and prognosis is debatable and only scarce direct evidence supporting or refuting such an
472 impact [108, 109, 115]. Similarly, the association between post-diagnosis weight gain and BC mortality is
473 unclear.

474 With regard to body composition parameters, the majority of evidence support a prognostic role of muscle
475 and fat mass. Particularly, the sarcopenia, a frequent underrecognized condition in both metastatic and early
476 BC patients, seems to be associated with an increased risk of recurrence and death. Understanding the

477 relevance of sarcopenia and body composition in BC also highlights the need for timely interventions to
478 increase or prevent further loss of MM during and after treatment [146]. Intervention studies to date has
479 focused on physical exercise, Mediterranean diet, vitamin D and omega-3 fatty acid dietary supplementation,
480 even if the aim of these study is not always focused on BC outcome or treatment toxicity. Further research
481 exploring the impact of these interventions on efficacy and toxicity and how to incorporate them into clinical
482 practice is needed.

483 The methodological limitations of the majority of studies exploring the role of obesity and body composition
484 in BC, due to the retrospective design, the small sample size, the heterogeneity in terms of patients'
485 characteristics, cut-offs' definitions and methods adopted, may justify the differences in terms of results and
486 make the derived interpretation unreliable. Thus, the development of well-design prospective studies in order
487 to identify reliable prognostic and predictive body composition biomarkers together with the validation of
488 effective intervention strategies, would allow to improve the BC prognosis and reduce treatment toxicity.

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