Breast Cancer Research and Treatment (2019) 177:569–579
https://doi.org/10.1007/s10549-019-05352-3

REVIEW

Muscle composition and outcomes in patients with breast cancer: meta-analysis and systematic review

G. F. P. Aleixo[1,2] · G. R. Williams[3] · K. A. Nyrop[1] · H. B. Muss[1] · S. S. Shachar[4]

Received: 2 July 2019 / Accepted: 5 July 2019 / Published online: 11 July 2019

Abstract

Purpose Breast cancer is the most common cancer and leading cause of cancer death in women. Body composition parameters, especially those related to muscle, have become a growing focus of cancer research. In this review, we summarize the literature on breast cancer and muscle parameters as well as combine their outcomes for overall survival (OS), time to tumor progression (TTP), and chemotherapy toxicity in a meta-analysis.

Methods A systematic search of the literature for randomized controlled trials and observational studies was conducted on MEDLINE, Cochrane CENTRAL, and EMBASE through May 1, 2019. Two reviewers independently searched and selected. Meta-analysis was conducted using a random-effects model. The risk of bias was evaluated using the Newcastle–Ottawa quality assessment for cohorts and GRADE summary of findings tool from Cochrane.

Results A total of 754 articles were screened from which 6 articles and one abstract were selected. Using skeletal muscle index (SMI), patients classified as sarcopenic had a 68% greater mortality risk compared to non-sarcopenic patients (HR 1.68 95% CI 1.09–2.59, 5 studies) ($p = .02$) ($i^2 = 70\%$). Low muscle density was not predictive of OS (HR 1.44 95% CI 0.77–2.68, 2 studies) ($p = .25$) ($i^2 = 87\%$)**.** Patients with sarcopenia (56%) had more grade 3–5 toxicity compared to non-sarcopenic (25%) (RR 2.17 95% CI 1.4–3.34, 3 studies) ($p = .0005$) ($i^2 = 0\%$). TTP was nearly 71 days longer in advanced/metastatic patients classified as non-sarcopenic compared to patients with sarcopenia (MD − 70.75 95% CI − 122.32 to − 19.18) ($p = .007$) ($i^2 = 0\%$).

Conclusion Our synthesis of the literature shows that patients with sarcopenia have more severe chemotherapy toxicity as well as shorter OS and TTP, and that low muscle density is prognostic of OS for women with metastatic breast cancer. Our findings suggest that in clinical practice, body composition assessment is valuable as a prognostic parameter in breast cancer.

Keywords Breast cancer · Sarcopenia · Myosteatosis · Muscle measures

Abbreviations

SMI	Skeletal muscle index
SMD	Skeletal muscle density
SMG	Skeletal muscle gauge
VAT	Visceral adipose tissue
SAT	Subcutaneous adipose tissue
CT	Computer tomography
MRI	Magnetic resonance imaging
DEXA	Dual X-ray absorptiometry
BIA	Bioelectrical impedance analysis

Introduction

Breast cancer is the most common cancer and leading cause of cancer deaths in women. World Health Organization (WHO) data from 2018 report over 2 million new cases per

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10549-019-05352-3) contains supplementary material, which is available to authorized users.

✉ G. F. P. Aleixo
gfpa@email.unc.edu

[1] Division of Hematology-Oncology, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, 170 Manning Drive, Campus Box 7305, Chapel Hill, NC 27599-7305, USA

[2] Unoeste Universidade do Oeste Paulista, Presidente Prudente, SP, Brazil

[3] Division of Hematology/Oncology, University of Alabama at Birmingham, Birmingham, AL, USA

[4] Oncology Institute, Rambam Health Care Campus, Haifa, Israel

year worldwide about 627,000 deaths from breast cancer [1]. In the United States, there were about 250,000 new cases and over 40,000 deaths per year [2, 3] in 2016. The majority of breast cancers are diagnosed at an early stage (I–III) and 20–30% will eventually develop metastases [4]. Breast cancer research leading to more effective treatment options has reduced mortality in all stages of disease [5], and the pursuit of new prognostic parameters coupled with personalized therapies holds the promise of further reductions in recurrence and mortality.

Body composition parameters, especially muscle quantity and density, have become a growing focus of research in cancer prognosis. Sarcopenia is the progressive degeneration of muscle mass [6] and is a well-known condition in older persons [7]. It is typically assessed using diagnostic imaging techniques such as computed tomography (CT), dual-energy X-ray absorptiometry (DEXA), and magnetic resonance imaging (MRI) or bioelectrical impedance analysis (BIA). Systematic reviews and meta-analysis of sarcopenia in patients with cancer have shown that sarcopenia is associated with poorer survival in pancreatic [8], esophageal [9], gastric [10], colorectal [11], and lung cancer [12]. Muscle density is another measure of body composition and pertains to fatty infiltration of the muscle [13]. It can be assessed indirectly through CT imaging evaluation of mean skeletal muscle density (SMD) expressed in Hounsfield Units (HU) [14]. Similar to sarcopenia, low SMD is associated with a poorer prognosis in multiple cancers, [15] specifically colorectal [14], pancreatic [16], and ovarian [17] cancer.

Starting in 2009 but especially over the past 3 years, a growing number of studies have evaluated body composition and prognosis in women with breast cancer. However, there have been no meta-analyses correlating body composition parameters with key outcome events in patients with breast cancer. The aim of this systematic review and meta-analysis is to summarize the literature and evaluate the strength of the evidence for the prognostic value of sarcopenia and low muscle density in breast cancer prognosis, severe chemotherapy toxicity, time to tumor progression, and OS. Should these measures prove to be important prognostic parameters, they could be incorporated into clinical practice to assist in personalized treatment decisions and better outcomes.

Materials and methods

Search strategy

This systematic review is registered at PROSPERO (international database of prospectively registered systematic reviews) [18] (CRD42019131280). With the help and guidance of the University of North Carolina Health Sciences Library in the use of Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia), two reviewers (GFA and KN) independently performed a search of the literature in several databases (PubMed/Medline, Cochrane Central Register for Clinical Trials, and EMBASE) with a publication cut-off date of May 1, 2019. References from published systematic reviews of sarcopenia that included breast cancer patients were included in the review.

The search strategy (see Supplementary Material/Appendix 1 for search terms) followed the PICO framework [19], using combined terms and MeSH (Medical Subject Headings of the National Library of Medicine) descriptors and the following criteria:

- Population: women diagnosed with breast neoplasia +18 years old
- Interest: patients with sarcopenia or low skeletal muscle density
- Comparison or control: non-sarcopenic or normal skeletal muscle density patients
- Outcomes: primary outcome—overall survival. Secondary outcomes: treatment toxicity and time to tumor progression
- Study design: observational or randomized controlled trial (including abstracts)
- Timing: any time after diagnosis

Two independent reviewers (GFA and KN) selected the articles, extracted the data, and analyzed the data. Any discrepancies were resolved by consensus between the reviewers or after discussion with a third author (GRW). The reviewers evaluated the title and abstract for all studies that were identified through the COVIDENCE search strategy. Full texts were evaluated when there was insufficient information in the title and abstract to make a decision about inclusion or exclusion. References in reviewed and excluded articles were examined to identify studies that may not have been identified through the primary search strategy. The search was not limited to the English language. A list of potential studies for inclusion in the systematic review was generated through this process.

Data extraction

Extracted data included details regarding authors, year of publication, country of the study population, inclusion/exclusion criteria (patient characteristics), and stage of cancer. Data were also extracted regarding the definition of sarcopenia (cut-points) and study outcomes (e.g., overall survival, toxicity, time to tumor progression).

Data synthesis and statistical analysis

A random-effects meta-analysis model was applied to take into account that patient populations in the included studies were in different disease stages and received different treatments. Estimation of a common effect size was not possible in light of the heterogeneity of the studies. Therefore, inverse-variance weighting was used to pool estimates from the included studies. Rev-Man 5.3 was used (Cochrane Collaboration) to combine the results across studies. Heterogeneity was evaluated using Q test (c^2 Chi-square test) to assess whether observed differences in results are compatible with chance alone. A low p value (or a large Chi squared statistic relative to its degree of freedom) provides evidence of heterogeneity (variation in effect estimates beyond chance) and is expressed in the i^2 statistic [20, 21]. According to the Cochrane handbook, [22] a guide to interpretation of the i^2 statistic is as follows: 0% to 39%—might not be important, 40% to 59%—may represent moderate heterogeneity, 60% to 89%—may represent substantial heterogeneity, 90% to 100%—considerable heterogeneity. The importance of the observed value of i^2 depends on the magnitude and direction of effects and the strength of evidence for heterogeneity. Statistical significance was defined at the 0.05 level.

Dichotomous data were used to assess inverse variance and risk ratio (RR). Generic inverse variance was expressed in log hazard ratios (HR) with 95% confidence intervals (CI) for overall survival. For continuous data, we used standard deviation (SD) that was either available in the text or calculated using data from the text, expressed as mean difference (MD) between groups with 95% CI. Subgroup analysis was done according to cancer stage (e.g., stage I–III vs. metastatic) when possible.

Outcome definitions

Outcomes included (a) overall survival (OS)—time from sarcopenia diagnosis until death from any cause, (b) time to tumor progression (TTP)—length of time from date of diagnosis or start of treatment for a disease until the disease starts to worsen or spread to other parts of the body (not applicable to early stages), and (c) toxicity grades 3–5 according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE; Version 4.03) including hematologic toxicity (neutropenia, thrombocytopenia, anemia), febrile neutropenia, and common non-hematologic toxicities such as neurotoxicity and gastrointestinal (GI) toxicity (stomatitis, diarrhea, vomiting).

Quality assessment

The Newcastle–Ottawa Quality (NOQ) [23] assessment form for cohort analysis was used by two independent researchers (GFA and GRW) to assess methodological quality and standard of outcome reporting in the included studies [24]. The quality of evidence was assessed using the GRADE (Cochrane Group) analysis of findings which summarizes the level of evidence and the relative or absolute impact of each analyzed outcome.

Results

Literature search

A total of 754 articles were identified through the search strategy. Figure 1 presents the PRISMA diagram (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [25]. After duplicates were removed, the two primary reviewers screened titles and abstracts for 657 articles. For the articles that remained after the initial screen, 21 full texts were reviewed for eligibility. Most articles were excluded because they did not include information on outcomes selected for our review or did not include comparison groups [26–34]. Ultimately, seven studies were selected for inclusion in the systematic review—six articles [29, 35–39] and one abstract [40] with a total of 4065 patients.

Overview of included studies

Table 1 provides an overview of the included studies. Patients in four studies were early-stage breast cancer [35, 36, 38] and in four studies they were advanced/metastatic [29, 37, 39, 40]. Two studies focused on capecitabine/taxane treatment [29, 39] (both in patients with metastatic breast cancer), while all other studies entailed multiple chemotherapy treatments. Six studies used lumbar L3 CT scans to assess sarcopenia [29, 35–37, 39, 40] and one study used DEXA scan [38]. The mean proportion of patients with sarcopenia was 39.8% (range 25–66.9%).

Body composition definitions

Sarcopenia using Skeletal Muscle Index (SMI) and cut-points varied across the studies. Three studies used < 41 cm^2/m^2 [29, 36, 37], one study used < 40 cm^2/m^2 [35], one study used < 38.5 cm^2/m^2 [39] and in one study the sarcopenia cut-point was not defined [40]. The seventh study used DEXA with a cut-point of < 5.45 kg/m^2 [38]. Low skeletal muscle density (SMD) using mean attenuation in Hounsfield Units (HU) was assessed in three studies, with one study using < 37.8 HU [35] and two using < 41 HU for BMI < 25 and < 33 HU for BMI > 25 [37, 39] as cut-points.

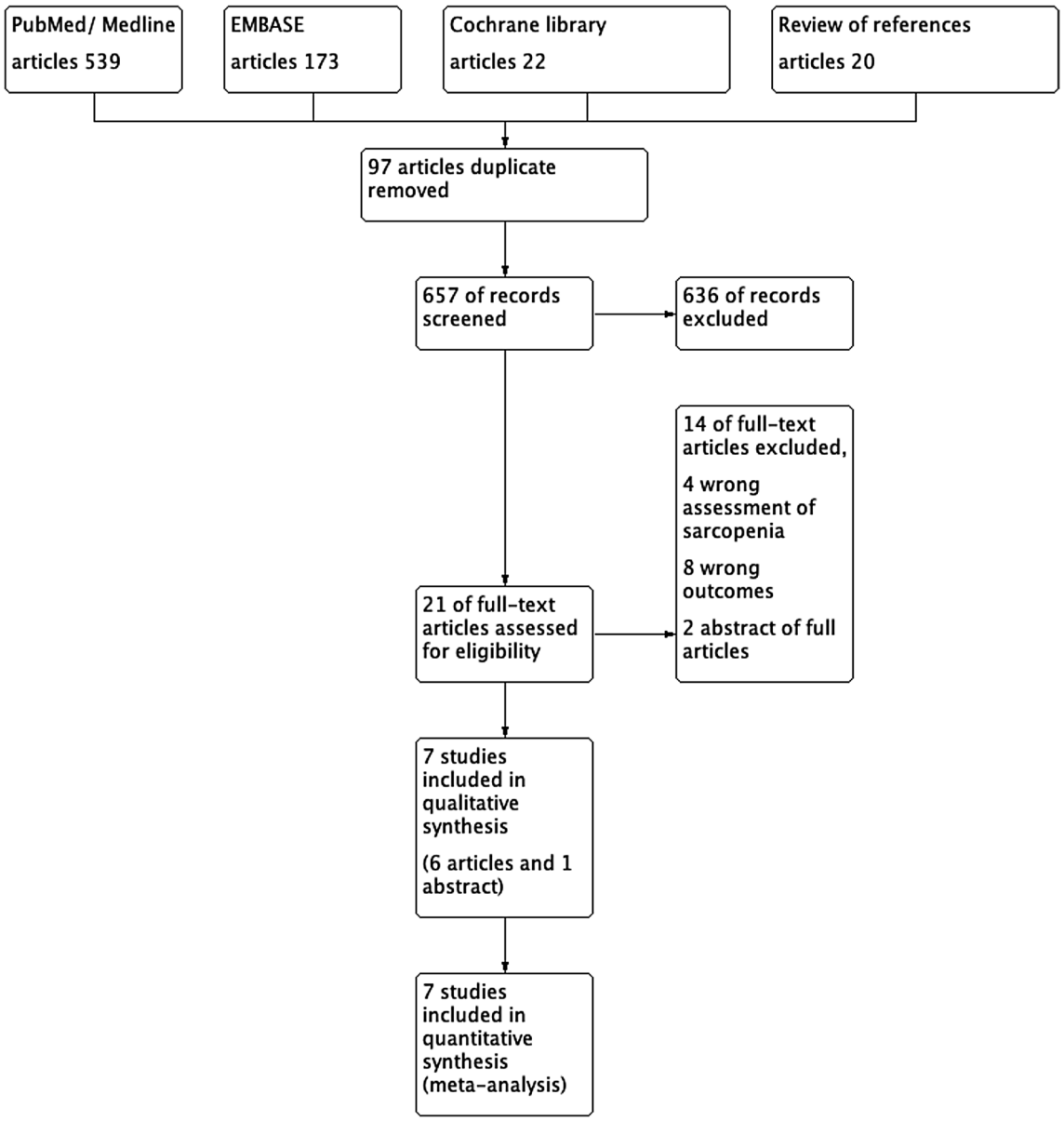

Fig. 1 Prisma search strategy

Primary outcome

Overall survival

Using skeletal muscle index (SMI) for all patients in five studies, patients classified as sarcopenic had a 68% greater mortality risk compared to patients with non-sarcopenic patients (HR 1.68 95% CI 1.09–2.59, 5 studies) ($p = .02$) ($i^2 = 70\%$) (Fig. 2). Subgroup analysis by stage showed that sarcopenia was of prognostic value in early breast cancer ($p = .05$) but not prognostic in metastatic ($p = .44$).

Low muscle density was not predictive of overall survival (HR 1.44 95% CI 0.77–2.68, 2 studies) ($p = .25$) ($i^2 = 87\%$) (Fig. 3). However, in subgroup analysis, low muscle density was significantly related to shortened survival in patients with metastatic breast cancer ($p = .0009$) but not for early breast cancer ($p = .38$).

Secondary outcomes

Metastatic patients with sarcopenia (56%) had more grade 3–5 toxicity compared to patients classified as non-sarcopenic (25%) (RR 2.17 95% CI 1.4–3.34, 3 studies) ($p = .0005$) ($i^2 = 0\%$) (Fig. 4).

Time to tumor progression in patients with advanced/metastatic breast cancer was nearly 71 days longer in

Table 1 Characteristics of included studies

Author date (country)	(n)	Participants	Treatment	Cancer stage	CTMRI DXA BIA	Sarcopenia	Low SMD	Sarcopenia %	NOQ	Outcomes
Lee 2019 [40] (USA)	53	Retrospective data	Multiple	Metastatic	CT	L3 analysis Sarcopenia cut-point not defined	Not assessed	30	Fair	Sarcopenia is a predictor for grade 3-4 toxicity 60% versus 35% ($p=.04$) and time to tumor progression 223.6 days versus 156.4 days ($p=.05$)
Caan et al. 2018 [35] (USA)	3241	Retrospective data Women age 18–80	Multiple	II and III	CT	Slice O Matic 5.0 (Canada). SMI derived from L3 muscle mass/height in m^2 Sarcopenia SMI < 40 cm^2/m^2	Low SMD < 37.8 HU	34	Good	Sarcopenic women had higher overall mortality HR 1.41 95% CI 1.18 − 1.69
Deluche et al. 2017 [36] (France)	119	Retrospective data Women age +18 years	Multiple	I–III	CT	Slice O Matic 4.3 (Canada) SMI derived from L3 muscle mass/height in m^2. Sarcopenia SMI < 41 cm^2/m^2	Not assessed	48.8	Good	Sarcopenic patients has shorter disease-free survival HR 0.3 95% CI 0.1–0.8 $p=.03$ and worse overall survival HR 0.3 95% CI 0.1–0.99 $p=.05$
Shachar et al. 2017 [29] (USA)	40	Retrospective data Women age 34-80	Taxane based	Metastatic	CT	Impax radiological software SMI derived from L3 muscle mass/height in m^2 (AGFA version 6, Belgium) SMI < 41 cm^2/m^2	Not assessed	58	Good	Sarcopenia is associated with G3-4 toxicities 57% versus 18% ($p=.02$), higher toxicity-related hospitalizations ($p=.02$). No changes in Overall survival and adverse event
Rier et al. 2017 [37] (Netherlands)	166	Retrospective data Women age +18 years old (range 30–86)	Multiple	Metastatic	CT	Slice O Matic 5.0 (Canada) SMI derived from L3 muscle mass/height in m^2 Sarcopenia SMI < 41 cm^2/m^2	< 41 HU for BMI < 25 < 33 HU for BMI > 25	66.9	Good	No changes in overall survival (OS) and time to next treatment (TNT) with SMI data. Low muscle quality was associated with

Table 1 (continued)

Author date (country)	(n)	Participants	Treatment	Cancer stage	CTMRI DXA BIA	Sarcopenia	Low SMD	Sarcopenia %	NOQ	Outcomes
Villasen et al. 2012 [38] (USA)	471	Prospective data Women age +18 years old	Multiple	In situ or I–IIIA	DXA	Sarcopenia < 5.45 kg/m^2	Not calculated	16	Good	Sarcopenia is increased risk for overall mortality (HR 2.86 95% CI.1.67–4.89). No difference in cancer-specific mortality
Prado et al. 2009 [39] (Canada)	55	Retrospective data Women age +18 Breast cancer resistant to anthracycline or taxane	Capecitabine	Metastatic	CT	Slice O Matic 5.0 (Canada). SMI derived from L3 muscle mass/height in m^2 Sarcopenia SMI < 38.5 cm^2/m^2	< 41 HU for BMI < 25 < 33 HU for BMI > 25	25	Good	Sarcopenia is a predictor for grade 3–4 toxicity 50% versus 20% ($p = .03$) and time to tumor progression 101.4 days versus 173 days ($p = .05$)

SMI skeletal muscle index, *SMD* skeletal muscle density, *HU* Hounsfield units, *NOQ* newcastle–ottawa quality, *CT* computer tomography, *MRI* magnetic resonance imaging, *DEXA* Dual X-Ray Absorptiometry

non-sarcopenic compared to sarcopenic patients (Mean Deviation − 70.75 95% CI − 122.32 to − 19.18) ($p = .007$) ($i^2 = 0\%$) (Fig. 5).

Quality assessment

Table 2 summarizes the NOQ results for studies included in the review. Six studies were rated "good" [29, 35–39] and one "fair" [40]. The grade summary of findings (Table 3) shows that the certainty of the effect estimate was moderate for all outcomes.

Discussion

This systematic review and meta-analysis evaluated the evidence of body composition—specifically sarcopenia and low muscle density. An important finding is that adverse outcomes varied between women with early breast cancer and those with metastatic breast cancer. Specifically, SMI was prognostic for mortality risk in early breast cancer but not in metastatic, while low muscle density was prognostic for OS in women with metastatic but not with early breast cancer. Risk for grade 3–5 chemotherapy toxicity was significant for both early and metastatic breast cancer.

Interest continues to grow in exploring multiple body composition parameters of prognosis in patients with cancer [8, 10, 16]. This interest is evident in the publishing dates for most studies included in our meta-analysis. It is also evident in a recently published systematic review of sarcopenia and breast cancer using CT scans that included 15 articles [41] and other recent publications exploring the influence of body composition in breast cancer patients [30]. Research will continue to expand as advances in the use artificial intelligence for body imaging analysis [42, 43] make the assessment of multiple parameters of body composition increasingly reliable and accessible in clinical practice.

Sarcopenia (low SMI) was the first body composition parameter to provide independent prognostic information in cancer patients in general (e.g., overall survival, chemotherapy toxicity, surgical toxicity) and is the reason for its widespread use in body composition research. Our finding that sarcopenia is prognostic for OS, TTP, and high-grade chemotherapy toxicity in breast cancer has been observed in prior meta-analyses of sarcopenia in other cancer types [8, 10]. However, our subgroup analyses showed that sarcopenia was not always significant in early breast cancer compared to metastatic breast cancer. We hypothesize that the small number of patients in each group may be affecting these results. Of note, two studies not included in our analysis because they did not have data necessary for this analysis showed linear correlation between muscle density

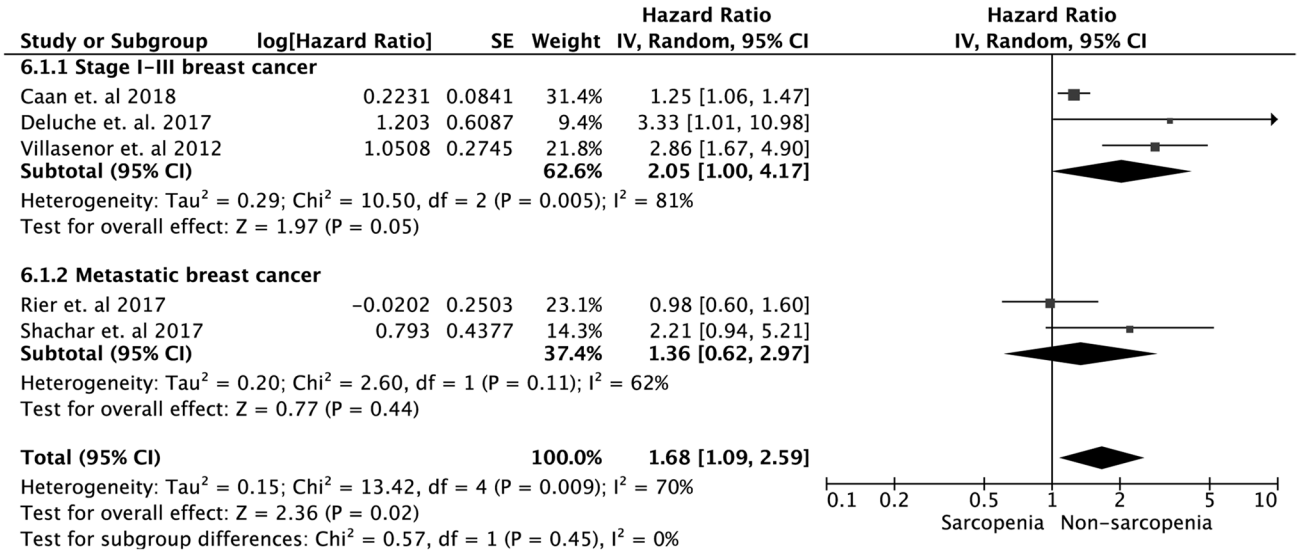

Fig. 2 Sarcopenia and overall survival: Forest plot

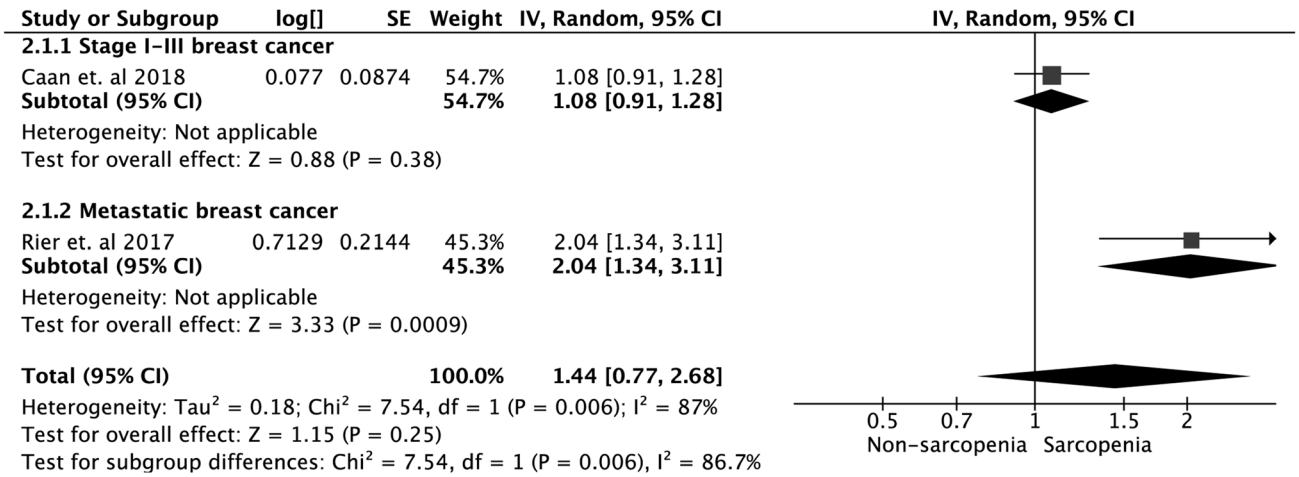

Fig. 3 Low muscle density and overall survival. Forest plot

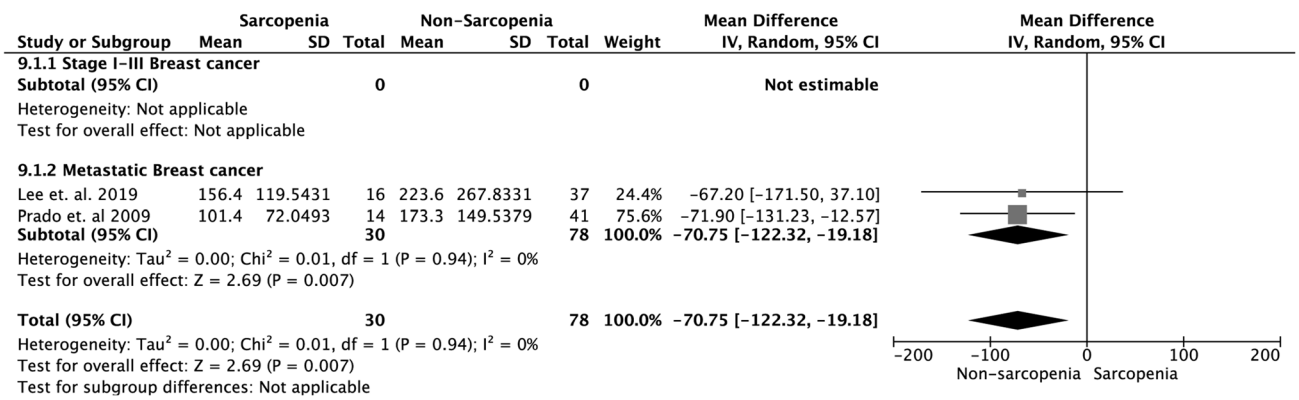

Fig. 4 Sarcopenia and high-grade chemotherapy toxicity. Forest plot

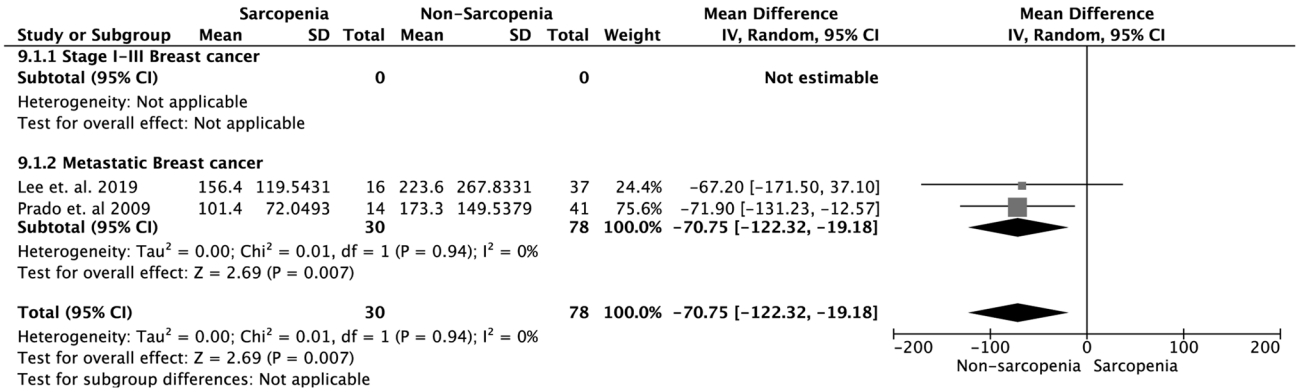

Fig. 5 Sarcopenia and time to tumor progression. Forest plot

Table 2 Newcastle–Ottawa quality assessment of cohort trials

	Caan et al. 2018 [35]	Prado et al. 2009 [39]	Deluche et al. 2017 [36]	Shachar et al. 2017 [29]	Rier et al. 2017 [37]	Lee et al. 2018 [40]	Villasenor et al. 2012 [38]
Selection							
Representative of the cohort?	*	*	*	*	*	*	*
Selection of the non-exposed	*	*	*	*	*	*	*
Ascertainment of exposure	*	*	*	*	*	*	*
Demonstration that outcome was not present at start of study							
Comparability							
Comparability on the basis of design or analysis	*	*	*	*	*		*
Outcome							
Assessment of outcome	*	*	*	*	*	*	*
Was follow-up long enough for outcomes to occur	*	*	*	*	*	*	*
Adequacy of follow-up of cohorts	*	*	*	*	*	*	*
Result	Good	Good	Good	Good	Good	Fair	Good

Asterisks are the equivalent of "yes"

and mortality as well as chemotherapy toxicity in patients with breast cancer [28, 44].

It has been hypothesized that sarcopenia is prognostic because muscle acts as an energy storage compartment which may be used in catabolic periods such as cancer and chemotherapy [45]. The impact of sarcopenia may be due to a combination of vulnerability to cancer and its treatment, due to low physical reserves or in more advanced cases due to sub-optimal treatment options in patients with limited physical reserve [7]. Low SMD, which reflects high muscle fat content rather than low muscle mass, has been associated with poor survival in some cancers [14–16, 36] as it promotes higher systemic inflammation and insulin resistance which may reduce body defenses and stimulate neoplasia growth [46, 47]. Our evaluation did not find a statistically significant difference for OS in low SMD compared to normal SMD patients with breast cancer; however, this may be due to the heterogeneity of outcomes and the small number of studies eligible for our analysis. A large observational study showed that low muscle attenuation was associated with dose reductions and that women whose doses were reduced had a higher chance of dying from breast cancer [48].

Body composition markers other than SMI and SMD have been analyzed for outcomes in a variety of cancer populations. For example, Weinberg et al. [33] combined SMI and SMD to create skeletal muscle gauge (SMG) which was shown to be a strong predictor of outcomes in patients with cancer [29, 44]. Visceral adipose tissue (VAT) area, which increases insulin resistance and inflammation [49], is associated with poor outcomes in patients with colorectal cancer who are receiving bevacizumab or undergoing surgery [50, 51]. A recent abstract showed that low muscle density is associated with dose reductions in patients with

Table 3 GRADE summary of findings

Sarcopenia/low SMD compared to no sarcopenia/normal SMD in women with breast cancer						
Patient or population: women with breast cancer						
Setting: at any time after diagnosis						
Interest: sarcopenia/low SMD						
Comparison: non-sarcopenia/normal SMD						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Sarcopenia/low SMD	Non-sarcopenia/normal SMD				
Overall survival SMI	–	–	HR 1.68 (1.09 to 2.59)	4217 (5 observational studies)	⨁⨁⨁◯ Moderate	
Overall survival SMD	–	–	HR 1.44 (0.77 to 2.68)	3407 (2 observational studies)	⨁⨁⨁◯ Moderate	
Toxicity	56%	25%	RR 2.17 (1.40 to 3.34)	148 (3 observational studies)	⨁⨁⨁◯ Moderate	
Time to tumor progression	The mean time to tumor progression was 127 days	The mean time to tumor progression was 198 days	The mean time to tumor progression in the sarcopenia group was 70.75 days higher (19.18 higher to 122.32 higher)	108 (2 observational studies)	⨁⨁⨁◯ Moderate	

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

CI confidence interval, *HR* hazard ratio, *SMI* skeletal muscle index, *SMD* skeletal muscle density

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

breast cancer receiving taxanes [48]. One study also showed that VAT correlated with OS [27]; however, other studies have not associated VAT with prognosis [31, 36]. A large observational trial found an association between low subcutaneous adipose tissue area and prognosis for patients with various solid neoplasia [52], and in breast cancer an increase in both VAT and SAT was associated with poor survival [53]. Despite studies identifying sarcopenic obesity as a risk factor for poor outcomes in multiple cancers [54], our search identified only one study to date in breast cancer that analyzed sarcopenic obesity [37] and which showed poor overall survival in women with metastatic breast cancer.

Most studies included in our analysis were rated as good on the Newcastle–Ottawa Quality assessment of cohorts. However, the GRADE summary of findings was moderate in all outcomes either because of high heterogeneity or the limited the number of trials available for analysis, thereby creating a high risk for bias. It is of concern that several excellent studies could not be included in our analysis because of the heterogeneous manner in which their data were assessed. For example, two trials could not be included in our analysis because they did not provide cut-points for defining patients with sarcopenia or low muscle density [28, 44]. In another study, the outcome "time to progression" could not be evaluated because low SMD was not defined [29]. We also note that both sarcopenia and low muscle density had some variation in cut-points among the studies that could influence final results. A consensus on definitions and cut-points would improve the quality of future studies and the trustworthiness of results. Despite the existence of European [55] and Asian [56] guidelines for sarcopenia, the lack of consensus in other parameters remains problematic for body composition research in oncology [7].

Conclusion

To our knowledge, this is the first systematic review with a meta-analysis pertaining to the importance of muscle mass parameters in women with breast cancer. Our findings suggest that in clinical practice body composition assessment could prove valuable as a prognostic parameter in breast cancer. Future research is needed to explore additional body composition measures, such as visceral adipose tissue area, subcutaneous adipose tissue area, and sarcopenic obesity to deepen our understanding of the extent to which body composition affects outcomes in women with breast cancer. Further research is also needed to understand the mechanisms by which body composition affects cancer outcomes.

Acknowledgements We thank for the help and guidance on our search from the University of North Carolina Health Sciences Library.

Compliance with ethical standards

Conflict of interest The authors declare they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent This study did not entail direct contact with humans and therefore did not entail obtaining informed consent.

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