



Review Article

Fracture risk in breast cancer: Does obesity have an effect? A scoping review

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ABSTRACT

Background: Metastasis from breast cancer (BC) has a predilection for the skeleton. Due to its osteolytic nature, breast cancer bone metastasis (BCBM) appears to increase fracture risk. The association between obesity and its effect on bone seems to be skeletal site-specific. The incidence of pathological fractures often involves the axial skeleton even though the most debilitating effects of fractures are caused in the appendicular skeleton. Whether obesity increases fracture risk in BCBM remains inconclusive, however. At present, there is no literature that examines the effects of obesity on BCBM, and fracture risk are as such we sought to determine the effect of obesity on fracture risk in BC. This is the focus of the review.

Objectives: This scoping review aims to examine the link between fracture outcomes of women with BC and obesity as reported by Body Mass Index (BMI). The purpose of this study is to determine if current literature suggests obesity increases fracture risk in women with BC.

Design: We conducted a comprehensive literature search for breast cancer bone metastasis, obesity, and fracture risk in PubMed, Cochrane Library, NIH Clinical Trials, and OpenGrey. Articles that included BC, obesity, and fracture risk were included for analysis. Data were pooled, charted, analysed, and reported according to PRISMA-ScR standards.

Data synthesis and results: Each outcome was stratified by BMI (obese or non-obese) status in women with breast cancer. Five studies were eligible for analysis and relevant data was charted to allow results to be synthesised. We found four out of five studies reported a positive association between BMI and fracture risk in females with breast cancer.

Conclusions: We found a potential association of obesity and fracture risk in breast cancer. However, as we conducted this study it was evident that there is limited literature available on this topic and none for breast cancer bone metastasis. This poses an important direction for future research. Larger and robust pre-clinical and clinical randomized control trials are needed to better understand the relation between obesity and metastatic breast cancer.

1. Introduction

Breast cancer (BC) is the most common cancer affecting women worldwide. It was estimated that in 2018 alone there were more than 2 million new cases of breast cancer [1]. Advanced cancers often result in metastatic disease. The spread begins with epithelial to mesenchymal transition of invasive cancer cells which then enter the lumina of blood vessels. Subsequently, they travel to metastatic sites and initiate their proliferative programs [2]. The skeleton is the most common organ of distant metastasis in BC patients. Up to 73 % of stage 4 BC patients develop skeletal-related metastases [3]. The ‘seed and soil’ hypothesis (Stephen Paget, 1889) suggested that bone offers a fertile ground for

cancer cells to proliferate. Cancer cells invade the rich arterial supply in the red marrow of the long bones, ribs, sternum, vertebrae, and pelvis. These malignant cells disrupt bone homeostasis, structural integrity, and bone remodelling, leading to an increased risk for skeletal-related events (SREs) such as pathological fracture, spinal cord compression, malignant hypercalcemia, and decreased quality of life [3,4].

As BC is a serious health concern, it is important to investigate its risk factors. Epidemiological evidence suggests an interplay between obesity and incidence and severity of multiple cancers including BC [5–7]. Obese women are observed to have 41 % higher risk of all-cause mortality and 35 % breast cancer specific mortality [8]. Interestingly, when it comes to the relationship between obesity and fracture risk, the

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association remains uncertain. Obesity may protect bones [9] due to higher mechanical loading by increasing bone formation [10]. However, there are arguments that due to lesser mobility and greater impact during a fall, higher body weight may cancel out these potential benefits [11]. The interplay between obesity and fracture risk and the varying effects on different body sites further complicates this relationship [12].

If we were to ask a question about what is known about the direct effect of obesity on BCBM fracture risk, there is little knowledge reported on this relationship. This scoping review's initial plan was to answer the question "Does obesity increase the risk of metastatic fracture in breast cancer bone metastasis?" After conducting a review of literature on this pressing issue it was found that there are no available relevant studies that explore this connection. With this in mind, we expanded our search to include breast cancer as a primary disease, obesity, and fracture risk with the aim to provide some insight into whether there may be an interaction with obesity and BCBM and direct future research.

2. Methods and materials

2.1. Protocol

This scoping review applied the methodological framework developed by Arksey and O'Malley and integrated additional scoping review recommendations made by Levac et al. [13,14]. We reported our results according to the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and meta-Analyses extension for Scoping Reviews). Eligibility criteria and analysis are also described in the following sections of the manuscript.

This scoping review was conducted in the five broad stages outlined below.

Stage 1: Identify the research questions.

Our initial hypothesis was to test whether obesity increases risk of metastatic fracture in breast cancer bone metastasis.

After conducting an intensive search of current literature on databases listed in *Step 2 and 3*, we found no relevant articles making a direct conclusion supporting or disputing the initial hypothesis. The team discussed an alternative hypothesis: Obesity increases risk of fracture in breast cancer, and identified a new research question: "Does obesity increase risk of fracture in breast cancer?".

Stages 2 and 3: Identifying and selecting relevant studies.

The database search was run by the author. Study selection and review took approximately 4 weeks. The following electronic databases were searched: (1) PubMed, (2) Cochrane, (3) NIH Clinical Trials, (4) Google Scholar. We also conducted a scan of relevant gray literature (OpenGrey). We limited our search to those with English language published between 2000 and 2021.

The review team started the process by reviewing together a small sample of studies to ensure that there was a collective agreement on inclusion and exclusion criteria which is shown in [Table 1](#). The selection process and search flow are shown in [Supplementary Fig. 1](#).

Stage 4: Charting the data.

The data reported in the eligible papers were charted in an Excel spreadsheet. Characteristics included publication details, authors, year of publication, study location, study type (i.e., clinical trial), aims of the study, overview of methods, outcome measures, and results.

Stage 5: Collating, summarizing, and reporting the results.

A broad overview of all material including (1) analysis of descriptive numerical summary; (2) reporting the results and producing the outcome that refers to the overall purpose of the research question; (3) discussing implication for future research and practice.

The review presents the main points of research within the research questions described above. Subsequently, the review will conclude outlining the knowledge gaps that exist in addressing the primary question.

2.2. Eligibility criteria

Eligibility criteria were defined using an adaptation of the PICOS approach (Population, Exposure, Comparator, Outcomes and Study design).

2.3. Population

The study population were women of any ethnicity or setting with BC. Only studies that included a majority of adults (i.e., at least 80 % of the sample was aged 18 years or older, which is an arbitrary criterion commonly used in systematic reviews) [15] were selected, as findings among the paediatric population may differ due to incomplete and ongoing bone development [16]. Studies including individuals who experienced BC with bone metastasis (BM) were excluded. Studies without data on BMI exposure group categories or waist circumference, or bone biomarkers were also disregarded. We also excluded studies that were not in written in English.

2.4. Exposure

Studies included those with an exposure group that was composed of individuals with obesity, characterized as a BMI greater than 30 kg/m² [17]. Therefore, when results were reported for obese weight range and healthy weight range individuals' exposure groups data were pooled for assessment of eligibility.

2.5. Comparator

Studies were included when the comparison group was composed of individuals without obesity (BMI < 30).

2.6. Information sources

Online databases were used to identify papers published between 2000 and 2021. PubMed, Cochrane Library, NIH Clinical Trials, Google Scholar and OpenGrey were searched from the inception databases until the 6th of January 2022.

2.7. Search strategies

Studies were identified by searching electronic databases, scanning the reference list of included studies for possible relevant information and consulting project's supervisor. The search strategy ([Table 1](#): Inclusion criteria and search strategy) was revised by project's supervisor. Highly sensitive filters were used on PubMed, Cochrane Library, NIH Clinical Trials, Google Scholar and OpenGrey. Restrictions were imposed on publication date, publication status and language. Results from different databases were merged and duplicates were manually removed using Paperpile version 1.5.305 reference software when title, authors, journal, and year of publication were identical. Results were checked for errata, retraction, and expression of concern.

2.7.1. Selection of sources of evidence

To increase consistency among the team, both reviewer and supervisor screened the same 12 publications, discussed the results, evaluated the titles, abstracts and then full texts of all publications. We resolved any disagreements on study selection and data extraction by consensus and discussion on most applicable studies.

2.7.2. Data charting process

A data-charting form was jointly developed by the reviewer and the supervisor to determine which variables to extract. Data from eligible studies were charted using data abstraction tool designed for this study. The tool captured the relevant information on key study characteristics and detailed information on all metrics used to evaluate fracture risk

Table 1

Analysis of included manuscripts in scoping review. Journal article’s lead author, year of publication, title, study type, population, age group, aim of study, overview of methods, outcome measures, main results and alignment with aim of this study as indicated by the authors.

Lead author, year	Title	Study type	Population	Aim of the study	Overview of methods	Outcome measures	Main results	Positive association BMI with fracture risk
Fraenkel, 2015	Breast cancer survivors are at an increased risk for osteoporotic fractures not explained by lower BMD: a retrospective analysis	Observational study	Mature females n = 1193	Assess fracture risk adjusted for BMD in women with and without BC, and to assess whether fracture risk in BC patients is attributed to BMD or BC characteristics.	A retrospective analysis, statistical analysis, meta analysis	BMD, PTH Assay, 25-hydroxyvitamin D assay,	a qualitative defect in bone of BC patients that is not apparent with BMD testing similar to other processes that affect bone quality such as diabetes and obesity. See table BMI p value is <	Yes
Pedersini, 2019	Association of Fat Body Mass With Vertebral Fractures in Postmenopausal Women With Early Breast Cancer Undergoing Adjuvant Aromatase Inhibitor Therapy.	Observational, cross sectional study	Mature females n = 556	To determine whether fat body mass (FBM), as measured by dual-energy X-ray absorptiometry, is associated with vertebral fracture prevalence in postmenopausal women undergoing adjuvant aromatase inhibitor therapy for breast cancer.	A cross sectional study, statistical analysis	Vertebral fracture prevalence associated with FBM in aromatase inhibitor-naive and aromatase inhibitor-treated patients.	High fat body mass was associated with a numerically but not significantly lower proportion of vertebral fractures in aromatase inhibitor-naive women and a significantly higher proportion of vertebral fractures in aromatase inhibitor-treated women high fat body mass was associated with a numerically but not significantly lower proportion of vertebral fractures in aromatase inhibitor-naive women and a significantly higher proportion of vertebral fractures in aromatase inhibitor-treated women.	Yes, for some subgroups
Chen, 2005	Fracture Risk among Breast Cancer Survivors: Results from the Women’s Health Initiative Observational Study.	Observational study	Mature females n = 5298 BCE, n = 80848 no BC as ref group	Postmenopausal survivors of breast cancer have a higher risk for fractures compared with women who have no cancer history.	Prospective analysis with follow up	Fracture outcomes and fracture sites	The increased risk for clinical vertebral fracture was statistically significant only among survivors who had a breast cancer diagnosis before age 55 years (HR, 1.78; 95 % CI, 1.28–2.46). After adjusting for factors related to hormone levels, risk of fall, fracture history, medication use, comorbidity, and lifestyle, the increased risk for all fractures studied among survivors was reduced to 15 % (HR, 1.15; 95 % CI, 1.05–1.25).	No
Melton, 2012	Fracture risk in women with breast cancer: A	Retrospective Analysis	Mature females n = 608	Determine whether long-term fracture risk, exclusive of	A retrospective analysis, statistical	Fracture records and fracture risks assessment	Age-adjusted fracture risk is increased modestly, if at all, among	Yes

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Table 1 (continued)

Lead author, year	Title	Study type	Population	Aim of the study	Overview of methods	Outcome measures	Main results	Positive association BMI with fracture risk
	population-based study			pathologic fractures, is now greater than expected (and as compared with the Rochester women diagnosed with breast cancer in an earlier era)	analysis, meta analysis		women with breast cancer. BC patients in general are not at greatly increased risk of fracture, neither are they protected from fractures despite any determinants that breast cancer and high bone density may have in common. Obesity hazard ratio is 1.8	
Zheng, 2019	Soy Food Consumption, Exercise, and Body Mass Index and Osteoporotic Fracture Risk Among Breast Cancer Survivors: The Shanghai Breast Cancer Survival Study	Prospective, Experimental Study	Mature females n = 5042. note that this study is the first include such a large number of pre-/perimenopausal breast cancer survivors for research on osteoporotic fracture.	Incidence of bone fracture and its associations with soy food consumption, exercise, and body mass index among breast cancer survivors	Prospective analysis with follow up	any fracture and osteoporotic fracture that occurred during the 10 years following diagnosis. Osteoporotic fractures were defined as low-trauma fractures (eg, due to falls from standing height), occurring in anatomic sites commonly associated with osteoporosis	Soy isoflavone intake is inversely associated with osteoporotic fracture risk, and overweight/obesity with increased osteoporotic fracture risk. Exercise and tamoxifen use were inversely associated with the risk for osteoporotic fracture	Yes

and/or bone quality anywhere in the article, including metrics that were not mentioned in the narrative explicitly.

The author charted the data from eligible article and discussed charting results with the supervisor. Any disagreement was resolved by going through objectives of the review. Data charting was implemented using Excel spreadsheet.

2.7.3. Data items

We abstracted data on article characteristics e.g., country of origin, publication journal, author, engagement characteristics and contextual factors e.g., study type, population of the study, age group, aim of study, overview of methods, outcome measures, main results, and future suggestions for further investigations.

2.7.4. Synthesis of results

We grouped the studies by the types of behaviour they analysed, and summarized the type of settings, populations, and study designs for each group, along with the outcome measures used and broad findings. We counted the number of studies that potentially met our inclusion criteria and noted how many studies had been missed by our search and checked whether they would yield valuable and relevant information to our research question.

3. Results

3.1. Selection of sources of evidence

After a thorough search of literature on this topic, a total of 1,780 citations were identified from searches of selected electronic databases. Based on the titles and abstracts, 1,345 studies were excluded, with 435 full text articles to be retrieved and assessed for eligibility. Of these, 423 studies were excluded for the following reasons: studies that do not contain information on either BMI or obesity or fracture risk, studies that

are systematic reviews, or studies with no association of BMI or obesity and fracture risk that could be compared to control group, and duplicated studies.

We excluded 7 studies due to the lack of quantifiable association between BMI and fracture risk. These studies focused on bone biomarkers which could infer fracture risk and bone quality yet making an inferential conclusion is outside of the scope of this review. The remaining 5 were considered eligible for this review.

3.2. Characteristics of sources of evidence

The search flow is demonstrated in [Supplementary Fig. 1](#). We identified 5 studies from 4 countries. One study was retrospective, 2 were prospective and 2 cross-sectional studies. There was one study concerning vertebral fractures, 4 others concerning general fracture risk on any sites of the skeleton such as hip, humerus, ribs, spine, radius. In total, 5 studies included more than 92, 642 patients. The journal’s lead author, year of publication, study type, population, age group, aim of study, overview of methods, outcome measures and main results related to each study are presented in [Table 1](#).

Fraenkel and colleagues viewed electronic medical records of patients who underwent dual-energy X-ray bone mineral density (BMD) to identify a subsequent diagnosis of osteoporotic fractures. BC status, demographic, health characteristics, BMD, and other laboratory finds were assessed. It was suggested that BC survivors are at an increased risk of fracture. Hazard ratio (HR) for any osteoporotic fracture in women with BC was 1.34 (P = 0.026) that was not explained by bone mineral density (BMD) but other processes that affect bone quality such as obesity [18]. In a single-centre, cross-sectional study examining the association of fat body mass with vertebral fractures in postmenopausal women with BC, Pedersini et al. stratified participants treatment according to whether they were aromatase inhibitor naive or had been taking aromatase inhibitors for at least 2 years. The results showed no

significant difference in fracture risk in the low-fat body mass (FBM) group regardless of whether they used aromatase inhibitors (AI) or not (19.2 % vs 13.3 %; $P = 0.13$). There was however, a significant difference in fracture risk within the AI-treated group between the low FBM and high FBM proportion of vertebral fractures in the AI-treated group (20.0 % in patients with low FBM vs 33.3 % in patients with high FBM ($P = 0.04$)) [19].

Two other studies by Melton and Zheng yielded the same results showing an increase in fracture risk in pre/perimenopausal women but no significant increase in their post-menopausal counterparts [20,21]. Melton conducted a population-based historical cohort study [20] of 608 women with invasive breast cancer. Pre-menopausal women with obesity were at an increased hazard ratio (HR) of 1.8 for any fracture and 1.8 for pathological fracture compared to the post-menopausal HR of 0.7 and 0.5, respectively. A prospective, longitudinal study by Zheng et al [21] involving a large population-based cohort of 5042 women complemented Melton's conclusion. It was observed that obesity was associated with increased relative risk of osteoporotic fractures among premenopausal breast cancer patients (HR 1.81 osteoporotic fractures) compared to postmenopausal women (HR 0.67 for osteoporosis fractures). Interestingly, the study by Chen et al produced an opposing result that BMI was not significantly associated with total fracture risk in breast cancer survivors [22]. In this prospective study with 5.1 year's follow up, women who reported a history of breast cancer ($n = 5298$) were compared to a reference group of women who had no cancer history at baseline ($n = 80848$). Fracture risk was significantly and positively associated with age among breast cancer survivors if they had any of the following characteristics: race, an indication of depression, a fracture history, diabetes, arthritis, hip replacement, emphysema or chronic bronchitis, and osteoporosis. BMI, number of years since menopause, age and hormonal therapy use were not significantly associated with total fracture risk in breast cancer survivors.

3.3. Synthesis of results

All 5 studies examined the association between BMI and fracture risk [18–22]. Two studies were from the US [20,22], one from Italy [19], one from Israel [18] and one from China [21]. All studies were conducted among mature females with breast cancer (over 18).

Two of the studies used cross-sectional analyses [19,21]. Both studies reported results from longitudinal and pre/post analysis to examine associations between BMI and fracture risk. These studies used objective measures to assess bone quality. Fracture risk was assessed in conjunction with menopausal status, exercise, weight, use of chemotherapy, stage and grade of cancer.

Overall, four studies [18–21] ($n = 4$, 80 %) reported a positive association between BMI and fracture risk in females with BC. However, one of these results [19] ($n = 1$) reported mixed results for women with different treatment interventions (control vs treatment of AI). Among the AI naive patients (control group), the vertebral fracture prevalence was higher in the subgroup with low FBM than in those with high FBM, but the difference was not statistically significant (19.2 % vs 13.3 %; $P = 0.13$). It was clear that among AI treated females, those with higher FBM were those with higher fracture risk whilst low FBM patients had similar fracture prevalence.

Our charting exercise (Table 1) revealed several branches within the topic of fracture risk in obese females with BC: use of chemotherapy, exercise, site of fractures, diagnosis factor, age trend, stage and grade of BC, history of fracture and additional characters of bone quality. These issues were most indicated as the focus of the studies. Additional topics less frequently mentioned were as follows: use of supplements, smoking status, comorbidities such as myocardial infarction, diabetes.

4. Discussion

The skeleton is the most common site of breast cancer metastasis.

The majority of individuals (up to 85 %) with advanced disease harbour bone metastases [23]. Metastatic cancer cells tend to populate the highly vascularized area of the axial skeleton where they disrupt bone physiology and haematopoiesis as well as the immune system [24]. Most breast cancer metastases cause eventual bone loss. The most frequent clinical outcomes are bone pain, nerve compression, hypercalcemia and the typical sequela is skeletal fracture [3].

It is of general concern that obesity has the propensity for several types of cancers including the breast [5]. Obesity has been a debatable subject in relation to fracture risk. Whether obesity increases skeletal-related events have inspired a plethora of studies. However, the results are conflicting [10,11,25]. De Laet et al. suggested that obesity may protect bones and low BMI may confer a higher fracture risk [9]. Other studies by Premaor and Palermo argued that even though obesity might provide greater protection due to fat tissue padding around the bones, restriction of mobility and higher impact of weight during a fall might mitigate these potential benefits [11,25]. Given the exponential growing rate of obesity and its association with a wide spectrum of comorbidity such as diabetes and cancers [26] that could affect bone quality, there is still surprisingly little that we know about the association between obesity and fracture risk in BC. It is of utmost importance to focus on this topic. To date there is no literature exploring the link between obesity, breast cancer bone metastasis and fracture risk. This scoping review therefore explored the relationship between obesity, breast cancer primary disease and fracture risk with the aim to inform future research directions.

In this scoping review, we found that four out of five selected studies eligible for analysis showed an association between obesity and an increased in fracture risk in breast cancer. Fraenkel and colleagues conducted a retrospective study in a large cohort of 17 110 women in Israel with the primary objective to compare the rates of osteoporotic fractures adjusted for BMD [18]. The patients were then further evaluated to determine whether fracture risk was attributed to BMD or BC treatment. The results showed that BC survivors were at a 34 % increased risk of osteoporotic fracture. This risk is not explained by loss of BMD. However, they did report that, age, BMI, and BC play a significant role in increased fracture risk. This finding supports our hypothesis of a positive relationship between obesity and fracture risk in BC.

Whilst examining the association of FBM with vertebral fractures in postmenopausal women with breast cancer undergoing adjuvant aromatase inhibitor therapy, Pedersini et al conducted a study of 556 women in Italy [19]. The results indicated that there is no statistically significant difference in fracture risk in low FBM women regardless of AI treatment groups or within the AI naive patients. Interestingly, FBM in obese females with BC may be a factor associated with vertebral fractures on postmenopausal women with breast cancer receiving AI therapy (p -value < 0.04). At closer inspection considering the covariates, it was clear that older age in AI-treated patients also played a significant role ($p < 0.001$). They were also less likely to engage in physical activity ($p < 0.03$) and consume fewer alcoholic beverages ($p < 0.001$). Even though we are unable to draw a conclusively positive association between obesity and fracture risk, it could be deduced that higher incidence of fracture might be explained in these patients due to their more sedentary lifestyle, higher FBM and/or seniority of age [27,28].

Two selected studies by Melton and Zheng [20,21] found an increased risk of fracture with obesity in pre-menopausal women with a hazard ratio (HR) of 1.8 [20] and 1.36 [21] for any fractures, and 1.8 [20] and 1.81 [21] for osteoporotic fractures. However, this relationship was not linear and took a U shape turn for post-menopausal patients. Obesity seemed to play a protective role for this subset of population of these studies. This result may be attributable in part to the small number of obese patients included in the studies. It might be beneficial to consider that with increased age, post-menopausal women are already at higher risk of fractures and have greater potential that they would be classified as at risk of osteoporotic [29]. Therefore, these patients are

more likely to be treated with bisphosphonates which decrease bone resorption and consequentially increases bone quality [30]. Of note, bone marrow adipocytes found abundantly in bone marrow tissue account for 15 % of the bone marrow volume in young adults, increasing significantly to 60 % by the age of 65 years old, irrespective of BMI [31]. This might explain the less apparent effect of obesity on bone.

Standing out among the selected studies was research by Chen et al. with a prospective, observational study [22]. It concluded that postmenopausal survivors of breast cancer are at increased risk for fractures. However, BMI, among other covariates such as number of years since menopause, age at breast cancer diagnosis and hormone therapy use, were not significantly associated with fracture risk in breast cancer survivors. Regrettably, detailed data was not available on the published article.

All analysed studies had the following indicated focuses: use of chemotherapy, exercise, site of fractures, diagnosis factor, age trend, stage and grade of BC, history of fracture and additional characters of bone quality. Three studies [19,20,22] confirmed the use of chemotherapy and an increase in fracture risk whilst two studies [18,21] provided a negative association. Concerning the use of exercise, 4 studies [19–22] claimed a positive impact on reducing fracture risk. Sites of fracture were explored in 4 studies [18,19,20,22] with vertebrae being the most sensitive sites for fracture. History of fracture was examined in 3 studies [19,20,22] indicating a negative effect on fracture risk.

All studies considered age in conjunction with fracture risk with 4 out of 5 studies [18,19,20,22] conferring a higher risk in postmenopausal women. Most studies except one [22] recorded stages and grades of BC, but only two [18,21] offered insights of fracture risk with opposing results. Fraenkel noted that women with fractures had a trend toward less advanced BC (lower tumour node metastasis stage and grade) whereas Zheng reported no differences in risk.

Two studies [18,19] mentioned additional characters of bone quality such BMD measurements on different sites of the skeleton. Fraenkel drew a conclusion that fracture risk was independent of BMD on all three sites, lumbar spine, femur neck and total hip [18] whilst Pedersini reported lower femoral neck and total hip BMD and T score values correlated significantly with the occurrence of vertebral fracture compared with no vertebral fracture in the AI naïve patients, but not the AI treated patients [19].

These 5 selected studies offered valuable insight into the interaction between obesity and its effect on fracture risk in BC, however, none of the studies provided in-depth details for readers to make a conclusive association.

Using the scoping review methodology, we were not restricted to tight inclusion criteria. However, there are several limitations to our study. The most challenging issue we met was the limited information on the topic in current literature. Furthermore, studies that were able to be included often lacked raw data for analysis and/or omission of data that would aid the decision-making process. A quantitative synthesis may have revealed additional insights [32]. Not being able to encompass all studies concerning breast cancer, obesity, and fracture risk in other languages as well as limited access to restricted valuable information on more relevant articles hindered our ability to fully analyse the topic in the context of higher quality studies.

This scoping review attempted to establish a positive association between obesity and its effect on fracture risk in females with BC. However, the question whether this association remains unclear in females with bone metastasis. Future research is needed to shed light on this pressing issue as obesity is on the rise and its effect on breast cancer is self-evident [33].

It is also crucial to note that all selected studies support the use of physical activity in the attempt to attenuate fracture risk. Research in exercise oncology has made tremendous progress in the last few decades. Structured exercise was found to improve physical functioning in breast cancer patients compared to usual care [34]. There is a large body

of evidence to show that the effect of physical activity interventions on upper and lower body strength post cancer treatment, and moderate effects on fatigue and breast cancer-specific concerns. In these studies, exercise was well tolerated during and post treatment without adverse events. It should not be neglected that physical activity has a positive effect during treatment increasing aerobic fitness, muscular strength, functional quality of life, mental health, and self-esteem [34–39]. A regular exercise program can enhance bone strength and mobility in cancer patients at risk for bone loss [40].

5. Conclusions

In summary, we found novel indication that obesity may be associated with increased fracture risk in females with breast cancer. Further, exercise appears to have an inverse association with the risk for fracture. To our best knowledge this is the first study to review the association between obesity, breast cancer and fracture risk. To date, there is no research on this topic concerning breast cancer bone metastasis. This presents a crucial area for further research and an exciting opportunity for potential inclusion of exercise as adjuvant treatment.

These findings help guide further research into this area and in time the potential development of comprehensive fracture risk reduction strategies in this vulnerable population.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jbo.2022.100449>.

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