Universidade Federal do Rio Grande do Sul
Faculdade de Medicina
Programa de Pós-Graduação em Ciências Médicas: Endocrinologia

Tese de Doutorado

Adiposidade corporal em pacientes com câncer de mama: revisões sistemáticas das mudanças na adiposidade corporal durante o tratamento antineoplásico e relação dessa com desfechos da doença

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Porto Alegre, 2024

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Tese apresentada ao Programa de Pós-graduação em Ciências Médicas: Endocrinologia da Faculdade de Medicina da Universidade Federal do Rio Grande do Sul como requisito parcial para a obtenção do título de doutora em Endocrinologia.

Porto Alegre, 2024

Ficha catalográfica

CIP - Catalogação na Publicação

Poltronieri, Taiara
Adiposidade corporal em pacientes com câncer de mama: revisões sistemáticas das mudanças na adiposidade corporal durante o tratamento antineoplásico e relação dessa com desfechos da doença / Taiara Poltronieri. -- 2024.
120 f.
Orientadora: Luciana Viana.

Tese (Doutorado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Porto Alegre, BR-RS, 2024.

1. Composição corporal. 2. Distribuição da gordura corporal. 3. Neoplasias da mama. 4. Antineoplásicos. I. Viana, Luciana, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

Esta Tese de Doutorado será apresentada no formato sugerido pelo Programa de Pós-Graduação em Ciências Médicas: Endocrinologia. Ela é constituída de resumo da tese, uma introdução em português, dois artigos em inglês (o primeiro publicado na *Nutrition and Cancer* em 2022 e o segundo na *Clinical Nutrition* em 2024), além de considerações finais em português.

Dedicatória

À minha família por me ensinar a perseverar.

Às mulheres com câncer que cruzaram meu caminho por me mostrar a sua força.

Agradecimentos

À minha orientadora, Profa. Dra. Luciana Verçoza Viana, a qual me acolheu de braços abertos. Agradeço pela sua contribuição ao meu crescimento pessoal e profissional durante esses 4 anos através da sua ilustre capacidade de unir didática à ética docente e científica. Obrigada pela sua paciência e orientações.

Agradeço aos colegas da UFRGS e da Universidade de Alberta, no Canadá, pelo companheirismo nas tarefas, nas alegrias e nas dificuldades.

Agradeço aos professores e funcionários do Programa de Pós-graduação em Ciências Médicas: Endocrinologia por me receberem tão bem, pela qualidade do ensino e pelo suporte. Assim como os professores dos demais Programas de Pós-Graduação com os quais tive oportunidade de cursar excelentes disciplinas.

Agradeço as funcionárias do Serviço de Biblioteca da UFRGS, as quais foram imprescindíveis para o rigor da minha coleta de dados ao longo da construção da minha tese.

Agradeço a CAPES e à Universidade de Alberta, em especial a Profa. Dra. Carla Prado pela receptividade e oportunidade de vivenciar a pesquisa no exterior.

À minha família, em especial ao meu esposo Cássio, meus pais, minha tia Wilma, e minhas filhas de quatro patas Amora e Carmela. Obrigada pelo amor, compreensão e apoio.

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Capítulo 3 - *Body adipose tissue depots and treatment outcomes for women with breast cancer: a systematic review*

Lista de Abreviaturas

ADP - Air displacement plethysmography
BAT - Brown adipose tissue
BC – Breast cancer
BIA - Bioelectrical impedance / Impedância bioelétrica
BMI - Body mass index
CDK - Cyclin-dependent kinase
CHT – Chemotherapy
CI – Confidence interval
CT - Computed tomography
DDFS – Distant disease-free survival
DEXA – Análise por dupla emissão de raios-X
DFS – Disease-free survival
DSS – Disease-specific survival
DXA - Dual energy X-ray absorptiometry
FBM - Fat body mass
GFAT – Gluteofemoral adipose tissue
HU – Hounsfield Units
HR – Hazard ratio
IMAT - Intermuscular adipose tissue
MRI - Magnetic resonance imaging
PCR – Pathologic complete response
PDA - Pletismografia por deslocamento de ar
PET-CT - Positron emission tomography – computed tomography
PFS – Progression-free survival
OR – Odds ratios
OS – Overall survival
SAT - Subcutaneous adipose tissue
SERMS - Selective estrogen receptor modulators
TAAT - Total abdominal adipose tissue
TAGF - Tecido adiposo gluteofemoral
TAIM – Tecido adiposo intermuscular

TAS – Tecido adiposo subcutâneo

TAT - Total adipose tissue

TAV – Tecido adiposo visceral

TBF - Total body fat

TC - Tomografia computadorizada

USG - Ultrasound

VAT - Visceral adipose tissue

Resumo

O excesso de adiposidade corporal é uma condição comum em mulheres com câncer de mama, a qual gera um ambiente propício à neoplasia. A presente tese buscou avaliar as alterações na adiposidade corporal em mulheres com câncer de mama e sua relação com o tratamento antineoplásico, assim como, os possíveis impactos dos compartimentos adiposos corporais (visceral, subcutâneo, intermuscular e gluteofemoral) em desfechos dessas pacientes. **Métodos:** Estudo 1) Revisão de escopo de estudos clínicos e observacionais avaliando mulheres diagnosticadas com câncer de mama que tiveram a adiposidade corporal quantificada pelo menos duas vezes durante o seguimento; Estudo 2) Revisão sistemática de estudos observacionais com mulheres diagnosticadas com câncer de mama submetidas à análise do tecido adiposo corporal por tomografia computadorizada, relacionando esses dados a desfechos de interesse. **Resultados:** Dados insuficientes e heterogêneos impossibilitaram análises quantitativas em ambos os estudos. O estudo 1 mostrou aumento significativo da adiposidade corporal durante o tratamento oncológico na maioria dos estudos; quimioterapia e hormonioterapia com moduladores seletivos do receptor de estrogênio estiveram relacionados a maior adiposidade corporal, diferentemente dos inibidores da aromatase. O estudo 2 encontrou que, ao contrário do tecido adiposo gluteofemoral, maiores quantidades de tecido adiposo visceral e subcutâneo foram associadas a piores desfechos na população analisada. Já o tecido adiposo intermuscular apresentou resultados conflitantes. **Conclusão**: Os achados dessa tese indicam que, embora tenha sido observado um aumento significativo da adiposidade corporal durante o tratamento oncológico, diferentes modalidades terapêuticas impactam a adiposidade de forma distinta. Além disso, é crucial considerar não apenas a quantidade, mas também a distribuição corporal do tecido adiposo, devido às diferentes características dos seus depósitos e, consequentemente, impacto prognóstico. Essas informações propiciam um manejo clínico mais precoce e eficaz para essa população. São necessários estudos futuros empregando aspectos clínicos e métodos de análise da adiposidade corporal mais homogêneos.

Capítulo 1

Introdução

O câncer de mama é a neoplasia mais comum entre mulheres e a mais frequente em geral [1]. Mundialmente, em 2020, foram registrados mais de 2,26 milhões de novos casos de câncer de mama entre a população feminina [1]. No Brasil, excluindo tumores de pele não melanoma, o câncer de mama feminino é o mais incidente em todas as regiões do país. De acordo com o Instituto Nacional de Câncer, para cada ano do triênio de 2023 a 2025, estimam-se 73.610 casos novos da doença [2].

Diante dos números alarmantes do câncer de mama e do seu amplo impacto na saúde das mulheres, é crucial a busca continuada por avanços clínicos e na qualidade de vida dessa população [3]. Nesse sentido, a integralidade na assistência, que envolve diferentes aspectos do cuidado e profissionais de saúde, tem ganhado destaque como estratégia para otimizar os resultados de pacientes diagnosticadas com câncer [4-6].

O avanço da nutrição oncológica tem possibilitado uma avaliação mais ampla do estado nutricional, através de uma análise detalhada dos componentes da massa corporal [7]. O termo composição corporal se refere aos tecidos presentes no corpo, como por exemplo, o muscular e o gorduroso [8,9]. A presença de um fenótipo de composição corporal desfavorável, caracterizado por massa muscular reduzida e/ou excesso de gordura, está associado com um pior prognóstico do câncer de mama. Os estudos apontam para maior recorrência da doença, menor resposta ao tratamento antineoplásico e redução na sobrevida [9-11].

Esta tese concentra-se primordialmente na interação entre a adiposidade corporal, os tratamentos antineoplásicos para o câncer de mama e desfechos relacionados ao câncer de mama em mulheres. Esse foco é justificado pela relação bidirecional entre o excesso de adiposidade corporal e o câncer de mama. O excesso de adiposidade corporal não é apenas um fator de risco para o desenvolvimento do câncer de mama [12], mas também pode ser resultado do tratamento antineoplásico [13,14]. Medicamentos de suporte, como os corticosteroides, frequentemente utilizados durante o tratamento antineoplásico, também podem contribuir para alterações na adiposidade corporal [15].

A análise da composição corporal e, por conseguinte, da adiposidade corporal, pode ser realizada em cinco níveis (atômico, molecular, celular, tecidual/órgão e corpo inteiro), dependendo do método de avaliação empregado [16-18]. Os níveis mais comumente avaliados pelos estudos em pacientes com câncer de mama são o molecular e o tecidual/órgão. No nível molecular, é possível avaliar a massa de gordura, enquanto no nível tecidual/órgão, o tecido adiposo. A massa de gordura é composta por triglicerídeos e representa aproximadamente 80% do tecido adiposo [16,17]. Este último, é um tecido conectivo formado por adipócitos, fibras colágenas e elásticas, fibroblastos, células imunes, vasos sanguíneos e fluído extracelular [16,17,19].

Nesta tese, o termo adiposidade corporal é exclusivamente utilizado ao referir-se aos depósitos de gordura corporal de maneira abrangente, sem considerar os níveis em análise. Faz-se importante a correta utilização das terminologias e interpretação de dados, pois a função e o metabolismo da adiposidade corporal variam em cada nível devido às suas diferentes composições e organizações [16-18].

As localizações anatômicas da adiposidade corporal também precisam ser levadas em consideração. A literatura demonstra, por exemplo, que os compartimentos de tecido adiposo, como o visceral, o subcutâneo e o intermuscular, são metabolicamente heterogêneos [20-22]. O tecido adiposo visceral (TAV) encontra-se ao redor dos órgãos na cavidade peritoneal [22]. Já o tecido adiposo subcutâneo (TAS) está localizado logo abaixo da pele e se distribui por todo o corpo. O TAS concentra-se principalmente na região anterior e posterior da parede abdominal (TAS abdominal) e na região gluteofemoral (referido nesta tese como tecido adiposo gluteofemoral [TAGF]) [22,23]. O tecido adiposo intermuscular (TAIM) se encontra intercalado entre e ao redor dos grupos musculares esqueléticos, também em diferentes partes do corpo [21].

O tecido adiposo da região abdominal, em contraste com o da região gluteofemoral [24,25], demonstrou ser mais favorável ao desenvolvimento e à progressão tumoral, por ser pró-inflamatório, hiperglicêmico e hiperinsulinêmico [26-28]. Além disso, distinções significativas podem ser observadas entre os compartimentos abdominais. Quando comparado ao TAS abdominal, o TAV também apresenta mais células inflamatórias e imunes, e maiores vascularização e resistência à ação da insulina [23,29,30].

Até mesmo o TAS abdominal exibe variações com base na sua localização em relação à fáscia de Scarpa. A fáscia de Scarpa é uma camada delgada e firme de tecido conjuntivo localizada na parede anterior do abdome que divide o TAS abdominal em uma porção mais externa e outra mais interna. O TAS acima da fáscia (mais externo) compartilha características similares com o TAGF, enquanto o TAS que está abaixo dela (mais interno) assemelha-se mais ao TAV [31-34]. Há indícios de que o TAIM também seja funcionalmente semelhante ao TAV, e contribua para a ocorrência de inflamação, resistência à ação da insulina e desregulação glicêmica. No entanto, suas propriedades ainda não foram completamente esclarecidas. Permanece incerto se o TAIM é capaz de predizer riscos metabólicos de forma independente ao tecido adiposo abdominal [21].

Em mulheres, o acúmulo e a distribuição da adiposidade corporal estão relacionados a fatores fisiológicos, como o envelhecimento e a menopausa. A queda nos níveis de estrogênio e o aumento do hormônio folículo estimulante durante a menopausa influenciam o metabolismo lipídico e insulinêmico, além de reduzir o gasto energético, levando ao acúmulo de adiposidade abdominal e visceral [35-38].

A relação entre a adiposidade corporal e o câncer de mama ocorre principalmente devido às alterações metabólicas negativas causadas pelo excesso de tecido gorduroso. Exemplos são a promoção de um estado pró-inflamatório e modificações no metabolismo glicêmico e insulinêmico [24,27,39,40]. Pacientes que apresentam excesso de adiposidade corporal ao serem submetidas ao tratamento antineoplásico para o câncer de mama tendem a enfrentar mais complicações cirúrgicas, radioterápicas e quimioterápicas [11]. No caso da quimioterapia, por exemplo, a adiposidade corporal excessiva oportuniza o acúmulo de drogas antineoplásicas lipofílicas no tecido adiposo, o que pode comprometer a eficácia e causar maior toxicidade [41,42].

Em contrapartida, o próprio tratamento antineoplásico também pode afetar os tecidos corporais [13,14]. É possível que os quimioterápicos reduzam o gasto energético, facilitando o ganho de adiposidade corporal [43]. Além disso, os efeitos colaterais oriundos dos antineoplásicos podem afetar a ingestão alimentar e a funcionalidade das pacientes, favorecendo o ganho de adiposidade corporal [44]. Já as terapias hormonais, a depender do seu mecanismo de ação, podem tanto exacerbar o ganho de adiposidade corporal pela supressão

estrogênica, quanto reduzir a adiposidade corporal em mulheres na pós-menopausa ao beneficiar os hormônios androgênicos [45,46].

Dada essa complexa relação metabólica, estudos têm investigado o comportamento da adiposidade corporal durante o tratamento antineoplásico [14,47,48], bem como o impacto clínico da quantidade ou distribuição da adiposidade corporal em mulheres com câncer de mama [47,49,50].

Diversos métodos não invasivos estão disponíveis para predizer a adiposidade corporal em humanos [11,51-53]. Estes baseiam-se em técnicas e métricas específicas, variando em precisão e acurácia, e apresentando vantagens e desvantagens [16,52,54]. Dentre os métodos aplicados pelos estudos incluídos nesta tese estão a pletismografia por deslocamento de ar (PDA), a impedância bioelétrica (BIA), a análise por dupla emissão de raios-X (DEXA), e a tomografia computadorizada (TC), que permitem predizer a adiposidade corporal nos níveis molecular e tecidual/órgão [16,52,54].

A PDA avalia a densidade corporal e, a partir disso, prediz a gordura total, mas não a sua distribuição corporal. Fatores de confusão como variações no conteúdo mineral ósseo e na hidratação e o excesso de pelos faciais ou corporais podem interferir nos resultados [52,54]. Esse método carece de baixa complexidade técnica, porém tem alto custo e não é portátil [54,55].

Já a BIA utiliza as propriedades condutivas elétricas do corpo para estimar a gordura corporal [52,54,56-58]. Esse método é atualmente o mais utilizado na prática clínica, tem custo relativamente baixo, fácil aplicação e é portátil [54,56,58]. Contudo, os resultados obtidos devem ser interpretados com cautela devido à sua limitada precisão. Variações no comprimento dos membros, atividade física recente, hidratação corporal, equações preditivas e protocolos de medição aplicados podem contribuir para possíveis erros [52,54-58].

A DEXA e a TC são métodos de imagem, e utilizam as diferenças na atenuação de raios-X entre os tecidos corporais para estimar a adiposidade corporal total e regional [52,54,57]. Ambos são considerados métodos de referência em predizer a composição corporal em níveis molecular (DEXA) e de tecidos/órgãos (TC), sendo atualmente, a ressonância magnética o método de imagem considerado padrão ouro para essa análise [59,60]. No entanto, esses não são equipamentos portáteis e necessitam expertise técnica [52,54,55,57-59,61,62]. A DEXA tem menor exposição à radiação, é mais rápida e tem maior

disponibilidade [54,57]. Já a TC ainda é considerada ferramenta estritamente de pesquisa para avaliação da composição corporal, pelo seu alto custo, complexidade e elevada exposição à radiação. É um exame de conveniência clínica em pacientes com câncer e diferencia-se por estimar não só a quantidade como também a qualidade do tecido adiposo [55,58,61,62].

Há poucas revisões de literatura abordando a relação entre mudanças e distribuição da adiposidade corporal, tratamento antineoplásico e desfechos do câncer de mama [63-65]. Dessa forma, são necessárias revisões atuais seguindo critérios sistemáticos de desenvolvimento, focadas na adiposidade corporal em mulheres com câncer de mama e que também abordem protocolos terapêuticos mais recentes.

Devido à importância clínica da adiposidade corporal em pacientes com câncer de mama e considerando as lacunas existentes na literatura e a necessidade de revisão e atualização do tema, essa tese teve como objetivos: 1) Investigar através de revisão de escopo as alterações na adiposidade corporal em mulheres com câncer de mama e sua relação com o tratamento antineoplásico; 2) Avaliar através de revisão sistemática o impacto da distribuição do tecido adiposo (visceral, subcutâneo, gluteofemoral e intermuscular) nos desfechos de sobrevida, complicações, toxicidades e resposta ao tratamento antineoplásico nessa mesma população.

Esta tese busca aprofundar a compreensão da interação entre o câncer de mama, suas intervenções terapêuticas e os efeitos na adiposidade corporal. Assim como, visa contribuir para a aplicação da avaliação da adiposidade corporal no prognóstico de pacientes com câncer de mama. Espera-se que essa abordagem possibilite intervenções nutricionais e de estilo de vida mais precoces e eficazes, potencialmente resultando na redução de efeitos colaterais e na melhoria dos resultados clínicos.

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Capítulo 2

Artigo 1

Changes in body adiposity in women undergoing breast cancer treatment: a scoping review

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Artigo publicado no periódico *Nutrition and Cancer*
Fator de Impacto 2.816 – doi: 10.1080/01635581.2022.2081341

Abstract

Antineoplastic treatments can negatively affect body composition, leading to metabolic derangements and worse clinical outcomes in breast cancer patients. This scoping review assesses body adiposity changes during breast cancer therapy. We included clinical and observational studies, published until the last search date in any language, with women aged >18 years, after breast cancer diagnosis, at any clinical stage and with any history of breast cancer treatment, who had body adiposity quantified at least twice during follow-up. In total, 17 studies were included (n=1,009 individuals), six of which found a significant increase in body adiposity during treatment and two found a significant decrease. One studies presented divergent findings according to the method and the analyzed body adiposity depots and eight found no significant changes. Hormone therapy using selective estrogen receptor modulators were associated with increased body adiposity, whereas aromatase inhibitors were associated with its decrease (n=3). Chemotherapy alone or in combination with hormone therapy was associated with increased body adiposity (n=2). When combined with monoclonal antibody, chemotherapy was linked to reduced brown adipose tissue activity (n=1). Breast cancer treatment may have different effects on body adiposity, according to its mechanisms and protocols. Further studies are necessary to better elucidate this scenario.

Keywords: Adiposity, Antineoplastic Protocols, Body Composition, Breast Neoplasms, Nutritional Status

Introduction

Breast cancer is the most common malignant disease worldwide among women (1), with an incidence of over two million new cases in 2018 (2). Fortunately, breast cancer overall survival rates have improved (3) due to diagnosis and therapeutic improvements, including surgery, radiotherapy, chemotherapy, hormone treatment, and target therapy. Besides, treatment advances have enabled fewer side effects and a better quality of life (4,5).

Body composition refers to the amount of body fat and lean tissues (6). Body mass index (BMI) is the most used measurement to evaluate adiposity, but it may not accurately provide information about the contributions of each tissue to body mass nor depict specific changes in these body depots. Assessing different body depots provides a more in-depth evaluation of the nutritional status (6–8), and it may be essential under some clinical conditions, such as cancer, psoriasis, cardiovascular and liver diseases, and others (9–12). Cancer treatment may lead to unfavorable changes in body composition, such as increased or redistributed adiposity (13,14), contributing to a poor prognosis (15–18).

The most commonly used methods among the innovative approaches for assessing body composition in the literature are dual energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), ultrasonography (USG), computed tomography (CT), and magnetic resonance imaging (MRI). These methods can be applied in different contexts and applications, presenting advantages and disadvantages (Figure S1) (6,19–30). Different organizational levels and metrics, as well as types of adipose tissues and adipose depots, can be evaluated using these tools (Chart S1) (6,27,31–40).

Currently, the lack of available literature evaluating the relationship between body adiposity changes, breast cancer treatment and the methodological diversity of the existing studies are significant limitations. To our knowledge, only a few reviews have evaluated this relationship (14,15,41). This study updates the topic with an appropriate methodological criterion, focusing on body adiposity and new antineoplastic drugs and protocols.

Due to the apparent clinical importance of body adiposity in cancer patients, a greater understanding of the complex interaction between the cancer itself, its therapeutic interventions and metabolic effects is necessary. We hope that understanding the changes in body adiposity during cancer treatment will

provide a useful instrument to tailor medicine to the individual. Treatment options could provide early and more effective interventions, seeking positive clinical outcomes and less side effects if body composition becomes a part of it in the future.

Given this context, this study analyzes body adiposity changes during clinical follow-up of breast cancer patients and their relationship with the applied antineoplastic treatments.

Materials and methods

Study Design and Research Question

A scoping review is a type of literature review that, focusing on wide research topics, can identify gaps on a given subject, contributing to science in a systematic, transparent, and methodologically rigorous manner (42).

This scoping review was developed according to the Joanna Briggs Institute (42) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews (PRISMA-ScR) guideline (43), to systematize and improve the study quality.

The research question was: Do antineoplastic treatments affect body adiposity in women diagnosed with breast cancer during their clinical follow-up?

Search strategy

A literature search was performed in the U.S. National Library of Medicine (PubMed), Embase, Cochrane Library, Web of Science and Scopus databases from May 2020 to November 2020, according to the mnemonic Population, Concept and Context and using all index terms and keywords selected from PubMed Medical Subject Headings (MESH). Boolean operators “OR” and “AND” were used to combine terms within the strategy conceptual blocks, and to combine the blocks with each other, respectively, truncating terms whenever necessary.

Specific search methods for each database were also applied and the initial search comprised title, abstract, and keywords. Manual searches were made in the reference list of the selected articles. Table S1 shows the complete list of applied strategies and the number of studies found in each database.

Eligibility Criteria and Study Selection

Eligibility criteria consisted of clinical and observational studies published in any language until the last search date, with women aged >18 years after breast cancer diagnosis, at any stage of the disease, and who had body adiposity quantified at least twice during the follow-up. Studies evaluating patients undergoing adjuvant and/or neoadjuvant antineoplastic treatments with body adiposity analysis prior, during, or after treatments were included. Antineoplastic treatments comprised surgery, radiotherapy, chemotherapy, hormone therapy, or target therapy (4). The following exams for evaluating body adiposity were included in this study: DXA, CT, USG, BIA, MRI, air displacement plethysmography (ADP) and positron emission tomography/computed tomography (PET/CT).

Case series, case reports, and reviews were excluded. Clinical studies with interventions in the whole sample that could affect body adiposity were excluded. In studies including more than one group, with an intervention beyond the cancer treatment itself and that aimed to modify body composition (i.e., exercise or dieting), only the nonintervention group was included in this review.

Selection was carried out by two independent researchers (TSP and RSP): first, a screening based on title and abstract reading was performed; then, the eligibility of each study previously selected was independently analyzed by the researchers. When necessary, a third researcher (LVV) resolved disagreements regarding study eligibility.

Data Extraction

Data from the included studies were independently computed by each researcher and refined during the extraction process. A standard form was specifically developed for this review, and was previously tested in a pilot study.

This tool included the following items: authors, year and country of publication, study design, sample size, clinical variables (age, ethnicity, menopausal status, BMI, types of tumor, staging, hormone receptors), treatments used for breast cancer, antineoplastic treatment status at each body adiposity assessment, methods used and frequency, presence of body adiposity changes during the study, and possible relations with antineoplastic treatments.

If the included study did not specify which body fat depot was analyzed, it was considered as total body fat (TBF), according to the method used. Moreover, if patients had already undergone antineoplastic treatments, including surgery, prior to the current antineoplastic treatment under study, body adiposity analyses were considered as “assessed during the antineoplastic treatment”.

Whenever possible, in studies that evaluated body adiposity more than twice during follow-up, only the initial and final measurements were considered in this review. In articles without specific information related to body adiposity, the respective authors were contacted and WebPlotDigitizer Software v4.3 (Pacifica, California, USA) was applied to the necessary graphs to read specific body adiposity changes. Both reviewers independently performed the analysis, and the results were subsequently compared.

Results

Search Results

Figure 1 details the search process. The major exclusion criterion was body adiposity evaluation made only once during follow-up. Physical activity interventions between adiposity assessments and studies that evaluated body composition but did not assess body adiposity were excluded.

Study characteristics

Table 1 describes the main characteristics of the 17 studies included (total population = 1,009 patients) (34,44–59). Most studies were conducted in the United States (47,53,54,56,57,59), from 1997 to 2020. Of these, six were clinical trials analyzing the effect of interventions on body composition, such as bisphosphonates, chemotherapy, radiotherapy, hormone therapy, and physical activity (control group) (44,52–55,58).

Population characteristics

Mean age of the total sample was 51.3 years old, mostly including postmenopausal women (34,47–49,51,53–56,59). Only five studies reported the participants’ ethnicity and more than 80% declared themselves white (51,54,56–58).

A total of 15 studies included exclusively or a greater number of patients with early-stage disease (44–49,51–59). Eight articles had the entire sample or most of it composed by estrogen-positive tumors (34,45,46,48,49,51,52,55), and six studies showed progesterone receptor-positive tumors for more than 64% of the patients (45,46,48,51,52,55).

Antineoplastic treatments

In total, 13 studies clearly informed the inclusion of patients subjected to previous antineoplastic treatments (45–47,49–58). Of these, six evaluated individuals previously subjected to surgery (45,49,56–58) or to chemotherapy (53); the remaining seven included patients previously subjected to polytherapy, combining surgery, chemotherapy, radiotherapy, or hormone therapy, according to the respective protocols (46,47,50–52,54,55).

During studies follow-up, hormone therapy was the most used treatment, alone (47,49,51–55,59) or combined with other treatments, such as target therapy (34) and chemotherapy (49,56,57), also according to the respective protocols. Table S2 details information about treatments.

Anthropometric parameters

Among the 17 studies included, eight analyzed the initial and final BMI. A BMI uptrend was suggested (44–47,52,54,57,58), varying from 25.7kg/m² to 25.8kg/m², respectively. Hojan et al. found an increase in BMI after six months of treatment (52). Cheney et al. divided patients according to weight loss: the weight loss group showed a BMI decrease of -0.4kg/m² (-0.2 to -1.0), whereas the weight gain group had a BMI increase of 1.7kg/m² (1.0 to 2.3) (not statistically significant) (59).

Two studies statically analyzed the relationship between changes in body adiposity and BMI (44,52). Hojan et al. showed a significant correlation between BMI and body adiposity depots, with an increase in both during the study (52).

Body adiposity analysis

Table 2 summarizes the different methodologies used to evaluate body adiposity. DXA featured as the most used tool among the included studies (n=10) (46–48,52–58). Overall, the time between body adiposity assessments ranged

from one to 24 months, and ten studies performed more than three evaluations during follow-up (34,45,46,48,49,53–57).

Regardless of the method used, six authors observed an increase in body adiposity between the first and final analysis (46,47,49,52,53,58) and two studies reported body adiposity decrease in the follow-up (48,55). One study presented divergent findings according to the method and the analyzed body adiposity depots (56) and eight studies found no significant changes or did not report a p-value (34,44,45,50,51,54,57,59).

Six articles reported an increase in TBF by DXA (46,47,52,53,56,58), ranging from 0.9% to 11.3% (47,52,53,56,58). Van den Berg et al. and Hojan et al. also found an increase in fat body mass (FBM) (46,52), whereas Gadéa et al. and Francini et al. showed FBM decrease (48,55).

A study described no significant changes in subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), intermuscular adipose tissue (IMAT), and total adipose tissue (TAT) indexes by abdominal CT (34). On the other hand, patients evaluated by Battisti et al. showed an increase in all adipose tissue depots: total abdominal adipose tissue (TAAT), VAT and SAT, regardless of weight gain or loss (p-value not available) (51). Freedman et al. found a not statistically significant increase in SAT and a decrease in VAT (56). Rier et al. reported a TAT decrease in the paclitaxel group, but its increase in the 5-fluorouracil plus doxorubicin and cyclophosphamide group. All patients showed a decrease in SAT, a stable VAT, and an increase in IMAT (none statistically significant) (50). Two studies evaluated the VAT/SAT ratio: one showed a 21.8% increase (p-value not available) (51), whereas the other found its decrease ($p=0.02$), reflex of a SAT increase (56).

Cheney et al. applied CT scans to different body sites, and both patient groups (weight loss and weight gain) showed VAT decrease and SAT increase (p-value not available) (59). Using PET/CT, Ginzac et al. observed a tendency ($p=0.056$) towards a 4.38% decrease in brown adipose tissue (BAT) metabolic activity after a treatment cycle (44).

Table S3 shows changes in body adiposity according to the menopausal status, as it is a significant factor to be considered when assessing body adiposity during the antineoplastic treatment.

A total of 11 studies evaluated the relationship between body adiposity changes and antineoplastic treatments (chemotherapy, radiotherapy, target therapy, and hormone therapy) (44,45,49–51,53–58). Five of these did not find significant associations (45,50,51,56,58). Three studies found an association between hormonal therapies and changes in body adiposity (53–55). Van Londen et al. observed an increase in the TBF of aromatase inhibitors non-users (users of drugs such as SERMs) versus users during follow-up ($p \leq 0.05$) (53). Similarly, Francini et al. found a FBM decrease in aromatase inhibitors users, but not in non-users (users of SERM) ($p<0.01$) (55). Irwin et al. showed in six-month data that TBF decreased among patients using aromatase inhibitors, increased in those undergoing SERM, and even more so among those without hormone therapy (p-value not available) (54).

Studies showed that chemotherapy alone or combined with other treatments was related to an increase in body adiposity (49,57). Comparing patients treated with local treatment (surgery with or without radiotherapy) and chemotherapy, Demark-Wahnefried et al. reported a TBF and FBM increase ($p=0.001$ and $p=0.002$, respectively) in the chemotherapy group. It remained statistically significant ($p=0.04$ for both) after adjusting for age, ethnicity, radiotherapy, and baseline BMI (57). When chemotherapy was combined with hormone therapy, patients also presented an increase in FBM ($p=0.001$) (49). Similarly, Ginzac et al. found a reduction in BAT activity during chemotherapy plus target therapy (monoclonal antibody) use. After excluding other factors, they observed that antineoplastic treatment seems to be the only factor affecting BAT activity (statistics not shown) (44).

Discussion

Most studies reported an increase in body adiposity during breast cancer treatment, regardless of the method, with DXA being the most often employed tool. Results were mixed for CT scans, according to depots and metrics (as indexes) used to assess adipose tissue during different treatment approaches.

Previous studies (60–64) showed that higher body adiposity is related to adverse outcomes, such as increased mortality, cardiovascular disease, glycemic disorders, shorter distant disease-free survival, among others. So far, there is no specific value that serves as a cut-off point for this matter. More data

are still needed on the prognostic effect of different body adiposity depots and the amount of body adiposity gained considered significant in this population. We must also consider the patients' menopausal status, tumor characteristics, and cancer treatments when evaluating body adiposity (14,65,66).

Body adiposity distribution and quantity seem to be affected by antineoplastic drug use (45). Chemotherapy could negatively affect energy expenditure, which could predispose individuals to greater adiposity during cancer treatment (67). Proportion of body adiposity can affect the clearance and distribution volume of lipophilic antineoplastic drugs, such as docetaxel or paclitaxel. These compounds can accumulate in adipose tissue, compromising efficacy and increasing toxicity levels (68–70). The most common side effects are nausea, vomiting, dysgeusia, diarrhea, constipation, and pain. This conditions can affect patients' food intake and functional status, favoring loss of lean mass and gain of body adiposity (14,67,71–73).

Hormonal changes can also affect body adiposity, occurring as treatment and/or physiological consequence of the disease. Temporary amenorrhea or chronic ovarian failure induced by cytotoxic drugs may be related to metabolic effects and to body adiposity increase or change in its distribution (45,74). Menopause itself is associated with an increase in visceral adiposity (75,76). Hormone therapies—as aromatase inhibitors—can exacerbate this phenotype via additional suppression of estrogen production, but can also prolong the presence of higher levels of androgens, which are associated with lower body fat in postmenopausal women (77–79).

In our review, aromatase inhibitors were the most closely related to body adiposity decrease; hitherto, hormone therapy has provided conflicting outcomes regarding its effect on body composition (53,79). Gibb et al. showed that postmenopausal patients treated with aromatase inhibitors had a higher percentage of body adiposity compared to women without this treatment (77). Akyol et al. found a similar—but not statistically significant—increase of body adiposity percentage in both SERM and aromatase inhibitor patient groups (79). Regardless of the treatment side effects, exercise and eating habits must be considered, and lifestyle behavior changes should be encouraged to ameliorate these side effects (79,80).

In our study, patients using SERMs tended to show an increase in body adiposity, as described in previous studies in which SERM, such as tamoxifen, seem to increase body adiposity (14,72,81,82). Serum leptin levels could explain this finding, since these levels are positively correlated with FBM (83), and are higher in breast cancer patients treated with tamoxifen (84,85). However, we have found conflicting results by the latest clinical and experimental studies, showing a decrease in FBM with tamoxifen use (86,87). Several hypotheses could explain this outcome, such as reduction of lipoprotein lipase activity (88), production of reactive oxygen species at the cellular level (89), and others (87).

Lastly, the combination of a cyclin-dependent kinase (CDK) 4–6 inhibitor with hormone therapy, a modern protocol for breast cancer treatment, seems to positively contribute to body adiposity (34,90,91). This target therapy can act on body composition by suppressing a transcription factor related to CDK-6 activity, which negatively regulates the conversion of stored fat cells into burned status (92). In mice, these drugs were associated with fat mass reduction by increasing lipid oxidation (34,93). In this review, only Franzoi et al. evaluated the effect of this treatment protocol, and observed no significant differences regarding body composition parameters after treatment, but the authors emphasized the possibility of a later effect (34). Further studies are necessary to better clarify this new scenario, since these modern drugs will probably be part of the future of cancer treatment and their mechanisms may impact body composition.

Insufficient data precluded a quantitative analysis of the impact of antineoplastic treatments on body adiposity of the evaluated population. Other limitations included older studies, small and heterogenic samples, frequent lack of a comparison group and scarce information about previous treatments and institutional differences in treatment protocols. The studies also varied in terms of design, methodologies applied to assess body adiposity (such as scanned body regions, cut-off point divergences for body adiposity, and others) and nomenclature referring to body adiposity. We found different lengths of follow-up, which may hinder the detection of changes in body adiposity; a minimum and standardized follow-up period could allow for a better measurement.

On the other hand, most papers were prospective studies. Body adiposity evaluations were performed three or more times and most patients were postmenopausal women, facilitating total sample homogenization. The novelty of

our scoping review has important future implications, such as more predictable chemotherapy doses and sides effects based on body composition. The approach of new breast cancer therapies is also a strong point of this study.

In conclusion, most studies observed significant increase in body adiposity during breast cancer treatment, regardless of the analysis method used. Patients using aromatase inhibitors had better results on body adiposity changes, while SERMs and chemotherapy was related to a negative impact. Due to very limited data on the effects of treatment on body adiposity, the results of this review should be interpreted cautiously. Further prospective studies, with a larger sample size and more homogeneous methods will further elucidate this scenario, aiding in even better nutritional approaches and clinical outcomes for this population.

Funding and Acknowledgments: Research Incentive Fund (FIPE) – Hospital de Clinicas de Porto Alegre (HCPA) and Coordination for the Improvement of Higher Education Personnel (CAPES).

Institutional Review Board Statement: Study approved by the Research Ethics Committee of the Hospital de Clinicas de Porto Alegre (HCPA) under registration no. 31772720.5.0000.5327, and by the internal group responsible for research in HCPA - Research and Graduate Group (GPPG) under registration no. 2020-0224.

Conflict of interest: The authors report no conflict of interest.

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Figure 1. Search process of the studies

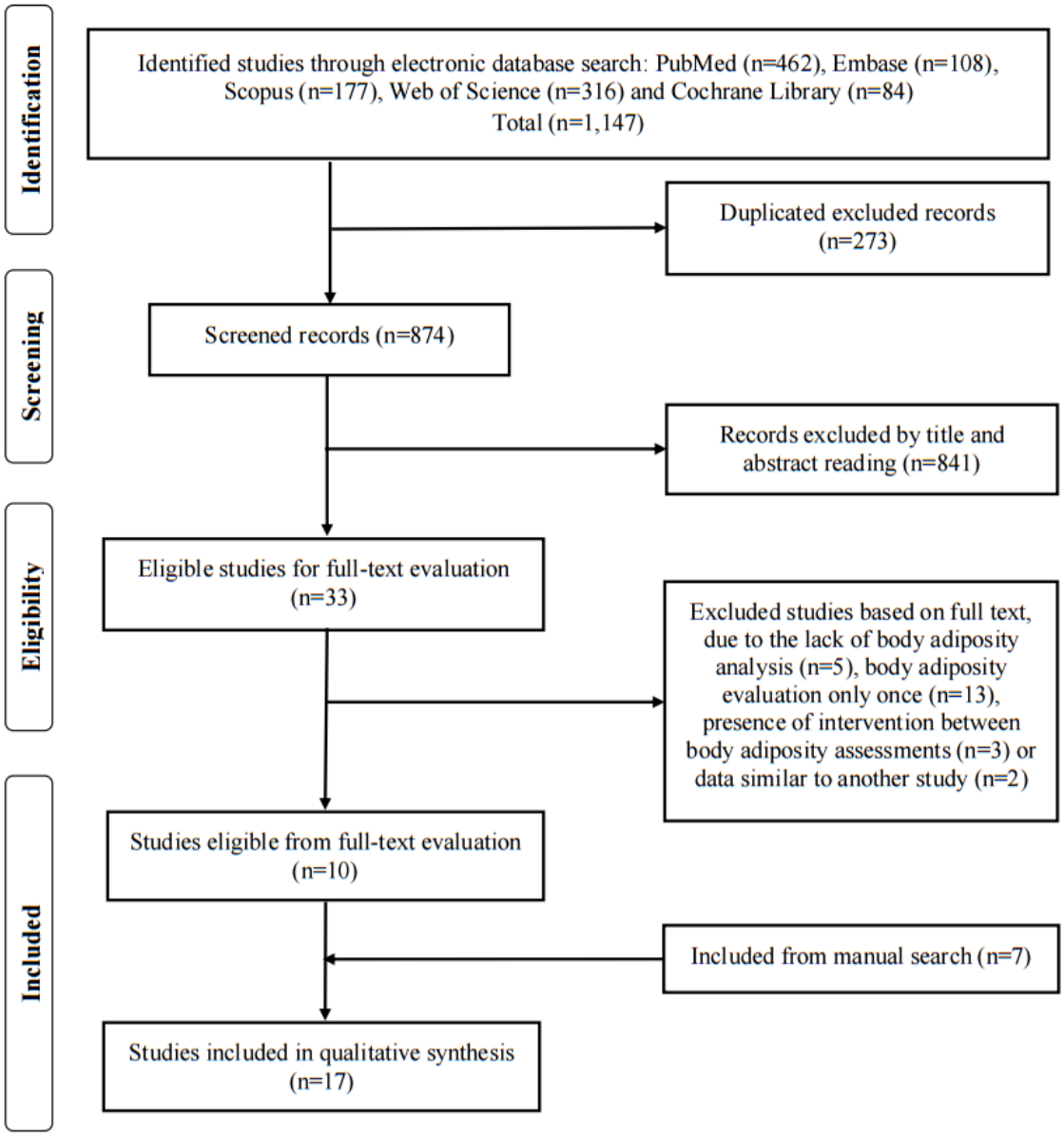


Table 1. Study information and patient's clinical characteristics (n=17).

Authors and Study		Patients		Tumor and Antineoplastic treatments		
Authors **Year** **Country**	**Design** **Sample size**	**Age** **Ethnicity** **Menopausal status**	**BMI**	**Tumor stage** **Hormone receptor** **HER-2**	**Previous treatments**	**Treatments used during e study**
Ginzac et al. 2020 (44) France	RCT / CHT[a] n=109	48 (25–74) yrs NA Premenopausal: 56.9%	Initial: 25.1 ± 5.7 kg/m² Final: 25.5 ± 5.3 kg/m²	Early tumors NA HER-2 (+): 100%	No previous treatment	CHT + TT (monoclonal antibody): 100%
Franzoi et al. 2020 (34) Belgium	Retrospective Initial: n=50 Final: n=20	61.2 (39–83) yrs NA Postmenopausal: 94%	NA	IV: 100% ER (+): 100% PR (+): NA HER-2 (+): 100%	NA	1st line therapy: 78% 2nd line therapy: 22% HT + TT (CDK 4/6 inhibitors): 100%
Jung et al. 2020 (45) South Korea	Prospective n=37	50.9 ± 9.4 yrs NA Premenopausal: 56.8%	Initial: 23.4 ± 3.0 kg/m² Final: 23.5 ± 2.9 kg/m²	II: 59.5% ER (+): 59.5% PR (+): 64.9% HER-2 (-): 73%	Surgery: 100%	CHT: 100%
van den Berg et al. 2020 (46) Netherlands	Prospective n=181[b]	51.8 (46.7–58.9) yrs NA Premenopausal: 57.5%	Initial: 25.6 ± 0.2 kg/m² Final: 25.9 ± 0.3 kg/m²	II: 60.8% ER (+): 79% PR (+): 66.9% HER-2 (-): 80.1%	NA	CHT: 100% Adjuvant: 64.6% Neo-adjuvant: 35.4%
Artese et al. 2018 (47) United States	Prospective n=10[b]	57.9 ± 5.7 yrs NA Postmenopausal: 100%	Initial: 24.9 ± 2.9 kg/m² Final: 25.2 ± 3.3 kg/m²	I: 50% NA HER-2: NA	Surgery: 100% RT: 60% | CHT: 40% AI: 80% | Some combination: 100%	Some patients could have used HT
Gadéa et al. 2018 (48) France	Prospective Initial: n=50 Final: n=48	60 (56–66) yrs NA Postmenopausal: 100%	Initial: 26 (23–31) kg/m² Final: NA	II-III: 100% ER (+): 90% PR (+): 76% HER-2 (+): 88%	NA	CHT: 100% TT (monoclonal antibody): 12%
Pedersen et al. 2017 (49) Denmark	Prospective n=95	58 (28–82) yrs NA Postmenopausal: 60%	NA	I: 62.1% ER (+): 94.7% PR (+): NA HER-2 (-): 95.8%	Surgery: 100%	HT only: 49.5% CHT + HT: 50.5%

Table 1 (continuation)**.** Study information and patient's clinical characteristics (n=17).

Authors and Study		Patients		Tumor and Antineoplastic treatments		
Authors **Year** **Country**	**Design** **Sample size**	**Age** **Ethnicity** **Menopausal status**	**BMI**	**Tumor stage** **Hormone receptor** **HER-2**	**Previous treatments**	**Treatments used during e study**
Rier et al. 2017 (50) Netherlands	Retrospective n=98	FAC: 57 (49.5–67.0) yrs Paclitaxel: 56 (48.0–62.5) yrs NA NA	**FAC** Initial: 26.8 (23.5–30.6) kg/m² Final: NA **Paclitaxel** Initial: 25.9 (22.9–30.6) kg/m² Final: NA	**FAC** IV: 100% HR (+): 76% HER-2 (-): 92% **Paclitaxel** IV: 100% HR (+): 74% HER-2 (-): 50.7%	(Neo)Adjuvant CHT: 40.8% (Neo)Adjuvant HT: 21.4% Palliative HT:14.3% Adjuvant + Palliative HT: 12.2%	1st line palliative CHT: 100%
Battisti et al. 2014 (51) Italy	Retrospective n=64	55.9 ± 11.7 yrs Caucasian: 100% Postmenopausal: 100%	Initial: 26.3 ± 4.2 kg/m² Final: NA	IIB: 35.9% ER (+): 98.4% PR (+): 93.8% HER-2: NA	Surgery: 100% Adjuvant CHT: 85.9%	HT: 100%
Hojan et al. 2013 (52) Poland	NRCT / Exercise[c] n=41	44.3 ± 4.9 yrs NA Premenopausal: 100%	Initial: 22.3 ± 3.1 kg/m² Final: 24.3 ± 4.2 kg/m²	IIA: 48.8% ER (+): 100% PR (+): 82.9% HER-2: NA	Surgery: 100% RT: 100%	HT: 100%
van Londen et al. 2011 (53) United States	RCT / Risedronate[a] n=82	AI: 51.2 ± 2.1 yrs No-AI: 49.8 ± 0.6 yrs NA Postmenopausal: 100%	NA	Nonmetastatic tumors NA HER-2: NA	Polyadjuvant CHT: 100%	HT: 74% No Adjuvant HT: 26%
Irwin et al. 2009 (54) United States	RCT / Exercise[d] Initial: n=38 Final: n=23	55.1 ± 7.7 yrs Caucasian: 84% Postmenopausal: 100%	Initial: 29.7 ± 7.3 kg/m² Final: 29.9 ± 7.6 kg/m²[e]	II: 46% NA HER-2: NA	CHT: 19% RT: 24% CHT + RT: 43% No treatment: 14%	HT: 70% No treatment: 30%

Table 1 (continuation)**.** Study information and patient's clinical characteristics (n=17).

Authors and Study		Patients		Tumor and Antineoplastic treatments		
Authors Year Country	**Design Sample size**	**Age Ethnicity Menopausal status**	**BMI**	**Tumor stage Hormone receptor HER-2**	**Previous treatments**	**Treatments used during e study**
Francini et al. 2006 (55) Italy	RCT / HT[a] n=55	No-AI: 61.1 ± 2.7 yrs AI: 61.8 ± 4.4 yrs NA Postmenopausal: 100%	**No-AI** Initial: 28.9 ± 1.8 kg/m² Final: NA **AI** Initial: 29.1 ± 2.1 kg/m² Final: NA	**No-AI** I: 46% ER (+): 100% PR (+): 72% **AI** II: 40% ER (+): 100% PR (+): 65% HER-2: NA	Surgery: 100% HT: 100% CHT: NA RT: NA	HT: 100%
Freedman et al. 2004 (56) United States	Prospective n=20[b]	48.2 ± 8.8 yrs Caucasian: 80% Postmenopausal: 50%	Initial: 24.1 ± 3.9 kg/m² Final: NA	II: 70% NA HER-2: NA	Surgery: 100%	CHT: 100% RT after CHT: 75% Tamoxifen after CHT: 75%
Demark-Wahnefried et al. 2001 (57) United States	Prospective n=53	LT: 41.5 ± 4.8 yrs CHT: 41.4 ± 6.2 yrs Caucasian: 83% Premenopausal: 100%	**LT** Initial: 21.5 ± 1.0 kg/m² Final: 21.9 ± 1.0 kg/m² **CHT** Initial: 25.8 ± 0.8 kg/m² Final: 26.9 ± 0.9 kg/m²	**LT** 0: 65% **CHT** I: 33% NA HER-2: NA	**LT** Surgery: 100% **CHT** Surgery: 100%	**LT** RT: 41% **CHT** RT: 69% CHT: 64% CHT + HT: 36%
Kutynec et al. 1999 (58) Canada	NRCT / CHT-RT[a] n=18	CHT: 44 ± 6.0 yrs RXT: 42 ± 5.0 yrs Caucasian: 88.9% Premenopausal: 77.8%	**CHT** Initial: 22.9 ± 2.8 kg/m² Final: 22.9 ± 2.6 kg/m² **RT** Initial: 24.4 ± 3.5 kg/m² Final: 25.0 ± 4.3 kg/m²	I: 66.7% ER (+): 38.9% ER (-): 22.2% Unknown: 38.9% HER-2: NA	Surgery: 100%	CHT: 44.5% RT: 55.5%

Table 1 (continuation)**.** Study information and patient's clinical characteristics (n=17).

Authors and Study		Patients		Tumor and Antineoplastic treatments		
Authors **Year** **Country**	**Design** **Sample size**	**Age** **Ethnicity** **Menopausal status**	**BMI**	**Tumor stage** **Hormone receptor** **HER-2**	**Previous treatments**	**Treatments used during e study**
Cheney et al. 1997 (59) United States	Prospective n=8[f]	LW: 54 (49–56) yrs GW: 61 (46–66) yrs NA Postmenopausal: 75%	**LW** Initial: 23.8 (22.0–27.4) kg/m² **GW** Initial: 26.1 (22.2–32.3) kg/m²	Early tumors ER (+): 37.5% ER (-): 50% ER unknown:12.5% PR (+): 25% PR (-): 50% PR unknown:25% HER-2: NA	NA	CHT: 50% HT only: 25% Corticotherapy only: 12.5% RT only: 12.5%[g]

AI: aromatase inhibitors; AC: doxorubicin and cyclophosphamide; BCT: brachytherapy; BMI: body mass index; CAF/AC: cyclophosphamide, doxorubicin, fluorouracil/doxorubicin and cyclophosphamide; CMF: cyclophosphamide, methotrexate and fluorouracil; ECT: epirubicin, cyclophosphamide and docetaxel; ER: estrogen receptor positive; FAC: 5-fluorouracil, doxorubicin and cyclophosphamide; FEC: fluorouracil, epirubicin and cyclophosphamide; GW: gained weight; HER-2: human epidermal growth factor receptor 2; HR: hormonal receptor; HT: hormone therapy; LT: local treatment (surgery with or without radiotherapy); LW: lost weight; NA: not available; NRCT: nonrandomized clinical trial; PR: progesterone receptor positive; RCT: randomized clinical trial; SERM: selective estrogen receptor modulator; TC: docetaxel and cyclophosphamide; TT: target therapy

[a]all sample considered; [b]breast cancer patients group only; [c]patients before intervention only; [d]control group only; [e]analysis at 6 months; [f]prospective analysis only; [g]adjuvant treatment

Table 2. Methodologies used to assess body adiposity changes and their relation with antineoplastic treatments (n=17).

Authors Year Design	Body adiposity assessment				Relation between body adiposity changes and antineoplastic treatments (p-value)
	Method Body region	Frequency Interval between initial and final measurements	Changes between measurements (p-value)	Status of assessment	
Ginzac et al. 2020 (44) RCT	PET/CT Cervical and supraclavicular	2 times 1 mo	Δ BAT (%): −4.38 ± 34.07 (p=0.056) [a]	1st: Pre-treatment 2nd: During treatment	CHT + TT seems to be the only factor affecting BAT activity
Franzoi et al. 2020 (34) Retrospective	CT Abdominal	3 times 12 mo	Δ SAT Index (cm²/m²): −1.18 (95% CI: −7.21 to 4.84) (p=0.68) [b] Δ SAT Density (HU): 1.28 (95% CI: −0.56 to 3.13) (p=0.16) Δ VAT Index (cm²/m²): −1.77 (95% CI: −5.05 to 1.50) (p=0.27) Δ VAT Density (HU): 0.64 (95% CI: −1.48 to 2.76) (p=0.53) Δ TAT Index (cm²/m²): −27.7 (95% CI: −72.6 to 17.06) (p=0.21)	1st: Pre-treatment 3rd: During treatment	Not evaluated
Jung et al. 2020 (45) Prospective	BIA Whole body	3 times Not clear	FBM Increased (kg) (p=0.308) FBM Increased (%) (p=0.276)	1st: During treatment 3rd: After treatment	Not statistically significant (p=0.992)
van den Berg et al. 2020 (46) Prospective	DEXA Whole body	3 times 10.8 mo	FBM Increased (kg) (p<0.05)	1st: Pre-treatment for some and during treatment for others 3rd: After treatment	Not evaluated
Artese et al. 2018 (47) Prospective	DEXA Whole body	2 times 13.6 mo	TBF Increased (%): 3.4 (p=0.013)[c]	1st and 2nd: During treatment for some and after for others	Not evaluated

Table 2 (continuation). Methodologies used to assess body adiposity changes and their relation with antineoplastic treatments (n=17).

Authors Year Design	Body adiposity assessment				Relation between body adiposity changes and antineoplastic treatments (p-value)
	Method Body region	Frequency Interval between initial and final measurements	Changes between measurements (p-value)	Status of assessment	
Gadéa et al. 2018 (48) Prospective	DEXA Whole body	3 times 6 mo	FBM Overall Decreased (p=0.003) **Weight gain (n=10)** FBM Increased (%): 15.4 ± 19.0 (p=0.008) **Weight loss (n=10)** FBM Decreased (%): -18.3 ± 8.1 (p<0.0001)	1st: During treatment 3rd: After treatment	Not evaluated.
Pedersen et al. 2017 (49) Prospective	BIA Whole Body	4 times 18 mo	**Total patients** FBM Increased (kg): 0.8 (95% CI: 0.2 to 1.3) (p=0.006) **HT** FBM Increased (kg): 0.2 (95% CI: -0.5 to 0.9) (p=0.587) **CHT plus or not HT** FBM Increased (kg): 1.4 (95% CI: 0.5 to 2.3) (p=0.001)	1st: During treatment 4th: Not clear	The authors suggest attention to younger premenopausal women treated with CT plus HT with tamoxifen
Rier et al. 2017 (50) Retrospective	CT Abdominal	2 times Not clear	**FAC** SAT Decreased (cm²): -6.3 (IQR: -26.7 to 9.0) (p=0.31) VAT Stable (cm²): 0.0 (IQR: -17.0 to 13.2) (p=0.82) IMAT Increased (cm²): 2.1 (IQR:-2.3 to 3.7) (p=0.15) TAT Increased (cm²): 1.0 (IQR: -35.4 to 27.0) (p=0.71) **Paclitaxel** SAT Decreased (cm²): -4.8 (IQR: -22.1 to 19.3) (p=0.75) VAT Decreased (cm²): -0.1 (IQR: -18.2 to 12.3) (p=0.84) IMAT Increased (cm²): 0.9 (IQR: -1.8 to 3.9) (p=0.10) TAT Decreased (cm²): -2.4 (IQR: -28.7 to 37.9) (p=0.94)	1st: Not clear 2nd: After treatment	VAT remained stable in both groups

Table 2 (continuation). Methodologies used to assess body adiposity changes and their relation with antineoplastic treatments (n=17).

Authors Year Design	Body adiposity assessment				Relation between body adiposity changes and antineoplastic treatments (p-value)
	Method Body region	Frequency Interval between initial and final measurements	Changes between measurements (p-value)	Status of assessment	
Battisti et al. 2014 (51) Retrospective	CT Abdominal	2 times 6 mo	TAAT Increased (mm^3): 9.1% VAT Increased (mm^3): 18.0% SAT Increased (mm^3): 1.9% Total VAT/SAT Ratio Increased: 21.8% (p: NA)	1st: During treatment 2nd: Not clear	Not statistically significant (p-value NA)
Hojan et al. 2013 (52) NRCT	DEXA Whole body	2 times 6 mo	FBM Increased (g): 16.45% (p<0.01) TBF Increased (%): 11.3 (p<0.01) Android fat Increased (%): 19.9 (p<0.01) Gynoid fat Increased (%): 2.4 (p>0.05)	1st: During treatment 2nd: During treatment	Not evaluated
van Londen et al. 2011 (53) RCT	DEXA Whole body	5 times 24 mo	TBF No-AI Increased (%): 1.2 (0.4) (p<0.05) TBF AI Remained Stable (%) (p >0.05)	1st to 5th: During treatment for some and after for others	TBF was significantly different between the AI and no-AI groups for 24 months (p≤0.05) and for all periodic measurements (p≤0.05)
Irwin et al. 2009 (54) RCT	DEXA Whole body	3 times 12 mo	TBF Increased (%): 0.8 (p: NA)	1st to 3rd: During treatment	HT - AI patients: TBF decreased 0.54% HT - Tamoxifen patients: TBF increased 0.15% No-HT patients: TBF increased 4.15%*
Francini et al. 2006 (55) RCT	DEXA Whole body	3 times 12 mo	**No-AI** FBM Increased (%): 0.5 (p>0.05) **AI** FBM Decreased (%): -7.8 (p<0.01)	1st to 3rd: During treatment	FBM significantly decreased in AI group, but not in No-AI group (p<0.01)

Table 2 (continuation). Methodologies used to assess body adiposity changes and their relation with antineoplastic treatments (n=17).

Authors Year Design	Body adiposity assessment				Relation between body adiposity changes and antineoplastic treatments (p-value)
	Method Body region	Frequency Interval between initial and final measurements	Changes between measurements (p-value)	Status of assessment	
Freedman et al. 2004 (56) Prospective	DEXA, BIA ADP, CT Whole body and Abdominal (CT)	3 times 6 mo	**DEXA** TBF (1st and 2nd) (p: non-significant) TBF (2nd and 3rd) Increased (%): 0.9 ± 1.6 (p=0.02) **BIA** TBF (1st and 2nd) Decreased (%): 1.2 ± 3.0 (p=0.09) TBF (2nd and 3rd) Increased (%): 1.7 ± 3.0 (p=0.02) **ADP** TBF (1st and 3rd) Increased (%): 3.8 ± 6.0 (p=0.01) **CT [d]** SAT (1st and 3rd) Increased (p=0.38) VAT (1st and 3rd) Decreased (p=0.65) VAT/SAT ratio (1st and 3rd) Decreased (cm^3): 0.02 ± 0.05 (p=0.02)	1st to 3rd: During treatment	No associations between TBF (DEXA or BIA) and RT, HT (tamoxifen) for all measures
Demark-Wahnefried et al. 2001 (57) Prospective	DEXA Whole body	3 times 12 mo	**LT** TBF (%): -0.1 ± 0.4 (p=NA) FBM (kg): 0.1 ± 0.3 (p=NA) **CHT** TBF (%): 2.2 ± 0.6 (p=NA) FBM (kg): 2.3 ± 0.7 (p=NA)	1st: During treatment 3rd: Not clear	LT vs. CHT groups: TBF and FBM increased (p=0.001 and p=0.002, respectively) in CHT group, and remained significant after adjustment (p=0.04 for both)

Table 2 (continuation). Methodologies used to assess body adiposity changes and their relation with antineoplastic treatments (n=17).

Authors Year Design	Body adiposity assessment				Relation between body adiposity changes and antineoplastic treatments (p-value)
	Method Body region	Frequency Interval between initial and final measurements	Changes between measurements (p-value)	Status of assessment	
Kutynec et al. 1999 (58) NRCT	DEXA Whole body	2 times 3 mo	**CHT and RT** TBF Increased (%): 1.3 (p=0.04)[e]	1st: During treatment 2nd: After treatment	No statistically significant difference in TBF or FBM comparing CHT and RT groups
Cheney et al. 1997 (59) Prospective	CT T12 vertebral level, Iliac crest and Mid pelvis	2 times 6 mo	**Weight loss (p= NA) [f]** FBM Stable (%): 0.0 (Min-Max: -1.0 to 1.0) FBM Increased (kg): 0.1 (Min-Max: -0.8 to 0.2) VAT Decreased (cm²): -7.4 SAT Increased (cm²): 1.1 **Weight gain (p= NA) [g]** FBM Increased (%): 4.0 (Min-Max: 1.0 to 8.0) FBM Increased (kg): 4.4 (Min-Max: 0.7 to 7.9) VAT Decreased (cm²): 14.9 (Min-Max: 10.7 to 28.8) SAT Increased (cm²): 19.5 (Min-Max: -7.6 to 32.0)	1st and 2nd: During treatment	Not evaluated

ADP: air displacement plethysmography; BAT: brown adipose tissue; BIA: bioelectrical impedance analysis; CHT: chemotherapy; CI: confidence interval; CT: computed tomography; DEXA: dual-energy X-ray absorptiometry; FBM: fat body mass; F-FDG: fluorine-18 fluorodeoxyglucose; HT: hormone therapy; HU: hounsfield unit; IMAT: intermuscular adipose tissue; IQR: interquartile range; LT: local treatment (surgery with or without radiotherapy); MAX: maximum; MIN: minimum; NA: not available; NRCT: nonrandomized clinical trial; PET/CT: positron emission tomography/computed tomography; RCT: randomized clinical trial; SAT: subcutaneous adipose tissue; TAAT: total abdominal adipose tissue; TAT: total body adipose tissue; TBF: total body fat; TT: target therapy; VAT: visceral adipose tissue;

[a]Consider ^{18}F-FDG uptake; [b]Results from all measures available in the supplementary material; [c]TBF data available for 9 patients; [d]Data for 17 patients; [e]Changes in FBM not shown; [f]2nd scan data available for 1 patient; [g]2nd scan data available for 5 patients; *6 months data only

Figure S1. Characteristics of tools for body composition assessment.

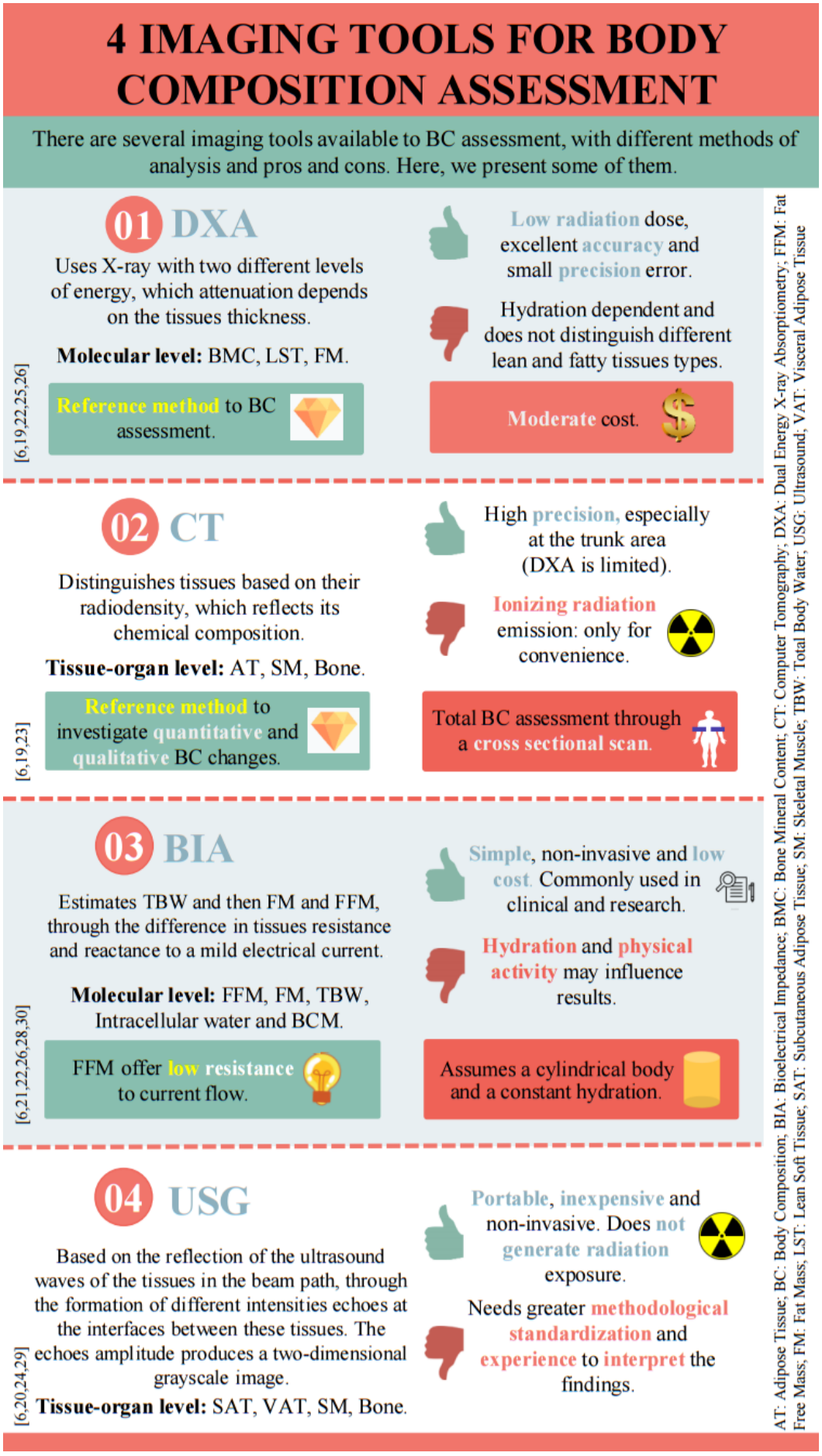
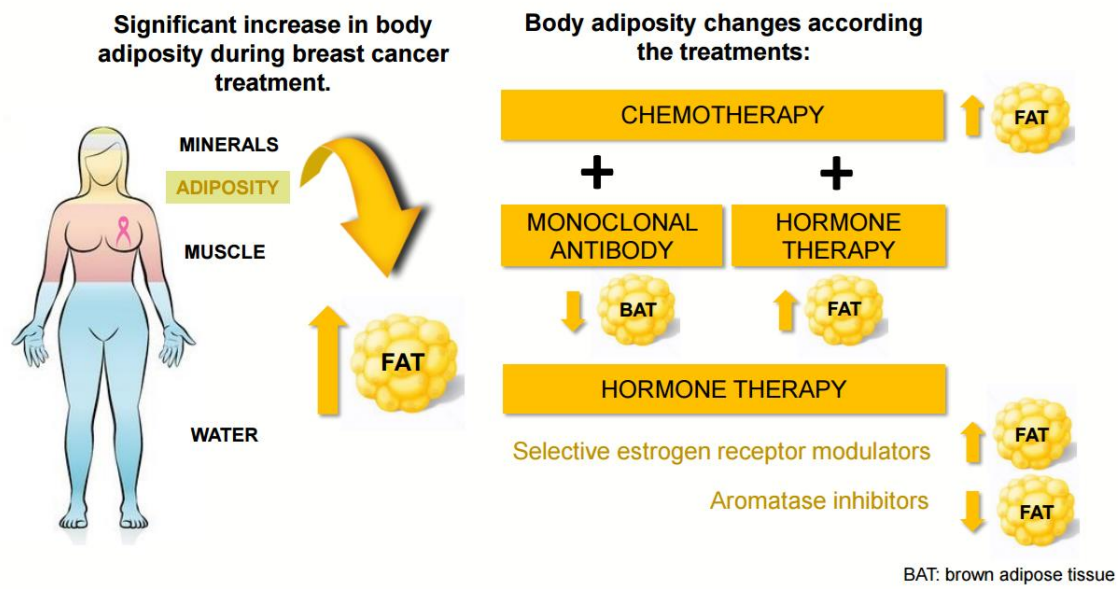


Figure S2. Graphical abstract of the review.



BAT: brown adipose tissue

Chart S1. Definitions of terms related to body adiposity.

Adipose tissue	Adipose tissue is a connective tissue formed by adipocytes, collagenous and elastic fibers, fibroblasts, immune cells, blood vessels and extracellular fluid. It is part of the tissue-organ level (IV) in body composition analysis (6,27,31).
Adipose tissue density	Analysis of adipose tissue radiodensity expressed by Hounsfield units. It can be assessed by computed tomography (CT) and measures the x-ray tissue radiodensity expressed as a linear attenuation in relation to air and water (6). Increased adipose radiodensity (closer to zero) means that the composition of the tissue is relatively low in lipid content, high in vascularity and high in extracellular matrix (32,33).
Adipose tissue indexes	Subcutaneous (SAT), visceral (VAT) and total adipose tissues (TAT) areas (cm^2) normalized for the square of height (m^2), as indexes (cm^2/m^2) (34).
Body adiposity	A general concept approached in this study referring to all body adipose depots and anatomical levels of the five-level model body composition analysis.
Body fat	Family of lipids composed by triglycerides which represents approximately 80% of adipose tissue. It can be expressed by fat body mass (FBM) (the actual weight of fat in the body) or total body fat (TBF) percentage. It is part of the molecular level (II) in body composition analysis (6,27,35).
Brown adipose tissue (BAT)	A type of body adipose tissue involved in controlling the energy balance and whole body metabolism (36).
Intermuscular adipose tissue (IMAT)	A depot of adipose tissue located between muscle groups (6,37).
Subcutaneous adipose tissue (SAT)	A depot of adipose tissue located beneath the skin (6,38).
Total adipose tissue (TAT)	Total adipose tissue in the body, considering all the body adipose depots (39,40).
Visceral adipose tissue (VAT)	A depot of adipose tissue located in the abdomen, lining internal organs (6,38).

Table S1. Total results found and bibliographic search strategy used for each database.

Database	Total results found	Final date	Search strategy
PUBMED	462 articles	5/28/2020	(((Overweight[mh] OR Overweight[tiab] OR Adipose Tissue[mh] OR Adipose Tissue[tiab] OR Adiposity[mh] OR Adiposity[tiab] OR Body Composition[mh] OR Body Composition[tiab] OR Obesity[mh] OR Obesity[tiab] OR Intra-Abdominal Fat[mh] OR Visceral Adipose Tissue[tiab] OR Subcutaneous Fat[mh] OR Subcutaneous Adipose Tissue[tiab]) AND (Breast neoplasms[mh] OR ((breast[tiab] OR mamma*[tiab]) AND (neoplas*[tiab] OR cancer[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR oncol*[tiab] OR malignan*[tiab])))) AND ("Tomography X-Ray Computed"[tiab] OR Tomography, X-Ray Computed[mh] OR "X-Ray Computed Tomography"[tiab] OR "CT X Ray"[tiab] OR "computed tomography"[tiab] OR "x ray tomography"[tiab] OR Absorptiometry, Photon[mh] OR "Dual Energy X Ray Absorptiometry Scan"[tiab] OR "Dual-Energy X-Ray Absorptiometry Scan"[tiab] OR Magnetic Resonance Imaging[mh] OR "Magnetic Resonance Imaging"[tiab] OR "CT Scan*"[tiab] OR "DXA Scan*"[tiab] OR "MRI Scan*"[tiab] OR Ultrasonography[mh] OR Ultrasonography[tiab]))
EMBASE	108 articles	5/28/2020	(obesity/exp OR obesity:ti,ab OR Overweight:ti,ab OR Adipose Tissue/exp OR 'Adipose Tissue':ti,ab OR Adiposity:ti,ab OR 'Body Composition'/exp OR 'Body Composition':ti,ab OR Intra-Abdominal Fat/exp OR 'Visceral Adipose Tissue':ti,ab OR Subcutaneous Fat/exp OR 'Subcutaneous Fat':ti,ab OR 'Subcutaneous Adipose Tissue':ti,ab) AND ('Breast tumor'/exp OR 'Breast tumo*':ti,ab OR 'Breast neoplasms':ti,ab OR ((breast:ti,ab OR mamma*:ti,ab) AND (neoplas*:ti,ab OR câncer:ti,ab OR tumo*:ti,ab OR carcinoma*:ti,ab OR oncol*:ti,ab OR malignan*:ti,ab))) AND ('x-ray computed tomography'/exp OR 'Tomography, X-Ray Computed':ti,ab OR 'X-Ray Computed Tomography':ti,ab OR 'CT X Ray':ti,ab OR 'computed tomography':ti,ab OR 'x ray tomography':ti,ab OR 'photon absorptiometry'/exp OR 'Dual Energy X Ray Absorptiometry Scan':ti,ab OR 'Dual-Energy X-Ray Absorptiometry Scan':ti,ab OR 'Nuclear Magnetic Resonance'/exp OR 'Magnetic Resonance Imaging':ti,ab OR 'CT Scan*':ti,ab OR 'DXA Scan*':ti,ab OR 'MRI Scan*':ti,ab OR echography/exp OR Ultrasonography:ti,ab)
COCHRANE LIBRARY	84 articles	5/28/2020	(Overweight OR "Adipose Tissue" OR Adiposity OR "Body Composition" OR Obesity OR "Intra-Abdominal Fat" OR "Visceral Adipose Tissue" OR "Subcutaneous Fat" OR "Subcutaneous Adipose Tissue") AND ((breast OR mamma*) AND (neoplas* OR cancer OR tumor* OR tumour* OR carcinoma* OR oncol* OR malignan*)) AND ("Tomography X-Ray Computed" OR "X-Ray Computed Tomography" OR "CT X Ray" OR "computed tomography" OR "x ray tomography" OR "Dual Energy X Ray Absorptiometry Scan" OR "Dual-Energy X-Ray Absorptiometry Scan" OR "Magnetic Resonance Imaging" OR "CT Scan*" OR "DXA Scan*" OR "MRI Scan*" OR Ultrasonography)

Table S1 (continuation)**.** Total results found and bibliographic search strategy used for each database.

Database	Total results found	Final date	Search strategy
WEB OF SCIECE	316 articles	5/28/2020	ALL=(Overweight OR "Adipose Tissue"OR Adiposity OR "Body Composition" OR Obesity OR "Intra-Abdominal Fat" OR "Visceral Adipose Tissue" OR "Subcutaneous Fat" OR "Subcutaneous Adipose Tissue") AND ALL=("Breast neoplasms" OR ((breast OR mamma*) AND (neoplas* OR cancer OR tumor* OR tumour* OR carcinoma* OR oncol* OR malignan*))) AND ALL=("Tomography X-Ray Computed" OR "X-Ray Computed Tomography" OR "CT X Ray" OR "computed tomography" OR "x ray tomography" OR "Absorptiometry, Photon" OR "Dual Energy X Ray Absorptiometry Scan" OR "Dual-Energy X-Ray Absorptiometry Scan" OR "Magnetic Resonance Imaging" OR "CT Scan*" OR "DXA Scan*" OR "MRI Scan*" OR Ultrasonography OR Echography)
SCOPUS	177 articles	5/28/2020	TITLE-ABS(Overweight OR "Adipose Tissue"OR Adiposity OR "Body Composition" OR Obesity OR "Intra-Abdominal Fat" OR "Visceral Adipose Tissue" OR "Subcutaneous Fat" OR "Subcutaneous Adipose Tissue") AND TITLE-ABS("Breast neoplasms" OR ((breast OR mamma*) AND (neoplas* OR cancer OR tumor* OR tumour* OR carcinoma* OR oncol* OR malignan*))) AND TITLE-ABS ("Tomography X-Ray Computed" OR "X-Ray Computed Tomography" OR "CT X Ray" OR "computed tomography" OR "x ray tomography" OR "Absorptiometry, Photon" OR "Dual Energy X Ray Absorptiometry Scan" OR "Dual-Energy X-Ray Absorptiometry Scan" OR "Magnetic Resonance Imaging" OR "CT Scan*" OR "DXA Scan*" OR "MRI Scan*" OR Ultrasonography OR Echography)

Table S2. Data from specific treatment protocols and initial and final body adiposity measures performed during the studies evaluated (n=17).

Authors	Specific descriptions of the treatments used by the studies	Body adiposity measures
Ginzac et al. 2020 (44)	CHT + TT: 100% Docetaxel + Trastuzumab	BAT ^{18}F-FDG uptake intensity – Initial: 1.16 (0.88) | Final: 1.02 (0.9)
Franzoi et al. 2020 (34)	1st line therapy: 78% 2nd line therapy: 22% HT + TT (CDK 4/6 inhibitors): 100% Letrozol + Palbociclib: 66% Fulvestran + Palbociclib: 30% Letrozol + Ribociclib: 4%	**Changes in measures 1 compared to measure 2:** SAT index: 1.23 (−2.11 to +4.58) SAT density: −0.88 (−1.95 to +0.17) VAT index: −0.28 (−2.25 to +1.67) VAT density: 0.24 (−1.48 to +1.53) IMAT index: −0.42 (−0.93 to +0.08) IMAT density: 0.01 (−2.22 to +2.25) TAT index: 0.51 (−3.61 to +4.64)
Jung et al. 2020 (45)	CHT: 100% AC: 37.8% TC: 62.2%	BFM - Initial: 15.82kg ± 5.79 | Final: 16.75kg ± 5.31 (p=0.308) BFP - Initial: 26.85% ± 7.44 | Final: 28.17% ± 6.59 (p=0.276)
van den Berg et al. 2020 (46)	CHT Adjuvant: 64.6% Neo-adjuvant: 35.4% *Protocols: anthracyclines plus or not taxanes (not specified)	FBM - Initial: 30.0kg ± 0.9 | Final: 31.0kg ± 0.9[a] (p<0.05) **Initial:** TFM: 25.9kg (20.2-34.4) TFM: 36.6% (31.2-42.1)) Arm fat: 2.6kg (2.0-3.6) Leg fat: 9.5kg (8.1-11.9) Trunk fat: 12.0kg (8.8-17.0)
Artese et al. 2018 (47)	Some patients could have used HT (not specified)	TBF - Initial: 38.3 (6.1) | Final: 39.6 (6.2)[b] FBM - Initial: 22.4kg (6.1) | Final: 23.2kg (6.7)
Gadéa et al. 2018 (48)	CHT: 100% FEC + Docetaxel: 96% TC: 4% TT (monoclonal antibody): Trastuzumab: 12%	**FBM** Overall population (n=48) - Initial: 25.8kg | Final: 25.2kg (1.21) (p=0.03) Weight gain (n=10) – Initial: 20.7kg | Final: 23.6kg (2.44) (p 0.008) Weight loss (n=10) - Initial: 28.6kg | Final: 23.3kg (1.66) (p<0.0001) Stable weight (n=28) - Initial: 26.5kg | Final: 26.4kg (1.77) (p: non-significant) **TRUNK FAT MASS** Overall population (n=48) - Initial: 11.8kg | Final: 11.7kg (0.78) (p: non-significant) Weight gain (n=10) - Initial: 8.4kg | Final: 9.7kg (1.25) (p=0.02) Weight loss (n=10) – Initial: 13.2kg | Final: 10.1kg (0.87) (p<0.0001) Stable weight (n=28) - Initial: 12.5kg | Final: 13.0kg (1.20) (p: non-significant)

Table S2 (continuation)**.** Data from specific treatment protocols and initial and final body adiposity measures performed during the studies evaluated (n=17).

Authors	Specific descriptions of the treatments used by the studies	Body adiposity measures
Pedersen et al. 2017 (49)	HT only: 49.5% CHT: 50.5% ECT only: 12.6% ECT plus HT: 37.9%	**TOTAL** FBM - Initial: 24.3kg (22.5-26.0) **HT** FBM - Initial: 24.1kg (21.6-26.7) **CHT+/- HT** FBM - Initial: 24.4kg (22.1-26.8)
Rier et al. 2017 (50)	1st line palliative CHT: 100% Paclitaxel: 74.5% FAC: 25.5%	**FAC** SAT – Initial: 181.8cm² (148.7–225.1) VAT – Initial: 109cm² (51.8–126) IMAT – Initial: 17cm² (11.7–22) TAT – Initial: 314.1cm² (211.3–364) **PACLITAXEL** SAT – Initial: 206.9cm² (147.3–237) VAT – Initial: 105.4cm² (65.1–147.2) IMAT – Initial: 14.7cm² (10.2–23.8) TAT – Initial: 308.1cm² (256.9–389.5)
Battisti et al. 2014 (51)	HT - AI: 100% Anastrazol: 51.6% Letrozol: 48.4%	TAAT - Initial: 16,280.3mm³ (6953.3) | Final: 17,763.6mm³ (6850.8) VAT - Initial: 9024.4mm³ (4630.0) | Final: 10,651.9mm³ (4371.7) SAT - Initial: 7255.8mm³ (3376.6) | Final: 7111.6mm³ (3372.0) Total VAT/SAT ratio – Initial: 1.38 (0,9) | Final: 1.69 (0,83)
Hojan et al. 2013 (52)	HT: 100% Goserelin + Tamoxifen: 100%	FBM - Initial: 21058,7g | Final: 24792,8g TBF - Initial: 33,7% | Final: 37,8% Android fat - Initial 34,2% | Final: 41,3% Gynoid fat - Initial: 40,8% | Final: 42,2%
van Londen et al. 2011 (53)	HT: 74% AI: 13% (Anastrazol, Letrozol, Exemestane) No-AI: 61% (Tamoxifen, Fulvestrant, Toremifen) No Adjuvant HT: 26%	TBF - Initial AI group: 36.99% (1.21) TBF - Initial no-AI group: 37.7% (0.78)
Irwin et al. 2009 (54)	HT: 70% AI: 40% SERM: 30% (Tamoxifen) No treatment: 30%	TBF initial: 39,18% (5,90) | After 6 months: 39,60% (5,97) TBF initial: 39,53% (6,14) | After 12 months: 39,50% (6,14)

Table S2 (continuation)**.** Data from specific treatment protocols and initial and final body adiposity measures performed during the studies evaluated (n=17).

Authors	Specific descriptions of the treatments used by the studies	Body adiposity measures
Francini et al. 2006 (55)	HT: 100% AI: 51% (Exemestane) SERM: 49% (Tamoxifen)	NA
Freedman et al. 2004 (56)	CHT: 100% AC: 40% AC + paclitaxel: 50% AC + docetaxel: 10% RT after CHT: 75% HT (Tamoxifen) after CHT: 75%	**DEXA** TBF – Initial: NA | T2: 33.6% (6.2) | Final: 34.6% (6.5) FBM – Initial: NA | T2: 22.5kg (7.4) | Final: 23.6kg (8.2) **BIA** TBF – Initial: 30.8% (8.0) | Final: 31.4% (7.0) **ADP** TBF – Initial: 33.8% (9.0) | Final: 37.9% (8.0) FBM – Initial: 22.8kg (9.5) | Final: 25.3kg (8.7) **CT** SAT – Initial: 243.5cm³ (110.5) | Final: 252.8cm³ (110.9) VAT – Initial: 64.0cm³ (30.6) | Final: 62.3cm³ (31.2) VAT/SAT ratio – Initial: 0.29cm³ (0.13) | Final: 0.26cm³ (0.13)[c]
Demark-Wahnefried et al. 2001 (57)	*LT group* RT: 41% *CHT group* RT: 69% CHT: 100% Doxorubicin protocols: 47% (ACTX; ACTX and Paclitaxel; Doxorubicin and CMF) Doxorubicin protocols + HT: 33% (ACTX and Tamoxifen; ACTX and Paclitaxel + Tamoxifen; Doxorubicin and CMF + Tamoxifen; CAF + Tamoxifen) CMF protocol: 17% CMF + Tamoxifen: 3%	**TBF** LT: baseline: 28.6% (1.6) | 6 months: 28.3% (1.6) | 12 months: 28.5% (1.7) CHT: baseline: 33.6% (1.4) | 6 months: 35.4% (1.5) | 12 months: 35.8% (1.5) **FBM** LT: baseline: 16.9kg (2.1) | 6 months: 16.9kg (2.0) | 12 months: 17.0kg (1.9) CHT: baseline: 24.0kg (1.6) | 6 months: 26.0kg (1.9) | 12 months: 26.3kg (1.8)
Kutynec et al. 1999 (58)	CHT: 44.5% AC: 100% RT: 55.5%	**TBF** RT - Initial: 38.8% (5.4) | Final: 39.8% (5.4) CHT - Initial: 41.7% (6.8) | Final: 43.1% (6.7) **FBM** CHT - Initial: 25.8kg (6.8) | Final: 26.4kg (6.2) RT - Initial: 25.9kg (6.1) | Final: 26.7kg (6.9)

Table S2 (continuation)**.** Data from specific treatment protocols and initial and final body adiposity measures performed during the studies evaluated (n=17).

Authors	Specific descriptions of the treatments used by the studies	Body adiposity measures
Cheney et al. 1997 (59)	CAF/AC: 25% Tamoxifen only: 25% CMF: 25% Prednisone: 12.5% RT only: 12.5%	**LW group** TAT: Initial 34% (30 to 39) | Final: NA FBM: Initial 23.6kg (17.9 to 28.1) | Final: NA[d] **GW group** TAT: Initial: 47% (34 to 55) | Final: NA FBM: Initial: 38.1kg (33.1 to 46.6) | Final: NA[e]

AI: aromatase inhibitors; AC: doxorubicin and cyclophosphamide; ACTX: doxorubicin and cyclophosphamide; ADP: air displacement plethysmography; BAT: brown adipose tissue; BIA: bioelectrical impedance analysis; CAF/AC: cyclophosphamide, doxorubicin, fluorouracil/doxorubicin and cyclophosphamide; CDK: cyclin-dependent kinase; CHT: chemotherapy; CMF: cyclophosphamide, methotrexate and fluorouracil; CT: computed tomography; DEXA: dual-energy X-ray absorptiometry; ECT: epirubicin, cyclophosphamide and docetaxel; FBM, fat body mass; F-FDG: fluorine-18 fluorodeoxyglucose; FEC, fluorouracil, epirubicin and cyclophosphamide; HT: hormone therapy; IMAT: intermuscular adipose tissue; LT: local treatment (surgery with or without radiotherapy); NA: not available; RT: radiotherapy; SAT: subcutaneous adipose tissue; SERM: selective estrogen receptor modulator; TAAT: total abdominal adipose tissue; TAT: total body adipose tissue; TBF: total body fat; TC: docetaxel and cyclophosphamide; TT: target therapy; VAT: visceral adipose tissue

[a]Initial data available for 178 patients and final available for 163 patients; [b]Data available for 9 patients; [c]CT data available for 17 patients; [d]2st scan data available for 1 patient; [e]2st scan data available for 5 patients

Table S3. Changes in body adiposity during treatment according to the menopausal status of patients (n=16*).

Authors	Menopausal status	Changes in body adiposity between measurements (p-value)
Both pre- and postmenopausal patients		
Ginzac et al. 2020 (34)	Premenopausal: 56.9%	Δ BAT (%): −4.38 ± 34.07 (p=0.056)[a] BAT Increased (%): 43.0
Jung et al. 2020 (45)	Premenopausal: 56.8%	FBM Increased (kg) (p=0.308) FBM Increased (%) (p=0.276)
van den Berg et al. 2020 (46)	Premenopausal: 57.5%	FBM Increased (kg) (p<0.05)
Pedersen et al. 2017 (49)	Postmenopausal: 60%	**Total patients** FBM Increased (kg): 0.8 (95% CI: 0.2 to 1.3) (p=0.006) **HT** FBM Increased (kg): 0.2 (95% CI: -0.5 to 0.9) (p=0.587) **CHT plus or not HT** FBM Increased (kg): 1.4 (95% CI: 0.5 to 2.3) (p=0.001)
Freedman et al. 2004 (56)	Postmenopausal: 50%	**DEXA** TBF (1st and 2nd) (p: non-significant) TBF (2nd and 3rd) Increased (%): 0.9 ± 1.6 (p=0.02) **BIA** TBF (1st and 2nd) Decreased (%): 1.2 ± 3.0 (p=0.09) TBF (2nd and 3rd) Increased (%): 1.7 ± 3.0 (p=0.02) **ADP** TBF (1st and 3rd) Increased (%): 3.8 ± 6.0 (p=0.01) **CT[b]** SAT (1st and 3rd) Increased (p=0.38) VAT (1st and 3rd) Decreased (p=0.65) VAT/SAT ratio (1st and 3rd) Decreased (cm^3): 0.02 ± 0.05 (p=0.02)
All or most premenopausal patients (>70%)		
Hojan et al. 2013 (52)	Premenopausal: 100%	FBM Increased (g): 16.45% (p<0.01) TBF Increased (%): 11.3 (p<0.01) Android fat Increased (%): 19.9 (p<0.01) Gynoid fat Increased (%): 2.4 (p>0.05)
Demark-Wahnefried et al. 2001 (57)	Premenopausal: 100%	**LT** TBF (%): -0.1 ± 0.4 (p=NA) FBM (kg): 0.1 ± 0.3 (p=NA) **CHT** TBF (%): 2.2 ± 0.6 (p=NA) FBM (kg): 2.3 ± 0.7 (p=NA)
Kutynec et al. 1999 (58)	Premenopausal: 77.8%	**CHT and RT** TBF Increased (%): 1.3 (p=0.04)[c]

Table S3 (continuation)**.** Changes in body adiposity during treatment according to the menopausal status of patients (n=16*).

Authors	Menopausal status	Changes in body adiposity between measurements (p-value)
	Both pre- and postmenopausal patients	
All or most postmenopausal patients (>70%)		
Artese et al. 2018 (47)	Postmenopausal: 100%	TBF Increased (%): 3.4 (p=0.013)[d]
Franzoi et al. 2020 (34)	Postmenopausal: 94%	Δ SAT Index (cm²/m²): −1.18 (95% CI: −7.21 to 4.84) (p=0.68)[e] Δ VAT Index (cm²/m²): −1.77 (95% CI: −5.05 to 1.50) (p=0.27) Δ TAT Index (cm²/m²): −27.7 (95% CI: −72.6 to 17.06) (p=0.21)
Gadéa et al. 2018 (48)	Postmenopausal: 100%	FBM Overall Decreased (p=0.003)
Battisti et al. 2014 (51)	Postmenopausal: 100%	TAAT Increased (mm³): 9.1% VAT Increased (mm³): 18.0% SAT Increased (mm³): 1.9% Total VAT/SAT Ratio Increased: 21.8% (p: NA)
van Londen et al. 2011 (53)	Postmenopausal: 100%	TBF No-AI Increased (%): 1.2 (0.4) (p<0.05) TBF AI Remained Stable (%) (p >0.05)
Irwin et al. 2009 (54)	Postmenopausal: 100%	TBF Increased (%): 0.8 (p: NA)
Francini et al. 2006 (55)	Postmenopausal: 100%	**No-AI** FBM Increased (%): 0.5 (p>0.05) **AI** FBM Decreased (%): -7.8 (p<0.01)
Cheney et al. 1997 (59)	Postmenopausal: 75%	**Weight loss (p= NA)** [f] FBM Stable (%): 0.0 (Min-Max: -1.0 to 1.0) FBM Increased (kg): 0.1 (Min-Max: -0.8 to 0.2) VAT Decreased (cm²): -7.4 SAT Increased (cm²): 1.1 **Weight gain (p= NA)** [g] FBM Increased (%): 4.0 (Min-Max: 1.0 to 8.0) FBM Increased (kg): 4.4 (Min-Max: 0.7 to 7.9) VAT Decreased (cm²): 14.9 (Min-Max: 10.7 to 28.8) SAT Increased (cm²): 19.5 (Min-Max: -7.6 to 32.0)

AI: aromatase inhibitors; BAT: brown adipose tissue; BIA: bioelectrical impedance analysis; CHT: chemotherapy; CT: computed tomography; DEXA: dual-energy X-ray absorptiometry; FBM, fat body mass; LT: local treatment (surgery with or without radiotherapy); NA: not available; RT: radiotherapy; SAT: subcutaneous adipose tissue; TAAT: total abdominal adipose tissue; TAT: total body adipose tissue; TBF: total body fat; TT: target therapy; VAT: visceral adipose tissue

[a]Consider ^{18}F-FDG uptake; [b]Data for 17 patients; [c]Changes in FBM not shown; [d]TBF data available for 9 patients; [e]Results from all measures available in the supplementary material; [f]2nd scan data available for 1 patient; [g]2nd scan data available for 5 patients; *Only 16 studies presented the menopausal status

Capítulo 3

Artigo 2

Body adipose tissue depots and treatment outcomes for women with breast cancer: a systematic review

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Artigo publicado no periódico *Clinical Nutrition*
Fator de Impacto 6.3 – doi: 10.1016/j.clnu.2024.03.010

Abstract

Background & Aims: Excessive adipose tissue is associated with poorer prognosis in women with breast cancer (BC). However, several body adiposity depots, such as visceral (VAT), subcutaneous (SAT), intermuscular (IMAT), and gluteofemoral adipose tissues (GFAT) may have heterogeneous metabolic roles and health effects in these patients. This systematic review aims to evaluate the impact of different body adipose tissue depots, assessed via computed tomography (CT), on treatment outcomes for women with BC. We hypothesize that distinct body adipose tissue depots may be associated differently with outcomes in patients with BC. **Methods:** A comprehensive bibliographical search was conducted using PubMed, Embase, Cochrane Library, Scopus, and Web of Science databases (until January 2024). The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale. **Results:** The final sample comprised 23 retrospective studies (n=12,462), with fourteen presenting good quality. A lack of standardization in measuring CT body adipose tissue depots and outcomes presentation precluded quantitative analysis. Furthermore, most included studies had heterogeneous clinical characteristics. Survival and treatment response were the most prevalent outcomes. VAT (n=19) and SAT (n=17) were the most frequently evaluated depots and their increase was associated with worse outcomes, mainly in terms of survival. IMAT (n=4) presented contradictory findings and a higher GFAT (n=1) was associated with better outcomes. **Conclusion:** This systematic review found an association between increased VAT and SAT with worse outcomes in patients with BC. However, due to the heterogeneity of the included studies, further research with homogeneous methodologies is necessary to better understand the impact of body adipose tissue depots on treatment outcomes. Such knowledge could lead to improved care for this patient population.

Keywords: Adipose tissue, Body Composition, Breast Neoplasms, Nutritional Status, Prognosis

1. Introduction

Obesity is associated with a greater risk of developing breast cancer (BC) and a poorer prognosis for female patients with BC [1–3]. Body mass index (BMI) is the main anthropometric parameter used in clinical practice and in the literature to evaluate the relationship between obesity and outcomes in patients with BC [4–9]. However, it is important to note that BMI is an unreliable indicator to measure body adiposity in terms of quantity, quality, and distribution [1,10].

Although primarily used in research setting, computed tomography (CT) has become a reference method to assess body composition in patients with BC. This imaging technique estimates total body composition through an abdominal cross-sectional scan, presenting good accuracy for body depot evaluations (quantity and quality of tissues). Computed tomography is also convenient, making up most disease staging evaluation in patients with BC [11–15].

Body adipose depots, including visceral, subcutaneous, intermuscular and gluteofemoral adipose tissues (VAT, SAT, IMAT and GFAT, respectively), play heterogeneous metabolic roles. These depots differ regarding the profile of secreted inflammatory cytokines [16,17], energy storage, and health effects. For instance, abdominal body adipose tissue is associated with a higher inflammatory state, hyperglycemia, hyperinsulinemia, hypertriglyceridemia, whereas the GFAT presents contrasting association [3,10,18–20].

Despite data on body adipose tissue influence on outcomes in women with BC, the impact of its distribution (VAT, SAT, IMAT, and GFAT) on cancer treatment outcomes is still poorly stablished. Other reviews evaluated the matter [21,22], but to our knowledge, this is the first systematic review on the subject. Hence, this study evaluates the impact of different body adipose tissue depots on cancer treatment outcomes in women with BC regarding overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), mortality, surgical complications, cancer treatment toxicities and response. We hypothesized that distinct body adipose tissue depots may be associated differently with outcomes in this population. This systematic review may provide insights to support the future use of body composition in assessing the prognosis of patients with BC.

2. Methods and materials

This systematic review was conducted using a protocol based on the Cochrane Handbook [23] and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24]. It was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under no. CRD42020185771. This research was also approved by the Federal University of Rio Grande do Sul (UFRGS) Ethics Committee under no. 2020-0224.

2.1 Search strategy

Bibliographical search was conducted in the U.S. National Library of Medicine (Pubmed) (via website), Embase (via website), Cochrane Library (via website), Scopus (via website), and Web of Science (via website) databases until January 2024, to identify observational studies reporting outcomes related to body adipose tissue in patients with BC.

A librarian developed search strategies based on the Population, Intervention, Control and Outcome (PICO) framework. Three relevant studies were used to identify records, from which candidate search terms were extracted by looking at words in the titles, abstracts and subject indexing. The PubMed's Medical Subject Headings (MeSH) was also consulted to select other candidate terms. A draft search strategy was then developed, whose results pointed to additional terms. We used no search filter or previously developed search strategy available in the literature. Boolean operators “OR” and “AND” were used to combine terms within the strategy conceptual blocks, and to combine these blocks with each other, respectively, with term truncation when necessary.

A specific search method was applied to each database, concerning title, abstract and keywords. We also performed a manual search in the reference lists of the included articles. Table S1 lists the complete strategies applied, and the number of studies found in each database.

2.2 Inclusion and exclusion criteria and study selection

Inclusion criteria consisted of observational studies published in any language, without time restriction, with women >18 years old after BC diagnosis, at any stage of the disease, and body adipose tissue assessed via CT during

follow-up. Studies evaluating patients undergoing adjuvant and/or neoadjuvant cancer treatments with body adipose tissue analysis before or after treatments were included.

Conference abstracts were also included. Clinical studies, case series, case reports, and reviews were excluded. In studies with more than one publication involving the same population, only the most recent was included. Cancer treatments comprised surgery, radiotherapy, chemotherapy (CHT), hormone therapy, target therapy, and immunotherapy [25].

Outcomes of interest included OS, DFS, PFS, mortality, surgical complications, cancer treatment toxicities and response, as specified by the studies methodologies. We developed a glossary to standardize the main definitions used in the studies (Table S2). In this review, intra-abdominal adipose tissue is presented alongside with VAT, as both are defined as the adipose tissue area within the abdominal wall [26].

Quantitative analysis of adipose tissue involves measuring area (in cm^2) or volume (in cm^3) to capture the entire amount of tissue within the depot [26–28]. Index analysis (in cm^2/m^2) normalizes adipose tissue area (in cm^2) by the square of the height (in m^2) [27,29]. Higher values indicate greater adipose tissue presence. Adipose tissue quality assessment utilizes CT evaluation of tissue radiodensity (in HU). Increased density/radiodensity may suggest more inflammation and vascularity [29,30].

2.3 Data extraction

Using the StArt® software (São Carlos, São Paulo, Brazil), two independent investigators (TSP and RSP) initiated the selection process by evaluating titles and abstracts. Papers that met the inclusion criteria were selected for full-text analysis, in which both investigators independently analyzed the data. A third reviewer (LVV) resolved any disagreements.

Next, we conducted a pilot standardized form with three manuscripts, to improve the data extraction, which was independently performed by the same two reviewers. Extracted data included: authors, year and country of publication, study design, CT-analyzed body adipose tissue depots and their cut-off points, previous and subsequent cancer treatments, sample size, patient and cancer characteristics (age, ethnicity, menopausal status, BMI, tumor types and staging,

hormone receptors and human epidermal growth factor receptor type 2 status), and outcome-related findings. If menopausal status was not specified, those over 50 years of age were considered as postmenopausal patients.

2.4 Risk of bias in individual studies

Quality of the included papers was assessed via Newcastle-Ottawa scale (NOS) [31], using stars for selection (0–4 stars), comparability (0–2), and outcome (0–3). The studies were classified into three quality levels: good, fair, or poor, based on the number of stars awarded [32,33].

2.5 Data synthesis

Lack of homogeneity in methodology, sample size and patient characteristics among the included studies allowed only for qualitative data analysis. Thus, the hazard ratios (HR) or odds ratios (OR) along with their respective confidence interval (CI) and p-values, were used to summarize the findings for each outcome.

Weighted averages for age and BMI were calculated using Microsoft Excel (2010). Graphs with clinically relevant information were analyzed by Web Plot Digitizer® Software v4.3 (Pacifica, California, USA). Manuscript authors were contacted by e-mail to request more information in case of unavailable data.

3. Results

3.1 Study characteristics and quality assessment

Of the 2,266 titles retrieved by the search strategy, 41 manuscripts were read in full (Figure 1) and 23 were included in the final sample (n=12,462) [19,26–30,34–50]. Most studies were conducted in the United States (published between 2012 and 2023), all with a retrospective design. Seventeen were published as complete studies [19,26–30,34–37,39,41–44,46,47] and six as conference abstracts [38,40,45,48–50]. Table S3 describes their main characteristics.

Newcastle-Ottawa scale assessment classified fourteen studies as good quality (low risk of bias) [19,27–30,34–37,39,41,43,44,46], four studies as fair quality [26,42,47,50], and five studies as low quality (high risk of bias) [38,40,45,48,49].

3.2 Population characteristics

Among the included studies, those involving postmenopausal patients were the most commonly represented (n=17) [19,26–30,34,36,37,41–44,46,48–50]. The weighted average age was 47.5 years (ranging from 21 to 87 years) [19,22,26–30,34,36,37,39,41–44,46,47,49,50] and six studies reported a higher percentage of white patients [30,39,43,45,47,48].

Nineteen studies reported the disease stage. Of these, 52.6% included patients with early stage disease [19,29,30,34–37,43,46,47]. Fourteen articles had their entire sample, or most of it, made up of patients with hormone-positive tumors [19,27–30,34–36,39–41,43,44,46], and twelve studies found negative human epidermal growth factor receptor type 2 for more than 45% of patients [19,28–30,34–36,39–41,43,46].

3.3 Cancer treatments

Eleven studies clearly reported inclusion of patients without any prior cancer treatments [26,29,35,37,39,40,44–46,48,50]. During follow-up, neoadjuvant CHT was the most commonly used treatment, alone [19,35,37,39,42,45–49] or combined with other treatments, such as surgery plus adjuvant CHT, according to the respective protocols [26,40,50].

3.4 Anthropometric parameters

Five studies described the obesity ratio among included patients (from 24.6% to 66%) [34,39,40,45,48] and eleven papers described BMI, with a weighted average of 26.9 kg/m² (ranging from 14.5 to 45.7 kg/m²) [19,29,35–37,41–44,46,50].

3.5 Computed tomography analysis

All studies used abdominal CT [19,26–30,34–50]. Visceral adipose tissue (n=21) [19,26–30,34–37,39–49] and SAT (n=19) [26–30,34,35,37–44,46–48,50] were the mainly analyzed body depots. Most CT images were acquired before cancer treatments (n=20) [19,26–30,34–37,39–44,46,47,49,50].

Regarding technical aspects of CT application, most articles used the whole cross-sectional area of the body adipose tissue depot under analysis [19,26–30,34–37,39,41–44,46,47,50]. Twelve studies did not report the number of axial

CT slices used to assess body adipose tissue [19,36,39–43,45,47–50]. However, among the studies that did report it, the use of a single slice was the most common approach [28–30,34,35,37,38].

Adipose tissue radiodensity (measured in Hounsfield Units [HU]) described in the studies ranged from -190HU to -30 HU [29,37,39,41,42], -195HU to -45 HU [19], -200HU to -50 HU [44], -300HU to -10HU [26], -300HU to -50HU [36]. Only four studies reported different ranges for each adipose tissue depot (−190HU to –30HU for SAT and –150HU to –50HU for VAT) [27,30,35,47] and from -190HU to -30HU for IMAT [35]. For the remaining ten studies, this information was unavailable [28,34,38,40,43,45,46,48–50].

Thirteen articles evaluated body adipose tissue as a continuous variable [19,26,34–36,39,42–44,47–50] and twelve applied different cut-off points, according to the authors' description [27–30,35,37,39–41,44–46].

Finally, eleven studies referred to adjust their outcome analysis to consider confounding variables that might impact adipose tissue results [19,30,34,36,39,43,44,48,49]. The most common adjusted variables for tumors were stage [30,34,36,44,48,49], grade [36,43,44,48], estrogen and progesterone receptor status [30,36,43,44,48], human epidermal growth factor receptor 2 status [30,36,43,44,48], as well as cancer treatment [26,36,43,48]. Additionally, some studies accounted for variables such as BMI, body composition [19,30,34,43,44], and age [30,43,44,47,49].

3.6 Body adipose tissue and outcomes

Most studies analyzed survival-related outcomes, including OS (n=6) [29,39–41,46,48], PFS (n=5) [27,38,39,44,48], distant disease-free survival (DDFS) (n=3) [19,39,45], DFS (n=5) [22,36,37,40,46] and disease-specific survival (DSS) (n=2) [29,48]. Treatment response was also a common analyzed outcome (n=7) [19,28,35,39,45,48,50]. Table 1 presents CT methodological approaches and outcomes according to the adipose tissue depots assessed by each study. Figure S1 and Table S4 summarize these main body adipose tissue results for each outcome.

3.6.1 Visceral Adipose Tissue (VAT)

In a total of 19 studies, increased VAT has been linked with unfavorable outcomes in 36.8% (n=7) and 68.40% (n=13) had neutral results. VAT area was an independent predictor for poor DFS [35]. As well as, a higher VAT area was also associated with diminished DFS (p=0.009) [35], lower DDFS (HR 1.39, 95% CI: 1.11–1.75; p<0.05, in the neoadjuvant group) [19,45], and higher mortality risk (HR 2.04, 95% CI 1.33–3.12, in white patients) [45]. Additionally, a higher VAT area was linked to decreased probability of achieving pathologic complete response (PCR) (OR 0.52, 95% CI 0.36–0.75; p<0.001 and OR 0.55, 95% CI 0.32–0.96) [45,48] and elevated risk of cancer recurrence (HR 1.91, CI 1.30-2.79, in white patients) [45]. A high VAT index was also an independent predictor for worse OS (HR 2.55, 95% CI 1.26–5.16; p=0.01) [29] and lower DSS (HR 2.55; 95% CI 1.10–5.95; p=0.03) [29]. Furthermore, an elevated VAT index was associated with the occurrence of neutropenia (p=0.038) [34]. Increased intra-abdominal adipose tissue volume was associated with the occurrence of high-grade leukopenia (grade 4) (p=0.014) [26].

Only three studies yielded disparate findings, indicating that a higher VAT area was associated with good treatment response (p=0.008) and absence of axillary lymphadenopathies (p=0.028) [28]. Similarly, a high VAT index and density were linked to longer PFS (HR 0.40, 95% CI 0.16–0.99; p=0.041 and HR 2.46, 95% CI 0.99–6.12; p=0.045, respectively) [27], and a lower VAT density was significantly associated with worse DDFS (HR 1.20, 95% CI 1.01–1.43; p<0.05, for the neoadjuvant CHT group) [19].

Despite the associations, VAT density was not identified as an independent predictor for DSS [29]. Moreover, studies found no significant association between VAT density/radiodensity and OS [29,39,41], PCR [19,39], overall mortality [30], and treatment toxicity [47]. VAT area was also not associated with OS [39,41], DFS [37,40], risk of death from any cause [43], PCR [19,39], and treatment toxicity [42,47,49]. Lastly, studies found no association between VAT index and DFS [46], and occurrence of thrombocytopenia [34].

3.6.2 Subcutaneous Adipose Tissue (SAT)

In a total of 17 studies, SAT was associated with worse outcomes in 35.3% (n=6) and 64.7% (n=11) had neutral results. Notably, SAT area exhibited an independent association with OS (p=0.003) (no absolute data presented) [40]. An

increase in SAT area was associated with greater risk of death from any cause (HR 1.13, 95% CI 1.02–1.26) [43] and elevated residual cancer burden score (OR 0.38, 95% CI 0.04–0.72; p=0.03) [50]. Additionally, an increase in abdominal SAT volume and a high SAT index were significantly associated with worse PFS (HR 1.02, 95% CI 1.01–1.03; p=0.002 and HR 2.04, 95% CI 1-4.17; p=0.047, respectively) [38,44]. Moreover, a higher SAT radiodensity was associated with increased risk of overall mortality (HR 1.45, 95% IC 1.15-1.81, p=0.003) [30].

On the contrary, a lower SAT area was independently associated with lower probability of achieving PCR (OR 0.56, 95% CI 0.39–0.81; p=0.002) [48], and a decrease in SAT index was linked to the occurrence of anemia (p=0.0008) [34].

Other studies failed to identify significant associations between SAT area and outcomes, including OS [39,41], DFS [36,40], PCR [28,39], and treatment toxicity [42,47]. Similarly, SAT index was not associated with OS [29], DSS [29], DFS [46], PFS [27], and occurrence of thrombocytopenia [34]. SAT density also did not exhibit associations with OS [29,39], DSS [29], PFS [27], and treatment toxicity [47].

3.6.3 Visceral Adipose Tissue (VAT)/Subcutaneous Adipose Tissue (SAT) ratio (n=4)

The analysis of the distribution between VAT and SAT yielded conflicting results. A higher VAT/SAT ratio area emerged as an independent predictor for lower OS (HR 2.18, 95% CI 1.52–3.13; p<0.001) [48], poor DSS (HR 1.71, 95% CI 1.20–2.44; p=0.003) [48], and worse PFS (HR 1.41, 95% CI 1.05–1.89; p=0.02) [48]. Contrastingly, other studies showed that low VAT/SAT ratio area was associated with shorter DFS (HR 4.38, 95% CI 1.2–15.5, p=0.022) [37], poor DDFS (HR 0.64, 95% CI 0.52–0.74; p=0.001) [39], worse OS (HR 2.00, 95% CI 1.07–3.74; p=0.03) [39], and lower PFS (HR 0.63, 95% CI 0.51–0.73; p<0.001) [39]. Notably, one study reported no significant association between VAT/SAT ratio index and OS and DFS [46].

3.6.4 Total Abdominal Adipose Tissue (TAAT) (n=3)

The whole abdominal adipose tissue, referred as TAAT, encompasses both VAT and SAT area in the abdomen [26]. The results showed that a high TAAT index was associated with worse PFS (HR 2.17, 95% CI 1.06-4.46; p=0.030) [38].

In the distribution analysis between intra-abdominal adipose tissue and TAAT, it was observed that a higher intra-abdominal adipose tissue/TAAT volume ratio was linked to the occurrence of high-grade leukopenia (grade 4) (p=0.012) [26].

3.6.5 Intermuscular Adipose Tissue (IMAT) (n=4)

The IMAT also presented conflicting findings between the studies. Elevated IMAT density emerged as a significant prognostic factor for poor OS (HR 2.28, 95% CI 1.22–4.26; p=0.01) [29] and lower DSS (HR 2.95; 95% CI 1.34–6.46, p=0.007) [29]. Moreover, a high IMAT index was associated with worse OS (HR 3.6, 95% CI 1.2–10.8; p=0.02) [46] and poor DFS (HR 2.8, 95% CI 1.0–7.8; p=0.04) [46]. In contrast, studies failed to find associations between IMAT index and DSS [29], OS [29], and PFS [27]. As well as, no significant link was observed between IMAT density and PFS [27], nor between IMAT area and PCR [35].

3.6.6 Total Adipose Tissue (TAT) (n=1)

When combining the indices of SAT, VAT, and IMAT, into what is referred as TAT index, no significant differences in PFS were observed (p=0.204) [27].

3.6.7 Gluteofemoral Adipose Tissue (GFAT) (n=1)

The GFAT analysis, conducted by a single study and distinct from the previously discussed adipose tissue depots, revealed promising associations with favorable outcomes. The results demonstrated that a 1.0 cm^3 increase in GFAT volume was significantly linked to longer PFS (HR 0.98, 95% CI 0.96–0.99; p<0.001) [44]. Moreover, delving into the distribution between abdominal adipose tissue and GFAT, showed that a 1.0 cm^3 increase in abdomen/GFAT volume ratio was also significantly associated with worse PFS (HR 2.50, 95% CI 1.64–3.81; p<0.001) [44].

4. Discussion

This systematic review evaluated 23 studies, showing that VAT and SAT were the most frequently assessed body adipose tissue depots. In cases where associations between VAT and SAT with outcomes were identified, most studies found that an increase in these depots was linked to worse outcomes. The results regarding IMAT were conflicting, whereas greater GFAT was associated with

better outcomes. Limited studies evaluating IMAT and GFAT hindering drawing conclusive results (Figure 2). These findings are consistent with our initial hypothesis that differing adipose tissue depots may contribute to diverse prognosis in women with BC and align with previous literature [15,20,43,44,51,52].

Visceral adipose tissue, surrounding the abdominal viscera, is highly vascular, sensitive to lipolysis, and insulin resistant. It contains elevated inflammatory and immune cells producing inflammatory cytokines [19,51,53]. These mediators exacerbate pro-inflammatory and pro-tumorigenic environments, thus explaining the found association with worse outcomes [16,43,51,53].

The inflammatory characteristics of excess body adipose tissue can also promote chemoresistance [54,55] and affect the pharmacokinetics of antineoplastic agents by altering tissue distribution and drug elimination [55,56]. Limited data exist on these aspects, requiring further research. Conversely, patients with higher body adipose tissue levels may exhibit better clinical outcomes with targeted therapies, such as cyclin-dependent kinase (CDK) 4/6 inhibitors [27,28]. Individuals with higher levels of body adipose tissue might express greater CDK 4/6, which plays an important role in adipogenesis, glycolysis and mitochondrial function, processes also involved in tumor progression [27,28,56,57].

Excessive energy intake often leads to body adiposity redistribution. In such cases, abdominal SAT may not expand properly, causing adipocyte hypertrophy and immune cells infiltration, thus altering adipokine secretion. Once the storage capacity of hypertrophic adipocytes is exceeded, excess lipids can be redirect to other ectopic sites, such as VAT and skeletal muscle (IMAT) [20,58–60]. Lower body depots (GFAT) may prevent or reduce this ectopic fat accumulation. Besides, abdominal SAT is divided into superficial and deep layers by Scarpa's Fascia. Deep SAT exhibits a pro-inflammatory profile similar to VAT, while superficial SAT resembles GFAT, secreting less inflammatory cytokines [20,43,61–64]. However, CT scans cannot distinguish between these layers, making it difficult to conduct a more specific metabolic analysis of SAT [19].

The results of this review may have been affected by CT technical issues, including variations in the ranges and cut-off points used to assess adipose tissue

radiodensity [16,65,66], as established standards are lacking [3,16,46]. The inconsistent reporting of axial CT slices numbers further compounds this issue. While a single abdominal cross-sectional CT image correlates strongly with total body adiposity and muscularity measurements [16,67,68], its accuracy may be affected by surrounding structures [19,69]. Discrepancies also exist regarding the optimal lumbar vertebrae for analysis [16,65,67,68,70].

Due to the heterogeneity of the included papers, quantitative analysis could not be conducted. Variations in sample sizes and patient characteristics that can affect body composition, such as age, BMI, menopause status, cancer staging, and treatment, may have influenced our results. Establishing a causal link between body adiposity and BC outcomes within this systematic review is challenging due to limited evidence and the reliance on observational studies.

Stage and type of cancer can impact the predictability capacity of CT. For example, in a study involving patients with renal cancer (n=1,039), a lower VAT index exhibited a non-linear association with worse OS and DFS in stages I-III, while a higher VAT index was associated with better OS in stage IV [71]. In advanced colorectal cancer (n=217), low SAT and VAT indexes, along with high SAT and VAT densities were linked to an increased risk of mortality. Notably, a high VAT density emerged as the primary predictor of poor survival [72].

Many studies in this review explored the relationship between BMI and body adipose tissue depots, often stratifying or adjusting analyses based on BMI categories [19,26,27,29,30,34,35,39,43,44,46]. Body mass index serves as an indicator of obesity degree but does not reflect body components [19,39]. Furthermore, consideration of distinct underlying pathophysiological processes of each adipose tissue depot is important. For instance, IMAT may be more closely associated with the decline in muscle mass quality and function compared to other depots. This might contribute to the divergent findings observed in this review, compounded by variations in CT methodology [29,73].

Our paper presents a systematic review of a novel approach to evaluating body compartments and their relationship with outcomes in BC, despite the challenges of summarizing the results. It plays a crucial role in future research by providing a valuable data source and foundation for hypotheses. Notably, to the best of our knowledge, this marks the initial exploration of the relationship between CT-evaluated body adipose tissue depots and BC outcomes. Computed

tomography is considered a reference method for assessing body composition in research and is routinely utilized in medical follow-up examinations. Its ongoing advancement and integration into clinical practice hold tremendous potential for benefiting patients, particularly concerning cancer outcomes.

The findings of this review shed light on the diverse outcomes regarding BC across different body adipose tissue depots assessed by CT. Specially, when associations were identified, higher VAT and SAT were linked to worse outcomes. Additional research is required to analyze homogeneous clinical samples and use standardized CT analysis to investigate body adipose tissue. The challenge lies in stablishing methodological criteria for the application of CT imaging and in comprehending the unique characteristics of different body adipose tissue depots. Such studies will contribute to enhancing our understanding of the implications of body adipose tissue in improving the health outcomes of patients with BC.

In conclusion, the heterogeneity of the included studies in this systematic review reinforces the need of homogeneous methodologies to better understand the impact of body adipose tissue depots on BC outcomes. Despite this, association between increased VAT and SAT with worse outcomes in patients with BC was observed.

Acknowledgment: The authors have no acknowledgment to declare.

Grants and founding: This work was supported by the Research Incentive Fund (FIPE) – Hospital de Clinicas de Porto Alegre (HCPA); and Coordination for the Improvement of Higher Education Personnel (CAPES) (no. 88887.483699/2020-00).

Authors contributions: All authors should have made substantial contributions to all of the following: **TSP:** Project administration, design of the study, practical performance, data analysis, preparation of the manuscript, critical review and editing, final approval of the version to be submitted; **RSP:** Design of the study, practical performance, data analysis, preparation of the manuscript, critical review and editing, final approval of the version to be submitted; **LVV:** Design of the study, practical performance, data analysis, preparation of the manuscript, critical review and editing, final approval of the version to be submitted.

Conflict of interest statement: The authors report no conflict of interest.

Institutional Review Board Statement: Study approved by the Research Ethics Committee of Hospital de Clinicas de Porto Alegre (HCPA) under registration no. 31772720.5.0000.5327, and by the internal research group at HCPA - Research and Graduate Group (GPPG) under registration no. 2020-0224.

CAPTIONS TO ILLUSTRATIONS

Figure 1. Flowchart showing the selection process of the studies. Two independent investigators performed a literature search in Pubmed, Embase, Cochrane Library, Scopus, and Web of Science databases to identify observational studies reporting outcomes related to body adipose tissue in patients with BC. After all phases of the screening process, 23 studies were included in the final sample (n=12,462).

Figure 2. Summary of the most important and rational findings of this systematic review. VAT and SAT increases were associated with worse outcomes, greater GFAT was associated with better outcomes, and the findings for IMAT were controversial. VAT and GFAT results can be explained by its pro-inflammatory and its less inflammatory profile, respectively. The findings for SAT may be affected by CT scans inability to distinguish between its deeper (more inflammatory) and superficial layers (less inflammatory). Meanwhile, the results for IMAT could be influenced by the methodological variability in CT techniques and the possible underling pathophysiological processes related to muscle mass.

Figure S1. Major positive and negative associations for each adipose tissue depot and BC treatment outcomes. This figure shows data on area, index and volume of adipose tissue depots. Adipose tissue density data are not presented here with the main associations, as the literature on its assessment is still unclear. Completed information can be found in the text and tables.

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Figure 1. Flowchart showing the selection process of the studies.

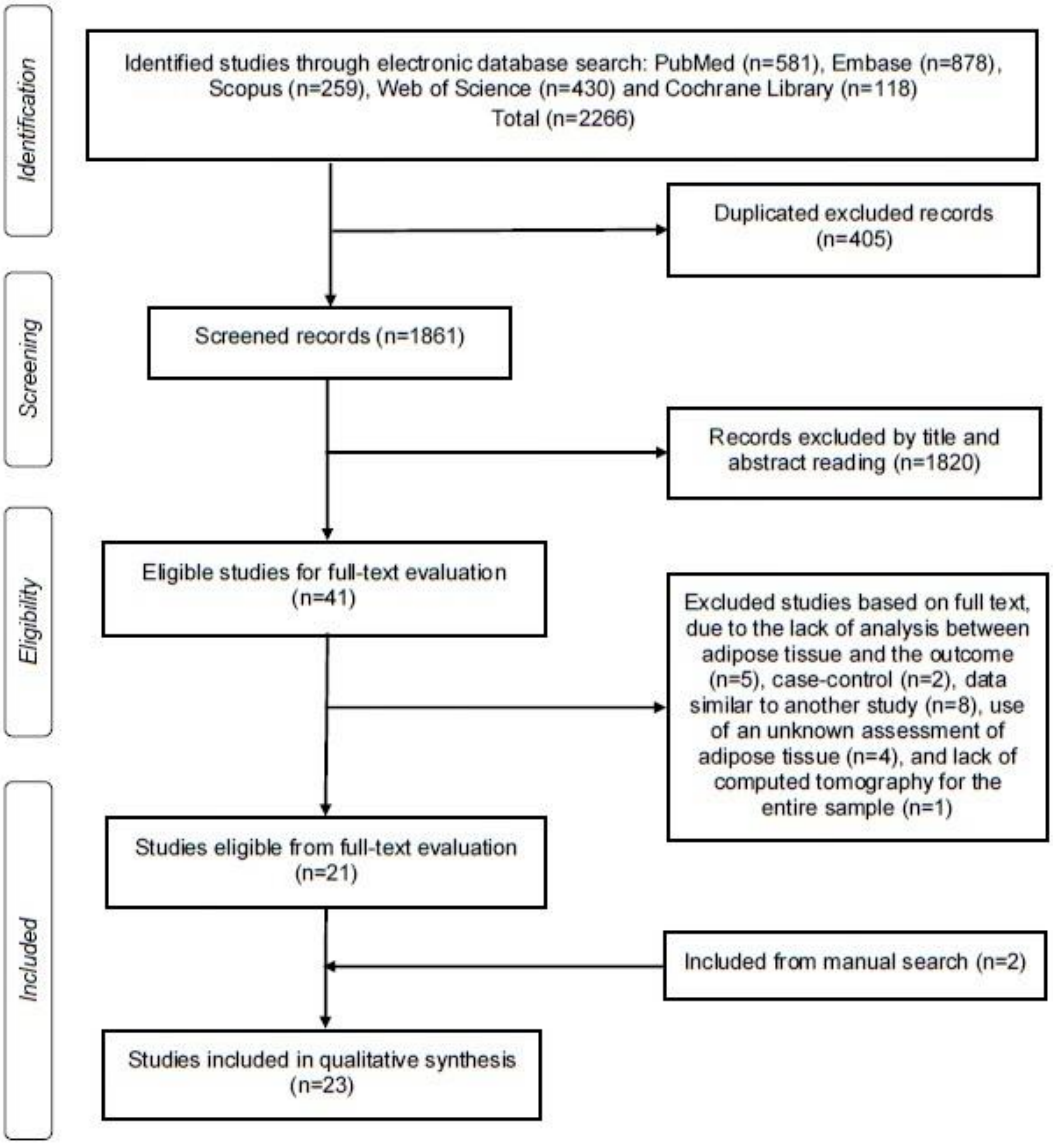
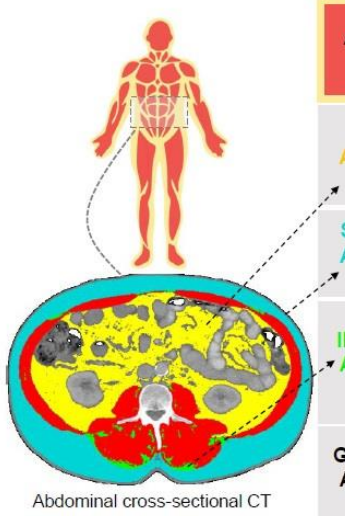


Figure 2. Summary of the most important and rational findings of this systematic review.



Adipose tissue depots	Clinical Outcomes	Inflammatory status
VISCERAL ADIPOSE TISSUE (n=19)	↓ Overall survival ↓ Disease-free survival ↓ Distant disease-free survival ↓ Progression-free survival ↑ Cancer burden ↑ Mortality	↑ Inflammatory and immune cells: pro-inflammatory and pro-tumorigenic environment
SUBCUTANEOUS ADIPOSE TISSUE (n=17)		Superficial SAT: ↓ inflammatory vs. deep SAT: ↑ inflammatory
INTERMUSCULAR ADIPOSE TISSUE (n=4)	Contradictory finds	Possible underlying pathophysiological processes related to muscles + CT methodological differences
GLUTEOFEMORAL ADIPOSE TISSUE (n=1)	↑ Progression-free survival	↑ Favorable adipokines and ↓ inflammatory cytokines: health protector effect

CT: computed tomography; SAT: subcutaneous adipose tissue

Table 1. Methodological approaches and results according to adipose tissue compartments and outcomes in women with BC assessed by each observational study (n=23).

Authors Year	Body region of CT Methods for AT analysis by CT HU range for AT compartment	Cut-off points used for AT compartments Cut-off points development	Results according AT compartments and outcome
		OVERALL SURVIVAL	
Iwase et al. 2021 [39]	Abdominal Whole cross-sectional area of SAT and VAT -190HU to -30 HU	Continuous for VAT (density and area) and SAT area. Cut-off point for VAT/SAT ratio >34 Cut-off point developed by statistical analysis	SAT and VAT (areas and densities) = no association with OS <VAT/SAT ratio (area) = worse OS
Jeon et al. 2021 [29]	Abdominal Whole cross-sectional area of SAT, VAT and IMAT -190HU to -30 HU	Cut-off points (cm/m²) for SAT: 49.3, VAT: 31.1 and IMAT: 2.1 (indexes) Cut-off points (HU) for SAT: -98.4, VAT: -83.3 and IMAT: -57.2 (densities) Cut-off points developed by statistical analysis	>VAT (index) = independent predictor of poor OS >IMAT (density) = significant prognostic factor for worse OS SAT (index and density), VAT (density) and IMAT (index) = no association with OS
Brennan et al. 2020 [40]	Abdominal NA NA	NA	SAT (area) = independently associated with OS
Huh et al. 2020 [41]	Abdominal Whole cross-sectional area of SAT and VAT −190HU to −30 HU	Cut-off points (cm²) for SAT: >134.39 and VAT: >85.56 Cut-off points developed by statistical analysis	SAT and VAT (areas) = not associated with OS
Deluche et al. 2018 [46]	Abdominal Whole cross-sectional area of SAT, VAT and IMAT (except AT in the psoas) NA	Cut-off points (cm²/m²) for VAT/SAT ratio: >0.69 and IMAT index: >3.5 Cut-off for VAT/SAT ratio: 50th percentiles Cut-off points for VAT, SAT, IMAT: median	VAT/SAT ratio (index) = not associated with OS >IMAT (index) = worse OS
Dalal et al. 2014 [48]	Abdominal NA NA	Continuous	>VAT/SAT ratio (area) = worse OS

AT: adipose tissue; CT: computed tomography; HU: Hounsfield Units; IMAT: intermuscular adipose tissue; NA: not available; OS: overall survival; SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue

Table 1 (continuation)**.** Methodological approaches and results according to adipose tissue compartments and outcomes in women with BC assessed by each observational study (n=23).

Authors Year	Body region of CT Methods for AT analysis by CT HU range for AT compartment	Cut-off points used for AT compartments Cut-off points development	Results according AT compartments and outcome
		DISEASE-FREE SURVIVAL	
Trestini et al. 2023 [35]	Abdominal Whole cross-sectional area of SAT, VAT and IMAT -190 to -30 HU for SAT and IMAT, and -150 to -50 HU for VAT	Cut-off point (%) for VAT gain: ≥10 Cut-off point developed by statistical analysis Continuous for SAT (area)	VAT (area) = independent predictor of worse DFS >VAT (area) = worse DFS
Oliveira et al. 2022 [37]	Abdominal Whole cross-sectional area of SAT and VAT −190 to −30 HU for SAT and VAT	Cut-off point (cm^2) for VAT: >100 Cut-off point for VAT/SAT ratio: 0.47 Cut-off point for VAT available at literature, for VAT/SAT ratio developed by statistical analysis Cut-off point for SAT: NA	VAT (area) = not associated with DFS <VAT/SAT (area) = associated with shorter DFS
Kwon et al. 2022 [36]	Abdominal Whole cross-sectional area of VAT -300 to -50 HU	Continuous	VAT (area) = not associated with DFS
Brennan et al. 2020 [40]	Abdominal NA NA	Cut-off point (cm^2) for VAT: >80.1 Development of VAT cut-off point: NA Cut-off point for SAT: NA	SAT and VAT (areas) = not predictors for DFS
Deluche et al. 2018 [46]	Abdominal Whole cross-sectional area of SAT, VAT and IMAT (except AT in the psoas) NA	Cut-off points (cm^2/m^2) for SAT: >107.7; VAT: >55.6; IMAT: >3.5 (indexes); VAT/SAT ratio: >0.69 Cut-off for VAT/SAT ratio: 50th percentiles Cut-off points for VAT, SAT, IMAT: median	>IMAT (index) = worse DFS SAT, VAT and VAT/SAT ratio (indexes) = not associated with DFS

AT: adipose tissue; CT: computed tomography; DFS: disease-free survival; HU: Hounsfield Units; IMAT: intermuscular adipose tissue; NA: not available; SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue

Table 1 (continuation)**.** Methodological approaches and results according to adipose tissue compartments and outcomes in women with BC assessed by each observational study (n=23).

Authors Year	Body region of CT Methods for AT analysis by CT HU range for AT compartment	Cut-off points used for AT compartments Cut-off points development	Results according AT compartments and outcome
		DISTANT DISEASE-FREE SURVIVAL	
Iwase et al. 2021 [39]	Abdominal Whole cross-sectional area of SAT and VAT -190HU to -30 HU	Cut-off for VAT/SAT ratio: >34 Cut-off point developed by statistical analysis	<VAT/SAT ratio (area) = worse DDFS
Iwase et al. 2020 [19]	Abdominal Whole cross-sectional area of VAT -195HU to − 45 HU	Continuous	>VAT (area) and <VAT (density) = shorter DDFS
Dalal et al. 2018 [45]	Abdominal NA NA	Cut-off point for VAT: NA Development of VAT cut-off point: NA	>VAT (area) = worse DDFS
		DISEASE-SPECIFIC SURVIVAL	
Jeon et al. 2021 [29]	Abdominal Whole cross-sectional area of SAT, VAT and IMAT -190HU to -30 HU	Cut-off points (cm/m²) for SAT: 49.3, VAT: 31.1 and IMAT: 2.1 (indexes) Cut-off points (HU) for SAT: -98.4, VAT: -83.3 and IMAT: -57.2 (densities) Cut-off point developed by statistical analysis	>VAT (index) = independent predictor of DSS >IMAT (density) = significant prognostic factor for DSS SAT (index and density), VAT (density) and IMAT (index) = no significant prognostic factors for DSS
Dalal et al. 2014 [48]	Abdominal NA NA	Continuous	>VAT/SAT ratio (area) = independent predictor for lower DSS

AT: adipose tissue; CT: computed tomography; DDFS: distant disease-free survival; DSS: disease-specific survival; GFAT: gluteofemoral adipose tissue; HU: Hounsfield Units; IMAT: intermuscular adipose tissue; NA: not available; PFS: progression-free survival; SAT: subcutaneous adipose tissue; TAAT: total abdominal adipose tissue; TAT: total adipose tissue; VAT: visceral adipose tissue

Table 1 (continuation)**.** Methodological approaches and results according to adipose tissue compartments and outcomes in women with BC assessed by each observational study (n=23).

Authors Year	Body region of CT Methods for AT analysis by CT HU range for AT compartment	Cut-off points used for AT compartments Cut-off points development	Results according AT compartments and outcome
		PROGRESSION-FREE SURVIVAL	
Iwase et al. 2021 [39]	Abdominal Whole cross-sectional area of SAT and VAT -190HU to -30 HU	Cut-off for VAT/SAT ratio: >34 Cut-off point developed by statistical analysis	<VAT/SAT ratio (area) = worse PFS
Palleschi et al. 2022 [38]	Abdominal NA NA	NA	>SAT (index) = worse PFS >TAAT (index) = worse PFS
Franzoi et al. 2020 [27]	Abdominal Whole cross-sectional area of VAT, SAT and IMAT SAT: −190HU to –30HU VAT: −150HU to – 50HU	Cut-off point for SAT, VAT, TAT, IMAT (indexes and densities): NA Cut-off points for SAT, VAT, TAT, IMAT (indexes and densities): median	>VAT (index and density) = longer PFS SAT and IMAT (indexes and densities) and TAT (index) = not associated with PFS
Lee et al. 2019 [44]	Abdominal and thigh Whole cross-sectional area of VAT, SAT and GFAT -200HU to -50 HU	Continuous and cut-off points (cm^3) for abdominal SAT: 90.00; GFAT: 88.00 and abdomen/GFAT volume ratio: 1.50 (volumes) Cut-off points developed by statistical analysis	>Abdominal SAT and >Abdomen/GFAT ratio (volumes) = worse PFS >GFAT (volume) = increase in PFS
Dalal et al. 2014 [48]	Abdominal NA NA	Continuous	>VAT/SAT ratio (area) = independent predictor of lower PFS

AT: adipose tissue; CT: computed tomography; DSS: disease-specific survival; GFAT: gluteofemoral adipose tissue; HU: Hounsfield Units; IMAT: intermuscular adipose tissue; NA: not available; PFS: progression-free survival; SAT: subcutaneous adipose tissue; TAAT: total abdominal adipose tissue; TAT: total adipose tissue; VAT: visceral adipose tissue

Table 1 (continuation)**.** Methodological approaches and results according to adipose tissue compartments and outcomes in women with BC assessed by each observational study (n=23).

Authors Year	Body region of CT Methods for AT analysis by CT HU range for AT compartment	Cut-off points used for AT compartments Cut-off points development	Results according AT compartments and outcome
		MORTALITY	
Cheng et al. 2022 [30]	Abdominal Whole cross-sectional area of VAT and SAT -190 to -30 HU for SAT and -150 to -50 HU for VAT	Cut-off points (HU) for SAT and VAT: <mean minus 1 SD), mean ± 1 SD and >1 mean plus SD (radiodensities) Cut-off points for SAT and VAT developed by statistical analysis	>SAT radiodensity = increased risk of overall mortality VAT radiodensity = not associated with overall mortality
Bradshaw et al. 2019 [43]	Abdominal Whole cross-sectional area of VAT and SAT NA	Continuous	>SAT (area) = greater risk of death from any cause >VAT (area) = not associated with risk of death from any cause
Dalal et al. 2018 [45]	Abdominal NA NA	Cut-off point for VAT: NA Development of VAT cut-off point: NA	>VAT (area) = higher mortality risk
		TREATMENT RESPONSE	
Trestini et al. 2023 [35]	Abdominal Whole cross-sectional area of SAT, VAT and IMAT -190 to -30 HU for SAT and IMAT, and -150 to -50 HU for VAT	Continuous	<IMAT (area) = not associated with PCR
Kripa et al. 2022 [28]	Abdominal Whole cross-sectional area of SAT and VAT NA	Cut-off point for VAT: >130cm^2 Cut-off point for VAT available at literature Development of SAT cut-off point: NA	>VAT (area) = good treatment response and absence of axillary lymphadenopathies SAT (area) = not associated with treatment response

AT: adipose tissue; CT: computed tomography; HU: Hounsfield Units; IMAT: intermuscular adipose tissue; NA: not available; SAT: subcutaneous adipose tissue; SD: standard deviation; VAT: visceral adipose tissue

Table 1 (continuation)**.** Methodological approaches and results according to adipose tissue compartments and outcomes in women with BC assessed by each observational study (n=23).

Authors Year	Body region of CT Methods for AT analysis by CT HU range for AT compartment	Cut-off points used for AT compartments Cut-off points development	Results according AT compartments and outcome
		TREATMENT RESPONSE	
Iwase et al. 2021 [39]	Abdominal NA Whole cross-sectional area of SAT and VAT -190HU to -30 HU	Continuous	VAT and SAT (areas and densities) = not associated with PCR
Iwase et al. 2020 [19]	Abdominal Whole cross-sectional area of VAT -195HU to − 45 HU	Continuous	VAT (area and density) = not associated with PCR
Dalal et al. 2018 [45]	Abdominal NA NA	Cut-off points for VAT: NA Development of VAT cut-off point: NA	>VAT (area) = lower chance of PCR
Dalal et al. 2014 [48]	Abdominal NA NA	Continuous	<SAT and >VAT (area) = lower probability of achieving PCR
Tanner et al. 2012 [50]	Abdominal Whole cross-sectional area of SAT NA	Continuous	>SAT (area) = increase in residual cancer burden score

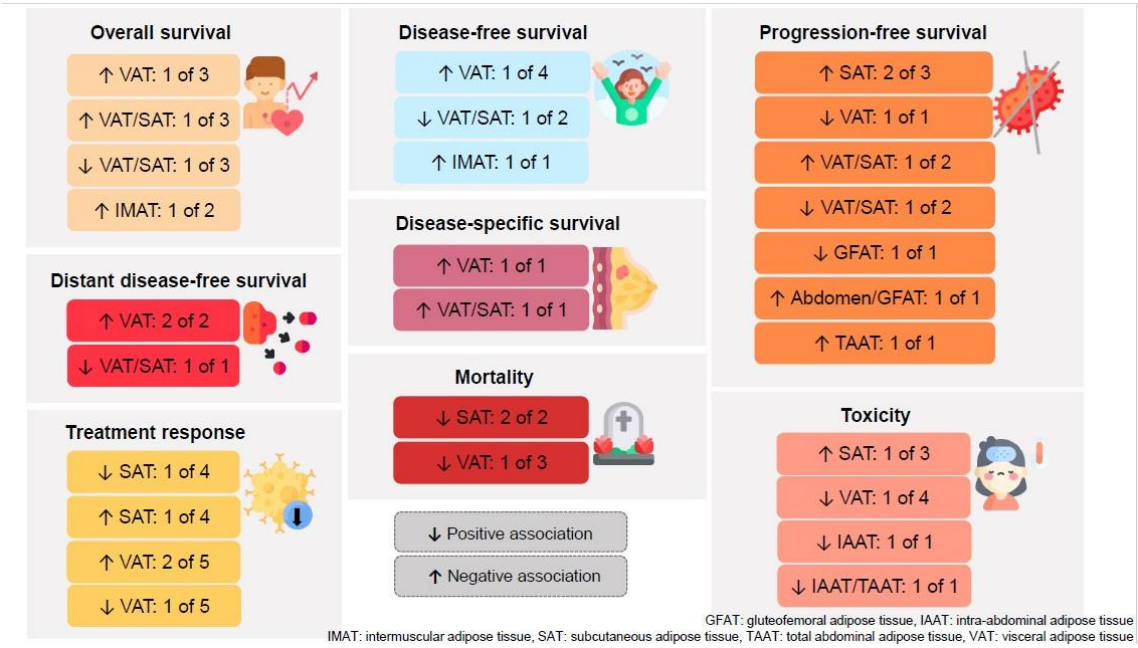
AT: adipose tissue; CT: computed tomography; HU: Hounsfield Units; IMAT: intermuscular adipose tissue; NA: not available; SAT: subcutaneous adipose tissue; SD: standard deviation; VAT: visceral adipose tissue

Table 1 (continuation)**.** Methodological approaches and results according to adipose tissue compartments and outcomes in women with BC assessed by each observational study (n=23).

Authors Year	Body region of CT Methods for AT analysis by CT HU range for AT compartment	Cut-off points used for AT compartments Cut-off points development	Results according AT compartments and outcome
		TREATMENT TOXICITY	
Jang et al. 2023 [34]	Abdominal Whole cross-sectional area of SAT and VAT NA	Continuous	<SAT (index) = associated with anemia >VAT (index) = associated with neutropenia VAT and SAT (index) = not associated with thrombocytopenia
Ueno et al. 2020 [42]	Abdominal Whole cross-sectional area of SAT and VAT -190 to -30 HU	Continuous	SAT and VAT (areas) = not associated with treatment toxicity
Shachar et al. 2017 [47]	Abdominal Whole cross-sectional area of SAT and VAT -190 to -30 HU for SAT and -150 to -50 HU for VAT	Continuous	SAT and VAT (areas or density) = not associated with treatment toxicity
Wong et al. 2014 [26]	Abdominal Whole cross-sectional area of SAT and VAT -300HU to -10HU	Continuous	>Intra-abdominal AT and >intra-abdominal AT/total abdominal AT ratio (volumes) = higher degree of leukopenia
Sabel et al. 2012 [49]	Abdominal NA NA	Continuous	>VAT (area) = reduced chemotherapy completion

AT: adipose tissue; CT: computed tomography; HU: Hounsfield Units; IMAT: intermuscular adipose tissue; NA: not available; SAT: subcutaneous adipose tissue; TAAT: total abdominal adipose tissue; TAT: total adipose tissue; VAT: visceral adipose tissue

Figure S1. Major positive and negative associations for each adipose tissue depot and BC treatment outcomes.



GFAT: gluteofemoral adipose tissue, IAAT: intra-abdominal adipose tissue
IMAT: intermuscular adipose tissue, SAT: subcutaneous adipose tissue, TAAT: total abdominal adipose tissue, VAT: visceral adipose tissue

Table S1. Total results found and bibliographic search strategy used for each database.

Database	*Total results found*	*Final date*	*Search strategy*
PUBMED	581 articles	01/09/2024	(((Overweight[mh] OR Overweight[tiab] OR Adipose Tissue[mh] OR Adipose Tissue[tiab] OR Body fat[tiab] OR total body fat[tiab] OR fatness[tiab] OR fat body mass[tiab] OR body fat distribution[mh] OR body fat distribution[tiab] OR Body Fat Patterning[tw] OR Adiposity[mh] OR Adiposity[tiab] OR Body Composition[mh] OR Body Composition[tiab] OR Obesity[mh] OR Obesity[tiab] OR Intra-Abdominal Fat[mh] OR Visceral Adipose Tissue[tiab] OR Subcutaneous Fat[mh] OR Subcutaneous Adipose Tissue[tiab]) AND (Breast neoplasms[mh] OR ((breast[tiab] OR mamma*[tiab]) AND (neoplas*[tiab] OR cancer[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR oncol*[tiab] OR malignan*[tiab])))) AND ("Tomography X-Ray Computed"[tiab] OR Tomography, X-Ray Computed[mh] OR "X-Ray Computed Tomography"[tiab] OR "CT X Ray"[tiab] OR "computed tomography"[tiab] OR "x ray tomography"[tiab] OR Absorptiometry, Photon[mh] OR "Dual Energy X Ray Absorptiometry Scan"[tiab] OR "Dual-Energy X-Ray Absorptiometry Scan"[tiab] OR Magnetic Resonance Imaging[mh] OR "Magnetic Resonance Imaging"[tiab] OR "CT Scan*"[tiab] OR "DXA Scan*"[tiab] OR "MRI Scan*"[tiab] OR Ultrasonography[mh] OR Ultrasonography[tiab]))
EMBASE	878 articles	01/09/2024	(Obesity/exp OR Overweight:ti,ab,kw OR 'Adipose Tissue'/exp OR 'Adipose Tissue':ti,ab,kw OR 'Body fat':ti,ab,kw OR 'total body fat':ti,ab,kw OR fatness:ti,ab,kw OR 'fat body mass':ti,ab,kw OR 'body fat distribution'/exp OR 'body fat distribution':ti,ab,kw OR 'Body Fat Patterning':ti,ab,kw OR Adiposity:ti,ab,kw OR 'Body Composition'/exp OR 'Body Composition':ti,ab,kw OR Obesity:ti,ab,kw OR 'Intra-Abdominal Fat'/exp OR 'Visceral Adipose Tissue':ti,ab,kw OR 'Subcutaneous Fat'/exp OR 'Subcutaneous Adipose Tissue':ti,ab,kw)AND ('Breast tumor'/exp OR 'Breast neoplasm*':ti,ab,kw OR ((breast:ti,ab,kw OR mamma*:ti,ab,kw) AND (neoplas*:ti,ab,kw OR cancer:ti,ab,kw OR tumor*:ti,ab,kw OR tumour*:ti,ab,kw OR carcinoma*:ti,ab,kw OR oncol*:ti,ab,kw OR malignan*:ti,ab,kw))) AND ('x-ray computed tomography'/exp OR 'Tomography X-Ray Computed':ti,ab,kw OR 'X-Ray Computed Tomography':ti,ab,kw OR 'CT X Ray':ti,ab,kw OR 'computed tomography':ti,ab,kw OR 'x ray tomography':ti,ab,kw OR 'photon absorptiometry'/exp OR 'photon absorptiometry':ti,ab,kw OR 'Dual Energy X Ray Absorptiometry Scan':ti,ab,kw OR 'Dual-Energy X-Ray Absorptiometry Scan':ti,ab,kw OR 'nuclear magnetic resonance imaging'/exp OR 'Magnetic Resonance Imaging':ti,ab,kw OR 'CT Scan*':ti,ab,kw OR 'DXA Scan*':ti,ab,kw OR 'MRI Scan*':ti,ab,kw OR echography/exp OR Ultrasonography:ti,ab,kw)
COCHRANE LIBRARY	118 articles	01/09/2024	#1 MeSH descriptor: [Overweight] explode all trees 16880 #2 MeSH descriptor: [Adipose Tissue] explode all trees 2536 #3 MeSH descriptor: [Body Fat Distribution] explode all trees 943 #4 MeSH descriptor: [Adiposity] explode all trees 765 #5 MeSH descriptor: [Body Composition] explode all trees 5227 #6 MeSH descriptor: [Obesity] explode all trees 14210

			#7 MeSH descriptor: [Intra-Abdominal Fat] explode all trees 310 #8 MeSH descriptor: [Subcutaneous Fat] explode all trees 256 #9 Overweight OR "Adipose Tissue" OR "Body fat" OR "total body fat" OR fatness OR "fat body mass" OR "body fat distribution" OR "Body Fat Patterning" OR Adiposity OR "Body Composition" OR Obesity OR "Intra-Abdominal Fat" OR "Visceral Adipose Tissue" OR "Subcutaneous Fat" OR "Subcutaneous Adipose Tissue" 60682 #10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 60745 #11 MeSH descriptor: [Breast Neoplasms] explode all trees 13386 #12 breast OR mamma* 53458 #13 neoplas* OR cancer OR tumor* OR tumour* OR carcinoma* OR oncol* OR malignan* 243332 #14 #12 AND #13 40904 #15 #11 OR #14 40904 #16 MeSH descriptor: [Tomography, X-Ray Computed] explode all trees 5099 #17 MeSH descriptor: [Absorptiometry, Photon] explode all trees 1907 #18 MeSH descriptor: [Magnetic Resonance Imaging] explode all trees 7924 #19 MeSH descriptor: [Ultrasonography] explode all trees 13854 #20 "Tomography X-Ray Computed" OR "X-Ray Computed Tomography" OR "CT X Ray" OR "computed tomography" OR "x ray tomography" OR "Dual Energy X Ray Absorptiometry Scan" OR "Dual-Energy X-Ray Absorptiometry Scan" OR "Magnetic Resonance Imaging" OR "CT Scan*" OR "DXA Scan*" OR "MRI Scan*" OR Ultrasonography 57612 #21 #16 OR #17 OR #18 OR #19 OR #20 64022 #22 #10 AND #15 AND #20
WEB OF SCIECE	430 articles	01/09/2024	TS=(Overweight OR "Adipose Tissue" OR "Body fat" OR "total body fat" OR fatness OR "fat body mass" OR "body fat distribution" OR "Body Fat Patterning" OR Adiposity OR "Body Composition" OR Obesity OR "Intra-Abdominal Fat" OR "Visceral Adipose Tissue" OR Subcutaneous Fat OR "Subcutaneous Adipose Tissue") AND TS=("Breast neoplasms" OR ((breast OR mamma*) AND (neoplas* OR cancer OR tumor* OR tumour* OR carcinoma* OR oncol* OR malignan*))) AND TS=("Tomography X-Ray Computed" OR "X-Ray Computed Tomography" OR "CT X Ray" OR "computed tomography" OR "x ray tomography" OR "Dual Energy X Ray Absorptiometry Scan" OR "Dual-Energy X-Ray Absorptiometry Scan" OR "Magnetic Resonance Imaging" OR "CT Scan*" OR "DXA Scan*" OR "MRI Scan*" OR Ultrasonography)
SCOPUS	259 articles	01/09/2024	TITLE-ABS(Overweight OR "Adipose Tissue" OR "Body fat" OR "total body fat" OR fatness OR "fat body mass" OR "body fat distribution" OR "Body Fat Patterning" OR Adiposity OR "Body Composition" OR Obesity OR "Intra-Abdominal Fat" OR "Visceral Adipose Tissue" OR Subcutaneous Fat OR "Subcutaneous Adipose Tissue") AND TITLE-ABS("Breast neoplasms" OR ((breast OR mamma*) AND (neoplas* OR cancer OR tumor* OR tumour* OR carcinoma* OR oncol*

	OR malignan*))) AND TITLE-ABS("Tomography X-Ray Computed" OR "X-Ray Computed Tomography" OR "CT X Ray" OR "computed tomography" OR "x ray tomography" OR "Dual Energy X Ray Absorptiometry Scan" OR "Dual-Energy X-Ray Absorptiometry Scan" OR "Magnetic Resonance Imaging" OR "CT Scan*" OR "DXA Scan*" OR "MRI Scan*" OR Ultrasonography)

Table S2. Glossary of terms as described by included studies.

Terms	Definitions
Breast cancer-specific survival	The time from breast cancer diagnosis until death [29].
Disease-free survival	The time from the date of diagnosis or from the date of surgery until disease progression or relapse; the date of death from any cause, the date last known to have no evidence of disease, or the date of the most recent follow-up [36,40,46].
Disease-specific survival	NA [40,48].
Distant disease-free survival	The time from initial treatment to relapse at any distant site/organ [19].
Distant progression-free survival	The time from the initial diagnosis to recurrence in distant organs[a] [39].
Overall mortality	Follow-up time from CT scan to death from any cause or last date of contact [43].
Overall survival	The time from the date of diagnosis to the date of death from any cause or the date of last follow-up or the end of the study [29,39,40,41,46,48].
Pathologic complete response	Either an absence of residual tumor or noninvasive in situ residual tumor remaining in the surgical specimen from the primary tumor and axillary lymph nodes [19,39,48].
Progression-free survival	The time from the day of the initial treatment to the day of the detection of cancer recurrence[b] [27,44] or the time from the date of the diagnosis to the date of the first documented relapse [39].
Residual cancer burden	NA [50].
Treatment toxicity	Laboratory adverse events were graded according to the Common Terminology Criteria for Adverse Events version 4.0. and version 2.0 [26,42].

NA: not available

[a]Includes also the term distant recurrence-free survival.

[b]Includes also the term recurrence-free survival.

Table S3. Description of the main characteristics of the observational studies included evaluating women with BC (n=23).

Authors Year Country	Study type Evaluated outcome Sample size Follow-up	Age BMI (kg/m²) Menopausal status	Tumor stage	Hormone receptor status HER2 status	Previous treatments	Treatments used during the study
Jang et al. 2023 [34] South Korea	Retrospective Treatment toxicity n = 298 5 mo	52.9 (NA) yrs No sarcopenia - Obese: 39.7% Sarcopenia - Normal: 71.6% NA	II: 73.6%	ER (+) / PR (+): 50.7% HER2 (-): 65.8%	NA	NA
Trestini et al. 2023 [35] Italy	Retrospective DFS and treatment response n = 93 47 mo	47 (30-72) yrs 24.9 (21.9-28.9) kg/m² Pre-menopause: 63.4%	II: 53.8%	ER (+): 72% PR (+): 60.2% HER2 (-): 66.7%	No previous treatment	Neoadjuvant CHT: 98.9%
Cheng et al. 2022 [30] United States	Retrospective Mortality n = 2868 91 mo	56 (48-65) yrs High SAT radiodensity: 18.5-24.9 kg/m²: 60.5% NA	II: 45.6%	High SAT radiodensity: ER (+): 80.7% PR (+): 57.5% HER2 (-): 78.5%	NA	NA
Kwon et al. 2022 [36] Korea	Retrospective DFS n = 627 83 (75–90) mo	53.6 ± 8.3 yrs 23.7 ± 3.1 kg/m² Post-menopause: 59.3%	I: 48.3%	ER (+): 75% PR (+): 68.4% HER2 (-): 78.6%	Surgery: 100%	Adjuvant CHT: 60.8% Adjuvant RT: 78.9% HT: 75.8%
Kripa et al. 2022 [28] Italy	Retrospective Treatment response n = 30 6 mo	53 ± 12 yrs NA Post-menopause: 63.3%	IV: 100%	ER (+): 100% HER2 (-): 100%	NA	CDK 4/6 inhibitors + HT: 100%
Oliveira et al. 2022 [37] Brasil	Retrospective DFS n = 262 32.8 ± 1.8 mo	51.9 ± 12.4 yrs 27.4 ± 5.1 kg/m² NA	II: 38.5%	NA HER2 (+): 13.4%	No previous treatment	Neoadjuvant CHT: 38.2% Surgery: 67.9% Adjuvant CHT: 64.5% Adjuvant RT: 80.9% Adjuvant HT: 78.2%

BMI: body mass index; CDK: cyclin-dependent kinase; CHT: chemotherapy; DFS: disease-free survival; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; HT: hormone therapy; NA: not available; PR: progesterone receptor; RT: radiotherapy; SAT: subcutaneous adipose tissue

Table S3 (continuation). Description of the main characteristics of the observational studies included evaluating women with BC (n=23).

Authors Year Country	Study type Evaluated outcome Sample size Follow-up	Age BMI (kg/m²) Menopausal status	Tumor stage	Hormone receptor status HER2 status	Previous treatments	Treatments used during the study
Palleschi et al. 2022 [38] Italy	Retrospective PFS n = 43 NA	NA NA NA	IV: 100%	NA NA HER2 (+): 100%	NA	1st Line therapy (dual HER2 inhibitors): 100%
Iwase et al. 2021 [39] United States	Retrospective OS, DDFS, PFS, and treatment response n = 198 4.7 yrs	49 (22-80) yrs NA Pre-menopause: 56.6%	Locally advanced	ER (+): 74.7% PR (+): 58.1% HER2 (-): 74.7%	No previous treatment	Neoadjuvant CHT: 100%
Jeon et al. 2021 [29] Korea	Retrospective OS and DSS n = 479 79 (6-173) mo	51 (21-87) yrs 24.2 (14.5–37.5) kg/m² NA	II: 49.5%	ER (+): 62.6% PR (-): 51.8% HER2 (-): 68.9%	No previous treatment	Surgery: 100% Adjuvant CHT: 100%
Brennan et al. 2020 [40] NA	Retrospective OS and DFS n = 83 NA	NA NA NA	Locally advanced	ER (+) / PR (+): 100% HER2 (-): 100%	No previous treatment	Neoadjuvant CHT: 100% Surgery: 100%
Franzoi et al. 2020 [27] Belgium	Retrospective PFS n = 50 14.4 (3.1–33) mo	61.2 yrs (39–83) NA Post-menopause: 94%	IV: 100%	ER (+): 100% HER2 (+): 100%	NA	1st Line therapy: 78% 2nd Line therapy: 22% HT + Target therapy (CDK 4/6 inhibitors): 100%
Huh et al. 2020 [41] Korea	Retrospective OS n = 577 74 (7–90) mo	48.9 ± 10.2 yrs 23.8 ± 3.7 kg/m² Post-menopause: 42%	I-III: 100%	ER (+): 73.3% PR (+): 64.8% HER2 (-): 81.5%	Neoadjuvant CHT: 22.5%	Surgery: 100%. Adjuvant CHT: 57.7% Adjuvant RT: 80.6%

BMI: body mass index; CDK: cyclin-dependent kinase; CHT: chemotherapy; DDFS: distant disease-free survival; DSS: disease-specific survival; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; HT: hormone therapy; NA: not available; PFS: progression-free survival; PR: progesterone receptor; OS: overall survival; RT: radiotherapy

Table S3 (continuation). Description of the main characteristics of the observational studies included evaluating women with BC (n=23).

Authors Year Country	Study type Evaluated outcome Sample size Follow-up	Age BMI (kg/m²) Menopausal status	Tumor stage	Hormone receptor status HER2 status	Previous treatments	Treatments used during the study
Iwase et al. 2020 [19] Japan	Retrospective DDFS and treatment response n = 271 112 mo	Neoadjuvant CHT: 54.5 (30–76) yrs 22.2 (16–37) kg/m² Post-menopause: 57% Adjuvant CHT: 50.6 (30–72) yrs 22.1 (16–29) kg/m² Pre-menopause: 58%	Early stage	Neoadjuvant CHT: ER (+) / HER2 (−): 45% ER (+) / HER2 (+): 17% HER2 (+): 20% TN: 18% Adjuvant CHT: ER (+) / HER2 (−): 50% ER (+) / HER2 (+): 15% HER2 (+): 10% TN: 25%	NA	Neoadjuvant CHT: 62% Adjuvant CHT: 38%
Ueno et al. 2020 [42] Japan	Retrospective Treatment toxicity n = 82 NA	54 (44.3–66) yrs 22.4 (20.3–24.5) kg/m² NA	NA	NA NA	NA	Neoadjuvant or Adjuvant CHT: % NA
Bradshaw et al. 2019 [43] United States	Retrospective Mortality n = 3235 C1: 6.3 (0.0–12.6) yrs C2: 8.5 (0.2–16.5) yrs	54.1 ± 11.8 yrs 28.1 ± 6.3 kg/m² NA	II: 60.1%	ER (+) / PR (+): 73.5% HER2 (-): 73.5%	Surgery: 94.5%	NA
Lee et al. 2019 [44] Korea	Retrospective PFS n = 336 53.3 (6.1 – 88.9) mo	51 (30–85) yrs 23.7 (16.4–35.2) kg/m² Post-menopause: 57.4%	NA	ER (+): 74.4% PR (+): 61.9% HER2 (+): 50.3%	No previous treatment	CHT + RT + HT: 48.2% RT + HT: 28.9% CHT + HT: 5.7% CHT + RT: 1.5% HT: 8.0% CHT: 5.7% RT: 0.9% No: 1.2%
Dalal et al. 2018 [45] NA	Retrospective DDFS, mortality, and treatment response	NA NA NA	NA	NA NA	No previous treatment	Neoadjuvant CHT: 100%

	n = 1154
	NA

BMI: body mass index; C1: cohort 1; C2: cohort 2; CHT: chemotherapy; DDFS: distant disease-free survival; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; HT: hormone therapy; NA: not available; PFS: progression-free survival; PR: progesterone receptor; RT: radiotherapy; TN: triple-negative

Table S3 (continuation). Description of the main characteristics of the observational studies included evaluating women with BC (n=23).

Authors Year Country	Study type Evaluated outcome Sample size Follow-up	Age BMI (kg/m²) Menopausal status	Tumor stage	Hormone receptor status HER2 status	Previous treatments	Treatments used during the study
Deluche et al. 2018 [46] France	Retrospective OS and DFS n = 119 52.4 (2.0–108.4) mo	56 (21–87) yrs 26.6 ± 0.5 kg/m² Post-menopause: 59.5%	Early stage	ER (+): 74% PR (+): 55% HER2 (-): 90.5%	No previous treatment	Neoadjuvant CHT: 46.2% Adjuvant CHT: 54% Adjuvant RT: 90%
Shachar et al. 2017 [47] United States	Retrospective Treatment toxicity n =151 NA	49 (23-75) yrs NA NA	Early stage	NA NA NA	NA	(Neo)adjuvant CHT+ anti-HER2(+): 100%
Dalal et al. 2014 [48] United States	Retrospective OS, DSS, PFS, and treatment response n = 1237 NA	58 yrs NA Post-menopause: 100%	I-III: 100%	NA NA	No previous treatment	Neoadjuvant CHT: 100%
Wong et al. 2014 [26] Singapore	Retrospective Treatment toxicity n = 84 NA	50.4 ± 10.1 yrs NA NA	IV: 33.3%	NA NA	No previous treatment	Neoadjuvant CHT + Surgery: 48.8% Neoadjuvant CHT + Surgery + Adjuvant CHT: 51.2%
Sabel et al. 2012 [49] United States	Retrospective Treatment toxicity n = 129 NA	52 (24–83) yrs NA NA	NA	NA NA	NA	Neoadjuvante CHT: % NA Adjuvante CHT: % NA
Tanner et al. 2012 [50] United States	Retrospective Treatment response n = 56 NA	50.8 (29–73) yrs 31.2 (18.1–45.7) kg/m² NA	III: 54.7%	TN: 33.9%	No previous treatment	Neoadjuvant CHT + Surgery: 100%

BMI: body mass index; CHT: chemotherapy; DFS: disease-free survival; DSS: disease-specific survival; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; HT: hormone therapy; NA: not available; PFS: progression-free survival; PR: progesterone receptor; OS: overall survival; RT: radiotherapy; TN: triple-negative

Table S4. Summarizes the main results of body adipose tissue for each outcome in women with BC (n=23).

SAT	OS (n=6)	DFS (n=5)	DDFS (n=3)	DSS (n=2)	PFS (n=5)	Mortality (n=3)	Treatment response (n=7)	Treatment toxicity (n=5)
SAT area	NS (n=1) [40] ∅ (n=2) [39,41]	∅ (n=1) [40]	-	-	-	-	∅ (n=2) [28,39]	∅ (n=2) [42,45]
↑ SAT area	-	-	-	-	-	↑ (n=1) [42]	↓ (n=1) [50]	-
↓ SAT area	-	-	-	-	-	-	↓ (n=1) [47]	-
SAT index	∅ (n=1) [29]	∅ (n=1) [46]	-	∅ (n=1) [29]	∅ (n=1) [27]	-	-	∅ (n=1) [34]
↑ SAT index	-	-	-	-	↓ (n=1) [38]	-	-	-
↓ SAT index	-	-	-	-	-	-	-	↑ (n=1) [34]
↑ SAT volume	-	-	-	-	↓ (n=1) [44]	-	-	-
↑ SAT density	-	-	-	-	-	↑ (n=1) [30]	-	-
SAT density	∅ (n=2) [29,39]	-	-	∅ (n=1) [29]	∅ (n=1) [27]	-	-	∅ (n=1) [47]

DFS: disease-free survival; DDFS: distant disease-free survival; DSS: disease-specific survival; NS: association between the body adipose depot and the outcome under analysis not specified; OS: overall survival; PFS: progression-free survival; SAT: subcutaneous adipose tissue; ∅: no association between the body adipose depot and the outcome under analysis; ↑ the body adipose depot increased the outcome under analysis; ↓: the body adipose depot decreased the outcome under analysis;

Table S4 (continuation)**.** Summarizes the main results of body adipose tissue for each outcome in women with BC (n=23).

VAT	OS (n=6)	DFS (n=5)	DDFS (n=3)	DSS (n=2)	PFS (n=5)	Mortality (n=3)	Treatment response (n=7)	Treatment toxicity (n=5)
VAT area	∅ (n=2) [39,41]	∅ (n=3) [36,37,40]	-	-	-	-	∅ (n=2) [19,39]	∅ (n=3) [42,47,49]
↑ VAT area	-	↓ (n=1) [35]	↓ (n=2) [19,45]	-	-	↑ (n=1) [45] ∅ (n=1) [43]	↓ (n=2) [45,48] ↑ (n=1) [28]	-
VAT index	-	∅ (n=1) [46]	-	-	-	-	-	∅ (n=1) [34]
↑ VAT index	↓ (n=1) [29]	-	-	↓ (n=1) [29]	↑ (n=1) [27]	-	-	↑ (n=1) [34]
VAT density	∅ (n=3) [39,29,41]	-	-	∅ (n=1) [29]	-	∅ (n=1) [30]	∅ (n=2) [19,39]	∅ (n=1) [47]
↓ VAT density	-	-	↓ (n=1) [19]	-	-	-	-	-
↑ VAT density	-	-	-	-	↑ (n=1) [27]	-	-	-
↑ VAT/SAT ratio area	↓ (n=1) [48]	-	-	↓ (n=1) [47]	↓ (n=1) [48]	-	-	-
↓ VAT/SAT ratio area	↓ (n=1) [39]	↓ (n=1) [37]	↓ (n=1) [39]	-	↓ (n=1) [39]	-	-	-
VAT/SAT ratio index	∅ (n=1) [46]	∅ (n=1) [46]	-	-	-	-	-	-

DFS: disease-free survival; DDFS: distant disease-free survival; DSS: disease-specific survival; OS: overall survival; PFS: progression-free survival; VAT: visceral adipose tissue; ∅: no association between the body adipose depot and the outcome under analysis; ↑ the body adipose depot increased the outcome under analysis; ↓: the body adipose depot decreased the outcome under analysis;

Table S4 (continuation)**.** Summarizes the main results of body adipose tissue for each outcome in women with BC (n=23).

IMAT	OS (n=6)	DFS (n=5)	DDFS (n=3)	DSS (n=2)	PFS (n=5)	Mortality (n=3)	Treatment response (n=7)	Treatment toxicity (n=5)
↓ IMAT area	-	-	-	-	-	-	∅ (n=1) [35]	-
IMAT index	-	-	-	∅ (n=1) [29]	∅ (n=1) [27]	-	-	-
↑ IMAT index	↓ (n=1) [46]	↓ (n=1) [46]	-	-	-	-	-	-
IMAT density	-	-	-	-	∅ (n=1) [27]	-	-	-
↑ IMAT density	↓ (n=1) [34]	-	-	↓ (n=1) [34]	-	-	-	-
TAAT, TAT, GFAT	**OS (n=6)**	**DFS (n=3)**	**DDFS (n=3)**	**DSS (n=2)**	**PFS (n=5)**	**Mortality (n=3)**	**Treatment response (n=7)**	**Treatment toxicity (n=5)**
↑ TAAT index	-	-	-	-	↓ (n=1) [38]	-	-	-
TAT index	-	-	-	-	∅ (n=1) [27]	-	-	-
↑ GFAT volume	-	-	-	-	↑ (n=1) [44]	-	-	-
↑ Abdomen/GFAT ratio volume	-	-	-	-	↓ (n=1) [44]	-	-	-
↑ Intra-abdominal AT volume	-	-	-	-	-	-	-	↑ (n=1) [26]
↑ Intra-abdominal AT/TAAT ratio volume	-	-	-	-	-	-	-	↑ (n=1) [26]

AT: adipose tissue; DFS: disease-free survival; DDFS: distant disease-free survival; DSS: disease-specific survival; GFAT: gluteofemoral adipose tissue; IMAT: intermuscular adipose tissue; OS: overall survival; PFS: progression-free survival; TAAT: total abdominal adipose tissue; TAT: total adipose tissue; ∅: no association between the body adipose depot and the outcome under analysis; ↑ the body adipose depot increased the outcome under analysis; ↓: the body adipose depot decreased the outcome under analysis

Capítulo 4

Considerações finais

A avaliação da composição corporal e, consequentemente, da adiposidade corporal (AC), representa um avanço significativo para a nutrição clínica. Ao longo dos anos, diferentes métodos foram desenvolvidos e aprimorados para esse propósito [1-4]. Analisar a AC, em contraposição a somente o peso corporal, detém uma importância clínica crucial, principalmente no contexto do câncer de mama (CM), em que a adiposidade corporal está estreitamente associada. O excesso de gordura corporal é reconhecido como um fator de risco para o desenvolvimento da doença e, por isso, muitas vezes se faz presente já ao diagnóstico [5]. A presença de adiposidade corporal elevada pode contribuir para que as pacientes enfrentem mais toxicidade durante o tratamento ou complicações pós-operatórias. Por outro lado, tanto o tumor quanto o seu tratamento podem afetar a adiposidade corporal por meio de alterações metabólicas e efeitos adversos que influenciam negativamente a ingestão alimentar e a capacidade funcional das pacientes [6-9].

Apesar da complexa interação entre a adiposidade corporal e o CM, a literatura ainda carece de revisões abordando o tema de forma sistemática. Isso se deve principalmente ao amadurecimento do estudo da adiposidade corporal. Diante desse cenário, o desenvolvimento de revisões sistemáticas dos dados disponíveis na literatura é fundamental para proporcionar uma compreensão mais ampla do tema, assegurando a análise da maior quantidade possível de dados e um maior número de pacientes.

Esta tese foi desenvolvida com base em um racional clínico, visando avaliar inicialmente as mudanças na adiposidade corporal em mulheres com câncer de mama e sua relação com o tratamento antineoplásico. Posteriormente, investigou-se como a distribuição do tecido adiposo corporal (visceral, subcutâneo, gluteofemoral e intermuscular) impacta os desfechos dessa mesma população, especialmente em termos de sobrevida, complicações, toxicidades e resposta ao tratamento antineoplásico.

A primeira revisão revelou que a maioria dos estudos incluídos observou um aumento significativo na adiposidade corporal durante o tratamento para o

câncer de mama, independentemente do método de avaliação utilizado. Confirmando a hipótese inicial, pacientes submetidos à quimioterapia sozinha ou combinada à hormonioterapia ou terapia alvo (anticorpo monoclonal) apresentaram um aumento na adiposidade corporal. Já para o uso de hormonioterapia sozinha, os achados variaram conforme o tipo de medicação utilizada. As pacientes tratadas apenas com moduladores seletivos do receptor de estrogênio apresentaram um aumento da adiposidade corporal, enquanto as que receberam inibidores da aromatase tiveram uma redução. Por fim, o uso combinado de terapia alvo (inibidores de quinases dependentes de ciclina) com hormonioterapia não demonstrou diferenças na adiposidade corporal. Os dados disponíveis para esse tipo de terapia alvo ainda são iniciais, mas com base nos seus mecanismos de ação e em achados prévios, é possível que levem à uma redução tardia na adiposidade corporal.

A segunda revisão representa um avanço significativo no entendimento da adiposidade corporal no contexto do câncer de mama, sendo a primeira a explorar os diferentes depósitos de tecido adiposo em relação ao prognóstico da doença. Identificaram-se associações em que maiores quantidades de tecidos adiposos visceral (TAV) e subcutâneo (TAV) estavam relacionadas a piores desfechos. Já um maior tecido adiposo gluteofemoral (TAGF) foi associado a melhores resultados, enquanto os dados para tecido adiposo intermuscular (TAIM) foram conflitantes. Porém, devido à limitação dos dados disponíveis para TAGF e TAIM não foi possível chegar a conclusões definitivas. Este estudo demonstra a necessidade de, na prática clínica, considerar não apenas a quantidade, mas também a distribuição corporal do tecido adiposo, dada as diferentes características e consequente impacto prognóstico de cada depósito.

Destaca-se, a inclusão de terapias modernas para o tratamento do câncer de mama neste trabalho, acompanhando o contínuo avanço da oncologia. Ainda, do ponto de vista metodológico, as revisões sistemáticas seguem como ferramentas essenciais para explorar e sumarizar dados, especialmente em campos em expansão, como é o caso do tema estudado aqui. Entretanto, os achados ficam sujeitos e podem diferir a depender do desenho e da qualidade dos estudos incluídos, bem como das técnicas e metodologias científicas empregadas por deles.

Há muito a ser estudado e considerado em relação à adiposidade corporal no câncer de mama. Isso inclui a definição de pontos de corte para classificar níveis elevados ou reduzidos de adiposidade corporal e avaliar alterações quantitativas consideradas clinicamente significativas. Além disso, é importante padronizar as técnicas e metodologias empregadas para avaliação da adiposidade corporal, aprimorar de forma contínua a qualidade dos estudos e considerar os protocolos de tratamento antineoplásico atuais.

Em termos práticos, os resultados obtidos nessa tese lançam luz para que profissionais de saúde possam antecipar possíveis ganhos de adiposidade corporal em mulheres com câncer de mama, conforme o tratamento antineoplásico necessário, o que pode resultar em mais efeitos adversos. Além disso, os achados apontam para a importância de considerar na prática clínica a redistribuição de tecido adiposo, que pode vir como consequência de alterações na adiposidade corporal, visando assim prevenir desfechos menos favoráveis. Isso permite um manejo precoce e eficaz.

As perspectivas futuras envolvem tornar a avaliação da composição corporal cada vez mais acessível na prática clínica, utilizando métodos de fácil acesso e ainda mais confiáveis. Para tal, esse campo está em constante evolução. Durante meu doutorado sanduíche na Universidade de Alberta, no Canadá, tive a oportunidade de vivenciar isso em uma das mais importantes unidades de pesquisa em nutrição humana do mundo, referência no estudo da composição corporal.

Lá presenciei avanços significativos, tanto no desenvolvimento de estudos robustos visando qualidade e padronização dos dados, quanto no aprimoramento de técnicas já existentes para análise da composição corporal. Um exemplo é o uso da inteligência artificial para avaliação de imagens de tomografia computadorizada, tornando o processo mais rápido e preciso, o que pode facilitar a aplicação futura na prática clínica. Além disso, nos últimos anos têm surgido novas tecnologias, como aplicativos para dispositivos móveis que podem predizer a composição corporal, tema no qual me aprofundei durante minha estada no exterior.

Um terceiro artigo de minha autoria que contará com renomados pesquisadores Canadenses e Americanos como coautores está sendo desenvolvido a partir da experiência na Universidade de Alberta. Os aplicativos

para predição da composição corporal prontamente chamaram minha atenção devido à sua acessibilidade e à capacidade de aprimorar a análise corporal, especialmente ao incorporar a inteligência artificial em seu funcionamento. Por meio desse método, a composição corporal pode ser avaliada a partir de fotografias de corpo inteiro feitas com a câmera de *smartphones* e *tablets* convencionais. Esses aplicativos empregam técnicas computacionais de análise, como imagens tridimensionais do corpo humano e/ou a já referida inteligência artificial [10-14].

Quando finalizado, este estudo inédito contribuirá significativamente para a literatura científica ao descrever o funcionamento técnico dessas ferramentas, apresentar dados iniciais de análise da composição corporal em indivíduos saudáveis e propor direções futuras. Essa tecnologia demonstra resultados promissores. No entanto, é essencial aprimorar sua precisão em nível individual, avaliá-la em diferentes populações, como a oncológica, e explorar sua capacidade prospectiva de monitorar as mudanças na composição corporal.

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Anexos

NUTRITION AND CANCER
https://doi.org/10.1080/01635581.2022.2081341

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REVIEW

Changes in Body Adiposity in Women Undergoing Breast Cancer Treatment: A Scoping Review

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ABSTRACT

Antineoplastic treatments can negatively affect body composition, leading to metabolic derangements and worse clinical outcomes in breast cancer patients. This scoping review assesses body adiposity changes during breast cancer therapy. We included clinical and observational studies, published until the last search date in any language, with women aged >18 years, after breast cancer diagnosis, at any clinical stage and with any history of breast cancer treatment, who had body adiposity quantified by imaging tools at least twice during follow-up. In total, 17 studies were included (n = 1,009 individuals), six of which found a significant increase in body adiposity during treatment, two found a significant decrease, one presented divergent findings according to the imaging method and the analyzed body adiposity depots, and eight studies found no significant change in the outcome. Selective estrogen receptor modulators were associated with increased body adiposity, whereas aromatase inhibitors were associated with its decrease (n = 3). Chemotherapy was associated with increased body adiposity (n = 1), and monoclonal antibody with reduced brown adipose tissue activity (n = 1). Breast cancer treatment may have different effects on body adiposity, according to its mechanisms and protocols. Further studies are necessary to better elucidate this scenario.

ARTICLE HISTORY
Received 1 July 2021
Accepted 19 May 2022

Introduction

Breast cancer is the most common malignant disease worldwide among women (1), with an incidence of over two million new cases in 2018 (2). Fortunately, breast cancer overall survival rates have improved (3) due to diagnosis and therapeutic improvements, including surgery, radiotherapy, chemotherapy, hormone treatment, and target therapy. Besides, treatment advances have enabled fewer side effects and a better quality of life (4, 5).

Body composition refers to the amount of body fat and lean tissues (6). Body mass index (BMI) is the most used measurement to evaluate adiposity, but it may not accurately provide information about the contributions of each tissue to body mass nor depict specific changes in these body depots. Assessing different body depots may provide a more in-depth evaluation of the nutritional status (6–8), and it may be essential under some clinical conditions, such as cancer, psoriasis, cardiovascular and liver diseases, and others (9–12). Cancer treatment may lead to unfavorable changes in body composition, such as increased or redistributed adiposity (13, 14), contributing to a poor prognosis (15–18).

The imaging methods currently available for assessing body composition are dual energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), ultrasonography (USG), computed tomography (CT), and magnetic resonance imaging (MRI), which can be used in different contexts and applications, presenting advantages and disadvantages (Figure S1) (6, 19–30). Different organizational levels, types of adipose tissues, adipose depots, and metrics can be evaluated using these tools (Chart S1) (6, 27, 31–40).

Currently, the lack of available literature evaluating the relationship between body adiposity changes, breast cancer treatment and the methodological diversity of the existing studies are significant limitations. To our knowledge, only a few reviews have evaluated this relationship (14, 15, 41). This study updates the topic with an appropriate methodological criterion,

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Clinical Nutrition 43 (2024) 1033–1042

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Body adipose tissue depots and treatment outcomes for women with breast cancer: A systematic review

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ARTICLE INFO

Article history:
Received 30 March 2023
Accepted 16 March 2024

Keywords:
Adipose tissue
Body composition
Breast neoplasms
Nutritional status
Prognosis

SUMMARY

Background & aims: Excessive adipose tissue is associated with poorer prognosis in women with breast cancer (BC). However, several body adiposity depots, such as visceral (VAT), subcutaneous (SAT), intermuscular (IMAT), and gluteofemoral adipose tissues (GFAT) may have heterogeneous metabolic roles and health effects in these patients. This systematic review aims to evaluate the impact of different body adipose tissue depots, assessed via computed tomography (CT), on treatment outcomes for women with BC. We hypothesize that distinct body adipose tissue depots may be associated differently with outcomes in patients with BC.

Methods: A comprehensive bibliographical search was conducted using PubMed, Embase, Cochrane Library, Scopus, and Web of Science databases (until January 2024). The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale.

Results: The final sample comprised 23 retrospective studies (n = 12,462), with fourteen presenting good quality. A lack of standardization in CT body adipose tissue depots measurement and outcome presentation precluded quantitative analysis. Furthermore, most included studies had heterogeneous clinical characteristics. Survival and treatment response were the most prevalent outcomes. VAT (n = 19) and SAT (n = 17) were the most frequently evaluated depots and their increase was associated with worse outcomes, mainly in terms of survival. IMAT (n = 4) presented contradictory findings and a higher GFAT (n = 1) was associated with better outcomes.

Conclusion: This systematic review found an association between increased VAT and SAT with worse outcomes in patients with BC. However, due to the heterogeneity of the included studies, further research with homogeneous methodologies is necessary to better understand the impact of body adipose tissue depots on treatment outcomes. Such knowledge could lead to improved care for this patient population.

1. Introduction

Obesity is associated with a greater risk of developing breast cancer (BC) and a poorer prognosis for female patients with BC [1–3]. Body mass index (BMI) is the main anthropometric parameter used in clinical practice and in the literature to evaluate the relationship between obesity and outcomes in patients with BC [4–9]. However, it is important to note that BMI is an unreliable indicator to measure body adiposity in terms of quantity, quality, and distribution [1,10].

Currently, computed tomography (CT) has become a gold standard exam to assess body composition in patients with BC. This imaging technique estimates total body composition through an abdominal cross-sectional scan, presenting good accuracy for body depot evaluations (quantity and quality of tissues). Computed tomography is also convenient, making up most disease staging evaluation in patients with BC [11–15].

Body adipose depots, including visceral, subcutaneous, intermuscular and gluteofemoral adipose tissues (VAT, SAT, IMAT and GFAT, respectively), play heterogeneous metabolic roles. These

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https://doi.org/10.1016/j.clnu.2024.03.010