UNIVERSIDADE FEDERAL DO TRIÂNGULO MINEIRO
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE
MEDICINA TRANSLACIONAL
ASPECTOS CLÍNICOS, DIAGNÓSTICOS E TERAPÊUTICOS DAS DOENÇAS

ANSELMO ALVES DE OLIVEIRA

GORDURA INTRAMUSCULAR, SEUS PREDITORES E SUA ASSOCIAÇÃO COM A FUNÇÃO FÍSICA EM SOBREVIVENTES DE CÂNCER MAMA

UBERABA – MG
2020

ANSELMO ALVES DE OLIVEIRA

GORDURA INTRAMUSCULAR, SEUS PREDITORES E SUA ASSOCIAÇÃO COM A FUNÇÃO FÍSICA EM SOBREVIVENTES DE CÂNCER MAMA

Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde, área de concentração Medicina Translacional, linha de pesquisa Aspectos clínicos, diagnósticos e terapêuticos das doenças, da Universidade Federal do Triângulo Mineiro, como requisito parcial para a obtenção do título de Doutor em Ciências da Saúde.

Orientador: Prof. Dr. Fábio Lera Orsatti

UBERABA – MG

2020

Catalogação na fonte: Biblioteca da Universidade Federal do Triângulo Mineiro

O45g

Oliveira, Anselmo Alves de
Gordura intramuscular, seus preditores e sua associação com a função física em sobreviventes de câncer mama / Anselmo Alves de Oliveira. -- 2020.
65 f. : il., fig., tab.

Tese (Doutorado em Ciências da Saúde) -- Universidade Federal do Triângulo Mineiro, Uberaba, MG, 2020
Orientador: Prof. Dr. Fábio Lera Orsatti

1. Neoplasias da mama. 2. Gordura subcutânea. 3. Desempenho físico funcional. 4. Atividade física. 5. Força muscular. I. Orsatti, Fábio Lera. II. Universidade Federal do Triângulo Mineiro. III. Título.

CDU 618.19-006

Sônia Maria Rezende Paolinelli - CRB-6/1191

ANSELMO ALVES DE OLIVEIRA

Gordura intramuscular, seus preditores e sua associação com a função física em Sobreviventes de Câncer Mama

Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde, área de concentração Medicina Translacional, linha de pesquisa Aspectos clínicos, diagnósticos e terapêuticos das doenças, da Universidade Federal do Triângulo Mineiro, como requisito parcial para a obtenção do título de Doutor em Ciências da Saúde.

Orientador: Prof. Dr. Fábio Lera Orsatti

18 de fevereiro de 2020.

Banca examinadora:

_____

Prof. Dr. Fábio Lera Orsatti

_____

Prof. Dr. Guilherme Vannucchi Portari

_____

Prof. Dr. Jair Sindra Virtuoso Júnior

_____

Prof. Dr. Erick Prado de Oliveira

_____

Prof. Dr. Paulo Ricardo Prado Nunes

DEDICATÓRIA

Ao meu pai *(in memoriam)* que não pôde aguardar este momento, mas cujo brilho do olhar foi e será minha fonte de inspiração. À minha mãe, mulher guerreira, que nunca mediu esforços para amparar os filhos. À minha esposa Elaine, pelo amor, companheirismo e paciência. À minha filha Maria Luiza, a maior das minhas conquistas.

AGRADECIMENTOS

Agradeço inicialmente a Deus, pela minha vida e pela vida das pessoas que estiveram ao meu lado ao longo desta jornada.

Agradeço ao Centro Universitário do Planalto de Araxá, pelo apoio e confiança.

Agradeço a todos os funcionários do Hospital Hélio Angotti, em especial ao Dr. Vitor Lara, à Paula e à Cristiane, por todo apoio prestado.

Agradeço ao Dr. Luís Ronan pela parceria e suporte durante todo o desenvolvimento deste projeto, ao Dr. Giovanni pelas valiosas contribuições, ao funcionário Romeu pelos auxílios e a todos os outros funcionários da Clínica Radiológica de Uberaba pelo amparo e gentileza.

Agradeço a todos os meus amigos de Laboratório (BioEx), de hoje e de ontem, com os quais vivi momentos de aprendizagens e alegrias. Menção especial aos amigos Fernanda Martins e Gersiel Oliveira que me apoiaram incondicionalmente durante o desenvolvimento desta pesquisa.

Por fim, agradeço ao meu orientador, Prof. Dr. Fábio Orsatti, pessoa admirável e profissional incansável, minha maior referência como mestre e pesquisador. Obrigado pelo apoio irrestrito e pelos valiosos ensinamentos.

Meu muito obrigado!

EPÍGRAFE

"...Não é sobre chegar no topo do mundo e saber que venceu, é sobre escalar e sentir que o caminho te fortaleceu, é sobre ser abrigo e também ter morada em outros corações, e assim ter amigos contigo em todas as situações..."

(Ana Carolina Vilela da Costa)

RESUMO

Sobreviventes de câncer de mama (SCM) frequentemente apresentam baixa função física (FF). De preocupação importante é o fato que a menor FF está associado à incapacidades funcionais, riscos de quedas e mortalidade. Estudos anteriores têm reportado associação entre a baixa FF e conteúdo de gordura intramuscular (CGI), elevado em SCM. No entanto, estes estudos não levaram em consideração a massa e força musculares e nível de atividade física (AF) nas associações, que são importantes preditores da FF e podem estar reduzidos em SCM. Além disso, o tempo de AF tem sido considerado o fator mais fortemente associado às alterações de CGI em populações específicas, o que indica um papel moderador da condição (doença/tratamento) na relação entre tempo de AF e CGI. No entanto, o papel moderador da condição SCM ainda não foi investigado. Portanto, os objetivos do presente estudo foram: (estudo 1) verificar se a massa e força musculares e o tempo de AF estão concomitantemente alterados com o CGI em SCM, e, se o CGI é um mediador da relação entre SCM e baixa FF, independentemente de fatores de confusão, e, (estudo 2) verificar se a relação entre o tempo de AF e o CGI é moderado pela condição SCM. Para tanto, após seleção por critérios de inclusão e exclusão, se voluntariaram 56 mulheres SCM e 23 mulheres com idade similar às SCM, mas sem histórico de câncer, como o grupo controle (GC). O CGI foi mensurado por tomografia computadorizada. Os níveis de AF, dados sociodemográficos e as características do tratamento de câncer de mama foram avaliadas por questionários. Também foram realizadas medidas antropométricas e testes de FF (i.e. sentar e levantar, velocidade da marcha em 4 metros e o *Timed Up and Go Test*– TUG). Nossos resultados indicaram maior CGI ($p = 0,002$), menor força muscular ($p = 0,006$) e pior desempenho em todos os testes de FF ($p < 0,001$) em SCM quando comparado ao GC. No entanto, não foram observadas diferenças entre SCM e GC para a massa muscular ($p = 0,930$) e tempo de AF ($p = 0.132$). Além disso, o CGI foi negativamente associado ($p \leq 0,05$) com o desempenho em todos os testes de FF, sendo que, em SCM o pior desempenho na marcha, TUG e sentar e levantar foram mediados, pelo menos em parte, pelo CGI. Ademais, modelos de regressão indicaram que a inclusão da variável de interação (condição SCM e tempo de atividade física) representou significante proporção da variância do CGI ($\Delta R^2 = 0,05$, $P = 0,031$, $B = 0,004$; CI – 95% = 0,001; 0,008). Portanto, concluímos que a baixa FF de SCM é mediada, pelo menos em parte, pelo CGI; e que a relação entre tempo de AF e CGI é moderada pela condição SCM.

Palavras chave: gordura muscular, Câncer de Mama, capacidade funcional, atividade física, força muscular

ABSTRACT

Breast cancer survivors (BCS) often have low physical capacity (PC). Of major concern is the fact that lower PC is associated with functional disabilities, risks of falls and mortality. Previous studies have reported association between low PC and intramuscular fat content (IMFC), increased in BCS. However, these studies did not take into account muscle mass and strength and physical activity (PA) time in the associations, which are important predictors of PC and may be reduced in BCS. In addition, PA time has been considered the factor most strongly associated with IMFC changes in specific populations, which indicates a moderating role of the disease/treatment condition in the relationship between PA time and IMFC. However, this moderating role of the BCS condition has not yet been investigated. Therefore, the objectives of the present study were: (study 1) to verify if the muscle mass and strength and the PA time are concomitantly altered with IMFC in BCS, and, if IMFC is a mediator of the relationship between BCS and low PC, regardless of confounding factors, and, (study 2) to verify if the relationship between the PA time and IMFC is moderated by BCS condition. For this purpose, after selection by inclusion and exclusion criteria, 56 BCS women and 23 women aged similar to BCS, but without a history of cancer (control group - CG) volunteered. IMFC was measured by computed tomography, and PA time, sociodemographic data and characteristics of breast cancer treatment were assessed using questionnaires. Anthropometric measurements and PC tests were also performed (i.e. sit-to-stand, gait speed at 4 meters and the Timed Up and Go Test - TUG). Our results indicated higher IMFC ($p = 0.002$), less muscle strength ($p = 0.006$) and worse performance in all PC tests ($p < 0.001$) in BCS when compared to CG. However, no differences were observed between BCS and CG for muscle mass ($p = 0.930$) and PA time ($p = 0.132$). In addition, IMFC was negatively associated with performance in all PC tests ($p \leq 0.05$), and in BCS worse performance in walking, TUG and sit-to-stand were mediated, at least in part, by IMFC. In addition, regression models indicated that the inclusion of the interaction variable (i.e. BCS condition and PA time) represented a significant proportion of the IMFC variance ($\Delta R^2 = 0.05$, $P = 0.031$, $B = 0.004$; CI - 95% = 0.001; 0.008). Therefore, we conclude that the low PC in BCS is mediated, at least in part, by IMFC; and that the relationship between PA time and IMFC is moderated by the BCS condition.

Keywords: muscle fat, breast cancer, functional capacity, physical activity, muscle strength

LISTA DE ILUSTRAÇÕES

ARTIGO 1

ARTIGO 2

LISTA DE TABELAS

ARTIGO 1

ARTIGO 2

LISTA DE ABREVIATURAS

AF: atividade física

a.u.: arbitrary units

B: non-standard regression coefficient

BC: Breast Cancer

BCS: Breast Cancer Survivors

BioEx: Laboratório de Biologia do Exercício

BMI: body mass index

CAAE: certificado de apresentação para apreciação ética

CG: control group

CGI: conteúdo de gordura intramuscular

CI: confidence interval

CM: Câncer de Mama

cm: centimeters

cm^2: square centimeters

COPD: Chronic Obstructive Pulmonary Disease

CT: computed tomography

DPOC: Doença Pulmonar Obstrutiva Crônica

FF: função física

GC: grupo controle

GLM: generalized linear models

HC: hip circumference

HU: Hounsfield Units

ICC: intra-class correlation coefficient

IMFC: intramuscular fat content

INCA: Instituto Nacional de Câncer

IPAQ: International Physical Activity Questionnaire

Kg.f: kilogram force

Kg/m^2: kilograms per square meter

Kg: kilograms

Km: quilômetros

KVp: Peak kilovoltage

m: meters

mm: millimeters

mA: miliampere

min/week: minutes per week

PA: physical activity

PC: physical capacity

s: seconds

SCM: Sobreviventes de Câncer de Mama

TC: tomografia computadorizada

TUG: Timed up and go test

UFTM: Universidade Federal do Triângulo Mineiro

WC: waist circumference

WHR: waist-to-hip ratio

WS: walking speed

SUMÁRIO

1. INTRODUÇÃO

As estatísticas atuais demonstram que o câncer de mama (CM) é aquele que mais acomete a população feminina no Brasil e no mundo. Nas últimas décadas os avanços tecnológicos, sobretudo dos mecanismos de diagnóstico e das terapias de tratamento, têm contribuído para o maior tempo de sobrevida após o diagnóstico de CM (INCA, 2019). Consequentemente, observa-se um número crescente de pacientes sobreviventes de câncer de mama (SCM). Contudo, nestes pacientes, frequentemente são observados efeitos colaterais associados ao tratamento que podem se prolongar por toda a vida, como por exemplo, a redução da função física (FF) (SHAPIRO, 2019). A avaliação da FF é um componente importante para avaliar a saúde geral e a reserva fisiológica dos sobreviventes de câncer e vem sendo sugerida como uma ferramenta para distinguir a idade funcional da idade cronológica (BASU P; LUCAS E; CARVALHO AL; SAUVAGET C *et al.*, 2019; FERRUCCI; COOPER; SHARDELL; SIMONSICK *et al.*, 2016; GUIDA; AHLES; BELSKY; CAMPISI *et al.*, 2019; SOTO-PEREZ-DE-CELIS; LI; YUAN; LAU *et al.* 2018; WILDIERS; HEEREN; PUTS; TOPINKOVA *et al.*, 2014). A baixa FF em SCM está associada à suscetibilidade de quedas e hospitalizações, à desfechos negativos relacionados ao tratamento, além de estar associada à mortalidade (WINTERS-STONE; HORAK; JACOBS; TRUBOWITZ *et al.*, 2017). Diante deste cenário, são necessários estudos que investiguem possíveis alvos terapêuticos que possam evitar comprometimentos funcionais em SCM.

1.1 CÂNCER DE MAMA

1.1.1 Epidemiologia

No Brasil, as estimativas de incidência de CM para o ano de 2019 foram de 59.700 novos casos, com uma taxa bruta de incidência de 56,33 a cada 100.000 mulheres. Isto representa 29,5% dos cânceres em mulheres, excetuando-se o câncer de pele não melanoma (INCA, 2019). Estes dados são semelhantes aos observados na população dos Estados Unidos, cuja estimativa para 2019 foi de 268.600 novos casos, representando 30% dos cânceres em mulheres. Estimativas mundiais indicam que em 2018 ocorreram 2,1 milhões de novos casos de CM (BRAY; FERLAY; SOERJOMATARAM; SIEGEL *et al.*, 2018).

Os mais recentes dados do Instituto Nacional de Câncer (INCA), indicam que em 2016 foram registradas 16.069 mortes de mulheres por CM no país. A análise temporal indica uma tendência de aumento das taxas de mortalidade por CM entre 1980 e 2016 nas diferentes regiões do Brasil. No

entanto, quando a análise se restringe a grandes cidades, observa-se uma manutenção ou mesmo redução destas taxas (INCA, 2019). Estes dados indicam que o acesso a procedimentos de diagnóstico e tratamento são medidas essenciais para minimizar a taxa de mortalidade de CM. Corroborando com esta inferência, países desenvolvidos vêm apresentando declínios na taxa de mortalidade por CM de 1,8% ao ano (AMERICAN CANCER SOCIETY, 2019). Outro indicador melhorado pelas evoluções relacionadas, sobretudo, às técnicas de diagnóstico e das terapias de tratamento de CM, é o tempo de sobrevida de pacientes após o diagnóstico da doença (BRAY; FERLAY; SOERJOMATARAM; SIEGEL *et al.*, 2018). No Brasil, a estimativa de sobrevida mínima de cinco anos foi de 75,2% para o período de 2010 a 2014 (INCA, 2019). Estes resultados são inferiores aqueles observados em países desenvolvidos como os Estados Unidos, onde a taxa relativa de sobrevida mínima de 5 e 10 anos para mulheres com CM invasivo é de 90% e 83%, respectivamente (AMERICAN CANCER SOCIETY, 2019). A alta prevalência do CM somada às estimativas de tempo de sobrevida após o diagnóstico da doença indicam um número cada vez maior de pacientes SCM.

1.1.2 Sobreviventes de câncer de mama

Atualmente, dados epidemiológicos indicam aproximadamente 3,8 milhões de SCM nos Estados Unidos (AMERICAN CANCER SOCIETY, 2019). Estes resultados levam em consideração pacientes que estão sendo tratadas e aquelas que já finalizaram o tratamento, uma vez que, segundo o *National Cancer Institute*, o período de sobrevida começa no momento do diagnóstico e dura ao longo de toda vida útil da paciente (NATIONAL CANCER INSTITUTE, 2018). Esta definição holística incentiva os profissionais da saúde a pensar que o atendimento a SCM deve iniciar no momento do diagnóstico e seguir por todo período de vida adicional da paciente. No entanto, após o término do tratamento, SCM apresentam reduções na frequência de contato com sua equipe de saúde o que dificulta o gerenciamento dos efeitos colaterais remanescentes do tratamento (DE MOOR; MARIOTTO; PARRY; ALFANO *et al.*, 2013).

Mesmo diante dos avanços relacionados ao diagnóstico e tratamento de CM, efeitos colaterais de longo prazo (i.e. começam durante e se estendem além do tratamento) e/ou tardios (i.e. iniciam após o término do tratamento) são frequentemente reportados por SCM após a finalização do tratamento (SHAPIRO, 2018). Dados da Pesquisa Nacional de Entrevista em Saúde dos Estados Unidos, na qual mais de 60% das SCM tinham cinco ou mais anos após o diagnóstico, sugeriram que aproximadamente 30% das SCM estavam com razoável ou má condição de saúde, 17% não conseguiam trabalhar devido a problemas de saúde e 58% apresentavam uma ou mais limitações funcionais (i.e. baixa FF) (HEWITT; ROWLAND; YANCIK, 2003).

1.1.3 Função física de sobreviventes de câncer de mama

A FF está relacionada à capacidade de realizar de forma independente ações cotidianas. Um estudo retrospectivo de coorte com base populacional, indicou que pacientes, mesmo após 5 anos do final do tratamento oncológico (amostra composta majoritariamente por pacientes SCM) apresentavam incapacidades relacionadas a realização de trabalhos domésticos, para caminhar uma milha (i.e. 1,609km) e para subir e descer escadas (SWEENEY; SCHMITZ; LAZOVICH; VIRNIG *et al.*, 2006). Assim, quando reduzida, a FF pode implicar na perda de autonomia e incapacidades físicas (MANINI; CLARK, 2012).

A observação da alta prevalência de prejuízos observados na FF de SCM tem sido acompanhada de um número crescente de estudos realizados para identificar as consequências deste acometimento (HEWITT; ROWLAND; YANCIK, 2003; NEIL-SZTRAMKO; KIRKHAM; HUNG; NIKSIRAT *et al.*, 2014). Estudos prévios indicaram que a baixa FF está associada ao maior risco de quedas, de mortalidade por todas as causas, além de mortalidade relacionada ao CM (BRAITHWAITE; SATARIANO; STERNFELD; HIATT *et al.*, 2010; MANINI; CLARK, 2012; MARINAC; PATTERSON; VILLASENOR; FLATT *et al.*, 2014; WINTERS-STONE; HORAK; JACOBS; TRUBOWITZ *et al.*, 2017). Diante das repercussões negativas relacionadas à baixa FF, torna-se necessário identificar fatores mediadores da baixa FF em SCM.

1.2 GORDURA NO MÚSCULO ESQUELÉTICO

A habilidade única dos adipócitos em se expandir e liberar mensageiros químicos, faz com que o tecido adiposo seja reconhecido como um dos maiores órgãos endócrinos do corpo humano. Inicialmente considerado um inerte estoque do excesso de calorias, importante somente para a homeostase energética, agora é conhecido que o tecido adiposo expressa e secreta hormônios e citocinas pro-inflamatórias agindo de maneira autócrina, parácrina e endócrina, a partir de sinalizações aos sistemas cardíaco, musculoesquelético, nervoso central e metabólico. Embora o aumento acentuado nos depósitos de gordura possam resultar em um estado de inflamação crônica, levando ao diabetes e à doenças cardíacas, os depósitos de gordura podem agir de modo distinto (STEHNO-BITTEL, 2008). Estudos prévios indicam que a localização do tecido adiposo excedente, mais do que simplesmente a quantidade, pode ser importante no aumento sistêmico de citocinas circulantes e no aumento de doenças metabólicas como o diabetes (GOODPASTER; KRISHNASWAMI; RESNICK; KELLEY *et al.*, 2003; MARCUS; ADDISON; KIDDE; DIBBLE *et al.*, 2010). Neste sentido, o aumento de gordura subcutânea, particularmente na região do quadril, é

um preditor negativo da Síndrome Metabólica, além de cardioprotetor. No entanto, o tecido adiposo estocado no músculo esquelético, está relacionado com a inflamação crônica, intolerância à glicose, redução nos níveis de força e à baixa FF (ADDISON; MARCUS; LASTAYO; RYAN, 2014).

1.2.2 Gordura intramuscular: definição e medida

A gordura intramuscular é definida como a gordura localizada no interior ou em torno dos miócitos (ADDISON; MARCUS; LASTAYO; RYAN, 2014; KHOJA; MOORE; GOODPASTER; DELITTO *et al.*, 2018). Um estudo recente indicou que o conteúdo de gordura intramuscular (CGI) é uma medida fortemente associada com alterações funcionais (KHOJA; MOORE; GOODPASTER; DELITTO *et al.*, 2018).

O CGI é comumente medido por tomografia computadorizada (TC) (AMINI; BOYLE; BOUTIN; LENCHIK, 2019). A TC é um método de imagem rápido que utiliza raios-X para uma medição indireta do CGI com base na densidade, medida em unidades de Hounsfield (HU), dos tecidos de uma determinada área analisada. Em um *continuum* de densidade em que o osso é o mais denso e a gordura é a menos densa, a massa muscular magra varia entre estes dois extremos. Desta feita, uma determinada área muscular pode ser interpretada como tendo maior infiltração de gordura quando observada uma menor densidade (i.e. menores valores em HU) na área muscular analisada. Portanto, presume-se que um indivíduo com uma proporção maior de massa magra de baixa densidade tenha o CGI aumentado (AMINI; BOYLE; BOUTIN; LENCHIK, 2019).

1.2.2 Aspectos relacionados ao aumento do conteúdo de gordura intramuscular

Alguns autores sugeriram que o aumento do CGI é uma consequência indesejada, mas inevitável do envelhecimento, uma vez que estudos epidemiológicos, longitudinais e transversais demostraram relações positivas e significativas entre o envelhecimento e o CGI (MARCUS; ADDISON; KIDDE; DIBBLE *et al.*, 2010). No entanto, a maioria dos estudos que examinaram os efeitos do envelhecimento nos aumentos do CGI foram pequenos e transversais e falharam em explicar os níveis de atividade física e o status da doença ou investigaram apenas uma faixa etária restrita. Portanto, o efeito univariado e independente do envelhecimento na infiltração de gordura no músculo esquelético pode ser questionado (ADDISON; MARCUS; LASTAYO; RYAN, 2014) e não pode ser transportado para outras condições, tais como o câncer e desuso. O estudo de Wroblewski e colaboradores (2011) indicou que indivíduos com altos níveis de atividade física, mesmo idosos, não apresentam alterações no CGI quando comparados aos indivíduos mais jovens (i.e. 40 anos)

(WROBLEWSKI; AMATI; SMILEY; GOODPASTER *et al.*, 2011). Além disso, indivíduos jovens (i.e.18 a 29 anos) apresentam um aumento significativo do CGI quando submetidos a uma redução acentuada nos níveis de atividade física (MANINI; CLARK; NALLS; GOODPASTER *et al.*, 2007). Esses dados são clinicamente importantes porque sugerem que, embora o avanço da idade influencie no CGI, eles podem mudar com intervenções baseadas em atividades físicas.

1.2.3 Conteúdo de gordura intramuscular em sobreviventes de câncer de mama

Pacientes oncológicos frequentemente apresentam elevações do CGI (DELUCHE; LEOBON; DESPORT; VENAT-BOUVET *et al.*, 2018). Dois estudos recentes demonstram que entre 50-60% de pacientes SCM apresentam aumento do CGI (DELUCHE; LEOBON; DESPORT; VENAT-BOUVET *et al.*, 2018; RIER; JAGER; SLEIJFER; VAN ROSMALEN *et al.*, 2018). Cabe ressaltar que em SCM, o aumento do CGI está associado a um maior número de hospitalizações, comprometimento funcional, baixa tolerância ao tratamento e maior mortalidade (KUBO; NAITO; MORI; OSAWA *et al.*, 2017; SHACHAR; DEAL; WEINBERG; NYROP *et al.*, 2017; WILLIAMS; DEAL; MUSS; WEINBERG *et al.*, 2017). Diante destas evidências, compreender as alterações do CGI pode auxiliar na adoção de estratégias preventivas ou mesmo de intervenção.

Como previamente ressaltado, o envelhecimento é identificado como uma das principais causas do aumento do CGI (DELMONICO; HARRIS; VISSER; PARK *et al.*, 2009; GOODPASTER; CARLSON; VISSER; KELLEY *et al.*, 2001). No entanto, estudos mais recentes sugerem que as elevações do CGI são mais um produto da inatividade física do que de outros fatores (e.g. envelhecimento) (ADDISON; MARCUS; LASTAYO; RYAN, 2014). De fato o baixo tempo de atividade física tem sido associado a elevações no CGI, mas esta associação tem sido mais evidenciada em populações específicas (i.e. diabéticos, obesos e pacientes com artrite reumatoide) (ADDISON; MARCUS; LASTAYO; RYAN, 2014; KHOJA; MOORE; GOODPASTER; DELITTO *et al.*, 2018; MARCUS; ADDISON; KIDDE; DIBBLE *et al.*, 2010; TUTTLE; SINACORE; CADE; MUELLER, 2011). Tais evidências indicam que exista um efeito moderador de condições patológicas (i.e. doença e/ou tratamento) sobre a associação entre o tempo de atividade física e o CGI. Especificamente, SCM podem carregar consigo efeitos colaterais associados ao tratamento de CM. Tem sido indicado que a radioterapia e a quimioterapia podem mimetizar os efeitos do envelhecimento e promover alterações no metabolismo e na regeneração de tecidos como o músculo esquelético, e assim induzir elevações do CGI (AMAYA-MONTOYA; PEREZ-LONDONO; GUATIBONZA-GARCIA; VARGAS-VILLANUEVA *et al.*, 2020; HERRANZ; GIL, 2018; SHAPIRO, 2018). Tais alterações poderiam alterar a magnitude de acumulação do CGI em SCM em

níveis similares de atividade física, quando da comparação entre SCM e mulheres não submetidas ao tratamento de CM. Se evidenciada, esta hipótese pode indicar necessidades específicas relacionadas à prática de atividade física entre SCM para equalização do CGI.

1.2.4 Conteúdo de gordura intramuscular e implicações para a função física de sobreviventes de câncer de mama

Há uma quantidade crescente de evidências ligando o elevado CGI ao comprometimento da FF em indivíduos idosos, diabéticos, com DPOC e câncer. Nestes pacientes, elevado CGI está associada à diminuição da distância de caminhada percorrida em seis minutos, diminuição da velocidade da marcha, diminuição do desempenho físico, dificuldades para estímulos repetidos de sentar e levantar, subir e descer escadas, dentre outros (MARCUS; ADDISON; KIDDE; DIBBLE *et al.*, 2010; TUTTLE; SINACORE; CADE; MUELLER, 2011; VISSER; KRITCHEVSKY; GOODPASTER; NEWMAN *et al.*, 2002).

Vem sendo mostrado que SCM apresentam elevado CGI (DELUCHE; LEOBON; DESPORT; VENAT-BOUVET *et al.*, 2018). Embora não tenhamos conhecimento de estudos que analisaram a relação entre o CGI e FF após o tratamento de CM, dois estudos avaliaram esta associação em pacientes durante o tratamento oncológico. Estes estudos indicaram que elevado CGI estava associado negativamente aos testes de FF (i.e. testes de velocidade da marcha e TUG) (BARBALHO; GONZALEZ; BIELEMANN; DA ROCHA *et al.*, 2019; WILLIAMS; DEAL; MUSS; WEINBERG *et al.*, 2017). No entanto, estes estudos falharam em não levar em consideração outros fatores conhecidos por suas implicações na FF. Estudos prévios relataram que a redução da massa e força musculares e do nível de atividade física podem ser a causa subjacente da baixa FF (MANINI; CLARK, 2012; SHIN; SONG; JUNG; LEE *et al.*, 2017; VISSER; KRITCHEVSKY; GOODPASTER; NEWMAN *et al.*, 2002). Além disso, baixos níveis de atividade física estão associados ao aumento do CGI, enquanto a perda de força pode ser explicada em até 6% por aumentos do CGI (GOODPASTER; CHOMENTOWSKI; WARD; ROSSI *et al.*, 2008; MANINI; CLARK; NALLS; GOODPASTER *et al.*, 2007). Essa intrincada relação entre variáveis dificulta a interpretação da influência específica do CGI sobre a FF em SCM. A compreensão de fatores independentes associados à FF pode fornecer informações adicionais sobre possíveis alvos terapêuticos para evitar a incapacidade física em SCM.

1.3 JUSTIFICATIVA

O atual nível de conhecimento limita a interpretação do papel específico do CGI sobre a baixa FF de SCM. Neste sentido, a análise da associação independente entre o CGI e a FF pode contribuir com a identificação de mais um alvo terapêutico a ser levado em consideração por profissionais que trabalham em cuidados primários da saúde de SCM.

Paralelamente, mulheres SCM frequentemente apresentam o CGI aumentado, o que está associado a desfechos negativos relacionados ou não ao tratamento de CM. Neste sentido, a compreensão de como a condição SCM pode influenciar a associação entre o tempo de atividade física e o CGI, pode auxiliar na adoção de estratégias preventivas, ou de intervenção, direcionadas a SCM durante e após a finalização do tratamento.

2. OBJETIVOS

1.2 OBJETIVO GERAL

Compreender as alterações do CGI e interpretar suas implicações sobre a FF de mulheres SCM.

1.3 OBJETIVOS ESPECÍFICOS

Artigo 1

- Verificar quais fatores (i.e. massa e força musculares; e atividade física) são concomitantemente alterados com o CGI em SCM.
- Verificar se o CGI é um mediador da relação entre SCM e a FF mais baixa, independentemente de fatores de confusão.

Artigo 2

- Verificar se a relação entre o tempo de atividade física e o CGI é moderado pela condição SCM.

3. RESULTADOS

Os resultados desta tese são apresentados sob a forma de dois artigos.

A seção de materiais e métodos, resultados e discussão estão contemplados nos dois artigos científicos.

3.1 ARTIGO 1

Intramuscular fat contributes to lower physical performance in Breast Cancer Survivors: a cross-sectional study

Anselmo Alves de Oliveira[a], Fernanda Maria Martins[a], Gersiel Nascimento de Oliveira Júnior[a], Luís Ronan Marquez Ferreira de Souza[a,c], Giovanni Bessa Pereira Lima[c], Vítor Carvalho Lara[c], Rosekeila Simões Nomelini[d], Fábio Lera Orsatti[a,b*]

[a] Exercise Biology Research Group (BioEx), Federal University of Triangulo Mineiro, Uberaba, Minas Gerais, Brazil

[b] Department of Sport Sciences, Health Science Institute, Federal University of Triangulo Mineiro, Uberaba, Minas Gerais, Brazil

[c] Department of Radiology and Diagnostic Imaging, Federal University of Triangulo Mineiro, Uberaba, Minas Gerais, Brazil

[d] Department of Ginecology and Obstetrics, Federal University of Triangulo Mineiro, Uberaba, Minas Gerais, Brazil

*Exercise Biology Research Group (BioEx), 30, avenue Frei-Paulino, Uberaba, Minas Gerais 38025-180, Brazil

Email: fabiorsatti@gmail.com or fabio.orsatti@uftm.edu.br

ABSTRACT

Background: In Breast Cancer Survivors (BCS), a limited physical performance (PP) is associated with disabilities, falls, and higher all-cause mortality. Increased intramuscular fat content (IMFC) is associated with a low PP in BCS. However, this association did not take into account confounding factors, such as muscle mass and strength and physical activity, which are important predictors of PP and may be reduced in BCS.

Objective: To verify which factors (i.e. muscle mass and strength and physical activity) are concomitantly altered with IMFC in BCS. Then, to verify whether IMFC mediates the relationship between BCS and lower PP, regardless of confounding factors.

Design: Cross-sectional study.

Setting: Women from a cancer treatment center (BCS) and a neighborhood association (control women - CG).

Participants: 79 women (56 BCS and 23 with no history of cancer) were evaluated between June 2016 and March 2018.

Measurements: PP was assessed by walking speed, sit-to-stand, and timed up and go (TUG) tests. Muscle attenuation coefficient (IMFC) and muscle area (muscle mass) were analyzed in the quadriceps muscle by computed tomography. The muscle strength was assessed by handgrip dynamometer and the physical activity time was quantified by the international physical activity questionnaire (IPAQ).

Results: The BCS showed lower PP (for all tests) ($p < 0.001$) and muscle strength ($p = 0.006$), and higher IMFC ($p = 0.002$) when compared to CG. However, the quadriceps muscle area ($p = 0.930$) and physical activity time ($p = 0.132$) were similar between groups. In BCS, lower walking, TUG and sit-to-stand were mediated, at least in part, by IMFC and muscle strength (total indirect effect: 15%, 27.5% and 15.8%, respectively). However, these indirect effects were mainly attributed to IMFC than muscle strength in walking (75.4% and 24.6%, respectively) and TUG (58.0% and 42%, respectively) tests, but not to sit-to-stand (28.0% and 72.0%, respectively) test. Mediation models provided a good fit to the data ($\chi2 = 0.144$; $df = 1.00$; $p = 0.704$; RMSES = 0.00; CFI = 1.00).

Conclusion: The findings of the present study demonstrated that BCS have, concomitantly, higher IMFC and lower muscle strength. Moreover, we demonstrated that IMFC, muscle strength or both mediate a lower PP in BCS, at least in part.

Keywords: muscle attenuation, physical function, muscle strength, physical activity, walking speed

INTRODUCTION

Breast cancer is the most prevalent and the third leading cause of death among cancers (SOCIETY, 2018). The relative survival rates of 5 and 10 years for women diagnosed with invasive BC are currently 90% and 83%, respectively (DE MOOR; MARIOTTO; PARRY; ALFANO *et al.*, 2013; SOCIETY, 2018). High prevalence associated with longer life expectancy suggests a significant increase in the number of breast cancer survivors (BCS). However, BCS often experience a decline in physical performance (PP) (CAMPBELL; WINTERS-STONE; WISKEMANN; MAY

et al., 2019; SHAPIRO, 2018). Limited PP is associated with disabilities, falls and higher all-cause mortality in BCS (BRAITHWAITE; SATARIANO; STERNFELD; HIATT *et al.*, 2010; WINTERS-STONE; HORAK; JACOBS; TRUBOWITZ *et al.*, 2017). Thus, it is essential to understand the mediating factors of lower PP in BCS if we are to avoid physical disability.

Previous studies conducted in non-cancer survivors (i.e. healthy elderly and individuals with rheumatoid arthritis, COPD, and diabetes) have shown an association between increased intramuscular fat content (IMFC) and reduced PP (KHOJA; MOORE; GOODPASTER; DELITTO *et al.*, 2018; VISSER; KRITCHEVSKY; GOODPASTER; NEWMAN *et al.*, 2002), but not all (REINDERS; MURPHY; KOSTER; BROUWER *et al.*, 2015). Some studies have argued that inconsistencies in these findings may reflect population differences (KHOJA; MOORE; GOODPASTER; DELITTO *et al.*, 2018; REINDERS; MURPHY; KOSTER; BROUWER *et al.*, 2015). People with chronic conditions experience a lower PP, are less active, and have more loss of muscle strength and gain in IMFC compared to healthy adults. Regarding this, it has been reported increased IMFC in BCS (CAMPBELL; WINTERS-STONE; WISKEMANN; MAY *et al.*, 2019; DELUCHE; LEOBON; DESPORT; VENAT-BOUVET *et al.*, 2018; SHAPIRO, 2018). Although we are not aware of studies that analyzed the relationship between IMFC and PP in BCS, two studies evaluated the association between IMFC and PP in patients during cancer treatment. These studies indicated that increased IMFC was negatively associated with performance in PP tests (i.e. walking speed and Timed Up and Go tests) (BARBALHO; GONZALEZ; BIELEMANN; DA ROCHA *et al.*, 2019; WILLIAMS; DEAL; MUSS; WEINBERG *et al.*, 2017). However, in these studies, the associations did not take into consideration the muscle strength, muscle mass and physical activity levels, which may be reduced in BCS (BRAITHWAITE; SATARIANO; STERNFELD; HIATT *et al.*, 2010; CAMPBELL; WINTERS-STONE; WISKEMANN; MAY *et al.*, 2019; LUCAS; LEVINE; AVIS, 2017). Several literature reviews have reported that reduced muscle mass, muscle strength, and physical activity level may be the underlying causes of reduced PP (KIM; KIM; MOON; KIM *et al.*, 2017; MANINI; CLARK, 2012; TIELAND; TROUWBORST; CLARK, 2018; VISSER; KRITCHEVSKY; GOODPASTER; NEWMAN *et al.*, 2002). Moreover, a low level of physical activity and also of muscle strength have been associated with increased IMFC (GOODPASTER; CHOMENTOWSKI; WARD; ROSSI *et al.*, 2008; MANINI; CLARK; NALLS; GOODPASTER *et al.*, 2007). Thus, the current level of knowledge does not allow us to identify the independent effects of IMFC on the PP in BCS.

Understanding the independent factors associated with PP may provide additional information on possible therapeutic targets to avoid physical disability in BCS. Hence, this study aimed to verify which of these factors (i.e. muscle mass and strength and physical activity) are concomitantly altered

with IMFC in BCS. Then, to verify whether IMFC mediates the relationship between BCS and lower PP, regardless of confounding factors.

METHODS

Participants

BCS (women) who were patients of a cancer treatment center in the city were invited to participate in this study. Patients of all treatment modalities (surgery, radiotherapy, chemotherapy or combination) were included in the research. Inclusion criteria: the patient that completed BC treatment for breast cancer staging between I-III (early breast cancer) and performed the functional tests. Patients who had not completed BC treatment or had previously undergone another type of cancer treatment were excluded from the study. The Control Group (CG) consisted of women who had no functional limitations to perform the physical tests and who had not undergone any type of cancer treatment. Volunteers from both groups who underwent systematic exercise over the past 6 months, or who had taken any nutritional supplements that affected muscle measurements were also excluded from the study. This study was previously submitted and approved by the Research Ethics Committee of the Federal University of Triangulo Mineiro (UFTM) with protocol number (CAAE: 82691818.0.0000.5154).

Study design

This research is a cross-sectional analytical study that sought to examine the association between IMFC and PP in BCS. Initially, we use a case-control approach to verify whether covariables known for influencing the PP or confounding variables were changed in BCS when compared to CG. Thus, solely the covariates or confounding variables that were different between groups were used in the association model between IMFC and PP.

All evaluations were performed between June 2016 and March 2018. After verbal acceptance and signing an informed consent form, patients were directed to a reserved room and questioned about their sociodemographic data, smoking and alcohol habits, diseases and medications. Clinical data (staging and treatment performed) were self-reported and subsequently checked by hospital staff based on analysis of the patient's medical records. Sociodemographic, anthropometric, alcohol consumption, smoking, medicaments, diseases, and BC treatment regimen variables were used for sample characterization. After, PP and anthropometric evaluations were conducted.

The sample size was calculated using G*Power software (version 3.1.9.2) based on a previous study (KHOJA; MOORE; GOODPASTER; DELITTO *et al.*, 2018), which demonstrated that at least 77 participants are needed to detect a 13% determination (effect size $f^2 = 0.15$; medium effect size)

between dependent and predictor (independent) variables. The alpha error was defined as 0.05 with the power of 80% and the number predictor equal to three.

Intramuscular Fat Content - Computed Tomography (CT)

CT images of thing were obtained from multislices tomographys Siemens Somatom Emotion (Siemens Healthineers AG, Munich, Germany) and Toshiba Alexion Advance – TSX-034A (Toshiba Corporation, Tokyo, Japan). A radiologist specializing in musculoskeletal radiography (G.B.P.L) supervised initial collection and analysis of CT parameters. As described by Goodpaster et al. (2001), patients were positioned with their arms above their heads and legs extended on the table (GOODPASTER; CARLSON; VISSER; KELLEY *et al.*, 2001). An anteroposterior scout scan was used to determine the position of the first cut (7cm above the upper edge of the patella). Fifty images above the first section were collected, with thickness and spacing between sections of 2mm. The scanning parameters for this image were 120 kVp and 130 mA. Osirix MD ANVISA (version 8.5.2) software was used for analysis of the thigh muscle area and IMFC. Quality analysis was performed on each subject's images to ensure that all images were present, that the proper scanning techniques were used, and that the image was of adequate quality for analysis. For analysis of muscle measurements, we considered the first thigh section in which the rectus femoris muscle was completely visible. IMFC was measured in Quadriceps femoral muscle. For this, Quadriceps muscle was manually delimited being careful not to include pixels related to intermuscular fat and/or femoral bone. IMFC values were obtained from the muscle attenuation coefficient (the lower the muscle attenuation coefficient the higher the IMFC levels) within the regions delimited in the images and determined by the average pixel intensity in Hounsfield units (HU). All analyzes were performed by the same evaluator. To analyze the reliability of the muscle parameters reading, the intra-class correlation coefficient (ICC) was calculated. For this, the area and IMFC measurements of 10 volunteers were analyzed in triplicate. The ICC for quadriceps IMFC was 0.97.

Eligible covariates

Muscle area

To measure the Quadriceps muscle area, the same image and delimitation area described for IMFC were used, and the ICC for the quadriceps muscle area was 0.99.

Muscle strength measurement - Handgrip test

To quantify muscle strength levels, the handgrip test was performed. Handgrip test is a global indicator of muscle strength levels extensively used in clinical practice (CRUZ-JENTOFT; BAHAT;

BAUER; BOIRIE *et al.*, 2019; IBRAHIM; MAY; PATEL; BAXTER *et al.*, 2016). For this, was used a palmar dynamometer (JAMAR®). Three palm grips were performed in the right and left hands in the sitting position with the elbow flexed at 90 degrees and hand in neutral position. The volunteers were instructed to apply as much force as possible. A recovery interval of 30 seconds was observed between attempts. The mean of two best measures (right and left) was calculated to evaluate the strength levels (ROBERTS; DENISON; MARTIN; PATEL *et al.*, 2011).

Physical activity levels

To measure physical activity levels, the short version of the International Physical Activity Questionnaire (IPAQ) was applied. To determine the level of physical activity, the 25th percentile (192.5 min/week) was considered as the cutoff point for dichotomization between low or good level of physical activity.

Physical performance tests

- *Walking test*

The usual walking speed test was evaluated by the time walking at a distance of 4 m. To avoid the influence of acceleration and deceleration, 1-meter indentation and extension areas were considered in the test area (6m total). Two measures were taken and the minor time was considered as the valid measure.

- *Sit-to-stand test*

The five-time chair stand test was evaluated by the time spent on five maximal velocity squats in a chair with their arms folded across their chest. The technique consisted of full sit and stand positions and the women started in the sitting position (CRUZ-JENTOFT; BAHAT; BAUER; BOIRIE *et al.*, 2019). Sit-to-stand test also was used to assess lower-extremity muscle strength (SCHURR; SHERRINGTON; WALLBANK; PAMPHLETT *et al.*, 2012).

- *Timed up and go test (TUG)*

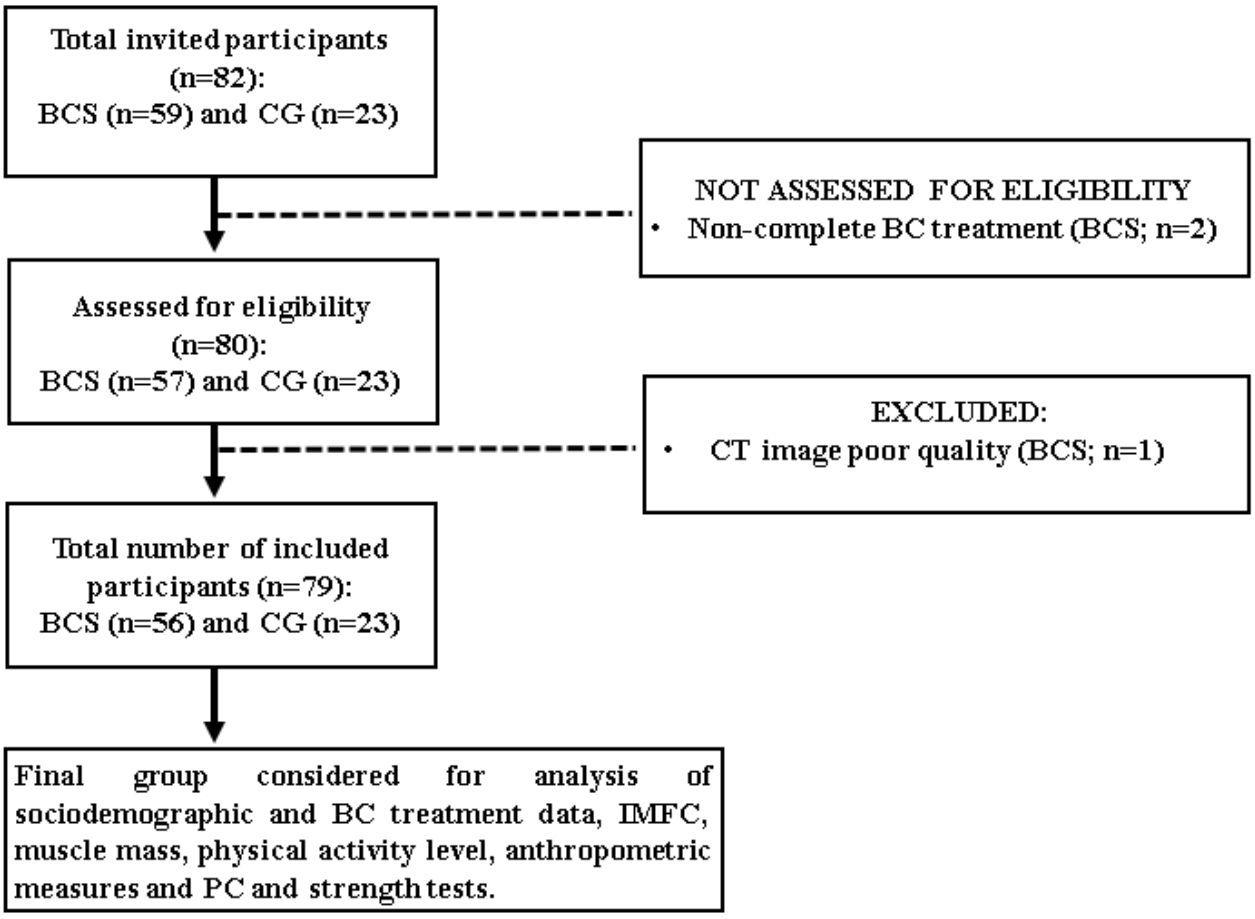
To perform the TUG test, a cone was placed 3 m away from the chair where the volunteer rested at the beginning of the test. After the “go” signal, the volunteers should get up from the chair and walk as quickly as possible to get around the cone and sit back in the chair. The time between the “go” signal and the full support in the chair after the course was considered (SPAGNUOLO; JURGENSEN; IWAMA; DOURADO, 2010).

Although we did not perform duplicate analyses for PP tests, previous studies demonstrated a high reproducibility of the tests used in the current study (FREIRE; GUERRA; ALVARADO; GURALNIK *et al.*, 2012; SPAGNUOLO; JURGENSEN; IWAMA; DOURADO, 2010).

Data analysis

Continuous variables are presented as mean and confidence interval of 95% (CI95%) while categorical variables were presented as frequency measures. Data normality was verified by the Kolmogorov-Smirnov test. Comparison between the conditions (groups) was performed in Generalized Linear Models (GLM) by selecting the functions as follows: parametric or nonparametric continuous variables were analyzed by the Linear function and the Log-linked Gamma function, respectively; dichotomous variables were analyzed by binary logistic function; count indicators were analyzed by Poisson linear log function; and ordinal variables by ordinal logistic function (table 1 and 2). Then, linear regression models (simple and multiple) between PP and HU and handgrip (eligible as variables because they were significantly different between the conditions) were interpreted considering for the analysis the non-standard regression coefficients (B) and the 95% confidence interval (CI) (Table 3). Finally, to estimate direct and indirect effects in single and multiple mediator models (mediation effect), we used a path analysis modeling tool termed Process (HAYES, 2017) (Table 4). In bootstrapping for indirect, the bootstrap sample used was 1000 with bias corrected. All analyses were performed on IBM SPSS version 23 software (IBM Corporation). Statistical difference was considered when $p < 0.05$.

Figure 1. Flow diagram



Legend:
BCS – breast cancer survivors; CG – control group; CT – computed tomography; BC – breast cancer; IMFC – intramuscular fat content; PP – physical performance.

RESULTS

Descriptive characteristics for BCS and CG are presented in Table 1. The results indicate that there were no differences between groups for sociodemographic, anthropometric, alcohol consumption, smoking, medicaments, and disease variables. Analysis of BC treatment characteristics indicates that 100% of BCS underwent breast cancer surgery, 92.9% of BCS underwent radiotherapy (the most prevalent adjuvant therapy) and that BCS had completed treatment on average 3.3 years ago (CI 95%, 2.6 – 4.1).

Table 1. Sample characteristics for CG and BCS

	CG (n=23)	BCS (n=56)	p value
Age, years	59.9 (56.9 ; 62.8)	58.5 (56.3 ; 60.6)	0.465
Menopause time, years	13.8 (8.9 ; 18.7)	11.1 (8.8 ; 13.4)	0.336
BMI, kg/m^2	26.2 (24.1 ; 28.4)	27.2 (25.9 ; 28.6)	0.432
WC, cm	89.9 (84.5 ; 95.4)	95.0 (91.4 ; 98.5)	0.131
HC, cm	101.1 (96.5 ; 105.7)	105.3 (102.8 ; 107.7)	0.116
WHR, a.u.	0.90 (0.87 ; 0.92)	0.90 (0.88 ; 0.92)	0.893
Number of diseases	1.4 (1.0 ; 2.0)	1.2 (1.0 ; 1.5)	0.489
Number of medicaments	1.5 (1.0 ; 2.3)	2.0 (1.6 ; 2.5)	0.239
Smokers, n (%)	5 (21.7)	21 (36.8)	0.382
Alcohol drinkers, n (%)	6 (26.1)	15 (26.3)	0.949
Marital status, n (%)			0.418
Omitted	2 (8.7)	0	
Single	2 (8.7)	13 (23.2)	
Married	11 (47.8)	25 (44.6)	
Divorced	3 (13.0)	5 (8.9)	
Widow	5 (21.7)	13 (23.2)	
Scholarity, n (%)			0.569
Omitted	2 (8.7)	1 (1.8)	
Elementary school	9 (39.1)	31 (55.3)	
High school	10 (43.5)	14 (25.0)	
College	2 (8.7)	10 (17.9)	
Treatment Characteristics		*BCS (n=56)*	
Time since end of treatment, years	-	3.3 (2.6 ; 4.1)	
Surgery, n(%)	-	56 (100)	
Radiotherapy, n(%)	-	52 (92.9)	
Quimiotherapy, n(%)	-	35 (62.5)	
Antihormonal Therapy, n(%)	-	41 (73.2)	

Comparison between groups by GLM. CG – control group; BCS – breast cancer survivors; BMI – body mass index; kg/m^2 – kilograms per square meter; WC – waist circumference; cm – centimeters; HC – hip circumference; WHR – waist-hip ratio; a.u. – arbitrary units.

The comparisons between the groups for PP tests, muscle attenuation coefficient, handgrip, physical activity time and quadriceps muscle area are shown in table 2. The statistical analysis showed that the BCS group was 0.80 s (IC95%: 0.50 ; 1.09 s), 2.00 s (IC95%: 11.38 ; 2.65s), 4.55 s (IC95%: 33.34 ; 5.77 s) significantly slower in walking, TUG, and sit-to-stand tests, respectively, that the CG. Also, the BCS group was 3.67 kg.f (IC95%: -6.27 ; -1.07 kg.f) and 3.85 HU (IC95%: -6.34 ; -1.36 HU) significantly slower in handgrip and muscle attenuation coefficient, respectively, then the CG. There were no significant differences between the groups for physical activity and quadriceps muscle area.

Table 2. Comparation of physical performance tests, muscle attenuation coefficient (IMFC), handgrip (muscle strength), physical activity time and muscle area between CG and BCS

Variable	CG (n=23)	BCS (n=56)	B (IC95%)	p value
Walking time, s	3.0 (2.8 ; 3.2)	3.8 (3.6 ; 4.0)	0.80 (0.50 ; 1.09)	<0.001
TUG, s	6.7 (6.3 ; 7.1)	8.7 (8.2 ; 9.2)	2.00 (1.38 ; 2.65)	<0.001
Sit-to-stand, s	7.7 (6.8 ; 8.5)	12.2 (11.3 ; 13.1)	4.55 (3.34 ; 5.77)	0.000
Muscle attenuation coefficient, HU	50.3 (48.7 ; 51.8)	46.4 (44.4 ; 48.4)	-3.85 (-6.34 ; -1.36)	0.002
Handgrip, kg.f	24.1 (22.1 ; 26.0)	20.4 (18.7 ; 22.1)	-3.67 (-6.27 ; -1.07)	0.006
Physical Activity, (min/wk)	918.1 (550,5; 1285,6)	608.4 (442,9; 773,8)	-309.72 (-712.83 ; 93.36)	0.132
Quadriceps muscle area, cm^2	41.7 (38.6 ; 44.9)	41.6 (39.5 ; 43.6)	-0.17 (-3.93 ; 3.60)	0.930

Comparison between groups by GLM. IMFC – intramuscular fat content; CG – control group; BCS – breast cancer survivors; B - regression coefficient; IC95% - 95% confidence interval; s – seconds; TUG – timed up and go test; HU – hounsfield unit; kg.f – kilogram-force; min/wk – minutes per week; cm^2 - square centimeters.

Two regression models were used to estimate the predictive power of muscle attenuation coefficient (IMFC) and handgrip (muscle strength) over PP (Table 3). Model 1 (no adjusted) and model 2 showed that muscle attenuation coefficient values (HU) were significantly and negatively associated with performance in all PP tests (walking, sit-to-stand, and TUG tests). Handgrip values (kg) were significantly and negatively associated only with performance in TUG and sit-to-stand tests (s), regardless of the model. There was no correlation between handgrip and muscle attenuation coefficient values ($r = 0.14$, $P = 0.214$).

Table 3. Association of muscle attenuation coefficient (IMFC) and handgrip (muscle) strength with physical performance tests.

Variable	Model 1 (n = 79)	Model 2 (n = 79)
Walking time, s		
Muscle attenuation coefficient, HU	-.036*	-0.031*
	(-.062 ; -.010)	(-0.059 ; -0.002)
Handgrip, kg.f	0.02	-0.022
	(-0.05 ; 0.005)	(-0.051 ; 0.007)
TUG, s		
Muscle attenuation coefficient, HU	-0.115*	-0.107*
	(-0.171 ; -0.060)	(-0.169 ; - 0.046)
Handgrip, kg.f	-0.102*	-0.103*
	(-0.165 ; -0.039)	(-0.116 ; - 0.040)
Sit-to-stand, s		
Muscle attenuation coefficient, HU	-0.130*	-0.154*
	(-0.250 ; -0.010)	(-0.286 ; -0.022)
Handgrip, kg.f	-0.216*	-0.236*
	(-0.340 ; -0.091)	(-0.363 ; -0.111)

Regression coefficient (B) and 95% confidence interval. IMFC – intramuscular fat content; PP – physical performance ; CG – control group; s – seconds; TUG – timed up and go test; HU – Hounsfield unit; kg.f – kilogram-force; cm^2 - square centimeters. *p ≤ 0,05.
Model 1 – no adjustment for other variables;
Model 2 – Adjusted for age, smokers and numbers of medicaments

Mediation analysis was proposed to investigate the mediating role of IMFC in the relationship between BC treatment and PP (table 4). The direct effects of the BCS treatment (controlling for muscle attenuation coefficient and handgrip) were 0.67 s (CI95%= 0.29 ; 1.05 s), 1.46 s (CI95% = 0.67 - 2.24 s) and 3.83 s (CI95% = 2.22 ; 5.45 s) for walking, TUG and sit-to-stand tests, respectively. Thus, comparing to total effect (table 2), the total indirect effects (muscle attenuation coefficient plus handgrip) were 0.12 s (CI95% = -0.01; 0.30s), 0.559 s (CI95% = 0.23; 1.06 s), and 0.72 s (CI95% = 0.15; 1.81 s) for walking, TUG and sit-to-stand tests, respectively. Specifically, indirect effects of muscle attenuation coefficient and handgrip were 0.09 s (CI95% = 0.00; 0.22 s) and 0.03 s (CI95% = -0.04; 0.19 s), 0.32 s (CI95% = 0.09; 0.63 s) and 0.23 s (CI95% = 0.02; 0.72s), and 0.20 s (CI95% = -0.04; 0.64 s) and 0.51 s (CI95% = 0.05; 1.59 s) for walking, TUG and sit-to-stand tests, respectively.

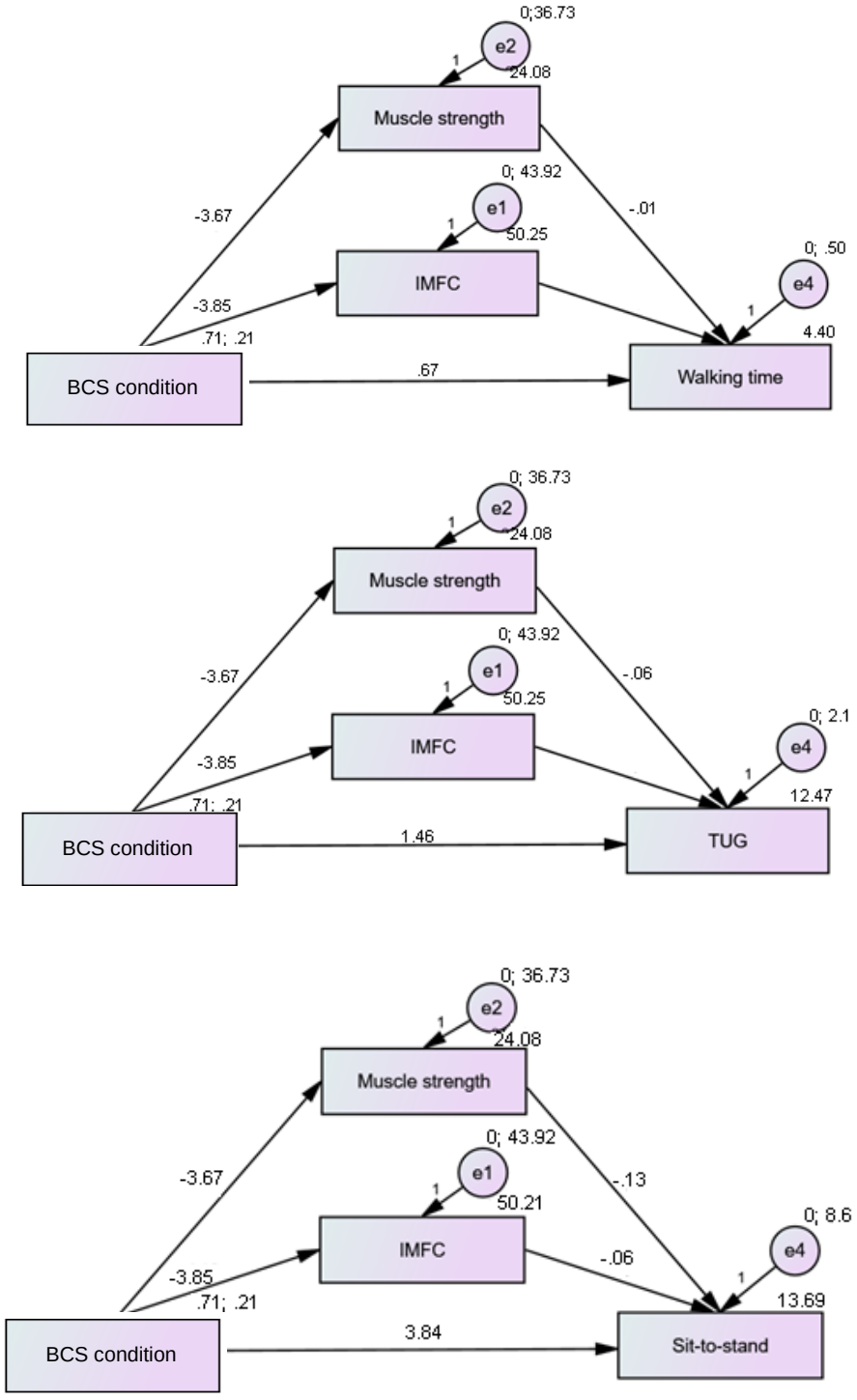
All mediation models (figure 2) provided a good fit to the data ($\chi 2 = 0.144$; df = 1.00; p = 0.704; RMSES = 0.00; CFI = 1.00).

Table 4. Estimation of direct and indirect (mediation) effects of BCS condition on physical performance tests.

	Walking time, s			**TUG, s**			**Sit-to-stand, s**		
	B	**R^2**	**P**	**B**	**R^2**	**P**	**B**	**R^2**	**P**
Model		0.24	<0.001		0.39	<0.001		0.38	<0.001
BCS condition (direct effect)	0.673 (0.290 ; 1.057)*			1.461 (0.677 ; 2.243)*			3.837 (2.220; 5.455)*		
Muscle attenuation coefficient, HU	-0.0239 (-0.049 ; -0.001)*			-0.084 (-0.134 ; -0.034)*			-0.056 (-0.159; 0.047)		
Handgrip, kg.f	-0.008 (-0.035 ; 0.019)			-0.064 (-0.119 ; -0.009)*			-0.134 (-0.246; -0.021)*		
Indirect effect of BCS condition									
Muscle attenuation coefficient, HU	0.092 (0.007 ; 0.224)*			0.324 (0.098 ; 0.639)*			0.203 (-0.046; 0.640)		
Handgrip, kg.f	0.030 (-0.048 ; 0.212)			0.235 (0.028 ; 0.729)*			0.518 (0.054; 1.590)*		
Total	0.122 (-0.009 ; 0.329)			0.559 (0.233 ; 1.063)*			0.721 (0.159; 1.811)*		

Regression coefficient (B) and 95% confidence interval. R^2 correlation coefficient; s – seconds; TUG – timed up and go test; HU – Hounsfield unit; kg.f – kilogram-force; cm^2 - square centimeters. *$p \leq 0.05$.

Figure 2. Diagram of models in which the effect of BCS condition on physical performance is mediated by IMFC and muscle strength.



Chi-square = ,144
Degrees of freedom = 1
Probability level = ,704
RMSES = 0,00
CFI = 1,00

DISCUSSION

In this study, reduced PP, greater IMFC, and lower muscle strength (but not reduced muscle mass and physical activity time) were concomitantly observed in BCS when compared to women of similar age never diagnosed with cancer. Our main findings were that the effects of BCS condition on PP were mediated, at least in part, by IMFC, muscle strength, or both However, these mediating effects were independent of each other and test-specific.

Previous studies indicate that cancer treatment can lead to reduced muscle mass that may compromise the PP of these individuals (CAMPBELL; WINTERS-STONE; WISKEMANN; MAY *et al.*, 2019; SHAPIRO, 2018). However, the results of our study showed higher levels of IMFC, but no muscle mass (indicated by quadriceps muscle area) in BCS when compared to CG (Table 2). Indeed, breast cancer treatment does not cause muscle mass reduction (RIER; JAGER; SLEIJFER; VAN ROSMALEN *et al.*, 2018). Also, previous studies have indicated that BCS may have low levels of physical activity (DE GROEF; GERAERTS; DEMEYER; VAN DER GUCHT *et al.*, 2018; LUCAS; LEVINE; AVIS, 2017). However, we observed high physical activity values in both groups. These high physical activity values are due to the employment situation of these women (cleaning women). Moreover, we did not observe significantly reduced levels of physical activity in the BCS when compared to the CG (Table 2). Indeed, a lower level of physical activity in BCS does not seem to be influenced by the treatment of BC (EMERY; YANG; FRIERSON; PETERSON *et al.*, 2009; MASON; ALFANO; SMITH; WANG *et al.*, 2013). Emery et al. (2009) showed a curvilinear behavior of physical activity levels after BC treatment, increasing in the first 18 months and decreasing after this period, with values similar to that pre-treatment in 36° month (similar period observed in the BCS in the present study) (EMERY; YANG; FRIERSON; PETERSON *et al.*, 2009). Taken together, these findings indicate that the reduction in physical activity levels in BCS observed by some studies may not be related to the treatment of BC, but may be a consequence of other factors. Collectively, these results led us to disregard the influence of muscle mass and physical activity on the relationship between IMFC and PP in the current study.

On the other hand, we also observed that BCS had lower muscle strength and greater IMFC that CG (Table 2). These findings are consistent with the literature that has shown increased IMFC and reduced muscle strength in BCS(CAMPBELL; WINTERS-STONE; WISKEMANN; MAY *et al.*, 2019; DELUCHE; LEOBON; DESPORT; VENAT-BOUVET *et al.*, 2018; KLASSEN; SCHMIDT; ULRICH; SCHNEEWEISS *et al.*, 2017; MANINI; CLARK, 2012; SHAPIRO, 2018). Thus, these results led us to consider the influence of muscle strength and IMFC on the relationship

between BCS condition and PP in the current study. Indeed, muscle strength and IMFC were associated with PP, even after adjustment to confounding factors (table 3)

The results of the current study indicated a lower PP (all PP test) in the BCS that the CG (Table 2). These results are in line with those of previous studies (CAMPBELL; WINTERS-STONE; WISKEMANN; MAY *et al.*, 2019; SHAPIRO, 2018). Specifically, we observed a reduction of 0.80 s, 2.00 s, 4.55 s in walking, TUG, and sit-to-stand tests, respectively, in BCS when compared to the CG (Table 2). After adjustment to muscle strength and IMFC, there was a decline in the BCS condition effects (table 4) on PP tests. The direct effects of the BCS condition (i.e. adjusted to muscle strength and IMFC) on walking, TUG, and sit-to-stand tests were 0.67, 1.46, and 3.83, respectively. That is, reductions of 0.12 s (15.0%), 0.55 s (27.5%), and 0.72 s (15.8%) assigned to indirect effects (total) of BCS condition. However, these indirect effects were mainly attributed to IMFC than muscle strength in walking and TUG tests, but not to sit-to-stand test. In the walking test, the IMFC significantly contributed 75.4% while the muscle strength contributed 24.6% (no significant) of the indirect effects (total). In the TUG test, the IMFC significantly contributed 58.0% while the muscle strength significantly contributed 42.0% of the indirect effects (total). However, in the sit-to-stand test, the IMFC contributed 28.0% (no significant) while the muscle strength significantly contributed 72.0% of the indirect effects (total). Thus, in our results, the effects of the BCS condition on PP were mediated, at least in part, by IMFC, muscle strength, or both, suggesting that these mediating effects may be specific to the test used.

Previous studies have reported an association between IMFC and PP in older adults during cancer treatment (BARBALHO; GONZALEZ; BIELEMANN; DA ROCHA *et al.*, 2019; WILLIAMS; DEAL; MUSS; WEINBERG *et al.*, 2017). However, although it has been reported increased IMFC in BCS (CAMPBELL; WINTERS-STONE; WISKEMANN; MAY *et al.*, 2019; DELUCHE; LEOBON; DESPORT; VENAT-BOUVET *et al.*, 2018; SHAPIRO, 2018), the association between IMFC and PP has also been observed in older adults in non-cancer conditions (KHOJA; MOORE; GOODPASTER; DELITTO *et al.*, 2018; VISSER; GOODPASTER; KRITCHEVSKY; NEWMAN *et al.*, 2005; VISSER; KRITCHEVSKY; GOODPASTER; NEWMAN *et al.*, 2002). Thus, the relationship between IMFC and PP may not be specific to BCS condition. Hence, the design of our study was to verify whether IMFC mediates the effect of BCS condition on PP, comparting with a group of similar age never diagnosed with cancer. Indeed, the effects of BCS condition on PP were mediated, at least in part, by IMFC in our study. Moreover, in these previous studies, the associations between IMFC and PP did not take into consideration muscle strength. Although IMFC is increased in BCS (CAMPBELL; WINTERS-STONE; WISKEMANN;

MAY *et al.*, 2019; DELUCHE; LEOBON; DESPORT; VENAT-BOUVET *et al.*, 2018; SHAPIRO, 2018), muscle strength is reduced in BCS (BRAITHWAITE; SATARIANO; STERNFELD; HIATT *et al.*, 2010; CAMPBELL; WINTERS-STONE; WISKEMANN; MAY *et al.*, 2019). As muscle strength has been associated with PP (KIM; KIM; MOON; KIM *et al.*, 2017; MANINI; CLARK, 2012; TIELAND; TROUWBORST; CLARK, 2018; VISSER; KRITCHEVSKY; GOODPASTER; NEWMAN *et al.*, 2002) and with IMFC, the effect of IMFC could just be the effects of muscle strength on PP. However, even with adjustment to muscle strength, there was a significant mediating effect of IMFC on the walking and TUG tests, but not on the sit-to-stand test.

The mechanism(s) that might explain the independent association and mediation role of IMFC on PP remains unclear, but some studies have indicated that excessive IMFC may interfere with muscle metabolism or neural factors by activating the inflammatory process and producing toxic lipid by-products (ADDISON; MARCUS; LASTAYO; RYAN, 2014; COEN; GOODPASTER, 2012; GILLIES; LIEBER, 2011). Specifically, Khoja and colleagues argue that the invasion of fat around the muscle spindles may affect intrafusal muscle fibers and consequently alter the neuromuscular adjustment for a given muscle action (KHOJA; MOORE; GOODPASTER; DELITTO *et al.*, 2018). Muscle spindles are encapsulated mechanosensory receptors within skeletal muscle tissue that inform the central nervous system about the contractile status of each muscle. This information is required for any coordinated movement and stable posture (KROGER, 2018).

The muscle strength, but not IMFC, was a significant mediator of the effect of the BCS condition on the sit-to-stand test (Table 4). Indeed, the sit-to-stand test is applied clinically to measure leg muscle strength (SCHURR; SHERRINGTON; WALLBANK; PAMPHLETT *et al.*, 2012) because greater muscle force is required to stand up from a chair (JANSSEN; BUSSMANN; STAM, 2002). This effect of muscle strength on performance to stand up from a chair could explain the mediating role that muscle strength has in the TUG test since stand up from a chair is part of the TUG test. Thus, our results suggest that muscle strength is the more important mediator of the effect of the BCS condition on the sit-to-stand test when compared to IMFC.

The results of the present study are clinically relevant because they suggest that high levels of IMFC may be also (together with lower muscle strength level) an alternative source of lower PP in BCS. From these findings, professionals involved in primary health care in BCS now need to consider interventions that can also reduce IMFC. Clinical interventions based on dietary manipulation and exercise seem to be effective in reducing muscle fat content in non-cancer populations (ADDISON; MARCUS; LASTAYO; RYAN, 2014). Thus, further randomized, controlled, clinical trials are required to develop effective therapies for avoiding or reduce IMFC accumulation in BCS.

The present study is not without its limitations. The cross-sectional design limits temporal inferences. Considering the influence of physical activity levels on quantitative and qualitative indicators of skeletal muscle, the use of an indirect measure to assess physical activity levels may have impaired the quantification of physical activity levels. However, the similarity between BCS and CG activity levels is in line with previous studies evidence (EMERY; YANG; FRIERSON; PETERSON *et al.*, 2009; MASON; ALFANO; SMITH; WANG *et al.*, 2013)

CONCLUSION

The findings of the present study indicate that IMFC and muscle strength, but not physical activity and muscle mass are concomitantly altered in BCS. Moreover, our results suggest that IMFC is a mediator of the relationship between BCS and lower PP; regardless of muscle strength. However, this mediating effect is test-specific.

REFERENCES

1. ADDISON, O.; MARCUS, R. L.; LASTAYO, P. C.; RYAN, A. S. Intermuscular fat: a review of the consequences and causes. **Int J Endocrinol**, 2014, p. 309570, 2014.

2. BARBALHO, E. R.; GONZALEZ, M. C.; BIELEMANN, R. M.; DA ROCHA, I. M. G. *et al.* Is skeletal muscle radiodensity able to indicate physical function impairment in older adults with gastrointestinal cancer? **Exp Gerontol**, 125, p. 110688, Oct 1 2019.

3. BRAITHWAITE, D.; SATARIANO, W. A.; STERNFELD, B.; HIATT, R. A. *et al.* Long-term prognostic role of functional limitations among women with breast cancer. **J Natl Cancer Inst**, 102, n. 19, p. 1468-1477, Oct 6 2010.

4. CAMPBELL, K. L.; WINTERS-STONE, K. M.; WISKEMANN, J.; MAY, A. M. *et al.* Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. **Med Sci Sports Exerc**, 51, n. 11, p. 2375-2390, Nov 2019.

5. COEN, P. M.; GOODPASTER, B. H. Role of intramyocelluar lipids in human health. **Trends Endocrinol Metab**, 23, n. 8, p. 391-398, Aug 2012.

6. CRUZ-JENTOFT, A. J.; BAHAT, G.; BAUER, J.; BOIRIE, Y. *et al.* Sarcopenia: revised European consensus on definition and diagnosis. **Age Ageing**, 48, n. 4, p. 601, Jul 1 2019.

7. DE GROEF, A.; GERAERTS, I.; DEMEYER, H.; VAN DER GUCHT, E. *et al.* Physical activity levels after treatment for breast cancer: Two-year follow-up. **Breast**, 40, p. 23-28, Aug 2018.

8. DE MOOR, J. S.; MARIOTTO, A. B.; PARRY, C.; ALFANO, C. M. *et al.* Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. **Cancer Epidemiol Biomarkers Prev**, 22, n. 4, p. 561-570, Apr 2013.

9. DELUCHE, E.; LEOBON, S.; DESPORT, J. C.; VENAT-BOUVET, L. *et al.* Impact of body composition on outcome in patients with early breast cancer. **Support Care Cancer**, 26, n. 3, p. 861-868, Mar 2018.

10. EMERY, C. F.; YANG, H. C.; FRIERSON, G. M.; PETERSON, L. J. *et al.* Determinants of physical activity among women treated for breast cancer in a 5-year longitudinal follow-up investigation. **Psychooncology**, 18, n. 4, p. 377-386, Apr 2009.

11. FREIRE, A. N.; GUERRA, R. O.; ALVARADO, B.; GURALNIK, J. M. *et al.* Validity and reliability of the short physical performance battery in two diverse older adult populations in Quebec and Brazil. **J Aging Health**, 24, n. 5, p. 863-878, Aug 2012.

12. GILLIES, A. R.; LIEBER, R. L. Structure and function of the skeletal muscle extracellular matrix. **Muscle Nerve**, 44, n. 3, p. 318-331, Sep 2011.

13. GOODPASTER, B. H.; CARLSON, C. L.; VISSER, M.; KELLEY, D. E. *et al.* Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. **J Appl Physiol (1985)**, 90, n. 6, p. 2157-2165, Jun 2001.

14. GOODPASTER, B. H.; CHOMENTOWSKI, P.; WARD, B. K.; ROSSI, A. *et al.* Effects of physical activity on strength and skeletal muscle fat infiltration in older adults: a randomized controlled trial. **J Appl Physiol (1985)**, 105, n. 5, p. 1498-1503, Nov 2008.

15. HAYES, A. F. **Introduction to mediation, moderation, and conditional process analysis: A regression-based approach**. Guilford publications, 2017. 1462534651.

16. IBRAHIM, K.; MAY, C.; PATEL, H. P.; BAXTER, M. *et al.* A feasibility study of implementing grip strength measurement into routine hospital practice (GRImP): study protocol. **Pilot Feasibility Stud**, 2, p. 27, 2016.

17. JANSSEN, W. G.; BUSSMANN, H. B.; STAM, H. J. Determinants of the sit-to-stand movement: a review. **Phys Ther**, 82, n. 9, p. 866-879, Sep 2002.

18. KHOJA, S. S.; MOORE, C. G.; GOODPASTER, B. H.; DELITTO, A. *et al.* Skeletal Muscle Fat and Its Association With Physical Function in Rheumatoid Arthritis. **Arthritis Care Res (Hoboken)**, 70, n. 3, p. 333-342, Mar 2018.

19. KIM, W. J.; KIM, J. W.; MOON, Y. J.; KIM, S. H. *et al.* The photoplethysmographic amplitude to pulse pressure ratio can track sudden changes in vascular compliance and resistance during liver graft reperfusion: A beat-to-beat analysis. **Medicine (Baltimore)**, 96, n. 22, p. e7045, Jun 2017.

20. KLASSEN, O.; SCHMIDT, M. E.; ULRICH, C. M.; SCHNEEWEISS, A. *et al.* Muscle strength in breast cancer patients receiving different treatment regimes. **J Cachexia Sarcopenia Muscle**, 8, n. 2, p. 305-316, Apr 2017.

21. KROGER, S. Proprioception 2.0: novel functions for muscle spindles. **Curr Opin Neurol**, 31, n. 5, p. 592-598, Oct 2018.

22. LUCAS, A. R.; LEVINE, B. J.; AVIS, N. E. Posttreatment trajectories of physical activity in breast cancer survivors. **Cancer**, 123, n. 14, p. 2773-2780, Jul 15 2017.

23. MANINI, T. M.; CLARK, B. C. Dynapenia and aging: an update. **J Gerontol A Biol Sci Med Sci**, 67, n. 1, p. 28-40, Jan 2012.

24. MANINI, T. M.; CLARK, B. C.; NALLS, M. A.; GOODPASTER, B. H. *et al.* Reduced physical activity increases intermuscular adipose tissue in healthy young adults. **Am J Clin Nutr**, 85, n. 2, p. 377-384, Feb 2007.

25. MASON, C.; ALFANO, C. M.; SMITH, A. W.; WANG, C. Y. *et al.* Long-term physical activity trends in breast cancer survivors. **Cancer Epidemiol Biomarkers Prev**, 22, n. 6, p. 1153-1161, Jun 2013.

26. REINDERS, I.; MURPHY, R. A.; KOSTER, A.; BROUWER, I. A. *et al.* Muscle Quality and Muscle Fat Infiltration in Relation to Incident Mobility Disability and Gait Speed Decline: the Age, Gene/Environment Susceptibility-Reykjavik Study. **J Gerontol A Biol Sci Med Sci**, 70, n. 8, p. 1030-1036, Aug 2015.

27. RIER, H. N.; JAGER, A.; SLEIJFER, S.; VAN ROSMALEN, J. *et al.* Changes in body composition and muscle attenuation during taxane-based chemotherapy in patients with metastatic breast cancer. **Breast Cancer Res Treat**, 168, n. 1, p. 95-105, Feb 2018.

28. ROBERTS, H. C.; DENISON, H. J.; MARTIN, H. J.; PATEL, H. P. *et al.* A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. **Age Ageing**, 40, n. 4, p. 423-429, Jul 2011.

29. SCHURR, K.; SHERRINGTON, C.; WALLBANK, G.; PAMPHLETT, P. *et al.* The minimum sit-to-stand height test: reliability, responsiveness and relationship to leg muscle strength. **Clin Rehabil**, 26, n. 7, p. 656-663, Jul 2012.

30. SHAPIRO, C. L. Cancer Survivorship. **N Engl J Med**, 379, n. 25, p. 2438-2450, Dec 20 2018.

31. SOCIETY, A. C. **American Cancer Society. Cancer Facts & Figures 2018**. American Cancer Society, p. 71. 2018.

32. SPAGNUOLO, D. L.; JURGENSEN, S. P.; IWAMA, A. M.; DOURADO, V. Z. Walking for the assessment of balance in healthy subjects older than 40 years. **Gerontology**, 56, n. 5, p. 467-473, 2010.

33. TIELAND, M.; TROUWBORST, I.; CLARK, B. C. Skeletal muscle performance and ageing. **J Cachexia Sarcopenia Muscle**, 9, n. 1, p. 3-19, Feb 2018.

34. VISSER, M.; GOODPASTER, B. H.; KRITCHEVSKY, S. B.; NEWMAN, A. B. *et al.* Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. **J Gerontol A Biol Sci Med Sci**, 60, n. 3, p. 324-333, Mar 2005.

35. VISSER, M.; KRITCHEVSKY, S. B.; GOODPASTER, B. H.; NEWMAN, A. B. *et al.* Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the health, aging and body composition study. **J Am Geriatr Soc**, 50, n. 5, p. 897-904, May 2002.

36. WILLIAMS, G. R.; DEAL, A. M.; MUSS, H. B.; WEINBERG, M. S. *et al.* Skeletal muscle measures and physical function in older adults with cancer: sarcopenia or myopenia? **Oncotarget**, 8, n. 20, p. 33658-33665, May 16 2017.

37. WINTERS-STONE, K. M.; HORAK, F.; JACOBS, P. G.; TRUBOWITZ, P. *et al.* Falls, Functioning, and Disability Among Women With Persistent Symptoms of Chemotherapy-Induced Peripheral Neuropathy. **J Clin Oncol**, 35, n. 23, p. 2604-2612, Aug 10 2017.

3.2 ARTIGO 2

Breast cancer survivor condition as moderator of the relationship between physical activity and intramuscular fat content

Anselmo Alves de Oliveira[a], Fernanda Maria Martins[a], Gersiel Nascimento de Oliveira Júnior[a], Jairo de Freitas Rodrigues Souza[a], Paulo Ricardo Prado Nunes[a], Luís Ronan Marquez Ferreira de Souza[a,c], Giovanni Bessa Pereira Lima[c], Fábio Lera Orsatti[a,b*]

[a] Exercise Biology Research Group (BioEx), Federal University of Triangulo Mineiro (UFTM), Uberaba, Minas Gerais, Brazil
[b] Department of Sport Sciences, Health Science Institute, Federal University of Triangulo Mineiro, Uberaba, Minas Gerais, Brazil
[c] Department of Radiology and Diagnostic Imaging, Federal University of Triangulo Mineiro, Uberaba, Minas Gerais, Brazil

*Exercise Biology Research Group (BioEx), 30, avenue Frei-Paulino, Uberaba, Minas Gerais 38025-180, Brazil
Email:fabiorsatti@gmail.com or fabio.orsatti@uftm.edu.br

ABSTRACT

Background: Low physical activity (PA) time has been associated with elevations in intramuscular fat content (IMFC) in specific populations (e.g. diabetics, obesity and rheumatoid arthritis). Such evidence indicates an effect of the pathological condition (i.e. disease and treatment) on the association between PA time and IMFC. However, it is not yet known whether breast cancer survivor (BCS) condition can be a moderator of the relationship between P.A and IMFC.

Objective: to verify whether the relationship between PA time and IMFC is moderate by BCS condition.

Design: Cross-sectional analytical study.

Setting: Women of a cancer treatment center and from a neighborhood association.

Participants: 56 women who had completed BCS (Breast Cancer Survivors - BCS) and 23 control women were volunteers for this study.

Measurements: We performed computed tomography on each study participant to determine IMFC. All volunteers answered questionnaires (sociodemographic data, treatment adopted and PA time) and they were submitted to anthropometric assessment.

Results: BCS and untreated women without a history of cancer presented similar anthropometric and sociodemographic data ($p > 0.05$). However, BCS have a higher IMFC ($p = 0.002$). In the first step of hierarchical regression analysis, the BSC condition and age, but not PA time, were associated IMFC. However, when the interaction term between PA time and BSC condition was added to the regression model, this represented a significant proportion of the variance in IMFC ($\Delta R^2 = 0.05$, $P = 0.031$, $B = 0.004$; CI – 95% = 0.001; 0.008). Examination of the interaction plot showed that at high PA time, IMFC was similar between the conditions (with or without BSC). However, women with low and moderate PA time and BCS had a higher IMFC.

Conclusion: The findings of the present study suggest that PA time and IMFC relationship is moderate, at least in part, by BCS condition.

Keywords: muscle attenuation, skeletal muscle fat, breast cancer survivors, moderation effect, Computed Tomography

INTRODUCTION

Fat accumulation into skeletal muscle can trigger metabolic and cardiovascular diseases as well as functional disabilities (ADDISON; MARCUS; LASTAYO; RYAN, 2014). Furthermore, in some populations (i.e. patients undergoing cancer treatment), elevated intramuscular fat content (IMFC) is associated with hospitalizations and increased mortality (KROENKE; PRADO; MEYERHARDT; WELTZIEN *et al.*, 2018).

Several studies have investigated the causes of elevated IMFC (ADDISON; MARCUS; LASTAYO; RYAN, 2014; MARCUS; ADDISON; KIDDE; DIBBLE *et al.*, 2010). In this sense, aging is identified as one of the main causes of increases in IMFC (DELMONICO; HARRIS; VISSER; PARK *et al.*, 2009; GOODPASTER; CARLSON; VISSER; KELLEY *et al.*, 2001). However, more recent work suggests that increases in IMAT may be more a product of physical inactivity than other factors (e.g. aging) (ADDISON; MARCUS; LASTAYO; RYAN, 2014). Regarding this, low physical activity (PA) time has been associated with elevations in IMFC in specific populations (i.e. diabetics, obesity and rheumatoid arthritis) (ADDISON; MARCUS; LASTAYO; RYAN, 2014; KHOJA; MOORE; GOODPASTER; DELITTO *et al.*, 2018; MARCUS; ADDISON; KIDDE; DIBBLE *et al.*, 2010; TUTTLE; SINACORE; CADE; MUELLER, 2011).

Thus, such evidence has indicated a moderating effect of the pathological condition (i.e. disease and treatment) on the association between PA time and IMFC.

Particularly, patients undergoing to breast cancer treatment (i.e. Breast Cancer Survivors – BCS) have a higher IMFC (BARBALHO; GONZALEZ; BIELEMANN; DA ROCHA *et al.*, 2019; WILLIAMS; DEAL; MUSS; WEINBERG *et al.*, 2017). Concomitantly, chemotherapy and radiotherapy (i.e. frequently therapies used in breast cancer treatment) can mimic the effect of aging and promote changes in metabolic and regenerative muscle cells function and induced an increase in IMFC (AMAYA-MONTOYA; PEREZ-LONDONO; GUATIBONZA-GARCIA; VARGAS-VILLANUEVA *et al.*, 2020; HERRANZ; GIL, 2018; SHAPIRO, 2018). Such changes could modify the magnitude of the late accumulation of IMFC in BCS under similar conditions of PA time. However, whether the BCS condition is a moderator of the relationship between PA time and IMFC has not yet been verified. The answer to this question can help to understand the causes of elevated IMFC in BSC and guide intervention strategies in future studies. Thus, this study aimed to verify whether the relationship between PA time and IMFC is moderate by BSC condition.

METHODS

Study design and participants

This research is an analytical cross-sectional study. For the development of the present study, we recruited patients who had completed BCS (Breast Cancer Survivors – BCS; n = 59) who were followed up at a cancer center, as well as women with the same characteristics (control women; n = 23) from a neighborhood association, both from the city of Uberaba-MG (Brazil). BCS were invited to participate in the study during routine visits to the cancer treatment center. BCS were eligible for the study if BC staging between I-III (early breast cancer). Patients who had not completed BCS were excluded from the study. After applying the eligibility criteria, 79 participants were considered for the analysis (Figure 1). All data were collected in a reserved room of the cancer treatment center (BCS) or a sports gym (control women) from June 2016 to March 2018. All women signed an informed consent form and this study was previously submitted and approved by the Research Ethics Committee of the Federal University of Triangulo Mineiro (UFTM) with protocol number (CAAE: 82691818.0.0000.5154).

Independent variable measurements

Questionnaires

Initially women were questioned about their socio-demographic data, smoking and alcohol habits, diseases and medications. To measure PA and sitting time, the short version of the International Physical Activity Questionnaire (IPAQ) was applied. Clinical data (staging and treatment performed) were self-reported and subsequently checked by hospital staff based on analysis of the patient's medical records.

Anthropometric measurements

Body mass was measured using a 100g precision digital scale (G-life®, São Paulo - Brazil). Height was measured using an inextensible tape measure (10mm accuracy) attached to the wall. Body Mass Index (BMI) was calculated as the ratio between body mass (kg) and height square (m^2) (Obesity: preventing and managing the global epidemic. Report of a WHO consultation, 2000). Waist circumference (WC) was measured as the midpoint between the last costal arch and the iliac crest. Hip circumference (HC) was measured at the largest circumference of the buttocks. The ratio between WC and HC was used to determine waist-to-hip ratio (WHR) (Obesity: preventing and managing the global epidemic. Report of a WHO consultation, 2000).

Measurement of dependent variable

Skeletal muscle fat – Computed Tomography

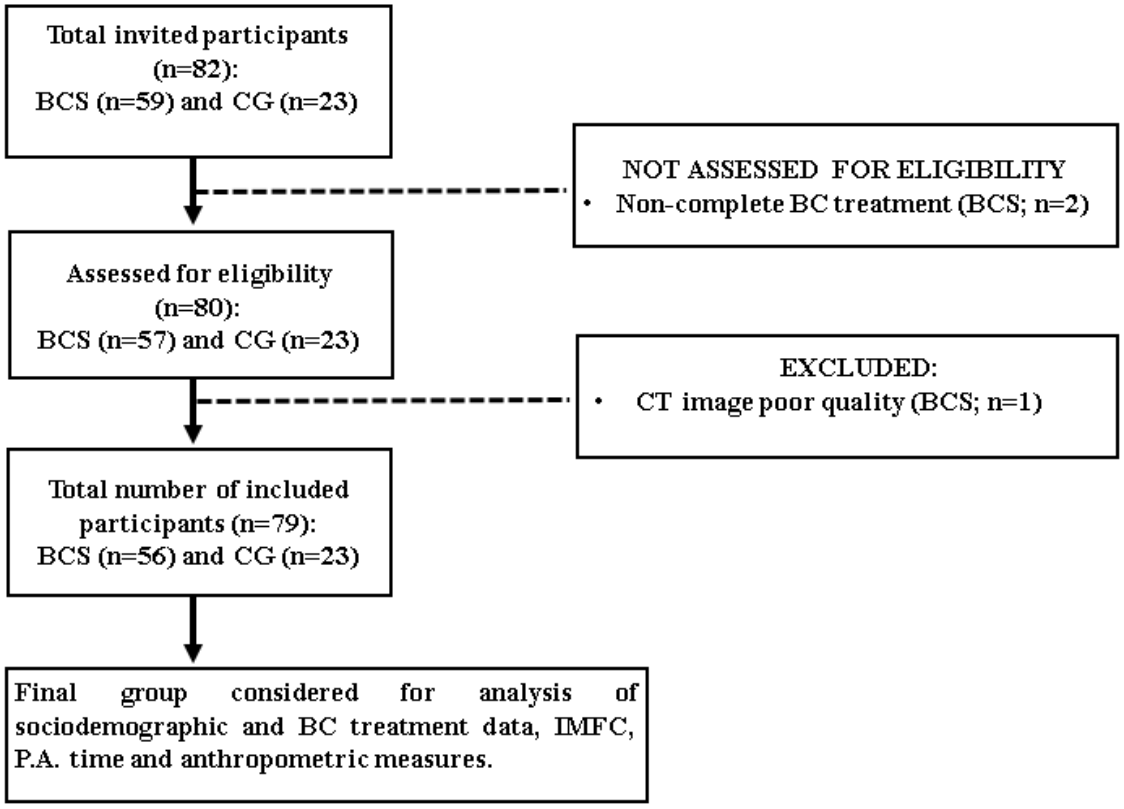
CT images of thing were obtained from multislices tomographys Siemens Somatom Emotion (Siemens Healthineers AG, Munich, Germany) and Toshiba Alexion Advance – TSX-034A (Toshiba Corporation, Tokyo, Japan). A radiologist specializing in musculoskeletal radiography (G.B.P.L) supervised initial collection and analysis of CT parameters. As described by Goodpaster et al. (2001), patients were positioned with their arms above their heads and legs extended on the table (GOODPASTER; CARLSON; VISSER; KELLEY *et al.*, 2001). An anteroposterior scout scan was used to determine the position of the first cut (7cm above the upper edge of the patella). An anteroposterior scout scan was used to determine the position of the first cut (7cm above the upper edge of the patella). Fifty images above the first section were collected, with thickness and spacing between sections of 2mm. The scanning parameters for this image were 120 kVp and 130 mA. Osirix MD ANVISA (version 8.5.2) software was used for analysis of the thigh muscle area and IMFC. Quality analysis was performed on each subject's images to ensure that all images were present, that the proper scanning techniques were used, and that the image was of adequate quality for analysis. For analysis of muscle measurements, we considered the first thigh section in which the rectus femoris muscle was completely visible. IMFC was measured in Quadriceps femoral muscle. For this,

Quadriceps muscle was manually delimited being careful not to include pixels related to intermuscular fat and/or femoral bone. IMFC values were obtained from the muscle attenuation coefficient (the lower the muscle attenuation coefficient the higher the IMFC levels) within the regions delimited in the images and determined by the average pixel intensity in Hounsfield units (HU). All analyzes were performed by the same evaluator. To analyze the reliability of the muscle parameters reading, the intra-class correlation coefficient (ICC) was calculated. For this, IMFC measurements of 10 volunteers were analyzed in triplicate, observing that ICC for quadriceps IMFC were 0.97.

Statistical methods

For sample characterization, continuous variables are presented as mean and standard deviation while categorical variables were presented as frequency measures. Data normality was verified by the Kolmogorov-Smirnov test. Comparison between the conditions was performed in Generalized Linear Models (GLM) by selecting the functions as follows: parametric or nonparametric continuous variables were analyzed by the Linear function and the Log-linked Gamma function, respectively; dichotomous variables were analyzed by binary logistic function; count indicators were analyzed by Poisson linear log function; and ordinal variables by ordinal logistic function (table 1). Then, a hierarchical multiple regression analysis was performed to explain the changes in IMFC. In the first model, PA time, age and BCS condition were considered. In the second model, the P.A time and BCS interaction was added to the first model (Table 2). To estimate the moderation effect, we used a path analysis modeling tool termed Process (HAYES, 2017). The bootstrap sample used was 1000 with bias corrected. Finally, the tertiles of PA time were used for testing the conditional effect of BCS condition on IMFC (table 3 and figure 2). All statistical procedures were performed on IBM SPSS version 23 software (IBM Corporation). Statistical difference considered when $p < 0.05$.

Figure 1. Flow diagram



Legend:
BCS – Breast Cancer Survivors; CG – control group; BC – Breast Cancer; CT – Computed Tomography; IMFC – Intramuscular fat content.

RESULTS

Descriptive characteristics for BCS and CG are presented in Table 1. The results indicate that there was no difference between groups for sociodemographic, anthropometric data and PA time. However, the BCS group had a greater IMFC (i.e. lower muscle attenuation) than CG.

Table 1. Sample characteristics for CG and BCS

	CG (n=23)	BCS (n=56)	p value
Age, years	59.9 ± 7.5	58.5 ± 8.3	0.465
Menopause time, years	13.8 ± 12.3	11.1 ± 8.9	0.336
BMI, kg/m^2	26.2 ± 5.2	27.2 ± 5.1	0.432
WC, cm	89.9 ± 13.1	95.0 ± 13.4	0.131
HC, cm	101.1 ± 10.8	105.3 ± 9.2	0.116
WHR, a.u.	0.90 ± 0.06	0.90 ± 0.09	0.893
Muscle attenuation coefficient, HU	50.3 ± 3.8	46.4 ± 7.6	0.002
PA time, min/week	918.1 ± 919.6	608.4 ± 637.5	0.132
Sitting time, min/week	2660.9 ± 1096.3	2492.1 ± 1264.0	0.554
Number of diseases	1.4 ± 1.2	1.2 ± 1.0	0.489
Number of medicaments	1.5 ± 1.6	2.0 ± 1.5	0.239
Smokers, n (%)	5 (21.7)	21 (36.8)	0.382
Smoked in the past, n (%)	5 (21.7)	21 (36.8)	0.382
Alcohol drinkers, n (%)	6 (26.1)	15 (26.3)	0.949
Marital status, n (%)			0.418
Omitted	2 (8.7)	0	
Single	2 (8.7)	13 (23.2)	
Married	11 (47.8)	25 (44.6)	
Divorced	3 (13.0)	5 (8.9)	
Widow	5 (21.7)	13 (23.2)	
Scholarity, n (%)			0.569
Omitted	2 (8.7)	1 (1.8)	
Elementary school	9 (39.1)	31 (55.3)	
High school	10 (43.5)	14 (25.0)	
College	2 (8.7)	10 (17.9)	
Treatment Characteristics		*BCS (n=56)*	
Time since end of treatment (years)	-	3.3 ± 2.9	
Surgery, n(%)	-	56 (100)	
Radiotherapy, n(%)	-	52 (92.9)	
Quimiotherapy, n(%)	-	35 (62.5)	
Antihormonal Therapy, n(%)	-	41 (73.2)	

Continuous data are presented as mean and standard deviation. Categorical data are presented as a measure of frequency. Normality verified by the Kolmogorov-Smirnov test. Comparison between groups by GLM. CG – Control Group; BCS – Breast Cancer Survivors; kg/m^2 – kilograms per square meter; cm – centimeters; a.u. – arbitrary units; HU – hounsfield unit; PA – physical activity; min/week – minutes per week.

A hierarchical multiple regression analysis was conducted (1 and 2 - table 2) to test whether increased IMFC is a function of multiple risk factors, and more specifically whether BCS condition moderates the relationship between PA time and IMFC. Model 1 indicates that BCS condition and age, but not P.A time (p = 0.587), are independently associated with IMFC and together explain the variance of IMFC in 24%. However, in model 2, the interaction variable (treatment*PA Time) was

independently associated with IMFC (B = 0.004; CI – 95% = 0.001; 0.008) and increased the model's predictive power by 5% (p = 0.031) (moderator effect).

Table 2. Hierarchical multiple regression analysis to explain changes in the muscle attenuation coefficient (IMFC)

	B	R^2	P
Model 1		0.24	<0.001
Treatment	-4.179 (-6.870; -1.530)		0.009
PA time	0.001 (-0.001; 0.003)		0.587
Age	-0.563 (-0.513; -0.200)		<0.001
Model 2		0.29	<0.001
Treatment	-4.535 (-7.308; -1.761)		0.002
PA time	0.001 (-0.001; 0.004)		0.338
Treatment*PA time	0.004 (0.001; 0.008)		0.039
Age	-0.375 (-0.530; -0.221)		<0.001
Increase due to interaction		0.05	0.031

Models of multiple linear regression. Statistical data of the model: B - non-standardized coefficient; CI – 95% - 95% confidence interval; R^2 determination coefficient. IMFC – intramuscular fat content; PA – physical activity; *interaction variable between treatment and PA time.

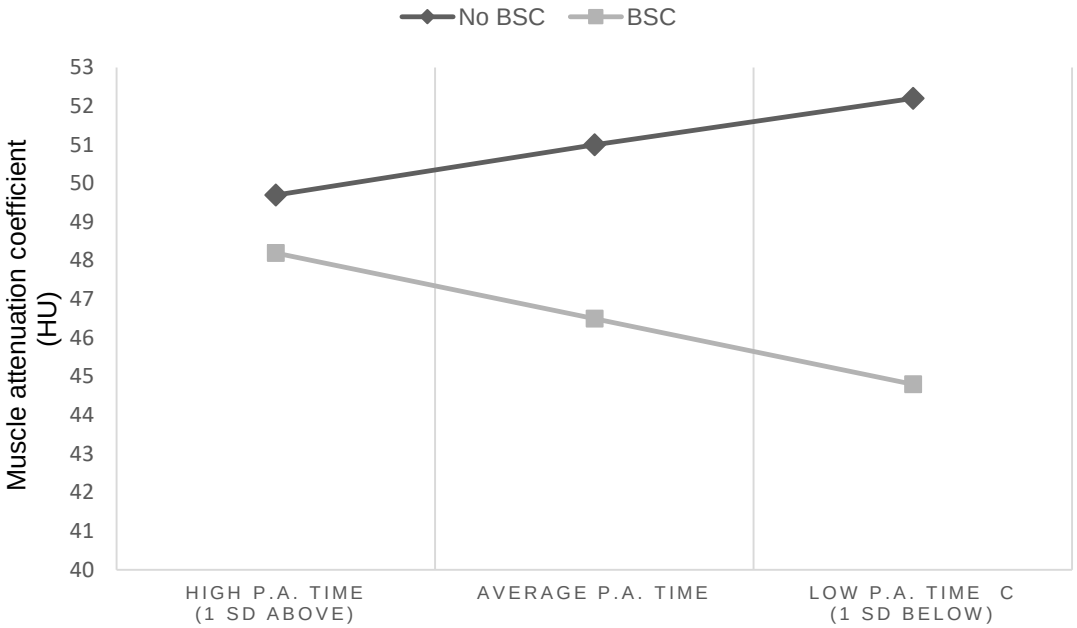
Examination of the interaction plot showed (Figure 2) an enhancing effect that as PA time decreased, IMFC increased in BCS. At high PA time, IMFC was similar between the conditions (with or without BSC). However, BCS with lower PA time had a higher IMFC (Table 3).

Table 3. Difference between groups in muscle attenuation coefficient (IMFC) at tertiles of the PA time

Tertiles of PA time	B (IC of 95%)
Low PA time (1 S.D. below)	-7.4 (-11.7; -3.2)
Average PA time	-4.5 (-7.5; -1.5)
High PA time (1 S.D. above)	-1.5 (-5.4; 2.4)

Single linear regression. Statistical data of the model: B - non-standardized coefficient; CI – 95% - 95% confidence interval; S.D. – standart deviation) IMFC – intramuscular fat content; PA – physical activity.

Figure 2. Muscle attenuation coefficient (IMFC) at tertiles of the PA time in both groups.



Correlation coefficient. IMFC – intramuscular fat content; HU – Hounsfield unit; PA – physical activity; SD – standard deviation

DISCUSSION

The finding of our study suggests that the relationship between PA time and IMFC is moderate by BCS condition. Given the implications related to the increase in IMFC, the findings of our study are clinically relevant. Health professionals must be aware of the implications of PA time on IMFC in BCs. Thus, our findings may help to guide intervention strategies in BCs in future studies.

In the current study, the comparison between the groups revealed a greater IMFC in the BCS when compared to the CG (table 1). Other studies have also identified elevations in IMFC in BCS (RIER; JAGER; SLEIJFER; VAN ROSMALEN *et al.*, 2018; WEINBERG; SHACHAR; MUSS; DEAL *et al.*, 2018). Other pathological conditions are also associated with an increase in IMFC, which suggests negative implications of the disease / treatment condition on muscle composition (i.e. on IMFC) (ADDISON; MARCUS; LASTAYO; RYAN, 2014; KHOJA; MOORE; GOODPASTER; DELITTO *et al.*, 2018; TUTTLE; SINACORE; CADE; MUELLER, 2011).

To our knowledge, to date, no study has assessed the moderating role of specific conditions (e.g. BCS) in the relationship between PA time and IMFC. In this sense, our data demonstrated that there was no relationship between PA time and IMFC when all women (i.e. BCS condition and control group) were analyzed together (table 2 - model 1). We also did not observe a direct (i.e. bivariate) relationship between PA time and IMFC (table 2 - models 1 and 2). However, the BCS condition* PA time interaction variable was associated with changes in IMFC ($p = 0.039$) in model 2 (i.e. moderating effect) and its inclusion increased the predictive power of IMFC of this model by 5% when compared to the model without the interaction variable ($p = 0.031$). Moreover, such moderating effect (i.e. by BCS condition) was observed even after adjusting for age, a factor previously associated with increased IMFC (ADDISON; MARCUS; LASTAYO; RYAN, 2014; DELMONICO; HARRIS; VISSER; PARK *et al.*, 2009; GOODPASTER; CARLSON; VISSER; KELLEY *et al.*, 2001). Interestingly, we observed that after standardization for tertiles of the PA time, BCS condition had a higher IMFC for low and moderate PA time (table 3 and figure 2). These results support our hypothesis that the relationship between PA time and IMFC is moderated by BCS condition. It has been indicated that therapies frequently used in the BC treatment (i.e. chemotherapy and radiotherapy) can generate damage to cellular DNA and favor the accumulation of senescent cells (AMAYA-MONTOYA; PEREZ-LONDONO; GUATIBONZA-GARCIA; VARGAS-VILLANUEVA *et al.*, 2020; HERRANZ; GIL, 2018). Indeed, chemotherapy can perpetuate changes in tissue function similar to aging (SHAPIRO, 2018). Cell senescence has been associated with changes in metabolic and stem cells (e.g. satellite cells) function (AMAYA-MONTOYA; PEREZ-LONDONO; GUATIBONZA-GARCIA; VARGAS-VILLANUEVA *et al.*, 2020). Satellite Cells are

population of small mononucleated muscle stem cells crucial for skeletal muscle growth and regeneration (DUMONT; WANG; RUDNICKI, 2015). It has been suggested that in pathological conditions and aging, satellite cells may enter an alternative route, differentiate into adipogenic cells and lead to an increase in IMFC (VETTOR; MILAN; FRANZIN; SANNA *et al.*, 2009). Although we can only speculate, the previous findings indicate that BC treatment therapies can mimic the effect of aging and perpetuate changes (i.e. metabolic and satellite cells function) that induce an increase in IMFC. Such remodeling in muscle tissue may explain the fact that BCS condition has a higher IMFC than a population not submitted to BC treatment when PA time (i.e. low and moderate) are equalized. However, randomized clinical trials are needed to test whether BC treatment increases IMFC even when PA time is standardized. We also observed that for high PA time, BCS have similar values of IMFC. These findings indicate that BCS may require longer PA time than healthy individuals to equalize IMFC.

Taking into account the negative implications related to the increase in the IMFC, our results point to the need for intervention strategies aimed at stimulating the increase in the time of PA to reduce the IMFC in BCS. In fact, a higher volume of weekly PA can reduce body fat indicators (FRIEDENREICH; NEILSON; O'REILLY; DUHA *et al.*, 2015). However, randomized clinical studies are needed to verify whether high volumes of PA time can reduce IMFC among BCS.

The present study is not without its limitations. Considering the influence of PA time on IMFC, the use of an indirect measure to assess PA time may have impaired the quantification. In fact, IPAQ measures may overestimate the amount of PA among cancer survivors (RUIZ-CASADO; ALEJO; SANTOS-LOZANO; SORIA *et al.*, 2016). However, even if overestimated, we demonstrated that the PA time among BCS women was similar to that performed by a standard population (i.e. CG). Such PA measures, allowed us to understand the moderation effect of BCS about PA time and IMFC relation. Even so, studies with objective measures of PA are necessary and, our hypothesis is that these studies can further strengthen our findings.

CONCLUSION

The findings of the present study suggest that the relationship between PA time and IMFC is moderate by BCS condition.

REFERENCES

1. ADDISON, O.; MARCUS, R. L.; LASTAYO, P. C.; RYAN, A. S. Intermuscular fat: a review of the consequences and causes. **Int J Endocrinol**, 2014, p. 309570, 2014.

2. AMAYA-MONTOYA, M.; PEREZ-LONDONO, A.; GUATIBONZA-GARCIA, V.; VARGAS-VILLANUEVA, A. *et al.* Cellular Senescence as a Therapeutic Target for Age-Related Diseases: A Review. **Adv Ther**, 37, n. 4, p. 1407-1424, Apr 2020.

3. BARBALHO, E. R.; GONZALEZ, M. C.; BIELEMANN, R. M.; DA ROCHA, I. M. G. *et al.* Is skeletal muscle radiodensity able to indicate physical function impairment in older adults with gastrointestinal cancer? **Exp Gerontol**, 125, p. 110688, Oct 1 2019.

4. DELMONICO, M. J.; HARRIS, T. B.; VISSER, M.; PARK, S. W. *et al.* Longitudinal study of muscle strength, quality, and adipose tissue infiltration. **Am J Clin Nutr**, 90, n. 6, p. 1579-1585, Dec 2009.

5. DUMONT, N. A.; WANG, Y. X.; RUDNICKI, M. A. Intrinsic and extrinsic mechanisms regulating satellite cell function. **Development**, 142, n. 9, p. 1572-1581, May 1 2015.

6. FRIEDENREICH, C. M.; NEILSON, H. K.; O'REILLY, R.; DUHA, A. *et al.* Effects of a High vs Moderate Volume of Aerobic Exercise on Adiposity Outcomes in Postmenopausal Women: A Randomized Clinical Trial. **JAMA Oncol**, 1, n. 6, p. 766-776, Sep 2015.

7. GOODPASTER, B. H.; CARLSON, C. L.; VISSER, M.; KELLEY, D. E. *et al.* Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. **J Appl Physiol (1985)**, 90, n. 6, p. 2157-2165, Jun 2001.

8. HAYES, A. F. **Introduction to mediation, moderation, and conditional process analysis: A regression-based approach**. Guilford publications, 2017. 1462534651.

9. HERRANZ, N.; GIL, J. Mechanisms and functions of cellular senescence. **J Clin Invest**, 128, n. 4, p. 1238-1246, Apr 2 2018.

10. KHOJA, S. S.; MOORE, C. G.; GOODPASTER, B. H.; DELITTO, A. *et al.* Skeletal Muscle Fat and Its Association With Physical Function in Rheumatoid Arthritis. **Arthritis Care Res (Hoboken)**, 70, n. 3, p. 333-342, Mar 2018.

11. KROENKE, C. H.; PRADO, C. M.; MEYERHARDT, J. A.; WELTZIEN, E. K. *et al.* Muscle radiodensity and mortality in patients with colorectal cancer. **Cancer**, 124, n. 14, p. 3008-3015, Jul 15 2018.

12. MARCUS, R. L.; ADDISON, O.; KIDDE, J. P.; DIBBLE, L. E. *et al.* Skeletal muscle fat infiltration: impact of age, inactivity, and exercise. **J Nutr Health Aging**, 14, n. 5, p. 362-366, May 2010.

13. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. **World Health Organ Tech Rep Ser**, 894, p. i-xii, 1-253, 2000.

14. RIER, H. N.; JAGER, A.; SLEIJFER, S.; VAN ROSMALEN, J. *et al.* Changes in body composition and muscle attenuation during taxane-based chemotherapy in patients with metastatic breast cancer. **Breast Cancer Res Treat**, 168, n. 1, p. 95-105, Feb 2018.

15. RUIZ-CASADO, A.; ALEJO, L. B.; SANTOS-LOZANO, A.; SORIA, A. *et al.* Validity of the Physical Activity Questionnaires IPAQ-SF and GPAQ for Cancer Survivors: Insights from a Spanish Cohort. **Int J Sports Med**, 37, n. 12, p. 979-985, Nov 2016.

16. SHAPIRO, C. L. Cancer Survivorship. **N Engl J Med**, 379, n. 25, p. 2438-2450, Dec 20 2018.

17. TUTTLE, L. J.; SINACORE, D. R.; CADE, W. T.; MUELLER, M. J. Lower physical activity is associated with higher intermuscular adipose tissue in people with type 2 diabetes and peripheral neuropathy. **Phys Ther**, 91, n. 6, p. 923-930, Jun 2011.

18. VETTOR, R.; MILAN, G.; FRANZIN, C.; SANNA, M. *et al.* The origin of intermuscular adipose tissue and its pathophysiological implications. **Am J Physiol Endocrinol Metab**, 297, n. 5, p. E987-998, Nov 2009.

19. WEINBERG, M. S.; SHACHAR, S. S.; MUSS, H. B.; DEAL, A. M. *et al.* Beyond sarcopenia: Characterization and integration of skeletal muscle quantity and radiodensity in a curable breast cancer population. **Breast J**, 24, n. 3, p. 278-284, May 2018.

20. WILLIAMS, G. R.; DEAL, A. M.; MUSS, H. B.; WEINBERG, M. S. *et al.* Skeletal muscle measures and physical function in older adults with cancer: sarcopenia or myopenia? **Oncotarget**, 8, n. 20, p. 33658-33665, May 16 2017.

4. CONSIDERAÇÕE FINAIS

O objetivo geral deste trabalho foi compreender as alterações do CGI e interpretar suas implicações sobre a FF de mulheres SCM. Para responder a este objetivo nós conduzimos dois estudos (artigos 1 e 2). Os objetivos específicos do artigo 1 foram: verificar quais fatores (i.e. massa e força musculares; e atividade física) são concomitantemente alterados com o CGI em SCM; e verificar se o CGI é um mediador da relação entre SCM e a FF mais baixa, independentemente de fatores de confusão. Neste sentido, nossos resultados (artigo 1) indicaram que a elevação do CGI ocorre simultaneamente à redução dos níveis de força, mas que o CGI é um mediador da relação entre SCM e baixa FF, independentemente da força muscular. No entanto, este efeito mediador é influenciado pela especificidade do teste realizado. Considerando as implicações da baixa FF sobre a qualidade e tempo de sobrevida de SCM, estes achados sugerem que estratégias de prevenção e intervenção precisam ser adotadas no intuito de reduzir o CGI em SCM. Adicionalmente, o objetivo específico do artigo 2 foi: verificar se a relação entre o tempo de atividade física e o CGI é moderado pela condição de SCM. Neste sentido, nossos resultados (artigo 2) indicaram que a condição SCM atua como um fator moderador da relação entre o CGI e o tempo de atividade física; evidenciado com a identificação de maior CGI entre SCM para níveis semelhantes de atividade física de mulheres não tratadas para o Câncer de Mama. Estes achados sugerem que SCM podem requerer intervenções específicas, baseadas em altos níveis de atividade física, para equalização do CGI. Juntos estes achados indicam que o CGI está associado a uma menor FF em SCM, e que, a prática de altos níveis de AF pode ser um importante fator preventivo ou de intervenção para evitar/tratar elevações do CGI em SCM.

5. CONCLUSÃO

A partir do previamente exposto, concluímos que o CGI é um mediador da relação entre SCM e a baixa FF, independentemente dos níveis de força muscular. Ademais, concluímos que a condição SCM é moderador da relação entre CGI e tempo de atividade física.

6. REFERÊNCIAS BIBLIOGRÁFICAS

ADDISON, O.; MARCUS, R. L.; LASTAYO, P. C.; RYAN, A. S. Intermuscular fat: a review of the consequences and causes. **Int J Endocrinol**, 2014, p. 309570, 2014.

AMAYA-MONTOYA, M.; PEREZ-LONDONO, A.; GUATIBONZA-GARCIA, V.; VARGAS-VILLANUEVA, A. *et al.* Cellular Senescence as a Therapeutic Target for Age-Related Diseases: A Review. **Adv Ther**, 37, n. 4, p. 1407-1424, Apr 2020.

AMINI, B.; BOYLE, S. P.; BOUTIN, R. D.; LENCHIK, L. Approaches to Assessment of Muscle Mass and Myosteatosis on Computed Tomography: A Systematic Review. **J Gerontol A Biol Sci Med Sci**, 74, n. 10, p. 1671-1678, Sep 15 2019.

AUBREY, J.; ESFANDIARI, N.; BARACOS, V. E.; BUTEAU, F. A. *et al.* Measurement of skeletal muscle radiation attenuation and basis of its biological variation. **Acta Physiol (Oxf)**, 210, n. 3, p. 489-497, Mar 2014.

BARBALHO, E. R.; GONZALEZ, M. C.; BIELEMANN, R. M.; DA ROCHA, I. M. G. *et al.* Is skeletal muscle radiodensity able to indicate physical function impairment in older adults with gastrointestinal cancer? **Exp Gerontol**, 125, p. 110688, Oct 1 2019.

BASU P; LUCAS E; CARVALHO AL; SAUVAGET C *et al.* **Cancer Screening in Five Continents**. 2019. Disponível em: https://canscreen5.iarc.fr.

BRAITHWAITE, D.; SATARIANO, W. A.; STERNFELD, B.; HIATT, R. A. *et al.* Long-term prognostic role of functional limitations among women with breast cancer. **J Natl Cancer Inst**, 102, n. 19, p. 1468-1477, Oct 6 2010.

BRAY, F.; FERLAY, J.; SOERJOMATARAM, I.; SIEGEL, R. L. *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. **CA Cancer J Clin**, 68, n. 6, p. 394-424, Nov 2018.

CAMPBELL, K. L.; WINTERS-STONE, K. M.; WISKEMANN, J.; MAY, A. M. *et al.* Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. **Med Sci Sports Exerc**, 51, n. 11, p. 2375-2390, Nov 2019.

COEN, P. M.; GOODPASTER, B. H. Role of intramyocelluar lipids in human health. **Trends Endocrinol Metab**, 23, n. 8, p. 391-398, Aug 2012.

CRUZ-JENTOFT, A. J.; BAHAT, G.; BAUER, J.; BOIRIE, Y. *et al.* Sarcopenia: revised European consensus on definition and diagnosis. **Age Ageing**, 48, n. 4, p. 601, Jul 1 2019.

DE MOOR, J. S.; MARIOTTO, A. B.; PARRY, C.; ALFANO, C. M. *et al.* Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. **Cancer Epidemiol Biomarkers Prev**, 22, n. 4, p. 561-570, Apr 2013.

DELMONICO, M. J.; HARRIS, T. B.; VISSER, M.; PARK, S. W. *et al.* Longitudinal study of muscle strength, quality, and adipose tissue infiltration. **Am J Clin Nutr**, 90, n. 6, p. 1579-1585, Dec 2009.

DELUCHE, E.; LEOBON, S.; DESPORT, J. C.; VENAT-BOUVET, L. *et al.* Impact of body composition on outcome in patients with early breast cancer. **Support Care Cancer**, 26, n. 3, p. 861-868, Mar 2018.

FERRUCCI, L.; COOPER, R.; SHARDELL, M.; SIMONSICK, E. M. *et al.* Age-Related Change in Mobility: Perspectives From Life Course Epidemiology and Geroscience. **J Gerontol A Biol Sci Med Sci**, 71, n. 9, p. 1184-1194, Sep 2016.

FREIRE, A. N.; GUERRA, R. O.; ALVARADO, B.; GURALNIK, J. M. *et al.* Validity and reliability of the short physical performance battery in two diverse older adult populations in Quebec and Brazil. **J Aging Health**, 24, n. 5, p. 863-878, Aug 2012.

GILLIES, A. R.; LIEBER, R. L. Structure and function of the skeletal muscle extracellular matrix. **Muscle Nerve**, 44, n. 3, p. 318-331, Sep 2011.

GOODPASTER, B. H.; CARLSON, C. L.; VISSER, M.; KELLEY, D. E. *et al.* Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. **J Appl Physiol (1985)**, 90, n. 6, p. 2157-2165, Jun 2001.

GOODPASTER, B. H.; CHOMENTOWSKI, P.; WARD, B. K.; ROSSI, A. *et al.* Effects of physical activity on strength and skeletal muscle fat infiltration in older adults: a randomized controlled trial. **J Appl Physiol (1985)**, 105, n. 5, p. 1498-1503, Nov 2008.

GOODPASTER, B. H.; KRISHNASWAMI, S.; RESNICK, H.; KELLEY, D. E. *et al.* Association between regional adipose tissue distribution and both type 2 diabetes and impaired glucose tolerance in elderly men and women. **Diabetes Care**, 26, n. 2, p. 372-379, Feb 2003.

GUIDA, J. L.; AHLES, T. A.; BELSKY, D.; CAMPISI, J. *et al.* Measuring Aging and Identifying Aging Phenotypes in Cancer Survivors. **J Natl Cancer Inst**, 111, n. 12, p. 1245-1254, Dec 1 2019.

HERRANZ, N.; GIL, J. Mechanisms and functions of cellular senescence. **J Clin Invest**, 128, n. 4, p. 1238-1246, Apr 2 2018.

HEWITT, M.; ROWLAND, J. H.; YANCIK, R. Cancer survivors in the United States: age, health, and disability. **J Gerontol A Biol Sci Med Sci**, 58, n. 1, p. 82-91, Jan 2003.

HUY, C.; SCHMIDT, M. E.; VRIELING, A.; CHANG-CLAUDE, J. *et al.* Physical activity in a German breast cancer patient cohort: one-year trends and characteristics associated with change in activity level. **Eur J Cancer**, 48, n. 3, p. 297-304, Feb 2012.

IBRAHIM, K.; MAY, C.; PATEL, H. P.; BAXTER, M. *et al.* A feasibility study of implementing grip strength measurement into routine hospital practice (GRImP): study protocol. **Pilot Feasibility Stud**, 2, p. 27, 2016.

INCA. A situação do câncer de mama no Brasil: síntese de dados dos sistemas de informação. 2019.

INSTITUTE, N. C. National Cancer Institute. Office of Cancer Survivorship 2018.

KHOJA, S. S.; MOORE, C. G.; GOODPASTER, B. H.; DELITTO, A. *et al.* Skeletal Muscle Fat and Its Association With Physical Function in Rheumatoid Arthritis. **Arthritis Care Res (Hoboken)**, 70, n. 3, p. 333-342, Mar 2018.

KIM, W. J.; KIM, J. W.; MOON, Y. J.; KIM, S. H. *et al.* The photoplethysmographic amplitude to pulse pressure ratio can track sudden changes in vascular compliance and resistance during liver graft reperfusion: A beat-to-beat analysis. **Medicine (Baltimore)**, 96, n. 22, p. e7045, Jun 2017.

KLASSEN, O.; SCHMIDT, M. E.; ULRICH, C. M.; SCHNEEWEISS, A. *et al.* Muscle strength in breast cancer patients receiving different treatment regimes. **J Cachexia Sarcopenia Muscle**, 8, n. 2, p. 305-316, Apr 2017.

KROGER, S. Proprioception 2.0: novel functions for muscle spindles. **Curr Opin Neurol**, 31, n. 5, p. 592-598, Oct 2018.

KUBO, Y.; NAITO, T.; MORI, K.; OSAWA, G. *et al.* Skeletal muscle loss and prognosis of breast cancer patients. **Support Care Cancer**, 25, n. 7, p. 2221-2227, Jul 2017.

LUCAS, A. R.; LEVINE, B. J.; AVIS, N. E. Posttreatment trajectories of physical activity in breast cancer survivors. **Cancer**, 123, n. 14, p. 2773-2780, Jul 15 2017.

MALENFANT, P.; JOANISSE, D. R.; THERIAULT, R.; GOODPASTER, B. H. *et al.* Fat content in individual muscle fibers of lean and obese subjects. **Int J Obes Relat Metab Disord**, 25, n. 9, p. 1316-1321, Sep 2001.

MANINI, T. M.; CLARK, B. C. Dynapenia and aging: an update. **J Gerontol A Biol Sci Med Sci**, 67, n. 1, p. 28-40, Jan 2012.

MANINI, T. M.; CLARK, B. C.; NALLS, M. A.; GOODPASTER, B. H. *et al.* Reduced physical activity increases intermuscular adipose tissue in healthy young adults. **Am J Clin Nutr**, 85, n. 2, p. 377-384, Feb 2007.

MARCUS, R. L.; ADDISON, O.; KIDDE, J. P.; DIBBLE, L. E. *et al.* Skeletal muscle fat infiltration: impact of age, inactivity, and exercise. **J Nutr Health Aging**, 14, n. 5, p. 362-366, May 2010.

MARINAC, C.; PATTERSON, R. E.; VILLASENOR, A.; FLATT, S. W. *et al.* Mechanisms of association between physical functioning and breast cancer mortality: evidence from the Women's Healthy Eating and Living Study. **J Cancer Surviv**, 8, n. 3, p. 402-409, Sep 2014.

MILJKOVIC, I.; ZMUDA, J. M. Epidemiology of myosteatosis. **Curr Opin Clin Nutr Metab Care**, 13, n. 3, p. 260-264, May 2010.

NEIL-SZTRAMKO, S. E.; KIRKHAM, A. A.; HUNG, S. H.; NIKSIRAT, N. *et al.* Aerobic capacity and upper limb strength are reduced in women diagnosed with breast cancer: a systematic review. **J Physiother**, 60, n. 4, p. 189-200, Dec 2014.

Obesity: preventing and managing the global epidemic. Report of a WHO consultation. **World Health Organ Tech Rep Ser**, 894, p. i-xii, 1-253, 2000.

REINDERS, I.; MURPHY, R. A.; KOSTER, A.; BROUWER, I. A. *et al.* Muscle Quality and Muscle Fat Infiltration in Relation to Incident Mobility Disability and Gait Speed Decline: the Age, Gene/Environment Susceptibility-Reykjavik Study. **J Gerontol A Biol Sci Med Sci**, 70, n. 8, p. 1030-1036, Aug 2015.

RIER, H. N.; JAGER, A.; SLEIJFER, S.; VAN ROSMALEN, J. *et al.* Changes in body composition and muscle attenuation during taxane-based chemotherapy in patients with metastatic breast cancer. **Breast Cancer Res Treat**, 168, n. 1, p. 95-105, Feb 2018.

ROBERTS, H. C.; DENISON, H. J.; MARTIN, H. J.; PATEL, H. P. *et al.* A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. **Age Ageing**, 40, n. 4, p. 423-429, Jul 2011.

SCHMIDT, M. E.; WISKEMANN, J.; ULRICH, C. M.; SCHNEEWEISS, A. *et al.* Self-reported physical activity behavior of breast cancer survivors during and after adjuvant therapy: 12 months follow-up of two randomized exercise intervention trials. **Acta Oncol**, 56, n. 4, p. 618-627, Apr 2017.

SCHURR, K.; SHERRINGTON, C.; WALLBANK, G.; PAMPHLETT, P. *et al.* The minimum sit-to-stand height test: reliability, responsiveness and relationship to leg muscle strength. **Clin Rehabil**, 26, n. 7, p. 656-663, Jul 2012.

SHACHAR, S. S.; DEAL, A. M.; WEINBERG, M.; NYROP, K. A. *et al.* Skeletal Muscle Measures as Predictors of Toxicity, Hospitalization, and Survival in Patients with Metastatic Breast Cancer Receiving Taxane-Based Chemotherapy. **Clin Cancer Res**, 23, n. 3, p. 658-665, Feb 1 2017.

SHAPIRO, C. L. Cancer Survivorship. **N Engl J Med**, 379, n. 25, p. 2438-2450, Dec 20 2018.

SHAPIRO, C. L. Cancer Survivorship. Reply. **N Engl J Med**, 380, n. 14, p. 1382, Apr 4 2019.

SHIN, W. K.; SONG, S.; JUNG, S. Y.; LEE, E. *et al.* The association between physical activity and health-related quality of life among breast cancer survivors. **Health Qual Life Outcomes**, 15, n. 1, p. 132, Jun 30 2017.

SOCIETY, A. C. **American Cancer Society. Cancer Facts & Figures 2018**. American Cancer Society, p. 71. 2018.

SOCIETY, A. C. Cancer facts and figures. **American Cancer Society.** 2019.

SONG, M. Y.; RUTS, E.; KIM, J.; JANUMALA, I. *et al.* Sarcopenia and increased adipose tissue infiltration of muscle in elderly African American women. **Am J Clin Nutr**, 79, n. 5, p. 874-880, May 2004.

SOTO-PEREZ-DE-CELIS, E.; LI, D.; YUAN, Y.; LAU, Y. M. *et al.* Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer. **Lancet Oncol**, 19, n. 6, p. e305-e316, Jun 2018.

SPAGNUOLO, D. L.; JURGENSEN, S. P.; IWAMA, A. M.; DOURADO, V. Z. Walking for the assessment of balance in healthy subjects older than 40 years. **Gerontology**, 56, n. 5, p. 467-473, 2010.

STEHNO-BITTEL, L. Intricacies of fat. **Phys Ther**, 88, n. 11, p. 1265-1278, Nov 2008.

SWEENEY, C.; SCHMITZ, K. H.; LAZOVICH, D.; VIRNIG, B. A. *et al.* Functional limitations in elderly female cancer survivors. **J Natl Cancer Inst**, 98, n. 8, p. 521-529, Apr 19 2006.

TIELAND, M.; TROUWBORST, I.; CLARK, B. C. Skeletal muscle performance and ageing. **J Cachexia Sarcopenia Muscle**, 9, n. 1, p. 3-19, Feb 2018.

TUTTLE, L. J.; SINACORE, D. R.; CADE, W. T.; MUELLER, M. J. Lower physical activity is associated with higher intermuscular adipose tissue in people with type 2 diabetes and peripheral neuropathy. **Phys Ther**, 91, n. 6, p. 923-930, Jun 2011.

VISSER, M.; GOODPASTER, B. H.; KRITCHEVSKY, S. B.; NEWMAN, A. B. *et al.* Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. **J Gerontol A Biol Sci Med Sci**, 60, n. 3, p. 324-333, Mar 2005.

VISSER, M.; KRITCHEVSKY, S. B.; GOODPASTER, B. H.; NEWMAN, A. B. *et al.* Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the health, aging and body composition study. **J Am Geriatr Soc**, 50, n. 5, p. 897-904, May 2002.

WEINBERG, M. S.; SHACHAR, S. S.; MUSS, H. B.; DEAL, A. M. *et al.* Beyond sarcopenia: Characterization and integration of skeletal muscle quantity and radiodensity in a curable breast cancer population. **Breast J**, 24, n. 3, p. 278-284, May 2018.

WILDIERS, H.; HEEREN, P.; PUTS, M.; TOPINKOVA, E. *et al.* International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. **J Clin Oncol**, 32, n. 24, p. 2595-2603, Aug 20 2014.

WILLIAMS, G. R.; DEAL, A. M.; MUSS, H. B.; WEINBERG, M. S. *et al.* Skeletal muscle measures and physical function in older adults with cancer: sarcopenia or myopenia? **Oncotarget**, 8, n. 20, p. 33658-33665, May 16 2017.

WINTERS-STONE, K. M.; HORAK, F.; JACOBS, P. G.; TRUBOWITZ, P. *et al.* Falls, Functioning, and Disability Among Women With Persistent Symptoms of Chemotherapy-Induced Peripheral Neuropathy. **J Clin Oncol**, 35, n. 23, p. 2604-2612, Aug 10 2017.

WROBLEWSKI, A. P.; AMATI, F.; SMILEY, M. A.; GOODPASTER, B. *et al.* Chronic exercise preserves lean muscle mass in masters athletes. **Phys Sportsmed**, 39, n. 3, p. 172-178, Sep 2011.