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INTERVENCIÓN MULTIMODAL EN LA FATIGA INDUCIDA POR EL CÁNCER DE MAMA MEDIANTE UN PROGRAMA DE FISIOTERAPIA Y EJERCICIO FÍSICO

MULTIMODAL INTERVENTIONS IN FATIGUE-RELATED BY BREAST CANCER THROUGH A PROGRAM OF PHYSICAL THERAPY AND PHYSICAL EXERCISE

DEPARTAMENTO DE FISIOTERAPIA

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Que la tesis doctoral titulada: "***Intervención multimodal en la fatiga inducida por el cáncer de mama mediante un programa de fisioterapia y ejercicios***" que presenta D. Irene Cantarero Villanueva al superior juicio del Tribunal que designe la Universidad de Granada, ha sido realizada bajo mi dirección durante los años 2009-2011, siendo expresión de la capacidad técnica e interpretativa de su autora en condiciones tan aventajadas que le hacen merecedora del Título de Doctor con mención Europea, siempre y cuando así lo considere el citado Tribunal.

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En Granada, 9 de Noviembre de 2011

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A mi gran familia

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Cantarero-Villanueva I, Fernández-Lao C, Fernández-DE-Las-Peñas C, Díaz-Rodríguez L, Sanchez-Cantalejo E, Arroyo-Morales M. Associations among musculoskeletal impairments, depression, body image and fatigue in breast cancer survivors within the first year after treatment. Eur J Cancer Care (Engl). 2011 Sep;20(5):632-9

Fernández-Lao C, Cantarero-Villanueva I, Fernández-de-Las-Peñas C, Del Moral-Ávila R, Castro-Sánchez AM, Arroyo-Morales M. Effectiveness of a Multidimensional Physical Therapy Program on Pain, Pressure Hypersensitivity, and Trigger Points in Breast Cancer Survivors: A Randomized Controlled Clinical Trial. Clin J Pain. 2011 Jun 23

Galiano-Castillo N, Fernández-Lao C, Cantarero-Villanueva I, Fernández-de-Las-Peñas C, Menjón-Beltrán S, Arroyo-Morales M. Altered pattern of cervical muscle activation during performance of a functional upper limb task in breast cancer survivors. Am J Phys Med Rehabil. 2011 May;90(5):349-55

Fernández-Lao C, Cantarero-Villanueva I, Díaz-Rodríguez L, Cuesta-Vargas AI, Fernández-De-las-Peñas C, Arroyo-Morales M. Attitudes towards massage modify effects of manual therapy in breast cancer survivors: a randomised clinical trial with crossover design. Eur J Cancer Care (Engl). 2011 Nov[Epub ahead of print]

Cantarero-Villanueva I, Fernández-Lao C, Del Moral-Avila R, Fernández-de-Las-Peñas C, Feriche-Fernández-Castanys MB, Arroyo-Morales M. Effectiveness of core stability exercises and recovery myofascial release massage on fatigue in breast cancer survivors: a randomized controlled clinical trial. Evid Based Complement Alternat Med. 2012;2012:620619. Epub 2011 Jul 17

Fernández-de-Las-Peñas C, Fernández-Lao C, Cantarero-Villanueva I, Ambite-Quesada S, Rivas-Martínez I, Del Moral-Avila R, Arroyo-Morales M. Catechol-O-methyltransferase genotype (Val158met) modulates cancer-related fatigue and pain sensitivity in breast cancer survivors. Breast Cancer Res Treat. 2011 Sep 4

Fernández-de-Las-Peñas C, Cantarero-Villanueva I, Fernández-Lao C, Ambite-Quesada S, Díaz-Rodríguez L, Rivas-Martínez I, Moral-Avila RD, Arroyo-Morales M. Influence of catechol-o-methyltransferase genotype (Val158Met) on endocrine, sympathetic nervous and mucosal immune systems in breast cancer survivors. Breast. 2011 Oct 4

Fernández-Lao C, Cantarero-Villanueva I, Díaz-Rodríguez L, Fernández-de-Las-Peñas C, Sánchez-Salado C, Arroyo-Morales M. The Influence of Patient Attitude Toward Massage on Pressure Pain Sensitivity and Immune System after Application of Myofascial Release in Breast Cancer Survivors: A Randomized, Controlled Crossover Study. J Manipulative Physiol Ther. 2011 Oct 20

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Cantarero-Villanueva I, Fernández-Lao C, Díaz-Rodríguez L, Fernández-de-las-Peñas C, Ruiz JR,Arroyo-Morales M. The handgrip strength test as a measure of function in breast cancer survivors: relationship with quality of life, cancer related symptoms, physical and physiological parameters. Eur J Phys Rehabil. **Submitted**.

Cantarero-Villanueva I, Fernández-Lao C, Fernández-de-las-Peñas C López-Barajas IB, Del-Moral-Ávila R, ; de-la-Llave-Rincón AI, Arroyo-Morales M. Effectiveness of water physical therapy on pain, pressure pain sensitivity and myofascial trigger points in breast cancer survivors: a randomized controlled clinical trial. J Pain. **Submitted**.

Participación en Proyectos y Contratos de Investigación

2011-13

- **PROYECTO:** *E-CUIDATE: Eficacia sobre el dolor musculoesquelético de una plataforma de telefisioterapia en mujeres con cáncer de mama.* Entidad Financiadora: Fondo de Investigaciones Sanitarias. Instituto de Salud Carlos III. Investigador Principal: Manuel Arroyo Morales.

2011-13

- **PROYECTO:** *Eficacia de una plataforma de telefisioterapia en mujeres con cáncer de mama durante la quimioterapia*. Entidad Financiadora: Servicio Andaluz de Salud. Investigador Principal: Manuel Arroyo Morales.

2009-10

- **PROYECTO:** *Efectos Psicofisiológicos y sobre la Supervivencia de la Cinesiterapia Activa y la Masoterapia en Supervivientes de Cáncer de Mama***.** Entidad financiadora: Fondo de Investigaciones Sanitarias. Instituto de Salud Carlos III. Investigador Principal: Manuel Arroyo Morales.

Premios

2011

- **Primer premio de Investigación 2011 del Ilustre Colegio de Fisioterapia de Andalucía**: *Influencia de las actitudes de los pacientes sobre la terapia manual en mujeres con fatiga inducida por cáncer de mama: un diseño cruzado aleatorizado con enmascaramiento simple*. Fernández-Lao C, Cantarero-Villanueva I, Arroyo-Morales, M.

2010

- **Galardón de Accesit de premio de Investigación 2010 del Ilustre Colegio de Fisioterapia de Andalucía**: *Eficacia de un programa de Fisioterapia (Cuídate)*. Cantarero-Villanueva I, Fernández-Lao C, Arroyo-Morales, M.

2010

- **Primer premio comunicación presentada en las II Jornadas Internacionales y VI nacionales en ciencias de la Salud:** *Metodología de estudio de los desajustes del control motor en pacientes tratadas por cáncer de mama.* Galiano-Castillo N, Fernández Lao C, Cantarero Villanueva I, Olea Serrano N, Arroyo-Morales M.

2009

- **Primer premio comunicación presentada en el XII Congreso Andaluz de Psicología de la Actividad Física y el Deporte:** *Estudio descriptivo del estado de ánimo en mujeres con cáncer de mama previo a un programa de cinesioterapia activa.* Cantarero Villanueva I., Fernández Lao C., Feriche-Fernández Castanys B., Arroyo Morales M.

RESUMEN

La supervivencia a un cáncer de mama se ha incrementado cuantiosamente en estos años. Estas mujeres arrastran numerosas secuelas, entre las que destaca la fatiga, un síntoma de naturaleza multifactorial que merma su calidad de vida. Con esta memoria de Tesis se persiguió mejorar la comprensión sobre la fatiga inducida por el cáncer de mama estudiando su relación con distintos factores, así como analizar la efectividad de un programa multimodal de ejercicio terapéutico.

Las 95 participantes habían finalizado en tratamiento por cáncer de mama, tenían un estadío I-IIIa de la enfermedad y no presentaban contraindicación para la práctica deportiva.

Los resultados de la memoria de Tesis indican que: a) Un estado psicológico caracterizado por depresión y mala imagen corporal, una mayor sensibilidad al dolor cervical y una disminución de la movilidad del hombro, se relacionan con la fatiga, confirmando su carácter multidimensional. b) La fuerza evaluada mediante dinamometría, está fuertemente correlacionada con la calidad de vida y la salud general en supervivientes de cáncer de mama. c) Un programa multimodal de terapia física fue efectivo para la disminución de la fatiga y de la α-amilasa, y la mejora del rango de movimiento cervical, la fuerza muscular y el estado de ánimo en mujeres con cáncer de mama.

Hay una fuerte asociación entre desórdenes del estado de ánimo y de tipo musculoesquelético y la fatiga, lo que muestra el carácter multifactorial de ésta. Los programas multimodales tienen un efecto favorable para reducir la fatiga y otras alteraciones relacionadas con el proceso oncológico.

ABSTRACT

Survival from breast cancer has increased in recent years. These women have numerous side effects. Fatigue is one of the most important symptoms with a multifactorial nature, which reduce quality of life. The aim of this PhD was improve understanding of fatigue-induced breast cancer and their relation to various factors, and analyze the effectiveness of a multimodal therapeutic exercise program.

The 95 participants had completed treatment for breast cancer had stage I-IIIa disease and had no contraindication to the physical activity practice.

The results indicate: a) A psychological condition characterized by depression and poor body image, increased sensitivity to neck pain and decreased shoulder mobility, are associated with fatigue, confirming that has multidimensional nature. b) The strength assessed by dynamometry, is strongly correlated with the quality of life and overall health in breast cancer survivors. c) A multimodal physical therapy program was effective in decreasing fatigue and α-amylase, and improving cervical range of motion, muscle strength and mood in women with breast cancer.

There is a strong association among both mood and musculoskeletal disorders and fatigue, which shows the multifactorial nature of it. Multimodal programs have a favorable effect in reducing fatigue and other disorders related to the cancer process.

ABREVIATURAS [ABBREVIATIONS]

ACSM	American Collage of Sport Medicine
AHA	American Herat Association
ANCOVA	Co-variance
ANOVA	Analysis of variance
BC	Breast Cancer
BCS	Breast Cancer Survivors
CM	Cáncer de Mama
CSEs	Core Stability Exercise
ECG	Electrocardiogram
EE	Energy Expenditure
EORTC	European Organization for Research and Treatment of Cancer
FIC	Fatiga Inducida por el Cáncer
FRC	Fatigue-Related Cancer
HF	High Frequency
HGS	Hand Grip Score
HHS	Hipotálamo-Hipófisiario-Suprarrenal

HPA	Hypothalamic-Pituitary-Adrenocortical
HRV	Heart Rate Variability
LF	Low Frequency
MET	Metabolic Equivalent of Task
MLTPAQ	Minnesota Leisure Time Physical Activity Questionnaire
NCCN	National Comprehensive Cancer Network
PFS	Piper Fatigue Scale
POMS	Profile of Mood State
PPT	Pressure Pain Thresholds
QLQ-BR23	Breast Cancer-Specific Quality of Life Questionnaire
s-AA	Salivary Alfa-Amylase
SCM	Supervivientes de Cáncer de Mama
s-IgA	Secretory ImmunoglobulinA
SNS	Sistema Nervioso Simpático
TDE	Tesis Doctoral Europea
UHVN	University Hospital Virgen de las Nieves
VAS	Visual Analogue Scale

INTRODUCCIÓN

El cáncer de mama y las alteraciones derivadas de su tratamiento: fatiga inducida.

El cáncer es hoy día uno de los mayores problemas de la salud pública en Europa[1], debido al aumento de casos y el número de muertes relacionadas con la enfermedad[2]. Según un estudio reciente[3], una de cada tres personas tendrá cáncer a lo largo de su vida en los países desarrollados. Esta situación preocupante es trasladable al cáncer de mama (CM), el tumor más frecuente entre la población femenina[4,5,6]. La incidencia global del CM según un estudio realizado en 187 países ha aumentado un 3,1% entre 1980 y 2010[7], de tal forma que actualmente supone el 28,2% de los casos de cáncer entre las mujeres españolas, seguido del colorectal (13,7%) y de pulmón (6,7%). En Andalucía los datos están en la misma línea que los anteriores, en 2002 se dieron 2.500 nuevos casos (67 casos por cada 100.000 mujeres) según datos de la Consejería de Salud de la Junta de Andalucía[8].

Actualmente, a pesar de que la incidencia aumenta lentamente[7,9], la tasa de mortalidad ha disminuido[6]. En nuestro país el índice de supervivencia esta en el 85% a los cinco años de intervención[4], algo más alto que en el resto de Europa y, en un estudio realizado en las provincias de Granada y Almería, se estimó una supervivencia similar, situándola en el 83% a los cinco años y en el 71% a los diez años después de la intervención[10].

El aumento de la supervivencia se ha relacionado con mejoras en los tratamientos[11], la prevención de la recurrencia[12] y el diagnóstico precoz[4,13]. Aunque en Andalucía esta última explicación parece improbable puesto que las campañas de detección precoz se iniciaron a mediados de los años noventa y hay autores que consideran que es pronto para comprobar su efecto[14]. El sistema de salud tiene que dar respuesta a este grupo poblacional portador de un gran número de alteraciones derivadas del proceso oncológico[7].

En este contexto, el CM se considera hoy día como una enfermedad crónica[12,15]. Las supervivientes de CM (SCM) padecen numerosas manifestaciones clínicas, incluidos síntomas físicos y psicológicos que tienen un gran impacto sobre su estado de salud[16]. Una vez superada la enfermedad en primera instancia, la paciente comienza una etapa difícil hacia la recuperación de su calidad de vida anterior, que puede verse impregnada por la aparición de alteraciones músculoesqueléticas[17], fatiga, estrés psicosocial, depresión, disturbios del sueño, miedo a la recurrencia[18, 19], ganancia de peso, enfermedades recurrentes y un riesgo incrementado de otras enfermedades crónicas[20]. Entre éstas destaca por su elevada frecuencia la presencia de fatiga, entre el 60 y el 96 % de las pacientes la sufren durante y tras el tratamiento[21,22].

La National Comprehensive Cancer Network (NCCN), define la fatiga inducida por el cáncer (FIC) como una sensación angustiosa persistente y subjetiva de cansancio físico, emocional y/o cognitivo relacionado con el tratamiento del cáncer que no es proporcional a la actividad realizada y que interfiere en el funcionamiento normal de la persona que tiene o han tenido

cáncer[23]. Es un síntoma multifactorial[24] que puede estar presente durante años después del cáncer[25,26], teniendo impacto físico, emocional, económico[27], y estando por tanto relacionada con factores bioquímicos, fisiológicos, psicológicos y comportamentales. La fatiga tiene, por tanto, gran impacto en cualquier persona[28] pero, en personas con cáncer, es más severa, más angustiosa[29] y más difícil de aliviar con el descanso[30].

Etiología de la fatiga inducida por cáncer

La FIC es un problema muy limitante presente tanto durante como después del tratamiento[31,32,33,34]. Su etiología no está clara[35], lo que indica un origen ligado a diferentes factores potencialmente desencadenantes, relacionados con la propia enfermedad o su tratamiento. Entre éstos, destacan los asociados al tratamiento farmacológico, a aspectos psicosociales y a alteraciones neuromusculares. Hay estudios que han relacionado la FIC con alteraciones endocrinas derivadas directamente del tratamiento[36], como la inducción de amenorrea o menopausia prematura debida a la toxicidad ovárica[37], o la anemia causada por la quimioterapia y la radioterapia[38].

Por otro lado, diferentes investigaciones han señalado una relación de la FIC con factores psicosociales, como el apoyo social[39], la imagen corporal[40], la angustia y la ansiedad[41,42] o la depresión[43,44]. Kim et al.[44] encontró una relación significativa entre fatiga, depresión, calidad de vida, y preocupaciones funcionales y emocionales en supervivientes de CM, lo que señala que es posible la influencia del estado psicológico en la percepción de fatiga, y que

debamos por tanto considerar su posible influencia a la hora de llevar a cabo su abordaje.

Además, se ha encontrado que las SCM padecen una hiperalgesia manifestada por un aumento de la sensibilidad dolorosa a la presión después de la cirugía[16,45]. Este proceso doloroso se manifiesta en la región cervical y escapulohumeral implicadas en el acto quirúrgico. Esta relación entre hiperalgesia y fatiga puede tener diferentes explicaciones. Fernández-Lao et al.[16] mostró la existencia de numerosos puntos gatillo con mayor intensidad de dolor en el cuello en SCM. Estos puntos gatillo están presentes en diferentes síndromes, como la fibromialgia, muy frecuente en SCM[46]. Esta experiencia de dolor a distancia puede ocurrir por una alteración neuroendocrina o por efecto directo sobre el sistema nervioso central (SNC). Las alteración de neurotransmisores a nivel del SNC se ha asociado a al aparición de FIC[21], por tanto es factible establecer una relación entre la hiperalgesia y la FIC. De confirmar esta asociación causal, habría que considerarla para planificar las estrategias terapéuticas dirigidas a mejorar la FIC.

La FIC guarda, por tanto, relación con aspectos psicológicos, como la ansiedad, y físicos, como con la pérdida de movimiento tras la cirugía o la aparición de dolor. Estas complejas relaciones dificultan su entendimiento y abordaje. A pesar de que existe un creciente cuerpo de investigación sobre la fatiga relacionada con el cáncer de mama y su gestión, actualmente hay lagunas en la comprensión de los mecanismos que la provocan[37]. Por lo tanto, es necesario profundizar en este sentido para llevar a cabo esfuerzos dirigidos a realizar un tratamiento adecuado.

Relación de la fatiga y la condición física

Desde una perspectiva de fisiología del ejercicio, se entiende la fatiga física como una disminución de la capacidad de tensión muscular con la estimulación repetida[47]. Tradicionalmente, la estrategia utilizada para combatir la FIC ha sido el descanso [31]. Sin embargo, de acuerdo con un reciente panel de expertos[48], la actividad física muestra efectos beneficiosos en la prevención y en la reducción de la fatiga asociada con el cáncer, es más, hoy en día se sabe que la inactividad física es precisamente uno de los factores que se relacionan con la aparición de la fatiga. No obstante, este comité de expertos[48] otorgó un nivel de evidencia B (existencia de pocos artículos controlados randomizados o de muestra insuficiente con resultados inconsistentes), en cuanto a la eficacia del ejercicio físico sobre la FIC. Así, de los 16 estudios realizados 8 de ellos mostraron resultados positivos y 7 no encontraron efectos, sólo en uno de ellos la fatiga empeoró después del programa aplicado. Es por ello, que es necesario un mayor número de estudios clínicos para determinar la eficacia de diferentes protocolos para el abordaje de la FIC.

La disminución de la actividad conduce a la reducción de la masa muscular y de la capacidad cardiovascular, por tanto, a la pérdida de la condición física general, que aumenta la fatiga[15,50,51]. Cuando la capacidad física se reduce, se establece un desequilibrio entre los requerimientos energéticos de la actividad física y la capacidad del paciente para realizarla, ocasionando fatiga prematura ante actividades cotidianas ligeras, tal y como reportan muchos pacientes[49]. Se sabe que el tratamiento del cáncer produce anormalidades en el metabolismo del músculo cardiaco y esquelético[52]

manifestadas por un hipercatabolismo muscular que da como resultado la pérdida de fuerza en supervivientes de cáncer. En concreto, los pacientes oncológicos sufren una disminución de la fuerza isométrica de agarre que puede medirse objetivamente mediante test máximos y submáximos, entre ellos, uno de los más utilizados en la literatura es la fuerza isométrica de prensión a través de la dinamometría de mano. La evaluación de la fuerza muscular por la prueba de la fuerza de prensión se ha utilizado ampliamente en diferentes condiciones como la fibromialgia[53], diabetes[54], la diálisis crónica peritoneal[53], insuficiencia cardiaca congestiva[55] o en SCM[56].

De forma concreta, en SCM se ha comprobado que en el primer año después del tratamiento hay una disminución de la fuerza de prensión, asociado a un mal estado psicológico. En este sentido, Kaya et al[57] mostró que la fuerza de prensión se relaciona inversamente con la calidad de vida en un grupo de mujeres tratadas por CM, aunque no se confirmaron los resultados después del tratamiento con quimioterapia. Además, algunos estudios que han demostrado que la disminución de la función muscular y de la función física, conllevan una mayor posibilidad de mortalidad[58,59,60,61]. Es necesaria la realización de estudios para establecer de manera clara la posible relación entre el deterioro físico de la fuerza de prensión y la FIC.

El ejercicio terapéutico regular mejora el estado subyacente en personas que padecen gran variedad de enfermedades crónicas no transmisibles, entre ellas el cáncer[16]. Se sabe que las mejoras en la fuerza muscular mejora el perfil lipídico sanguíneo, reduce la presión sanguínea en reposo/ejercicio, mejora la tolerancia a la glucosa y la sensibilidad a la insulina, aumenta el gasto

energético y reduce potencialmente el porcentaje de grasa abdominal[62], siendo este último uno de los principales predictores de mortalidad en población oncológica[60].

La puesta en marcha de protocolos de práctica clínica en pacientes oncológicos en fase de secuelas exige la selección de procedimientos y medios instrumentales que faciliten el seguimiento y control en la evolución de estos pacientes de forma que se facilite su uso en la práctica habitual de los fisioterapeutas dedicados al trabajo con pacientes oncológicos. Aún no se ha comprobado si la prueba de fuerza de prensión puede utilizarse como una de estas herramientas si bien ha sido utilizado en otros contextos clínicos[53,54,55,56].

Existe necesidad de determinar los parámetros de la condición física que se relacionan con la fatiga para prescribir programas de ejercicio individualizados (tipo, duración, intensidad y frecuencia) que nos permitan entender las consecuencias que puede tener la mejora de la aptitud del paciente en su calidad de vida y salud general, aunque previamente sería necesario establecer si puede ser utilizada como un indicador de fatiga, dolor y calidad de vida en mujeres con cáncer de mama.

El abordaje de la fatiga relacionada con el cáncer de mama:

El ejercicio terapéutico de tipo aeróbico y de fuerza resistencia es una de las modalidades no farmacológicas más utilizadas para tratar las alteraciones de las personas que han sobrevivido a un cáncer[48,63], siendo de especial utilidad en el manejo de la FIC en estas pacientes[63,64,65]. Las intervenciones

mediante ejercicio y terapia física reducen el impacto de la fatiga en la funcionalidad y/o reducir la severidad de los síntomas[48]. El ejercicio terapéutico con suficiente frecuencia, intensidad y duración mejoran la capacidad física a través del incremento del volumen latido cardiaco y las mejora de capilarización, y el aumento del número de la actividad mitocondrial en la periferia, de tal modo que podría conducir a una reducción o a la prevención de la fatiga en mujeres tratadas por CM[15,26].

Una revisión llevada a cabo por Lucía et al.[21], mostró que estos programas se han llevado a cabo tanto durante como después del tratamiento, con una duración comúnmente entre 6 y 10 semanas y una frecuencia de entre 3 y 5 días por semana. El tiempo de cada sesión suele aumentar progresivamente desde los 30 minutos y se trabaja a intensidades moderadas desde el punto de vista de la fisiología del ejercicio, es decir, entre el 60-85% de la frecuencia cardiaca máxima.

No obstante, los resultados de estos estudios animan a los investigadores a realizar investigaciones que comprueben la efectividad de otras modalidades combinadas de ejercicio, con el objeto de mejorar el conocimiento sobre la dosificación y el tipo de ejercicio más efectivo su traslado a la práctica clínica habitual. La naturaleza multidimensional de la FIC y la necesidad de un actitud preactiva de las pacientes, exigen la implantación de intervenciones suplementadas con terapias cognitivo-conductuales[66], o de programas multimodales que se basan en el ejercicio físico como principal componente, ya que se han mostrado útiles para la disminución de la FIC y la mejora de la capacidad funcional[49,67,68,69].

Dado que las alteraciones derivadas del tratamiento oncológico afectan a la esfera física y mental de la mujer, una aproximación desde el punto de vista de la fisioterapia, combinando ejercicio con técnicas de recuperación de la fatiga como la masoterapia o las técnicas de relajación podrían alcanzar resultados satisfactorios. Un estudio reciente ha sugerido que 6 semanas de ejercicio diario o intermitente limita la respuesta del eje HHS al estrés[70]. Diferentes estudios resaltan la capacidad de la intervenciones cuerpo-mente, como el yoga o masajes, para mejorar el SNS-HHS respuesta del eje al estrés[71,72]. Sin embargo, los estudios que investigan la eficacia de la terapia física programas en la disfunción del eje HPA por marcadores salivales en SCM que sufren FIC son escasos.

A pesar de los efectos beneficiosos ya demostrados del ejercicio sobre el paciente oncológico, es bien sabido en la literatura que el nivel de adherencia de estos programas no consigue a veces resultados óptimos. Una posible razón es la dificultad para la recuperación tras la actividad física que pueden presentar estos pacientes. La introducción de técnicas de recuperación podría facilitar la mejora de la adherencia y cumplimentación de los programas de ejercicio dirigidos a pacientes oncológicos. Algunos estudios preliminares sobre la capacidad de la fisioterapia en este contexto deberán ser confirmados con ensayos clínicos que avalen la importancia de la fisioterapia en el tratamiento de la fatiga y los trastornos asociados al cáncer de mama. Entre dichos recursos se encuentra, con un especial interés para este grupo particular de pacientes el uso de masoterapia que ha mostrado enorme eficacia en procesos oncológicos, especialmente en la emesis asociada al tratamiento

con quimioterapia [73]. La masoterapia es un elemento imprescindible para favorecer la recuperación tras el ejercicio favoreciendo un estado de relajación de predominio vagal[74], una mejora del estado de animo y de la recuperación muscular[75], así como eliminando los efectos inmunosupresores del ejercicio[76]. Estos cambios fisiológicos a su vez pueden redundar en una mejora del estado psicológico de la paciente y por tanto favorecer la incorporación de la actividad física en su estilo de vida.

Resumiendo, entendemos la FIC como un estado de agotamiento físico, emocional y/o cognitivo, que incapacita para la realización de actividades cotidianas, mermando por tanto la calidad de vida, y que está determinado por factores de diferente naturaleza, entre los que destaca la inactividad física, puesto que además de inducir a la fatiga, la perpetua, ocasionando un círculo vicioso que sólo puede romperse con el ejercicio regular y adaptado.

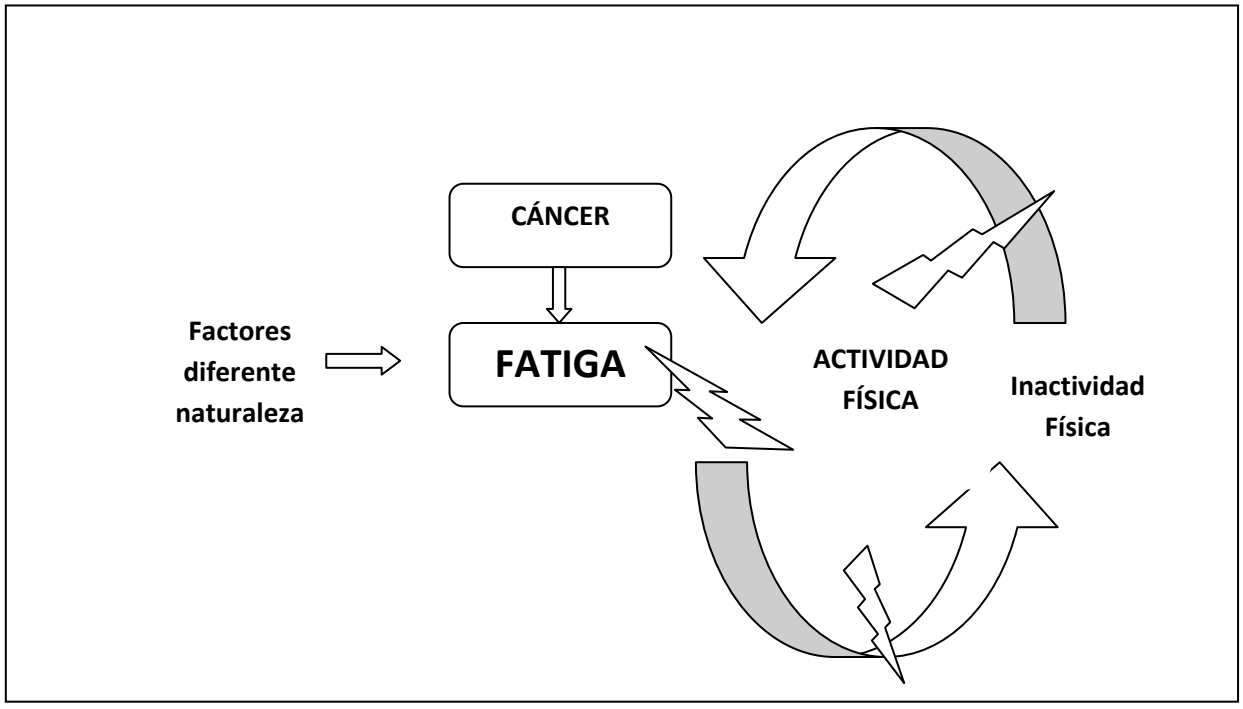

Figura 1: Relación de conceptos.

El objetivo principal de esta Tesis Doctoral Europea (TDE) ha sido mejorar la comprensión sobre la fatiga inducida por el cáncer de mama estudiando su relación con factores de distinta naturaleza, así como analizar la efectividad de un programa multimodal de ejercicio terapéutico en la fatiga en mujeres supervivientes de cáncer de mama.

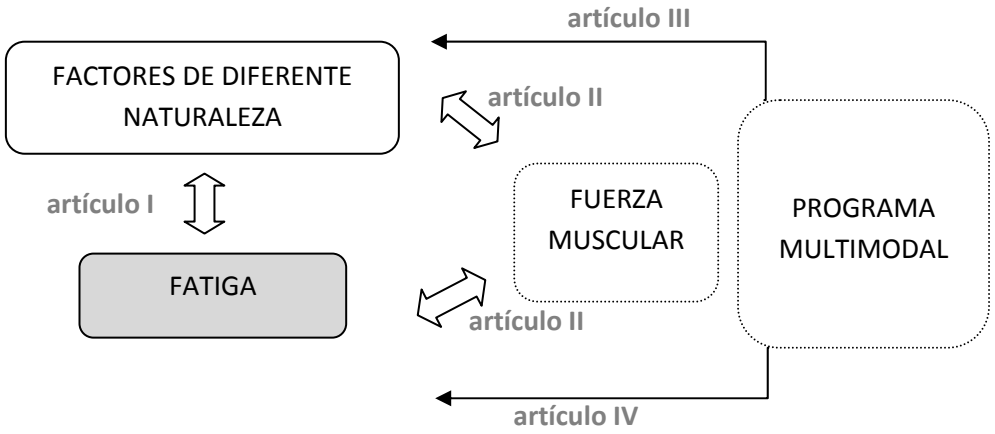

Figura 2: Conceptos abordados y artículos presentados en la memoria de Tesis.

Definición de conceptos:

Estado de ánimo

Estado emocional menos específico, intenso e influenciable de ser estimulado por un estímulo determinado que las emociones. Suele un carácter duradero en el tiempo[77]. McNair et al.[78] realizaron un cuestionario para su evaluación que incluía seis escalas; seis escalas: Tensión-Ansiedad, Depresión-Melancolía; Cólera-Hostilidad; Vigor, Fatiga-Inercia y Confusión-Desorientación. El estado de ánimo ha sido ampliamente estudiado en relación con el CM[48].

Calidad de vida

Concepto de reciente aparición y del que no existe un consenso en cuanto a su definición. Lawton[79] propone 4 categorías referentes a la calidad de vida: calidad de vida física, (relacionada con la salud), calidad de vida social (relacionada con el mundo externo), calidad de vida percibida (percepción subjetiva de la calidad de vida) y calidad de vida psicológica. Son numerosos los estudios que investigan sobre la calidad de vida tanto durante como después del tratamiento del CM[21], por la afectación que en ésta ejercen las secuelas derivadas del tratamiento y de la intervención.

Frecuencia cardiaca

Se refiere al número de veces que el corazón realiza un ciclo completo de llenado y vaciado de sus cavidades en un tiempo determinado, generalmente en un minuto. Es uno de los parámetros no invasivos más utilizados para cuantificar la intensidad del ejercicio físico. Ha sido ampliamente utilizado en la bibliografía como regulador de ejercicio en pacientes con CM[21].

Variabilidad de la frecuencia cardiaca

Hace referencia a la variación de la frecuencia del latido cardiaco durante un tiempo definido en un análisis de periodos circadianos consecutivos. Es un indicador no invasivo que se modifica con trastornos tanto fisiológicos[80], como psicológicos[81], siendo muy indicado para el estudio de la calidad de vida y el estado de salud en SCM.

Presión arterial

Hace referencia a la presión que ejerce la sangre sobre las paredes arteriales. La alteración de los valores establecidos como normales, indican un deterioro

del estado de salud. Es una forma eficaz y sencilla de control de la salud frecuentemente utilizada en la investigación en esta población[82] .

Rango de secreción salivar

El volumen de saliva producido en un tiempo determinado. Se sabe que el tratamiento relacionado con el cáncer puede producir una hipofunción de las glándulas salivares[83].

Cortisol

Hormona producida por la glándula suprarrenal, que se libera como respuesta al estrés y a un bajo nivel de glucocorticoides en sangre. Modificaciones en el ciclo circadiano del cortisol se asocia con alteraciones en el eje hipotálamo-hipófisis-suprarrenal en personas con fatiga relacionada con el cáncer[84, 85].

Alfa-amilasa

Enzima digestiva que ha sido señalada como un marcador para la actividad del SNS[86]. Diversos estudios demostraron que la concentración de alfa amilasa aumentó durante el estrés, cuando la activación autonómica se incrementa. De hecho, la alfa-amilasa se ha propuesto como marcador útil en el contexto del cáncer para diferentes síntomas, como dolor[87] o la alteración del sueño[88].

Inmunoglobulina A (IgA)

Glicoproteína importante para el sistema inmune, que actúa como defensa ante patógenos, presente en la sangre y en las secreciones. Su déficit se ha relacionado con alteraciones autoinmunes y atópicas y con una mayor suceptibilidad a las infecciones[89]. Diferentes estudios han encontrado una disminución de la secrección de IgA después del tratamiento del cáncer[90] .Se

ha comprobado que tanto el ejercicio físico, en adultos[91, 92], como el masaje[74], pueden ayudar a incrementar sus niveles.

Capacidad funcional

Hace referencia a la capacidad de realizar actividades diarias, que puede expresarse en METs. El ejercicio físico se ha mostrado muy útil para mejorar la capacidad funcional en mujeres con CM en numerosos estudios[21].

Rango de movimiento

Es la distancia de movimiento de una articulación en un eje determinado. Tras la cirugía y el tratamiento por CM existe una pérdida de la amplitud de movimiento[93].

INTRODUCTION

Breast cancer and the changes resulting from treatment: fatigue induced.

Cancer is now one of the biggest public health problems in Europe[1], due to increasing numbers of cases and deaths related to the disease[2]. According to a recent study[3], one in three people will have cancer during their life in developed countries. This alarming situation is particularly relevant to breast cancer (BC), the most common tumor among the female population[4,5,6]. The overall incidence of BC according to a study conducted in 187 countries has increased by 3.1% between 1980 and 2010[7], so that it currently accounts for 28.2% of cases of cancer among spanish women, followed by colorectal (13,7%) and lung (6.7%) cancer. In Andalusia, the data is similar as above, in 2002 there were 2,500 new cases (67 cases per 100,000 women) according to the Ministry of Health of the Junta de Andalucí[8].

Currently, although the incidence increasing slowly[7,9], the mortality rate has decreased[6]. In our country, the survival rate is 85% after five years intervention[4], somewhat higher than in the rest of Europe and, in a study conducted in the provinces of Granada and Almeria, similar survival was estimated, placing it in 83% at five years and 71% at ten years[10].

The increase in survival has been associated with improvements in treatments[11], prevention of recurrence[12] and early diagnosis[4,13]. Although in Andalusia the latter explanation seems unlikely since the early detection campaigns began in the mid-nineties and some authors believe that it is too soon to check their effect[14]. The health system must respond to this group of patients who have many side effects as a result of their biomedical treatment[7].

In this context, BC is now regarded as a chronic disease[12,15]. Survivors of BC (BCS) have many clinical manifestations, including physical and psychological symptoms that have a major impact on their state of health[16]. After the disease in the first instance, the patient begins a difficult time to recovery of their previous life quality, which can be affected by the appearance of musculoskeletal disorders[17], fatigue, psychosocial stress, depression, sleep disturbances, fear of recurrence[18,19], weight gain, recurrent disease and an increased risk of other chronic diseases[20]. Among these, one which stands out for its high frequency is the presence of fatigue, between 60- 96% of patients suffer during and after the treatment[21,22].

The National Comprehensive Cancer Network (NCCN) defines fatigue-related cancer (CRF) as a distressing persistent, subjective sense of physical fatigue, emotional and / or cognitive related to cancer treatment that is not proportional to the activity undertaken and that interferes with the normal functioning of the person who has or had cancer[23]. It is a multifactorial symptom[24] that may be present for years after cancer[25, 26], having a physical, emotional and economic impact[27], and being therefore linked to biochemical, physiological, psychological and behavioral. Fatigue therefore has a great impact on anyone[28] but in people with cancer, it is more severe, more distressing[29] and more difficult to relieve with rest[30].

Etiology of cancer induced fatigue

The CRF is a very limiting, present both during and after treatment[31,32,33,34]. Its etiology is not clear[35], indicating an origin linked to different trigger factors potentially related to the disease itself or its treatment. Among these include those associated with drug therapy, psychosocial aspects and neuromuscular disorders. There are studies that have also linked CRF to endocrine disruption CRF derived directly from treatment[36], such as induction of amenorrhea or premature menopause due to ovarian toxicity[37] or anemia caused by chemotherapy and radiotherapy[38].

On the other hand, several studies have indicated a relationship between CRF and psychosocial factors, such as social support[39], body image[40], anxiety and distress[41,42], or depression[43,44]. Kim et al.[44] found a significant relationship between fatigue, depression, quality of life and functional and emotional concerns in BCS. Therefore the influence of the psichological perception of fatigue should be considered when treating a patient.

In addition, BCS have been found that have hyperalgesia manifested by an increase in pressure pain sensitivity after surgery[16,45]. This painful process is manifested in the cervical region and is associated with involved shoulder surgery. This relationship between hyperalgesia and fatigue may have different explanations. Fernández-Lao et al.[16] showed the existence of numerous trigger points with greater intensity of pain in the neck in BCS. These trigger points are present in different syndromes such as fibromyalgia and are very frequent in BCS[46]. This experience of pain can occur for a distant neuroendocrine alteration or by direct effects on the Central Nervous System (CNS). The alteration of

neurotransmitters in the CNS has been associated with the appearance of CRF[21], so it is feasible to establish a relationship between hyperalgesia and CRF. To confirm this causal association, this should be considered when planning therapeutic strategies aimed at improving the CRF.

CRF is associated with psychological aspects, such as anxiety, and physical aspects such as the loss of motion after surgery or onset of pain. These complex relationships hinder their understanding and approach. Although there is a growing body of research on CRF and its management, there are currently gaps in the understanding of the mechanisms that cause CRF[37]. Therefore, work is required in this area to understand the causes to treatment CRF appropiately.

Relationship of fatigue and fitness

From the perspective of exercise physiology, physical fatigue is defined as a decrease in muscle tension capacity on repeated stimulation[47]. Traditionally, the strategy used to combat CRF has been rest [31]. However, according to a recent expert panel[48], physical activity shows beneficial effects in preventing and reducing the fatigue associated with cancer, and today it is known that physical inactivity is just one of the factors associated with the onset of fatigue. However, this committee gave a level of evidence B (there are few randomized or small sample with inconsistent results), concerning the boarding of on CRF by exercise Thus, of the 16 studies analyzed, 8 of them showed positive results and 7 found no effect, only one fatigue worsened following a program implemented after treatment. This is why it is necessary for more

studies to determine the effectiveness of different clinical protocols for addressing CRF.

The decrease in activity leads to reduced muscle mass and cardiovascular capacity, therefore, the loss of the general physical condition, which increases fatigue[15,50.51]. When the physical capacity is reduced, a mismatch is created between the energy requirements of physical activity and the patient's ability to perform it, premature fatigue is caused with daily activities, as many patients[49] report. It is known that cancer treatment causes abnormalities in the metabolism of heart and skeletal muscle[52] manifested by a hypercatabolism of muscle that results in loss of strength in cancer survivors. Specifically, cancer patients suffer a decrease in isometric grip strength which can be measured objectively by maximum and submaximal test, including one of the most used in the literature isometric grip strength by dynamometry hand. The assessment of muscle strength by testing grip strength has been widely used in different conditions such as fibromyalgia[53], diabetes[54], chronic peritoneal dialysis[53], failure heart[55] or BCS[56].

As a specific example in BCS it has been shown that in the first year after treatment there is a decrease in grip strength associated with poor psychological state. In this sense. Kaya et al[57] showed that handgrip strength is inversely related to quality of life in a group of women treated for BC, although the results were not confirmed after completing chemotherapy treatment. In addition, some studies have shown that the decrease in muscle function and physical function, carry a greater chance of mortality[58,59,60,61]. It is necessary for

studies to clearly establish the possible relationship between physical impairment of handgrip strength and the CRF.

Regular therapeutic exercise improves the condition in people with a variety of underlying chronic noncommunicable diseases, including cancer[16]. It is known that improvements in muscle strength improves blood lipid profile, reduce blood pressure at rest / exercise, improves glucose tolerance and insulin sensitivity, increases energy expenditure and potentially reduces the percentage of abdominal fat[62], the latter being one of the main predictors of mortality in the oncological population[60].

The implementation of practice guidelines in oncology patients undergoing follow up requires the selection of instrumental procedures and arrangements that facilitate the monitoring and control of the recovery of these patients in a way that facilitates its use in physiotherapy dedicated to working with cancer patients. It has not yet been proven if the grip strength test can be used as one of these tools but has been used in other clinical contexts[53,54,55,56].

There is a need to determine the parameters of physical fitness that are related to fatigue to prescribe individualized exercise programs (type, duration, intensity and frequency) that allow us to understand the consequences they may have in improving the ability of the patient, and their quality of life and general health. First of all it is necessary to establish whether it can be used as an indicator of fatigue, pain and quality of life in women with breast cancer.

The approach of fatigue related to breast cancer:

Therapeutic aerobic and resistance exercise is one of the most widely used non-pharmacological methods to treat disorders of the people who have survived a cancer[48,63], being particularly useful in the management of CRF in these patients[63,64 65]. Exercise and physical therapy interventions can reduce the impact of fatigue on the functionality and / or reduce the severity of symptoms[48]. Therapeutic exercise with sufficient frequency, intensity, can improve physical capacity by increasing cardiac stroke volume, improve capillarization, and increase the level of mitochondrial activity in the peripheral area, which could lead to a reduction or prevention of fatigue in women treated for BC[15, 26].

A review conducted by Lucia et al.[21] showed that these exercise programs have been carried out both during and after treatment, usually lasting between 6 and 10 weeks and a frequency of 3 to 5 days per week. The time of each session tends to increase gradually from 30 minutes moderate intensity are works from the viewpoint of exercise physiology, between 60-85% of maximum heart rate.

However, the results of these studies encourage researchers to conduct research that prove the effectiveness of other forms of exercise combined with the aim of improving knowledge about the amount and type of exercise to improve more transfer to clinical practice . The multidimensional nature of the CRF and the need for a proactive attitude of patients, requires the implementation of interventions supplemented with cognitive-behavioral[66] or multimodal programs which are based on physical exercise as the main

component, and which have proved useful for the decline of CRF and improving the functional ability [49,67,68,69].

Because cancer treatment-related changes affect the physical and mental sphere of women, an approach from the standpoint of physical therapy, combining exercise with recovery techniques such as massage therapy for fatigue or relaxation techniques can achieve satisfactory results. A recent study has suggested that 6 weeks of daily or intermittent exercise limited HPA axis response to stress[70]. Several studies highlight the ability of the mind-body interventions such as yoga or massage, to improve HHS-SNS axis response to stress[71,72]. However, studies investigating the efficacy of physical therapy programs in the HPA axis dysfunction in salivary markers in BCS that suffer from CRF are scarce.

The beneficial effects of exercise for cancer patients being reported in the literature, that the grip of these programs sometimes get results. One possible reason is the difficulty of recovery after physical activity may have these patients. The introduction of recovery techniques could help improve adherence and completion of the exercise programs aimed at cancer patients. Preliminary studies on the ability of physiotherapy in this context must be confirmed in clinical trials have confirmed the importance of physiotherapy in the treatment of disorders associated with fatigue and breast cancer. Among these resources are found, with a special interest for this particular group of patients is the use of massage therapy wich has shown great effectiveness in oncological processes, especially in the emesis associated with chemotherapy[73]. Massage therapy is an essential element to promote recovery

after exercise favoring a relaxed state of dominance vagal[74], improved mood and muscle recovery[75] and eliminating the immunosuppressive effects of exercise[76]. These physiological changes may in turn result in improved patient's psychological state and therefore favor the incorporation of physical activity into your lifestyle.

In short, we understand the CRF as a state of physical exhaustion, emotional and / or cognitive, which renders it incapable of carrying out daily activities, thus diminishing the quality of life, and is determined by different factors, among which is physical inactivity, as well as inducing fatigue, perpetual, causing a vicious cycle that can only be broken with regular exercise and adapted.

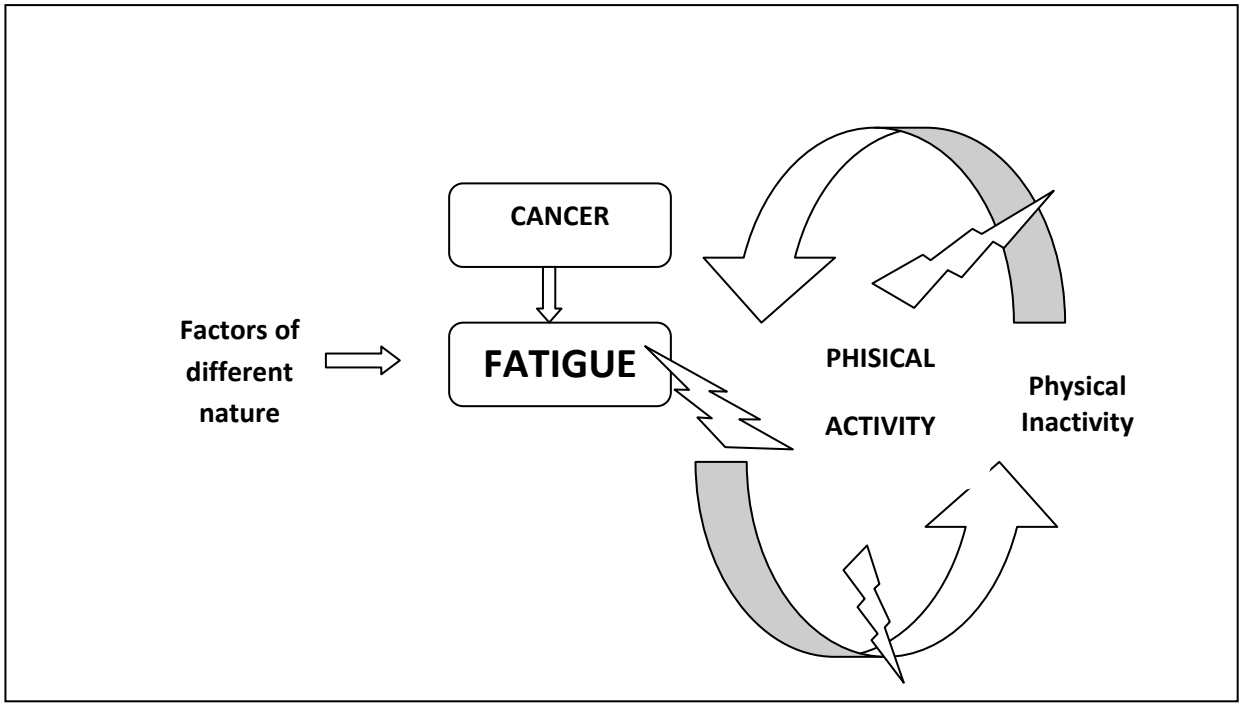

Figure 1: Relationship of concepts.

The main objective of this PhD has been to improve the understanding of CRF and the relationship between different factors, and to analyze the effectiveness of a multimodal therapeutic exercise program on fatigue in women survivors of breast cancer.

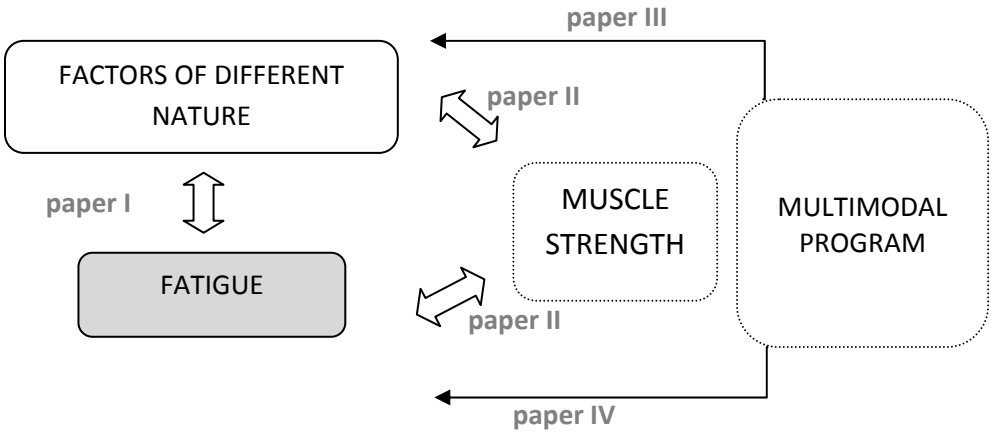

Figure 2: Concepts discussed and papers presented at the memory of PhD.

Definitions:

Mood

Less specific emotional state, intense and impressionable to be stimulated by a given stimulus than emotions. Usually a lasting nature in the time[77]. McNair et al.[78] conducted an evaluation questionnaire that included six scales, six scales: Tension-Anxiety, Depression, Melancholy, Anger-Hostility, Vigor, Fatigue-Inertia and Confusion, Disorientation. The mood has been extensively studied in relation to the BC[48].

Quality of life

Emerging concept and there is no consensus on its definition. Lawton[79] proposes 4 categories concerning the quality of life: physical quality of life (health related) quality of social life (related to the external world), perceived quality of life (self-reported quality of life) and quality of psychological life. Numerous studies investigating the quality of life both during and after treatment for BC[21], for involvement in this exercise the sequelae of the treatment and intervention.

Heart rate

Refers to the number of times the heart performs a complete cycle of filling and emptying their pockets at any given time, usually in a minute. One of the most widely used non-invasive parameters to quantify the intensity of exercise. It has been widely used in the literature as a regulator of exercise in patients with BC[21].

Heart rate variability

Refers to the variation in the frequency of the heartbeat during a defined time periods on an analysis of circadian running. It is a noninvasive indicator changes with both physiological[80] and psychological[81] disorders, being very suitable for studying the quality of life and health status in BCS.

Blood pressure

Refers to the pressure of blood against artery walls. Altering the values set as normal, indicating a deterioration of health. It is an effective and easy to control frequently used in health research in this population[82].

Range of salivary secretion

The volume of saliva produced in a given time. It is known that cancer-related treatment can produce a salivary gland hypofunction[83].

Cortisol

A hormone produced by the adrenal gland, which is released in response to stress and low levels of glucocorticoids in blood. Changes in the circadian rhythm of cortisol is associated with alterations in the hypothalamic-pituitary-adrenal axis in patients with cáncer83 related fatigue[84,85].

Alpha-amylase

Digestive enzyme that has been identified as a marker for SNS activity[86]. Studies have shown that alpha amylase concentration increased during stress, when the autonomic arousal increases. In fact, alpha-amylase

has been suggested as useful marker in the context of cancer for different symptoms, such as pain[87] or sleep disturbance[88].

Immunoglobulin A (IgA)

Glycoprotein important for the immune system, which acts as a defense against pathogens present in the blood and secretions. Its deficit has been associated with autoimmune and atopic disorders and a higher susceptibility to infections[89]. Different studies have found a decrease in IgA secretion after treatment cancer[90]. It has been found that both physical exercise in adults[91,92], like masssage[74] can help increase your levels.

Functional Capacity

Refers to the ability to perform daily activities, which can be expressed in METs. Physical exercise has been very helpful in improving functional capacity in women with BC in numerous studies[21].

Range of motion

The distance of movement of a joint in a particular axis. After surgery and treatment for BC there is a loss of range of movement[93].

BIBLIOGRAFÍA [REFERENCES]

1. Boyle P, Boley F. Cancer incidence and mortality in Europe, 2004. Annals of Oncology 2005;16: 481-488.
2. Jema l A, Siegel R, Ward E, Hao Y, Xu J, Thun M. Cancer Statistics, 2009. CA Cancer J Clin 2009;59:225-249.Ann Oncol
3. Signaleringscommissie K, Kankerbestrijding van KWF. Kanker in Nederland, Trends prognoses en implicaties voor zorgvraag. Amsterdam, Report of the Dutch Cancer Society, 2004.
4. Pollán M, Ramis R, Aragonés N, Pérez-Gómez B, Gómez D, Lope V, et al. Municipal distribution of breast cancer mortality among women in Spain. BMC Cancer 2007;7-78.
5. Ries LA, Wingo PA, Miller DS, Howe HL, Weir HK, Rosenberg HM, et al. The annual report to the nation on the status of cancer, 1973-1997 with a Special Section on Colorectal Cancer. Cancer 2000;88: 2398-2424.
6. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. EJC 2010;46:765 -781.
7. Forouzanfar MH, Foreman KJ, Delossantos AM, Lozano R, Lopez AD, Murray CJL, et al. Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. The Lancet 2011;378:1461-1484.
8. Plan Integral de Oncología de Andalucía 2002-2006. Consejería De Salud. Disponible en http://www.juntadeandalucia.es/salud/channels/temas/temas_es/P_2_ANDALUCIA_EN_SALUD_PLANES_Y_ESTRATEGIAS/plan_oncologia/pla

n_oncologia?perfil=org&desplegar=/temas_es/P_2_ANDALUCIA_EN_SALUD_PLANES_Y_ESTRATEGIAS/&idioma=es&tema=/temas_es/P_2_ANDALUCIA_EN_SALUD_PLANES_Y_ESTRATEGIAS/plan_oncologia/&contenido=/channels/temas/temas_es/P_2_ANDALUCIA_EN_SALUD_PLANES_Y_ESTRATEGIAS/plan_oncologia/plan_oncologia, acceso en acceso en 8 junio, 2010.

9. National Comprehensive Cancer Network (NCCN), Clinical Practice Guidelines in Oncology: Cancer Related-Fatigue, National Comprehensive Cancer Network, Fort Washington, Pa, USA, 2009.
10. Ocón O, Fernández MF, Pérez S, Dávila C, Expósito J, Olea N. Supervivencia en cáncer de mama tras diez años de seguimiento en las provincias de Granada y Almería. Rev Esp Salud Pública 2010;84:705-715.
11. Ganz PA. A teachable moment for oncologists: cancer survivors, 10 million strong and growing!. J Clin Oncol 2005;23,5458-5460.
12. Martín M, Mahillo E, Llombart-Cussac A,Lluch A, Munarriz B, PastorM, et al. The 'El Alamo' project (1990–1997): twoconsecutive hospital-based studies of breast cancer outcomes in Spain. Clin Transll Oncol 2006;8:508–518.
13. Cabanes A, Vidal E, Pérez-Gómez B, Aragonés N, López-Abente G, Pollán M. Age-specific breast, uterine and ovarian cancer mortality trends in Spain: changes from 1980 to 2006. Cancer Epidemiology 2009;33:169-175.

14. Ruiz-Ramos M, Expósito J. Tendencia de la mortalidad por cáncer en Andalucía entre 1975 y 2003. Med Clin (Barc) 2007;128:448-52.
15. Markes M, Brockow T, Resch KL. Exercise for women receiving adjuvant therapy for breast cancer. Cochrane Database Syst Rev 2006;18(4);CD005001.
16. Pinto BM, Trunzo JJ. Health behaviour during and after a cancer diagnosis.Cancer 2005;104:2614-2623.
17. Fernández-Lao C, Cantareno-Villanueva I, Fernández-de-las-Peñas C, Del-MoralÁvila R, Arendt-Nielsen L, Arroyo- Morales M. Myofascial trigger points in neck and shoulder muscles and widespread pressure pain hypersensitivity in patients with postmastectomy pain: evidence of central spreading sensitisation. Clinical Journalof Pain 2010;26:798–806.
18. Ganz PA, Desmond KA, Leedham B, Rowland JH, Meyerowitz BE, Belin TR. Quality of life in long-term, disease-free survivors of breast cancer: a follow-up study. J Natl Cancer Inst 2002;94(1):39-49.
19. Ganz PA, Guadagnoli E, Landrum MB, Lash TL, Rakowski W, Silliman RA. Breast cancer in older women: quality of life and psychosocial adjustment in the 15 months after diagnosis. J Clin Oncol 2003;21:4027-4033.
20. Aziz NM. Cáncer survivorship research: state of knowledge, challenges and opportunities. Acta Oncol 2007;46:417-432.
21. Lucia A, Earnest C, Perez M. Cancer-related fatigue: can exercise physiology assist oncologists? Lancet Oncol 2003;4:616-625.

22. Wagner LI, Cella D. Fatigue and cancer: causes, prevalence and treatment approaches. Br J Cancer 2004;91:822-828.
23. Mortimer JE, Barsevick AM, Bennett CL, Berger AM, Cleeland C, Devader SR, et al. Studying Cancer-Related Fatigue: Report of the NCCN Scientific Research Committee. J Natl Compr Canc Netw 2010; 8:1331-1339.
24. Denieffe S, Gooney M. A metasynthesis of women's symptoms experience and breast cancer.Eur J Cancer Care 2011;20(4):424-435.
25. Bower JE, Ganz PA, Desmond K, Bernaards C, Rowland J., Meyerowitz BE et al. Fatigue in long-term breast carcinoma survivors. A longitudinal investigation. Cancer 2006;106:751-758.
26. Bower JE, Ganz PA, Tao ML, Hu WH, Belin TR, Sepah S, et al. Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. Clin Cancer Res 2009:15;5534-5540.
27. Prue G, Rankin J, Allen J, Gracey J, Cramp F. Cancer-related fatigue: a critical appraisal. Eur J Cancer 2006;42:846-863.
28. Watt T, Groenvold M, Bjorner JB, Noerholm V, Rasmussen NA, Bech P. Fatigue in the Danish general population. Influence of sociodemographic factors and disease. J Epidemiol Commun H 2000;54:827-833.
29. Jacobsen PB, Donovan KA, Small BJ, Jim HS, Munster PN, Andrykowski MA. Fatigue After Treatment for Early Stage Breast Cancer: A Controlled Comparison. *Cancer* 2007;110(8):1851–1859.

30. Glaus A, Crow R, Hammond S. A qualitative study to explore the concept of fatigue/tiredness in cancer patients and in healthy individuals. Support Care Cancer 1996;4:82-96.
31. Irvine DM, Vincent L, Graydon JE, Bubela N. Fatigue in women with breast cancer receiving radiation therapy. Cancer Nurs 1998;21:127–35.
32. Hann DM, Jacobsen P, Martin S, Azzarello L, Greenberg H. et al. Fatigue and quality of life following radiotherapy for breast cancer: a comparative study. J Clin Psychol Med Settings 1998;5: 19-33.
33. Smets EM, Visser MR, Willems-Groot AF, Garssen AF, Shuster-Uitterhoeve AL, Haes JC. Fatigue and radiotherapy: B, experience in patients 9 months following treatment. Br J Cancer 1998;78:907-12.
34. Broeckel JA, Jacobsen PB, Horton J, Balducci L, Lyman GH. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. J Clin Oncol 1998; 16: 1689-96.
35. Barsevick AM, Cleeland CS, Manning DC, O'Mara AM, Reeve BB, Scott JA, et al. ASCPRO (Assessing Symptoms of Cancer Using Patient-Reported Outcomes). ASCPRO recommendations for the assessment of fatigue as an outcome in clinical trials. J Pain Symptom Manage 2010;39:1086-99.
36. Huang X, Zhang Q, Kang X, Song Y, Zhao W. Factor associated with cancer-related fatigue in breast cancer patients undergoing endocrine therapy in a urban setting: a cross-sectional study. BMC Cancer 2010; 10:453-460.

37. Holmes S. Preliminary investigations of symptom distress in two cancer patient population: evaluation of a measurement instrument. J Adv Nurs 1991;16:439-446.

38. Dicatto M. Anemia in cancer: some pathophysiological aspects. Oncologist 2003;8:19-21.

39. Jiang P, Wang S, Jiang D, Yu L, Tang L, Lai J. Association between cancer related fatigue and social support in patients after breast cancer chemotherapy in Changsha]. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2011;36(9):844-8.

40. Yilmazer N, Aydiner A, Ozkan S, Aslay I, Bilge N. A comparison of body image, self-esteem and social support in total mastectomy and breast-conserving therapy in Turkish women. Support Care Cancer 1994;2(4):238-41.

41. Schuler LA, Auger AP. Psychosocially influenced cancer: diverse early-life stress experiences and links to breast cancer. Cancer Prev Res (Phila) 2010;3:1365-70.

42. Geinitz H, Zimmermann FB, Thamm R, Keller M, Busch R, Molls M. Fatigue in patients with adjuvant radiation therapy for breast cancer: long-term follow-up. J Cancer Res Clin Oncol 2004;130: 327-333.

43. Okamura T, Akechi T, Kugaya A, Okamura H, Imoto S, Nakano T, et al. Factors correlated with fatigue in disease-free breast cancer patients: application of the Cancer Fatigue Scale. Support Care Cancer 2000; 8:215-222.

44. Kim SH, Son BH, Hwang SY, Han W, Yang J, Lee S. Fatigue and depression in disease-free breast cancer survivors: prevalence, correlates, and association with quality of life. J Pain Symptom Manag 2008;35:644-655.

45. Gottrup H, Andersen J, Arendt-Nielsen L, Jensen TS. Psychophysical examination in patients with postmastectomy pain. Pain 2000;87:275-284.

46. Eyigor S, Karapolat H, Kokmaz OK, Eyigor C, Durmaz B, Uslu R, et al. The frequency of fibromyalgia síndrome and quality of life in hospitalizad cancer patients. Eur J Cancer Care 2009;18:195-201.

47. McArdle WD, Katch FI, Katch VL. Exercise physiology. Energy, nutrition and performance, 5th edn. Philadelphia: LippincottWilliams & Wilkins, 2001.

48. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galva˜o DA, Pinto BM, et al. American College of Sports Medicine Roundtable on Exercise Guidelines for Cancer Survivors. Med Sci Sports Exerc 2010;42:1409-1426.

49. Dimeo F, Fetscher S, Lange W, Mertelsmann R, Keul J. Effects of aerobic exercise on the physical performance and incidence of treatment-related complications after high-dose chemotherapy. Blood 1997;90:3390-94.

50. Cramp F, Daniel J. Exercise for the management of cancer-related fatigue in adults.Cochrane Database Syst Rev 2008;6;(2):CD006145.

51. McNeely ML, Campbell KL, Rowe BH, Klassen TP, Mackey JR, Courneya KS. Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. CMAJ 2006;175:34-41.

52. Hayward R, Ruangthai R, Schneider CM, Hyslop RM, Strange R, Westerlind KC. Training enhances vascular relaxation after chemotherapy-induced vasoconstriction. Med Sci Sports Exerc 2004;36:428-434.

53. Aparicio VA, Ortega FB, Heredia JM, Carbonell-Baeza A, Sjostrom M, Delgado-Fernandez M: Handgrip strength test as a complementary tool in the assessment of fibromyalgia severity in women. Arch Phys Med Rehabil 2011;92:83-88.

54. van Sloten TT, Savelberg HH, Duimel-Peeters IG, Meijer K, Henry RM, Stehouwer CD, et al. Peripheral neuropathy, decreased muscle strength and obesity are strongly associated with walking in persons with type 2 diabetes without manifest mobility limitations. Diabetes Res Clin Pract 2011;91:32-39.

55. Wang AY, Sanderson JE, Sea MM, Wang M, Lam CW, Chan IH, et al. Handgrip strength, but not other nutrition parameters, predicts circulatory congestion in peritoneal dialysis patients. Nephrol Dial Transplant 2010;25:3372-3379.

56. Izawa KP, Watanabe S, Osada N, Kasahara Y, Yokoyama H, Hiraki K, et al. Handgrip strength as a predictor of prognosis in japanese patients

with congestive heart failure. Eur J Cardiovasc Prev Rehabil 2009;16:21-27.

57. Kaya T, Karatepe AG, Gunaydn R, Yetis H, Uslu A. Disability and healthrelated quality of life after breast cancer surgery: Relation to impairments. South Med J 2010;103:37-41.

58. Lipscombe LL, Hux JE. Trends in diabetes prevalence, incidence, and mortality in Ontario, Canada 1995-2005: a population-based study. Lancet 2007;369:750-6.

59. Saydah SH, Fradkin J,CowieCC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA 2004;291:335-42.

60. Ruiz J, Sui X, Lobelo F, Lee DC, Morrow JR, Jackson AW, et al. Muscular strength and adiposity as predictors of cáncer mortality in men. Cancer Epidemiol Biomarkers Prev 2009;18:1468-1476.

61. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, et al. Explaining the decrease in U.S. deaths fromcoronary disease, 1980-2000. N Engl J Med 2007;356:2388-98.

62. Warburton DER, Gledhill N, Quinney A. Musculoskeletal fitness and health. Can J Appl Physiol 2001;26(2):217-37.

63. Taylor NF, Dodd KJ, Shields N, Bruder A. Therapeutic exercise in physiotherapy practice is beneficial: a summary of systematic reviews 2002–2005. Aust J Physiother 2007;53:7-16.

64. Pedersen BK, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. Scand J Med Sci Sports 2006;16(1):3-63.

65. Kujala UM. Evidence for exercise therapy in the treatment of chronic disease based on at least three randomized controlled trials d summary of published systematic reviews. Scand J Med Sci Sports 2004;14:339-345.
66. Al-Majid S, Gray P. A Biobehavioral Model for the Study of Exercise Interventions in Cancer-related Fatigue. BRN 2009;10(4):381-391.
67. MacVicar MG, Winningham ML, Nickel JL. Effects of aerobic interval training on cancer patients' functional capacity. Nurs Res 1989;38:348-51.
68. Dimeo FC, Stieglitz RD, Novelli-Fischer U, Fetscher S, Keul J. Effects of physical activity on the fatigue and psychologic status of cancer patients during chemotherapy. Cancer 1999; 85: 2273–77.
69. Burham TR, Wilcox A. Effects of exercise on physiological and psychological variables in cancer survivors. Med Sci Sports Exerc 2002; 34:1863–67.
70. Campeau S, Nyhuis TJ, Sasse SK, Kryskow EM, Herlihy L, Masini CV, et al. Hypothalamic pituitary adrenal axis responses to low-intensity stressors are reduced after voluntary wheel running in rats. J Neuroendocrinol 2010;22:872–88.
71. Moyer CA, Rounds J, Hannum J. A meta-analysis of massage therapy research. Psychol Bull 2004;130:3–18.
72. Ross A, Thomas S. The health benefits of yoga and exercise: a review of comparison studies. J Altern Complement Med 2010;16:3–12.

73. Dibble SL, Luce J, Cooper BA, Israel J, Cohen M, Nussey B, et al. Acupressure for chemotherapy-induced nausea and vomiting: a randomized clinical trial. Oncol Nurs Forum 2007;34(4):813-20.

74. Arroyo-Morales M, Olea N, Martínez MM, Hidalgo-Lozano A, Ruiz-Rodríguez C, Díaz-Rodríguez, L. Psychophysiological effects of massage-myofascial release after exercise: a randomized sham-control study. J Altern Complem Med 2008;14 (10):1223–1229.

75. Arroyo-Morales, M, Olea N, Moreno-Lorenzo C, Martinez M, Díaz Rodríguez L, Hidalgo-Lozano, A. Effects of myofascial release after high intensity exercise. A randomized clinical trial**.** J Manip Physiol Ther 2008;31(3):217-223.

76. Arroyo-Morales M, Olea N, Ruíz C, del Castilo JD, Martínez M, Lorenzo C, et al. Massage after exercise—responses of immunologic and endocrine markers: a randomized single-blind placebo-controlled study. J Strength Cond Res 2009;23:638-44.

77. Thayer, Robert E. The biopsychology of mood and arousal. New Yok: Oxford University Press, 1989.

78. McNair DM, Lorr M, Droppleman LF. Manual for the Profile of Mood States. San Diego: Educational and Industrial Testing Services, 1971.

79. Lawton MP. Quality of life and the end of life. En Birren JM, Schaie KW(Eds.). Handbook of the psychology of aging. San Diego: Academic Press, 2001

80. Tsuji H, Venditti FJ, Manders ES, Evans JC, Larson MG, Feldman CL, et al. Reduced heart rate variability and mortality risk in an elderly cohort. the Framingham heart study. Circulation 1994;90:878-83.

81. Dishman RK, Nakamura Y, Garcia ME, Thompson RW, Dunn AL, Blair SN. Heart rate variability, trait anxiety, and perceived stress among physically fit men and women. Int J Psychophysiol 2000;37:121-33.

82. Manjer J, Kaaks R, Riboli E, Berglund G. Risk of breast cancer in relation to anthropometry, blood pressure, blood lipids and glucose metabolism: a prospective study within the Malmö Preventive Project. Eur J Cancer Prev 2001;10(1):33-42.

83. Jensen SB, Mouridsen HT, Reibel J, Brünner N, Nauntofte B. Adjuvant chemotherapy in breast cancer patients induces temporary salivary gland hypofunction. Oral Oncology 2008;44:162–173.

84. Bender CM, Sereika SM, Brufsky AM, Ryan CM, Vogel VG, Rastogi P, et al. Memory impairments with adjuvant anastrozole versus tamoxifen in women with early stage breast cancer. Menopause 2007;14:995–998.

85. Bower JE, Ganz PA, Aziz N, Bower JE, Ganz PA, Aziz N. Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue.Psychosom Med 2005;67:277-280.

86. Nater UM, Rohleder N. Salivary alpha-amylase as a noninvasive biomarker for the sympathetic nervous system: Current state of research. Psychoneuroendocrinology 2009;34:486-496.

87. Shirasaki S, Fujii H, Takahashi M, Sato T, Ebina M, Noto Y, et al. Correlation between salivary alpha-amylase activity and pain scale in patients with chronic pain. Reg Anesth Pain Med 2007;32**:**120-123.

88. Seugnet L, Boero J, Gottschalk L, Duntley SP, Shaw PJ. Identification of a biomarker for sleep drive in flies and humans*.* Proc Natl Acad Sci. 2006;103**:**19913-19918.

89. Conde ME, Sileo E, Aldrey O. Estandarización de niveles de IgAs en saliva de 269 niños anos del Hospital J.M de los Ríos de Caracas. Alergia, Asma e Inmunología 2001;3:119-28.

90. Jensen SB, Mouridsen HT, Reibel J, Brünner N, Nauntofte B. Adjuvant chemotherapy in breast cancer patients induces temporary salivary gland hypofunction. Oral Oncol 2008;44:162-73.

91. Martins RA, Cunha MR, Neves AP, Martins M, Teixeira-Veríssimo M, Teixeira AM. Effects of aerobic conditioning on salivary IgA and plasma IgA, IgG and IgM in older men and women. Int J Sports Med 2009;30:906-12.

92. Lim YM, Hong GR. Effect of 16-week Kouk-Sun-Do exercise on physical fitness, emotional state, and immunoglobulin A in community-dwelling elders in Korea. Appl Nurs Res 2010;23:91–100.

93. Bendz I, Fagevik Olsen M. Evaluation of immediate versus delayed shoulder exercises after breast cancer surgery including lymph node dissection—a randomised controlled trial. Breast 2002;11:241–248.

OBJETIVOS

General:

Con esta Tesis Doctoral Europea (TDE) se ha perseguido mejorar la comprensión sobre la fatiga inducida por el cáncer de mama estudiando su relación con factores de distinta naturaleza, así como analizar la efectividad de un programa multimodal de ejercicio terapéutico en la fatiga en mujeres supervivientes de cáncer de mama.

Específicos:

- Estudiar la relación entre umbrales de dolor a la presión, la movilidad del hombro, el estado de ánimo, la percepción de dolor, la resistencia muscular y la calidad de vida con la fatiga en supervivientes de cáncer de mama para establecer un modelo explicativo sobre este síntoma (**Artículo I**).
- Examinar la relación entre la fuerza isométrica de prensión con el dolor, la condición física, el estado psicológico, la calidad de vida, la fatiga y el estado de ánimo en supervivientes con cáncer de mama (**Artículo II**).
- Determinar la eficacia de un programa de actividad terapéutica multimodal de ocho semanas sobre la fatiga inducida por el cáncer de mama (**Articulo III y IV**).
- Analizar la eficacia de un programa de actividad terapéutica multimodal sobre parámetros físicos, fisiológicos y psicológicos relacionados con la FIC (**Articulo III y IV**).

AIMS

Overall:

With this European PhD Thesis has sought to improve the understanding of fatigue-induced breast cancer and their relation to factors of different nature, and to analyze the effectiveness of a multimodal therapeutic exercise program on fatigue in women breast cancer survivors.

Specific:

- Study the relationship between pain thresholds to pressure, shoulder mobility, mood, perception of pain, muscular endurance and quality of life with fatigue in breast cancer survivors to establish a model explaining this symptom (**Paper I**).
- Examine the relationship between isometric grip strength with pain, physical condition, psychological status, quality of life, fatigue and mood in breast cancer survivors (**Paper II**).
- Determine the effectiveness of a multimodal therapeutic activity of eight weeks on the cancer-related fatigue. (**Papers III and IV**).
- Analyze the effectiveness of a multimodal therapeutic activity program on physical parameters, physiological and psychological issues related to cancer-related fatigue (**Papers III and IV**).

MATERIAL Y MÉTODOS [MATERIAL AND METHODS]

En la **tabla 1** se muestra el material y los métodos utilizados en los diferentes artículos que constituyen la presente memoria de Tesis.

Tabla 1: Tabla resumen del material y métodos utilizados en esta memoria de Tesis.

PAPER	STUDY DESIGN	PARTICIPANTS	INTERVENTION	MAIN VARIABLES STUDIED	METHODS - INSTRUMENTS
I.Associatios among musculoskeletal impairments, depression, body image and fatigue in breast cancer survivors within the first year after treatment	A cross-sectional	59 BCS	Not aplicable	Fatigue PPT index Mood Quality of life Shoulder range of motion Isometric endurance of trunk flexors Spontaneous neck, axillary/shoulder pain	PFS Standard pressure algometer POMS QLQ-BR23 Standard goniometric Trunk curl static endurance test 11-point numerical point rate scale
II. The handgrip strength test as a measure of physical function in breast cancer survivors: relationship with quality of life, cancer related symptoms, physical and phycological parameters.	A cross-sectional	95 BCS	Not aplicable	Upper body muscular strength Llower body muscular strength Shoulder and cervical active range of motion Functional capacity Lower body endurance Endurance of trunk flexors Mood Fatigue Quality of life Spontaneous neck and axillary/shoulder pain PPT index, Heart rate and heart rate variability Blood Pressure Salivary flow rate.	Handgrip test Vertical jump Standard goniometric 6-minutes walk test Multiple sit-to-stand test Trunk curl static endurance test POMS PFS QLQ-BR23 11-point numerical point rate scale Standard pressure algometer Holter Tensiometer 3 minutes saliva samplimg (passive drooling technique). Determination by luminescence

PAPER	STUDY DESIGN	PARTICIPANTS	INTERVENTION	MAIN VARIABLES STUDIED	METHODS - INSTRUMENTS
III. A multimodal exercise program and multimedia support reduce cancer-related fatigue in breast cancer survivors: a randomized controlled clinical trial.	A randomized controlled clinical trial.	78 BCS Experimental group (n=38) Control group (=40)	8 weeks multimodal physical therapy CUIDATE program: physical training and physical recovery procedures, 3 times/week. Multimedia instructional package with CUIDATE exercise (experimental group) Usual care with physical activity control (control group)	Shoulder and cervical active range of motion Salivary flow rate Cortisol, Iga and α-Amylase secretions	Standard goniometric 3 minutes saliva samplimg (passive drooling technique). Determination by luminescence
IV. Effectiveness of core estability exercise and recovery myofascial release massage on fatigue in breast cancer survivors: a randomized controlled clinical trial.	A randomized controlled clinical trial.	78 BCS Experimental group (n=38) Control group (=40)	8 weeks multimodal physical therapy CUIDATE program: physical training and physical recovery procedures, 3 times/week. Multimedia instructional package with CUIDATE exercise (experimental group) Usual care (control group)	Mood (fatigue) Endurance of trunk flexors Lower body muscular strength,	POMS Trunk curl static endurance test Multiple sit-to-stand test.

RESULTADOS Y DISCUSIÓN [RESULTS AND DISCUSSION]

En los siguientes artículos publicados y/o sometidos se exponen tanto los resultados como la discusión de los mismos.

I. ETIOLOGÍA DE LA FATIGA INDUCIDA POR EL CÁNCER

Artículo I

"Associations among musculoskeletal impairments, depression, body image and fatigue in breast cancer survivors within the first year after treatment".

Cantarero-Villanueva I, Fernández-Lao C, Fernández-DE-Las-Peñas C, Díaz-Rodríguez L, Sánchez-Cantalejo E, Arroyo-Morales M.

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Original article

Associations among musculoskeletal impairments, depression, body image and fatigue in breast cancer survivors within the first year after treatment

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CANTARERO-VILLANUEVA I., FERNÁNDEZ-LAO C., FERNÁNDEZ-DE-LAS-PEÑAS C., DÍAZ-RODRÍGUEZ L., SANCHEZ-CANTALEJO E. & ARROYO-MORALES M. (2011) *European Journal of Cancer Care* **20**, 632–639
Associations among musculoskeletal impairments, depression, body image and fatigue in breast cancer survivors within the first year after treatment

The aim of the current study was to investigate the relationship between pressure pain thresholds, shoulder movement, mood state, pain perception, muscle endurance, quality of life and fatigue in breast cancer survivors (BCS). Fifty-nine BCS reporting fatigue were examined at 6 months post-treatment. Women completed the Piper Fatigue Scale, the Breast Cancer-Specific Quality of Life Questionnaire, the Profile of Mood State, and neck–shoulder visual analogue scale. Additionally, shoulder flexion range of motion, the McQuade test (trunk flexor endurance) and pressure pain thresholds over the C5-C6 joint, the deltoid muscle, the second metacarpal and tibialis anterior muscle were assessed. Fatigue was greater in those patients with higher depression ($r = 0.45$, $P < 0.05$), higher shoulder pain ($r = 0.39$, $P < 0.05$), higher neck pain ($r = 0.46$, $P < 0.01$), lower body image ($r = -0.34$, $P < 0.05$) and reduced shoulder movement ($r = -0.32$, $P < 0.05$). Regression analyses demonstrated that depression, cervical pain intensity, body image and shoulder mobility were associated with fatigue ($r = 0.55$, $P < 0.001$). A psychological state characterised with higher depression and reduced body image and a physical impairment with higher cervical pain intensity and reduced shoulder mobility confirm multidimensional character of fatigue in BCS.

Keywords: fatigue, breast cancer, pain, depression, body image, range of motion.

INTRODUCTION

Breast cancer is increasingly considered a chronic disease because of the high survival rate (Markes *et al.* 2006). In Spain the survival rate for breast cancer survivors is 83% at 5 years after intervention (Pollán *et al.* 2007), slightly higher than in Europe (Istituto Superiore di Sanita', Centro Nazionale di Epidemiologia, and Istituto Nazionale per la cura e lo studio dei Tumori 2009). The high 5-year survival rate is related to improvements in effectiveness of treatment (Ganz 2005), an increase in early diagnosis (Pollán *et al.* 2007; Cabanes *et al.* 2009) and recurrence prevention (Martín *et al.* 2006).

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Breast cancer survivors suffer from clinical manifestations, including physical and psychological symptoms that have an impact on their health status (Pinto & Trunzo 2005; Pollán *et al*. 2007). In fact, breast cancer results in fatigue in up to 66% of individuals after treatment (Kim *et al*. 2008). Fatigue is a multidimensional symptom (Denieffe & Gooney 2010) which can be present for years after the cancer (Bower *et al*. 2006, 2009), inducing a physical, emotional, social and economic impact (Prue *et al*. 2006).

To assist patients in coping with fatigue, it is necessary to understand its mechanism and relationships with other associated risk factors, such as, socio-economic habits (Akechi *et al*. 1999), treatment received (Mast 1998), anxiety (Geinitz *et al*. 2004), pain (Bower *et al*. 2000; Kim *et al*. 2008), sleep disruption (Ancoli-Israel *et al*. 2001) or depression (Okamura *et al*. 2000; Geinitz *et al*. 2001; Reuter & Harter 2004; Bower *et al*. 2006). Relationships among variables such as sensory hypersensitivity and movement impairments have not been examined in these studies. Evidence has shown that breast cancer survivors suffer swelling of the arm or shoulder, paraesthesia, phantom sensations (Peuckmann *et al*. 2009), pressure hypersensitivity and myofascial pain (Fernández-Lao *et al*. 2010). It is currently not known if these variables may have an influence in perceived fatigue after breast cancer surgery.

Finally, we cannot rule out the possible influence of psychological factors in the development of fatigue. Some studies have found disorders related to self-esteem, body image and self-hatred (Yilmazer *et al*. 1994) after breast cancer; however, no study has previously investigated the relationships of these variables with fatigue. Kim *et al*. found a significant relationship between fatigue, depression, quality of life, functionality and emotional concerns in breast cancer survivors (Kim *et al*. 2008). It may be possible that psychological status also has an influence in fatigue perception.

To the best of the authors' knowledge, no previous study has investigated the association between sensory hypersensitivity, movement impairments and psychological factors with fatigue in breast cancer survivors. The aim of this study was to investigate the relationship between pressure pain thresholds (PPTs), shoulder movement, mood state, pain perception, muscle endurance and quality of life with fatigue in breast cancer survivors.

METHODS

Study population

A cross-sectional design was used in this study. Fifty-nine women from the Breast Oncology Unit of University Hospital Virgen de las Nieves, Granada (Spain) participated. Eligible women had a diagnosis of breast cancer (grades I–IIIA), were between 18 and 75 years and were at least 1 month from primary treatment for breast cancer (surgery, radiation, chemotherapy). Women were excluded if they were receiving radiation or chemotherapy for cancer at the time of the study or any physical limitation that prevented participation in performance tests. Participants were recruited if the oncologist who referred patients identified three to five of the following physical findings: neck–shoulder pain, reduced range of motion in neck shoulder complex, reduced physical capacity, psychological problems, increased fatigue, sleep disturbances or problems in coping with reduced physical/psychosocial functioning. All measurements were conducted at the Faculty of Health Sciences, University of Granada. The Ethical approval for this study was granted by the Ethics Committee of the University Clinic Hospital San Cecilio Granada (Spain).

Data collection

Eligible patients were contacted by telephone by two oncologists of the Breast Oncology Unit of University Hospital Virgen de las Nieves, and those who agreed to participate were scheduled for an initial testing appointment. Upon arrival, patients received a complete explanation of the study protocol and signed the consent form. Demographic and clinical characteristics, including stage, date of diagnosis, and the date and type of breast cancer treatment were self-reported. Medical records were obtained from their oncologist. If clinical and self-reported data were not consistent, we gave precedence to the clinical data.

Measures

Individuals completed the following questionnaires and scales: Piper Fatigue Scale (PFS), European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer-Specific Quality of Life Questionnaire (QLQ-BR23), Profile of Mood State (POMS) and cervical and shoulder visual analogue scale (VAS). After the questionnaires were completed, they underwent the following testing: goniometric shoulder measurement, McQuade test and PPT levels. The same assessor (a physiotherapist with more than 10 years of experience on musculoskeletal pain rehabilitation), blinded to the participants' fatigue score, carried out the physical measurements.

The VAS provides a continuous scale for subjective pain estimation and consists of a straight line, the limits of

which carry a verbal description of each extreme of the symptom (0: no pain; 10: very severe pain). The VAS has been widely used as an exact and reliable measurement of pain.

Fatigue was measured with the Spanish version of PFS (López-Delgado *et al.* 2003). PFS is a validated tool measuring cancer-related fatigue (Piper *et al.* 1998) and it was selected for its particular focus on fatigue and pain (Giacalone *et al.* 2010). The PFS consists of 22 numerical items assessing fatigue experienced by the patients. Using a 0–10 numeric scale, the PFS measures four dimensions of subjective fatigue: behavioural/severity, affective meaning, sensory and cognitive/mood (Piper *et al.* 1998). The total fatigue score is calculated by adding the four subscale scores and dividing this sum by four. The reliability of PFS has been found to be high (Cronbach's α = 0.96; Piper *et al.* 1998; López-Delgado *et al.* 2003).

The Spanish version of QLQ-BR23 is a 23-item breast cancer questionnaire assessing the quality of life in breast cancer (Sprangers *et al.* 1996; Arrarás *et al.* 2001). It incorporates two functional scales (body image and sexual functioning) and three symptom scales (arm symptoms, breast symptoms and systematic therapy side effects). Furthermore, the remaining items assess sexual enjoyment and shock due to hair loss. The reliability of the QLQ-BR23 has been found moderate to high (Cronbach's α range 0.46–0.94; Sprangers *et al.* 1996).

The POMS questionnaire consists of 63 items on mood state. Scores are grouped into six subscales: tension–anxiety, depression–dejection, anger–hostility, vigour, fatigue and confusion. Each subscale score is evaluated on a 5-point scale (0–4). Depression subscale score was converted into *t*-scores for the statistical analysis (Hernández-Mendo & Ramos-Pollán 1996). The reliability of Spanish version used has been found high (Cronbach's α range 0.76–0.91; Andrade *et al.* 2002).

A plastic 41-cm universal two-arm goniometer was used to measure the passive movement of shoulder flexion, abduction and lateral rotation of the affected arm. Patients were seated in an upright position with their thumb facing upwards. The assessor moved the limb upwards to the end of range of passive motion into flexion, abduction and lateral rotation. The angle of movement was assessed with the goniometer using anatomical bony landmarks of the patient (American Medical Association 2008). The intra-test reliability of goniometer used to measure shoulder movement has been found to be excellent (ICC = 0.94, 95% CI = 0.91–0.99; Mullaney *et al.* 2010).

To test isometric endurance of trunk flexors, participants were supine with their arms crossed over the chest, hands on the opposite shoulders, hips bent, and knees and feet apart. Participants were asked to nod and continue to lift their head and shoulders until the inferior angle of the scapula was lifted from the table and were instructed to maintain the position as long as possible. The number of seconds that the position was maintained with a maximum of 120 s was recorded. The test proved reliable with reliability coefficients of >0.97 for the repeated tests (McGill *et al.* 1999).

Pressure pain threshold, defined as the minimal amount of pressure where a sensation of pressure changes to pain (Vanderweeën *et al.* 1996) was also assessed on affected side. An electronic algometer (Somedic AB, Farsta, Sweden) was used to measure PPT (kPa). The pressure was applied at approximately rate of 30 kPa/s. Participants were instructed to press the switch when the sensation first changed from pressure to pain. The mean of three trials (intra-examiner reliability) was calculated and used for the main analysis. A 30-s rest period was allowed between each trial. The reliability of pressure algometry has been found to be high the same day (ICC = 0.91, 95% CI = 0.82–0.97; Chesterson *et al.* 2007) and between four separate days (ICC = 0.94–0.97; Jones *et al.* 2007). PPTs were assessed over the C5-C6 zygapophyseal joint, deltoid muscle, second metacarpal and tibialis anterior muscle. The order of point assessment was randomised between participants.

Statistics

Means and standard deviations were calculated to describe the sample. Pearson product–moment correlation coefficients were calculated to determine relationships between the dependent measure (fatigue) and the following independent variables: age, time from the diagnosis, body image, depression, passive shoulder movement, VAS cervical, VAS shoulder, abdominal endurance, PPT C5-C6 joint, PPT deltoid, PPT second metacarpal and PPT tibialis anterior. Similar analyses were used to examine relationships between independent variables to check for multicollinearity and shared variance between the measures. Stepwise regression analysis was finally used to determine the independent variables that contributed significantly to variance in fatigue. The significance criterion of the critical *F*-value for entry into the regression equation was set at $P < 0.05$. Finally, the final model was validated using bootstrapping. Specifically, the bootstrapping method was carried out with repeated samples of the same size as the original samples in replacement. Two thousand replications were produced to estimate bootstrap bias-corrected and accelerated confidence intervals (bca CI). For statistical analyses, significance level was set at $P < 0.05$. All analyses were performed using R software (2.9.3).

RESULTS

Demographic data, sensory measures and questionnaires

Our sample consisted of 59 short-term breast cancer survivors with a mean age of 49.5 ± 8.9 years. Women had university level education (44.8%), were married (72.9%), Caucasian and from the Granada metropolitan area. Most women had breast cancer stage I (29%) or stage II (56%) cancer, and received both radiation and chemotherapy (84.8%) as adjuvant treatment after surgery. Forty-one (70%) women had received lumpectomy, whereas the remaining 18 (30%) had received mastectomy surgery. In addition, 18 (30.5%) women were taken antagonist of estrogen receptors (tamoxifen), 22 (37.3%) aromatase inhibitors (anastrozole) and 6 (10.2%) monoclonal antibody HER2 (trastuzumab). Additionally, 11% of the participants were taken analgesics (paracetamol) to control increased pain. None patient received rehabilitation treatment. Participants showed moderate fatigue (mean ± SD: 5.8 ± 1.9), high depression (mean ± SD: 51.1 ± 10.9) and reduced body image (mean ± SD: 63.8 ± 30.0). The intensity of neck pain was moderate (mean ± SD: 5.6 ± 3.2), whereas the intensity of shoulder pain was low to moderate (mean ± SD: 3.9 ± 3.7). Table 1 summarises the demographic and clinical data of the patients.

Correlational analyses

Significant negative correlations between fatigue and body image ($r = –0.34$, $P < 0.01$), fatigue and passive shoulder flexion ($r = –0.32$, $P = 0.01$), fatigue and PPT levels over the deltoid muscle ($r = –0.40$, $P < 0.01$) and fatigue and PPT levels over the second metacarpal ($r = –0.41$, $P < 0.01$) were found: the greater the self-reported fatigue, the lower the self-perception of body image, the passive shoulder flexion or the PPT levels. In addition, significant positive correlations between fatigue and depression ($r = 0.45$, $P < 0.001$), fatigue and neck pain intensity ($r = 0.46$, $P < 0.001$), and fatigue and shoulder pain intensity ($r = 0.39$, $P < 0.01$) were also found: the greater the fatigue, the higher the level of depression, or the higher the intensity of neck or shoulder pain.

In addition, significant correlations existed among the independent variables ($r = –0.33 < r < 0.63$; Table 2), but none was considered to be multi-collinear (defined as $r > 0.80$); therefore, each one was included in regression analyses.

Regression analyses

Stepwise regression analyses revealed that passive shoulder flexion, depression, body image and cervical pain intensity were independent and significant predictors of fatigue, and when combined, they explained 54.3% of the variance in fatigue scores (see Table 3).

DISCUSSION

The objective of the current study was to investigate the relationships between fatigue, pressure pain sensitivity, movement impairments and psychological factors in breast cancer survivors. We found significant low to moderate negative associations between fatigue, body image, passive shoulder flexion and PPTs over the deltoid muscle and the second metacarpal. We also found positive associations between fatigue, depression, and neck and shoulder pain intensity. In fact, results from the regression analyses showed that body image, depression, neck pain

Table 1. Demographics data and baseline variable scores

	Mean (95% CI)	SD	Range
Age (years)	49.5 (47.1–51.8)	8.9	30–73
Time since diagnosis (months)	12.1 (10.9–13.3)	4.5	6–35
Fatigue score*	5.8 (5.2–6.3)	1.9	1.0–9.8
Body image†	63.8 (56.0–71.6)	30.0	0–100
Depression POMS	51.1 (48.2–54.0)	10.9	37–80
Passive flexion shoulder (°)	157.4 (152.9–161.8)	16.7	90–175
VAS cervical (0–10)	5.6 (4.7–6.6)	3.2	1–10
VAS shoulder (0–10)	3.9 (2.8–4.9)	3.7	1–9
McQuade test (s)	27.3 (21.9–32.6)	20.6	4.1–90
PPT C5-C6 zygapophyseal (kPa)	151.1 (131.7–171.6)	68.5	52.0–318.3
PPT deltoid muscle (kPa)	178.7 (153.7–203.7)	88.8	23.3–414.3
PPT second metacarpal (kPa)	195.1 (171.5–218.7)	82.9	50.3–431.0
PPT tibialis anterior (kPa)	288.9 (257.2–320.5)	112.6	257.2–320.5

*Measured by the Fatigue Global Piper Scale.
†Measured by European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire.
POMS, Profile of Mood State; VAS, neck and shoulder visual analogue scale; PPT, pressure pain threshold.

Table 2. Pearson product–moment correlation matrix for study variable

Variable	Fatigue Piper	Age	Time diagnosis	Body image	Depression POMS	Passive flexion shoulder	VAS cervical	VAS shoulder	McQuade test	PPT deltoid	PPT hand	PPT tibialis anterior	PPT C5-C6 joint
Fatigue Piper	1.00	–	–	–	–	–	–	–	–	–	–	–	–
Age	–0.02	1.00	–	–	–	–	–	–	–	–	–	–	–
Time diagnosis	–0.22	0.14	1.00	–	–	–	–	–	–	–	–	–	–
Body image	–0.34*	0.20	0.01	1.00	–	–	–	–	–	–	–	–	–
Depression POMS	0.45**	–0.02	0.01	–0.20	1.00	–	–	–	–	–	–	–	–
Flexion shoulder	–0.32*	–0.09	0.22	0.08	0.08	1.00	–	–	–	–	–	–	–
VAS cervical	0.46**	–0.05	0.18	–0.12	0.09	–0.20	1.00	–	–	–	–	–	–
VAS shoulder	0.39*	–0.09	0.17	–0.28*	0.32*	–0.23	0.57**	1.00	–	–	–	–	–
McQuade test	–0.20	–0.13	0.08	0.17	–0.01	0.37**	0.15	0.07	1.00	–	–	–	–
PPT deltoid	–0.40*	0.26	0.12	–0.08	–0.27	0.27*	–0.35**	–0.23*	–0.02	1.00	–	–	–
PPT hand	–0.41*	0.13	–0.10	0.15	–0.33*	0.08	–0.40**	–0.33*	–0.09	0.60**	1.00	–	–
PPT tibialis	0.19	0.19	0.20	–0.02	–0.19	0.24	–0.16	–0.04	0.15	0.63**	0.48**	1.00	–
PPT C5-C6	–0.6	0.23	–0.19	–0.03	–0.00	–0.15	–0.16	–0.18	0.00	0.62**	0.57**	0.56**	1.00

*$P < 0.05$; **$P < 0.01$.
POMS, Profile of Mood State; VAS, neck and shoulder visual analogue scale; PPT, pressure pain threshold.

Table 3. Summary of stepwise regression analyses to determine predictors of fatigue ($r^2 = 55.5\%$)

Independent variable	β	95% CI	t	P	Bootstrap β	Bootstrap bias-corrected and accelerated 95% CI
Intercept	5.26	0.20–10.31	2.03	0.04	5.26	(–0.13)–10.63
Shoulder passive flexion	–0.02	(–0.04)–0	–2.06	0.04	–0.03	(–0.05)–0.003
Body image	–0.01	(–0.02)–0	–2.07	0.04	–0.02	(–0.02)–0.006
Neck pain intensity	0.21	0.10–0.33	3.50	<0.001	0.21	0.08–0.33
Depression	0.09	0.07–0.11	4.90	<0.001	0.09	0.05–0.13

intensity and shoulder flexion were significant predictors of fatigue, whereas clinical characteristics, trunk muscle endurance and PPTs were not. Current findings suggest that self-reported psychological data (body image, depression), neck pain intensity and shoulder mobility have a relevant contribution to fatigue in breast cancer survivors.

In our sample size, 82% of breast cancer survivors reported fatigue (32% severe) following the criteria previously reported by Winters-Stone *et al.* (2008). Our results showed higher prevalence of fatigue with respect to previous studies (Kim *et al.* 2008; Winters-Stone *et al.* 2008). Differences between these studies and the current one may be related to the fact that time from the diagnosis in our sample of breast cancer survivors was shorter (mean: 4.5 months) than in previous studies. Fatigue related to breast cancer may be caused by the disease itself, the treatment received, the physical symptoms or conditions resulting from the disease. Our study is the first to specifically examining fatigue determinants related to musculoskeletal impairments resulting from breast cancer. Since rehabilitation strategies are focused in reducing pain and clinical repercussions from breast cancer, particularly fatigue, understanding potential determinants for fatigue may assist in the rehabilitation process in these patients.

The multiple regression analysis showed that the intensity of neck pain and shoulder mobility contributed to cancer-related fatigue in our sample of breast cancer survivors. This was reflected by higher neck pain intensity and reduced shoulder range of motion in breast cancer survivors reporting greater fatigue. These results are in accordance with previous studies (Bower *et al.* 2000). Bower (2007) has suggested that increased pain sensitivity associated with pro-inflammatory cytokines may be a possible aetiologic factor of fatigue-related breast cancer. Neck pain may lead to fatigue through its effects on mood state, activity level and sleep (Bower *et al.* 2000; Ancoli-Israel *et al.* 2004). Besides, the fatigue–pain association could be mediated by the belief that pain is indicative of progressive disease or recurrence. In fact, our model reflects a depressed mood and increased pain perception associated with higher fatigue scores, which supports this hypothesis. Kim *et al.* (2008) found arm/shoulder impairments as a risk factor common to fatigue and depression in breast cancer survivors. Therefore, a reduction of neck pain combined with an improvement in mobility of the shoulder–cervical complex could contribute to reducing fatigue perception. Future studies are in progress to determine if fatigue is influenced by improving shoulder–cervical function in breast cancer survivors.

Different factors can explain the relationship between cervical and/or shoulder impairments and fatigue. Fernández-Lao *et al*. (2010) showed the existence of multiple active trigger points in neck and shoulder muscles related to greater neck pain intensity in breast cancer survivors. In fact, trigger points are present in different syndromes such as fibromyalgia, which is frequent in cancer survivors (Eyigor *et al*. 2009). We suggest that breast cancer may enhance the experience of pain at distant sites presumably via alterations in neuroendocrine profiles or direct sensitising effects on the central nervous system. These effects could be in relation with fatigue.

We also found a relationship between pressure pain sensitivity and fatigue in breast cancer survivors, although the regression analysis did not identify this association. Previous studies suggested the presence of hyperexcitability of the central nervous system in breast cancer survivors (Gottrup *et al*. 2000; Fernández-Lao *et al*. 2010). We do not know if the management of muscle impairments may be an appropriate strategy to influence fatigue in breast cancer survivors. Future studies are now needed to elucidate the role of pressure pain hypersensitivity in breast cancer-related fatigue.

The fact that fatigue is also associated with depression in breast cancer survivors is not new (Geinitz *et al*. 2004; Reuter & Harter 2004). The relationship between fatigue and depression is bidirectional and a complex process; as fatigue is a symptom of depression, fatigue can induce depression and both fatigue and depression may be symptoms of an underlying biologic disease (Bower *et al*. 2000). Drug-induced neurotoxicity during treatment can constitute a common origin to fatigue and depression in breast cancer survivors. From a clinical point of view, these findings highlight the importance of carefully screening for depression in fatigued breast cancer survivors.

Finally, data from the current study suggest that body image dissatisfaction is also related to fatigue. Breast cancer survivors perceiving body image dissatisfaction had more fatigue than those who were satisfied with their body image. These results confirm that body image is a human behaviour which depends on vitality and physical functioning (Mock 1993). In fact, better body image and reduced fatigue assist with coping with breast cancer (Pikler & Winterowd 2003). Breast cancer survivors have expressed the need for support in changing body image (Chung *et al*. 2009) and fatigue (Winters-Stone *et al*. 2008) with multidimensional exercise programmes (Adamsen *et al*. 2004).

We should recognise some limitations of the study. First, we included a relative small sample size ($n = 59$) and used a cross-sectional design. However, because of the small sample size, the number of independent variables entered in the regression analysis was limited to reduce the likelihood of a type II error. Second, pain could be underestimated because reluctance to report pain, fear of side effects and the belief that pain is indicative of progressive disease. Third, other relevant outcomes such as anxiety or cytokine levels should be examined in future research to provide more global information about relationship between pain and fatigue. Additionally, due to the cross-sectional study design, a cause and effect relationships between those variables associated with fatigue cannot be suggested.

CONCLUSION

The current study described significant associations between fatigue, body image, passive shoulder flexion, pressure pain sensitivity, depression, and neck and shoulder pain intensity in breast cancer survivor. Body image, depression, neck pain intensity and shoulder passive flexion were significant predictors of fatigue in breast cancer survivors. Current findings suggest that self-reported psychological data (body image, depression), neck pain intensity and shoulder mobility can have a relevant contribution to fatigue in women with breast cancer. Therapists and/or specialist nurses working with a breast cancer population should take in account these relationships to improve the management of fatigue-related cancer. Multidimensional programmes with pain control strategies, mobility exercise and cognitive behavioural therapy could help patients to cope with fatigue-related cancer.

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REFERENCES

Adamsen L., Midtgaard J., Andersen C., Quist M., Moeller T. & Roerth M. (2004) Transforming the nature of fatigue through exercise: qualitative findings from a multidimensional exercise programme in cancer patients undergoing chemotherapy. *European Journal of Cancer Care* **13**, 262–270.

Akechi T., Kugaya A., Okamura H., Yamawaki S. & Uchitomi Y. (1999) Fatigue and its associated factors in ambulatory cancer patients: a preliminary study. *Journal of Pain and Symptom Management* **17**, 42–48.

American Medical Association (2008) *Guides to the Evaluation of Permanent*

Impairment, 6 edn. AMA, Chicago, IL, USA.

Ancoli-Israel S., Moore P.J. & Jones V. (2001) The relationship between fatigue and sleep in cancer patients: a review. *European Journal of Cancer Care* **10**, 245–255.

Ancoli-Israel S., Soares C.N., Gaeta R. & Benca R.M. (2004) Insomnia in special populations: effects of aging, menopause, chronic pain, and depression. *Postgraduate Medicine* **116**, 33–47.

Andrade E.M., Arce C. & Seoane G. (2002) Adaptación al español del cuestionario 'Perfil de los Estados de Ánimo' en una muestra de deportistas. *Psicothema* **14**, 708–713.

Arrarás J.L., Tejedor M., Illaramendi J.J., Vera R., Pruja E., Marcos M., Arias F. & Valerdi J.J. (2001) El cuestionario de calidad de vida para cáncer de mama de la EORTC, QLQ-BR23: estudio psicométrico con una muestra española. *Psicología Conductal* **9**, 81–97.

Bower J.E. (2007) Cancer-related fatigue: links with inflammation in cancer patients and survivors. *Brain, Behavior, and Immunity* **21**, 863–871.

Bower J.E., Ganz P.A., Desmond K., Bernaards C., Rowland J., Meyerowitz B. & Belin T.R. (2000) Fatigue in Breast cancer survivors: occurrence, correlates, and impact on quality of life. *Journal of Clinical Oncology* **18**, 743–753.

Bower J.E., Ganz P.A., Desmond K., Bernaards C., Rowland J., Meyerowitz B.E. & Belin T.R. (2006) Fatigue in long-term breast carcinoma survivors. A longitudinal investigation. *Cancer* **106**, 751–758.

Bower J.E., Ganz P.A., Tao M.L., Hu W.H., Belin T.R., Sepah S., Cole S. & Aziz N. (2009) Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. *Clinical Cancer Research* **15**, 5534–5540.

Cabanes A., Vidal E., Pérez-Gómez B., Aragonés N., López-Abente G. & Pollán M. (2009) Age-specific breast, uterine and ovarian cancer mortality trends in Spain: changes from 1980 to 2006. *Cancer Epidemiology* **33**, 169–175.

Chesterson L.S., Sim J., Wright C.C. & Foster N.E. (2007) Inter-rater reliability of algometry in measuring pressure pain thresholds in healthy humans, using multiple raters. *Clinical Journal of Pain* **23**, 760–766.

Chung L.K., Cimprich B., Janz N.K. & Mills-Wisneski S.M. (2009) Breast Cancer Survivorship Program: testing for cross-cultural relevance. *Cancer Nursing* **32**, 236–245.

Denieffe S. & Gooney M. (2010) A meta-synthesis of women's symptoms experience and breast cancer. *European Journal of Cancer Care* **6**, doi: 10.1111/j.1365-2354.2010.01223.x [Epub before print].

Eyigor S., Karapolat H., Kokmaz O.K., Eyigor C., Durmaz B., Uslu R. & Uyar M. (2009) The frequency of fibromyalgia syndrome and quality of life in hospitalized cancer patients. *European Journal of Cancer Care* **18**, 195–201.

Fernández-Lao C., Cantareno-Villanueva I., Fernández-de-las-Peñas C., Del-Moral-Ávila R., Arendt-Nielsen L. & Arroyo-Morales M. (2010) Myofascial trigger points in neck and shoulder muscles and widespread pressure pain hypersensitivity in patients with post-mastectomy pain: evidence of central spreading sensitisation. *Clinical Journal of Pain* **26**, 798–806.

Ganz P.A. (2005) A teachable moment for oncologists: cancer survivors, 10 million strong and growing! *Journal of Clinical Oncology* **23**, 5458–5460.

Geinitz H., Zimmermann F.B., Stoll P., Thamm R., Kaffenberger W., Ansorg K., Keller M., Busch R., van Beuningen D. & Molls M. (2001) Fatigue, serum cytokine levels, and blood cell counts during radiotherapy of patients with breast cancer. *International Journal of Radiation Oncology, Biology, Physics* **51**, 691–698.

Geinitz H., Zimmermann F.B., Thamm R., Keller M., Busch R. & Molls M. (2004) Fatigue in patients with adjuvant radiation therapy for breast cancer: long-term follow-up. *Journal of Cancer Research and Clinical Oncology* **130**, 327–333.

Giacalone A., Polesel J., De Paoli A., Colussi A.M., Sartor I., Talamini R. & Tirelli U. (2010) Assessing cancer-related fatigue: the psychometric properties of the Revised Piper Fatigue Scale in Italian cancer inpatients. *Supportive Care in Cancer* **18**, 1191–1197.

Gottrup H., Andersen J., Arendt-Nielsen L. & Jensen T.S. (2000) Psychophysical examination in patients with post-mastectomy pain. *Pain* **87**, 275–284.

Hernández-Mendo A. & Ramos-Pollán C. (1996) Herramienta 2: Informatización del Profile of Mood Status de MacNair, Lorr y Dropleman. In: *Introducción a la Informática Aplicada a la Psicología del Deporte* (eds Hernández Mendo A. & Ramos Pollán R.), pp. 55–85. Ra-Ma, Madrid, Spain.

Istituto Superiore di Sanita', Centro Nazionale di Epidemiologia, and Istituto Nazionale per la cura e lo studio dei Tumori (2009) *The EUROCARE-4 database on cancer survival in Europe*. Available at: http://www.eurocare.it/Results/tabid/79/Default.aspx#longsurv0002

Jones D.H., Kilgour R.D. & Comtois A.S. (2007) Test-retest reliability of pressure pain threshold measurements of the upper limb and torso in young healthy women. *Journal of Pain* **8**, 650–656.

Kim S.H., Son B.H., Hwang S.Y., Han W., Yang J., Lee S. & Yun Y.H. (2008) Fatigue and depression in disease-free breast cancer survivors: prevalence, correlates, and association with quality of life. *Journal of Pain and Symptom Management* **35**, 644–655.

López-Delgado T., O'Keally Pérez P. & Madrid-Reques M. (2003) La fatiga en el cáncer: impacto y alcance del problema. *Enfermeria Actual* **2**, 1–14.

McGill S.M., Childs A. & Liebenson C. (1999) Endurance times for low back stabilization exercises: clinical targets for testing and training from a normal database. *Archives of Physical Medicine and Rehabilitation* **80**, 941–944.

Markes M., Brockow T. & Resch K.L. (2006) Exercise for women receiving adjuvant therapy for breast cancer. *Cochrane Database of Systematic Reviews* (4), CD005001.

Martín M., Mahillo E., Llombart-Cussac A., Lluch A., Munarriz B., Pastor M., Alba E., Ruiz A., Antón A. & Bermejo B. (2006) The 'El Alamo' project (1990–1997): two consecutive hospital-based studies of breast cancer outcomes in Spain. *Clinical and Translational Oncology* **8**, 508–518.

Mast M.E. (1998) Correlates of fatigue in survivors of breast cancer. *Cancer Nursing* **21**, 136–142.

Mock V. (1993) Body image in women treated for breast cancer. *Nursing Research* **42**, 153–157.

Mullaney M.J., McHugh M.P., Johnson C.P. & Tyler T.F. (2010) Reliability of shoulder range of motion comparing a goniometer to a digital level. *Physiotherapy Theory and Practice* **26**, 327–333.

Okamura T., Akechi T., Kugaya A., Okamura H., Imoto S., Nakano T., Hosaka T. & Uchitomi Y. (2000) Factors correlated with fatigue in disease-free breast cancer patients: application of the Cancer Fatigue Scale. *Supportive Care in Cancer* **8**, 215–222.

Peuckmann V., Ekholm O., Rasmussen N.K., Groenvold M., Christiansen P., Møller S., Eriksen J. & Sjøgren P. (2009) Chronic pain and other sequelae in long-term breast cancer survivors: nationwide survey in Denmark. *European Journal of Pain* **13**, 478–485.

Pikler V. & Winterowd C. (2003) Racial and body image differences in coping for women diagnosed with breast cancer. *Health Psychology* **22**, 632–637.

Pinto B.M. & Trunzo J.J. (2005) Health behaviour during and after a cancer diagnosis. *Cancer* **104**, 2614–2623.

Piper B.F., Dibble S.L., Dodd M.J., Weiss M.C., Slaughter R.E. & Paul S.M. (1998) The revised Piper Fatigue Scale: psycho-

metric evaluation in women with breast cancer. *Oncology Nursing Forum* **25**, 677–684.

Pollán M., García-Mendizabal M.J., Pérez-Gómez B., Aragonés N. & Lope V. (2007) Situación epidemiológica del cáncer de mama en España. *Psico-oncología* **4**, 231–248.

Prue G., Rankin J., Allen J., Gracey J. & Cramp F. (2006) Cancer-related fatigue: a critical appraisal. *European Journal of Cancer* **42**, 846–863.

Reuter K. & Harter M. (2004) The concepts of fatigue and depression in cancer. *European Journal of Cancer Care* **13**, 127–134.

Sprangers M.A., Groenvold M., Arraras J.I., Franklin J., te Velde A., Muller M., Franzini L., Williams A., de Haes H.C., Hopwood P., Cull A. & Aaronson N.K. (1996) The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *Journal of Clinical Oncology* **14**, 2756–2768.

Vanderweeën L., Oostendorp R.B., Vaes P. & Duquet W. (1996) Pressure algometry in manual therapy. *Manual Therapy* **1**, 258–265.

Winters-Stone K.M., Bennet J.A., Nail L. & Schwartz A. (2008) Strength, physical activity, and age predict fatigue in older breast cancer survivors. *Oncology Nursing Forum* **35**, 815–821.

Yilmazer N., Aydiner A., Ozkan S., Aslay I. & Bilge N. (1994) A comparison of body image, self-esteem and social support in total mastectomy and breast-conserving therapy in Turkish women. *Supportive Care in Cancer* **2**, 238–241.

II. RELACIÓN DE LA FATIGA Y LA CONDICIÓN FÍSICA

Artículo II

"The handgrip strength test as a m easure of physical function in breast cancer survivors: relationsh ip with quality of life, cancer related symptoms, physical and physiological parameters".

Submitted

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Title: The handgrip strength test as a measure of physical function in breast cancer survivors: relationship with quality of life, cancer related symptoms, physical and physiological parameters

Short Title: Force Handgrip test in breast cancer survivors

Article Type: Original Research Study

Keywords: breast cancer, handgrip strength, pain, symptoms, quality of life, fatigue, women, heart rate variability

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Cover Letter

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At Cancer Nursing:

We remit the entitled manuscript: *"**The handgrip strength test as a measure of physical function in breast cancer survivors: relationship with quality of life, cancer related symptoms, physical and physiological parameters**",* to consider this manuscript for publication in your prestigious journal. There are not previous reports that might be regarded as redundant publication of the same or very similar work. The manuscript has been read and approved by all the authors, the requirements for authorship in this document have been met, and each author believes that the manuscript represents honest work.

Your sincerely

Manuel Arroyo Morales (PhD)

University of Granada. Faculty of Health Sciences

TITLE PAGE

The handgrip strength test as a measure of physical function in breast cancer survivors: relationship with quality of life, cancer related symptoms, physical and physiological parameters

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***Abstract**

Background: Whether the handgrip strength test can be used as an indicator of fatigue, pain and quality of life in breast cancer survivors (BCS) remains to be elucidated.

Objective: To examine the relationship of handgrip strength (HGS) with pain,fitness, physiological state, quality of life, fatigue and mood in BCS.

Methods: The study comprised a total of 95 BCS. We measured heart rate variability (HRV), pressure pain thresholds (PPTs) of neck, shoulder, hand and tibia of affected side and fitness level (HGS of affected side, 6-min walk test, neck-shoulder mobility, vertical jump, sit-to-stand test, trunk curl test). Participants completed the Fatigue Piper Scale (FPS), EORTC quality of life questionnaire Br23 (QLQ Br-23) and profile of mood state (POMS) questionnaires and the neck-shoulder visual analogue scale.

Results: We observed a weak relationship between HGS and HRV(high-frequency domain) ($P=0.049$). Likewise, the relationship between HGS and POMS subscales ranged between weak to fair (all $P<0.001$). HGS showed a fair relationship with symptoms subscales of QLQ-Br23 (all $P<0.01$), and a weak relationship with FPS (all $P<0.01$). HGS showed a fair relationship with PPTs (all $P<0.01$), and a moderate to fair relationship with fitness (all $P<0.01$).

Conclusions: These results suggest that strength, as assessed by the HGS test on the affected side, is an important correlate of quality of life and overall health in BCS.

Implications for Practice: These findings may help nurses to better understand the usefulness of HGS as an additional tool when planning the assessment, treatment and monitoring of BCS.

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INTRODUCTION

There is increasing evidence that breast cancer is considered a chronic disease due to the high survival rate [1]. The majority of all breast cancer survivors suffer from one or more cancer-related symptoms such as fatigue, pain, anxiety, sleep disruption, depression and hypersensitivity [2]. These symptoms affect patient's quality of life and activities of daily living [3]

Cancer and cancer-related treatment is known to induce lean tissue degradation and abnormalities in the metabolic system in both cardiac and skeletal muscle [4], resulting in loss of muscular strength in cancer survivors. It was reported that handgrip strength is reduced in malnourished preoperative colorectal cancer patients [5], and in prostate cancer patients [6]. Kaya et al. [7] showed that handgrip strength was inversely associated with quality of life in a group of surgically treated breast cancer survivors, yet this was not confirmed after complete chemotherapy treatment.

The assessment of muscle strength by the handgrip strength test have been widely used in different conditions such as fibromyalgia [8], diabetes [9], chronic peritoneal dialysis [10], congestive heart failure [11], survivors of critical illness [12] and in breast cancer survivors [7]. Whether the handgrip strength test could be employed as a complement tool in the armamentarium used in the clinical examination when planning the treatment and monitoring of breast cancer survivors remains to be investigated. Before that, more research in needed to better understand whether

handgrip strength can be used as an indicator of fatigue, pain and quality of life in breast cancer survivors.

The purpose of this study was to examine the relationship of handgrip strength with pain, fitness, physiological state, quality of life, fatigue and mood in breast cancer survivors.

METHODS

Patients

A total of 95 women from the Breast Oncology Unit of University Hospital *Virgen de las Nieves* (UHVN), Granada (Spain), participated in the present cross-sectional study. Eligible women had a diagnosis of breast cancer (grades I-IIIA), were between 18 to 75 years, and had at least one month from primary treatment for breast cancer (surgery, radiation, chemotherapy). Women were not included in the study if they were receiving radiation or chemotherapy for cancer at the time of the study or had any physical limitation that prevented participation in the fitness tests. Participants were recruited if the oncologist who referred patients identified 3 to 5 of the following physical problems: neck-shoulder pain, reduced range of motion in neck shoulder complex, reduced physical capacity, psychological problems, increased fatigue, sleep disturbances, or problems in coping with reduced physical/psychosocial functioning. All measurements were conducted at the School of Health Sciences, University of Granada, Granada (Spain). The Ethics Committee of the UHVN (Spain) approved the study design, study protocols and informed consent procedure.

Data collection

Eligible patients were contacted by telephone by two nurses of the Breast Oncology Unit of UHVN, and those who agreed to participate were scheduled for an initial testing

appointment. Upon arrival, patients received a complete explanation of the study protocol and signed the consent form. Demographic and clinical characteristics, including stage, date of diagnosis, and the date and type of breast cancer treatment were self-reported. Medical records were obtained from their oncologist. If clinical and self-reported data were not consistent, we gave precedence to the clinical data. All the data were obtained between 8.00 to 11.00 pm to avoid circadian influences in measurements [i.e. heart rate variability (HRV) or salivary flow rate]. The study was carried out in the laboratories of the School of Health Sciences of the University of Granada, Granada (Spain).

Measurements

Physical measurements

Upper body muscular strength: Handgrip strength of affected side was measured using a digital dynamometer (TKK 5101 Grip-D; Takey, Tokyo, Japan) as previously described [13]. The patient performed the test twice, allowing a 3-minute rest period between measures. The mean value of two trials was scored. This test is valid and reliable [14].

Lower body muscular strength: Vertical jump performance was assessed by a squat jump with infrared photocell mat (Ergo-jump Globus, Codogne, Italy) as indicated elsewhere [15]. The jumps were performed with hands held on the hips and attaining 90° knee flexion at the start of the push-off phase. Participants performed 3 trials of each jump, and the best attempt was retained for the analysis.

Shoulder and cervical active range of motion: A 41cm plastic universal 2-arm goniometer was used to assess active movement of shoulder flexion, extension, horizontal abduction and external rotation of the affected arm. Patients were seated in an upright position with their thumb facing upwards. The assessor moved the limb to the end-range of active motion into flexion, abduction, and external rotation. The angle of movement was calculated with the universal goniometer using anatomical bony landmarks [16]. The physical measurements were conducted by an experienced physiotherapist. The intra-rater reliability of the test has been found to be excellent (ICC 0.94, 95%CI 0.91-0.99) [17].

Cervical mobility was assessed as reported elsewhere [18] with a cervical goniometric device manufactured by Performance Attainment Associates (St. Paul, MN). Cervical mobility was recorded as the total range of motion for flexion and extension movements. Participants were asked to sit comfortably on a chair with both feet flat on the floor, the hips and knees positioned at 90º, and buttocks positioned against the back of the chair. Once the goniometer was set in neutral position, participants were asked to move the head as far as possible in a standard form: forwards (flexion), backwards (extension). Three measurements for each movement were recorded and the mean was used in the analysis. The intra-rater reliability of the test has been found to be excellent (ICC 0.96, 95%CI 0.91-0.98) [19].

Functional capacity: The 6-minutes walk test is a valid and reliable test [20] that consists of determining the maximum distance (meters) that can be walked in 6 min along a 45.7 meters rectangular course [21].

Lower-body endurance: Multiple sit-to-stand test was used to assess general lower-extremity endurance [22]. Participants were asked, while sitting at the front of the chair, to rise until they reached full knee extension and sit back 10 times as fast as possible. The number of times that the participant was able to sit and stand was recorded. This test was shown to be reliable [23].

Trunk curl static endurance test: This test requires a wedged piece of wood to support the patient at a fixed angle of 60º. The patients maintained both knees and hips flexed at 90º, the arms were folded across chest and the toes are anchored by the tester. The wood was pulled back 10 cm and the subject held the isometric posture as long as possible. This test has shown to be reliable [24].

Psychological measurements

***Profile of Mood States (POMS) questionnaire*.** The POMS questionnaire consists of 63 items on mood state. Scores (on a five-point scale of 0–4) are grouped into six subscales: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor, Fatigue, and Confusion. Subscale scores were converted into T-scores for the statistical analysis. The reliability has been found high (Cronbach´s α ranged between 0.76-0.91) [25].

Fatigue Piper Scale (PFS). The PFS is a valid tool to assess cancer related fatigue, and it was selected for its particular focus on related-fatigue and pain. The PFS consists of 22 numerical items assessing fatigue experienced by the patient. Using a 0-10 numerical scale, PFS measures 4 dimensions of subjective fatigue: behavioral/severity, affective meaning, sensory and cognitive/mood. The total fatigue score is calculated by adding

the 4 subscale scores and dividing this sum by 4. The reliability of Piper Fatigue Sacle has been found high (Cronbach´s α=0.96) [26].

Quality of Life (QLQ-Br23). The European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life questionnaire (EORTC QLQ-BR23) consists of 23 items, which are rated on a four-point scale ranging from 1 (not at all)–4 (very much). Items assess therapy side-effects, arm symptoms, breast symptoms, body image and sexual functioning; in addition, there are single items to assess sexual enjoyment, anxiety caused by hair loss and future outlook. Scores range between 0–100. For scales evaluating function, a higher score indicates a higher level of functioning. For scales evaluating symptoms, a higher score indicates more problems and a higher level of symptoms. We had permission to use the Spanish version of QLQ-BR23 from the EORTC Quality of Life Group. The reliability of version used has been found high to moderate (Cronbach´s α ranged between 0.46-0.94) [27].

Pain measurements

Visual Analogue Scale (VAS) was used to assess the intensity of spontaneous neck and shoulder/axillary pain. The VAS is a 100mm line anchored with a 0 at one end representing no pain and 100 at the other end representing the worst pain imaginable. The VAS has been shown to be a reliable and valid instrument for assessing pain [28].

Pressure pain threshold (PPT) defined as the minimal amount of pressure where a sensation of pressure first changes to pain [29] was assessed with an electronic algometer (Somedic AB, Farsta, Sweden). The pressure was applied approximately at rate of 30 kPa/seconds by a 1 cm^2 probe. Participants were instructed to press the switch

when the sensation first changed from pressure to pain. The mean of 3 trials was calculated and used for the analysis. A 30seconds resting period was allowed between each trial. PPT levels was assessed over C5-C6 zygapophyseal joint (cervical), deltoid muscle (shoulder), second metacarpal (hand) and tibialis anterior muscle (tibial) of affected side by an experienced physician.

Phsyiological measurements

Heart rate and Heart Rate Variability (HRV): Short-term HRV in time (SDNN, square root of mean squared differences of successive normal-to-normal intervals and HRV index [number of all normal-to-normal intervals/maximum of the all normal-to-normal intervals]) and frequency [low frequency (LF) component, 0.04-0.15 Hz; high frequency (HF) component, 0.15-0.40 Hz, and LF/HF ratio) domains was obtained using a 3-channel (1, right manubrial border of sternum-left anterior auxiliary line of the sixth rib; 2, left manubrial border of sternum 1 in to the right of xiphoid process; 3, center of manubrium-left midclavicular line of the sixth rib) ECG (Norav Holter DL 800; Braemar, Burnsville, Minn), taking 5-minute recordings with the subject at rest and with no external stimulation at 2 time points: baseline and after 8-weeks. The spectral analysis was calculated with NH300 Software (Norav, v.2.70) using Fast Fourier transform algorithms. The sampling rate was 256 samples per second, and the frequency filter was set at 0.05 to 60 Hz. Because of the low sampling rate, the software used an interpolation algorithm to improve r-peak detection.

***Blood Pressure*:** An Omron HEM-737 validated automatic oscillometric device (Kyoto, Japan) was used for blood pressure measurements. Measurements were performed in duplicate and the average used for data analysis.

Salivary flow rate: Participants were asked to sit and chewing paraffin for 3 minutes expectorating periodically into a pre-weighed plastic container the saliva accumulated in the floor of the mouth. Salivary samples were collected on ice, and the volume was determined gravimetrically and calculated to the nearest 0.1 ml. Salivary flow rate (ml·min-1) was determined by dividing volume by collection time.

Data Analysis

The relationship of the handgrip strength test with mood, quality of life, fatigue, pain, fitness, and physiological measurements was analyzed with the Spearman correlation coefficient. A correlation from 0 to 0.25 indicates an absence or weak relationship, a correlation from 0.25 to 0.50 indicates a fair relationship, a correlation from 0.50 to 0.75 indicates a moderate to good relationship, and a correlation >0.75 indicates a very good relationship [30]. Statistical analysis was conducted using the SPSS (v. 16.0 for WINDOWS, Chicago), and significance level was 5%.

RESULTS

Demographic and clinical data

Our sample consisted of 95 short-term breast cancer survivors with a mean age of 49.1 ± 8.2 years. Most women had breast cancer stage I (30%) or stage II (52.56%) cancer, and received both radiation and chemotherapy (88.4%) as adjuvant treatment after surgery. A total of 68.4% women had received lumpectomy whereas 31.6% had received mastectomy surgery. In addition, 44% women were taken antagonist of estrogen receptors (tamoxifen), 34.4% aromatase inhibitors (anastrozole), and 11.6 % monoclonal antibody HER2 (trastuzumab).

Tables 1-3 show the medians and lower and upper quartiles of the study variables. Handgrip strength showed a weak relationship with the HF domain of HRV (ρ= 0.227, P=0.049) **(Table 4)**. Likewise, the relationship between handgrip strength and POMS subscales were weak (ρ= -0.226 and -0.221) for tension and depression, and fair (ρ=-0.364 and -0.348 for fatigue and confusion, respectively, all P<0.001) dimensions **(Table 4)**.

Table 5 shows the relationship of handgrip strength with QLQ-Br23 and FPS in breast cancer survivors. Handgrip strength showed a fair relationship with arm symptoms, breast symptoms and systemic side effects scales of QLQ-Br23 (ρ= -0.327, -0.272 and -0.304, respectively, all P<=0.01), and a fair relationship with sexual enjoyment scale (ρ= -0.246, P=0.045). Handgrip strength showed a weak relationship with all subscales (severity, sensorial, affective and cognitive) and total score of FPS (ρ= -0.298, -0.283, -0.335, -0.283 and -0.351; respectively, all P<0.01).

Table 6 shows the relationship of handgrip strength with pain, range of motion and fitness level in breast cancer survivors. Handgrip strength showed a fair relationship with shoulder pain (ρ= -0.368; P<0.001) and cervical (ρ= 0.300; P=0.003), shoulder (ρ=

0.317; P=0.002), and tibial PPTs (ρ= 0.295, P=0.004), and a fair relationship with hand PPT (ρ= 0.246, P=0.016). Handgrip strength showed a moderate relationship with flexion shoulder ROM (ρ= 0.531, P<0.001) and a fear relationship with extension shoulder (ρ= 0.397, P<0.001), shoulder external rotation (ρ= 0.358, P<0.001), shoulder horizontal abduction (ρ= 0.475, P<0.001) and neck extension (ρ= 0.273, P=0.007). Handgrip strength showed a moderate relationship with trunk curl static endurance test (ρ= 0.519, P<0.001) and fair relationship with 6-m walk test (ρ= -0.334; P=0.002), vertical jump (ρ= 0.434; P<0.001) and multiple sit to stand test (ρ= -0.302; P=0.003).

DISCUSSION

The present study shows significant relationships, ranging from moderate to fair, of the handgrip strength with mood, quality of life, fatigue, pain, hypersensitivity, neck-shoulder mobility, fitness level and physiological parameters as HF domain of HRV in breast cancer survivors. These findings indicate that strength, as assessed by the handgrip strength test on the affected side, might be important when planning the assessment, treatment and monitoring of breast cancer survivors. Resistance exercise of light intensity (e.g. Pilates) is known to enhance strength in breast cancer survivors and is recommended for the management of cancer-related symptoms [31,32]. To adequately prescribe individualized exercise programs (type, duration, intensity and frequency), it is important to know the patients' initial strength levels as well as to understand the potential implications that enhancing fitness may have of patient's quality of life and overall health.

At physical level, the strongest associations observed in the present study were between handgrip strength and the flexion shoulder range of motion and trunk curl static endurance test. These findings suggest that patients with higher handgrip strength are likely to develop also higher core strength and increased range of motion in neck-shoulder complex. A reduction of neck-shoulder range of motion could be associated with radiation and surgery procedures mediated by fibrotic damage to soft and/or contractile tissue [33]. Reduction of shoulder range of motion could also reduce the ability of surrenders muscles to develop strength and it affects distal-hand muscles.

We also observed a positive association between handgrip strength and trunk endurance. Cancer treatment, particularly chemotherapy, promotes disruption in muscle metabolism (adenosine triphosphate dysregulation, cytokine dysregulation, deprivation of satellite cells) wasting which may impair muscle strength [34]

We observed a negative association between handgrip strength and mood/fatigue, which indicates that the lower performance in handgrip strength the higher perceived fatigue, confusion, anger and depression. These findings are of relevance and informative. It was reported that a reduction in handgrip strength is associated with a poor psychological state in breast cancer survivors in the first year after treatment. A peripheral muscle dysfunction as a manifestation of muscle wasting and remodelling associated to clinical situations as chronic obstructive pulmonary disease [35] could induce similar changes in breast cancer survivors. Physical inactivity because of wrong psychological state (depression, fatigue) and treatment side effects could also alter protein metabolism, and therefore drive to muscle weakness [36].

Recent research [37-39] showed the relevance of myofascial neck-shoulder pain in breast cancer survivors and its contribution to perceived pain and other related symptoms as fatigue [39]. Interesting results of the present study shows a positive association of handgrip strength with PPT in proximal to distal muscles and even at distance (tibia) of affected region.

Higher values of PPT reflect widespread mechanical pain hypersensitivity in breast cancer survivors. This hypersensitivity might be produced by changes in central and peripheral mechanisms, which might produce different alterations as hyperexcitability of the central nervous system [40] or an increased thalamo-insular. These changes may affect the ability to develop muscle strength [41].

Detection and treatment of cancer-related symptoms are important parts of daily clinical practice in the exercise and rehabilitation setting of breast cancer survivors. Simple and rapid screening tools as handgrip strength with a relationship with quality of life need to be implemented to improve self-efficacy [42] . In this sense, we observed a

weak negative relationship between handgrip strength and several aspect of quality of life as breast, arm symptoms and systemic side effects. To note is that both breast and -arm symptoms scales (measured by QLQ-Br23) include items related to functioning of this corporal region, which may explain the stronger relationships observed compared to the other scales.

We also observed a positive (weak) relationship between HF domain of HRV and handgrip strength. HRV is a predictor of cardiovascular morbidity [43], and well-being [44]. The relation between HRV and handgrip strength may help to better understand the recovery processes after exercise. A recent study reported a similar relationship between HF domain and strength performance during recovery after exercise [45].

Due to the study design (i.e. cross-sectional) it is not possible to establish the direction of the associations. Another limitation include the restriction to only one tumor type and the fact that the patients had just completed their primary oncology treatment and thus could be expected to have a moderate level of force handgrip.

In summary, the present study shows a moderate to fair associations of handgrip strength with cancer-related symptoms, quality of life, hypersensitivity, HF domain of HRV, neck-shoulder mobility and fitness level measured by the distance in the 6-min walk test, abdominal endurance, vertical jump and leg strength in breast cancer survivors.

IMPLICATIONS FOR PRACTICE

Hand grip dynamometer is a feasible, quick and non expensive choice for measuring muscle strength in an objective manner. The findings of the present study may help nurses implied in exercises or rehabilitation programs to better understand the

usefulness of handgrip strength as an additional tool when planning the assessment, treatment and monitoring of breast cancer survivors, as it has already been shown in other chronic diseases [8].

REFERENCES

1. Markes M, Brockow T, Resch KL: Exercise for women receiving adjuvant therapy for breast cancer. Cochrane Database Syst Rev 2006:CD005001.

2. Mortimer JE, Barsevick AM, Bennett CL, Berger AM, Cleeland C, Devader SR, Escalante C, Gilreath J, Hurria A, Mendoza TR, Rugo HS: Studying cancer-related fatigue: Report of the nccn scientific research committee. J Natl Compr Canc Netw 2010;8:1331-1339.

3. Paim CR, de Paula Lima ED, Fu MR, de Paula Lima A, Cassali GD. Post lymphadenectomy complications and quality of life among breast cancer patients in Brazil. Cancer Nurs. 2008; 31:302-9

4. Hayward R, Ruangthai R, Schneider CM, Hyslop RM, Strange R, Westerlind KC: Training enhances vascular relaxation after chemotherapy-induced vasoconstriction. Med Sci Sports Exerc 2004;36:428-434.

5. Burden ST, Hill J, Shaffer JL, Todd C: Nutritional status of preoperative colorectal cancer patients. J Hum Nutr Diet 2010;23:402-407.

6. Soyupek F, Soyupek S, Perk H, Ozorak A: Androgen deprivation therapy for prostate cancer: Effects on hand function. Urol Oncol 2008;26:141-146.

7. Kaya T, Karatepe AG, Gunaydn R, Yetis H, Uslu A: Disability and health-related quality of life after breast cancer surgery: Relation to impairments. South Med J 2010;103:37-41.

8. Aparicio VA, Ortega FB, Heredia JM, Carbonell-Baeza A, Sjostrom M, Delgado-Fernandez M: Handgrip strength test as a complementary tool in the assessment of fibromyalgia severity in women. Arch Phys Med Rehabil 2011;92:83-88.

9. van Sloten TT, Savelberg HH, Duimel-Peeters IG, Meijer K, Henry RM, Stehouwer CD, Schaper NC: Peripheral neuropathy, decreased muscle strength and obesity are strongly associated with walking in persons with type 2 diabetes without manifest mobility limitations. Diabetes Res Clin Pract 2011;91:32-39.

10. Wang AY, Sanderson JE, Sea MM, Wang M, Lam CW, Chan IH, Lui SF, Woo J: Handgrip strength, but not other nutrition parameters, predicts circulatory congestion in peritoneal dialysis patients. Nephrol Dial Transplant 2010;25:3372-3379.

11. Izawa KP, Watanabe S, Osada N, Kasahara Y, Yokoyama H, Hiraki K, Morio Y, Yoshioka S, Oka K, Omiya K: Handgrip strength as a predictor of prognosis in japanese patients with congestive heart failure. Eur J Cardiovasc Prev Rehabil 2009;16:21-27.

12. Ali NA, O'Brien JM, Jr., Hoffmann SP, Phillips G, Garland A, Finley JC, Almoosa K, Hejal R, Wolf KM, Lemeshow S, Connors AF, Jr., Marsh CB: Acquired weakness, handgrip strength, and mortality in critically ill patients. Am J Respir Crit Care Med 2008;178:261-268.

13. Ruiz-Ruiz J, Mesa JL, Gutierrez A, Castillo MJ: Hand size influences optimal grip span in women but not in men. J Hand Surg [Am] 2002;27:897-901.

14. Espana-Romero V, Ortega FB, Vicente-Rodriguez G, Artero EG, Rey JP, Ruiz JR: Elbow position affects handgrip strength in adolescents: Validity and reliability of jamar, dynex, and tkk dynamometers. J Strength Cond Res 2010;24:272-277.

15. Bosco C, Mognoni P, Luhtanen P: Relationship between isokinetic performance and ballistic movement. Eur J Appl Physiol Occup Physiol 1983;51:357-364.

16. American Medical Association: Guides to the evaluation of permanent impairment Chicago, 2008.

17. Mullaney MJ, McHugh MP, Johnson CP, Tyler TF: Reliability of shoulder range of motion comparing a goniometer to a digital level. Physiother Theory Pract 2010;26:327-333.

18. Fernandez-de-las-Penas C, Alonso-Blanco C, Cuadrado ML, Pareja JA: Forward head posture and neck mobility in chronic tension-type headache: A blinded, controlled study. Cephalalgia 2006;26:314-319.

19. Fletcher JP, Bandy WD: Intrarater reliability of crom measurement of cervical spine active range of motion in persons with and without neck pain. J Orthop Sports Phys Ther 2008;38:640-645.

20. Solway S, Brooks D, Lacasse Y, Thomas S: A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. Chest 2001;119:256-270.

21. Rikli RE, Jones CJ: Assessing physical performance in independent older adults: Issues and guidelines. J Aging Phys Act 1997;5:244-261.

22. Netz Y, Ayalon M, Dunsky A, Alexander N: 'the multiple-sit-to-stand' field test for older adults: What does it measure? Gerontology 2004;50:121-126.

23. Ritchie C, Trost SG, Brown W, Armit C: Reliability and validity of physical fitness field tests for adults aged 55 to 70 years. J Sci Med Sport 2005;8:61-70.

24. McGill SM, Childs A, Liebenson C: Endurance times for low back stabilization exercises: Clinical targets for testing and training from a normal database. Arch Phys Med Rehabil 1999;80:941-944.

25. Andrade EM, Arce C, Seoane G: Adaptación al español del cuestionario “perfil de los estados de ánimo” en una muestra de deportistas. Psicothema 2002; 14, 708-713. Psicothema 2001.

26. Piper BF, Dibble SL, Dodd MJ, Weiss MC, Slaughter RE, Paul SM: The revised piper fatigue scale: Psychometric evaluation in women with breast cancer. Oncol Nurs Forum 1998;25:677-684.

27. Sprangers MA, Groenvold M, Arraras JI, Franklin J, te Velde A, Muller M, Franzini L, Williams A, de Haes HC, Hopwood P, Cull A, Aaronson NK: The european organization for research and treatment of cancer breast cancer-specific quality-of-life questionnaire module: First results from a three-country field study. J Clin Oncol 1996;14:2756-2768.

28. Bijur PE, Silver W, Gallagher EJ: Reliability of the visual analog scale for measurement of acute pain. Acad Emerg Med 2001;8:1153-1157.

29. Vanderweeen L, Oostendorp RA, Vaes P, Duquet W: Pressure algometry in manual therapy. Man Ther 1996;1:258-265.

30. Colton T: Statistics in medicine. Boston, Little Brown, 1974.

31. Speck RM, Gross CR, Hormes JM, Ahmed RL, Lytle LA, Hwang WT, Schmitz KH: Changes in the body image and relationship scale following a one-year strength training trial for breast cancer survivors with or at risk for lymphedema. Breast Cancer Res Treat 2010;121:421-430.

32. Keays KS, Harris SR, Lucyshyn JM, MacIntyre DL: Effects of pilates exercises on shoulder range of motion, pain, mood, and upper-extremity function in women living with breast cancer: A pilot study. Phys Ther 2008;88:494-510.

33. Stricker CT, Jacobs LA: Physical late effects in adult cancer survivors. Oncology (Williston Park) 2008;22:33-41.

34. Clarkson PM, Kaufman SA: Should resistance exercise be recommended during breast cancer treatment? Med Hypotheses 2010;75:192-195.

35. Gosker HR, Wouters EF, van der Vusse GJ, Schols AM: Skeletal muscle dysfunction in chronic obstructive pulmonary disease and chronic heart failure: Underlying mechanisms and therapy perspectives. Am J Clin Nutr 2000;71:1033-1047.

36. Wolin KY, Ruiz JR, Tuchman H, Lucia A: Exercise in adult and pediatric hematological cancer survivors: An intervention review. Leukemia 2010;24:1113-1120.

37. Fernandez-Lao C, Cantarero-Villanueva I, Fernandez-de-las-Penas C, Del-Moral-Avila R, Menjon-Beltran S, Arroyo-Morales M: Widespread mechanical pain hypersensitivity as a sign of central sensitization after breast cancer surgery: Comparison between mastectomy and lumpectomy. Pain Med 2010;12:72-78.

38. Fernandez-Lao C, Cantarero-Villanueva I, Fernandez-de-Las-Penas C, Del-Moral-Avila R, Arendt-Nielsen L, Arroyo-Morales M: Myofascial trigger points in neck and shoulder muscles and widespread pressure pain hypersensitivtiy in patients with postmastectomy pain: Evidence of peripheral and central sensitization. Clin J Pain 2011;26:798-806.

39. Cantarero-Villanueva I, Fernandez-Lao C, Fernandez DEL-PC, Diaz-Rodriguez L, Sanchez-Cantalejo E, Arroyo-Morales M: Associations among musculoskeletal impairments, depression, body image and fatigue in breast cancer survivors within the first year after treatment. Eur J Cancer Care (Engl) 2011.

40. Shy ME, Frohman EM, So YT, Arezzo JC, Cornblath DR, Giuliani MJ, Kincaid JC, Ochoa JL, Parry GJ, Weimer LH: Quantitative sensory testing: Report of the therapeutics and technology assessment subcommittee of the american academy of neurology. Neurology 2003;60:898-904.

41. Hilty L, Jancke L, Luechinger R, Boutellier U, Lutz K: Limitation of physical performance in a muscle fatiguing handgrip exercise is mediated by thalamo-insular activity. Hum Brain Mapp 2010.

42. Haas BK. Fatigue, self-efficacy, physical activity, and quality of life in women with breast cancer. Cancer Nurs. 2010 Nov 24.

43. Kristal-Boneh E, Raifel M, Froom P, Ribak J: Heart rate variability in health and disease. Scand J Work Environ Health 1995;21:85-95.

44. Hanson EK, Godaert GL, Maas CJ, Meijman TF: Vagal cardiac control throughout the day: The relative importance of effort-reward imbalance and within-day measurements of mood, demand and satisfaction. Biol Psychol 2001;56:23-44.

45. Chen JL, Yeh DP, Lee JP, Chen CY, Huang CY, Lee SD, Chen CC, Kuo TB, Kao CL, Kuo CH: Parasympathetic nervous activity mirrors recovery status in weightlifting performance after training. J Strength Cond Res 2011.

Table 1

Outcomes	n	Median	25th and 75th percentiles	
Affected side handgrip (Kg)	95	18.30	13.00	23.00
Pain				
VAS cervical	95	6.00	0.00	8.00
VAS shoulder	95	4.00	0.00	7.00
Pressure pain threshold (Kpa)				
Cervical	95	144.00	109.00	185.00
Shoulder	95	186.00	133.00	265.00
Hand	95	206.00	165.00	275.00
Tibial	95	233.33	202.63	265.33
Shoulder Range of Motion (º)				
Flexion	95	160.0	148.0	165.0
Extension	95	50.0	42.0	60.0
External Rotation	95	52.0	45.0	62.0
Horizontal Abduction	95	32.0	25.0	40.0
Neck Range of Motion (º)				
Flexion	95	50.0	40.0	58.0
Extension	95	60.0	55.0	72.0
6min distance walked (m)	95	486	408	573
Vertical jump (cm)	94	12.95	10.50	15.95
Multiple sit to stand test (s)	95	26.25	22.40	29.13
Trunk curl static endurance test (s)	95	24.24	12.23	46.70

Abbreviations: VAS, Visual Analogue Scale

Table 1. Descriptive characteristics of the study sample.

Table 2

Outcomes	n	Median	25th and 75th percentiles	
EORTC QLQ-Br23				
Body Image	95	75.00	41.66	91.66
Sexual Functioning	92	66.66	37.50	95.83
Arm symptoms	95	33.33	11.11	55.55
Breast symptoms	95	41.66	25.00	50.00
Systemic side effects	91	28.57	19.04	33.88
Sexual enjoyment	67	66.66	33.33	76.62
Future perspective	95	33.33	0.00	66.67
Upset hair loss	27	33.33	0.00	100.00
Fatigue Piper Scale				
Severity / Behaviour	95	5.80	3.33	7.60
Sensorial	95	5.60	3.60	7.60
Affective	95	6.40	4.40	8.00
Cognitive	95	4.83	3.00	6.60
Global Score	95	5.30	4.09	7.10

Abbreviations: EORTC QLQ Br23, European Organization for Research and Treatment of Cancer, Quality of Life questionnaire module for Breast Cancer Patient 23

Table 2. Quality of life and fatigue of the study participants

Table 3

Outcomes	n	Median	25th and 75th percentiles	
HRV				
SDNN (ms)	91	34.12	23.26	48.77
RMSSD (ms)	91	23.78	16.56	38.09
Index HRV	91	7.90	5.66	10.15
Total Power (ms^2)	91	553.17	496.73	607.58
LF(ms^2)	91	159.42	119.70	204.50
HF(ms^2)	91	133.81	92.41	178.02
LF/HF	91	1.18	0.72	1.88
Systolic blood pressure (mm Hg)	94	123.50	111.75	135.25
Diastolic blood pressure (mm Hg)	94	84.0	74.0	89.25
Heart Rate (beat/min)	94	75.0	69.0	85.25
Profile of Mood State				
Tension	95	47.0	40.0	58.0
Depression	95	47.0	41.0	56.0
Anger	95	52.0	44.0	61.0
Vigour	95	51.0	44.0	57.0
Fatigue	95	52.0	45.0	58.0
Confusion	95	39.0	33.0	48.0

Abbreviations: HF, high frequency; HRV, heart rate variability; LF, low frequency; LF/HF, ratio low frequency / high frequency; RMSD, the square root of the mean squared difference of successive NNs; SDNN, the standard deviation normal of NN intervals.

Table 3. Heart rate variability and mood state of the study participants.

Table 4

Outcomes	n	rho	P value
Heart Rate Variability			
Temporal Domain			
SDNN (ms)	95	0.019	.861
RMSSD (ms)	95	0.063	.555
Index HRV	95	-0.010	.922
Frequency Domain			
Total Power (ms^2)	95	0.086	.421
HF (ms^2)	95	0.227	**.049**
LF (ms^2)	95	0.098	.356
LF/HF ratio	95	-0.069	.515
Physiological measurements			
Systolic blood pressure (mm Hg)	94	-0.070	.505
Diastolic blood pressure (mm Hg)	94	-0.035	.738
Heart Rate (beat/min)	94	-0.075	.471
Salivary flow rate (ml/min)	94	0.143	.170
Profile of Mood State			
Tension	95	-0.197	.056
Depression	95	-0.226	**.028**
Anger	95	-0.221	**.031**
Vigour	95	0.087	.400
Fatigue	95	-0.364	**.000**
Confusion	95	-0.348	**.001**

Abbreviations: HF, high frequency; HRV, heart rate variability; LF, low frequency; LF/HF, ratio low frequency / high frequency; RMSD, the square root of the mean squared difference of successive NNs; SDNN, the standard deviation normal of NN intervals.

Table 4. Relationship of handgrip strength with physiological parameters and profile of mood state in breast cancer survivors.

Table 5

Outcomes	n	rho	P value
EORTC QLQ-Br23			
Body Image	95	0.066	.524
Sexual Functioning	92	-0.042	.693
Arm symptoms	95	-0.327	**.001**
Breast symptoms	95	-0.272	**.008**
Systemic side effects	95	-0.304	**.003**
Sexual enjoyment	67	-0.246	**.045**
Future perspective	95	0.143	.167
Upset hair loss	27	0.069	.733
Fatigue Piper Scale			
Severity / Behaviour	95	-0.298	**.003**
Sensorial	95	-0.283	**.016**
Affective	95	-0.335	**.001**
Cognitive	95	-0.283	**.005**
Global Score	95	-0.351	**<.001**

Abbreviations: EORTC QLQ Br23, European Organization for Research and Treatment of Cancer, Quality of Life questionnaire module for Breast Cancer Patient 23

Table 5. Relationship of force handgrip affected side with QLQ-Br23 and Fatigue Piper Scale in breast cancer survivors.

Table 6

Outcomes	n	rho	P value
Pain			
VAS cervical	95	-0.136	.187
VAS shoulder	95	-0.368	**<.001**
Pressure pain threshold (Kpa)			
Cervical	95	0.300	**.003**
Shoulder	92	0.317	**.002**
Hand	95	0.246	**.016**
Tibial	95	0.295	**.004**
Shoulder Range of Motion (º)			
Flexion	95	0.531	**<.001**
Extension	95	0.397	**<.001**
External Rotation	95	0.358	**<.001**
Horizontal Abduction	95	0.475	**<.001**
Neck Range of Motion (º)			
Flexion	95	0.114	.270
Extension	95	0.273	**.007**
6min distance walked (m)	95	0.334	**.002**
Vertical jump (cm)	95	0.434	**<.001**
Multiple sit to stand test (s)	95	-0.302	**.003**
Trunk curl static endurance test (s)	95	0.519	**<.001**

Abbreviations: VAS, Visual Analogue Scale

Table 6. Relationship of force handgrip affected side with pressure pain threshold, range of motion in neck-shoulder complex, strength and distance 6-min walking test

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III. ABORDAJE DE LA FATIGA MEDIANTE PROGRAMAS MULTIMODALES

Artículo III

"A multimodal exercise program and multi media support reduce cancer-related fati gue i n breast ca ncer survivors: A randomized controlled clinical trial".

Cantarero-Villanueva I, Fernández-Lao C, Díaz-Rodriguez L, Fernández-de-las-Peñas C,del Moral-Avila R, Arroyo-Morales M.
European Journal of Integrative Medicine. Epub 2011 August 2.

Journal Citation Reports Area:
Integrative and Complementary Medicine: 13/21 T2

Artículo IV

"Effectiveness of Core Stability Ex ercises and RecoveryMyofascial ReleaseMassage on Fatigue in Breast Cancer Survivors: A Randomized Controlled Clinical Trial".

Cantarero-Villanueva I, Fernández-Lao C, Del Moral-Avila R, Fernández-de-Las-Peñas C, Feriche-Fernández-Castanys MB, Arroyo-Morales M.
Evid Based Complement Alternat Med. 2012. Epub 2011 Jul 17.

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Integrative and Complementary Medicine: 2/21 T1

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Original article

A multimodal exercise program and multimedia support reduce cancer-related fatigue in breast cancer survivors: A randomised controlled clinical trial

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Abstract

Aim of the study: To evaluate the effects of an 8-week multimodal physical therapy program with multimedia support on cancer-related fatigue, cortisol and IgA salivary concentrations, α-amylase activity and neck-shoulder mobility, in breast cancer.
Methods: This was a prospective randomised clinical trial using between-groups design. Seventy-eight breast cancer survivors during first year after treatment participated. Participants were assigned into 2 groups: CUIDATE group (multimodal program) or control group (usual care). CUIDATE program consisted of 24 h of individual physical training and 12 h of stretching and massage interventions. Measurements included the Piper Fatigue Scale, cortisol and IgA salivary levels, α-amylase activity and active cervical-shoulder range of motion.
Results: Compared to the control group, CUIDATE group showed a estimated improvement for total fatigue score of −2.49 points immediately after treatment (between-group effect size 0.68; $P < 0.001$) and −1.43 at 6 month follow-up (between group effect size: 0.43; $P < 0.01$). CUIDATE group showed a decrease in α-amylase activity of −41.77 U/ml immediately after treatment compared to the control group (between-group effect size: 0.24; $P = 0.046$). Further, significant between-group improvements for shoulder flexion, horizontal abduction, cervical extension and lateral-flexion (between-group effect sizes ranging 0.30–0.75; all $P < 0.05$) after treatment were also found.
Conclusions: An 8-week multimodal physical therapy program was effective at short and 6 month follow-up for decreasing fatigue in breast cancer survivors. The program was also effective in decreasing α-amylase activity and improving shoulder and cervical range of motion.

Keywords: Breast cancer; Fatigue; Sympathetic nervous system; Exercise; Mobility; Alpha-amylase

Introduction

Cancer related fatigue (CRF) has been recently defined as the perception of unusual tiredness that varies in pattern of severity and has a negative impact on ability to function in people who have or have had cancer [1]. An extensive group of symptoms are associated with CRF, such as anxiety, pain, sleep disruption, and altered body image and have been reported by breast cancer survivors (BCS) after treatment [2]. The high incidence of fatigue is coupled with distress; as BCS report fatigue as the most distressing symptom they have experienced [3]. Almost 50% of breast cancer patients suffer from moderate to severe psychological distress; even if they have early-stage breast cancer with a relatively good prognosis [4]. Different studies have reported that distress can play a relevant role in the development of cancer recurrence or cancer genesis [5]. It has been demonstrated that stress activates the hypothalamic-pituitary-adrenocortical (HPA) axis and sympathetic nervous system (SNS) [6]. Reduction and altered circadian response of cortisol concentration,

Abbreviations: CRF, cancer related fatigue; BCS, breast cancer survivors; HPA, hypothalamic-pituitary-adrenocortical; SNS, sympathetic nervous system; s-AA, salivary α-amylase; s-IgA, salivary immunoglobulin A; PFS, Piper Fatigue Scale.

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which is associated with dysfunction of the HPA axis, has been identified in BCS reporting CRF [7,8]. A recent study has suggested that 6 weeks of daily or intermittent exercise constrains the HPA axis response to stress [9]. Different studies report the ability of body-mind interventions, such as yoga or massage, to improve SNS-HPA axis response to stress [10,11]. Nevertheless, studies investigating the effectiveness of physical therapy programs in dysfunction of the HPA axis by salivary markers in BCS suffering from CRF are scarce.

Despite an increasing body of research investigating CRF and its management, there are gaps in understanding the mechanisms [1]. There are few published studies investigating SNS influence on CRF in BCS. One potential reason is that SNS reactivity is more difficult to assess than HPA-axis. Salivary α-amylase (s-AA) has been suggested as a non-invasive saliva based marker for SNS activity [12]. Different studies showed that s-AA is increased during stress, when autonomic activation is increased. In fact, s-AA has been proposed as useful marker in the context of different cancer-related symptoms, such as pain [13] or sleep alteration [14]. No study has previously studied the effects of a multimodal physical therapy program on SNS-HPA axis in BCS. We expected a multimodal physical therapy program to reduce SNS activation. Therefore, a reduction in s-AA would be expected after the intervention.

Additionally, different studies found a decrease in secretory immunoglobulin A (s-IgA) and non-stimulated salivary flow rate after cancer treatment [15,16]. Some studies demonstrated that exercise interventions may protect against the deterioration of s-IgA in elders [17,18]. An old study reported that 10 min of massage had a positive effect on s-IgA levels in the elderly [19]. Arroyo-Morales et al. have recently reported the ability of massage, as a recovery method after exercise, to increase s-IgA [20]. We can hypothesize that a multimodal physical therapy approach, combining exercise and recovery techniques such as massage, can improve s-IgA levels in BCS suffering from CRF.

Following breast cancer surgery, a common post-operative complication is neck-shoulder dysfunction. The reported prevalence of decreased range of motion in the shoulder varies from 2% to 51% [21]. Pain and restricted mobility in the arm-shoulder are significantly associated with poor quality of life at long-term in breast cancer [22]. Further, pressure pain hypersensitivity has been found in the neck-shoulder complex in BCS after surgery [23,24]. Recently, the contribution of shoulder range of motion to CRF in BCS has been identified [25]. Several studies have shown improvements in shoulder mobility after physical therapy [26–28]. However, cervical dysfunction associated with shoulder pain has not been previously evaluated. It would be expected that a multimodal program targeting cancer-related symptoms may be associated with improvements in neck-shoulder mobility.

To the best of the authors' knowledge, no study has previously investigated fatigue, HPA axis, SNS and immune changes after a multimodal physical therapy program in BCS suffering from CRF. Therefore, the aims of this randomised controlled study were: 1, to determine the effectiveness of a multimodal physical therapy program in CRF with fatigue as the main outcome; and, 2, to investigate changes in cortisol (HPA axis function), s-AA activity (SNS), s-IgA (immune system) salivary concentrations and neck-shoulder mobility induced by a physical therapy program in BCS suffering from CRF.

Materials and methods

Subjects

Participants were recruited from the Breast Oncology Unit of Hospital Virgen de las Nieves de Granada (Spain) from December 2008 to June 2010. Participants were eligible if they: 1, had a diagnosis of breast cancer (stage I-IIIA); 2, were aged between 25–65 years; 3, had finished co-adjuvant treatment except hormone-therapy; 4, were not having active cancer; 5, had an interest in improving their lifestyle and increasing physical activity; and, 6, present 4 or 5 of the following physical findings, judged by the oncologist who referred the patient: neck or shoulder pain symptoms, reduced range of motion in neck-shoulder area, reduced physical capacity, any psychological problem, increased fatigue, sleep disturbances, or any problem in coping with reduced physical-psychosocial functioning.

Patients were excluded if they: 1, were receiving chemotherapy or radiotherapy treatment at the time of the study; 2, had chronic or orthopedic disease which did not permit them to follow the physical program; or, 3, had uncontrolled hypertension (diastolic pressure > 95 mm Hg).

Potential eligible participants were contacted by two oncologists of the Hospital Virgen de las Nieves. Those interested were invited for an appointment and received a complete explanation of the study protocol and signed the consent form. The ethical approval for the study was granted by the Ethics Committee of the Hospital Virgen de las Nieves (Spain). After inclusion, participants were scheduled to a medical visit which included a history, physical examination, and medical questionnaire to establish cardiac risk and a rest ECG.

Design, randomisation, and allocation

A randomised controlled trial was conducted. Participants, after providing written informed consent, were randomly assigned into 2 groups: the CUIDATE group, who received a physical therapy program; or the CONTROL group who received usual care. We allocated patients to CUIDATE or CONTROL group in 4 randomisation cycles, using computer-generated random numbers (EPIDAT 3.1®, Organización Panamericana de Salud, 2005). The sequence was entered into numbered opaque envelopes by an external researcher and they were opened after completion of baseline assessment.

Intervention condition: the CUIDATE program

The multimodal physical therapy CUIDATE program consisted of a total of 24 h of physical training and 12 h of physical therapy recovery procedures, conducted 3 times per week for 90 min each. The physical program is described in Table 1. The intensity of the aerobic training was established following the recommendations of the American College of Sport Medicine [29].

Table 1
Description of the CUIDATE (intervention) program.

CUIDATE program		
Weeks 1–4		
Material	Small soft ball, mats, fit-ball	
Endurance program	Unspecific work during sessions	
Exercise program	Content	Dosage and progression
1	Half squat with arm movement	wk.1: Learning proposal. Assessment maximum load
2	Standing rows with leg semi-flexion maintained	wk.2–3: 75% Maximum load
3	Wall push-ups	Increase 5% per week
4	Abdominal with lower limb movement	Continue progression between exercises:
5	All tours with hip and knee movement	2 sets/30 s pause
6	Abdominal with adductor isometric contraction and arms movement	wk.4: 75% Maximum load. Increase number series (3 sets)
7	Standing hip circumduction	Medium velocity execution exercises
8	Supine on fit-ball with arms movements	Increase range of joint motion
9	Superman on fit-ball	
10	Oblique partial sit-up	
CUIDATE program		
Weeks 5–8		
Materials	Fit-ball, elastic band, mats, small soft ball	
Endurance program	10–25 min of fast working with arms movement two days per week	
Exercise program	Content	Dosage and progression
1	Chest press on fit-ball with elastic band	wk.5: 10–12 repetitions × 2 sets
2	Squat with elastic band	wk.6: 12–15 repetitions × 2 sets
3	Seated rows on fit-ball with elastic band	wk.7: 10–12 repetitions × 3 sets
4	Isometric abdominal sitting on fit-ball with arms and legs movement	wk.8: 10–12 repetitions × 2 sets
5	Biceps curl on fit-ball with elastic band	Increase resistance with elastic band and positions that require more body control
6	Biceps curl with elastic band and leg semi-flexion maintained	
7	Leg curl with fit-ball	
8	Sit-up with lower limb movement	

Multimodal physical training was followed by 30–40 min of low intensity interventions for improving recovery after exercise. This period included stretching of the muscles used during previous exercise and massage (myofascial release techniques), which has the ability to improve recovery after exercise [20]. The CUIDATE program had a higher ratio of supervision with 2–4 therapists for 6–8 patients (ratio therapist/patient: 1/3–4). This high therapist/patient ratio of the CUIDATE program was designed to promote social and environmental support, and satisfaction to the patients.

After finishing 8-weeks of supervised CUIDATE program, participants received a multimedia instructional package with the CUIDATE exercise program which included aerobic exercise progression, resistance exercise, neck-shoulder mobility exercises, self-massage and some relaxation techniques. The DVD included safety precautions related to exercise, and health advice related to promote a healthy lifestyle. This approach has shown the ability to improve quality of women undergoing adjuvant therapy for breast cancer [30].

Control conditions

Participants followed usual care recommended by the oncologist in relation to healthy lifestyle. A follow-up of the physical activity was used to control possible bias detected in previous clinical trials with exercise in BCS [31,32]. For that purpose, we used the Spanish version of Minnesota Leisure Time Physical Activity Questionnaire [33].

Cancer-related fatigue assessment (Piper Fatigue Scale, PFS)

CRF was the main outcome of this study. Therefore, the Piper Fatigue Scale was used following recent guidelines [1]. The PFS is a validated tool assessing CRF, and it was selected for its particular focus on related fatigue and pain [34]. The PFS consists of 22 numerical items assessing fatigue experienced by the patient. Using a 0–10 numerical scale, PFS measures 4 dimensions of subjective fatigue: behavioural/severity, affective meaning, sensory and cognitive/mood. The total fatigue score is calculated by adding the 4 subscale scores and dividing by 4.

The PFS was completed prior to the beginning of the program (pre-intervention), immediately after the 8-weeks intervention (post), and 6 months after discharge (follow-up period).

Minnesota Leisure Time Physical Activity Questionnaire, MLTPAQ

The MLTPAQ was administered by a trained interviewer who had detailed instructions and a list of clearly defined physical activities. The assessor asked the participants about what type of leisure-time physical activities they had been doing during the last year. Then, the participants estimated the duration of the

activities performed in min/week for each season. To be able to calculate energy expenditure (EE) for leisure-time physical activity, the time reported for each activity was multiplied by a MET value [35].

Shoulder and cervical active range of motion assessment

A 41 cm plastic universal 2-arm goniometer was used to assess active movement of shoulder flexion, extension, horizontal abduction and external rotation of the affected arm. Patients were seated in an upright position with their thumb facing upwards. The assessor moved the limb to the end-range of active motion into flexion, abduction, and external rotation. The angle of movement was calculated with the universal goniometer using anatomical bony landmarks [36]. The intra-rater reliability of the goniometer has been found to be excellent (ICC 0.94, 95%CI 0.91–0.99) [37]. The same assessor, a physiotherapist with 10 years of experience on musculoskeletal rehabilitation, who was blinded to participants fatigue score, conducted physical measurements.

Cervical mobility was assessed following a previous guideline [38]. A cervical goniometric device manufactured by Performance Attainment Associates (St. Paul, MN) was used. A recent study found intratester reliability ranging from 0.87 to 0.96 and standard error of measurements between 2.3° and 4.1° [39]. Cervical mobility was recorded as the total range of motion for different types of movement, i.e. flexion/extension, lateral flexion, and rotation; as well as for half-cycles, movements in a single direction, i.e. flexion or extension, lateral-flexion/rotation to the surgical side/to the non-surgical side. For that purpose, all participants were asked to sit comfortably on a chair with both feet flat on the floor, the hips and knees positioned at 90°, and buttocks positioned against the back of the chair. Once the goniometer was set in neutral position, participants were asked to move the head as far as possible in a standard form: forwards (flexion), backwards (extension), right and left lateral flexion, right and left rotation. Three measurements for each movement were recorded and the mean was employed in the statistical analysis.

Shoulder and cervical range of motion were collected before the program (pre-intervention) and immediately after the 8-week intervention (post-intervention) by an assessor blinded to the treatment allocation of the patients.

Saliva sample collection and measurements

Non-stimulated saliva samples were collected from each participant for assessment of HPA axis, SNS, and immune system functions according to standardised procedures [12]. Saliva collections were made with patients seated, leaning forward and with their heads tilted down.

The process was done for 3 min. All saliva sampling was performed between 10 and 12 am and always 4 h after waking to control possible fluctuation associated to daily output and diurnal rhythms on cortisol and α-amylase secretions [12]. It has been found that 4 h after waking α-amylase secretion reaches its highest level of the day. Participants were asked not to eat, drink or chew gum for 1 h before sampling. The volume of the sample was calculated (nearest 0.1 ml) and saliva flow rate (ml min^{-1}) was determined by dividing the volume of saliva by the collection time. Concentration of cortisol and IgA, and α-amylase activity were assessed in thawed samples.

Salivary cortisol and IgA concentrations, and α-amylase activity were calculated using a commercial luminescence immune assay (Salimetrics, State College, PA, USA), reading the luminescence units with automatic luminometers (Sunrise, TECAN Group, Mannedorf, Switzerland). Saliva samples were analyzed in a single batch to eliminate inter-assay variance and they were measured in duplicate. In fact, adequate intra-assay accuracy was obtained with a coefficient of variance between 6.3% and 8.9%.

Saliva was collected at pre-intervention and immediately after the 8 week program (post-intervention). Saliva analysis was conducted by an external investigator blinded to the treatment allocation of the patients.

Sample size calculation

Based on a previous pilot study [40] the sample size was calculated on an 80% power to detect a mean difference of 3 points, with a standard deviation of 1.5 (15%), on the fatigue total score of PFS, using a type 1 error (α) of 5%, and a type 2 error (β) of 20%. This power calculation resulted in 29 patients in each group. To accommodate expected dropouts before study completion, a total of 78 participants were included.

Statistical analyses

Statistical analysis was performed using SPSS statistical software, version 16.0, and it was conducted following intention-to-treat analysis. Participants who dropped out before the completion of the study were asked to return for post-testing. When post-intervention data were missing, baseline scores were used. To determine the effectiveness of the randomisation procedure, Student's *t*-tests and chi-square tests were used to examine the differences in baseline socio-demographic and medical features between included and excluded patients, as well as between participants who completed the study and those who dropped-out. A one-way analysis of variance (ANOVA) was conducted to compare the degree of fatigue of our sample of BCS with healthy women recruited from the Hospital Virgen de las Nieves influence area ($n = 43$, age: 47 ± 12 years).

The main analysis examined whether differences (mean differences) at baseline, 8-weeks and 6 months follow-up existed between CUIDATE-CONTROL groups in all outcomes. A 2×3 mixed-model repeated-measure analysis of co-variance (ANCOVA) with time (pre-, post-intervention, 6 months follow-up) as the within-subjects variable, intervention (CUIDATE, CONTROL group) as the between-subjects variable and age, civil status, educational level and clinical features as covariates was used to examine the effects of the intervention on the each subscale of the PFS.

Secondary outcomes were analyzed using 2×2 mixed-model repeated-measures ANCOVA with time (pre-, post-intervention)

as within-subjects variable, intervention (CUIDATE, CONTROL group) as the between-subjects variable and age, civil status, educational level and clinical features as covariates. Separate ANCOVAs were done with each outcome as dependent variable. The hypothesis of interest was intervention × time interaction. Inter-group effect sizes were calculated according to Cohen *d* statistic [41].

Results

Participants

One hundred and four patients were eligible for pre-screening and 78 (75%) were included (Fig. 1). All patients underwent axillary lymph node dissection during the surgery. No significant differences in socio-demographic or medical features were found between the 78 patients (75%) included and the 26 patients (25%) who were excluded or declined to participate, except that a greater number of excluded/declined patients were married (20% vs. 68.7%, $P < 0.05$). Further, participants who completed the study did not show differences in fatigue baseline than those patients who dropped out. The ANOVA revealed that BCS of both groups exhibited significant fatigue in all dimensions of the PFS as compared to healthy women (Table 2). No differences in age, clinical features, and PFS existed between CUIDATE and CONTROL groups (Tables 2 and 3), so it can be assumed that they were comparable at the beginning of the study.

Adherence and adverse events

Adherence to intervention and adverse events were recorded in a clinical history for each participant after each session.

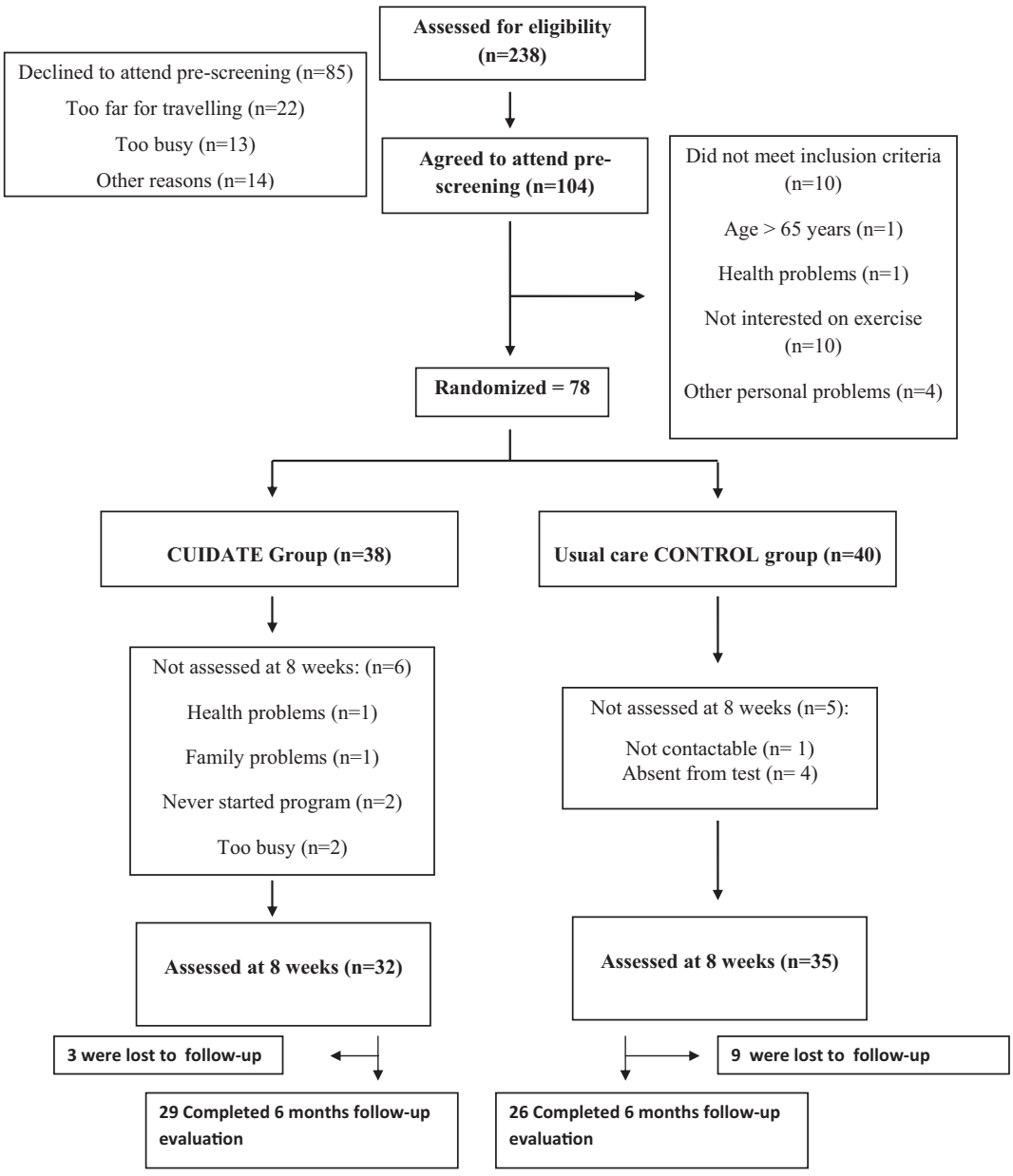

Fig. 1. Flow diagram of subject recruitment and retention throughout the course of the study.

Table 2
Comparison of Piper Fatigue Score data among healthy reference women and breast cancer survivors at baseline.

Piper Fatigue	Healthy women ($n=43$)	CUIDATE program ($n=32$)	CONTROL group ($n=35$)	P CUIDATE vs. CONTROL
Behavioural/severity[a]	1.33 ± 0.53	5.59 ± 1.89	6.75 ± 2.18	0.20
Affective/meaning[a]	1.60 ± 0.97	6.49 ± 2.25	6.71 ± 2.04	0.74
Sensory[a]	1.46 ± 0.66	5.90 ± 2.51	5.53 ± 1.64	0.49
Cognitive/mood[a]	1.61 ± 0.75	5.61 ± 2.39	5.01 ± 2.69	0.48
Total Fatigue Score[a]	1.51 ± 0.64	5.88 ± 1.91	5.89 ± 1.64	0.98

[a] $P<0.001$ for ANOVA analysis among breast cancer survivors at baseline and healthy women.

Patients within the CUIDATE group completed 83.3% of the 24 physical therapy treatments (mean ± SD number of sessions: 20 ± 4.2), showing a high adherence rate to the physical therapy program. Three participants in the CUIDATE group showed an increase of neck-shoulder pain after one session, but this event disappeared one day after. None participant reported increased fatigue during the sessions. One participant developed cancer within her non-affected breast during the program and, consequently, left the program. No further adverse events were reported.

Effects of physical therapy program CUIDATE in fatigue and physical activity

The ANCOVA found significant group × time interactions for all dimensions of fatigue (PFS): affective ($F=7.347$; $P=0.002$); sensory ($F=5.199$; $P=0.010$) cognitive (9.001; $P=0.001$), severity ($F=3.377$; $P=0.044$) and total fatigue score ($F=10.002$; $P<0.001$). The CUIDATE group experienced a greater decrease of fatigue as compared to the CONTROL group in all dimensions and the total score (Table 4) The inter-group effect size after treatment was moderate for severity (*d*: 0.55, 95%CI 0.30–0.85), sensory (*d*: 0.51, 95%CI 0.19–0.83), cognitive (*d*: 0.61, 95%CI 0.37–0.85) dimensions, and for total fatigue score (*d*: 0.68, 95%CI 0.57–1.05). The intergroup effect size for the affective dimension was small (*d*: 0.25, 95%CI 0.05–0.59).

The CUIDATE group maintained the improvements of fatigue in all dimensions and total score of PFS after 6 months follow-up (Table 4). The inter-group effect size after 6 months follow-up was small for affective (*d*: 0.21, 95%CI 0.04–0.51), severity (*d*: 0.45, 95%CI 0.12–0.78), sensory (*d*: 0.34, 95%CI 0.02–0.67), cognitive (*d*: 0.44, 95%CI 0.12–0.77) dimensions

Table 3
Patient's characteristics and comparisons between both breast cancer survivor groups.

Variable	Control group ($n=35$)	CUIDATE program ($n=32$)	P value
Age (y), mean (SD)	48 (9)	49 (9)	0.415
Time post-treatment, *n* (%)			
<12 months	29 (82.9)	22 (68.8)	0.176
>12 months	6 (17.1)	10 (31.3)	
Civil status, *n* (%)			
Married	21 (60)	20 (62.5)	
Unmarried	8 (22.9)	5 (15.6)	0.718
Divorced	6 (17.1)	7 (21.9)	
Educational level, *n* (%)			
Low	13 (37.1)	11 (34.4)	
Medium	6 (17.1)	8 (25.0)	0.481
University level	16 (45.7)	13 (40.6)	
Employment status, *n* (%)			
Home employed	8 (22.9)	7 (21.9)	0.586
Employed	14 (40.0)	10 (31.3)	
Non employed	13 (37.1)	15 (46.9)	
Tumor stage, *n* (%)			
I	12 (34.3)	4 (12.5)	
II	16 (45.7)	23 (71.9)	0.145
IIIA	7 (20.0)	5 (15.6)	
Type of surgery, *n* (%)			
Tumerectomy	21 (60.0)	21 (65.6)	0.596
Mastectomy	14 (40.0)	11 (34.4)	
Type of treatment *n* (%)			
Radiation	1 (2.9)	1 (3.1)	0.991
Chemotherapy	3 (8.6)	3 (9.4)	
Radiation + chemotherapy	31 (88.6)	28 (87.5)	
Menopause, *n* (%)			
Yes	20 (57.1)	24 (75.0)	0.197
Not	15 (42.9)	8 (25.0)	

P values for comparisons among group based on chi-square and analysis of variance tests.

Table 4
Pre-intervention, post-intervention, 6 months follow-up and change scores for MEAN values of Fatigue Piper Score.

Group	CUIDATE program	Control	Between-group differences
Behavioural/severity			
Pre-intervention	5.59 ± 1.89	6.75 ± 2.18	
Post-intervention	3.17 ± 1.77	6.01 ± 2.10	
6 months follow-up	3.60 ± 2.18	5.75 ± 2.55	
Within group change scores			
Pre-post intervention	−2.42 (−3.18; −1.74)	−0.74 (−1.58; 1.17)	−1.68 (−2.90; −0.66)*
Pre intervention–6 months follow up	−1.99 (−3.03; −0.94)	−1.00 (−1.80; 0.27)	−1.00 (−2.22; 0.30)*
Affective/meaning			
Pre-intervention	6.49 ± 2.25	6.71 ± 2.04	
Post-intervention	3.81 ± 2.33	6.24 ± 2.21	
6 months follow-up	4.18 ± 2.18	5.98 ± 2.53	
Within group change scores			
Pre-post intervention	−2.68 (−3.70; −1.65)	−0.47 (−1.19; 0.32)	−2.21 (−3.61; −0.80)*
Pre intervention–6 months follow up	−2.31 (−3.16; −1.45)	−0.73 (−1.43; 0.02)	−1.58 (−2.73; −0.44)*
Sensory			
Pre-intervention	5.90 ± 2.51	5.53 ± 1.64	
Post-intervention	3.92 ± 2.11	5.95 ± 2.26	
6 months follow-up	4.03 ± 2.23	5.09 ± 1.98	
Within group change scores			
Pre-post intervention	−1.98 (−3.17; −0.74)	0.42 (−0.58; 1.42)	−2.40 (−3.54; −1.17)*
Pre intervention–6 months follow up	−1.87 (−2.85; −0.89)	−0.44 (−1.32; 0.44)	−1.43 (−2.75; −0.10)*
Cognitive/mood			
Pre-intervention	5.61 ± 2.39	5.01 ± 2.69	
Post-intervention	3.42 ± 1.69	5.78 ± 2.02	
6 months follow-up	3.97 ± 2.19	5.10 ± 2.88	
Within group change scores			
Pre-post intervention	−2.19 (−3.15; −1.44)	0.77 (−0.76; 1.84)	−2.96 (−4.06; −1.76)*
Pre intervention–6 months follow up	−1.64 (−2.72; −0.62)	0.09 (−0.29; 0.88)	−1.73 (−2.95; −0.55)*
Total Fatigue score			
Pre-intervention	5.88 ± 1.91	5.89 ± 1.64	
Post-intervention	3.54 ± 1.74	6.04 ± 1.89	
6 months follow-up	3.92 ± 1.96	5.36 ± 2.00	
Within group change scores			
Pre-post intervention	−2.34 (−3.18; −1.59)	0.15 (−0.22; 0.72)	−2.49 (−4.00; −2.17)*
Pre intervention–6 months follow up	−1.96 (−2.77; −1.14)	−0.53 (−1.13; 0.11)	−1.43 (−3.57; −1.62)*

Values are expressed as mean ± standard deviation for pre- and post-intervention data and as mean (95% confidence interval) for within- and between-group change scores.

* Significant group × time interaction (repeated ANCOVA test, $P < 0.05$).

and total fatigue score (*d*: 0.43, 95%CI 0.12–0.74) related to pre-intervention values.

In addition, a significant group × time interaction ($F = 49.896$; $P < 0.001$) for MLTPAQ was also found: the CUIDATE group increased physical activity during the 8 weeks of the program (Table 5). The inter-group effect size was large (*d*: 0.98, 95%CI 0.68–1.33).

Effects of physical therapy program CUIDATE in salivary markers

The ANCOVA revealed a significant group × time interaction for α-amylase activity ($F = 4.002$; $P = 0.047$): breast cancer survivors in the CUIDATE group showed a higher decrease in α-amylase activity as compared to those within the CONTROL group (Table 5). The inter-group effect size was small (*d*: 0.24, 95%CI 0–0.49). No significant group × time interactions for cortisol ($F = 1.122$; $P = 0.729$), IgA concentration ($F = 1.805$; $P = 0.184$) and salivary flow rate ($F = 0.184$; $P = 0.679$) were found. Inter-group effect sizes were negligible for cortisol (*d*: 0.03, 95%CI −0.26; 0.38), IgA (*d*: −0.17, 95%CI −0.43; −0.08) and salivary flow rate (*d*: −0.05 95%CI −0.26; 0.17).

Effects of physical therapy program CUIDATE in neck-shoulder mobility

The ANCOVA revealed a significant group × time interaction for shoulder flexion ($F = 0.151$; $P = 0.004$) and horizontal abduction ($F = 5.691$; $P = 0.020$). Patients within the CUIDATE group experienced greater increases in flexion and horizontal abduction than those within the CONTROL group (Table 6). Inter-group effect size was moderate for active flexion (*d*: 0.75, 95%CI 0.25–0.75) and small for active horizontal abduction (*d*: 0.30, 95%CI 0.04–0.55) of the shoulder.

The ANCOVA did not find a significant group × time interaction for shoulder extension ($F = 0.840$; $P = 0.363$) or external rotation ($F = 2.140$; $P = 0.149$). In fact, inter-group effect sizes were negligible for both, extension (*d*: 0.04, 95%CI −0.13/0.27)

Table 5
Pre-, post-intervention, and change scores for saliva measurements and MLTPAQ condition values.

Group	Pre-intervention	Post-intervention	Within group change scores	Between-group differences
α-Amylase activity (U/ml)				
CUIDATE program	208.49 ± 130.65	165.70 ± 91.13	−42.78 (−77.95; −7.60)	
Control	195.58 ± 132.32	194.47 ± 126.98	−1.01 (−26.46; 24.40)	−41.77 (−83.51; −0.02)*
Cortisol (μg/ml)				
CUIDATE program	0.30 ± 0.25	0.27 ± 0.11	−0.02 (−0.06; 0.11)	
Control	0.30 ± 0.27	0.24 ± 0.18	−0.05 (−0.11; 0.22)	0.03 (−0.15; 0.21)
Salivary IgA (mg ml^{-1})				
CUIDATE program	20.41 ± 8.01	17.15 ± 9.87	−3.25 (−6.97; 0.46)	
Control	21.87 ± 9.60	22.26 ± 10.40	0.38 (−3.45; 4.23)	−2.87 (−4.65; 0.34)
Salivary flow rate (ml min^{-1})				
CUIDATE program	1.23 ± 0.29	1.22 ± 0.39	−0.01 (−0.10; 0.11)	
Control	1.24 ± 0.56	1.27 ± 0.49	0.04 (−0.13; 0.22)	0.05 (−0.26; 0.17)
MLTPAQ (METS/h/days)				
CUIDATE program	8.90 ± 6.59	37.11 ± 15.29	28.53 (22.53; 34.54)	
Control	8.41 ± 6.05	12.12 ± 8.26	4.17 (0.03; 8.30)	24.36 (17.44; 31.99)*

Values are expressed as mean ± standard deviation for pre- and post-intervention data and as mean (95% confidence interval) for within- and between-group change scores.
* Significant group × time interaction (repeated ANCOVA test, $P < 0.05$).

Table 6
Pre-intervention, post-intervention, and change scores for active range of motion within the affected (surgical) shoulder.

Group	Pre-intervention	Post-intervention	Within group change scores	Between-group differences
Flexion (°)				
CUIDATE program	146.25 ± 23.50	162.25 ± 13.97	16.00 (9.63; 22.36)	
Control	144.62 ± 15.04	148.09 ± 18.46	3.46 (−2.08; 9.02)	12.53 (4.25; 20.81)*
Extension (°)				
CUIDATE program	44.90 ± 16.14	47.34 ± 10.02	2.43(−2.25; 7.12)	
Control	45.25 ± 9.85	45.18 ± 12.23	−0.06 (−3.05; 2.92)	2.50 (−2.95; 7.95)
External rotation (°)				
CUIDATE program	45.25 ± 16.48	52.59 ± 12.90	7.34 (−2.62; 12.05)	
Control	44.50 ± 15.11	46.53 ± 14.34	2.03 (−3.68; 7.74)	5.31 (−1.94; 12.57)
Horizontal abduction (°)				
CUIDATE program	27.84 ± 9.52	31.87 ± 8.78	4.03 (−1.22; 6.77)	
Control	29.56 ± 11.32	27.71 ± 10.67	−1.84 (−5.99; 3.91)	5.84 (0.94; 10.72)*

Values are expressed as mean ± standard deviation for pre- and post-intervention data and as mean (95% confidence interval) for within- and between-group change scores.
* Significant group × time interaction (repeated ANCOVA test, $P < 0.05$).

and horizontal abduction (*d*: 0.08, 95%CI −0.06/0.23) of the shoulder.

The ANCOVA revealed a significant group × time interaction for neck extension ($F = 6.382$; $P = 0.014$), both lateral-flexion (surgical side: $F = 9.389$; $P = 0.003$; non-surgical: $F = 18.479$; $P < 0.001$), and non-surgical rotation ($F = 7.966$; $P = 0.006$). Patients within the CUIDATE group experienced greater increases in cervical mobility in these movements than those within the CONTROL group (Table 7). Inter-group effect sizes were small for cervical extension (*d*: 0.31, 95%CI 0.06–0.56), lateral-flexion towards the surgical side (*d*: 0.37, 95%CI 0.13–0.62), and rotation towards the non-surgical side (*d*: 0.35, 95%CI 0.10–0.60), and moderate for lateral-flexion towards the non-surgical side (*d*: 0.52, 95%CI 0.28–0.77).

No significant group × time interactions for cervical flexion ($F = 0.128$; $P = 0.721$), or rotation to the surgical side ($F = 2.749$; $P = 0.102$) were found. Inter-group effect sizes were negligible for active cervical flexion (*d*: −0.18, 95%CI −0.43; 0.0) and rotation to the surgical side (*d*: 0.09, 95%CI −0.04; 0.28).

Discussion

The current study found that an 8-week supervised multimodal physical therapy program, including core stability exercises, endurance exercises, neck-shoulder mobility procedures, relaxation interventions and manual massage, exerts broad effects in BCS. It has been recently proposed that the interaction among fatigue, pain, sleep, and distress is investigated in clinical trials assessing CRF [42]. The current study assessed the effects of physical therapy, following a psycho-neuro-immunology perspective, and demonstrated significant and potential effects in different dimensions of self-perceived fatigue associated with changes in distress markers as α-amylase activity and functional status in neck-shoulder mobility. The effects over fatigue were maintained at 6 months after completion of the individualised sessions.

The effect sizes of the improvement in fatigue suggest medium clinically important changes immediate after the program and at 6-months follow-up. Our results differ from the

Table 7
Pre-intervention, post-intervention, and change scores for active cervical range of motion.

Group	Pre-intervention	Post-intervention	Within group change scores	Between-group differences
Flexion (°)				
CUIDATE program	43. 80 ± 9.30	41.06 ± 8.07	−2.73 (−1.23; 6.70)	
Control	41.06 ± 11.07	42.25 ± 11.22	1.18(−2.54; 4.90)	−3.92 (−9.25; 1.41)
Extension (°)				
CUIDATE program	56.54 ± 12.75	63.48 ± 10.01	6.93 (2.10; 11.77)	
Control	56.08 ± 13.34	54.44 ± 10.64	−1.64 (−6.57; 3.27)	8.58 (1.79; 15.37)*
Lateral-flexion towards the surgical side (°)				
CUIDATE program	33.65 ± 7.39	36.93 ± 9.11	3.28 (−5.61; −0.97)	
Control	33.88 ± 8.06	31.94 ± 8.48	−1.94 (−4.48; 0.60)	5.22 (1.83; 8.60)*
Lateral-flexion towards the non-surgical side (°)				
CUIDATE program	33.06 ± 8.15	37.75 ± 8.71	4.68 (−2.15; 7.28)	
Control	34.82 ± 7.14	31.54 ± 6.45	−3.28(−6.05; 0.51)	7.97 (4.25; 11.65)*
Rotation towards the surgical side (°)				
CUIDATE program	53.53 ± 17.14	61.13 ± 10.94	7.60 (−0.24; 34.54)	
Control	53.11 ± 11.06	53.64 ± 14.37	0.52 (−5.50; 4.44)	7.07 (−1.45; 15.59)
Rotation towards the non-surgical side (°)				
CUIDATE program	52.74 ± 14.90	63.06 ± 9.99	10.32 (5.03; 15.61)	
Control	56.11 ± 10.96	54.94 ± 14.70	−1.17 (−7.46; 5.11)	11.49 (3.35; 19.64)*

Values are expressed as mean ± standard deviation for pre- and post-intervention data and as mean (95% confidence interval) for within- and between-group change scores.
* Significant group × time interaction (repeated ANCOVA test, $P < 0.05$).

findings of a recent meta-analysis which indicated that the magnitude of the effects of exercise interventions on CRF was small (effect size 0.31, 95%CI 0.22–0.40) [43,44]. Most of these trials applied one-modality exercise approach for the management of BCS; however, the current randomised controlled trial is included in the generation of studies demonstrating the effects of different modalities of exercises and recovery strategies, following a body-mind approach, which have demonstrated their effectiveness when used alone [45].

Our results may be explained due to the high rate supervision and the nature of the CUIDATE program. To the best of the authors' knowledge, no study has previously incorporated recovery strategies (massage) immediately after the exercise intervention. The application of massage after an exercise demonstrated the ability to reduce psycho-physiological deleterious effects of the exercise [20] by improving the recovery process. Recovery techniques applied after exercise program may reduce CRF after each session, increasing the effectiveness of these programs. The results obtained at post-intervention were maintained after 6 months follow-up within the CUIDATE group. Current results and the program adherence during the follow-up period are superior to a similar study using multimedia support [30]. These results may be related to the supervision received with a high therapist/patient ratio during the main program which can improve exercise performance during the follow-up period.

An interesting result of this randomised controlled trial was a clinical, although small, reduction of SNS activity, as reflected by reduced α-amylase activity, within the CUIDATE group. Despite profuse research supporting high and low intensity exercise programs for improving psychological and physical outcomes in BCS; only a few studies have reported biological effectiveness of these programs [29]. In fact, this is the first randomised controlled trial reporting clinical effects of a physical therapy program in α-amylase activity. This recently incorporated biological SNS marker, i.e. α-amylase, is considered a promising outcome for treatment trials [12], but with few precedents showing positive effects [46,47]. Therefore, reduced SNS activity induced by exercise can exert modulatory positive influences on several biological systems relevant for BCS (e.g., immune, metabolic, cardiovascular) explaining the psychophysical improvements reported in this study.

Further, considering that cancer therapies impair immune and endocrine function in BCS [29], restorative procedures should be included in clinical practice to respond to expectations of patients with these types of programs [48]. Nevertheless, our clinical trial failed to show ability to improve HPA axis and immune function in BCS. Insufficient numbers of studies [29,47] have tested the effects of exercise on immune factors after breast cancer treatment. The CUIDATE program, in agreement with some previous studies [49–51], was not able to improve immune function; nevertheless, the program did not negatively impact immune function either. However, two studies [52,53] observed significant improvements after longer applications of aerobic exercises. We do not know if a longer application of the CUIDATE program would be also able to induce these changes. Therefore, based in current and previous results, it seems that chronic changes in immune response induced by exercise programs are small, and their clinical relevance is, at least at this moment, limited.

Our study supports results from previous studies which indicate that moderate exercise does not modify cortisol concentrations in cancer survivors [54,55]. Alterations of HPA-axis, that is, a flattened diurnal cortisol slope [56], present in BCS with CRF, could reduce the ability of exercise to change salivary cortisol concentrations. Future studies including cortisol slope changes and other HPA-axis biomarkers altered during breast cancer treatment, such as serotonin, should be conducted

to investigate the ability of physical therapy programs to improve endocrine function in BCS. Different response patterns between SNS (α-amylase) and HPA-axis (cortisol) are non-anecdotic, because different tendencies in these systems associated to biological cost of caring for cancer patients have been previously reported [12].

We also found significant and clinical improvements in active cervical-shoulder mobility. Improvement in shoulder mobility was similar to previous studies focussed on shoulder mobility exercises [21,27,28,57]. It is known that shoulder area dysfunction is a consequence of surgery by limiting the motion of the side that has been operated on. This dysfunction reduces ability of BCS to perform daily activities, such as reaching above the head or fastening clothes from behind [28]. The current study reports positive effects of physical therapy on the neck-shoulder complex. A broad treated area strategy and the combination of core stability with mobility can reduce adverse outcomes, such as spasm of the muscles surrounding the joint, muscle atrophy, tightening of the shoulder capsule and decreased functional joint mobility [59]. Core stability exercises used in this study have shown optimal production, transfer, and control of the force and motion to the arm during functional tasks of daily life [60]. We could hypothesize a summative effect of both neck-shoulder mobility exercises (dynamic movement) and core stability exercises (isometric muscle endurance training) inducing greater clinical effects. Future studies investigating these summation effects are warranted.

Strengths of the current trial include supervised and structured exercise program, multimodal cancer approach, use of validated objective measurements; intention-to-treat analyses and a high therapist/patient ratio which could improve the well-being of BCS; however, we should recognize some weaknesses. Particularly, one weakness of this study was that the control group did not include a sham hands-on intervention. Future studies should compare manual techniques used in the current study to placebo interventions including any manual contact with patients. A second weakness is that we only assessed the main outcome (fatigue), but not the remaining outcomes, at 6 month follow-up period. This is needed to establish long-term effects of the CUIDATE program on neck-shoulder mobility and salivary markers. Finally, high supervision levels of this type of programs can imply high cost, which may threaten the financial viability of such programs; however, large clinical effects obtained with this type of program should be considered in order to respond high demand of integrative medicine resources in breast patients [61].

Conclusions

An 8-week multimodal program was clinically effective for decreasing cancer-related fatigue, reducing α-amylase activity and increasing shoulder and cervical active range of motion compared to usual health care in breast cancer survivors. The effects in fatigue were maintained at 6 months follow-up using an exercise program multimedia support.

Conflict of interest

No competing financial interests exist.

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References

[1] Barsevick AM, Cleeland CS, Manning DC, O'Mara AM, Reeve BB, Scott JA, et al. (Assessing Symptoms of Cancer Using Patient-Reported Outcomes) ASCPRO recommendations for the assessment of fatigue as an outcome in clinical trials. J Pain Symptom Manage 2010;39:1086–99.

[2] Kröz M, Zerm R, Kuhnert N, Brauer D, von Laue HB, Bockelbrink A, et al. The influence of self- and autonomic regulation on cancer-related fatigue and distress in breast and colorectal cancer patients—a prospective study. Eur J Integr Med 2009;1:182.

[3] Lawrence DP, Kupelnick B, Miller K, Devine D, Lau J. Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients. J Natl Cancer Inst Monogr 2004;32:40–50.

[4] Bleike EM, Pouwer F, van der Ploeg HM, Leer JW, Ader HJ. Psychological distress two years after diagnosis of breast cancer: frequency and prediction. Patient Educ Couns 2000;40:209–17.

[5] Schuler LA, Auger AP. Psychosocially influenced cancer: diverse early-life stress experiences and links to breast cancer. Cancer Prev Res (Phila) 2010;3:1365–70.

[6] Gunnar MR, Quevedo K. The neurobiology of stress and development. Annu Rev Psychol 2007;58:145–73.

[7] Bender CM, Sereika SM, Brufsky AM, Ryan CM, Vogel VG, Rastogi P, et al. Memory impairments with adjuvant anastrozole versus tamoxifen in women with early stage breast cancer. Menopause 2007;14:995–8.

[8] Bower JE, Ganz PA, Aziz N, Bower JE, Ganz PA, Aziz N. Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. Psychosom Med 2005;67:277–80.

[9] Campeau S, Nyhuis TJ, Sasse SK, Kryskow EM, Herlihy L, Masini CV, et al. Hypothalamic pituitary adrenal axis responses to low-intensity stressors are reduced after voluntary wheel running in rats. J Neuroendocrinol 2010;22:872–88.

[10] Moyer CA, Rounds J, Hannum J. A meta-analysis of massage therapy research. Psychol Bull 2004;130:3–18.

[11] Ross A, Thomas S. The health benefits of yoga and exercise: a review of comparison studies. J Altern Complement Med 2010;16:3–12.

[12] Nater UM, Rohleder N. Salivary alpha-amylase as a noninvasive biomarker for the sympathetic nervous system: current state of research. Psychoneuroendocrinology 2009;34:486–96.

[13] Shirasaki S, Fujii H, Takahashi M, Sato T, Ebina M, Noto Y, et al. Correlation between salivary alpha-amylase activity and pain scale in patients with chronic pain. Reg Anesth Pain Med 2007;32:120–3.

[14] Seugnet L, Boero J, Gottschalk L, Duntley SP, Shaw PJ. Identification of a biomarker for sleep drive in flies and humans. Proc Natl Acad Sci 2006;103:19913–8.

[15] Harrison T, Bigler L, Tucci M, Pratt L, Malamud F, Thigpen JT, et al. Salivary sIgA concentrations and stimulated whole saliva flow rates among women undergoing chemotherapy for breast cancer: an exploratory study. Spec Care Dentist 1998;18:109–12.

[16] Jensen SB, Mouridsen HT, Reibel J, Brünner N, Nauntofte B. Adjuvant chemotherapy in breast cancer patients induces temporary salivary gland hypofunction. Oral Oncol 2008;44:162–73.

[17] Martins RA, Cunha MR, Neves AP, Martins M, Teixeira-Veríssimo M, Teixeira AM. Effects of aerobic conditioning on salivary IgA and

plasma IgA, IgG and IgM in older men and women. Int J Sports Med 2009;30:906–12.
[18] Lim YM, Hong GR. Effect of 16-week Kouk-Sun-Do exercise on physical fitness, emotional state, and immunoglobulin A in community-dwelling elders in Korea. Appl Nurs Res 2010;23:91–100.
[19] Groer M, Mozingo J, Droppleman P, Davis M, Jolly ML, Boynton M, et al. Measures of salivary secretory immunoglobulin A and state anxiety after a nursing back rub. Appl Nurs Res 1994;7:2–6.
[20] Arroyo-Morales M, Olea N, Ruíz C, del Castilo JdeD, Martínez M, Lorenzo C, et al. Massage after exercise—responses of immunologic and endocrine markers: a randomized single-blind placebo-controlled study. J Strength Cond Res 2009;23:638–44.
[21] McNeely ML, Campbell K, Ospina M, Rowe BH, Dabbs K, Klassen TP, et al. Exercise interventions for upper-limb dysfunction due to breast cancer treatment. Cochrane Database Syst Rev 2010;16:CD005211.
[22] Nesvold IL, Reinertsen KV, Fosså SD, Dahl AA. The relation between arm/shoulder problems and quality of life in breast cancer survivors: a cross-sectional and longitudinal study. J Cancer Surviv 2010. Ahead of print.
[23] Fernández-Lao C, Cantarero-Villanueva I, Fernández-de-Las-Peñas C, Del-Moral-Ávila R, Menjón-Beltrán S, Arroyo-Morales M. Widespread mechanical pain hypersensitivity as a sign of central sensitization after breast cancer surgery: comparison between mastectomy and lumpectomy. Pain Med 2011;12:72–8.
[24] Fernández-Lao C, Cantarero-Villanueva I, Fernández-de-Las-Peñas C, Del-Moral-Ávila R, Arendt-Nielsen L, Arroyo-Morales M. Myofascial trigger points in neck and shoulder muscles and widespread pressure pain hypersensitivtiy in patients with postmastectomy pain: evidence of peripheral and central sensitization. Clin J Pain 2010;26:798–806.
[25] Cantarero-Villanueva I, Férnandez-Lao C, Díaz-Rodríguez L, Férnandez-de-las-Peñas C, Sánchez-Cantalejo E, Arroyo Morales M. Associations among musculoskeletal impairments, depression, body image and fatigue in breast cancer survivors within the first year after treatment. Eur J Cancer Care 2011;17. Ahead of print.
[26] Ahmed RL, Thomas W, Yee D, Schmitz KH. Randomized controlled trial of weight training and lymphedema in breast cancer survivors. J Clin Oncol 2006;24:2765–72.
[27] Beurskens CHG, Van Uden CJT, Strobbe LJA, Oostendorp RAB, Wobbes T. The efficacy of physiotherapy upon shoulder function following axillary dissection in breast cancer, a randomized controlled trial. BMC Cancer 2007;7:166.
[28] Chan DN, Lui LY, So WK. Effectiveness of exercise programmes on shoulder mobility and lymphoedema after axillary lymph node dissection for breast cancer: systematic review. J Adv Nurs 2010;66:1902–14.
[29] Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvão DA, Pinto BM, et al. American College of Sports Medicine. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010;42:1409–26.
[30] Haines TP, Sinnamon P, Wetzig NG, Lehman M, Walpole E, Pratt T, et al. Multimodal exercise improves quality of life of women being treated for breast cancer, but at what cost? Randomized trial with economic evaluation. Breast Cancer Res Treat 2010;124:163–75.
[31] Mock V, Frangakis C, Davidson NE, Ropka ME, Pickett M, Poniatowski B, et al. Exercise manages fatigue during breast cancer treatment: a randomized controlled trial. Psychooncology 2004;14:464–77.
[32] Pickett M, Mock V, Ropka ME, Cameron L, Coleman M, Podewils L, et al. Adherence to moderate-intensity exercise during breast cancer therapy. Cancer Pract 2002;10:284–92.
[33] Elosua R, Garcia M, Aguilar A, Molina L, Covas MI, Marrugat J. Validation of the Minnesota leisure time physical activity questionnaire in Spanish women. Investigators of the MARATDON Group. Med Sci Sports Exerc 2000;32:1431–7.
[34] Giacalone A, Polesel J, De Paoli A, Colussi AM, Sartor I, Talamini R, et al. Assessing cancer-related fatigue: the psychometric properties of the Revised Piper Fatigue Scale in Italian cancer inpatients. Support Care Cancer 2010;18:1191–7.
[35] Ainsworth BE, Haskell WL, Leon AS, Jacobs Jr DR, Montoye HJ, Sallis JF, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 1993;225:71–80.
[36] American Medical Association. Guides to the evaluation of permanent impairment. 6th ed. Chicago: AMA; 2008.
[37] Mullaney MJ, McHugh MP, Johnson CP, Tyler TF. Reliability of shoulder range of motion comparing a goniometer to a digital level. Physiother Theory Pract 2010;26:327–33.
[38] Fernandez-de-las-Peñas C, Alonso Blanco C, Cuadrado ML, Pareja JA. Forward head posture and neck mobility in chronic tension type headache: a blinded, controlled study. Cephalalgia 2006;26:314–9.
[39] Fletcher JP, Bandy WD. Intrarater reliability of CROM measurement of cervical spine active range of motion in persons with and without neck pain. J Orthop Sports Phys Ther 2008;38:640–5.
[40] Turner J, Hayes S, Reul-Hirche H. Improving the physical status and quality of life of women treated for breast cancer: a pilot study of a structured exercise intervention. J Surg Oncol 2004;86:141–6.
[41] Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale, NJ: Lawrence Erlbaum Associates; 1998.
[42] Mortimer JE, Barsevick AM, Bennett CL, Berger AM, Cleeland C, Devader SR, et al. Studying cancer-related fatigue: report of the NCCN Scientific Research Committee. J Natl Compr Canc Netw 2010;8:1331–9.
[43] Brown JC, Huedo-Medina TB, Pescatello LS, Pescatello SM, Ferrer RA, Johnson BT. Efficacy of exercise interventions in modulating cancer-related fatigue among adult cancer survivors: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2010;(November). Ahead of print.
[44] Velthuis MJ, Agasi-Idenburg SC, Aufdemkampe G, Wittink HM. The effect of physical exercise on cancer-related fatigue during cancer treatment: a meta-analysis of randomised controlled trials. Clin Oncol (R Coll Radiol) 2010:26. Ahead of print.
[45] Spahn G, Kennemann C, Lüdtke R, Franken U, Paul A, Dobos G. Moderate walking exercise versus a multimodal mind-body programme: report of an RCT in breast cancer patients affected by severe long-term tumour associated fatigue. Eur J Integr Med 2008;1:13.
[46] Arai YC, Sakakibara S, Ito A, Ohshima K, Sakakibara T, Nishi T, et al. Intra-operative natural sound decreases salivary amylase activity of patients undergoing inguinal hernia repair under epidural anesthesia. Acta Anaesthesiol Scand 2008;52:987–90.
[47] Hodgson NA, Andersen S. The clinical efficacy of reflexology in nursing home residents with dementia. J Altern Complement Med 2008;14:269–75.
[48] Büssing A, Fischer J, Fouladbakhsh JM, Ostermann T, Matthiessen PF. Perceived and expected effects of physical activity in female cancer survivors. Eur J Integr Med 2009;1:9–17.
[49] Spence RR, Heesch KC, Brown WJ. Exercise and cancer rehabilitation: a systematic review. Cancer Treat Rev 2010;36:185–94.
[50] Nieman DC, Cook VD, Henson DA, Suttles J, Rejeski WJ, Ribisl PM, et al. Moderate exercise training and natural killer cell cytotoxic activity in breast cancer patients. Int J Sports Med 1995;16:334–7.
[51] De Backer IC, Schep G, Backx FJ, Vreugdenhil G, Kuipers H. Resistance training in cancer survivors: a systematic review. Int J Sports Med 2009;30:703–12.
[52] Hayes SC, Rowbottom D, Davies PS, Parker TW, Bashford J. Immunological changes after cancer treatment and participation in an exercise program. Med Sci Sports Exerc 2003;35:2–9.
[53] Fairey AS, Courneya KS, Field CJ, Bell GJ, Jones LW, Mackey JR. Randomized controlled trial of exercise and blood immune function in postmenopausal breast cancer survivors. J Appl Physiol 2005;98:1534–40.
[54] Hutnick NA, Williams NI, Kraemer WJ, Orsega-Smith E, Dixon RH, Bleznak AD, et al. Exercise and lymphocyte activation following chemotherapy for breast cancer. Med Sci Sports Exerc 2005;37:1827–35.
[55] Galvão DA, Nosaka K, Taaffe DR, Spry N, Kristjanson LJ, McGuigan MR, et al. Resistance training and reduction of treatment side effects in prostate cancer patients. Med Sci Sports Exerc 2006;38:2045–52.
[56] Payne JK, Held J, Thorpe J, Shaw H. Effect of exercise on biomarkers, fatigue, sleep disturbances, and depressive symptoms in older women with breast cancer receiving hormonal therapy. Oncol Nurs Forum 2008;35:635–42.

[57] Bower JE, Ganz PA, Dickerson SS, Petersen L, Aziz N, Fahey JL. Diurnal cortisol rhythm and fatigue in breast cancer survivors. Psychoneuroendocrinology 2005;30:92–100.

[59] Kilgour RD, Jones DH, Keyserlingk JR. Effectiveness of a self-administered, home-based exercise rehabilitation program for women following a modified radical mastectomy and axillary node dissection: a preliminary study. Breast Cancer Res Treat 2008;109:285–95.

[60] Okada T, Huxel KC, Nesser TW. Relationship between core stability, functional movement, and performance. J Strength Cond Res 2011;25:252–61.

[61] Micke O, Bruns F, Glatzel M, Schönekaes K, Micke P, Mücke R, et al. Predictive factors for the use of complementary and alternative medicine (CAM) in radiation oncology. Eur J Integr Med 2009;1:19–25.

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Research Article

Effectiveness of Core Stability Exercises and Recovery Myofascial Release Massage on Fatigue in Breast Cancer Survivors: A Randomized Controlled Clinical Trial

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The purpose of the present paper was to evaluate the effects of an 8-week multimodal program focused on core stability exercises and recovery massage with DVD support for a 6-month period in physical and psychological outcomes in breast cancer survivors. A randomized controlled clinical trial was performed. Seventy-eight ($n = 78$) breast cancer survivors were assigned to experimental (core stability exercises plus massage-myofascial release) and control (usual health care) groups. The intervention period was 8 weeks. Mood state, fatigue, trunk curl endurance, and leg strength were determined at baseline, after the last treatment session, and at 6 months of followup. Immediately after treatment and at 6 months, fatigue, mood state, trunk curl endurance, and leg strength exhibited greater improvement within the experimental group compared to placebo group. This paper showed that a multimodal program focused on core stability exercises and massage reduced fatigue, tension, depression, and improved vigor and muscle strength after intervention and 6 months after discharge.

1. Introduction

Almost all breast cancer survivors (BCS) suffer from one or more cancer-related symptoms that impact their quality of life. Multimodal therapeutic programs can ameliorate and reduce the patient's impairments by improving their ability to carry out daily tasks [1]. Nevertheless, health care practitioners feel that their practice is usually affected by the lack of exercise guidance for cancer population suffering from fatigue-related cancer [2].

One principal component of a multimodal program is the therapeutic exercise. Similar levels of physical activity as general people have been recommended in BCS [3]. This recommendation was reviewed by American College Sports Medicine experts in exercise for cancer who suggested the necessity to individualize the programs to cancer populations [4]. A recent meta-analysis concluded that exercise interventions should be multidimensional, including both exercise and behavioral interventions [3].

In fact, there is evidence that exercise and massage can be beneficial when tested as separate interventions for improving physical function in BCS [3]. A recent study has reported psychological and physical improvements after the application of a multimodal physical therapy program including in patients with different types of cancer [5]. Although conventional exercise programs [3] and alternative medicine approachs [6] applied on BCS with cancer-related fatigue have been previously studied, the application of core

stability exercises (CSEs) as the main component of the program has not yet been investigated.

CSEs are defined as exercises developing the ability to control the position and motion of the trunk during end-range segment in integrated kinetic chain activities [7]. It is known that BCS exhibit reduction in muscle strength associated with cancer-related symptoms [8], which could be improved with an exercise program including CSEs.

Finally, disturbances of mood state have been reported as a frequent symptom in BCS [9]. Massage, which has been shown to be effective as a psychological resource [10, 11] and a recovery method after exercise [12] could be a main component of recovery process. Therefore, the aim of the current randomized controlled trial was to investigate the effectiveness of an 8-week physical therapy program focused on CSEs and recovery massage in physical (muscle strength) and psychological (mood state) outcomes in BCS.

2. Methods

2.1. Subjects. Participants were recruited from the Breast Oncology Unit of Hospital Virgen de las Nieves, Granada, Spain from December 2008 to June 2010. The patients were approached and enrolled by physicians and nurses from two treatment departments. Participants were eligible if they (1) had a diagnosis of breast cancer (stage I–IIIA), (2) were 25–65 years, (3) finished coadjuvant treatment except hormone therapy, (4) not do have active cancer, and (5) present 4 or 5 of the following physical findings, judged by the oncologist who referred the patient: neck or shoulder pain, reduced range of motion in neck-shoulder region, reduced physical capacity, psychological problems, increased fatigue, sleep disturbances, or any problem in coping with physical and psychosocial functioning. They were excluded if they were receiving chemotherapy or radiotherapy treatment at the time of the study or they had chronic or orthopedic diseases which do not permit following the physical program.

Potential participants were contacted by phone by 2 oncologists of the hospital. Those interested were cited for an appointment, received a complete explanation of the protocol and signed the consent form. The ethical approval for the study was granted by the Ethics Committee of the Hospital Virgen de las Nieves (no. 0890418, Granada, Spain). After inclusion, participants were scheduled for a medical visit including a history, physical examination, and a medical questionnaire. This visit had the goal of discovering conditions which justified any medical exclusion.

2.2. Design, Randomization, and Allocation. A randomized controlled clinical trial was conducted. Eligible participants, after providing written informed consent, were randomly assigned into 2 groups: multimodal exercise group or a control group who received the usual care treatment for breast cancer. For ethical implications, those participants allocated to the control group, who finished the period of 6 months for the current study, were invited to be included into a new multimodal program or received an intervention by multimedia electronic document including exercises of all therapeutic sessions. We allocated patients to a multimodal program or control group in 4 randomization cycles, using computer-generated numbers. The sequence was entered into numbered opaque envelopes by an external member and they were opened after completion of the baseline assessment.

2.3. Treatment: Multimodal Program. Multimodal program consisted of 24 hours of individual physical training and 12 hours of recovery procedures, conducted 3 times/week for 90 min each (Table 1). The intensity of the aerobic training was conducted following ACSM and AHA recommendations [13].

Physical training was followed by 30–40 min of low intensity interventions for improving recovery after exercise. This period included stretching of the muscles used during exercise and massage (myofascial release techniques) which has the ability to improve recovery after exercise [12].

After finish the 8 weeking supervised multimodal program, participants received an instructional DVD with the same exercise program which included aerobic exercise progression, resistance exercise, neck-shoulder mobility exercises, self-massage, and some relaxation techniques. The DVD included safety precautions related to exercise and health advice related to maintain and promote healthy lifestyle.

2.4. Control Condition. Participants followed usual care recommended by the oncologist in relation with healthy lifestyle. A followup of the physical activity during control period was used to control possible bias detected in previous studies on exercise in BCS [3]. For that purpose, we used the Spanish version of Minnesota Leisure Time Physical Activity Questionnaire [14].

2.5. Data Analysis—Outcomes. The primary outcome was fatigue assessed using the fatigue subscale of Profile of Mood State (POMS) questionnaire. The POMS questionnaire (Spanish version) consists of 63 items on mood state. Scores (on a 5-point scale from 0 to 4) are grouped into six subscales: tension-anxiety, depression-dejection, anger-hostility, vigor, fatigue, and confusion. Subscale scores were converted into T-scores for the analysis, and the overall mood disturbance was also calculated. The reliability of the Spanish version of the POMS has been found to be high (Cronbach's α ranging 0.76–0.91) [15]. Assessors, participants, and therapists were blinded to the POMS scores during all the trial.

Secondary outcome measures included the following physical tests.

(1) Trunk Curl Static Endurance Test. This test requires a wedged piece of wood to support the patient at a fixed angle of 60°. The patients maintain both knees and hips flexed at 90°, the arms are folded across the chest and toes are anchored by the tester. The wood is pulled back 10 cm and the subject holds the isometric posture as long as possible.

Table 1: Description of the CUIDATE (intervention) program.

CUIDATE program		
Week 1–4		
Material	Small soft ball, mats, and fit-ball	
Endurance program	Unspecific work during sessions	
Exercise Program	Content	Dosage and progression
	(1) Half squat with arm movement (2) Standing rows with leg semiflexion maintained (3) Wall push-ups (4) Abdominal with lower limb movement (5) All tours with hip and knee movement (6) Abdominal with adductor isometric contraction and armmovement (7) Standing hip circumduction (8) Supine on fit-ball with arm movements (9) Superman on fit-ball (10) Oblique partial sit-up	weekk 1: Learning proposal. Assessment maximum load week 2-3: 75% maximum load Increase 5% per week Continue progression between exercises: 2 sets/30 sec pause week 4: 75% maximum load. Increase number series (3 sets) Medium velocity execution exercises Increase range of joint motion
Week 5–8		
Materials	Fit-ball, elastic band, mats, and small soft ball	
Endurance program	10–25 min of fast working with arms movement two days per week	
Exercise Program	Content	Dosage and progression
	(1) Chest press on fit-ball with elastic band (2) Squat with elastic band (3) Seated rows on fit-ball with elastic band (4) Isometric abdominal sitting on fit-ball with arm and leg movement (5) Biceps curl on fit-ball with elastic band (6) Biceps curl with elastic band and leg semiflexion maintained (7) Leg curl with fit-ball (8) Sit-up with lower limb movement	week 5: 10–12 repetitions × 2 sets week 6: 12–15 repetitions × 2 sets week 7: 10–12 repetitions × 3 sets week 8: 10–12 repetitions × 2 sets Increase resistance with elastic band and positions that require more body control

This test has proved to be reliable with coefficients of >0.97 for repeated tests [16].

(2) Multiple Sit-to-Stand Test. Participants were asked, while sitting at the front of a chair, to rise until they reached full knee extension and sit back 10 times as fast as they can. This test was used to assess general lower-extremity endurance [17]. This test has been showed reliable in similar age population [18].

All outcomes were completed before the program (pre-), immediately after the 8-week intervention (post-), and 6 months after discharge (followup).

Based on a previous pilot study the sample size was calculated on an 80% power to detect a mean difference of 5 points, with a standard deviation of 4 (7%), on the POMS fatigue subscale, using a type 1 error (α) of 5%, and a type 2 error (β) of 20%. This power calculation resulted in 35 patients on each group. To accommodate expected dropouts before study completion, a total of 78 participants were included.

2.6. Statistics. Statistical analysis was performed using SPSS statistical software, version 19.0, and it was conducted according to intention to treat analysis principle. We used *t*-tests and Chi-square tests to examine differences in baseline sociodemographic and medical features between included and excluded patients, as well as between participants who completed the study and those who dropped out. A one-way ANOVA was used to compare both groups of BCS with healthy women from Hospital Virgen de las Nieves influence area ($n = 43$, age: 47 ± 12 years).

The main analysis examined whether differences in outcomes (mean differences) among baseline, 8 weeks, and 6 months of followup existed between the groups. A 2×3 repeated-measure ANCOVA with intervention (experimental and control) as between-subjects variable, time (pre-, post-, and 6 months) as within-subjects variable, and age, status, educational level, and clinical features as covariates was used to examine the effects of the intervention on the main outcome.

Intergroup effect sizes were calculated (*Cohen d*). An effect size <0.2 reflects a negligible difference, between ≥0.2

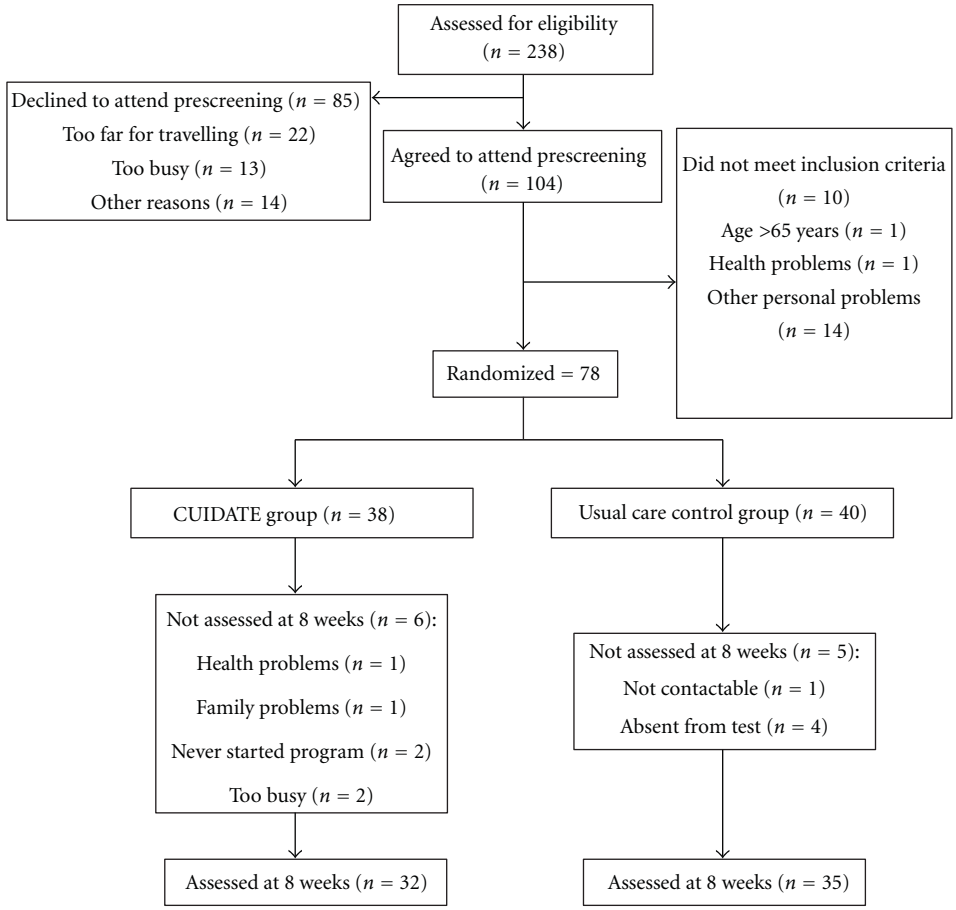

Figure 1: Flow diagram of subject recruitment and retention throughout the course of the study.

and ≤0.5 a small difference, between ≥0.5 and ≤0.8 a moderate difference, and ≥0.8 a large differences. The Pearson correlation test (r) was used to analyze the association between changes in mood state (mean differences) and in strength in the multimodal exercise group. A $P < 0.05$ was considered statistically significant.

3. Results

During the study period (from March 2009 to June 2010), 104 patients with cancer were agreed to attend prescreening (Figure 1). No differences in sociodemographic and medical features between the 78 patients (75%) included and the 26 patients (25%) who were excluded or declined to participate were found (Table 2). Participants who completed the study did not show differences in mood at baseline as compared to those who dropped out. The ANOVA revealed that patients in both groups had significantly disturbances of mood state in all subscales of the POMS as compared to healthy women (Table 3).

Patients who finished cancer treatment within the first 6 months before begining the multimodal exercise program completed 79.6% of the 24 physical therapy sessions (mean ± SD:19 ± 5) whereas patients incorporated >6 months after finishing cancer treatment completed 87.4% of the 24 sessions (mean: 21 ± 6). No adverse effect was reported during the study.

The ANCOVA found significant group × time interaction for the main outcome of the study, fatigue ($F = 4.506$; $P = 0.015$): the multimodal exercise group experienced a greater decrease of fatigue than the control group (Table 4). Intergroup effect sizes were moderate at postintervention (*d:* 0.52, 95% CI 0.14–0.81) and small at 6-month followup (*d:* 0.38, 95% CI 0.05–0.66).

Additionally, significant group × time interactions for the remaining domains of the POMS were also found: tension-anxiety ($F = 5.918$, $P = 0.005$); depression-dejection ($F = 5.214$, $P = 0.01$); anger-hostility ($F = 5.082$, $P = 0.010$); vigor ($F = 6.090$, $P = 0.004$), and also for total mood disturbance ($F = 3.512$, $P = 0.037$): the multimodal exercise group experienced a greater decrease of tension-anxiety, depression-dejection, or anger-hostility and a greater increase of vigor compared to the control group (Table 4). Intergroup effect sizes were large for both tension-anxiety (*d:* 1.05, 95% CI 0.54–1.55) and depression-dejection (*d:* 0.80, 95% CI 0.29–1.30) domains, and small for total mood disturbance (*d*: 0.40, 95% CI 0.16–0.65), anger-hostility (*d:* 0.40, 95% CI 0.16–0.63), and vigor (*d:* 0.35, 95% CI 0.18–0.67) domains after treatment. Intergroup effect sizes after 6-month followup

Table 2: Patient's characteristics and comparisons between both breast cancer survivor groups.

Variable	Control Group ($n = 35$)	CUIDATE program ($n = 32$)	P value
Age (y), mean (SD)	48 (9)	49 (9)	0.415
Time after treatment, n (%)			
<12 months	29 (82.9)	22 (68.8)	0.176
>12 months	6 (17.1)	10 (31.3)	
Civil status, n (%)			
Married	21 (60.0)	20 (62.5)	0.718
Unmarried	8 (22.9)	5 (15.6)	
Divorced	6 (17.1)	7 (21.9)	
Educational level, n (%)			
Low	13 (37.1)	11 (34.4)	0.481
Medium	6 (17.1)	8 (25.0)	
University level	16 (45.7)	13 (40.6)	
Employment status, n (%)			
Home employed	8 (22.9)	7 (21.9)	0.586
Employed	14 (40.0)	10 (31.3)	
Un employed	13 (37.1)	15 (46.9)	
Tumor stage, n (%)			
I	12 (34.3)	4 (12.5)	0.145
II	16 (45.7)	23 (71.9)	
IIIA	7 (20.0)	5 (15.6)	
Type of surgery, n (%)			
Tumorectomy	21 (60.0)	21 (65.6)	0.596
Mastectomy	14 (40.0)	11 (34.4)	
Type of treatment n (%)			
Radiation	1 (2.9)	1 (3.1)	0.991
Chemotherapy	3 (8.6)	3 (9.4)	
Radiation + chemotherapy	31 (88.6)	28 (87.5)	
Menopause, n (%)			
Yes	20 (57.1)	24 (75.0)	0.197
Not	15 (42.9)	8 (25.0)	
Physical activity (METS/h*day)	7.94 (3.37)	8.63 (3.85)	0.364

*P values for comparisons among group based on Chi-square and analysis of variance tests.

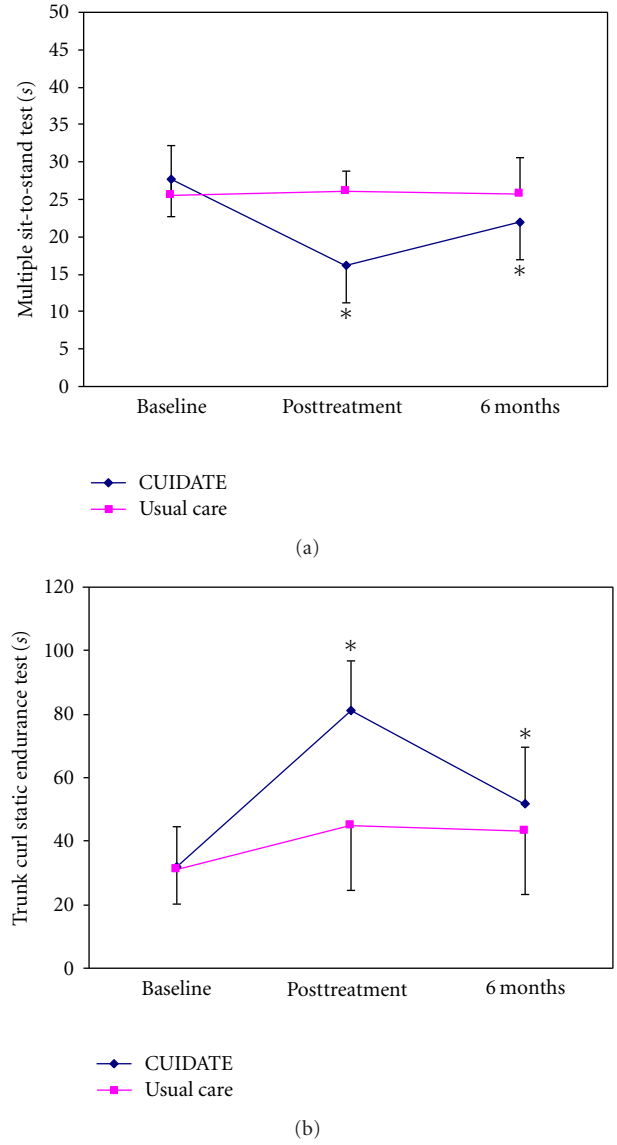

Figure 2: Multiple sit-to-stand test (*s*) and trunk curl static endurance test (*s*) changes after postintervention and 6 months followup, *significant changes respect baseline ($P < 0.05$).

were moderate for tension-anxiety (*d:* 0.76, 95% CI 0.20–1.31) and depression-dejection (*d*: 0.74, 95% CI 0.25–1.35), and small for anger-hostility (*d*: *0.39,* 95% CI 0.12–0.67), vigor (*d*: 0.41 95% CI 0.16–0.69) and total mood disturbance (*d*: 0.32 95% CI 0.05–0.60). No group x time interaction for confusion was found ($F = 0.831$; $P = 0.442$).

A significant group × time interaction for multiple sit-to-stand test ($F = 11.315$; $P < 0.001$) and trunk curl static endurance test ($F = 6.916$; $P = 0.002$) was also found (Figure 2). Intergroup effect sizes were large for multiple sit-to-stand test (*d:* 0.96, 95% CI 0.71–1.20) and trunk curl static endurance test (*d:* 0.89, 95% CI 0.71–1.19) at postintervention, but moderate (multiple sit-to-stand test, 0.50 95% CI 0.27–0.90) and small (trunk curl static endurance test, 0.21 95% CI 0.20–0.47) at 6 month followup.

A significant negative association ($r = -0.352$; $P = 0.046$) between changes in the total mood state and in the trunk curl static endurance test was found: the greater the decrease in mood, the higher the increase in muscle strength.

4. Discussion

The current study found that an 8-week supervised multimodal program induced physical and psychological improvements in BCS. We noted a greater decrease on fatigue

Table 3: Comparison of Profile of Mood State (POMS) data among healthy reference women and breast cancer survivors at baseline.

POMS	Healthy women ($n = 43$)	CUIDATE program ($n = 32$)	CONTROL group ($n = 35$)	P CUIDATE versus control
Tension-anxiety[a]	37.93 ± 8.71	49.00 ± 10.44	50.14 ± 10.18	0.65
Depression-dejection[a]	42.56 ± 7.14	52.39 ± 12.14	52.42 ± 11.01	0.99
Anger-hostility[a]	46.66 ± 6.89	55.17 ± 11.99	57.03 ± 14.12	0.53
Vigor[a]	57.43 ± 6.61	48.17 ± 7.08	49.19 ± 6.47	0.52
Fatigue[a]	39.90 ± 5.61	51.48 ± 10.85	54.19 ± 10.09	0.24
Confusion[a]	32.86 ± 4.53	42.35 ± 9.68	44.30 ± 9.70	0.53
Disturbance[a]	−14223 ± 2743	−19942.85 ± 5901.69	−20845.15 ± 5299.82	0.61

[a] $P < 0.001$ for ANOVA analysis among breast cancer survivors at baseline and healthy women.

as compared to usual breast cancer care. The effects over fatigue were maintained at 6 months after discharge using DVD support. We also observed significant effects on other aspects of mood and physical capacity.

The effect size of the improvement in fatigue (0.52) suggests a medium clinically important change. Our results are relatively better from the findings of a recent meta-analysis which indicates that the magnitude of the effects from exercise interventions on CRS is small (effect size 0.31, 95% CI 0.22–0.40) [3]. Our study used similar length of treatment (8 weeks) than previous studies investigating exercise in CRF [3, 19, 20], but we extended postural control by including CSEs and combined movement on extremities which could explain our results. The results of the current study also showed that BCS within the first year after treatment exhibit more disturbances of mood state and fatigue than healthy women. At postintervention, mood disturbance improved in BCS within the multimodal program, reaching similar values to healthy women. On the contrary, BCS included in the control group continued exhibiting altered mood state as compared to healthy women.

The POMS has been previously used to assess disturbance of mood state in oncology exercises studies [3]. Current results on mood state confirm the results from a previous pilot study using a similar exercise approach [21], since we found moderate-large effect sizes on several aspects of mood after the application of the multimodal program. Multimodal programs can help to BCS for coping with their cancer-related symptoms. Previous studies have suggested the necessity to apply interventions to better assist BCS for managing cancer related fatigue [19]. The multimodal program had a higher ratio of supervision with 2–4 therapists for 6–8 patients (ratio therapist/patient: 1/3–4). Only 60% of the exercise programs applied to reduce cancer related fatigue had employed therapist supervision [3], and the higher ratio therapist/patient of the multimodal program can promote social and environmental support, and satisfaction to the patients, both aspects which improve the mood state of BCS [22].

We also found significant and clinical improvement in muscle strength, which is consistent with recent studies on exercise [19, 20]. Current exercise guidelines for cancer apply minimal mention to muscle strength in BCS [23]. Our results suggest the necessity of including strength exercises in physical therapy programs for BCS. This may be related to the fact that cancer treatment, particularly chemotherapy, promotes disruption in muscle metabolism (i.e., adenosine triphosphate dysregulation, cytokine dysregulation, deprivation of satellite cells) wasting which may impair the maintenance of muscle mass [24]. CSEs were a major component of our program. Effectiveness of CSEs has been associated with modification of plasma levels of IL-6 and TNF-α by contraction of different muscles [25]. Interestingly, the current multimodal program produced large effect sizes in core-related muscles (trunk curl static endurance test) and also in nonrelated core muscles (leg muscles). These results may be explained because one of the principles of CSE is their ability to proximal muscle activation, providing interactive moments that would allow efficient distal muscle function [6]. Therefore, CSEs employed in our study may be also used for improving function of distal musculature through proximal (core-related) muscles.

One interesting result of our study was the relationship between the decrease in mood disturbance and the increase in strength of abdominal muscles. Cancer related fatigue constitutes a complex process involving both physical and psychosocial aspects [26]. Cancer patients who engage in negative beliefs about their cancer related symptoms (i.e., catastrophizing, fear of recurrence) are more likely to experience more intense symptoms [27]. It is possible that treatment programs combining preferred women's exercises [24] and recovery massage following an integrative oncology approach have a relevant role in mood improvement associated to increased functional state, as reflected in an increase of strength.

One of the most important results of this trial is the maintained effects in mood and strength, although slightly reduced, after 6-month followup using a DVD support. This kind of strategy based on multimedia supporting promote exercise in BCS had shown good results in previous studies [28]. A mixed intervention, including an initial supervised phase focussed on proper learning of the exercise program, promotes high improvements in BCS. Nevertheless, after the program, DVD support is needed for maintaining the improvements during the treatment. Future studies investigating effects of supervised programs with a follow-up period based on telerehabilitation are needed.

Table 4: Preintervention, postintervention, and change scores for mean values of POMS.

Group	CUIDATE program	Control	Between-group differences
	Tension-anxiety		
Preintervention	49.00 ± 10.44	50.14 ±10.18	
Postintervention	39.33 ± 8.08	49.80 ± 10.32	
6 months followup	43.53 ± 9.62	51.12 ±11.08	
Within group change scores			
Pre-post intervention	−9.66 (−13.45; −5.83)	−0.34 (−2.95; 2.26)	−9.32 (−13.79; −4.85)*
Pre intervention–6 months follow up	−5.89 (−2.53; −9.54)	−0.28 (−2.76; 6.26)	−6.17 (−1.71; −10.63)
	Depression-dejection		
Preintervention	52.39 ± 12.14	52.42 ± 11.01	
Postintervention	47.15 ± 9.34	52.40 ± 10.91	
6 months followup	48.17 ± 8.94	55.30 ± 12.12	
Within group change scores			
Pre-post intervention	−7.36 (−11.15; −3.57)	−0.02 (−2.84; 2.79)	−7.33 (−11.93; −2.73)*
Pre intervention–6 months follow up	−4.22 (−8.62; −0.87)	2.88 (0.73; 6.50)	−7.00 (−12.64; −0.77)
	Anger-hostility		
Preintervention	55.17 ± 11.99	57.03 ± 14.12	
Postintervention	46.82 ± 9.14	58.34 ± 11.65	
6 months followup	49.25 ± 8.07	58.76 ± 13.17	
Within group change scores			
Pre-post intervention	−7.87 (−12.16; −3.59)	1.31 (−2.05; 4.04)	−9.19 (−14.20; −3.65)*
Pre intervention–6 months follow up	−5.92 (−10.13; −1.72)	1.73 (−1.59; 5.06)	−7.65 (−12.95; −2.36)
	Vigor		
Preintervention	48.17 ± 7.08	49.19 ± 6.47	
Postintervention	53.46 ± 8.02	49.29 ± 7.31	
6 months followup	53.17 ± 8.41	48.00 ± 6.98	
Within group change scores			
Pre-post intervention	5.29 (3.40; 8.29)	0.17 (−2.57; 2.22)	5.12 (2.65; 9.38)*
Pre intervention–6 months follow up	5.00 (2.16; 7.83)	−1.19 (−3.94; 1.56)	6.19 (2.30; 10.06)
	Fatigue		
Preintervention	51.58 ± 10.85	54.19 ± 10.09	
Postintervention	43.93 ± 8.58	52.26 ± 10.09	
6 months followup	45.12 ± 10.31	53.34 ± 9.36	
Within group change scores			
Pre-post intervention	−8.03 (−11.19; −4.86)	−1.93 (−5.06; 0.20)	−6.10 (−9.12; −1.07)*
Pre intervention–6 months followup	−6.45 (−9.50; −3.39)	−0.84 (−3.44; −1.74)	−5.61 (−8.56; −0.35)
	Confusion		
Preintervention	42.35 ± 9.68	44.30 ± 9.70	
Postintervention	37.67 ± 7.08	42.90 ± 8.82	
6 months followup	39.85 ± 9.48	43.70 ± 9.44	
Within group change scores			
Pre-post intervention	−4.68 (−7.71; −1.55)	−1.40 (−4.55; 1.11)	−3.28 (−7.05; 1.22)
Pre intervention–6 months follow up	−2.50 (−5.36; 0.36)	−0.60 (−4.39; 3.19)	−2.91 (−6.42; 2.62)
	Total disturbance mood		
Preintervention	−19942.85 ± 5901.69	−20845.15 ± 5299.82	
Postintervention	−16000.00 ± 3532.28	−20353.84 ± 5888.03	
6 months followup	−17257.14 ± 4528.05	−20884.61 ± 6171.78	
Within group change scores			
Pre-post intervention	3442.85 (1623.71; 5353.11)	491.31 (−905.90; 1608.76)	2951.54 (754.29; 5124.67)*
Pre intervention–6 months follow up	2685.71 (986.08; 4835.34)	38.46 (−1553.29; 1630.21)	2647.25 (454.29; 4854.29)

Strengths of the current trial include supervised and structured exercise program, multimodal cancer approach, use of validated objective measurements and a validated questionnaire, and intention-to-treat analyses; however, we should recognize that the control group was allowed to freely increase physical activity during the study. The possible bias [3] associated to this weakness was controlled since our control group did not show significant increases in physical activity during the study.

5. Conclusions

In conclusion, an 8-week multimodal physical therapy program using CSE and massage recovery was clinically effective for improving physical (muscle strength) and psychological (mood state and fatigue) aspects in BCS as compared to usual treatment care.

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References

[1] L. S. Gilchrist, M. L. Galantino, M. Wampler, V. G. Marchese, G. S. Morris, and K. K. Ness, "A framework for assessment in oncology rehabilitation," *Physical Therapy*, vol. 89, no. 3, pp. 286–306, 2009.

[2] C. M. Donnelly, A. Lowe-Strong, J. P. Rankin, A. Campbell, J. M. Allen, and J. H. Gracey, "Physiotherapy management of cancer-related fatigue: a survey of UK current practice," *Supportive Care in Cancer*, vol. 18, no. 7, pp. 817–825, 2010.

[3] J. C. Brown, T. B. Huedo-Medina, L. S. Pescatello, S. M. Pescatello, R. A. Ferrer, and B. T. Johnson, "Efficacy of exercise interventions in modulating cancer-related fatigue among adult cancer survivors: a meta-analysis," *Cancer Epidemiology, Biomarkers and Prevention*, vol. 20, pp. 123–133, 2011.

[4] K. H. Schmitz, K. S. Courneya, C. Matthews et al., "American college of sports medicine roundtable on exercise guidelines for cancer survivors," *Medicine and Science in Sports and Exercise*, vol. 42, no. 7, pp. 1409–1426, 2010.

[5] L. Adamsen, M. Quist, C. Andersen et al., "Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial," *The British Medical Journal*, vol. 13, no. 339, p. b3410, 2009.

[6] J. E. Bower, D. Garet, and B. Sternlieb, "Yoga for persistent fatigue in breast cancer survivors: results of a pilot study," *Evidence-Based Complementary and Alternative Medicine*, vol. 2011, Article ID 623168, 8 pages, 2011.

[7] W. B. Kibler, J. Press, and A. Sciascia, "The role of core stability in athletic function," *Sports Medicine*, vol. 36, no. 3, pp. 189–198, 2006.

[8] K. M. Winters-Stone, J. A. Bennett, L. Nail, and A. Schwartz, "Strength, physical activity, and age predict fatigue in older breast cancer survivors," *Oncology Nursing Forum*, vol. 35, no. 5, pp. 815–821, 2008.

[9] J. E. Bower, "Behavioral symptoms in patients with breast cancer and survivors," *Journal of Clinical Oncology*, vol. 26, no. 5, pp. 768–777, 2008.

[10] J. Imanishi, H. Kuriyama, I. Shigemori et al., "Anxiolytic effect of aromatherapy massage in patients with breast cancer," *Evidence-Based Complementary and Alternative Medicine*, vol. 6, no. 1, pp. 123–128, 2009.

[11] C. A. Moyer, J. Rounds, and J. W. Hannum, "A meta-analysis of massage therapy research," *Psychological Bulletin*, vol. 130, no. 1, pp. 3–18, 2004.

[12] M. Arroyo-Morales, N. Olea, M. M. Martínez, A. Hidalgo-Lozano, C. Ruiz-Rodríguez, and L. Díaz-Rodríguez, "Psychophysiological effects of massage-myofascial release after exercise: a randomized sham-control study," *Journal of Alternative and Complementary Medicine*, vol. 14, no. 10, pp. 1223–1229, 2008.

[13] M. E. Nelson, W. J. Rejeski, S. N. Blair et al., "Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association," *Medicine and Science in Sports and Exercise*, vol. 39, no. 8, pp. 1435–1445, 2007.

[14] R. Elosua, M. Garcia, A. Aguilar, L. Molina, M. I. Covas, and J. Marrugat, "Validation of the Minnesota Leisure Time Physical Activity Questionnaire in Spanish Women. Investigators of the MARATDON Group," *Medicine and Science in Sports and Exercise*, vol. 32, no. 8, pp. 1431–1437, 2000.

[15] E. M. Andrade, C. Arce, and G. Seoane, "Adaptación al español del cuestionario Perfil de los Estados de Ánimo en una muestra de deportistas," *Psicothema*, vol. 14, no. 4, pp. 708–713, 2002.

[16] S. M. McGill, A. Childs, and C. Liebenson, "Endurance times for low back stabilization exercises: clinical targets for testing and training from a normal database," *Archives of Physical Medicine and Rehabilitation*, vol. 80, no. 8, pp. 941–944, 1999.

[17] Y. Netz, M. Ayalon, A. Dunsky, and N. Alexander, "The multiple-sit-to-stand field test for older adults: what does it measure?" *Gerontology*, vol. 50, no. 3, pp. 121–126, 2004.

[18] C. Ritchie, S. G. Trost, W. Brown, and C. Armit, "Reliability and validity of physical fitness field tests for adults aged 55 to 70 years," *Journal of Science and Medicine in Sport*, vol. 8, no. 1, pp. 61–70, 2005.

[19] M. J. Velthuis, S. C. Agasi-Idenburg, G. Aufdemkampe, and H. M. Wittink, "The effect of physical exercise on cancer-related fatigue during cancer treatment: a meta-analysis of randomised controlled trials," *Clinical Oncology*, vol. 22, no. 3, pp. 208–221, 2010.

[20] R. M. Speck, K. S. Courneya, L. C. Mâsse, S. Duval, and K. H. Schmitz, "An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis," *Journal of Cancer Survivorship*, vol. 4, no. 2, pp. 87–100, 2010.

[21] K. S. Keays, S. R. Harris, J. M. Lucyshyn, and D. L. MacIntyre, "Effects of pilates exercises on shoulder range of motion, pain, mood, and upper-extremity function in women living with breast cancer: a pilot study," *Physical Therapy*, vol. 88, no. 4,

pp. 494–510, 2008.

[22] A. Talley, L. Molix, R. J. Schlegel, and A. Bettencourt, "The influence of breast cancer survivors perceived partner social support and need satisfaction on depressive symptoms: a longitudinal analysis," *Psychology and Health*, vol. 25, no. 4, pp. 433–449, 2010.

[23] National Comprehensive Cancer Network (NCCN), *Clinical Practice Guidelines in Oncology: Cancer Related-Fatigue*, National Comprehensive Cancer Network, Fort Washington, Pa, USA, 2009.

[24] P. M. Clarkson and S. A. Kaufman, "Should resistance exercise be recommended during breast cancer treatment?" *Medical Hypotheses*, vol. 75, no. 2, pp. 192–195, 2010.

[25] N. Drela, E. Kozdron, and P. Szczypiorski, "Moderate exercise may attenuate some aspects of immunosenescence," *BMC Geriatrics*, vol. 29, pp. 4–8, 2004.

[26] I. Cantarero-Villanueva, C. Férnandez-Lao, C. Fernández-DE-Las-Peñas, L. Díaz-Rodríguez, E. Sanchez-Cantalejo, and M. Arroyo-Morales, "Associations among musculoskeletal impairments, depression, body image and fatigue in breast cancer survivors within the first year after treatment," *The European Journal of Cancer Care*. In press.

[27] C. Zaza and N. Baine, "Cancer pain and psychosocial factors: a critical review of the literature," *Journal of Pain and Symptom Management*, vol. 24, no. 5, pp. 526–542, 2002.

[28] T. P. Haines, P. Sinnamon, N. G. Wetzig et al., "Multimodal exercise improves quality of life of women being treated for breast cancer, but at what cost? Randomized trial with economic evaluation," *Breast Cancer Research and Treatment*, vol. 124, no. 1, pp. 163–175, 2010.

6

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CONCLUSIONES

I. Un estado psicológico caracterizado por una mayor depresión y una mala imagen corporal, y una alteración física caracterizada por mayor intensidad del dolor cervical y una disminución de la movilidad del hombro, se relacionan con la FIC, confirmando su carácter multidimensional en SCM (**Artículo I**).

II. La Fuerza, evaluada mediante dinamometría en el lado afectado, está correlacionada fuertemente con la calidad de vida y la salud general en SCM (**Artículo II**).

III. Un programa multimodal de 8 semanas de terapia física fue efectivo a corto plazo y tras 6 meses de seguimiento, para la disminución de la fatiga en SCM. El programa también fue eficaz en la disminución de α-amilasa y la mejora del rango de movimiento cervical. (**Artículo III**).

IV. Un programa multimodal centrado en ejercicios de estabilidad core y el masaje mejora el estado de ánimo y la fuerza muscular después de la intervención y 6 meses después de haber finalizado el tratamiento. (**Artículo IV**).

Conclusion Global

Hay una fuerte asociación entre desórdenes del estado de ánimo y de tipo musculoesquelético y la fuerza y la fatiga, lo que muestra su carácter multifactorial. Los programas multimodales tienen un efecto favorable para reducir la fatiga y otras alteraciones relacionadas con el proceso oncológico.

CONCLUSSIONS

I. A psychological state characterized with higher depression and reduced body image, and a physical impairment with higher cervical pain intensity and reduced shoulder mobility confirm multidimensional character of fatigue in BCS (**Paper I**).

II. Strength, as assessed by the HGS test on the affected side, is an important correlate of quality of life and overall health in BCS (**Paper II**).

III. An 8-week multimodal physical therapy program was effective at short and 6 month follow-up for decreasing fatigue in BCS. The program was also effective in decreasing Alfa-amylase activity and improving shoulder and cervical range of motion. (**Paper III**).

I. A multimodal program focused on core stability exercises and massage, improve mood and muscle strength after intervention and 6 months after discharge. (**Paper IV**).

Overall Conclusion

There is a strong association between mood disorders and musculoskeletal and fatigue strength, which shows its multifactorial nature. Multimodal programs have a favorable effect in reducing fatigue and other disorders related to the cancer process.

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"*La esencia de la sinergia es valorar las diferencias, respetarlas, construir sobre las fortalezas y compensar las debilidades*".

(Stephen R. Covey).

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Publicaciones científicas

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2. Fernández-Lao C, Cantarero-Villanueva I, Fernández-de-Las-Peñas C, Del-Moral-Ávila R, Arendt-Nielsen L, Arroyo-Morales M. Myofascial trigger points in neck and shoulder muscles and widespread pressure pain hypersensitivtiy in patients with postmastectomy pain: evidence of peripheral and central sensitization. Clin J Pain. 2010 Nov-Dec;26(9):798-806

3. Arroyo-Morales M, Fernández-Lao C, Ariza-García A, Toro-Velasco C, Winters M, Díaz-Rodríguez L, Cantarero-Villanueva I, Huijbregts P, Fernández-De-las-Peñas C. Psychophysiological effects of preperformance massage before isokinetic exercise. J Strength Cond Res. 2011 Feb;25(2):481-8

4. Cantarero-Villanueva I, Fernández-Lao C, Fernández-DE-Las-Peñas C, Díaz-Rodríguez L, Sanchez-Cantalejo E, Arroyo-Morales M. Associations among musculoskeletal impairments, depression, body image and fatigue in breast cancer survivors within the first year after treatment. Eur J Cancer Care (Engl). 2011 Sep;20(5):632-9

5. Fernández-Lao C, Cantarero-Villanueva I, Fernández-de-Las-Peñas C, Del Moral-Ávila R, Castro-Sánchez AM, Arroyo-Morales M. Effectiveness of a Multidimensional Physical Therapy Program on Pain, Pressure Hypersensitivity, and Trigger Points in Breast Cancer Survivors: A Randomized Controlled Clinical Trial. Clin J Pain. 2011 Jun 23

6. Galiano-Castillo N, Fernández-Lao C, Cantarero-Villanueva I, Fernández-de-Las-Peñas C, Menjón-Beltrán S, Arroyo-Morales M. Altered pattern of cervical muscle activation during performance of a functional upper limb task in breast cancer survivors. Am J Phys Med Rehabil. 2011 May;90(5):349-55

7. Cantarero-Villanueva I, Fernández-Lao C, Del Moral-Avila R, Fernández-de-Las-Peñas C, Feriche-Fernández-Castanys MB, Arroyo-Morales M. Effectiveness of core stability exercises and recovery myofascial release massage on fatigue in breast cancer survivors: a randomized controlled clinical trial. Evid Based Complement Alternat Med.

2012;2012:620619. Epub 2011 Jul 17

8. Fernández-de-Las-Peñas C, Fernández-Lao C, Cantarero-Villanueva I, Ambite-Quesada S, Rivas-Martínez I, Del Moral-Avila R, Arroyo-Morales M. Catechol-O-methyltransferase genotype (Val158met) modulates cancer-related fatigue and pain sensitivity in breast cancer survivors. Breast Cancer Res Treat. 2011 Sep 4

9. Fernández-de-Las-Peñas C, Cantarero-Villanueva I, Fernández-Lao C, Ambite-Quesada S, Díaz-Rodríguez L, Rivas-Martínez I, Moral-Avila RD, Arroyo-Morales M. Influence of catechol-o-methyltransferase genotype (Val158Met) on endocrine, sympathetic nervous and mucosal immune systems in breast cancer survivors. Breast. 2011 Oct 4

10. Fernández-Lao C, Cantarero-Villanueva I, Díaz-Rodríguez L, Fernández-de-Las-Peñas C, Sánchez-Salado C, Arroyo-Morales M. The Influence of Patient Attitude Toward Massage on Pressure Pain Sensitivity and Immune System after Application of Myofascial Release in Breast Cancer Survivors: A Randomized, Controlled Crossover Study. J Manipulative Physiol Ther. 2011 Oct 20

11. Díaz-Rodríguez L, Arroyo-Morales M, Cantarero-Villanueva I, Férnandez-Lao C, Polley M, Fernández-de-Las-Peñas C. The application of Reiki in nurses diagnosed with Burnout Syndrome has beneficial effects on concentration of salivary IgA and blood pressure. Rev Lat Am Enfermagem. 2011 Oct;19(5):1132-8

12. Fernández-Lao C, Cantarero-Villanueva I, Fernández-de-las-Peñas C, Del-Moral-Ávila R, Menjón-Beltrán S, Arroyo-Morales M. Development of active myofascial trigger

points in neck and shoulder musculature is similar after lumpectomy or mastectomy s

13. Fernández-Lao C, Cantarero-Villanueva I, Díaz-Rodríguez L, Cuesta-Vargas AI, Fernández-De-las-Peñas C, Arroyo-Morales M. Attitudes towards massage modify effects of manual therapy in breast cancer survivors: a randomised clinical trial with crossover design. Eur J Cancer Care (Engl). 2011 Nov[Epub ahead of print] urgery for breast cancer. J Bodyw Mov Ther. 2011 Jun

14. Arroyo-Morales M, Irene Cantarero-Villanueva I, Fernández-Lao C, Guirao-Piñeyro M, Castro-Martín E, Díaz-Rodríguez L. Efectiveness of a proposal based on e-learning (ecofisio.com) for acquisition of palpation and ultrasound abilities related to the locomotor apparatus: a single blind randomized controlled study. Man Ther. 2011. **Submitted**.

15. Cantarero-Villanueva I, Fernández-Lao C, Díaz-Rodríguez L, Fernández-de-las-Peñas C, Ruiz JR,Arroyo-Morales M. The handgrip strength test as a measure of function in breast cancer survivors: relationship with quality of life, cancer related symptoms, physical and physiological parameters. Eur J Phys Rehabil. **Submitted**.

16. Cantarero-Villanueva I, Fernández-Lao C, Fernández-de-las-Peñas C López-Barajas IB, Del-Moral-Ávila R, ; de-la-Llave-Rincón AI, Arroyo-Morales M. Effectiveness of water physical therapy on pain, pressure pain sensitivity and myofascial trigger points in breast cancer survivors: a randomized controlled clinical trial. J Pain. **Submitted**.

Capítulos de libros y Monografías

2011

- **CAPÍTULO DE LIBRO:** *Estudio de la satisfacción de los alumnos de Fisioterapia sobre la plataforma web ecofisio para la integración del a imagen ecográfica.* Carolina Fernández-Lao, Irene Cantarero-Villanueva, Eduardo Castro-Martín, Lourdes Díaz-Rodríguez, Miguel Guirao-Pyneiro, Manuel Arroyo-Morales. VIII Foro sobre la evaluación de la calidad de la investigación y de la educación superior (FECIES). Santander. ISBN: 978-84-694-3488-8.

2011

- **CAPÍTULO DE LIBRO:** *La comunicación como competencia en los docentes*. Lourdes Díaz Rodríguez, Irene Cantarero Villanueva, Carolina Fernández-Lao, Javier Ramos Torrecillas, De Luna Bertos Elvira, Olga García Martínez. VIII Foro sobre la evaluación de la calidad de la investigación y de la educación superior (FECIES). Santander.ISBN: 978-84-694-3488-8.

2011

- **CAPÍTULO DE LIBRO**: *Percepción del alumnado en torno al uso de las TICs para el desarrollo de competencias en valoración del aparato locomotor.* Irene Cantarero-Villanueva, Carolina Fernández-Lao, Lourdes Díaz- Rodríguez, Eduardo Castro-Martín, Bernabé Esteban-Moreno, Manuel Arroyo-Morales. VIII Foro sobre la evaluación de la calidad de la investigación y de la educación superior (FECIES). Santander ISBN: 978-84-694-3488-8.

2010

- **MONOGRAFÍA:** *Bases científicas y entrenamiento en la prevención laboral activa: control motor y condición física para el personal de*

prevención y extinción de incendios forestales. Martín A, Cuco I, Linari F, Fernández C, Arroyo M, Cantarero I, Cuadros J, Espinosa F, Fernández C, Galiano N, Jiménez D, López de Acebuche I. AIFEMA, Granada. ISBN: 978-84-614-3955-3

2009 • **CAPÍTULO DE LIBRO: La evaluación de las competencias: un logro a alcanzar.** Evaluación de la Calidad de la Educación Superior y de la Investigación. ISBN: 978-84-693-2096-9

2008 • **CAPÍTULO DE LIBRO:** *La lesión y sus repercusiones sobre el estado de ánimo en deportistas.* Educación Física y Ciencias Afines. Alternativas de integración y salud para el hombre y la mujer del S XXI Deposito legal: S.433-2008.

Participación en Proyectos y Contratos de Investigación

2011-13 • **PROYECTO:** *E-CUIDATE: Eficacia sobre el dolor musculoesquelético de una plataforma de telefisioterapia en mujeres con cáncer de mama.* Entidad Financiadora: Fondo de Investigaciones Sanitarias. Instituto de Salud Carlos III. Investigador Principal: Manuel Arroyo Morales.

2011-13 • **PROYECTO:** *Eficacia de una plataforma de telefisioterapia en mujeres con cáncer de mama durante la quimioterapia*. Entidad Financiadora: Servicio Andaluz de Salud. Investigador Principal: Manuel Arroyo Morales.

2011-12

- **PROYECTO:** *Utilización de la imagen ecográfica para el desarrollo de competencias de tratamiento del control motor en pacientes con lumbalgia.* Entidad Financiadora: Unidad de Innovación Docente. Universidad de Granada. Investigador Principal: Manuel Arroyo Morales.

2011

- **Contrato de Investigación:** "*Estudio de los parámetros funcionales para la prevención laboral activa: Prevención de lesiones, recuperación-readaptación del sistema músculo-esquelético, y acondicionamiento físico integral a través de un sistema funcional específico para los especialistas en prevención y extinción de incendios forestales"***.** Empresa Financiadora: Oficina de Transferencia de Resultados de Investigación UGR. Investigador Responsable: Manuel Arroyo Morales.

2010

- **Contrato de Investigación:** "*Estudio de los parámetros funcionales para la prevención laboral activa: Prevención de lesiones, recuperación-readaptación del sistema músculo-esquelético, y acondicionamiento físico integral a través de un sistema funcional específico para los especialistas en prevención y extinción de incendios forestales"***.** Empresa Financiadora: Oficina de Transferencia de Resultados de Investigación UGR. Investigador Responsable: Manuel Arroyo Morales.

2010-11

- **PROYECTO:** *Integración de la imagen ecográfica para la mejora de la adquisición de competencias de valoración musculoesquelética*. Entidad Financiadora: Unidad de Innovación Docente. Universidad de Granada. Investigador Principal: Manuel Arroyo Morales.

2009-10

- **PROYECTO:** *Efectos Psicofisiológicos y sobre la Supervivencia de la Cinesiterapia Activa y la Masoterapia en Supervivientes de Cáncer de Mama***.** Entidad financiadora: Fondo de Investigaciones Sanitarias. Instituto de Salud Carlos III. Investigador Principal: Manuel Arroyo Morales.

Premios

2011

- **Primer premio de Investigación 2011 del Ilustre Colegio de fisioterapia de Andalucía**: *Influencia de las actitudes de los pacientes sobre la terapia manual en mujeres con fatiga inducida por cáncer de mama: un diseño cruzado aleatorizado con enmascaramiento simple*. Fernández-Lao C, Cantarero-Villanueva I, Arroyo-Morales, M.

2010

- **Galardón de Accesit de premio de Investigación 2010 del Ilustre Colegio de fisioterapia de Andalucía**: *Eficacia de un programa de Fisioterapia (Cuídate)*. Cantarero-Villanueva I, Fernández-Lao C, Arroyo-Morales, M.

2010

- **Primer premio comunicación presentada en las II Jornadas Internacionales y VI nacionales en ciencias de la Salud:** *Metodología de estudio de los desajustes del control motor en pacientes tratadas por cáncer de mama.* Galiano-Castillo N, Fernández Lao C, Cantarero Villanueva I, Olea Serrano N, Arroyo-Morales M.

2009

- **Primer premio comunicación presentada en el XII Congreso Andaluz de Psicología de la Actividad Física y el Deporte:** *Estudio descriptivo del estado de ánimo en mujeres con cáncer de mama previo a un programa de cinesioterapia activa.* Cantarero Villanueva I., Fernández Lao C., Feriche-Fernández Castanys B., Arroyo Morales M.

Participación en Congresos

- La doctoranda ha participado como autora y coautora en más de 30 congresos nacionales e internacionales.
- La doctoranda ha participado en las II Jornadas Internacionales y VI Nacionales en Ciencias de la Salud como miembro del Comité Organizador celebradas en la Universidad de Granada.