TESIS DOCTORAL

PROGRAMA OFICIAL DE DOCTORADO EN MEDICINA CLÍNICA Y SALUD PÚBLICA

UNIVERSIDAD DE GRANADA

ESTADO FÍSICO Y ALTERACIONES DEL SUEÑO EN MUJERES CON CÁNCER DE MAMA: ENFOQUE DESDE LA FISIOTERAPIA

DEPARTAMENTO DE FISIOTERAPIA

FACULTAD DE CIENCIAS DE LA SALUD

ANGÉLICA ARIZA GARCÍA

2017

Editor: Universidad de Granada. Tesis Doctorales
Autora: Angélica Ariza García
ISBN: 978-84-9163-714-1
URI: http://hdl.handle.net/10481/48863

El doctorando / The *doctoral candidate* **[Carmen Angélica Ariza García]** y los directores de la tesis / and the thesis supervisor/s: **[Manuel Arroyo Morales, Irene Cantarero Villanueva]**

Garantizamos, al firmar esta tesis doctoral, que el trabajo ha sido realizado por el doctorando bajo la dirección de los directores de la tesis y hasta donde nuestro conocimiento alcanza, en la realización del trabajo, se han respetado los derechos de otros autores a ser citados, cuando se han utilizado sus resultados o publicaciones.

/

Guarantee, by signing this doctoral thesis, that the work has been done by the doctoral candidate under the direction of the thesis supervisor/s and, as far as our knowledge reaches, in the performance of the work, the rights of other authors to be cited (when their results or publications have been used) have been respected.

Lugar y fecha / Place and date:

Granada a 14 de junio de 2016

Director/es de la Tesis / *Thesis supervisor/s;*

Firma / Signed

Doctorando / *Doctoral candidate*:

Firma / Signed

ÍNDICE

Resumen.. **1**

Listado de Abreviaturas.. **2**

Introducción.. **3**

Bibliografía... **12**

Objetivos... **24**

Material y Métodos... **25**

Resultados y Discusión... **26**

Capítulo 1

Influence of physical inactivity in psychophysiolocigal state of breast cancer survivors (Artículo I).. **27**

Capítulo 2

Factors that explain the cancer-related insomnia (Artículo II).................. **36**

Capítulo 3

The 6-minute walk test as a measure of health in breast cancer patients (Artículo III).. **44**

Conclusiones... **53**

Currículum Vítae Abreviado... **55**

RESUMEN

El cáncer de mama (CM) es el segundo cáncer más común en el mundo, siendo el más frecuente entre las mujeres. Si bien la supervivencia de estas pacientes está aumentando de forma continua en los últimos años, debido principalmente a avances en el diagnóstico y en los tratamientos oncológicos, son muchos los efectos secundarios que sufren estas pacientes. Entre otros, el dolor, las alteraciones psicofisiológicas y del estado de ánimo, los cambios en la composición corporal o la disminución de la capacidad funcional, disminuyen la calidad de vida de estas pacientes.

Para poder iniciar estrategias de tratamiento eficaces tras la enfermedad, y mejorar la calidad de vida de estas pacientes, es necesario profundizar en el conocimiento de las alteraciones producidas por el cáncer y de las relaciones que se establecen entre ellas.

En esta memoria de Tesis se analizan tres de las alteraciones que suelen presentar las mujeres con CM, el nivel de inactividad, el insomnio y la capacidad funcional, así como los posibles factores, físicos, psicológicos y fisiológicos, relacionados con ellas.

Los resultados de esta memoria de Tesis indican: a) las supervivientes de cáncer de mama activas muestran menos disturbios del estado de ánimo, presión diastólica y α-amilasa salivar, relacionados con un mejor nivel de condición física, respecto a las inactivas; b) la fase y el tipo de tratamiento, la ansiedad, la severidad del dolor y la fuerza de tronco, son predictores del insomnio y en conjunto explican el 51,2 % de su variabilidad en mujeres con CM; c) existe una relación clara entre el test de la caminata de 6 minutos y el estado psicofisiológico, la calidad de vida, los síntomas relacionados con el cáncer y la composición corporal en mujeres con CM, constituyendo una herramienta eficaz para la monitorizar y posteriormente adaptar un programa de entrenamiento físico a estas pacientes.

LISTADO DE ABREVIATURAS

AVD	Actividades de la vida diaria
CBD	Cuestionario Breve del Dolor
CM	Cáncer de mama
EORTC	European Organization for Research and Treatment of Cancer
HADS	The Hospital Anxiety and Depression Scale
HHA	Hipotalámico-Hipofisario-Adrenal
INE	Instituto Nacional de Estadística
IRC	Insomnio relacionado con el cáncer
MLTPAQ	Minessotta Leisure Time of Physical Activity Questionnarie
OMS	Organización Mundial de la Salud
POMS	Profile of Mood State
PECP	Pruebas de ejercicio cardiopulmonar
QLQ-BR23	Breast Cancer-Specific Quality of Life Questionnaire
QLQ-C30	Quality of Life Questionnaire Core 30
QT	Quimioterapia
REDECAN	Red Española de Registros de Cáncer
RT	Radioterapia
SCM	Supervivientes de cáncer de mama
SEOM	Sociedad Española de Oncología Médica
SNS	Sistema nervioso simpático
TMT	The Trail Making Test
VO	Volumen de oxígeno

INTRODUCCIÓN

Contextualización

Según la Organización Mundial de la Salud (OMS), la palabra cáncer es un término genérico que designa a un gran grupo de enfermedades que pueden afectar a cualquier parte del cuerpo. Una de sus características definitorias es la rápida proliferación de células anormales que pierden sus mecanismos intrínsecos de regulación (1). El cáncer de mama (CM) es definido por la Sociedad Española de Oncología Médica (SEOM) como la proliferación acelerada e incontrolada de células del epitelio glandular mamario. Dichas células, pueden diseminarse a través de las sangre o de los vasos linfáticos, pudiendo llegar a otras partes del cuerpo y formar metástasis (2).

El cáncer es una de las principales causas de morbilidad y mortalidad en el mundo (1). Según los datos de GLOBOCAN, en el año 2012 se diagnosticaron aproximadamente 14,1 millones nuevos casos de cáncer en todo el mundo (3). Se espera un aumento del 70% en el número de nuevos casos aumente durante las próximas dos décadas (1), alcanzando los 22 millones de casos nuevos al año (4). En España se diagnosticaron 215.534 casos nuevos de cáncer en el año 2012 (5) y 247.771 en 2015 (4), ocupó el cuarto lugar entre los tipos de cáncer más frecuentemente diagnosticados, situándose por detrás del cáncer colorrectal, próstata y pulmón (41.441, 33.370 y 28.347 nuevos casos diagnosticados respectivamente en 2015). Se calcula que en 2020 se diagnosticarán 246.713 casos nuevos 2012 (5). Por tipología, el CM, según datos de GLOBOCAN, es el segundo cáncer más común en el mundo, tras el de pulmón. Se estima que en el año 2012, se diagnosticaron alrededor de 1,67 millones de nuevos casos, suponiendo el 25% de todos los cánceres (6). En España el CM, con 25.215 casos nuevos diagnosticados en el año 2012 (5) y 27.747 en 2015, En mujeres, el CM fue el mayormente diagnosticado con 27.747 casos, muy por encima del colorrectal (16.677 casos), cuerpo uterino (6.160 casos), pulmón (5.917 casos) y vejiga (3.654 casos) (4).

En relación a la mortalidad, el cáncer constituye la segunda causa de muerte en el mundo (1) por detrás de la cardiopatía isquémica y el accidente cerebrovascular (7). Las defunciones por cáncer aumentaron en 600.000 personas, pasando de 8,2 millones de defunciones en 2012 (3) a 8,8 millones en 2015, de forma que una de cada seis defunciones se debe a esta enfermedad (1). En España, en el año 2014, la mortalidad por cáncer fue de 106.039 fallecimientos, siendo también la segunda causa de muerte después de las enfermedades del aparato circulatorio y la primera causa de muerte en varones en España. Según datos de la Red Española de Registros de Cáncer (REDECAN), una de cada tres muertes en varones y una de cada cinco en mujeres en España, se debieron a tumores malignos en el año 2015. España, en números absolutos, es uno de los países europeos en los que se produce un mayor número de fallecimientos por cáncer, pero esto es debido a que cuenta con una de las mayores esperanzas de vida del mundo. Al ajustar la mortalidad por edad, se obtienen tasas similares a las europeas. Cabe destacar que según el Instituto Nacional de Epidemiología (INE), entre los años 2003-2012, la mortalidad por tumores se redujo un 1,32% al año a pesar del aumento global de la incidencia, debido a mejoras en la supervivencia de los pacientes con cáncer (4). Por tipo de cáncer, el CM fue responsable de 575.000 defunciones en el año 2015, ocupando el quinto lugar entre las causas más comunes de muerte por cáncer, situándose por detrás del cáncer de pulmón (1,69 millones de defunciones), hígado (788.000 defunciones), colorrectal (774.000 defunciones), y estómago (754.000 defunciones) (1). En España, el CM fue responsable de 6.213 fallecimientos en la población general, ocupando en 2014 el cuarto lugar, por detrás el cáncer de pulmón (21.220 defunciones), el cáncer colorrectal (15.449 defunciones) y el cáncer de páncreas (6.278 defunciones) (4).

Como se ha mencionado anteriormente, a pesar de que las cifras de mortalidad son muy elevadas, la supervivencia de los pacientes con cáncer está aumentando de forma continua en los últimos años, debido principalmente a las actividades preventivas y a los avances producidos tanto en el diagnóstico precoz como en el tratamiento (4, 5, 8). En España, la supervivencia de los pacientes con cáncer se sitúa en un 53 % a los 5 años, siendo similar a la del resto de países de nuestro entorno (4). Igualmente, la supervivencia por CM ha mejorado de forma importante en los últimos 20 años, viéndose incrementada anualmente en un 1,4% (9). En general, la tasa media de supervivencia a los 5 años es del 89%, del 83% a los 10 años y del del 78 % a los 15 años (10). En España, la cifra de supervivencia a los 5 años, se sitúa en el 82,7%, levemente por encima de la media europea (82%) (11).

Alteraciones en pacientes con CM

A pesar de esta esperanzadora tendencia al aumento de la supervivencia, el CM y los tratamientos aplicados, causan importantes efectos secundarios físicos, psicológicos y sociales, tanto a corto como a largo plazo, lo que lleva a considerar el periodo post-cáncer como una enfermedad crónica (12). Entre estos efectos secundarios se encuentran la fatiga (13-17), dolor (17-21), los trastornos psicológicos, incluyendo ansiedad y depresión (14, 22-28), la ganancia de peso (29-32), el deterioro de la imagen corporal (33), cambios en la función sexual (34), linfedema de la extremidad superior (35), déficits en la funcionalidad de la extremidad superior en relación a disminución de flexibilidad y fuerza (35), alteraciones del sueño (17, 36-39), y alteración de la función cardiopulmonar (40). Todas estas alteraciones contribuyen a una disminución de la calidad de vida (41-46).

Debido al aumento de su incidencia y a sus múltiples consecuencias clínicas y sociales, el CM constituye un verdadero problema de salud pública (12). En la actualidad asistimos a un encarecimiento considerable de los costes en atención médica, con previsiones de un continuo aumento en los próximos años. Este hecho pone de manifiesto la necesidad de centrar esfuerzos científicos y económicos para mejorar el conocimiento actual y optimizar las intervenciones que se ofrecen a los pacientes con CM, especialmente tras el padecimiento de la enfermedad.

Para poder iniciar estrategias de tratamiento eficaces tras la enfermedad, es necesario profundizar en el conocimiento de las secuelas y alteraciones producidas por el cáncer. El grupo de trabajo CUIDATE ha abordado a través de diferentes trabajos de investigación la mejora de síntomas como el dolor o la fatiga inducidos por el cáncer. Es motivo de esta tesis doctoral el profundizar en el conocimiento de otros síntomas y alteraciones del estilo de vida de las personas que han padecido cáncer de mama con el objeto de poder ser abordadas posteriormente de forma exitosa a través de la fisioterapia. En este caso nos centraremos en la inactividad física como un pilar importante en la génesis de un estilo de vida no saludable, que de manera directa pueden dar lugar a problemas en los pacientes derivados de la modificación de la composición corporal; así como alguno de los síntomas más prevalentes en esta población como el insomnio que junto con los ya abordados por nuestro grupo de investigación suponen los principales retos para la mejora de la calidad de vida en estos pacientes en un futuro próximo.

Inactividad Física

El nivel de inactividad física puede causar o exacerbar síntomas de diferentes patologías, como el síndrome metabólico (47), enfermedad de Parkinson (48), enfermedad coronaria y diabetes tipo 2 (49) además de relacionarse también con mayores niveles de depresión (50). Específicamente, la inactividad física contribuye al incremento del riesgo del CM y de cólon, dos de los cánceres más prevalentes del mundo (51). Además es importante resaltar que se espera el aumento en años futuros de la actual prevalencia de cáncer derivados de esta inactividad física (52).

A pesar de la fuerte evidencia de la inactividad física en el deterioro de la salud, los hábitos sedentarios están aumentando en la población mundial (49), lo que implica un problema global de salud en décadas futuras. Del mismo modo, las supervivientes de cáncer de mama (SCM) muestran mayor nivel de sedentarismo y participan en actividades menos intensas que mujeres sin cáncer (53). Aunque no tenemos un marco referencial exacto, es factible pensar que los síntomas producidos por el cáncer se relacionan con la perpetuación de estilos de vida poco saludables como la falta de actividad física y que por otro lado el padecimiento de estos síntomas pueden estar en el origen y perpetuación de estos síntomas favorecidos por un exceso de sedentarismo. La fatiga y el estrés se encuentran entre los efectos secundarios que sufren las SCM (13-17, 22-27). La posible influencia de la inactividad física en estas alteraciones sufridas por las SCM supone una laguna de la investigación que demanda especial atención en la actualidad desde el mundo de la investigación en el soporte sanitario de pacientes oncológicos.

Casi la mitad de las SCM sufren diferentes niveles de estrés psicológico (54), relacionándose este síntoma estrechamente con procesos dolorosos y limitaciones funcionales sufridas por esta población (55-56). El incremento de la actividad física y los efectos derivados del ejercicio terapéutico se han postulado como un medio adecuado para mejorar el dolor y el deterioro del estado de ánimo (57). Un mejor conocimiento sobre la influencia de la inactividad física en la depresión y otros aspectos del estado de ánimo, podría ayudar a los profesionales de la salud a implementar programas con el objetivo de promover y mejorar los niveles de actividad física en SCM.

En un intento por entender mejor las relaciones entre diferentes síntomas inducidos por el cáncer y el estilo de vida en estas pacientes, tenemos que destacar que algunos de estos síntomas como la depresión o la fatiga que sufren las mujeres con CM, podrían estar influenciados por el estrés (58). El estrés está mediado por el eje hipotalámico-hipofisario-adrenal (HHA) y el sistema nervioso simpático (SNS) (59). Las SCM que refieren fatiga persistente han mostrado una reducción de la concentración de cortisol (60) lo cual muestra un mecanismo fisiológico subyacente común a todos estos síntomas: el deterioro progresivo del eje HHA. En los últimos años ha crecido el interés por diferentes marcadores biológicos del eje HHA que superen los inconvenientes de sustancias como el cortisol muy sujeto a modulaciones circadianas. Entre estos marcadores ha tomado especial relevancia la α-amilasa. La actividad de la α-amilasa, es un marcador del SNS que podría ser modulado por la actividad física (61). No hay estudios previos que informen sobre marcadores biológicos como la actividad de la α-amilasa en SCM. La normalización de las concentraciones de cortisol y de la actividad de la α-amilasa inducida por un nivel adecuado de actividad física pueden ejercer influencias positivas en varios sistemas biológicos (ej. inmune, metabólico, cardiovascular) relevantes para las SCM (62).

Insomnio

Como se mencionó previamente, el insomnio es otro de los efectos secundarios que sufren las mujeres con CM (17, 36-39). Se describe como dificultad para conciliar el sueño, dificultad para permanecer dormido, o no tener un sueño reparador, a pesar de tener condiciones de sueño aceptables. Se asocia con alteraciones del funcionamiento temporal diario y se diagnostica cuando los síntomas persisten durante al menos 4 semanas (63). El insomnio se considera que es el trastorno del sueño más prevalente, y es más común en el mundo desarrollado (64). Al igual que la inactividad física, el insomnio se ha relacionado con la progresión de problemas físicos y psicológicos como la diabetes, las enfermedades cardiovasculares (65), la depresión, la ansiedad (66) y el cáncer (67).

En la población con cáncer, el insomnio es el trastorno más común entre los problemas de sueño (68) y es casi tres veces mayor en la población con cáncer que en la población general (69). La persistencia de este fenómeno se debe a que los pacientes con cáncer tienen factores precipitantes relacionados con la enfermedad, el tratamiento, los medicamentos o los síntomas concomitantes de cáncer, a los que se asocian factores predisponentes y de perpetuación como la edad, el género y los trastornos psiquiátricos (70), que pueden estar presentes en cualquier persona.

El insomnio relacionado con el cáncer (IRC) se ha vinculado ampliamente con la depresión, el dolor, el cansancio y la fatiga (71), siendo el síntoma psicológico más estresante (72). Sin embargo, no está claro como se desarrolla el insomnio, porque los factores precipitantes anteriormente mencionados contribuyen al insomnio, pero el insomnio en sí puede producir mayor fatiga, dolor y depresión, lo que puede convertirse en un círculo vicioso que es difícil de romper. Es necesaria una mayor comprensión del IRC ya que reduce el funcionamiento y la calidad de vida de los pacientes (73). En la literatura reciente, los modelos predictivos que explican el IRC son limitados; por lo tanto, se debe abordar esta brecha en la investigación.

En pacientes con CM, la prevalencia del insomnio fue mayor que en pacientes con otros tipos de cáncer, alcanzando una tasa del 42-69% (67), lo que podría deberse a que dichas pacientes tienen más factores predisponentes como el sexo femenino o la edad avanzada (69), así como factores precipitantes derivados del proceso patológico sufrido. El enfoque terapéutico para el CM es típicamente quimioterapia (QT), radioterapia (RT) y terapia hormonal como parte del tratamiento primario, además de la cirugía. Se sabe que hay un cambio en la prevalencia del insomnio durante el proceso oncológico, siendo más frecuente durante la etapa de tratamiento (67), especialmente durante la QT (69).

Respecto a la asociación que puede establecerse entre el estado físico y el insomnio, un estudio reciente con mujeres adultas jóvenes mostró una asociación inversa entre el insomnio y el estado físico y encontró que los sujetos con problemas de sueño tenían niveles más bajos de resistencia muscular, flexibilidad y condición cardiovascular (74). Las mujeres con CM, sufren deterioro del nivel de condición física (44, 75). Sin embargo, la influencia del nivel de condición física en el insomnio no se ha estudiado profundamente en pacientes con cáncer de mama.

Además, las pacientes con CM experimentan hiperalgesia y dolor (21), a menudo persistentemente, y estos problemas se asocian significativamente con trastornos del sueño después de la mastectomía (76). Junto a la hiperalgesia, el dolor y el deterioro físico, las pacientes con CM tienen trastornos psicológicos debido a la incertidumbre que experimentan durante el desarrollo de la enfermedad (77). Entre otros, presentan depresión, ansiedad y fatiga (78), que actualmente se consideran junto con el insomnio, como un conjunto de síntomas. La coexistencia de estos factores podría ayudar a que el insomnio se convierta en un problema persistente, que podría influir en la adherencia de los pacientes a los tratamientos (64).

Según nuestros datos, pocos estudios han investigado la asociación entre el insomnio y las variables sociodemográficas, psicológicas y de deterioro físico en pacientes con cáncer de mama. Un mayor entendimiento del IRC y su relación con otros factores podría mejorar el manejo de este problema en pacientes con cáncer de mama.

Capacidad funcional. Test de la caminata de 6 minutos

El ejercicio físico puede mejorar diferentes síntomas y alteraciones físicas relacionados con el cáncer como el nivel de fatiga (79-82), deterioro de la función cognitiva (81), la depresión (79, 80, 83), disminución de la función cardiorrespiratoria y la capacidad funcional (84), la reducción de la condición física, (81, 84, 85) la modificación de la composición corporal (85), las alteraciones del sueño (79), y sobre todo, la perdida de la calidad de vida. (80, 81, 83, 84, 87, 88). Por esta razón, el ejercicio se considera un componente fundamental de la recuperación en pacientes con esta enfermedad (88). Las guías clínicas, recomiendan una actividad semanal de 150 minutos de ejercicio aeróbico de intensidad moderada o 75 minutos de intensidad vigorosa o una combinación equivalente (89-90) para revertir los efectos secundarios negativos en esta población.

Sin embargo, la mayoría de las supervivientes no consiguen adherirse a estas recomendaciones debido a limitaciones individuales. Por tanto, las recomendaciones de ejercicio deberían individualizarse para adaptarse a las capacidades del paciente (91). Para facilitar la individualización de los programas de recuperación tras el cáncer basados en el ejercicio terapéutico es necesario contar con test adecuados que puedan facilitar una mayor compresión del estado de la condición física de estos pacientes y que permitan ser evaluados de forma sencilla en un contexto clínico.

Un adecuado test de capacidad funcional para evaluar las habilidades físicas de las SCM podría facilitar el desarrollo de programas de ejercicio adaptados a la paciente. El gold estándar para la estimar la condición cardiopulmonar de las SCM lo constituyen las pruebas de esfuerzo cardiopulmonar (PECP), realizadas normalmente en un cicloergómetro. Este método toma el consumo máximo de oxígeno (VO2 pico) como medida de rendimiento máximo para determinar la función cardiovascular y respiratoria generales durante el ejercicio (40). Sin embargo, muchas SCM no tienen acceso al equipo sofisticado que se requiere para realizar este test. En este sentido, una investigación previa (92), ha establecido que se alcanza un mejor rendimiento funcional en SCM cuando se usa un protocolo en cinta continua en lugar de un cicloergómetro. Más aún, realizar un test con incremento de la carga de trabajo hasta el agotamiento es factible en esta población y no provoca efectos adversos. De esta forma, este estudio establece un protocolo con cinta continua para estimar la condición cardiopulmonar de las SCM. Por tanto, un simple test de marcha, se ha usado ampliamente para testar la función cardiopulmonar en estos individuos (88), mostrando una adecuada fiabilidad.

El uso del test de la caminata de 6 minutos se ha ido incrementando tanto en la práctica clínica como en estudios de investigación como una medida objetiva de la capacidad funcional en pacientes con deterioro moderado-severo como la obesidad (93), enfermedad de Alzheimer (94), fibromialgia (95), o enfermedades cardiopulmonares (96). Adicionalmente, el test de la caminata de 6 minutos puede ser útil para la evaluación de la respuesta de un paciente a intervenciones médicas, pronóstico o estado funcional (97). Al ser una herramienta fiable, realizada con rapidez y barata para medir la condición cardiorrespiratoria, se ha usado previamente y ha mostrado tener buena correlación con otros aspectos de la salud en SCM (98). Se ha postulado que el test de la caminata de 6 minutos podría reflejar capacidad de una persona para realizar las actividades de la vida diaria (AVD) (99), pero actualmente, desconocemos las relaciones existentes entre el rendimiento en el test de la caminata de 6 minutos con datos clínicos, medidas antropométricas, tratamientos, función sexual, medidas físicas y dolor en mujeres con CM.

Para prescribir y lograr una programa de ejercicio adecuado en términos de tipo, duración, intensidad y frecuencia en pacientes con CM, se requiere conocer la capacidad funcional de las pacientes (que puede ser medida usando el test de la caminata de 6 minutos) y su influencia en la salud general de las mismas.

REFERENCIAS BIBLIOGRÁFICAS

1. Organización mundial de la Salud (OMS) [Internet]. Copenhagen: OMS. [Febrero 2017; Consultado 10 Marzo 2017]. Centro de Prensa. Cáncer. Nota Descriptiva. Datos y cifras. Febrero de 2017. Disponible en: http://www.who.int/mediacentre/factsheets/fs297/es/

2. Sociedad Española de Oncología Médica (SEOM) [Internet]. Madrid: SEOM. [8 Marzo 2017; Consultado 11 Marzo 2017]. Información sobre el cáncer. Cáncer de mama. Disponible en: http://www.seom.org/es/info-sobre-el-cancer/cancer-de-mama?showall=1

3. Stewart BW, Wild CP (eds.). World Cancer Report 2014. [Internet]. Lyon (Francia): International Agency for Research on Cancer (IARC); 2014 [Consultado 11 Marzo 2017]. Disponible en: http://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-2014

4. Sociedad Española de Oncología Médica (SEOM) [Internet]. Madrid: SEOM. [30 Enero 2017; Consultado 11 Marzo 2017]. Las cifras del Cáncer en España 2017. Disponible en: http://www.seom.org/es/prensa/el-cancer-en-espanyacom/105941-las-cifras-del-cancer-en-espana-2017?start=1#content

5. Sociedad Española de Oncología Médica (SEOM) [Internet]. Madrid: SEOM. [02 Febrero 2017; Consultado 12 Marzo 2017]. El Cáncer en España 2016. Disponible en: http://www.seom.org/es/prensa/el-cancer-en-espanyacom/105460-el-cancer-en-espana-2016?showall=1

6. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon (France): International Agency for Research on Cancer; 2013 [Consultado 12 Marzo 2017]. Disponible en: http://globocan.iarc.fr

7. Organización mundial de la Salud (OMS) [Internet]. Copenhagen: OMS. [Enero 2017; Consultado 10 Marzo 2017]. Centro de Prensa. Las 10 principales causas de defunción. Nota Descriptiva. Las 10 principales causas de defunción en el mundo. Disponible en: http://www.who.int/mediacentre/factsheets/fs310/es/

8. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. 2016 Jul; 66(4):271-89.

9. Asociación Española Contra el Cáncer (AECC) [Internet]. Madrid: AECC. [17 Febrero 2017; Consultado 15 Marzo 2017]. Sobre el cáncer. Cáncer de mama. Pronóstico (supervivencia y mortalidad). Disponible en: https://www.aecc.es/SobreElCancer/CancerPorLocalizacion/CancerMama/Paginas/pronostico.aspx

10. Cancer.net [Internet]. Alexandria (Virginia): Cancer.Net Editorial Board; c2005 [Agosto 2015; Consultado 15 Marzo 2017]. Tipos de cáncer. Cáncer de mama: Estadísticas [1 pantalla]. Disponible en: http://www.cancer.net/es/tipos-de-cáncer/cáncer-de-mama/estad%C3%ADsticas

11. Sant M, Chirlaque Lopez MD, Agresti R, Sánchez Pérez MJ, Holleczek B, Bielska-Lasota, et al.; EUROCARE-5 Working Group. Survival of women with cancers of breast and genital organs in Europe 1999-2007: results of the EUROCARE-5 study. Eur J Cancer. 2015 Sep 6. pii: S0959-8049(15)00702-9.

12. Leclerc AF, Jerusalem G, Devos M, Crielaard JM, Maquet D. Multidisciplinary management of breast cancer. Arch Public Health. 2016 Dec 5;74:50.

13. Fabi A, Falcicchio C, Giannarelli D, Maggi G, Cognetti F, Pugliese P. The course of cancer related fatigue up to ten years in early breast cancer patients: What impact in clinical practice? Breast. 2017 May 10;34:44-52.

14. Levkovich I, Cohen M, Pollack S, Drumea K, Fried G. Cancer-related fatigue and depression in breast cancer patients postchemotherapy: Different associations with optimism and stress appraisals. Palliat Support Care. 2015 Oct;13(5):1141-51. Erratum in: Palliat Support Care. 2016 Oct;14(5):596.

15. Bennett S, Pigott A, Beller EM, Haines T, Meredith P, Delaney C. Educational interventions for the management of cancer-related fatigue in adults. Cochrane Database Syst Rev. 2016 Nov 24;11:CD008144.

16. Berger AM, Gerber LH, Mayer DK. Cancer-related fatigue: implications forbreast cancer survivors. Cancer. 2012 Apr 15;118(8 Suppl):2261-9.

17. Berger AM, Visovsky C, Hertzog M, Holtz S, Loberiza FR Jr. Usual and worst symptom severity and interference with function in breast cancer survivors. J Support Oncol. 2012 May-Jun;10(3):112-8.

18. Wang L, Guyatt GH, Kennedy SA, Romerosa B, Kwon HY, Kaushal A, et al. Predictors of persistent pain after breast cancer surgery: a systematic review and meta-analysis of observational studies. CMAJ. 2016 Oct 4;188(14):E352-E361.

19. Andersen KG, Duriaud HM, Jensen HE, Kroman N, Kehlet H. Predictive factors for the development of persistent pain after breast cancer surgery. Pain. 2015 Dec;156(12):2413-22.

20. Ding YY, Yao P, Wu L, Han ZK, Hong T, Zhu YQ, et al. Body mass index and persistent pain after breast cancer surgery: findings from the women's healthy eating and living study and a meta-analysis. Oncotarget. 2017 May 17.

21. 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 Jan;12(1):72-8.

22. Kim YH, Choi KS, Han K, Kim HW. A psychological intervention program for patients with breast cancer under chemotherapy and at a high risk of depression: a randomized clinical trial. J Clin Nurs. 2017 May 30.

23. Gibbons A, Groarke A, Sweeney K. Predicting general and cancer-related distress in women with newly diagnosed breast cancer. BMC Cancer. 2016 Dec 3;16(1):935.

24. Bidstrup PE, Christensen J, Mertz BG, Rottmann N, Dalton SO, Johansen C. Trajectories of distress, anxiety, and depression among women with breast cancer: Looking beyond the mean. Acta Oncol. 2015 May;54(5):789-96.

25. Schmid-Büchi S, Halfens RJ, Müller M, Dassen T, van den Borne B. Factors associated with supportive care needs of patients under treatment for breast cancer. Eur J Oncol Nurs. 2013 Feb;17(1):22-9.

26. Mertz BG, Bistrup PE, Johansen C, Dalton SO, Deltour I, Kehlet H, et al. Psychological distress among women with newly diagnosed breast cancer. Eur J Oncol Nurs. 2012 Sep;16(4):439-43.

27. Ando N, Iwamitsu Y, Kuranami M, Okazaki S, Nakatani Y, Yamamoto K, et al. Predictors of psychological distress after diagnosis in breast cancer patients and patients with benign breast problems. Psychosomatics. 2011 Jan-Feb;52(1):56-64.

28. Lim CC, Devi MK, Ang E. Anxiety in women with breast cancer undergoing treatment: a systematic review. Int J Evid Based Healthc. 2011 Sep;9(3):215-35.

29. Sadim M, Xu Y, Selig K, Paulus J, Uthe R, Agarwl S, et al. A prospective evaluation of clinical and genetic predictors of weight changes in breast cancer survivors. Cancer. 2017 Feb 14.

30. Playdon MC, Bracken MB, Sanft TB, Ligibel JA, Harrigan M, Irwin ML. Weight gain after breast cancer diagnosis and all-cause mortality: systematic review and meta-Analysis. J Natl Cancer Inst. 2015 Sep 30;107(12):djv275.

31. Nyrop KA, Deal AM, Lee JT, Muss HB, Choi SK, Dixon S, et al. Weight changes in postmenopausal breast cancer survivors over 2 years of endocrine therapy: a retrospective chart review. Breast Cancer Res Treat. 2017 Apr;162(2):375-388.

32. Vance V, Mourtzakis M, McCargar L, Hanning R. Weight gain in breast cáncer survivors: prevalence, pattern and health consequences. Obes Rev. 2011 Apr;12(4):282-94.

33. Barsotti Santos D, Ford NJ, Dos Santos MA, Vieira EM. Breast cancer an sexuality: the impacts of breast cancer treatment on the sex lives of women in Brazil. Cult Health Sex. 2014 Jan 9.

34. Quintard B, Constant A, Lakdja F, Labeyrie-Lagardère H. Factors predicting sexual functioning in patients 3 months after surgical procedures for breast cancer: the role of the Sense of Coherence. Eur J Oncol Nurs. 2014 Feb;18(1):41-5.

35. Cheema B, Gaul CA, Lane K, Fiatarone Singh MA. Progressive resistance training in breast cancer: a systematic review of clinical trials. Breast Cancer Res Treat. 2008 May;109(1):9-26.

36. Lowery-Allison AE, Passik SD, Cribbet MR, Reinsel RA, O'Sullivan B, Norton L, et al. Sleep problems in breast cancer survivors 1-10 years posttreatment. Palliat Support Care. 2017 May 16:1-10.

37. Enderlin CA, Coleman EA, Cole C, Richards KC, Kennedy RL, Goodwin JA, et al. Subjective sleep quality, objective sleep characteristics, insomnia symptom severity, and daytime sleepiness in women aged 50 and older with nonmetastatic breast cancer. Oncol Nurs Forum. 2011 Jul;38(4):E314-25.

38. Enderlin CA, Coleman EA, Cole C, Richards KC, Hutchins LF, Sherman AC. Sleep across chemotherapy treatment: a growing concern for women older than 50 with breast cancer. Oncol Nurs Forum. 2010 Jul;37(4):461-A3.

39. Berger AM, VonEssen S, Kuhn BR, Piper BF, Agrawal S, Lynch JC, et al. Adherence, sleep, and fatigue outcomes after adjuvant breast cancer chemotherapy: results of a feasibility intervention study. Oncol Nurs Forum. 2003 May-Jun;30(3):513-22.

40. Klassen O, Schmidt ME, Scharhag-Rosenberger F, Sorkin M, Ulrich CM, Schneeweiss A, et al. Cardiorespiratory fitness in breast cancer patients undergoing adjuvant therapy. Acta Oncol. 2014 Oct;53(10):1356-65.

41. King MT, Winters ZE, Olivotto IA, Spillane AJ, Chua BH, Saunders C, et al. Patient-reported outcomes in ductal carcinoma in situ: A systematic review. Eur J Cancer. 2017 Jan;71:95-108.

42. Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. J Natl Cancer Inst. 2012 Mar 7;104(5):386-405.

43. Paraskevi T. Quality of life outcomes in patients with breast cancer. Oncol Rev. 2012 Jan 30;6(1):e2.

44. Penttinen HM, Saarto T, Kellokumpu-Lehtinen P, Blomqvist C, Huovinen R, Kautiainen H, et al. Quality of life and physical performance and activity of breast cancer patients after adjuvant treatments. Psychooncology. 2011 Nov;20(11):1211-20.

45. Groenvold M. Health-related quality of life in early breast cancer. Dan Med Bull. 2010 Sep;57(9):B4184. PubMed PMID: 20816024.

46. Montazeri A. Health-related quality of life in breast cancer patients: a bibliographic review of the literature from 1974 to 2007. J Exp Clin Cancer Res. 2008 Aug 29;27:32.

47. Sisson SB, Camhi SM, Church TS, Martin CK, Tudor-Locke C, Bouchard C, et al. Leisure time sedentary behavior, occupational/domestic physical activity, and metabolic syndrome in U.S. men and women. Metab Syndr Relat Disord. 2009 Dec;7(6):529-36.

48. Villar-Cheda B, Sousa-Ribeiro D, Rodriguez-Pallares J, Rodriguez-Perez AI, Guerra MJ, Labandeira-Garcia JL. Aging and sedentarism decrease vascularization and VEGF levels in the rat substantia nigra. Implications for Parkinson's disease. J Cereb Blood Flow Metab. 2009 Feb;29(2):230-4.

49. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT; Lancet Physical Activity Series Working Group. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 2012 Jul 21;380(9838):219-29.

50. Bishwajit G, O'Leary DP, Ghosh S, Yaya S, Shangfeng T, Feng Z. Physical inactivity and self-reported depression among middle- and older-aged population in South Asia: World health survey. BMC Geriatr. 2017 Apr 28;17(1):100.

51. Parkin DM. 9. Cancers attributable to inadequate physical exercise in the UK in 2010. Br J Cancer. 2011 Dec 6;105 Suppl 2:S38-41.

52. Wang D, Zheng W, Wang SM, Wang JB, Wei WQ, Liang H, et al. Estimation of cancer incidence and mortality attributable to overweight, obesity, and physical inactivity in China. Nutr Cancer. 2012;64(1):48-56.

53. Phillips SM, Dodd KW, Steeves J, McClain J, Alfano CM, McAuley E. Physical activity and sedentary behavior in breast cancer survivors: New insight into activity patterns and potential intervention targets. Gynecol Oncol. 2015 Aug;138(2):398-404.

54. Bleiker EM, Pouwer F, van der Ploeg HM, Leer JW, Adèr HJ. Psychological distress two years after diagnosis of breast cancer: frequency and prediction. Patient Educ Couns. 2000 Jun;40(3):209-17.

55. 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.

56. Charlier C, Pauwels E, Lechner L, Spittaels H, Bourgois J, De Bourdeaudhuij I, VAN Hoof E, et al. Physical activity levels and supportive care needs for physicalactivity among breast cancer survivors with different psychosocial profiles: a cluster-analytical approach. Eur J Cancer Care (Engl). 2012 Nov;21(6):790-9.

57. Sabiston CM, Brunet J, Burke S. Pain, movement, and mind: does physical activity mediate the relationship between pain and mental health among survivors of breast cancer? Clin J Pain. 2012 Jul;28(6):489-95.

58. Straub RH, Cutolo M. Psychoneuroimmunology-developments in stress research. Wien Med Wochenschr. 2017 Jun 9.

59. Gunnar M, Quevedo K. The neurobiology of stress and development. Annu Rev Psychol. 2007 58:145-73.

60. Bower JE, Ganz PA, Aziz N. Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. Psychosom Med. 2005 Mar-Apr;67(2):277-80.

61. Chatterton RT Jr, Vogelsong KM, Lu YC, Ellman AB, Hudgens GA. Salivary alpha-amylase as a measure of endogenous adrenergic activity. Clin Physiol. 1996 Jul;16(4):433-48.

62. Bower JE, Ganz PA, Aziz N, Olmstead R, Irwin MR, Cole SW. Inflammatory responses to psychological stress in fatigued breast cancer survivors: relationship to glucocorticoids. Brain Behav Immun. 2007 Mar;21(3):251-8.

63. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Arlington: American Psychiatric Publishing; 2013.

64. Sateia MJ, Doghramji K, Hauri PJ, Morin CM. Evaluation of chronic insomnia. An American Academy of Sleep Medicine review. Sleep. 2000 Mar 15;23(2):243-308.

65. Grandner MA, Jackson NJ, Pak VM, Gehrman PR. Sleep disturbance is associated with cardiovascular and metabolic disorders. J Sleep Res. 2012 Aug;21(4):427-33.

66. Taylor DJ, Lichstein KL, Durrence HH, Reidel BW, Bush AJ. Epidemiology of insomnia, depression, and anxiety. Sleep. 2005 Nov;28(11):1457-64.

67. Savard J, Ivers H, Villa J, Caplette-Gingras A, Morin CM. Natural course of insomnia comorbid with cancer: an 18-month longitudinal study. J Clin Oncol. 2011 Sep 10;29(26):3580-6.

68. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. J Clin Oncol. 2001 Feb 1;19(3):895-908.

69. Palesh O, Peppone L, Innominato PF, Janelsins M, Jeong M, Sprod L, et al. Prevalence, putative mechanisms, and current management of sleep problems during chemotherapy for cancer. Nat Sci Sleep. 2012 Dec 17;4:151-162.

70. Induru RR, Walsh D. Cancer-related insomnia. Am J Hosp Palliat Care. 2014 Nov;31(7):777-85.

71. Davis MP, Khoshknabi D, Walsh D, Lagman R, Platt A. Insomnia in patients with advanced cancer. Am J Hosp Palliat Care. 2014 Jun;31(4):365-73.

72. Bardwell WA, Profant J, Casden DR, Dimsdale JE, Ancoli-Israel S, Natarajan L, et al.; Women's Healthy Eating & Living (WHEL) Study Group. The relative importance of specific risk factors for insomnia in women treated for early-stage breast cancer. Psychooncology. 2008 Jan;17(1):9-18.

73. Romito F, Cormio C, De Padova S, Lorusso V, Berio MA, Fimiani F, et al. Patients attitudes towards sleep disturbances during chemotherapy. Eur J Cancer Care (Engl). 2014 May;23(3):385-93.

74. Lee AJ, Lin WH. Association between sleep quality and physical fitness in female young adults. J Sports Med Phys Fitness. 2007 Dec;47(4):462-7.

75. Juvet LK, Thune I, Elvsaas IKØ, Fors EA, Lundgren S, Bertheussen G, et al. The effect of exercise on fatigue and physical functioning in breast cancer patients during and after treatment and at 6 months follow-up: A meta-analysis. Breast. 2017 Jun;33:166-177.

76. Belfer I, Schreiber KL, Shaffer JR, Shnol H, Blaney K, Morando A, et al. Persistent postmastectomy pain in breast cancer survivors: analysis of clinical, demographic, and psychosocial factors. J Pain. 2013 Oct;14(10):1185-95.

77. Hall DL, Mishel MH, Germino BB. Living with cancer-related uncertainty: associations with fatigue, insomnia, and affect in younger breast cáncer survivors. Support Care Cancer. 2014 Sep;22(9):2489-95.

78. Bower JE. Behavioral symptoms in patients with breast cancer and survivors: Fatigue, insomnia, depression, and cognitive disturbance. J Clin Oncol. 2008 Feb 10;26(5):768-77.

79. Cramer H, Lauche R, Klose P, Lange S, Langhorst J, Dobos GJ. Yoga for improving health-related quality of life, mental health and cancer-related symptoms in women diagnosed with breast cancer. Cochrane Database Syst Rev. 2017 Jan 3;1:CD010802.

80. Stagl JM, Antoni MH, Lechner SC, Carver CS, Lewis JE. Postsurgical physical activity and fatigue-related daily interference in women with non-metastatic breast cancer. Psychol Health. 2014;29(2):177-98.

81. Furmaniak AC, Menig M, Markes MH. Exercise for women receiving adjuvant therapy for breast cancer. Cochrane Database Syst Rev. 2016 Sep 21;9:CD005001.

82. Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise interventions on health-related quality of life for people with cáncer during active treatment. Cochrane Database Syst Rev. 2012 Aug 15;(8):CD008465.

83. Fisher HM, Jacobs JM, Taub CJ, Lechner SC, Lewis JE, Carver CS, et al. How changes in physical activity relate to fatigue interference, mood, and quality of life during treatment for non-metastatic breast cancer. Gen Hosp Psychiatry. 2017 May 29. pii: S0163-8343(17)30080-4.

84. Markes M, Brockow T, Resch KL. Exercise for women receiving adjuvant therapy for breast cancer. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD005001.

85. Courneya KS, Segal RJ, Mackey JR, Gelmon K, Reid RD, Friedenreich CM, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. J Clin Oncol. 2007 Oct 1;25(28):4396-404.

86. Rufa'i AA, Muda WAMW, Yen SH, Abd Shatar AK, Murali BVK, Tan SW. Design of a randomised intervention study: the effect of dumbbell exercise therapy on physical activity and quality of life among breast cancer survivors in Malaysia. BMJ Glob Health. 2016 Jul 26;1(1):e000015.

87. Blair CK, Robien K, Inoue-Choi M, Rahn W, Lazovich D. Physical inactivity and risk of poor quality of life among elderly cancer survivors compared to women without cancer: the Iowa Women's Health Study. J Cancer Surviv. 2016 Feb;10(1):103-12.

88. Battaglini CL, Mills RC, Phillips BL, Lee JT, Story CE, Nascimento MG, et al. Twenty-five years of research on the effects of exercise training in breast cancer survivors: A systematic review of the literature. World J Clin Oncol. 2014 May 10;5(2):177-90.

89. 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 Jul;42(7):1409-26. Erratum in: Med Sci Sports Exerc. 2011 Jan;43(1):195.

90. NCCN Clinical Practice Guidelines in Oncology. Survivorship, https:// subscriptions.nccn.org/gl_login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf. Accesed 15 April 2017

91. Bourke L, Homer KE, Thaha MA, Steed L, Rosario DJ, Robb KA, et al. Interventions to improve exercise behaviour in sedentary people living with and beyond cancer: a systematic review. Br J Cancer. 2014 Feb 18;110(4):831-41.

92. Dolan LB, Lane K, McKenzie DC. Optimal mode for maximal aerobic exercise testing in breast cancer survivors. Integr Cancer Ther. 2012 Dec;11(4):321-6.

93. Beriault K, Carpentier AC, Gagnon C, Ménard J, Baillargeon JP, Ardilouze JL, et al. Reproducibility of the 6-minute walk test in obese adults. Int J Sports Med. 2009 Oct;30(10):725-7.

94. Ries JD, Echternach JL, Nof L, Gagnon Blodgett M. Test-retest reliability and minimal detectable change scores for the timed "up & go" test, the six-minute walk test, and gait speed in people with Alzheimer disease. Phys Ther. 2009 Jun;89(6):569-79.

95. Carbonell-Baeza A, Ruiz JR, Aparicio VA, Ortega FB, Delgado-Fernández M. The 6-minute walk test in female fibromyalgia patients: relationship with tenderness, symptomatology, quality of life, and coping strategies. Pain Manag Nurs. 2013

Dec;14(4):193-9.

96. Rasekaba T, Lee AL, Naughton MT, Williams TJ, Holland AE. The six-minute walk test: a useful metric for the cardiopulmonary patient. Intern Med J. 2009 Aug;39(8):495-501.

97. Salzman SH. The 6-min walk test: clinical and research role, technique, coding, and reimbursement. Chest. 2009 May;135(5):1345-1352.

98. 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 to cancer-related symptoms and physical and physiologic parameters. Am J Phys Med Rehabil. 2012 Sep;91(9):774-82.

99. Guazzi M, Dickstein K, Vicenzi M, Arena R. Six-minute walk test and cardiopulmonary exercise testing in patients with chronic heart failure: a comparative analysis on clinical and prognostic insights. Circ Heart Fail. 2009 Nov;2(6):549-55.

OBJETIVOS

General

El objetivo de esta Tesis Doctoral ha sido estudiar en pacientes con CM la relación del nivel de inactividad, del insomnio y de la capacidad funcional con diferentes variables físicas, psicológicas y fisiológicas relacionadas con la salud, que permita una mayor comprensión de las mismas y posibilite desarrollar programas que desde la fisioterapia, optimicen la calidad de vida de estas pacientes.

Específicos

1. Determinar la influencia de la inactividad física en el nivel de condición física, estado de ánimo y marcadores salivares del eje HHA (cortisol) y del SNS (α-amilasa) en SCM. Las hipótesis de las que partimos son: (1) las SCM con un nivel de inactividad física mostrarían un estado de ánimo deteriorado respecto a las SCM activas; y (2) que las SCM con un nivel de inactividad física mostrarían una concentración de cortisol y una actividad de la α-amilasa mas elevadas que las SCM activas en SCM **(Artículo I)**

2. Analizar la relación entre el insomnio y variables relacionadas con el tratamiento, variables sociodemográficas, la condición física relacionada con la salud, el dolor, la ansiedad y la depresión en pacientes con CM **(Artículo II)**.

3. Examinar las relaciones entre la capacidad funcional, evaluada con el test de la caminata de 6 minutos, y el nivel de condición física, el estado de salud fisiológico y psicológico, la calidad de vida, los síntomas relacionados con el cáncer y la composición corporal en pacientes con CM **(Articulo III)**.

MATERIAL Y MÉTODOS

En la siguiente tabla se muestra el material y los métodos utilizados en los diferentes artículos que componen esta memoria de Tesis

Tabla 1: Tabla resumen del material y métodos utilizados en esta memoria de Tesis (Artículos I, II y III)

ARTÍCULO	DISEÑO DEL ESTUDIO	PARTICIPANTES	PRINCIPALES VARIABLES DE ESTUDIO	METODOLOGÍA
I. Influence of physical inactivity in psychophysiological state of breast cancer survivors	Estudio trasversal	*N* = 108 SCM N= 39 (Grupo de inactivas) N=69 (Grupo de activas)	Estado de ánimo Nivel de Actividad Física Capacidad funcional Fuerza de prensión Tensión Arterial Marcadores salivares	POMS MLTPAQ Test de caminata de 6 min Dinamometría Tensiómetro Recolección no estimulada de saliva
II: Factors that explain the cancer-related insomnia	Estudio trasversal	*N* = 123 participantes	Insomnio Fase de tratamiento Tipo de tratamiento Resistencia de miembro inferior Resistencia abdominal Capacidad funcional Fuerza de tronco Dolor Ansiedad y Depresión	EORTC QLQ-C30 Autorregistro Autorregistro Test de sentarse y levantarse Test de flexión abdominal Test de caminata de 6 min Dinamometría CBD HADS
III. The 6-minute walk test as a measure of health in breast cancer patients	Estudio transversal	*N=87* SCM	Capacidad funcional Calidad de vida Función cognitiva Ansiedad y Depresión Composición corporal Resistencia abdominal Resistencia de miembro inferior Fuerza de tronco Dolor	Test de caminata de 6 min EORTC QLQ-C30 EORTC QLQ-BR23 TMT HADS Impedancia bioeléctrica Test de flexión abdominal Test de sentarse y levantarse Dinamometría CBD

SCM: Supervivientes de Cáncer de Mama; POMS: Profile of Mood State; MLTPAQ: Minessotta Leisure Time of Physical Activity Questionnarie; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 version; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality Questionnaire; TMT: The Trail Making Test; HADS: The Hospital Anxiety and Depression Scale; CBD: Cuestionario Breve del dolor.

RESULTADOS Y DISCUSIÓN

En los siguientes artículos publicados se presentan tanto los resultados como la discusión de los mismos.

CAPÍTULO 1

INFLUENCE OF PHYSICAL INACTIVITY IN PSYCHOPHYSIOLOCIGAL STATE OF BREAST CANCER SURVIVORS

Artículo I

Influencia de la inactividad física en el estado psicofisiológico de supervivientes de cáncer de mama

Ariza-García A, Galiano-Castillo N, Cantarero-Villanueva I,

Fernández-Lao C, Díaz-Rodríguez L, Arroyo-Morales M.

Eur J Cancer Care (Engl) 2013 Nov;22(6):738-45.

Journal Citation Reports

FI: 1.762 (16/106) Q1 (Nursing)

European Journal of Cancer Care

Original article

Influence of physical inactivity in psychophysiolocigal state of breast cancer survivors

A. ARIZA-GARCÍA, MSC, PHYSIOTHERAPIST, *Health Andalusian Service, University Hospital San Cecilio, Granada, and Physical Therapy Department, University of Granada, Granada,* N. GALIANO-CASTILLO, MSC, FELLOW, *Physical Therapy Department, University of Granada, Granada,* I. CANTARERO-VILLANUEVA, PHD, LECTURER, *Physical Therapy Department, University of Granada, Granada,* C. FERNÁNDEZ-LAO, PHD, *Physical Therapy Department, University of Granada, Granada,* L. DÍAZ-RODRÍGUEZ, PHD, ASSISTANT PROFESSOR, *Nursing Department, University of Granada, Granada,* & M. ARROYO-MORALES, PHD, PROFESSOR, *Physical Therapy Department, University of Granada, Granada, Spain*

ARIZA-GARCÍA A., GALIANO-CASTILLO N., CANTARERO-VILLANUEVA I., FERNÁNDEZ-LAO C., DÍAZ-RODRÍGUEZ L. & ARROYO-MORALES M. (2013) *European Journal of Cancer Care* **22**, 738–745
Influence of physical inactivity in psychophysiolocigal state of breast cancer survivors

Physical inactivity has been postulated as mediator of the relationship between cancer-related symptoms and psychoneurobiological alterations. The aim of the study was to evaluate the influence of physical inactivity level on mood state, fitness level as well as on salivary markers of the hypothalamic–pituitary–adrenal axis (cortisol) and the SNS (α-amylase) in breast cancer survivors. One hundred and eight breast cancer survivors (stages I–IIIa) participated in this cross-sectional study. Data were gathered on the following: Minnesota Leisure Time Physical Activity Questionnaire, profile of mood state, 6-min walk test, force handgrip, blood pressure, salivary cortisol concentration and salivary α-amylase activity. For our analysis, two groups were formed based on physical activity level measured as energy expenditure during diary leisure activities of the participants at the moment of the study, a physical inactivity level group (<3 METs × h/week) and an adequate physical activity level group (>3 METs × h/week). Fitness level was significantly higher in the active than the inactive group, while anger, fatigue, depression, confusion, mood disturbance, diastolic blood pressure and salivary α-amylase activity were significantly greater in the inactive than the active group. These results suggest that physical inactivity induces a worse psychoneurobiological state in inactive than in active breast cancer survivors.

Keywords: physical activity, mood state, blood pressure, cortisol, α-amylase activity.

INTRODUCTION

Physical inactivity level may cause or exacerbate symptoms of different conditions as metabolic syndrome (Sisson *et al*. 2009), Parkinson disease (Villar-Cheda *et al*. 2009), coronary heart disease and type 2 diabetes (Lee *et al*. 2012). Despite strong evidence over the deleterious health effects of physical inactivity, sedentary habits are increasing in world population (Lee *et al*. 2012), which imply a global health problem in future decades.

Specifically, physical inactivity contributes to big risk of breast and colon cancer, two of the most prevalent cancers in the world (Parkin 2010), even it is expected the increase in future years of the current burden of cancer associated with physical inactivity (Wang *et al*. 2012). Fortunately, major advances in oncology treatment and improvement of screening procedures have increased the survivorship after cancer (Nelson *et al*. 2009). However, this improvement of survivorship is associated with different functional limitations as cancer-related fatigue,

Correspondence address: Manuel Arroyo-Morales, Physical Therapy Department, Faculty of Health Sciences, University of Granada, Avda. Madrid s/n, 18071 Granada, Spain (e-mail: marroyo@ugr.es).

Accepted 25 June 2013
DOI: 10.1111/ecc.12101

European Journal of Cancer Care, 2013, **22**, 738–745

distress or pain (Braithwaite *et al*. 2010). If these alterations suffered by breast cancer survivors are influenced by physical inactivity is a gap of research which demands especial attention.

Almost a half of the breast cancer survivors suffer psychological distress (Bleike *et al*. 2000) which have a close relationship with pain processes and associated functional limitations suffered by this population (Cantarero-Villanueva *et al*. 2011a; Charlier *et al*. 2012). Physical activity has been postulated as a partial mediator of the relationship between pain, mood deterioration (Charlier *et al*. 2012; Sabiston *et al*. 2012) and sleep difficulties (Humpel & Iverson 2010). A better knowledge about the influence of physical inactivity in depression and others aspect of mood state could help health professionals to implement programmes with the objective to promote an increase of physical activity level in breast cancer survivors.

Cancer-related symptoms as pain, depression or fatigue, could be mediated by stress response. Stress response is mediated by the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS) (Gunnar & Quevedo 2007). Breast cancer survivors reporting persistent fatigue have shown a reduction of cortisol concentration (Bower *et al*. 2005). To the best of the authors' knowledge, there are not previous studies reporting biological markers as α-amilase activity in breast cancer survivors. α-Amilase activity is a marker of the SNS which could be modulated by physical activity (Chatterton *et al*. 1996). Normalisation of cortisol concentrations and α-amilase activity induced by adequate physical activity level can exert modulatory positive influences on several biological systems (e.g. immune, metabolic, cardiovascular) relevant for breast cancer survivors (Bower *et al*. 2007).

In the current study, we examined the influence of physical activity level on fitness level, mood state as well as on salivary markers of the HPA axis (cortisol) and the SNS (α-amylase) in breast cancer survivors. We hypothesised that: (1) breast cancer survivors with physical inactivity level would exhibit deteriorated mood with respect to active breast cancer survivors; and (2) breast cancer survivors with physical inactivity level would exhibit higher cortisol concentration and α-amylase activity than active breast cancer survivors.

METHODS

Patients were recruited from the Department of Oncology from both Hospitals, Virgen de las Nieves and Hospital Clínico San Cecilio (Granada, Spain) to participate in a cross-sectional study. Inclusion criteria were a primary diagnosis of breast cancer (grades I–IIIa), age between 18 and 65 years. and at least 1 month after finished post-primary oncology treatment (surgery, chemotherapy and radiotherapy). Exclusion criteria were active cancer and previous diagnosis of chronic musculoskeletal diseases (cervical pain, low back pain, fibromyalgia) or psychological limitation hindering test completion, and refusal to participate in the study. The study was approved by the Ethics Committee of the San Cecilio University Hospital of Granada.

Patients were contacted by phone by two oncologists of the hospitals. Those interested in joining the study were cited for an appointment, received a complete explanation of the protocol and signed the consent form. Those included in the study were cited for a second visit, for completing the medical history, physical examination and a medical questionnaire which included age, surgical side, comorbidity, socio-educational level, marital status and previous oncology treatments.

MEASURES

Psychologic state: Profile of mood states (POMS)

The Spanish version of the POMS questionnaire used in this study 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, Vigour, Fatigue, and Confusion. Subscale scores were converted into T-scores for the statistical analysis. A high reliability has been reported by this questionnaire (Andrade *et al*. 2002).

Physical activity level: Minnesota Leisure, Time Physical Activity Questionnaire, (MLTPAQ), 6-min walk test and force handgrip

The validated Spanish version of the MLTPAQ (Elosua *et al*. 2000) 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 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 Metabolic Equivalent of Task (MET) value (Ainsworth *et al*. 1993).

The 6-min walk test consists of determining the maximum distance (metres) that can be walked in 6 min along a 30-m rectangular course (Rikli & Jones 1997). This test has showed adequate reliability in different conditions (Kosak & Smith 2005).

Handgrip strength was measured bilaterally using a digital dynamometer (TKK 5101 Grip-D; Takey, Tokyo, Japan) as previously described (Ruiz-Ruiz *et al.* 2002). The patient performed the test three times for each hand, allowing a 1-min rest period between measures. The highest peak force per hand was selected. This test has been recently described as a reliable correlate of quality of life and health status in cancer survivors (Cantarero-Villanueva *et al.* 2012).

Physiological states: Blood pressure and salivary markers

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

Non-stimulated saliva samples were collected into collection tubes (by passive drooling technique) for 3 min. Saliva sampling was made with patients seated, leaning forward, and with their heads tilted down. All saliva sampling was performed in the 4 h after wake-up in order to control fluctuation associated to diurnal rhythms in cortisol and α-amylase secretions according to standardised international procedures (Rohleder & Nater 2009). Saliva samples were centrifuged at 3000 rpm for 15 min to remove sediments and were stored at –70°C until analysis. Salivary cortisol and α-amylase activity were analysed 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 analysed in a single batch to eliminate inter-assay variance and they were measured in duplicate. Adequate intra-assay accuracy was obtained with a coefficient of variance between 6 and 7.5%.

For our analysis, two groups were formed based on physical activity level measured as energy expenditure during diary leisure activities (MET, Metabolic Equivalent is a unit used to estimate the amount of oxygen used during physical activity) of the participants at the moment of the study, *a physical inactivity level* (<3 METs × h/week) and an *adequate physical activity level* (>3 METs × h/week). Physical activity values below this cut-off point have been associated with increased mortality risk in breast cancer patients (Holmes *et al.* 2005; Holick *et al.* 2008) and with less quality of life respect active women (Harrison *et al.* 2010).

Statistical analysis

Data were analysed with IBM-SPSS statistical package (19.0 version). Results are expressed as mean, standard deviation and 95% confidence interval. The Kolmogorov–Smirnov test showed that quantitative variables had a normal distribution of the data ($P > 0.05$). A one-way repeated measures ANCOVA was performed with group as between-subjects variable (inactive, active) and age, oncology treatment, grade of cancer, time since diagnostic, educational level, and marital status as co-variables. A $P < 0.05$ was considered statistically significant.

RESULTS

Our sample consisted of 108 breast cancer survivors with a mean age of 49.2 ± 8.2 years. There were not differences in clinical and socio-demographic values between inactive and active groups (Table 1).

Influence of physical activity level on mood state

The analysis revealed significant differences between groups for POMS values, specifically in Depression (F = 6.004; $P = 0.016$), Anger (F = 4.522; $P = 0.036$), Fatigue (F = 6.783; $P = 0.011$), Confusion (F = 4.331; $P = 0.040$) and Total Score (F = 3.958; $P = 0.049$) subscales; but no significant differences were found for Tension (F = 3.328; $P = 0.071$) and Vigour (F = 1.353; $P = 0.247$) subscales (Table 2). Inactive group showed a significantly higher level of fatigue, anger, confusion and total mood disturbance when compared with the active group (Fig. 1). The co-variables showed no influence on ANCOVA results.

Influence of physical activity on fitness level and physiological parameters

According to the ANCOVA results (Table 3), patients in the inactive group showed a significantly lower value in the force handgrip (affected side: F = 23.654; $P < 0.001$; non affected side: F = 12.237; $P < 0.001$) and 6-min walk test (F = 6.207; $P = 0.015$) respect active group. Besides patients in the inactive group showed a significantly higher value in diastolic blood pressure (F = 4.262; $P = 0.041$) respect active group. There were not significant differences between groups in systolic blood pressure (F = 1.569; $P = 0.213$).

Finally, patients in the inactive group showed a significantly higher activity of α-amylase activity (F = 6.366; $P = 0.016$) respect active group (Table 3). There were no significant differences between groups in cortisol concentration (F = 0.955; $P = 0.329$). The co-variables showed no influence on ANCOVA results.

DISCUSSION

Our study reveals that completing more than 3 METs × h/week is associated with better mood state, fitness level

Table 1. Patient's characteristics and comparisons between study groups

Variable	Inactive group (n = 39)	Active group (n = 69)	P value
Age (y), mean (SD)	49.51 ± 8.59 (95% CI 46.72–52.29)	49.00 ± 8.05 (95% CI 47.06–50.93)	0.757
Time since diagnosis(months), mean (SD)	9.98 ± 10.42 (95% CI 3.36–16.06)	10.65 ± 7.70 (95% CI 8.81–12.49)	0.805
Marital status, n (%)			
Married	25 (64%)	53 (76.8%)	0.896
Unmarried	6 (15.3%)	8 (11.6%)	
Divorced	6 (15.3%)	8 (11.6%)	
Widow	2 (5.12%)	0 (0%)	
Tumour stage, n (%)			
I	15 (38.4%)	26 (37.6%)	0.823
II	18 (46.1%)	31 (44.9%)	
IIIa	6 (15.4%)	12 (17.4%)	
Educational level, n (%)			
Primary schooling	15 (38.5%)	23 (33.3%)	0.196
Secondary schooling	6 (15.4%)	21 (30.4%)	
University	18 (46.2%)	25 (36.2%)	
Type of medical treatment, n (%)			
Radiotherapy	4 (10.3%)	3 (4.3%)	0.378
Chemotherapy	2 (5.1%)	4 (5.8%)	
Radiotherapy + chemotherapy	33 (84.6%)	62 (89.9%)	
Type of surgery, n (%)			
Lumpectomy	24 (61.5%)	50 (72.5%)	0.119
Unilateral mastectomy	13 (33.3%)	19 (27.5%)	
Bilateral mastectomy	2 (5.1%)	0 (0%)	
Body mass Index, mean (SD)	26.81 ± 3.65 (95% CI 20.60–34.10)	26.12 ± 3.59 (95% CI 19.30–38.10)	0.336

P values for inter-group comparisons using chi-squared test, and Mann–Whitney U-tests.

Table 2. Psychological values expressed as mean ±standard deviation with 95% confidence interval

Group	Inactive group (n = 39)	Active group (n = 69)	P value
Profile of mood state			
Tension	50.97 ± 11.35 (95% CI 47.24–54.70)	46.98 ± 10.57 (95% CI 44.46–49.50)	0.071
Depression	54.05 ± 11.40 (95% CI 53.07–60.82)	49.35 ± 10.25 (95% CI 46.34–51.23)	0.016*
Anger	56.94 ± 11.79 (95% CI 49.91–64.23)	52.04 ± 11.25 (95% CI 49.35–54.32)	0.036*
Vigour	49.31 ± 7.60 (95% CI 46.81–51.71)	51.11 ± 7.70 (95% CI 49.27–52.95)	0.247
Fatigue	55.47 ± 9.83 (95% CI 52.24–58.70)	50.40 ± 9.57 (95% CI 48.11–52.68)	0.011*
Confusion	44.31 ± 10.04 (95% CI 41.01–47.61)	40.22 ± 9.58 (95% CI 37.94–42.51)	0.040*
Total score	20 623.68 ± 5 965.95 (95% CI 18 662.72–22 584.64)	18 474.28 ± 5 008.18 (95% CI 17 280.12–19 668.44)	0.049*

*$P < 0.05$ for group × time interaction (Repeated ANOVA test).

and lower diastolic blood pressure and α-amylase activity in breast cancer survivors. In this study we found no differences between physical inactivity and physically active groups of breast cancer survivors in systolic blood pressure and cortisol concentration.

Lower levels of depression, fatigue, anger and confusion were associated with increased levels of physical activity, regardless of age, tumour stage, previous oncology treatment, time since diagnostic, educational level and marital status in breast cancer survivors, suggesting that the physical activity influences mood balance in this population. These results are in agreement with previous studies (Ochayon *et al.* 2010; Sabiston *et al.* 2012). One of the most interesting results is the increase of fatigue level (10%) in reduced physical activity group when compared with the active group. It is well known that inactivity induces muscle catabolism and causes further detraining (Schmitz 2010). As a result, a self-perpetuating detraining state with easily induced fatigue can persist in sedentary breast cancer survivors (Lucía *et al.* 2003). An increased level of depression was found in inactive breast cancer survivors with respect to the active group. Depression is a major health problem during survivorship phase of this condition which often leads patients to discontinue hormone-therapy (Giese-Davis *et al.* 2011). Similarly to our results, Mutrie *et al.* (2012) have confirmed that active women who previously participated in different exercise programmes for cancer survivors reported lower levels of depression and increased quality of life compared with those who were less active. A variety of biological pathways have been hypothesised to mediate the anti-depressant effects of adequate physical activity level

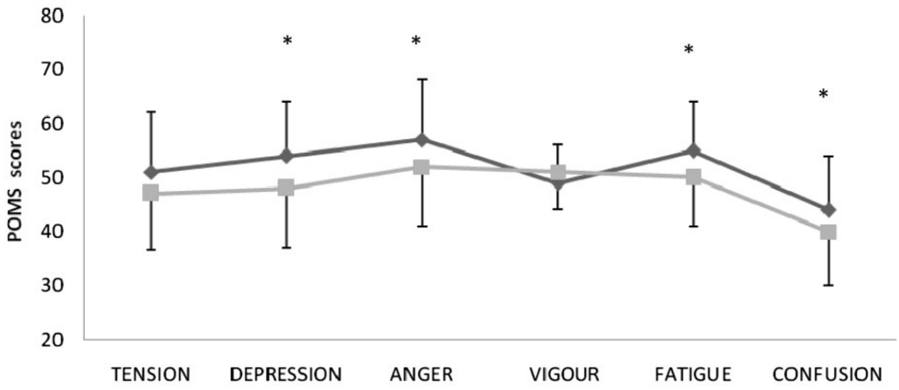

Figure 1. Difference in POMS score between inactive and active groups. *$P < 0.05$ for group × time interaction (ANOVA test). —◆—, inactive group; —■—, active group. POMS, profile of mood states.

Table 3. Physical and physiological values expressed as mean ±standard deviation with 95% confidence interval

Group	Inactive group (*n* = 39)	Active group (*n* = 69)	*P* value
Force Handgrip			
Affected side (kg)	13.76 ± 7.32 (95% CI 11.27–15.84)	21.31 ± 5.76 (95% CI 19.03–22.14)	<0.001*
Non-affected side (kg)	17.43 ± 7.67 (95% CI 14.91–20.36)	23.22 ± 4.87 (95% CI 21.32–24.65)	0.001*
Functional capacity			
6-min walk test (metres)	442.58 ± 116.36 (95% CI 399.89–485.26)	504.59 ± 111.54 (95% CI 476.46–532.36)	0.015*
Blood pressure			
Diastolic (mmHg)	84.46 ± 9.98 (95% CI 81.22–87.69)	80.92 ± 9.29 (95% CI 78.69–83.16)	0.130
Systolic (mmHg)	125.56 ± 15.70 (95% CI 120.47–130.65)	121.76 ± 14.79 (95% CI 118.21–125.32)	0.213
Salivary concentration			
Cortisol (μg/mL)	0.34 ± 0.33 (95% CI 0.14–0.54)	0.30 ± 0.23 (95% CI 0.21–0.40)	0.329
Alfa-amylase (U/mL)	256.55 ± 182.25 (95% CI 15.132–361.78)	142.68 ± 104.40 (95% CI 100.51–184.85)	<0.016*

*Significant interaction for group × time interaction (ANOVA test).

as regulation of central monoamines, regulation of the HPA axis or increased β-endorphin levels (Brosse *et al.* 2002), increased prefrontal cortex blood and improved brain mediators such as brain-derived neutrotrophic factor (Rozanski 2012). These results give support to promote strategies to reduce sedentary habits which could improve mood state in breast cancer survivors.

We have not found differences in diurnal cortisol concentration between groups included in this study. These results do not give support to the role of the hyperactivity of HPA axis function (McEwen 2006) to explain increased level of fatigue and depression in sedentary cancer survivors. Nevertheless, stress response in humans is mediated by two major components: the HPA axis and the sympathetic nervous system. One of the most interesting results of this study is the higher α-amylase activity of inactive with respect to the active group. These results support that there is a disturbed activity of the SNS in inactive breast cancer survivors (Nater & Rohleder 2009). Future studies should clarify the importance of these results in relation to wrong psychological state of this subgroup of patients. α-Amylase has a recognised role as immunological component of oral mucosa for its ability to bind to oral bacteria (Scannapieco *et al.* 1993). Physical activity is a major component of the adequate lifestyle in cancer survivors (Schmitz *et al.* 2010). Immuno-protector effect of moderate physical activity is well documented in literature (Neto *et al.* 2011). Recently, Cantarero-Villanueva *et al.* (2011b) reported effectiveness of a multimodal exercise programme to reduce α-Amylase activity in breast cancer survivors. Results of present study and previous research, give preliminary support to the immune role of adequate physical activity level in oral health of breast cancer survivors.

In this study, physically active group had a higher level of physical function than inactive group. The 12.5 and 35.5% of better functional capacity and force handgrip in active with respect to the inactive group could be associated with an increase of quality of life and survivorship (Cantarero-Villanueva *et al.* 2012). Explaining the mechanisms involved in the relationship between physical activity and fitness level in cancer survivors is beyond the scope of this study; but an adequate level of physical activity can attenuate the effects over muscle atrophy due to both cancer and the toxicity of cancer therapy through suppressing inflammatory responses and improving immune function, rates of protein synthesis, and antioxidant enzyme activities (Al-Majid & Waters 2008).

One of the most interesting results of this study is the reduced diastolic blood pressure of active compared with inactive group. These results are in line with previous studies about reduction of blood pressure in response to regular physical activity (Frisoli *et al*. 2011; Dimeo *et al*. 2012). Effects of adequate physical activity in blood pressure have been associated to a fitness level improvement (Carnethon *et al*. 2003). Different physiologic mechanisms as enhance prostaglandin mechanism, increase endothelium-dependent vasodilatation mediated by nitric oxide or reduction of sympathoadrenergic activity have been postulated as potential exercise mechanisms of action to reduce blood pressure (Goto *et al*. 2003). A possible relationship between reduction of α-amylase activity as marker of sympathetic nervous system and decrease of blood pressure in active breast cancer survivors warrant new research to clarify potential implication of these mechanisms in effects of physical activity level on blood pressure.

Study limitations include the possible bias from the use of self-reported measurements of physical activity level. Use of accelerometers to monitor physical activity in future studies should confirm the results presented in this report. Second, 3 METs × h/week is not a very high level of physical activity so the differences showed in this study could be validated by another physical activity measurement using different cut-off points. Third, not accounting for rhythmicity in the analysis and interpretation of salivary cortisol data can limit the interpretation of our results (Woods & Mentes 2011). Finally, the cross-sectional study design prevented exploration of cause-and-effect relationships. Nevertheless, we were able to present a broad view of the influence of physical activity in breast cancer survivors including a biological, psychological and physical perspective. Our results give support to previous Biobehavioural Model (Al-Majid & Gray 2009) which describes influence of biological, psychobehavioural, and functional mechanisms that contribute to cancer-related symptoms.

Nurse scientists and others interested professionals in supportive care in cancer are encouraged to use present results as a confirmation of biobehavioural model applied to cancer-related symptoms. The reported results in this study could develop a comprehensive understanding of the ways in which physical activity influences psychological state in cancer survivors. Multimodal exercise interventions could stimulate the increase of physical activity level in cancer survivors.

In summary, active breast cancer survivors showed reduced level of disturbance of mood, diastolic blood pressure and α-amylase activity with respect to inactive breast cancer survivors. This psychophysiological state was joined to a better fitness level in active respect to those inactive breast cancer survivors.

ACKNOWLEDGEMENTS

The authors are indebted to all participants without whom this work would not have been possible. This study was supported by a grant from the Health Institute Carlos III and PN I+D+I 2008-2011, Madrid, Spanish Government (FIS PI10/02749-02764), a grant from the Andalusian HealthService, Junta de Andalucia (PI-0457-2010) and a grant (Program FPU AP2010-6075) from Education Ministry, Madrid, Spanish Government.

REFERENCES

Ainsworth B.E., Haskell W.L., Leon A.S., Jacobs D.R. Jr, Montoye H.J., Sallis J.F. & Paffenbarger R.S. Jr (1993) Compendium of physical activities: classification of energy costs of human physical activities. *Medicine and Sciences in Sports and Exercise* **225**, 71–80.

Al-Majid S. & Gray D.P. (2009) A biobehavioral model for the study of exercise interventions in cancer-related fatigue. *Biological Research for Nursing* **10**, 381–391.

Al-Majid S. & Waters H. (2008) The biological mechanisms of cancer-related skeletal muscle wasting: the role of progressive resistance exercise. *Biological Research for Nursing* **10**, 7–20.

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.

Bleike E.M., Pouwer F., van der Ploeg H.M., Leer J.W. & Ader H.J. (2000) Psychological distress two years after diagnosis of breast cancer: frequency and prediction. *Patient Education and Counseling* **40**, 209–217.

Bower J.E., Ganz P.A. & Aziz N. (2005) Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. *Psychosomatic Medicine* **67**, 277–280.

Bower J.E., Ganz P.A., Aziz N., Olmstead R., Irwin M.R. & Cole S.W. (2007) Inflammatory responses to psychological stress in fatigued breast cancer survivors: relationship to glucocorticoids. *Brain Behaviour, and Immunology* **21**, 251–258.

Braithwaite D., Satariano W.A., Sternfeld B., Hiatt R.A., Ganz P.A., Kerlikowske K., Moore D.H., Slattery M.L., Tammemagi M., Castillo A., Melisko M., Esserman L., Weltzien E.K. & Caan B.J. (2010) Long-term prognostic role of functional limitations among women with breast cancer. *Journal of the National Cancer Institute* **102**, 1468–1477.

Brosse A.L., Sheets E.S., Lett H.S. & Blumenthal J.A. (2002) Exercise and the treatment of clinical depression in adults: recent findings and future directions. *Sports Medicine* **32**, 741–760.

Cantarero-Villanueva I., Fernandez-Lao C., Fernández-de-las-Peñas C., Díaz-Rodríguez L., Sánchez-Cantalejo E. & Arroyo-Morales M. (2011a) Associations among musculoskeletal imairments, depression, body image and fatigue in breast cancer survivors within the first year after treatment. *European Journal of Cancer Care* **20**, 632–639.

Cantarero-Villanueva I., Fernández-Lao C., Díaz-Rodriguez L., Fernández-de-las-Peñas C., Del Moral-Avila R. & Arroyo-Morales M. (2011b) A multimodal exercise program and multimedia support reduce cancer-related fatigue in breast cancer survivors: a randomised controlled clinical trial. *European Journal of Integrative Medicine* **3**, e189–e200.

Cantarero-Villanueva I., Fernández-Lao C., Díaz-Rodríguez L., Fernández-de-Las-Peñas C., Ruiz J.R. & Arroyo-Morales M. (2012) The handgrip strength test as a measure of function in breast cancer survivors: relationship to cancer-related symptoms and physical and physiologic parameters. *American Journal of Physical Medicine and Rehabilitation* **91**, 774–782.

Carnethon M.R., Gidding S.S., Nehgme R., Sidney S., Jacobs D.R., Jr & Liu K. (2003) Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. *JAMA: The Journal of the American Medical Association* **290**, 3092–3100.

Charlier C., Pauwels E., Lechner L., Spittaels H., Bourgois J., de Bourdeaudhuij I. & van Hoof E. (2012) Physical activity levels and supportive care needs for physical activity among breast cancer survivors with different psychosocial profiles: a cluster-analytical approach. *European Journal of Cancer Care* **21**, 790–799.

Chatterton R.T., Jr, Vogelsong K.M., Lu Y.C., Ellman A.B. & Hudgens G.A. (1996) Salivary alpha-amylase as a measure of endogenous adrenergic activity. *Clinical Physiology* **16**, 433–448.

Dimeo F., Pagonas N., Seibert F., Arndt R., Zidek W. & Westhoff T.H. (2012) Aerobic exercise reduces blood pressure in resistant hypertension. *Hypertension* **60**, 653–658.

Elosua R., Garcia M., Aguilar A., Molina L., Covas M.I. & Marrugat J. (2000) Validation of the Minnesota Leisure Time Physical Activity Questionnaire in Spanish women. Investigators of the MARATDON Group. *Medicine and Science in Sports and Exercise* **32**, 1431–1437.

Frisoli T.M., Schmieder R.E., Grodzicki T. & Messerli F.H. (2011) Beyond salt: lifestyle modifications and blood pressure. *European Heart Journal* **32**, 3081–3087.

Giese-Davis J., Collie K., Rancourt K.M.S., Neri E., Kraemer H.C. & Spiegel D. (2011) Decrease in depression symptoms is associated with longer survival in patients with metastatic breast cancer: a secondary analysis. *Journal of Clinical Oncology* **29**, 413–420.

Goto C., Higashi Y., Kimura M., Noma K., Hara K., Nakagawa K., Kawamura M., Chayama K., Yoshizumi M. & Nara I. (2003) Effect of difference intensities of exercise on endothelium-dependent vasodilation in humans: role of endothelium-dependent nitric oxide and oxidative stress. *Circulation* **108**, 530–535.

Gunnar M.R. & Quevedo K. (2007) The neurobiology of stress and development. *Annual Review of Psychology* **58**, 145–173.

Harrison S.A., Hayes S.C. & Newman B. (2010) Age-related differences in exercise and quality of life among breast cancer survivors. *Medicine and Sciences in Sports and Exercise* **42**, 67–74.

Holick C.N., Newcomb P.A., Trentham-Dietz A., Titus-Ernstoff L., Bersch A.J., Stampfer M.J., Baron J.A., Egan K.M. & Willett W.C. (2008) Physical activity and survival after diagnosis of invasive breast cancer. *Cancer Epidemiology, Biomarkers and Prevention* **17**, 379–386.

Holmes M.D., Chen W.Y., Feskanich D., Kroenke C.H. & Colditz G.A. (2005) Physical activity and survival after breast cancer diagnosis. *JAMA: The Journal of the American Medical Association* **293**, 2479–2486.

Humpel N. & Iverson D.C. (2010) Sleep quality, fatigue and physical activity following a cancer diagnosis. *European Journal of Cancer Care* **19**, 761–768.

Kosak M. & Smith T. (2005) Comparison of the 2-, 6-, and 12-minute walk tests in patients with stroke. *Journal of Rehabilitation Research and Development* **42**, 103–107.

Lee I.M., Shiroma E.J., Lobelo F., Puska P., Blair S.N., Katzmarzyk P.T. & Lancet Physical Activity Series Working Group (2012) Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *The Lancet* **380**, 219–229.

Lucía A., Earnest C. & Pérez M. (2003) Cancer-related fatigue: can exercise physiology assist oncologists? *Lancet Oncology* **4**, 616–625.

McEwen B.S. (2006) Sleep deprivation as a neurobiologic and physiologic stressor: allostasis and allostatic load. *Metabolism* **55**, S20–S23.

Mutrie N., Campbell A., Barry S., Hefferon K., McConnachie A., Ritchie D. & Tovey S. (2012) Five-year follow-up of participants in a randomised controlled trial showing benefits from exercise for breast cancer survivors during adjuvant treatment. Are there lasting effects? *Journal of Cancer Survivors* **6**, 420–430.

Nater U.M. & Rohleder N. (2009) Salivary alpha-amylase as a noninvasive biomarker for the sympathetic nervous system: current state of research. *Psychoneuroendocrinology* **34**, 486–496.

Nelson H.D., Tyne K., Naik A., Bougatsos C., Chan B.K. & Humphrey L.; U.S. Preventive Services Task Force. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. *Annals of Internal Medicine* **151**, 727–737, W237–W242.

Neto J.C., Lira F.S., de Mello M.T. & Santos R.V. (2011) Importance of exercise immunology in health promotion. *Amino Acids* **41**, 1165–1172.

Ochayon L., Zelker R., Kaduri L. & Kadmon I. (2010) Relationship between severity of symptoms and quality of life in patients with breast cancer receiving adjuvant hormonal therapy. *Oncology Nursing Forum* **37**, E349–E358.

Parkin D.M. (2010) 9. Cancers attributable to inadequate physical exercise in the UK in 2010. *British Journal of Cancer* **105**, S38–S41.

Rikli R.E. & Jones C.J. (1997) Assessing physical performance in independent older adults: issues and guidelines. *Journal of Aging Physical Activity* **5**, 244–261.

Rohleder N. & Nater U. (2009) Determinants of salivary α-amylase in humans and methodological considerations. *Psyconeuroendocrinology* **34**, 469–485.

Rozanski A. (2012) Exercise as medical treatment for depression. *Journal of American College of Cardiology* **60**, 1064–1066.

Ruiz-Ruiz J., Mesa J.L., Gutierrez A. & Castillo M.J. (2002) Hand size influences optimal grip span in women but not in men. *Journal of Hand Surgery* **27**, 897–901.

Sabiston C.M., Brunet J. & Burke S. (2012) Pain, movement, and mind: does physical activity mediate the relationship between pain and mental health among survivors of breast cancer? *The Clinical Journal of Pain* **28**, 489–495.

Scannapieco F.A., Torres G. & Levine M.J. (1993) Salivary α-amylase: role in dental plaque and caries formation. *Critical Reviews of Oral Biology Medicine* **4**, 301–307.

Schmitz K. (2010) Balancing lymphedema risk: exercise versus deconditioning for breast cancer survivors. *Exercise and Sport Sciences Reviews* **38**, 17–24.

Schmitz K.H., Courneya K.S., Matthews C., Demark-Wahnefried W., Galvão D.A., Pinto B.M., Irwin M.L., Wolin K.Y., Segal R.J., Lucia A., Schneider C.M., von Gruenigen V.E. & Schwartz A.L. (2010) American College of Sports Medicine. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Medicine and Science in Sports and Exercise* **42**, 1409–1426.

Sisson S.B., Camhi S.M., Church T.S., Martin C.K., Tudor-Locke C. & Bouchard

C. (2009) Leisure time sedentary behavior, occupational/domestic physical activity, and metabolic syndrome in U.S. men and women. *Metabolic Syndrome and Related Disorders* **7**, 529–536.

Villar-Cheda B., Sousa-Ribeiro D., Rodriguez-Pallares J., Rodriguez-Perez A.I., Guerra M.J. & Labandeira-Garcia J.L. (2009) Aging and sedentarism decrease vascularization and VEGF levels in the rat substantia nigra. Implications for Parkinson's disease. *Journal of Cerebral Blood Flow and Metabolism* **29**, 230–234.

Wang D., Zheng W., Wang S.M., Wang J.B., Wei W.Q., Liang H., Qiao Y.L. & Boffetta P. (2012) Estimation of cancer incidence and mortality attributable to overweight, obesity, and physical inactivity in China. *Nutrition and Cancer* **64**, 48–56.

Woods D.L. & Mentes J.C. (2011) Spit: saliva in nursing research, uses and methodological considerations in older adults. *Biological Research for Nursing* **13**, 320–327.

CAPÍTULO 2

FACTORS THAT EXPLAIN THE CANCER-RELATED INSOMNIA

Artículo II

Factores que explican el insomnio relacionado con el cáncer

Galiano-Castillo N, Arroyo-Morales M, **Ariza-García A,** Fernández-Lao C, Fernández-Fernández AJ, Cantarero-Villanueva I.

Breast J. 2017 Jan 24

Journal Citation Reports

FI: 2.297 (33/80) Q2 (Obstetrics & Gynecology)

The Breast Journal

ORIGINAL ARTICLE

Factors that Explain the Cancer-Related Insomnia

Noelia Galiano-Castillo, PhD,*,† Manuel Arroyo-Morales, MD, PhD,*,† Angélica Ariza-Garcia, MsC,†,‡ Carolina Fernández-Lao, PhD,*,† Andrés J. Fernández-Fernández, PT (Physiotherapist),† and Irene Cantarero-Villanueva, PhD*,†

*Instituto de Investigación Biosanitaria de Granada, Granada, Spain; †Department of Physical Therapy, Health Sciences Faculty, University of Granada, Granada, Spain; ‡Physical Medicine and Rehabilitation Department, Clinico Universitario San Cecilio, Granada, Spain

Abstract: A better understanding of cancer related insomnia and its relationship with other associated factors is necessary to improve its management. To clarify the relationship between insomnia and treatment related variables, sociodemographic data, health related fitness, pain, anxiety, and depression in breast cancer patients. One hundred twenty-three patients participated in this cross-sectional study. As a primary variable was insomnia using The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 version. Other variables included: stage of treatment, type of treatment, multiple sit to stand test, trunk curl test, 6-min walk test, back muscle strength test, the Brief Pain Inventory short form and the Hospital Anxiety and Depression Scale. Insomnia was negatively associated with the treatment stage ($p = 0.01$), the 6-min walk test ($p = 0.01$) and the back muscle strength test ($p = 0.01$), while it was positively associated with the type of treatment ($p = 0.01$) and the multiple sit-to-stand test ($p = 0.05$). In addition, higher levels of insomnia were associated with higher scores on the Brief Pain Inventory short form ($p = 0.01$) and the Hospital Anxiety and Depression Scale ($p = 0.01$). Anxiety, type of treatment, back muscle strength, pain severity and stage of treatment were predictors of insomnia, and when they were combined they explained 51.2% of insomnia in our sample. The variability in insomnia related breast cancer is explained by anxiety, type of treatment, pain, treatment stage, and back muscle strength. Clinicians should take these results into account when generating cancer care programs to control pain and health-related-fitness (Registration of Trials NCT01801527).

Key Words: breast cancer, chemotherapy, insomnia related cancer, survival

Insomnia is described as difficulty falling asleep, difficulty staying asleep or having no restorative sleep despite having acceptable sleep conditions. Insomnia is associated with impaired daytime functioning and is diagnosed when symptoms persist for at least 4 weeks (1). This disorder is considered to be the most prevalent sleep problem, and it is more common in the developed world (2). Insomnia has been related to the progression of physical and psychological problems such as diabetes, cardiovascular disease (3), depression, anxiety (4), and cancer (5).

Among sleep problems in the cancer population, insomnia is the most common (6), and it is almost three times higher in the population with cancer than among the general population (7). This phenomenon persists because cancer patients have precipitating factors related to the disease, treatment, medications or concomitant cancer symptoms. They may also have predisposing and perpetuation factors such as age, gender, and psychiatric disorders (8), which may be present in any person.

Cancer related insomnia (CRI) has been widely linked with depression, pain, tiredness, and fatigue (9), with psychological distress being the most highlighted (10). However, it is unclear how insomnia first develops because the previously mentioned precipitating factors contribute to insomnia, and the insomnia itself can produce greater fatigue, pain, and depression, which can become a vicious cycle that is difficult to break. A greater understanding of CRI is necessary because insomnia reduces the functioning and quality of life of patients (11). In recent literature, predictive models that explain insomnia related cancer are limited; therefore, this gap in research should be addressed.

The prevalence of insomnia was higher in breast cancer patients than in patients with other cancer

Address correspondence and reprint requests to: Irene Cantarero-Villanueva, Department of Physical Therapy, Health Sciences Faculty, University of Granada, Parque Tecnológico de la Salud, Avenida de la Ilustración s/n, 18016 Granada, Spain, or e-mail: irenecantarero@ugr.es

DOI: 10.1111/tbj.12759

types, reaching a rate of 42–69% (5). This higher rate could be due to having more predisposing factors such as female gender or older age (7), as well as precipitating factors. The therapeutic approach for breast cancer is typically chemotherapy, radiation therapy, and hormone therapy as part of the primary treatment, in addition to surgery. It is known that there is a change in insomnia prevalence during the oncology process; insomnia is more prevalent during the treatment stage (10), especially during chemotherapy (7).

Considering the association that may be established between fitness status and insomnia, a recent study with female young adults showed an inverse association between insomnia and fitness and found that subjects with sleep problems had lower levels of muscular endurance, flexibility, and cardiovascular fitness (12). It is known that women with breast cancer suffer deterioration in physical fitness. However, the influence of fitness level on insomnia has not been studied deeply in breast cancer patients.

Furthermore, breast cancer patients experience hyperalgesia and pain (13), often persistently, and these problems are significantly associated with sleep disturbance after mastectomy (14). In addition to physical deterioration, breast cancer patients have impaired mental health due to the uncertainty that is experienced (15). In addition, there is a very frequent presence of psychological disturbances including depression, anxiety and fatigue symptoms (16), which are currently considered as a “symptom cluster” with insomnia. The coexistence of these factors could help make insomnia a persistent problem, which could influence patients’ adherence to treatments (2). More research is needed for understanding CRI and its relationship with other associated factors to improve the management of this problem in breast cancer patients.

To the best of the authors’ knowledge, few studies have investigated the association between insomnia and sociodemographic, psychological and physical impairment variables in breast cancer patients. The aim of this study was to clarify the relationship between insomnia and treatment related variables, sociodemographic data, health related fitness, pain, anxiety, and depression in breast cancer patients.

MATERIALS AND METHODS

This cross-sectional study was approved by the Ethical Local Granada Hospital Committee following Declaration and The Biomedical Research (14/2007) currently in place.

Setting and Participants

One hundred and forty-two breast cancer patients were called by two nurses and one oncologist from the Oncology Department of Virgen de las Nieves and Clínico San Cecilio Hospital from Granada. Nineteen patients declined to participate. Finally, 123 breast cancer patients were included in the study (35.8%, $n = 44$ during chemotherapy; 64.2%, $n = 79$ after primary treatment), using the following enrolment criteria: (1) older than 18 years, (2) ability to complete the questionnaires and physical test, (3) an I–IIIa cancer stage.

Patients were given assessments in the Physical Therapy laboratory of Granada University. The informed consent was obtained from all individual participants included in the study. Also, they completed their sociodemographics and health data.

Variables

The primary variable was insomnia assessed by The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 version (EORTC QLQ-C30) version 3.0, which has 30 items and includes both multi-item scales and single-item measures. This test has shown reliability in breast cancer (17,18). Only the EORTC QLQ-C30 insomnia item was used in this study to measure sleep disturbance. Responses are transformed from 0 to 100 with higher scale/item scores meaning higher response level. This single item has been used in other studies based on cancer populations (19). Explanatory variables were as follows:

The Treatment Stage This variable shows which treatment stage our patients were in: primary treatment or survivorship.

Type of Treatment This variable describes whether breast cancer patients underwent chemotherapy, radiotherapy or both treatments.

The Multiple Sit to Stand Test This test, described by Netz et al. (20) assessed functional state and lower body endurance. Patients were asked to perform 10 sit-stand movements as fast as possible, and the required time (sec) was recorded. This test was shown to be reliable in similarly aged populations (21).

The Trunk Curl Test This test assessed the endurance of the abdominal flexors. It used a modification of the McQuade test described by Ljungquist et al. (22). Participants were laid supine with knees flexed and had to lift their body until the inferior angle of the scapula with arms collocated in knees level. The time in which the participants maintained this position was recorded in seconds. This test has been proven to be reliable for repeated tests (23).

The 6-min Walk Test Functional capacity was assessed by this test, which was performed on a treadmill (H-P-COSMOS for graphics; Germany). Patients had training for familiarity, and then they had to walk as fast as they were able to for 6 minutes. They could increase and decrease the speed voluntarily, and the distance (in meters) that they walked was used for the analysis. This test has previously been shown to be reliable (24).

The Back Muscle Strength Test This test assessed back muscle strength with a dynamometer (TKK 5002 Back-A; Takey, Tokyo, Japan), which has a precision of 1 kg. Breast cancer patients performed the test three times with a break of 1 minute, and the mean was recorded. The start position was in standing position with 30° of lumbar flexion (25). This test showed acceptable to good reliability (26).

The Brief Pain Inventory Short Form (BPI-SF) The BPI-SF test is more extensively used in the clinical setting due to its brevity (27). It was used to measure pain severity and pain interference using a recall period of 24 hours. The pain severity is measured by four items evaluated as the worst, least, or average and now uses a numeric rating scale from 0 (no pain) to 10 (pain as severe as you can imagine). It also measured the pain interference of seven items (general activity, mood, walking, work, relations with others, sleep, and enjoyment of life) with a numeric rating scale from 0 (no interference) to 10 (complete interference). Pain severity and pain interference were obtained from mean scores. This version also contains the front and back body diagrams and a question about percentage of pain relief by medications. The Spanish version showed rates that were considerated to be low and moderate (0.53 and 0.77) (28).

The Hospital Anxiety and Depression Scale (HADS) The HADS is the most widely validated scale for measuring emotional distress in the cancer population (29). The HADS is a self-assessment scale to evaluate symptoms of anxiety and depression. It consists of two 7-item subscales with a four-point Likert scale (ranging from 0 to 3) measuring anxiety (HADS-A) and depression (HADS-D). The score for each scale is from 0 to 21. The cut-off points are as follows: 0–7 (normal), 8–10 (borderline) and 11 or above (pathologic condition). The Spanish version was found to have good reliability (30).

Data Analyses

The IBM 20 SPSS software was used for data analysis, and a $p < 0.05$ was considered to be statistically significant. The normal distribution of continuous variables was tested using the Smirnov-Kolmogorov test. Categorical variables were analysed with the chi-square test. Pearson's correlation analyses were performed between QLQ-C30 insomnia and the other study variables. Stepwise multiple regression analysis was used to explore which variables could explain the variation in insomnia (dependent variables). The requirements for an independent variable to be included in the multiple regression analysis were as follows: (a) the correlation coefficients between the dependent variable and the independent variables were significant, and (b) the correlation coefficients between the independent variables were <0.75.

RESULTS

A total of 123 breast cancer patients were included in our study. Characteristics of patients and scores of the variables are shown in Tables 1 and 2.

Correlation Analyses

This analysis indicated that insomnia was negatively associated with the treatment stage ($r = -0.300$, $p = 0.01$), the 6-min walk test ($r = -0.265$, $p = 0.01$) and the back muscle strength ($r = -0.380$, $p = 0.01$). However, the level of insomnia was positively associated with the type of treatment ($r = 0.251$, $p = 0.01$) and the multiple sit-to-stand test ($r = 0.196$, $p < 0.05$).

Table 1. Demographic Data (n = 123)

Demographic data	Frequency (n)	Percentage (%)
Stage of treatment		
During Chemotherapy	44	35.8
After primary treatment	79	64.2
Educational level		
Primary schooling	53	43.1
Secondary schooling	37	30.1
University	33	26.8
Occupation		
Homemaker	35	28.5
Employed	24	19.5
Sick leave	59	48
Nonemployed	3	2.4
Retired	2	1.6
Alcohol intake frequency		
None	55	44.7
Monthly	24	19.5
Weekly	40	32.5
Daily	4	3.3
Menopause		
Premenopause	35	28.5
Postmenopause	88	71.5
Type of treatment		
Chemotherapy	48	39
Radiotherapy	4	3.3
Chemotherapy + Radiotherapy	71	57.7
Hormonal therapy		
None	58	47.2
Tamoxifen	36	29.3
Aromatase inhibitor	23	18.7
Fulvestrant	6	4.8

In addition, higher levels of insomnia were associated with higher scores on BPI (pain severity $r = 0.445$, p = 0.01; pain interference $r = 0.507$, p = 0.01) and HADS (HADS anxiety $r = 0.583$, p = 0.01; HADS depression $r = 0.423$, p = 0.01). Significant correlations were included in the regression analysis because none were considered to be multicollinear ($r = -0.728 < r < 0.770$) (Table 3).

Regression Analysis

Using stepwise regression analyses, it was revealed that anxiety, type of treatment, back muscle strength, pain severity and treatment stage were independent and significant predictors of insomnia, and all together they explained 51.2% of the variance in insomnia (Table 4).

DISCUSSION

This study is the first to focus on the factors contributing to insomnia including a fitness approach in breast cancer patients. The aim was to understand the association between insomnia and sociodemographic,

Table 2. Baseline Variable Scores of the Patients/ Characteristics of the Study Population (n = 123)

Baseline variable scores	Mean ± SD	95% CI	Range
Age (years)	47.74 ± 0.83	46.09–49.39	27–75
Multiple sit to stand test (seconds)	25.86 ± 5.94	24.79–26.93	17.80–50.07
Trunk curl test (seconds)	33.28 ± 32.00	27.51–39.64	1.51–174.94
6-min walk test (m)	342.96 ± 190.21	308.73–377.20	57.30–1,005.00
Back muscle strength (kg)	37.35 ± 1.43	34.51–40.20	6–76.33
BPI			
Pain severity	2.82 ± 0.18	2.45–3.19	0–8.25
Pain interference	2.91 ± 0.24	2.42–3.39	0–9.71
HADS			
HADS anxiety	4.35 ± 0.43	3.63–5.06	0–16
HADS depression	8.23 ± 0.36	7.37–9.09	0–20
Insomnia (EORTC QLQ-C30)	41.45 ± 3.2	35.10–47.80	0–100

BPI, Brief Pain Inventory; HADS, Hospital Anxiety and Depression Scale.

treatment, and psychophysiological variables in breast cancer patients. We found significant positive associations between insomnia and type of treatment, pain, anxiety and depression. In contrast, significant negative associations were found between insomnia and functional capacity and back muscle strength. Moreover, a low positive association was found between insomnia and lower body resistance. The other variables (age, educational level, occupation, alcohol intake frequency and abdominal resistance) were not associated with insomnia in breast cancer patients. Anxiety, pain, stage, type of treatment, and back strength explained 51.2% of insomnia related to breast cancer. These results indicate that psychological and physical factors play an important role in the development of insomnia. The percentage of insomnia for the patients in our sample was 39.8%. This rate is slightly lower than that found in previous studies with breast cancer patients that obtained a rate of 42–69% (5), but greater than the registered healthy population, whose range is 16–21% (31).

Among variables that explained our insomnia model, anxiety has a relevant contribution ($r = 0.583$, $p < .001$). This finding supported current models of insomnia which state that psychological disturbances are important factors in the development of insomnia in cancer patients (31). A relationship between insomnia and anxiety was found in breast cancer patients who underwent aromatase treatment (32). However, the relationship found in our study could be not

Table 3. Pearson-Product Moment Correlation Matrix for Study Variable

Variable	Insomnia QLQ-C30	Stage of treatment	Age (years)	Educational level	Occupation	Alcohol intake frequency	Type of treatment	Multiple sit-to-stand test (seconds)	Trunk curl test (seconds)	6-min walk test (m)	Back muscle strength (kg)	BPI pain severity	BPI pain interference	HADS anxiety	HADS depression
Insomnia QLQ-C30	1	−0.300**	0.036	0.000	0.135	−0.141	0.251**	0.196*	−0.174	−0.265**	−0.380**	0.445**	0.507**	0.583**	0.423**
Stage of treatment	−0.300[b]	—	−0.097	0.027	0.393**	−0.027	−0.728**	−0.261**	0.081	0.419**	0.309**	−0.488**	−0.498**	−0.321**	−0.261**
Age (years)	0.036	−0.097	—	−0.315**	−0.007	−0.170	0.110	0.332**	−0.137	−0.430**	−0.168	0.145	0.163	−0.002	0.216*
Educational level	0.000	0.027	−0.315**	—	0.063	0.291**	−0.090	−0.205*	0.205*	0.341**	0.175	−0.188**	−0.124	−0.036	−0.056
Occupation	0.135	0.393**	−0.007	0.063	—	−0.057	−0.326**	−0.051	0.116	0.151	−0.098	−0.148	−0.061	0.019	−0.003
Alcohol intake frequency	−0.141	−0.027	−0.170	0.291**	−0.057	—	−0.049	−0.141	0.089	0.218*	0.224*	−0.122	−0.179*	−0.034	−0.072
Type of treatment	0.251**	−0.728**	0.110	−0.090	−0.326**	−0.049	—	0.255**	−0.179*	−0.307**	−0.163	0.391**	0.352**	0.184*	0.184*
Multiple sit-to-stand test (seconds)	0.196*	−0.261**	0.332**	−0.205*	−0.051	−0.141	0.255**	—	−0.159	−0.417**	−0.271**	0.405**	0.434**	0.187*	0.242**
Trunk curl test (seconds)	−0.174	0.081	−0.137	0.205[a]	0.116	0.089	−0.179*	−0.159	—	0.309**	0.184*	−0.314**	−0.297**	−0.097	−0.220*
6-min walk test (m)	−0.265**	0.419**	−0.430**	0.341**	0.151	0.218*	−0.307**	−0.417**	0.309**	—	0.398**	−0.392**	−0.472**	−0.333**	−0.301**
Back muscle strength (kg)	−0.380**	0.309**	−0.168	0.175	−0.098	0.224*	−0.163	−0.271**	0.184*	0.398**	—	−0.431**	−0.428**	−0.237**	−0.146
BPI pain severity	0.445**	−0.488**	0.145	−0.188*	−0.148	−0.122	0.391**	0.405**	−0.314**	−0.392**	−0.431**	—	0.770**	0.405**	0.433**
BPI pain interference	0.507**	−0.498**	0.163	−0.124	−0.061	−0.179*	0.352**	0.434**	−0.297**	−0.472**	−0.428**	0.770**	—	0.533**	0.547**
HADS anxiety	0.583**	−0.321**	−0.002	−0.036	0.019	−0.034	0.184*	0.187*	−0.097	−0.333**	−0.237**	0.405**	0.533**	—	0.666**
HADS depression	0.423**	−0.261**	0.216*	−0.056	−0.003	−0.072	0.184*	0.242**	−0.220*	−0.301**	−0.146	0.433**	0.547**	0.666**	—

BPI, Brief Pain Inventory; HADS, Hospital Anxiety and Depression Scale.
*$p < 0.05$.
**$p < 0.01$.

Table 4. Summary of Stepwise Regression Analyses to Determine Predictors of Insomnia (r^2 = 51.2%)

Independent variable	β	*T*	p
Stage of treatment	0.20	1.89	0.06
Type of treatment	0.24	2.46	0.01**
Back muscle strength (kg)	−0.15	−2.06	0.04*
BPI Pain severity	0.236	2.714	0.008**
HADS anxiety	0.518	6.665	<0.001**

BPI, Brief Pain Inventory; HADS, Hospital Anxiety and Depression Scale.
*p < 0.05.
**p < 0.01.

explained by findings from Desai et al. (32) as almost half of our sample (47.2%) did not receive any hormone treatment and there were only a few patients (18.7%) who received aromatase inhibitor treatment. Our results indicate that there is a link between insomnia and anxiety in patients with breast cancer not only during hormone treatment, but also in other stages of treatment such as chemotherapy and the survivors of the phase. The anxiety-insomnia association could be mediated by biologic dysfunction. The role of cortisol could be a determinant in this relationship. It is known that anxiety or cancer worry causes an elevation in cortisol levels (33), which in addition to producing sleep disturbance decrease the response of the immune system against tumors (34), causing more worry. Multimodal programs based on physical activity and physiological support could break this cycle by improving sleep quality (35) and cortisol levels (36). Our results support the need to address psychological aspects for the improvement of insomnia in breast cancer patients.

The relationship observed between insomnia and pain was expected. It is known that there is a reciprocal relationship between these conditions (37), which forms a vicious cycle that should be avoided because it can influence the outcomes of therapeutic and supportive care measures (2). Breast cancer patients have a high prevalence of pain (32), which persists for a long period of time after surgery (14) and produces sleep problems (9). Furthermore, having sleep disturbance reduces pain thresholds (38) and pain increases the risk of having sleep problems (37). Pain and insomnia are part of a psychoneurological cluster symptom that has been identified after surgery and during breast cancer treatment (39). Therefore, pain is an important symptom that must be considered by clinicians in breast cancer treatment for improving insomnia.

In relation to the stage and type of treatment, the results revealed that these variables contributed to the model. The results showed that breast cancer patients who received chemotherapy and radiotherapy treatments had higher levels of insomnia. A longitudinal prospective study found that nearly 50% of breast cancer patients had sleep problems during and some months after radiotherapy treatment (40), although that study did not indicate whether patients had received chemotherapy treatment. Nevertheless, according to previous studies (7,41), linear regression analysis showed that receiving chemotherapy treatment was related with having more insomnia. However, the effect of time of treatment depended on other variables. A study by Savard et al. (41) reported that in the beginning of chemotherapy treatment, breast cancer patients have sleep disturbances and that these disturbances become progressively worse throughout the treatment. This point to psychological, physical, physiological, and behavioral factors such as worry, fatigue or decreased levels of estrogen and cortisol as potential mechanisms. Those findings are in line with our model and the results of the present study. We must consider that the women in our sample were 47.74 ± 0.83 years old, with 71.5% (n = 88) in the postmenopausal phase, which produces hormonal changes related to insomnia in breast cancer patients (42). Further studies are needed to improve knowledge about the influence of treatments on insomnia and its mechanism in breast cancer patients.

This is the first study to include fitness parameters in insomnia related to breast cancer. One of the most important findings was the independent association between insomnia and back strength (r = −0.380; p = 0.01), which was shown by the linear regression analysis. The inverse relationship between insomnia and physical status is well known (11), although most previous studies were focused on cardiorespiratory fitness (43). It has been shown that improvements in muscle strength lead to better sleep quality. Spira et al. (44) reported that a decline in strength in older woman was related to higher sleep distress (total sleep times, wake after sleep and sleep efficiency). However, a recent study during breast cancer chemotherapy showed that higher volumes of both aerobic activity and aerobic activity combined with resistance programs had better improvements than the recommended standard level for some aspect of sleep disturbances (45). Nevertheless, there is little research to explain strength factors related to insomnia in breast cancer patients. A possible relationship may exist between poor fitness and increased insomnia, which could be buffered with the inclusion of exercise as part of the supportive care plan for these patients. Our findings provide evidence that physical exercise programs for cancer patients must include cardiorespiratory and strength exercise. Further research is necessary on the mechanisms of how strength exercise can improve the quality of sleep.

This is the first study to analyse insomnia in breast cancer patients in search of an explanatory model. Our findings showed that anxiety, type of treatment, pain severity, treatment stage, and back muscle strength were predictors of insomnia in our sample of patients. These factors explained 51% of the insomnia observed, supporting its multifactorial nature in which psychological, physical factors related to cancer are mixed. Health specialists who work with breast cancer patients should consider this relationship with improve the treatment support for breast cancer patients.

Our study has some limitations. First, we used a cross-sectional design that studied a cause and effect relationship between the variables associated with insomnia. Our research team is already beginning a better longitudinal study to improve the understanding of insomnia in cancer patients, performing assessments prior to surgery. Second, our sample size was small ($n = 123$), which meant that we were not able to introduce more independent variables in the linear regression analysis to help decrease type II error. Third, we should have examined others factors which could be explained insomnia as mental- cognitive disorders.

The current study develops a comprehensive framework to understand factors that influence insomnia related breast cancer. The results demonstrate the need to use multimodal strategies, which include psychological and physical tools to improve insomnia problems in breast cancer patients. Future studies are needed to analyse the effects of these types of programs in insomnia-related breast cancer during the oncology process.

In summary, 51.2% of the variability in insomnia related breast cancer is explained by anxiety, type of treatment, pain, treatment stage and back muscle strength. Clinicians should take these results into account in order to generate cancer care programs for controlling pain and health related fitness deficits.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ACKNOWLEDGMENTS

The authors have no conflicts of interest to disclose. This work was supported by Health Institute Carlos III and PN I+D+I 2008-2011, Madrid, Spanish Government (FIS PI10/02749-02764), the Andalusian Health Service, Junta de Andalucia (PI-0457-2010).

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Arlington: American Psychiatric Publishing, 2013.
2. Sateia MJ, Doghramji K, Hauri PJ, Morin CM. Evaluation of chronic insomnia. An American Academy of Sleep Medicine review. *Sleep* 2000;23:243–308.
3. Grandner MA, Jackson NJ, Pak VM, Gehrman PR. Sleep disturbance is associated with cardiovascular and metabolic disorders. *J Sleep Res* 2012;21:427–33.
4. Taylor DJ, Lichstein KL, Durrence HH, Reidel BW, Bush AJ. Epidemiology of insomnia, depression, and anxiety. *Sleep* 2005;28:1457–64.
5. Savard J, Ivers H, Villa J, Caplette-Gingras A, Morin CM. Natural course of insomnia comorbid with cancer: an 18-month longitudinal study. *J Clin Oncol* 2011;29:3580–6.
6. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. *J Clin Oncol* 2001;19:895–908.
7. Palesh O, Peppone L, Innominato PF, *et al*. Prevalence, putative mechanisms, and current management of sleep problems during chemotherapy for cancer. *Nat Sci Sleep* 2012;4:151–62.
8. Induru RR, Walsh D. Cancer-related insomnia. *Am J Hosp Palliat Care* 2014;31:777–85.
9. Davis MP, Khoshknabi D, Walsh D, Lagman R, Platt A. Insomnia in patients with advanced cancer. *Am J Hosp Palliat Care* 2014;31:365–73.
10. Bardwell WA, Profant J, Casden DR, *et al*. The relative importance of specific risk factors for insomnia in women treated for early-stage breast cancer. *Psychooncology* 2008;17:9–18.
11. Romito F, Cormio C, De Padova S, *et al*. Patients attitudes towards sleep disturbances during chemotherapy. *Eur J Cancer Care (Engl.)* 2014;23:385–93.
12. Lee AJ, Lin WH. Association between sleep quality and physical fitness in female young adults. *J Sports Med Phys Fitness* 2007;47:462–7.
13. Fernández-Lao C, Cantarero-Villanueva I, Fernández-de-las-Peñas C, *et al*. 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.
14. Belfer I, Schreiber KL, Shaffer JR, *et al*. Persistent postmastectomy pain in breast cancer survivors: analysis of clinical, demographic, and psychosocial factors. *J Pain* 2013;14:1185–95.
15. Hall DL, Mishel MH, Germino BB. Living with cancer-related uncertainty: associations with fatigue, insomnia, and affect in younger breast cancer survivors. *Support Care Cancer* 2014;22:2489–95.

16. Bower JE. Behavioral symptoms in patients with breast cancer and survivors. *J Clin Oncol* 2008;26:768–77.

17. Zawisza K, Tobiasz-Adamczyk B, Nowak W, Kulig J, Jedrys J. Validity and reliability of the quality of life questionnaire (EORTC QLQ C30) and its breast cancer module (EORTC QLQ BR23). *Ginekol Pol* 2010;81:262–7.

18. Staren ED, Gupta D, Braun DP. The prognostic role of quality of life assessment in breast cancer. *Breast J* 2011;17:571–8.

19. Davidson JR, Waisberg JL, Brundage MD, MacLean AW. Nonpharmacologic group treatment of insomnia: a preliminary study with cancer survivors. *Psychooncology* 2001;10:389–97.

20. Netz Y, Ayalon M, Dunsky A, Alexander N. 'The multiple-sit-to-stand' field test for older adults: what does it measure? *Gerontology* 2004;50:121–6.

21. 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.

22. Ljungquist T, Fransson B, Harms-Ringdahl K, Björnham A, Nygren A. A physiotherapy test package for assessing back and neck dysfunction–discriminative ability for patients versus healthy control subjects. *Physiother Res Int* 1999;4:123–40.

23. 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: 941–4.

24. Laskin JJ, Bundy S, Marron H, *et al.* Using a treadmill for the 6-minute walk test: reliability and validity. *J Cardiopulm Rehabil Prev* 2007;27:407–10.

25. Imagama S, Matsuyama Y, Hasegawa Y, *et al.* Back muscle strength and spinal mobility are predictors of quality of life in middle-aged and elderly males. *Eur Spine J* 2011;20:954–61.

26. Gruther W, Wick F, Paul B, *et al.* Diagnostic accuracy and reliability of muscle strength and endurance measurements in patients with chronic low back pain. *J Rehabil Med* 2009;41:613–9.

27. Burton AW, Chai T, Smith LS. Cancer pain assessment. *Curr Opin Support Palliat Care* 2014;8:112–6.

28. Badia X, Muriel C, Gracia A, *et al.* Validation of the Spanish version of the Brief Pain Inventory in patients with oncological pain. *Med Clin (Barc)* 2003;120:52–9.

29. Vodermaier A, Millman RD. Accuracy of the Hospital Anxiety and Depression Scale as a screening tool in cancer patients: a systematic review and meta-analysis. *Support Care Cancer* 2011;19:1899–908.

30. Quintana JM, Padierna A, Esteban C, *et al.* Evaluation of the psychometric characteristics of the Spanish version of the Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 2003;107: 216–21.

31. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 2002;6:97–111.

32. Desai K, Mao JJ, Su I, *et al.* Prevalence and risk factors for insomnia among breast cancer patients on aromatase inhibitors. *Support Care Cancer* 2013;21:43–51.

33. Dettenborn L, James GD, Valdimarsdottir HB, Montgomery GH, Bovbjerg DH. Breast cancer-specific intrusions are associated with increased cortisol responses to daily life stressors in healthy women without personal or family histories of breast cancer. *J Behav Med* 2006;29:477–85.

34. Reiche EM, Nunes SO, Morimoto HK. Stress, depression, the immune system, and cancer. *Lancet Oncol* 2004;5:617–25.

35. 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.

36. Saxton JM, Scott EJ, Daley AJ, *et al.* Effects of an exercise and hypocaloric healthy eating intervention on indices of psychological health status, hypothalamic-pituitary-adrenal axis regulation and immune function after early-stage breast cancer: a randomized controlled trial. *Breast Cancer Res* 2014;16:R39.

37. Smith MT, Haythornthwaite JA. How do sleep disturbance and chronic pain interrelate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. *Sleep Med Rev* 2004;8: 119–32.

38. Tiede W, Magerl W, Baumgartner U, *et al.* Sleep restriction attenuates amplitudes and attentional modulation of pain-related evoked potentials, but augments pain ratings in healthy volunteers. *Pain* 2010;148:36–42.

39. Kim HJ, Barsevick AM, Tulman L, McDermott PA. Treatment-related symptom clusters in breast cancer: a secondary analysis. *J Pain Symptom Manage* 2008;36:468–79.

40. Knobf MT, Sun Y. A longitudinal study of symptoms and self-care activities in women treated with primary radiotherapy for breast cancer. *Cancer Nurs* 2005;28:210–8.

41. Savard J, Liu L, Natarajan L, *et al.* Breast cancer patients have progressively impaired sleep-wake activity rhythms during chemotherapy. *Sleep* 2009;32:1155–60.

42. Regestein QR, Friebely J, Shifren JL, *et al.* Self-reported sleep in postmenopausal women. *Menopause* 2004;11:198–207.

43. Strand LB, Laugsand LE, Wisløff U, *et al.* Insomnia symptoms and cardiorespiratory fitness in healthy individuals: the Nord-Trøndelag Health Study (HUNT). *Sleep* 2013;36:99–108.

44. Spira AP, Covinsky K, Rebok GW, *et al.* Poor sleep quality and functional decline in older women. *J Am Geriatr Soc* 2012;60: 1092–8.

45. Courneya KS, Segal RJ, Mackey JR, *et al.* Effects of exercise dose and type on sleep quality in breast cancer patients receiving chemotherapy: a multicenter randomized trial. *Breast Cancer Res Treat* 2014;144:361–9.

CAPÍTULO 3

THE SIX-MINUTE WALK TEST AS A MEASURE OF HEALTH IN BREAST CANCER PATIENTS

Artículo III

El test de la caminata de 6 minutos como medida de salud en supervivientes de cáncer de mama

Galiano-Castillo N, Arroyo-Morales M, **Ariza-García A,** Sánchez-Salado C, Fernández-Lao C, Cantarero-Villanueva I, Martín-Martín L.

J Aging Phys Act. 2016 Oct;24(4):508-515.

Journal Citation Reports

FI: 1.837 (33/81) Q2 (Sport Sciences)

Journal of Aging and Physical Activity, 2016, 24, 508-515
http://dx.doi.org/10.1123/japa.2015-0056

Human Kinetics
ORIGINAL RESEARCH

The Six-Minute Walk Test as a Measure of Health in Breast Cancer Patients

Noelia Galiano-Castillo, Manuel Arroyo-Morales, Angélica Ariza-Garcia, Carmen Sánchez-Salado, Carolina Fernández-Lao, Irene Cantarero-Villanueva, and Lydia Martín-Martín

This study examined the relationship between the 6-min walk test (6MWT) and fitness, psychological and physiologic states, quality of life, cancer-related symptoms, and body composition of 87 women with breast cancer. The assessment included the 6MWT and evaluations of Cancer Quality of Life (EORTC C-30 and EORTC BR-23), cognitive performance (Trail Making Test), the Hospital Anxiety and Depression Scale, body composition, health-related fitness (abdominal test, multiple sit-to-stand test, trunk dynamometry), and pain (Brief Pain Inventory). We observed the following correlations: moderate between 6MWT and pain interference; modest for cognitive and social functioning and the multiple sit-to-stand test; fair for several items on the Cancer Quality of Life, for anxiety, lean body mass, trunk dynamometry and pain intensity; and weak for role functioning, loss of appetite, cognitive performance and depression. Thus, the 6MWT could be used as a measure of the major components of global health in women with breast cancer.

Keywords: breast cancer, cardiopulmonary, functional capacity, quality of life.

Breast cancer is the most commonly diagnosed cancer among women and affects more than 1.2 million women per year worldwide (Eyigor et al., 2010). The survival rates are high, but many adverse side effects are associated with breast cancer and its treatment, including pain (Fernández-Lao et al., 2011), psychological distress, changes in sexual function (Quintard et al., 2014), negative body image (Barsotti Santos, Ford, Dos Santos, & Vieira, 2014), deficits in upper extremity function, decreased flexibility and strength (Cheema, Gaul, Lane, & Fiatarone Singh, 2008), and impaired cardiopulmonary function (Klassen et al., 2014). When these side effects are not adequately considered, the life expectancy of this group is reduced (Schmitz et al., 2010).

Exercise can effectively improve the functional capacity, fatigue level, depression, cardiorespiratory function, body composition, and overall quality of life in breast cancer survivors (BCS). For this reason, exercise is considered a fundamental component of recovery in patients with this disease (Battaglini et al., 2014). Clinical guidelines recommend 150 min of moderate-intensity aerobic exercise (Schmitz et al., 2010; NCCN Clinical Practice Guidelines in Oncology: Survivorship, 2014) to reverse the negative side effects in this population. Some of the negative and persistent effects of the cancer history include fatigue, pain, pulmonary changes, neurological changes, and effects on multiple body systems (musculoskeletal, cardiovascular, endocrine, nervous, and immune), which are relevant to exercise training (Schmitz et al., 2010). However, the majority of survivors do not achieve these recommendations because of individual limitations. Therefore, exercise recommendations should be individualized to accommodate the patient's capabilities (Bourke et al., 2014).

An adequate test of functional capacity to evaluate the physical abilities of BCS could facilitate the development of exercise programs that accommodate the patient. Previous research (Dolan, Lane, & McKenzie, 2012) has established that better functional performance is achieved in BCS when a graded treadmill protocol is used rather than a cycle ergometer. Furthermore, performing an incremental maximum workload test until exhaustion is feasible in this population and does not result in adverse events.

Cardiopulmonary exercise testing (CPET), usually performed on a cycle ergometer, is the gold standard for estimating the cardiopulmonary fitness of breast cancer patients; a graded treadmill protocol was also established in the aforementioned study.

This method yields the peak oxygen uptake (VO_{2peak}) as a maximal performance measure for determining the overall cardiovascular and respiratory function during exercise (Klassen et al., 2014). However, many BCS do not have access to the sophisticated equipment required to perform this test. Therefore, a simple walking test has been used broadly to test cardiopulmonary function in these individuals (Battaglini et al., 2014) and has shown adequate reliability.

The 6-min walk test (6MWT) has been increasingly used in clinical practice and research studies as an objective measure of functional status in patients with moderate-to-severe impairments, such as obesity (Beriault et al., 2009), Alzheimer's disease (Ries, Echternach, Nof, & Gagnon Blodgett, 2009), fibromyalgia (Carbonell-Baeza et al., 2013), or cardiopulmonary diseases (Rasekaba et al., 2009). In addition, the 6MWT may be useful for assessing a patient's response to medical interventions, prognosis, or functional status (Salzman, 2009). Because the 6MWT is a feasible, quickly performed, and inexpensive tool for measuring cardiorespiratory fitness, it has previously been used and shown to have good correlates with other aspects of the health in BCS (Cantarero-Villanueva et al., 2012). It is postulated that the 6MWT could closely approximate a

Galiano-Castillo, Arroyo-Morales, Ariza-Garcia, Fernández-Lao, and Cantarero-Villanueva are with the Physical Therapy Department, Instituto Investigación Biosanitaria (IBIS Granada), Universidad de Granada, Granada, Spain. Ariza-Garcia is also with University Hospital San Cecilio, Health Andalusian Service, Granada, Spain. Sánchez-Salado is with the Breast Oncology Unit, Hospital Virgen de las Nieves, Granada, Spain. Martín-Martín is with the Department of Physical Therapy, University of Granada, Granada, Spain. Address author correspondence to Lydia Martín-Martín at lydia@ugr.es.

person's capacity to perform the activities of daily living (Guazzi, Dickstein, Vicenzi, & Arena, 2009), but it is not currently known how well the 6MWT correlates with clinical data, anthropometric measurements, treatment, sexual functioning, physical measurement, and pain in women with breast cancer.

The patient's functional capacity (which can be measured using the 6MWT) and its influence on a patient's overall health are required for prescribing and achieving an adequate exercise program in terms of type, duration, intensity, and frequency. Thus, the aim of this study was to examine the relationship between the 6MWT and a patient's fitness, psychological and physiologic states, quality of life, cancer-related symptoms, and body composition.

Methods

Participants

Participants were selected from the Breast Oncology Unit of the University Hospital Virgen de las Nieves (Granada, Spain). The inclusion criteria included women between the ages of 18 and 75 years who had just received their initial therapy. The exclusion criteria included the following: (a) women receiving chemotherapy or radiation for cancer at the same moment the study was conducted and (b) those who had a physical limitation that prevented participation. Participants were contacted by phone by two nurses in the Breast Oncology Unit (University Hospital Virgen de las Nieves). The participants gave their informed consent to be included in the study after being informed about the study's aims and procedures. The ethics committee of the University Hospital Virgen de las Nieves (Spain) approved this study. Demographic and clinical data were recorded, and medical records were obtained.

A total of 87 women with a breast cancer (age: 48.33 ± 8.45) diagnosis of stage I, II, or IIIA were included in this cross-sectional study. Most women in the study had stage I (36.8%) or stage II (42.5%) breast cancer and had previously received an estrogen receptor antagonist (tamoxifen) (43.7%), aromatase inhibitors (29.9%), fulvestrant (3.4%), or other hormonal treatments (3.4%). A total of 19.5% of the women had not previously received any hormonal treatment. In total, 90.8% patients received radiotherapy and chemotherapy between six months and two years before the study started, 4.6% received only radiotherapy, and 4.6% received only chemotherapy. A total of 11.5% of the women had lymphedema in their affected limb.

Measurements

Functional Capacity. The 6MWT using a treadmill is a valid and reliable test (Laskin et al., 2007) which determines the maximum distance (meters) that a person can walk in 6 min. All participants were familiarized with the treadmill exercise protocol. They were instructed to set their own pace, to "walk as far as you can in 6 minutes", and to volitionally increase or decrease the speed of the treadmill. During the task standardized phrases of encouragement were given.

Psychological Measures

Quality of Life. Quality of life was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) version 3.0, a widely used tool for measuring quality of life in cancer patients (Aaronson et al., 1993). This instrument is composed of multi- and single-item measures, including functional scale (five items), symptom scale (three items), global health status scale (one item), and six single-item scales. The average of the items that contributed to the scale was estimated (raw score). Then, the raw score was subjected to linear transformation to standardize the scores in the range of 0–100. A higher score indicates a greater response level (Fayers et al., 2001).

Breast Module. We obtained data about perceived body image, sexual functioning, sex enjoyment, arm symptoms, breast symptoms, and systemic therapy side effects through the European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality questionnaire (EORTC QLQ-BR23). This test has previously been shown to have adequate reliability (Cronbach's alpha ranged between .46 and .94) (Sprangers et al., 1996).

Cognitive Function. The Trail Making Test (TMT) was employed to provide information on speed for attention, sequencing, mental flexibility, visual search, and motor function (Spreen & Strauss, 1998). After a practical example, the participant must complete two parts: to draw lines connecting consecutive numbers distributed on a sheet of paper (1–25) as fast as possible (part A) and to draw consecutive lines between numbers and letters (i.e., 1-A-2-B-3-C) (part B) without lifting the pen or pencil from the paper. Mistakes were corrected during the test and recorded even though the patient was allowed to correct them. The length of time required to finish each part was scored in seconds (the time to correct errors was included in the completion time). An average of 78 s or more to complete Trail A and 273 s or more to complete Trail B indicated deficient performance.

Anxiety and Depression. We used the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983; Herrero et al., 2003), a self-reporting tool for assessing the presence of anxiety and depression. This four-point Likert scale contains seven items for each subscale (14 items altogether) and ranges from 0 to 3. Given a global score from 0 to 21, the cut-off point for considering an anxiety and depression condition is 11 or above for both.

Body Composition

Fat Percentage and Lean Body Mass. Height was measured, and the bioelectrical impedance analysis (InBody 720; Biospace, Seoul, South Korea) was used to measure weight, body mass index, skeletal muscle mass, and body fat percentage.

Physical Measures

Abdominal Test. Muscle isometric strength was assessed with the patient lying on her back with her knees flexed and her heels approximately 0.30 m from her buttocks. The participant's arms were then lifted with guided palms to level the knees, with the inferior angle of the scapula being barely lifted from the ground. We recorded the number of seconds for which this position was maintained (McQuade, Turner, & Buchner, 1988).

Lower Body Endurance. General endurance was assessed using the multiple sit-to-stand test (Netz, Ayalon, Dunsky, & Alexander), which has previously been shown to be a reliable test (Ritchie, Trost, Brown, & Armit, 2005). Participants moved from a sitting position to a standing position until they reached full knee extension and sat back down. This process was repeated 10 times as fast as possible, and the time it took the participant to complete this process was measured in seconds.

Trunk Dynamometry. We measured back muscle strength using an analogic dynamometer (TKK 5002 Back-A; Takey, Tokyo, Japan) that was precise to 1 kg. Patients maintained a standing posture with a 30° lumbar flexion for as long as possible (Imagama et al., 2011). This test was repeated three times for each participant, and the mean from all three measurements was obtained.

Pain Measures

Brief Pain Inventory. Pain was measured using the Brief Pain Inventory (BPI) short form (Cleeland & Ryan, 1994; Badia et al., 2003). This test measures the severity of pain ('worst', 'least', 'average', and 'now'), the interference of pain on daily function (from 0: no interference to 10: complete interference), the location of the pain (body diagrams: front and back), pain medications, and the amount of pain relief in the past week or the past 24 hr. The pain severity and pain interference were averaged.

Statistical Analysis

A descriptive analysis of the studied variables was conducted using the medians, standard deviations, and percentiles. Partial correlation analysis after adjusting for age was used to assess the relationship between the 6MWT and the previously mentioned variables. A correlation of 0–0.25 indicated an absence or weak relationship, a correlation of 0.25–0.50 indicated a modest to fair relationship, a correlation of 0.50–0.75 indicated a moderate to good relationship, and a correlation greater than 0.75 indicated a very good relationship (Colton, 1974). A one-way analysis of variance (ANOVA) was used to determine the differences in mean estimates of the 6MWT across cancer stage, type of surgery, medical treatment and the presence of lymphedema. The Statistical Package for the Social Sciences (SPSS v. 20.0 for Windows; Chicago, IL, USA) was used to perform the statistical analyses, with significance set at 5%.

Results

The estimated mean 6MWT distance was not influenced by different clinical parameters: cancer stage ($F = 0.571$, $p = .381$), type of surgery ($F = 1.519$; $p = .678$), lymphedema ($F = 0.761$; $p = .419$), hormone therapy ($F = 1.574$; $p = .371$), or type of adjuvant therapy ($F = 0.420$; $p = .645$) (Table 1).

The relationship between the 6MWT and items on the EORTC QLQ-C30 was fair for overall health, physical functioning, and fatigue ($\rho = 0.393$; $\rho = 0.427$; and $\rho = -0.407$, respectively; all $p \leq .001$); emotional functioning and pain ($\rho = 0.350$ and $\rho = -0.349$, respectively; both $p = .001$); and dyspnea ($\rho = -0.336$, $p = .002$). The relationship was modest for cognitive ($\rho = 0.269$, $p = .014$) and social functioning ($\rho = 0.253$, $p = .021$) and weak for role functioning ($\rho = 0.238$, $p = .030$) and loss of appetite ($\rho = -0.220$, $p = .046$) (Table 2). The 6MWT had a weak relationship with the Trail Making test parts A ($\rho = -0.247$, $p = .024$) and B ($\rho = -0.238$, $p = .030$), as well as with HADS depression ($\rho = -0.227$, $p = .039$). The relationship between HADS anxiety and 6MWT was fair ($\rho = -0.381$, $p \leq .001$) (Table 3).

Considering body composition, we found a fair relationship between the 6MWT and lean body mass ($\rho = 0.340$, $p = .002$). Physical measures showed that the 6MWT had a modest relationship with the multiple sit-to-stand test ($\rho = -0.283$, $p = .010$), while it had a fair relationship with trunk dynamometry ($\rho = 0.434$, $p \leq .001$). The relationship between the 6MWT and the BPI was fair for pain intensity ($\rho = -0.418$, $p \leq .001$) and moderate for pain interference ($\rho = -0.518$, $p \leq .001$) (Table 3).

Table 1 Table of Means for Comparison of 6-Min Walk Test Across Clinical Parameters

	Mean (*SD*)
Cancer stage	
I	267.35 (205.29)
II	280.76 (149.51)
IIIA	355.08 (183.18)
IV	191.73 (118.17)
Type of surgery	
Lumpectomy	335.02 (199.89)
Quadrantectomy	220.46 (138.84)
Unilateral mastectomy	309.37 (169.09)
Bilateral mastectomy	241.90 (141.33)
Lymphedema	
Yes	277.04 (178.67)
No	347.56 (157.76)
Hormone therapy	
None	298.63 (260.65)
Tamoxifen	300.85 (147.80)
Aromatase inhibitors	268.06 (164.22)
Fulvestrant	281.00 (73.41)
Other	254.00 (255.36)
Type of adjuvant therapy	
Radiotherapy	399.15 (189.48)
Chemotherapy	250.30 (144.65)
Radiotherapy and	284.63 (179.26)
Chemotherapy	288.32 (178.26)

The unadjusted correlation analysis showed similar results.

Tables 4 and 5 display the medians and lower and upper quartiles of the study variables in women with breast cancer.

Discussion

Our study conducted on women with breast cancer exhibits significant relationships, ranging from weak to moderate, between the 6MWT and quality of life, cancer-related symptoms, cognitive performance, body composition, health-related fitness, and pain. Preliminary results suggest that the distance walked in 6 min is correlated with different aspects of health in breast cancer survivors. Thus, this test may be included as an acute clinical assessment and for prescribing exercise training for breast cancer survivors.

Our sample of BCS showed a low functional capacity in the 6MWT, with a reduction of close to 40% compared with 60-year-old healthy women (Bohannon, 2007). This reduction in functional capacity is combined with a low strength and endurance level, which indicates a clear deconditioned state of this sample of participants. Our BCS showed a low to moderate level of quality of life with respect to depression and pain. High anxiety was a principal concern in this population.

The strongest association between the 6MWT was found to be pain interference in this study. This finding suggests that patients who can walk longer distances suffer from less interference from

Table 2 Relationship of 6-Min Walk Test Distance with Quality of Life in Women with Breast Cancer

Outcomes	n	ρ	*P*
EORTC QLQ BR23			
Body image	87	0.466	.692
Sexual functioning	87	–0.486	.677
Sexual enjoyment	48	–0.466	.692
Future perspective	87	–0.429	.717
Systemic therapy side effects	87	–0.591	.598
Breast symptoms	87	–0.872	.325
Arm symptoms	87	–0.429	.717
Upset by hair loss	7	0.928	.243
EORTC QLQ-C30			
Global health status	87	0.393	< .001*
Physical functioning	87	0.427	< .001*
Role functioning	87	0.238	.030*
Emotional functioning	87	0.350	.001*
Cognitive functioning	87	0.269	.014*
Social functioning	87	0.253	.021*
Fatigue	87	–0.407	< .001*
Nausea and vomiting	87	–0.064	.566
Pain	87	–0.349	.001*
Dyspnoea	87	–0.336	.002*
Insomnia	87	–0.210	.056
Appetite loss	87	–0.220	.046*
Constipation	87	–0.112	.315
Diarrhea	87	–0.206	.061
Financial difficulties	87	–0.166	.134

Abbreviations: EORTC QLQ BR23 = European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality questionnaire; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

* $P < .05$.

pain. Cancer patients suffer from consistent pain and breakthrough pain, both of which are associated with decreased functional performance (Coleman et al., 2011). Our sample of BCS suffered from a moderate level of pain associated with different body location, including neck-shoulder syndrome after treatment, arthralgia induced by hormone therapy or other possible etiologies. It is important to consider that pain can have a nonphysiological origin and a direct negative influence on physical functioning. Namely, an increase in pain or fear of increased pain during a test performance can cause the patient to stop or to perform submaximally, resulting in a worse test score. Furthermore, according to the pain adaptation model, there may be a direct negative physiological influence on test performance from decreased agonist activity and increased antagonist activity. In addition, pain can have a physiological origin with additional negative effects (Huijnen, Verbunt, Wittink, & Smeets, 2013). It is plausible that BCS reduce their daily physical activity in an attempt to avoid pain, which directly influences physical performance. This reduction in activity could reinforce an increase in pain, as postulated by Vlaeyen and Linton's fear-avoidance model (Vlaeyen & Linton, 2000). Avoidance of activities can physically

Table 3 Relationship of 6-Min Walk Time Distance with Cognitive Performance, Psychological State, Body Composition, Physical Measurements, and Pain in Women with Breast Cancer

Outcomes	n	ρ	*P*
Cognitive performance			
Trial Making Test A (seconds)	87	–0.247	.024*
Trial Making Test B (seconds)	86	–0.238	.030*
Ratio Trial Making (B-A) (seconds)	86	–0.045	.680
HADS anxiety	87	–0.381	< .001*
HADS depression	87	–0.227	.039*
Body composition			
Fat percentage	87	–0.213	.053
Lean body mass percentage	87	0.340	.002*
Physical measurement			
Abdominal muscle strength (seconds)	85	0.161	.146
Multiple sit-to-stand test (seconds)	87	–0.283	.010
Trunk dynamometry (kg)	87	0.434	< .001*
Brief Pain Inventory			
Intensity	87	–0.418	< .001*
Interference	87	–0.518	< .001*

Abbreviations: HADS = Hospital Anxiety and Depression Scale.

* $P < .05$, significant level.

decondition patients, resulting in lower aerobic capacity and muscle strength (Huijnen et al., 2013).

The 6MWT was correlated with the multiple sit-to-stand test and trunk dynamometry, which makes sense considering these physical measures are related to the patient's functional status. There was a stronger association with trunk dynamometry. This finding suggests that patients who can walk longer distances have better trunk strength. Other authors have established a significant correlation between back muscle strength and physical functioning, as measured with the SF-36 test. These authors showed that sagittal balance requires good thoracic range of motion (ROM), lumbar ROM, and back muscle strength. Namely, back muscle strength deterioration with spinal ROM disorders can result in a gait disorder, abnormal posture, and a high risk of falling (Imagama et al., 2011). Consistent with this, deterioration of back muscle strength is one of the most important factors that decreases spinal ROM, which affects the patient's quality of life (QOL) (Miyakoshi et al., 2007). According to this statement, a worse performance on the 6MWT may be due to abnormalities in gait or posture that arise from diminished back muscle strength. Likewise, the influence of back muscle strength on the spinal ROM increases the likelihood of such abnormalities and worsens a patient's QOL. Trunk strength has both a direct influence on QOL (e.g., through its effects on spinal ROM), and a significant impact on QOL by itself (Imagama et al., 2011).

We observed a fair association between the 6MWT and lean body mass and trunk dynamometry as well as a modest association between the 6MWT and the multiple sit-to-stand test in this study. These findings suggest that patients who can walk longer distances have a higher lean body mass and better health-related fitness. These findings agree with those of other studies. Specifically, Pires, Oliveira, Parreira, and Brito (2007) demonstrated that better body

Table 4 6-Min Walk Test and Quality of Life Data of the Study Sample

Outcomes	n	Median	Percentile 25th	Percentile 75th
6-min distance walked	87	288.31	138.80	404.80
EORTC QLQ BR23				
Body image	87	63.31	33.33	91.66
Sexual functioning	87	21.45	0	33.33
Sexual enjoyment	48	43.75	33.33	66.66
Future perspective	87	38.31	0	66.66
Systemic therapy side effects	87	33.11	19.04	47.61
Breast symptoms	87	30.07	8.33	50.00
Arm symptoms	87	27.71	11.11	44.44
Upset by hair loss	7	38.09	0	66.66
EORTC QLQ-C30				
Global health status	87	56.70	41.66	66.66
Physical functioning	87	75.70	66.66	86.66
Role functioning	87	70.11	66.66	100.00
Emotional functioning	87	63.31	41.66	83.33
Cognitive functioning	87	63.02	50.00	83.33
Social functioning	87	63.60	33.33	83.33
Fatigue	87	44.44	33.33	66.66
Nausea and vomiting	87	6.51	0	0
Pain	87	40.80	16.66	66.66
Dyspnea	87	19.15	0	33.33
Insomnia	87	49.42	33.33	66.66
Appetite loss	87	13.41	0	33.33
Constipation	87	23.37	0	33.33
Diarrhea	87	7.66	0	0
Financial difficulties	87	27.20	0	33.33

Abbreviations: EORTC QLQ BR23 = European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality questionnaire; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

composition is associated with better performance on the 6MWT. They found a significant difference in the distance walked between individuals with a BMI of more than 35 kg/m^2 and below 25 kg/m^2 when comparing elderly subjects and young people (Pires et al., 2007). In fact, several authors have established that, following breast cancer treatment, most women experience significant body weight increases (McDonald, Bauer, Capra, & Coll, 2014), which has been found to be strongly associated with lower levels of physical activity (Dewey et al., 2007). Cantarero-Villanueva et al. (2012) also found a relationship between handgrip strength and several physical fitness parameters such as the 6MWT. Nevertheless, the limitations of the bioimpedance method for body composition assessment in patients exhibiting dehydration, water retention, or acute body mass changes (i.e., obesity or protein malnutrition) must be considered (Savegnago Mialich, Faccioli Sicchieri, & Jordao, 2014). Breast cancer survivors often undergo body mass changes and experience dehydration or lymphedema; thus, more accurate methods such as x-ray densitometry should be considered after weighing the benefit of utilizing additional radiation on a population previously exposed to radiotherapy.

A fair association was also noted between 6MWT and quality of life and their related components such as side effects from treatment (fatigue, pain or dyspnea) and emotional state. Some common side effects in cancer patients (such as fatigue, reduced functional capacity, pain, anxiety, or depression) have been found to be associated with physical and psychological conditions, as well as diminishing patient quality of life (Vardar Yağlı et al., 2015). Specifically, fatigue is related to decreased muscle strength and impaired cardiorespiratory function in cancer patients (Dimeo et al., 2004). In this regard, studies investigating the effects of aerobic exercise training and yoga in breast cancer patients have found that patients improve their functional capacity, according to the 6MWT (Campbell, Mutrie, White, McGuire, & Kearney, 2005), with decreased levels of fatigue, dyspnea, and leg fatigue (Vardar Yağlı et al., 2015). We suggest that better performance in the 6MWT decreases the side effects of cancer treatment due to the delayed onset of muscle fatigue as a result of improved aerobic capacity and the optimization of aerobic pathways as an energy source—adaptations broadly observed in response to exercise training (Rodrigues-Krause, Krause, & Reischak-Oliveira, 2015; Gillen et al., 2014).

Regarding cognitive functioning, it is known that cancer therapy may be related to cognitive impairment in specific cognitive domains (Mandilaras et al., 2013), better known as "chemobrain" (Hede, 2008). Meanwhile, anxiety and depression affect up to 50% of breast cancer patients (Burgess et al., 2005). Both cognitive changes and anxiety and depression symptoms have effects on the quality of life of BCS (Myers, 2012). In this respect, according to other studies, people with lower cognitive impairment are able to walk farther and thus have better scores on this assessment (Enright et al., 2003). Forte et al. (2013) also found that physical fitness parameters and their interaction with cognitive factors predict maximal walking speed; namely, executive functions moderate the physical fitness effects. The authors claim that high levels of cognitive flexibility seem necessary to take advantage of leg power for walking at maximal speed, which might be connected to better performance in the 6MWT (Forte et al., 2013).

The 6MWT has been previously used for the planning, assessment, treatment, and monitoring of women with fibromyalgia (Carbonell-Baeza et al., 2013). These authors performed a similar study in fibromyalgia patients and demonstrated significant relationships between the 6MWT and pain score, physical impairment, physical function, and bodily pain, among others. Similarly, this test has been widely used in breast cancer research, focusing on changes after exercise intervention (Eyigor et al., 2010; Milecki et al., 2013) and as an indicator of functional capacity in patients with breast cancer (Mustian, Katula, & Zhao, 2006), but not as a physiological parameter in terms of submaximal exercise. Our results suggest that the 6MWT could be a useful tool for assessing the functional capacity in BCS as it is related to different components of global health in this population.

Some limitations of our study must be considered. Because we used a cross-sectional design, causality could not be established. Further intervention studies are needed to establish the potential effect of an increase in the functional capacity of breast cancer patients on their overall health status. In addition, the patients were not familiar with the 6MWT, and other studies have shown a positive effect of learning this test (Wu, Sanderson, & Bittner, 2003). Because strength tests require time and instrumentation, walking is more clinically feasible and represents the most natural form of

Table 5 Cognitive Performance, Psychological Status, Body Composition, Physical Measurements, and Pain Data of the Study Sample

Outcomes	n	Median	Percentile	
			25th	75th
Trial Making Test A (seconds)	87	32.79	22.80	37.14
Trial Making Test B (seconds)	86	104.78	63.46	142.14
Ratio B-A (seconds)	86	3.37	2.44	4.03
HADS anxiety	87	9.37	6.00	13.00
HADS depression	87	5.1	2.00	8.00
Body composition				
Fat percentage	87	36.15	29.20	44.20
Lean body mass percentage	87	23.38	21.60	25.20
Physical measurement				
Abdominal muscle strength (seconds)	85	31.09	10.48	38.55
Multiple sit-to-stand test (seconds)	87	27.11	22.60	29.42
Trunk dynamometry (kg)	87	34.38	23.00	43.00
Brief Pain Inventory				
Intensity	87	3.67	2.25	5.00
Interference	87	3.94	1.43	6.00

Abbreviations: HADS = Hospital Anxiety and Depression Scale.

human locomotion (Morris & Hardman, 1997). A recent systematic review concluded that this method possessed excellent measurement properties, was better tolerated, and was more reflective of the activities of daily living compared with any other walking test used (Solway et al., 2001).

In conclusion, the 6MWT appears to be a useful tool for exercise program planning, assessment, treatment, and monitoring of BCS because it exhibits clear relationships with psychological and physiological state, quality of life, cancer-related symptoms, and body composition. The 6MWT protocol may serve as a reference to prescribe exercise training for BCS, as well as for acute assessments in clinical practice. Furthermore, the strong correlation between the 6MWT and pain variables as well as back muscle strength suggest that such variables should be considered for BCS exercise programs in long-term intervention studies.

References

Aaronson, N.K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N.J., . . . Takeda, F. (1993). The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute, 85,* 365–376. PubMed doi:10.1093/jnci/85.5.365

Badia, X., Muriel, C., Gracia, A., Núñez-Olarte, J.M., Perulero, N., Gálvez, R., . . . Cleeland, C.S. (2003). Validación española del cuestionario Brief Pain Inventory en pacientes con dolor de causa neoplásica. *Medicina Clínica, 120,* 52–59. PubMed doi:10.1016/S0025-7753(03)73601-X

Barsotti Santos, D., Ford, N.J., Dos Santos, M.A., & Vieira, E.M. (2014). Breast cancer and sexuality: the impacts of breast cancer treatment on the sex lives of women in Brazil. *Culture, Health & Sexuality,* Epub ahead of print. PubMed doi:10.1080/13691058.2013.867075

Battaglini, C.L., Mills, R.C., Phillips, B.L., Lee, J.T., Story, C.E., Nascimento, M.G., & Hackney, A.C. (2014). Twenty-five years of research on the effects of exercise training in breast cancer survivors: A systematic review of the literature. *World Journal of Clinical Oncology, 5*(2), 177–190. PubMed doi:10.5306/wjco.v5.i2.177

Beriault, K., Carpentier, A.C., Gagnon, C., Ménard, J., Baillargeon, J.P., Ardilouze, J.L., & Langlois, M.F. (2009). Reproducibility of the 6-minute walk test in obese adults. *International Journal of Sports Medicine, 30,* 725–727. PubMed doi:10.1055/s-0029-1231043

Bohannon, R.W. (2007). Six-minute walk test: a meta-analysis of data from apparently healthy elders. *Topics in Geriatric Rehabilitation, 23*(3):155–160

Bourke, L., Homer, K.E., Thaha, M.A., Steed, L., Rosario, D.J., Robb, K.A., . . . Taylor, S.J. (2014). Interventions to improve exercise behaviour in sedentary people living with and beyond cancer: a systematic review. *British Journal of Cancer, 110*(4), 831–841. PubMed doi:10.1038/bjc.2013.750

Burgess, C., Cornelius, V., Love, S., Graham, J., Richards, M., & Ramirez, A. (2005). Depression and anxiety in women with early breast cancer: five year observational cohort study. *BMJ (Clinical Research Ed.), 330,* 702. PubMed doi:10.1136/bmj.38343.670868.D3

Campbell, A., Mutrie, N., White, F., McGuire, F., Kearney, N. (2005). A pilot study of a supervised group exercise programme as a rehabilitation treatment for women with breast cancer receiving adjuvant treatment. *European Journal of Oncology Nursing, 9*(1), 56–63. PubMed doi:10.1016/j.ejon.2004.03.007

Cantarero-Villanueva, I., Fernández-Lao, C., Díaz-Rodríguez, L., Fernández-de-Las-Peñas, C., Ruiz, J.R., & Arroyo-Morales, M. (2012). The handgrip strength test as a measure of function in breast cancer survivors: relationship to cancer-related symptoms and physical and physiologic parameters. *American Journal of Physical Medicine & Rehabilitation, 91,* 774–782. PubMed doi:10.1097/PHM.0b013e31825f1538

Carbonell-Baeza, A., Ruiz JR, Aparicio VA, Ortega FB, Delgado-Fernández M. (2013). The 6-minute walk test in female fibromyalgia patients: relationship with tenderness, symptomatology, quality of life, and coping strategies. *Pain Management Nursing, 14,* 193–199. PubMed doi:10.1016/j.pmn.2011.01.002

Cheema, B., Gaul, C.A., Lane, K., Fiatarone Singh, M.A. (2008). Progressive resistance training in breast cancer: a systematic review of clinical trials. *Breast Cancer Research and Treatment, 109,* 9–26. PubMed doi:10.1007/s10549-007-9638-0

Cleeland, C.S., & Ryan, K.M. (1994). Pain assessment: global use of the Brief Pain Inventory. *Annals of the Academy of Medicine, Singapore, 23,* 129–138. PubMed

Coleman, E.A., Goodwin, J.A., Coon, S.K., Richards, K., Enderlin, C., Kennedy, R., . . . Barlogie, B. (2011). Fatigue, sleep, pain, mood, and performance status in patients with multiple myeloma. *Cancer Nursing, 34*(3), 219–227. PubMed doi:10.1097/NCC.0b013e3181f9904d

Colton, T. (1974). *Statistics in Medicine*. Boston: Little, Brown.

Dewey, A., Baughan, C., Dean, T., Higgins, B., & Johnson, I. (2007). Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. *Cochrane Database of Systematic Reviews, 24*(1), CD004597. PubMed

Dimeo, F.C., Thomas, F., Raabe-Menssen, C., Pröpper, F., & Mathias, M. (2004). Effect of aerobic exercise and relaxation training on fatigue and physical performance of cancer patients after surgery. A randomised controlled trial. *Supportive Care in Cancer, 12*(11), 774–779. PubMed doi:10.1007/s00520-004-0676-4

Dolan, L.B., Lane, K., & McKenzie, D.C. (2012). Optimal mode for maximal aerobic exercise testing in breast cancer survivors. *Integrative Cancer Therapies, 11*(4), 321–326. PubMed doi:10.1177/1534735411433202

Enright, P.L., McBurnie, M.A., Bittner, V., Tracy, R.P., McNamara, R., Arnold, A., & Newman, A.B. (2003). The 6-min walk test: a quick measure of functional status in elderly adults. *Chest, 123,* 387–398. PubMed doi:10.1378/chest.123.2.387

Eyigor, S., Karapolat, H., Yesil, H., Uslu, R., & Durmaz, B. (2010). Effects of pilates exercises on functional capacity, flexibility, fatigue, depression and quality of life in female breast cancer patients: a randomized controlled study. *European Journal of Physical and Rehabilitation Medicine, 46,* 481–487. PubMed

Fayers, P.M., Aaronson, N.K., Bjordal, K., Groenvold, M., Curran, D., & Bottomley, A. (2001). *The EORTC QLQ-C30 Scoring Manual* (3rd ed.). Brussels: European Organisation for Research and Treatment of Cancer.

Fernández-Lao, C., Cantarero-Villanueva, I., Fernández-de-las-Peñas, C., Del-Moral-Ávila, R., Menjón-Beltrán, S., & Arroyo-Morales, M. (2011). Widespread mechanical pain hypersensitivity as a sign of central sensitization after breast cancer surgery: comparison between mastectomy and lumpectomy. *Pain Medicine, 12,* 72–78. PubMed doi:10.1111/j.1526-4637.2010.01027.x

Forte, R., Pesce, C., Leite, J.C., De Vito, G., Gibney, E.R., Tomporowski, P.D., & Boreham, C.A. (2013). Executive function moderates the role of muscular fitness in determining functional mobility in older adults. *Aging Clinical and Experimental Research, 25*(3), 291–298. PubMed doi:10.1007/s40520-013-0044-7

Gillen, J.B., Percival, M., Skelly, L., Martin, B., Tan, R., Tarnopolsky, M.A., & Gibala, M.J. (2014). Three minutes of all-out intermittent exercise per week increases skeletal muscle oxidative capacity and improves cardiometabolic health. *PLoS One,* 9(11):e111489. PubMed doi:10.1371/journal.pone.0111489

Guazzi, M., Dickstein, K., Vicenzi, M., & Arena, R. (2009). Six-minute walk test and cardiopulmonary exercise testing in patients with chronic heart failure: a comparative analysis on clinical and prognostic insights. *Circulation: Heart Failure, 2,* 549–555. PubMed

Hede, K. (2008). Chemobrain is real but may need a new name. *Journal of the National Cancer Institute, 100,* 162–163. PubMed doi:10.1093/jnci/djn007

Herrero, M.J., Blanch, J., Peri, J.M., De Pablo, J., Pintor, L., & Bulbena, A. (2003). A validation study of the hospital anxiety and depression scale (HADS) in a Spanish population. *General Hospital Psychiatry, 25,* 277–283. PubMed doi:10.1016/S0163-8343(03)00043-4

Huijnen, I.P.J., Verbunt, J.A., Wittink, H.M., & Smeets, R.J.E.M. (2013). Physical performance measurement in chronic low back pain: measuring physical capacity or pain-related behaviour? *European Journal of Physics, 3,* 103–110.

Imagama, S., Matsuyama, Y., Hasegawa, Y., Sakai, Y., Ito, Z., Ishiguro, N., & Hamajima, N. (2011). Back muscle strength and spinal mobility are predictors of quality of life in middle-aged and elderly males. *European Spine Journal, 20,* 954–961. PubMed doi:10.1007/s00586-010-1606-4

Klassen, O., Schmidt, M.E., Scharhag-Rosenberger, F., Sorkin, M., Ulrich, C.M., Schneeweiss, A., . . . Wiskemann, J. (2014). Cardiorespiratory fitness in breast cancer patients undergoing adjuvant therapy. *Acta Oncologica (Stockholm, Sweden), 53,* 1356–1365. PubMed

Laskin, J.J., Bundy, S., Marron, H., Moore, H., Swanson, M., Blair, M., & Humphrey, R. (2007). Using a treadmill for the 6-minute walk test: reliability and validity. *Journal of Cardiopulmonary Rehabilitation and Prevention, 27,* 407–410. PubMed doi:10.1097/01.HCR.0000300270.45881.d0

Mandilaras, V., Wan-Chow-Wah, D., Monette, J., Gaba, F., Monette, M., & Alfonso, L. (2013). The impact of cancer therapy on cognition in the elderly. *Frontiers in Pharmacology, 4,* 48. PubMed doi:10.3389/fphar.2013.00048

McDonald, C., Bauer, J., Capra, S., & Coll, .J (2014). The muscle mass, omega-3, diet, exercise and lifestyle (MODEL) study - a randomised controlled trial for women who have completed breast cancer treatment. *BMC Cancer 16*(14):264.

McQuade, K.J., Turner, J.A., & Buchner, D.M. (1988). Physical fitness and chronic low back pain. An analysis of the relationships among fitness, functional limitations, and depression. *Clinical Orthopaedics and Related Research,* 233, 198–204. PubMed

Milecki, P., Hojan, K., Ozga-Majchrzak, O., & Molińska-Glura, M. (2013). Exercise tolerance in breast cancer patients during radiotherapy after aerobic training. *Contemporary Oncology (Poznan, Poland), 17,* 205–209. PubMed

Miyakoshi, N., Hongo, M., Maekawa, S., Ishikawa, Y., Shimada, Y., & Itoi, E. (2007). Back extensor strength and lumbar spinal mobility are predictors of quality of life in patients with postmenopausal osteoporosis. *Osteoporosis International, 18,* 1397–1403. PubMed doi:10.1007/s00198-007-0383-3

Morris, J.N., & Hardman, A.E. (1997). Walking to health. *Sports Medicine (Auckland, N.Z.), 23,* 306–332. PubMed doi:10.2165/00007256-199723050-00004

Mustian, K.M., Katula, J.A., & Zhao, H. (2006). A pilot study to assess the influence of tai chi chuan on functional capacity among breast cancer survivors. *The Journal of Supportive Oncology, 4,* 139–145. PubMed

Myers, J.S. (2012). Chemotherapy-related cognitive impairment: the breast cancer experience. *Oncology Nursing Forum, 39,* E31–E40. PubMed doi:10.1188/12.ONF.E31-E40

NCCN Clinical Practice Guidelines in Oncology. Survivorship. https://subscriptions.nccn.org/gl_login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf. Accesed 26 May 2014

Netz, Y., Ayalon, M., Dunsky, A., & Alexander, N. (2004). The multiple-sit-to-stand' field test for older adults: What does it measure? *Gerontology, 50,* 121–126. PubMed doi:10.1159/000076769

Pires, S.R., Oliveira, A.C., Parreira, V.F., & Brito, R.R. (2007). Teste de caminhada de seis minutos em diferentes faixas etárias e índices de massa corporal. *Rev Bras Fisioter, 11,* 147–151. doi:10.1590/S1413-35552007000200010

Quintard, B., Constant, A., Lakdja, F., & Labeyrie-Lagardère, H. (2014). Factors predicting sexual functioning in patients 3 months after surgical procedures for breast cancer: the role of the Sense of Coherence. *European Journal of Oncology Nursing, 18,* 41–45. PubMed doi:10.1016/j.ejon.2013.09.008

Rasekaba, T., Lee, A.L., Naughton, M.T., Williams, T.J., & Holland, A.E. (2009). The six-minute walk test: a useful metric for the cardiopulmonary patient. *Internal Medicine Journal, 39,* 495–501. PubMed doi:10.1111/j.1445-5994.2008.01880.x

Rodrigues-Krause, J., Krause, M., & Reischak-Oliveira, Á. (2015). Cardiorespiratory considerations in dance: from classes to performances. *Journal of Dance Medicine & Science : Official Publication of the International Association for Dance Medicine & Science, 19*(3), 91–102. PubMed doi:10.12678/1089-313X.19.3.91

Ries, J.D., Echternach, J.L., Nof, L., & Gagnon Blodgett, M. (2009). Test-retest reliability and minimal detectable change scores for the timed "up & go" test, the six-minute walk test, and gait speed in people with Alzheimer disease. *Physical Therapy, 89,* 569–579. PubMed doi:10.2522/ptj.20080258

Ritchie, C., Trost, S.G., Brown, W., & Armit, C. (2005). Reliability and validity of physical fitness field tests for adults aged 55 to 70 years. *Journal of Science and Medicine in Sport, 8,* 61–70. PubMed doi:10.1016/S1440-2440(05)80025-8

Salzman, S.H. (2009). The 6-min walk test: clinical and research role, technique, coding, and reimbursement. *Chest, 135,* 1345–1352. PubMed doi:10.1378/chest.07-1682

Savegnago Mialich, M., Faccioli Sicchieri, J.M., & Jordao, A.A., Junior. (2014). Analysis of Body Composition: A Critical Review of the Use of Bioelectrical Impedance Analysis. *Int J Clin Nutr, 2*(1), 1–10.

Schmitz, K.H., Courneya, K.S., Matthews, C., Demark-Wahnefried, W., Galvao, D.A., Pinto, B.M., . . . American College of Sports Medicine. (2010). American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Medicine & Science in Sports and Exercise, 42*:1409–1426

Solway, S., Brooks, D., Lacasse, Y., & Thomas, S. (2001). A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. Chest, *119,* 256–270. PubMed doi:10.1378/chest.119.1.256

Sprangers, M.A., Groenvold, M., Arraras, J.I., Franklin, J., te Velde, A., Muller, M., . . . 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. PubMed

Spreen, O., & Strauss, E. (1998). *A compendium of neuropsychological tests: administration, norms, and commentary* (2nd ed.). New York: Oxford University Press.

Vardar Yağlı, N., Şener, G., Arıkan, H., Sağlam, M., İnal İnce, D., Savcı, S., . . . Özışık, Y. (2015). Do yoga and aerobic exercise training have impact on functional capacity, fatigue, peripheral muscle strength, and quality of life in breast cancer survivors? Integrative Cancer Therapies, *14*(2), 125–132. PubMed doi:10.1177/1534735414565699

Vlaeyen, J.W., & Linton, S.J. (2000). Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain, *85,* 317–332. PubMed doi:10.1016/S0304-3959(99)00242-0

Wu, G., Sanderson, B., & Bittner, V. (2003). The 6-minute walk test: How important is the learning effect? American Heart Journal, *146,* 129–133. PubMed doi:10.1016/S0002-8703(03)00119-4

Zigmond, A.S., & Snaith, R.P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica, 67,* 361–370. PubMed doi:10.1111/j.1600-0447.1983.tb09716.x

CONCLUSIONES

1. Las SCM activas muestran menos alteraciones del estado de ánimo, presión diastólica y alfa amilasa salivar que el grupo de mujeres inactivas. Esta mejora del estado psicofisiológico está relacionada con un mejor nivel de condición física en el grupo de SCM activas respecto a las inactivas **(Artículo I)**.

2. La ansiedad, la fase y el tipo de tratamiento, la severidad del dolor y la fuerza de tronco, son predictores del insomnio en mujeres con CM, y en conjunto explican el 51,2 % del insomnio de nuestra muestra. Las diferentes formas en que padecen las mujeres el insomnio relacionado con el CM es explicado por la ansiedad, el tipo de tratamiento, el dolor, la fase de tratamiento y la fuerza de tronco. Estos resultados deben tenerse en cuenta por los clínicos a la hora de llevar a cabo programas de tratamiento para controlar el dolor y la condición física relacionada con la salud **(Artículo II)**.

3. El test de la caminata de 6 minutos es una herramienta eficaz que permite monitorizar y posteriormente adaptar el programa de entrenamiento físico en mujeres con CM, ya que existe una clara relación entre éste y el estado psicofisiológico, la calidad de vida, los síntomas relacionados con el cáncer, y la composición corporal. Además, la distancia recorrida mostró una fuerte correlación con el dolor y la fuerza de tronco, indicando que dichas variables deben considerarse en los programas de ejercicio de los estudios de intervención a largo plazo **(Articulo III)**.

CONCLUSIÓN GLOBAL

El CM y los tratamientos aplicados, causan importantes efectos secundarios tanto físicos como psicofisiológicos en las pacientes que lo padecen, disminuyendo su calidad de vida. Mantener un adecuado nivel de actividad física es fundamental en la recuperación de estas pacientes, ya que permite disminuir o revertir dichos efectos secundarios.

El conocimiento de la interrelación del insomnio y del nivel de actividad física de estas pacientes con parámetros fisiológicos, dolor, alteraciones del estado de ánimo, cambios en la composición corporal, fuerza, o fase y tipo de tratamiento, permitirá una planificación más efectiva de los programas de tratamiento. Además, la evaluación de la capacidad funcional de estas pacientes mediante el test de la caminata de 6 minutos, posibilitará el diseño de programas de ejercicio adaptados de forma individual a las pacientes con CM, lo que a su vez mejorará la calidad de vida de las mismas.