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ESTRATEGIA INTEGRAL DE SOPORTE PARA SUPERVIVIENTES DE CÁNCER DE MAMA: TERAPIA OCUPACIONAL Y MHEALTH. ESTUDIO BENECA

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Integral approach for breast cáncer survivors: Occupational therapy and m-Health. The BENECA study

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A mi yaya y yayo

To my grandmother and grandfather

"Aprendí que el coraje no era la ausencia de miedo, sino el triunfo sobre él. El valiente no es quien no siente miedo, sino aquel que conquista ese miedo."

"I learned that courage was not the absence of fear, but the triumph over it. The brave man is not he who does not feel afraid, but he who conquers that fear.

Nelson Mandela

(1918-2013) Johannesburgo"

TABLA DE CONTENIDO

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RESUMEN

La tasa de supervivencia del cáncer de mama se ha incrementado de forma exponencial durante los últimos años, principalmente debido a los avances en la detección precoz y en los tratamientos médicos y quirúrgicos habituales. De esta manera, el cáncer de mama ha pasado a considerarse una enfermedad crónica. Sin embargo, este aumento de la supervivencia ha conllevado un correspondiente incremento de los años de vida ajustados por discapacidad, principalmente debido a los efectos secundarios a largo plazo que suelen experimentar estas mujeres, principales afectadas de esta patología. Además, un elevado número de supervivientes de cáncer de mama no se adhieren a las recomendaciones internacionales de estilos de vida saludables, siendo el desequilibrio energético un factor de riesgo para la aparición de recidivas, segundos cánceres e incluso mortalidad por cáncer. La denominada *salud a distancia* o *telesalud* son un conjunto de herramientas que se han postulado como medidas complementarias y costo-efectivas dentro del soporte oncológico. Sin embargo, muchas son las limitaciones que se plantean en la literatura científica acerca de su validación, adherencia y eficacia. Por otro lado, la rehabilitación oncológica puede paliar estas secuelas mencionadas anteriormente, sin embargo, la evidencia científica es bastante limitada acerca de los beneficios de determinadas disciplinas como la terapia ocupacional. Por lo tanto, los objetivos de la presente Tesis Doctoral Internacional fueron i) proporcionar una nueva herramienta de monitorización del balance energético mediante una aplicación móvil de salud en mujeres supervivientes de cáncer de mama, comprobando su fiabilidad y factibilidad (**sección 1**) y ii) desarrollar e implementar un programa de rehabilitación presencial de terapia ocupacional para mujeres supervivientes de cáncer de mama, así como comprobar su eficacia junto con la herramienta de salud móvil propuesta (**sección 2**). Para ello, hemos desarrollado la aplicación móvil de salud BENECA (Balance ENErgético en CÁncer), comprobando que su fiabilidad en términos de dieta y actividad física en comparación con el *gold estándar* (**estudio I**). Además, hemos comprobado que se trata de una herramienta factible en términos de adherencia, usabilidad y satisfacción, y hemos valorado su efecto en la calidad de vida de estas mujeres (**estudio II**). Al mismo tiempo, hemos explorado la hipótesis de la asociación entre el uso de nuestra herramienta de salud móvil y posibles cambios biológicos en términos de inflamación sistémica (**estudio III**). Por otro lado, se desarrolló un programa de rehabilitación oncológica presencial de terapia ocupacional para mujeres supervivientes de cáncer de mama que, junto con la aplicación móvil, formaron parte de nuestro programa integral de soporte para estas mujeres (**estudio IV**). Por último, estudiamos la eficacia de dicho programa en la mejora de la calidad de vida y variables funcionales en mujeres

supervivientes de cáncer de mama (**estudio V**).

Los resultados de esta Tesis Doctoral Internacional aportan evidencia científica que apoya el uso de una nueva herramienta móvil de monitorización del balance energético en cáncer, válida y fiable. Se muestra también una posible asociación entre su uso y la reducción determinados marcadores de inflamación sistémica, presentando algunas variables predictoras de dicho cambio. Por último, estos resultados mejoran nuestro conocimiento sobre las diferentes formas de abordar las secuelas de las mujeres supervivientes de cáncer de mama, planteando la necesidad de incluir la terapia ocupacional como parte del equipo multidisciplinar de rehabilitación oncológica.

ABSTRACT

The survival rate of breast cancer has increased exponentially in recent years, mainly due to advances in early detection and usual medical and surgical treatments. In this way, breast cancer has been considered a chronic disease. However, this increase in survival has led to a corresponding increase in disability-adjusted life years, mainly due to the long-term side effects these women usually experience. Oncological rehabilitation can alleviate these consequences; however, scientific evidence is quite limited in certain disciplines such as occupational therapy. In addition, a high number of breast cancer survivors do not adhere to the international recommendations of healthy lifestyles, with energy imbalance being a risk factor for recurrence, second cancers and even cancer mortality. The so-called *distance health* or *telehealth* is a set of tools that have been postulated as complementary and cost-effective measures within the cancer support. However, there are many limitations that arise in the scientific literature about its validation, adherence and efficacy. Therefore, the objectives of this International Doctoral Thesis were i) to provide a new tool for monitoring the energy balance through a mobile health application in breast cancer survivors, verifying its reliability and feasibility (**section 1**) and ii) develop and implement a face-to-face rehabilitation program of occupational therapy for breast cancer survivors, as well as verify its effectiveness together with the proposed mobile health tool (**section 2**). For this, we have developed the mobile health application BENECA (ENERGY Balance in Cancer), checking that it is reliable in terms of diet and physical activity compared to the *gold standard* (**study I**). In addition, we have verified that it is a feasible tool in terms of adherence, usability and satisfaction, and we have assessed its effect on the quality of life of these women (**study II**). At the same time, we have explored the hypothesis of the association between the use of our mobile health tool and possible biological changes in terms of systemic inflammation (**study III**). On the other hand, a face-to-face occupational therapy oncology rehabilitation program for breast cancer survivors was developed and, together with the mobile application, was part of our integral support strategy for these women (**study IV**). Finally, we studied the effectiveness of this program in improving the quality of life and functional variables in women survivors of breast cancer (**study V**).

The results of this International Doctoral Thesis provide scientific evidence that supports the use of a new mobile tool for monitoring energy balance in cancer, valid and reliable. It also shows a possible association between its use and the reduction of certain markers of systemic inflammation, presenting some predictive variables of this change. Finally, these results improve our knowledge about the different ways to address the sequelae of breast cancer survivors, raising the need to

include occupational therapy as part of the multidisciplinary team of cancer rehabilitation.

Abreviaturas

AICR: American Institute of Cancer Research

ASCO: American Society of Clinical Oncology

ASE: American Society of Echocardiography

AVAD: Años de Vida Ajustados por Discapacidad

BENECA: Balance ENErgético en Cáncer

EACI: European Association of Cardiovascular Imagen

IL-1: Interleucina 1

IL-6: Interleucina 6

mHealth: mobile Health

PCR: Proteína C Reactiva

SCM: Supervivientes de Cáncer de Mama

TIC: Tecnologías de la Información y la Comunicación

WCRF: World Cancer Research Fund

INTRODUCCIÓN GENERAL
GENERAL INTRODUCTION

INTRODUCCIÓN GENERAL

Cáncer, también denominado *tumor maligno* o *neoplasia maligna*, es un término genérico que hace referencia a un amplio grupo de enfermedades que pueden llegar a afectar a cualquier parte del organismo. Se trata de la segunda causa principal de muerte a nivel mundial[1]. La incidencia mundial de cáncer aumentó hasta los 18.1 millones de casos nuevos en 2018, con 9.6 millones de muertes en dicho año. La Organización Mundial de la Salud (OMS) concluye que uno de cada cinco hombres y una de cada seis mujeres en todo el mundo desarrollarán cáncer a lo largo de su ciclo vital. De la misma manera, uno de cada ocho hombres y una de cada 11 mujeres mueren a causa de esta enfermedad. La prevalencia a los cinco años a nivel mundial, es decir, el número total de personas que siguen vivas a los cinco años tras el diagnóstico de cáncer se estima en 43.8 millones[2].

Son muchos los factores atribuibles a la creciente incidencia del cáncer, incluido el crecimiento de la población o el envejecimiento, pero estas cifras se han visto incrementadas en los últimos años debido, además, a otros factores vinculados al desarrollo social y económico, incluida la dieta, la nutrición y la actividad física[3]. De hecho, por ejemplo, Europa representa el 23.4% de los casos mundiales de cáncer, y el 20.3% de las muertes por cáncer, aunque solo constituye el 9% de la población mundial[2]. A tenor de estos datos, se hace necesario reflexionar sobre cómo los estilos de vida directamente relacionados con el índice de desarrollo humano pueden influir directamente en el crecimiento del cáncer; con el objetivo de poder adoptar y favorecer patrones de dieta y actividad física que puedan reducir la carga del cáncer en el futuro.

El proceso oncológico no solo afecta de una forma orgánica o sistémica, sino que la repercusión del cáncer y de su tratamiento médico y quirúrgico habitual en el desempeño ocupacional diario de las personas que lo padecen, puede afectar a todas las esferas de la vida cotidiana de los seres humanos, desde un punto de vista biopsicosocial[4, 5]. El rápido avance en los métodos de detección precoz y diagnóstico, así como el tratamiento oncológico, han favorecido que lo que antes se consideraba una enfermedad aguda, hoy en día, en muchas de sus variantes, se puede llegar a considerar como una enfermedad crónica, debido a las altas tasas de supervivencia[6]. Cuando se habla de superviviencia en cáncer, se hace referencia al *tiempo de vida libre de enfemerdad tras terminar el tratamiento oncológico*[7], aunque si bien es cierto que el término es muy discutido[8]. Los supervivientes de cáncer experimentan una importante morbilidad física, psicológica e incluso social que hace que minimizar su grado de discapacidad sea una prioridad en las políticas de salud. Requieren, por tanto, una atención continuada que esté coordinada y centrada en la prevención y vigilancia, mientras se minimizan y manejan los efectos a largo plazo del tratamiento y otras comorbilidades[9].

Situación actual del cáncer de mama

El cáncer de mama es el cáncer más común entre las mujeres a nivel mundial, uno de cada cuatro de todos los nuevos casos de cáncer diagnosticados en mujeres es cáncer de mama. En 2018, aproximadamente 2.1 millones de nuevos casos fueron diagnosticados, lo que consitituye el 11.6% del total de la incidencia de cáncer. De hecho, incluso haciendo una diferenciación geográfica entre países, el perfil de los cánceres diagnosticados con mayor frecuencia en las mujeres está marcado por su naturaleza dicotómica, con el cáncer de mama como el más frecuente en términos de nuevos casos en la mayoría de países, siendo el cáncer de cuello de útero el más frecuente entre las mujeres en los países restantes[2]. Sin embargo, las tasas de incidencia de cáncer de mama presentan una marcada tendencia geográfica de evolución en las últimas décadas: han aumentado en la mayoría de los países en transición, y algunos de los aumentos más rápidos se produjeron en países donde las tasas habían sido históricamente relativamente bajas, como países de América del Sur, África y Asia[10]. Estas tendencias objetivas son probablemente un reflejo de una combinación de factores demográficos asociados al desarrollo social y económico, como el aumento en la detección y concienciación, factores relacionados con la menstruación (edad temprana en la menarquia o avanzada en la menopausia), la reproducción (nuliparidad, edad tardía del primer nacimiento), la ingesta de hormonas exógenas, o los mayores niveles de obesidad e inactividad física[11].

El cáncer de mama es también la principal causa de muerte por cáncer en las mujeres (15%), seguido del cáncer de pulmón (13.8%) y cáncer colorrectal (9.5%)[2]. A pesar de esto, las tasas de mortalidad han ido disminuyendo desde la década de 1970[12], debido principalmente a las mejoras en el *screening* y en el tratamiento adyuvante[13, 14]. Como pone de manifiesto un artículo de 2019, el tratamiento oncológico es más efectivo cuanto más temprana es la detección. En este estudio, con mujeres de entre 40 y 69 años, se demostró que aquellas que participaban en mamografías organizadas tuvieron una reducción del riesgo de morir del 60% durante los 10 años posteriores al diagnóstico, y del 47% durante los 20 años posteriores al diagnóstico, en comparación con las mujeres que no participaron en la detección[15]. En este sentido, en la actualidad, el cáncer de mama presenta una tasa de supervivencia a los 5 años superior al 90%, situándose únicamente por detrás del cáncer de próstata (99%), tiroides (98%) y melanoma (93%)[16].

Centrándonos en España, el número de nuevos casos de cáncer de mama en 2018 en la mujer fue del 32,825, lo que supone un 28.7% del total de casos de cáncer, siendo el más incidente[2]. De la misma manera que a nivel mundial, la tasa de supervivencia a los 5 años del cáncer de mama en la mujer fue del 85.2%, siendo el que mejor pronóstico presenta al año tras el

diagnóstico con un 95% de supervivencia[17]. Terminando de delimitar esta patología en el contexto demográfico que concierne a esta Tesis, cabe destacar los datos publicados a nivel provincial, en Granada. Los datos del último estudio publicado en 2018 sobre un registro de cáncer de base poblacional en Granada muestran una tendencia creciente en la incidencia del cáncer de mama entre 1985 y 2012, situando la tasa de incidencia en 83.4 casos x 100,000 mujeres en 2012. Esta misma tendencia creciente es observable en la tasa de supervivencia a los 5 años, aunque se sitúa ligeramente por debajo de la media nacional, con un 83.7%, llegando a alcanzar una tasa de supervivencia a los 5 años del 96.6% en las mujeres diagnosticadas en estadio I.

En definitiva, la incidencia del cáncer de mama está aumentando: un vivo reflejo de la evolución y propagación de los factores de riesgo y el aumento de la presión diagnóstica de los últimos años. Afortunadamente, los datos también muestran un aumento equiparable de la tasa de supervivencia, de la mano de un incremento considerable de los años de vida ajustados por discapacidad (AVAD)[18]. Los AVAD secundarios a la supervivencia del cáncer están asociados con un coste sociosanitario muy elevado[19], así como con la pérdida de productividad, derivada de la temprana edad del diagnóstico, y los efectos secundarios a largo plazo (comorbilidades, trastornos emocionales y riesgos de recaida), relacionados con el propio cáncer o con el tratamiento recibido[8]. Todo esto plantea nuevas necesidades de abordaje tras la cronificación de esta patología, que abracen todas las esferas del quehacer diario de estas mujeres, con el objetivo de disminuir la morbimortalidad, mejorar las secuelas biopsicosociales y, en definitiva, su calidad de vida.

Equilibrio Energético y Cáncer. Una tarea pendiente

El exceso de grasa corporal, que caracteriza principalmente el sobrepeso y la obesidad, se considera en la actualidad uno de los principales problemas de salud pública. 1,970 millones de adultos viven con sobrepeso u obesidad en el siglo XXI, y según las estimaciones parece que la tendencia va en aumento[20, 21]. Esta creciente prevalencia de sobrepeso y obesidad tiene implicaciones económicas globales, tanto directas (como el coste sociosanitario generado), como indirectas (fruto del aumento del absentismo laboral)[22]. Además, todo parece indicar que tanto el inicio del sobrepeso como el de la obesidad se están produciendo cada vez en edades más tempranas, lo que aumenta la exposición de por vida a todos los riesgos derivados[23].

El mantenimiento del peso corporal en la edad adulta depende de la estrecha relación a largo plazo entre el gasto de energía (en términos de funciones básicas de nuestro organismo y la actividad física) y la ingesta de energía (mediante alimentos y bebidas). Es lo que se denomina equilibrio energético[24].

Además de diversos factores que influyen en el mantenimiento del equilibrio energético (como la genética, epigenénica, microbiota intestinal, o los factores psicosociales, políticos y del entorno), éste es el resultado de una interacción compleja entre los sistemas neurofisiológicos y gastrointestinales que influyen en la regulación de la ingesta de alimentos[24]. El nivel de actividad física, principal determinante modificable del gasto energético, influye directamente en el apetito, que a su vez promueve una mayor ingesta de alimentos y señales endógenas, como respuesta a la cantidad y características de los alimentos y bebidas consumidas. Como respuesta a la composición de éstos, numerosas hormonas son secretadas por el tracto gastrointestinal para estimular o inhibir el sistema central del apetito en el cerebro. Esta secreción de hormonas también está mediada por la actividad física, es decir, un aumento del gasto energético conduce a un aumento, en proporción, del apetito. Dado que las señales que promueven el hambre (como consecuencia de una reducción de la ingesta o un aumento del gasto) son más potentes que las que la suprimen (como consecuencia de una reducción del gasto de energía o un consumo excesivo de la misma), ante un reducido gasto energético, la regulación afectiva del apetito se ve comprometida aumentando la probabilidad de un consumo energético excesivo, principio que puede verse influenciado por la exposición a factores que tienden a promover el consumo excesivo, como alimentos y bebidas de mayor densidad energética. Por otro lado, el sistema central del apetito también está directamente influido por el aprendizaje, la memoria y la hedónica de alimentos, que a su vez están fuertemente modulados por el entorno y las experiencias, pudiendo estimular o inhibir el deseo de comer. Finalmente, la composición corporal influye en el gasto energético total (modificando el gasto energético en reposo) y la ingesta energética (modificando la demanda de energía y el impulso de comer)[25, 26]. Por lo tanto, se alcanza el equilibrio energético cuando la ingesta de energía coincide con la demanda de energía, y parece ser el resultado de una compleja interacción entre diversos factores endógenos y exógenos, de los cuales algunos son modificables.

El desequilibrio energético positivo ocurre cuando la ingesta de energía excede el gasto energético. En nuestra sociedad actual, también con un marcado carácter demográfico, el aumento del consumo de alimentos ricos en calorías, por la facilidad de acceso a comida de alta densidad calórica y baja calidad, junto con la reducción del gasto energético como consecuencia de la baja actividad física y/o al estilo de vida sedentario, provocan un desequilibrio energético positivo. Éste se manifiesta como un aumento de peso, y está implicado en el desarrollo y la progresión de varios tipos de cáncer más prevalentes en la actualidad: el cáncer de colon, el cáncer de mama, de esófago, renal, de hígado o pancreático, así como algunos linfomas[27]. Además, investigaciones

recientes han identificado una asociación entre la obesidad y el peor pronóstico en algunos pacientes con cáncer, particularmente aquellos con cáncer de mama, próstata, hígado y colon. Se cree que el exceso de peso corporal contribuye a una de cada cinco muertes relacionadas con el cáncer. De hecho, el exceso de peso se ha asociado con una mayor mortalidad por todos los cánceres combinados y por cánceres de varios sitios específicos. Un panel de expertos del *American Institute of Cancer Research* (AIRC) y del *World Cancer Research Fund* (WCRF) ha estimado que una reducción del consumo energético podría prevenir hasta el 40% de los casos de cáncer a nivel mundial[28]. Los riesgos relativos de los metaanálisis o de los análisis agrupados alcanzaron entre el 1.2 y 1.5 para el sobrepeso y entre 1.5 y 1.8 para la obesidad con respecto al cáncer de colon[29, 30], vesícula biliar[31], riñón[32], cardias gástrico[33], hígado[34] y páncreas[35], llegando a alcanzar el 4.8 para el adenocarcinoma esofágico[36].

En cuanto al cáncer de mama, la asociación positiva entre el cáncer de mama posmenopáusico y el exceso de peso corporal se ha demostrado en numerosos estudios, con un riesgo relativo de 1.1 especialmente en tumores de receptores de estrógeno positivo[29, 37]. La grasa corporal afecta directamente a los niveles de varias hormonas circundantes, como la insulina y los estrógenos, lo que crea un ambiente favorecedor de la carcinogénesis y la supresión de la apoptosis. En estas mujeres en las que la producción de estrógenos ha disminuido drásticamente, la conversión de andrógenos dentro del tejido adiposo se convierte en la principal fuente de estrógenos. Como consecuencia, las mujeres con sobrepeso u obesidad van a tener niveles circulantes de estrógenos más elevados, lo que está ampliamente asociado con el desarrollo de cáncer de mama. Por otro lado, la elevación de los niveles de insulina circulante se ha relacionado con el aumento de riesgo de cáncer de mama. En este sentido, el sobrepeso y la obesidad también se han asociado con hiperinsulinemia y resistencia a la insulina, por lo que se puede generar un círculo vicioso de riesgo de cáncer de mama.

La actividad física, entendida como gasto energético, constituye, como se ha visto con anterioridad, el otro eslabón para tener en cuenta en el equilibrio energético. Existe evidencia que respalda una asociación inversa entre la actividad física y la incidencia y mortalidad por cáncer. El mecanismo fisiológico que explica el efecto inhibitorio de la actividad física en el proceso cancerígeno incluye la reducción de las reservas de grasa, los cambios relacionados con la actividad en los niveles de hormonas sexuales, el efecto sobre la insulina y los factores de crecimiento similares a la insulina, la función inmune alterada, la generación reducida de radicales libres y el efecto directo sobre el tumor[38-40]. Un estudio realizado por Moore *et al.* en 2016 en 1.44 millones de adultos asoció la práctica de actividad física en tiempo libre con un menor riesgo de al menos 13 tipos diferentes de cáncer[41]. De la misma manera, estudios epidemiológicos

proporcionan evidencia de una reducción dependiente de la práctica de ejercicio físico en el riesgo de recurrencia del cáncer de mama, colon y cáncer de próstata[42-44].

Obesidad y sedentarismo también se han asociado con la denominada inflamación crónica de bajo grado. Se entiende por inflamación crónica de bajo grado a aquella inflamación constante y de bajo nivel que se produce en todo el cuerpo, según se juzga por un pequeño aumento en los marcadores del sistema inmunitario que se encuentran en la sangre o en los tejidos[45]. La obesidad promueve que el tejido adiposo secrete citoquinas y adipocinas proinflamatorias, que pueden promover el desarrollo de cáncer de mama. En concreto, está caracterizada por una elevación en los niveles circulantes de proteínas de fase aguda y citoquinas con actividad inflamatoria, como la proteína C reactiva (PCR) y las interleucinas 1 y 6 (IL-1, IL-6, respectivamente)[46]. Asimismo, se ha demostrado que la inflamación crónica de bajo grado produce, como se ha comentado, niveles altos de factores inflamatorios y células inmunes infiltradas, pero al mismo tiempo, no se exhiben alteraciones estructurales o pérdida de funciones primarias[47]. De la misma manera, la actividad física está vinculada a la protección contra el cáncer a través de reducciones en los factores de riesgo de cáncer dependientes del ejercicio, como las hormonas sexuales, la insulina y los marcadores inflamatorios[48].

Existe una relación bidireccional entre la inflamación crónica de bajo grado y el cáncer de mama ya que, por un lado, el tumor produce un ambiente inflamatorio y, por ende, una respuesta inmune sistémica, pero a su vez, la inflamación crónica también puede preceder y promover el desarrollo del cáncer[45, 49]. Hahan y Weinberg identificaron seis señales distintivas de esta enfermedad amplicamente reconocidas por la comunidad científica[50], y se habla de que la inflamación crónica de bajo grado se puede considerar como la séptima característica habilitadora del cáncer en general y del cáncer de mama en particular[51]. Los niveles circulantes de PCR, IL-1 e IL-6, así como el factor de necrosis tumoral son biomarcadores de inflamación sistémica ampliamente utilizados. Se ha demostrado que la presencia simultánea de niveles elevados de PCR e interleucinas se asocia con un mayor riesgo de cáncer colorrectal, pulmón y de mama, en una población de 84,000 sujetos con un periodo de seguimiento de 5 años[49].

En definitiva, parece existir una sólida evidencia sobre el carácter determinante del equilibrio energético, en términos de dieta y actividad física, en el riesgo de recidiva, segundos cánceres y mortalidad por cáncer, así como su relación con diversos parámetros sistémicos favorecedores o protectores de la inflamación. De igual modo, son numerosos los estudios que apoyan la eficacia y seguridad del ejercicio físico en esta población, así como la dieta saludable para mejorar la calidad de vida y reducir los efectos secundarios del tratamiento del

cáncer[52-56]. Sin embargo, los supervivientes de cáncer, y en concreto, las supervivientes de cáncer de mama (SCM) manifiestan la existencia de dificultades para adherise y mantener un adecuado estilo de vida y, por lo tanto, conseguir el equilibrio energético, especialmente debido a las limitaciones físicas asociadas a los efectos secundarios del tratamiento oncológico[57]. El conocimiento parece disponible, pero existe una clara debilidad a la hora de conseguir un calado social para una solución que aparenta ser sencilla: comer menos y moverse más[58]. A pesar de la aparente simplicidad del mensaje, una investigación reciente señala como, incluso conociendo los beneficios de las intervenciones dirigidas a promover el equilibrio energético entre los supervivientes de cáncer, es poco realista esperar que la mayoría de ellos, con un marcado hábito sedentario, se ajusten a las guías actuales de buenas prácticas relacionadas con el ejercicio y la nutrición en esta población[59].

Por otro lado, existen factores no achacables a los pacientes, que hacen referencia a las lagunas existentes a nivel asistencial y en la práctica clínica, en el manejo de diferentes tipos de cáncer, con respecto a la prescripción de programas basados en el ejercicio y la nutrición saludable[52]. Las razones potenciales para esta debilidad incluyen, entre otras, la impresión entre los clínicos de que el ejercicio puede incrementar el riesgo de lesión, fatiga y exacerbación de los síntomas; escasez de recursos en los programas clínicos, restricciones de espacios físicos y, sobre todo, la falta de clínicos con una formación y experiencia adecuada en relación a ejercicio y rehabilitación oncológica[58]. La principal salida a esta falta de adherencia terapéutica parece pasar por promover la prescripción indivudal de recomendaciones sobre equilibrio energético, basadas en el perfil específico del paciente[60]. Esta necesidad de promover intervenciones individualizadas exige una aproximación urgente desde la investigación que pueda ajustarse a las necesidades de los pacientes de una manera costo-efectiva.

Sin lugar a duda, un reto estimulante en la investigación de nuestros días es entender los principios de relación entre el desequilibrio energético y la génesis del cáncer, pero sin duda otro no menos relevante es conseguir hacer llegar al principal afectado, el paciente, todo el conocimiento desarrollado para reducir el impacto en la calidad de vida de esta enfermedad.

Estilos de vida saludables a través de las nuevas tecnologías: *mHealth.*

El cambio demográfico, la creciente incidencia de enfermedades crónicas y las necesidades insatisfechas de una atención más personalizada son tendencias que exigen un nuevo enfoque integral de la atención sanitaria y social. Durante la última década del siglo XX, y el inicio de este nuevo siglo XXI, las denominadas *Tecnologías de la Información y la*

Comunicación (TIC) han visto un crecimiento exponencial en todo el mundo, impulsado principalmente por el incesante avance tecnológico, la inversión económica y los cambios sociales y culturales que han facilitado la integración de las TIC en nuestra vida cotidiana[61, 62]. En el sector de la salud, las TIC se han convertido en una piedra angular de servicios eficientes y efectivos, principalmente debido a Internet, brindando una nueva oportunidad para lograr la integración de la atención. Internet está cambiando drásticamente la forma en que los consumidores interactúan con los servicios de salud, tanto en el acceso a la información, como en la capacidad de adquisición de productos o servicios[63].

No existe una definición que esté globalmente aceptada sobre el término *telemedicina* (en inglés, *telehealth*). Tomando su significado literal, se podría definir como «salud (atención) a distancia», por lo que puede representar una atención de cualquier ámbito de las ciencias de la salud en tiempo real o de forma asincrónica. De hecho, el término *telemedicina* ha sufrido una gran evolución a lo largo de su corta historia: desde su forma original se ha convertido sucesivamente en *telesalud*, *salud en línea*, *salud conectada*… Un esquema de *telesalud* bien diseñado puede mejorar el acceso a la atención sanitaria y la obtención de resultados, particularmente para el tratamiento de enfermedades crónicas y para grupos vulnerables. No solo reducen la demanda de instalaciones con personal, sino que favorecen el ahorro de costes y hacen que el sector de la salud sea más resistente[64]. El envejecimiento de la población, el desajuste geográfico o la cronificación de las patologías proporcionan una indudable justificación para la implementación y expansión de los servicios de telesalud, especialmente en oncología[65].

De entre los diferentes sistemas de telesalud disponibles, la salud móvil o *mHealth* se ha postulado como una herramienta crítica para la atención sanitaria y, en concreto, para oncología, desde la prevención[66] hasta los cuidados paliativos[67]. La tecnología *mHealth*, a menudo vinculada a aplicaciones móviles en teléfonos inteligentes, incluye una gran gama de recursos que pueden brindar a los pacientes compromiso, apoyo, monitorización y entrenamiento continuo[65]. Además, presenta muchas ventajas sobre los diferentes sistemas de *telesalud* disponibles, entre las que destacan la posibilidad de recibir un feedback instantáneo y personalizado, la recopilación en tiempo real y automatizada de gran cantidad de datos, el uso de interfaces más atractivas e intuitivas, la eliminación de algunos sesgos como el sesgo del evaluador o la reducción de costes derivada de la disminución de los procedimientos presenciales[68].

Se han desarollado multitud de aplicaciones móviles de salud en oncología. En concreto, más de 2,500 aplicaciones móviles se definen en la actualidad como aplicaciones relacionadas con el cáncer, pero esta relación puede ser periférica o basarse en afirmaciones no comprobadas, como las

aplicaciones de yoga y naturopatía que dicen ayudar a prevenir o incluso curar el cáncer[69]. A pesar de este gran número de aplicaciones destinadas a población con cáncer, en una reciente revisión sistemática en la que se consideraron 539 aplicaciones se concluyó que la efectividad de la mayoría de ellas no había sido validada científicamente, de las que el 47% estaban dedicadas a profesionales de la salud, el 31.5% a población general y el 21.5% a pacientes en particular[70]. Además, junto con éste, Collado-Borrell *et al.* en otra revisión sistemática publicada en 2016 también mostró la falta de participación de profesionales de salud cualificados en el desarrollo e implementación de estas aplicaciones móviles[70, 71]. Es curioso destacar, en este sentido, que en el año 2017, solo el 15% de los estudios realizados sobre *telesalud* en todo el mundo estaban destinados a la salud digital oncológica, y el 75% de estos estudios se realizaron en los Estados Unidos[69].

En la literatura científica se pueden encontrar aplicaciones móviles en oncología con diferentes objetivos o dianas terapéuticas como, por ejemplo, mejorar la adherencia a la medicación[72], realizar terapias grupales en adultos jóvenes con cáncer[73], evaluar el cuello uterino después de una detección anormal[74], facilitar el acceso a información sobre cuidados en oncología[75, 76], mejorar la calidad de vida de pacientes con cáncer a través del uso de las redes sociales[77], monitorizar algunos síntomas[78] o modificar estilos de vida en términos de dieta y actividad física[79]. Centrándonos en este último aspecto, son numerosas las aplicaciones móviles destinadas a promover estilos de vida saludables que se pueden encontrar en las diferentes tiendas de las plataformas móviles más extendidas en la actualidad (PlayStore, de Google, y App Store, de Apple), muchas de ellas con base científica. En los últimos años se puede observar un gran incremento en el número de publicaciones científicas acerca aplicaciones móviles y estilos de vida saludables, principalmente para población general. Se pueden encontrar diversos estudios que evalúan y/o sacan partido de las diferentes herramientas disponibles a través del *mHealth*. Algunos ejemplos en este sentido se resumen a continuación: el estudio realizado en 2016 por Keer *et al.* en el que utilizaron mensajes de texto para promocionar la ingesta de frutas y verduras en jóvenes adultos sanos[80]; el efectuado por Du *et al.* (2016) en el que se desarrolló una aplicación de *mHealth* llamada *Fittle* para potenciar el apoyo grupal en un programa de ejercicio y nutrición con el objetivo de producir cambios positivos en el comportamiento alimentario, la actividad física y el nivel de estrés en adultos sanos[81]; en la Universidad de Salamanca han llevado a cabo recientemente un estudio multicéntrico, en colaboración con otras universidades del territorio español, en el que desarrollaron una aplicación móvil de asesoramiento estandarizado para aumentar la actividad física y el cumplimiento de la dieta mediterránea a largo plazo[82]; en 2019 se ha publicado un trabajo del Karolinska Institutet en el que

implementaban una plataforma de *mHealth* multimodal con servicios en las áreas de dieta, actividad física, hábitos de sueño, estrés, consumo de alcohol y tabaco, estableciendo objetivos semanales[83]. Pero no solo se han desarollado en población sana o aparentemente sana, sino que también son diversas las aplicaciones móviles que se han presentado en la comunidad científica para promover estilos de vida saludables en algunas patologías: en cardiopatías, tanto para aumentar el nivel de actividad física complementaria a la rehabilitación presencial como se muestra en el estudio de Antypas *et al.* (2014)[84], como para potenciar la adherencia a dieta saludable y otros estilos de vida, como en el estudio de Lunde *et al.* (2019)[85]; en personas con sobrepeso u obesidad, Hass *et al.* (2019) evaluaron la eficacia de una plataforma *mHealth* que facilita la comunicación entre dietistas e individuos para el asesoramiento sobre pérdida de peso[86], y en la misma línea se desarrolla el trabajo publicado por Alnasser *et al.* (2019) para mujeres saudíes con sobrepeso u obesidad[87]; en diabetes, como los estudios realizados por Yan *et al.* (2018)[88] y Sun *et al.* (2019)[89] en los que se implementaron dos sistemas *mHealth* de manejo de síntomas y promoción de estilos de vida en población asiática; o en patología física, como el trabajo realizado por Rimmer *et al.* (2013) en Estados Unidos, en el que presentaron *POWERS*, una aplicación móvil para el control de peso de personas con diversas patologías físicas y/o neurológicas, entre las que se incluían esclerosis múltiple, espina bífida, parálisis cerebral, daño cerebral o lupus[90]. Focalizando en población oncológica, también son varios los estudios de aplicaciones móviles de salud destinadas de una u otra forma a la promoción de estilos de vida saludables en estos pacientes. Un estudio realizado por Ormel *et al.* y publicado en 2018 evaluó la viabilidad de la aplicación *Runkeeper* (pública y gratuita en las diferentes plataformas), para mejorar el nivel de actividad física en pacientes con cáncer, sin resultados concluyentes e instando a seguir investigando en el área[91]. Por otro lado, en 2016 Duman-Lubberding *et al.* desarrollaron y validaron una aplicación denominada Oncokompas para mejorar la supervivencia de pacientes con cáncer en general[75], y posteriormente adaptado a cáncer de mama en particular[76], mediante recomendaciones personalizadas sobre diversos aspectos de calidad de vida, fatiga y sueño, que incluían un apartado de estilos de vida, pero no una monitorización de los mismos. En la Universidad de Carolina del Norte, en Estados Unidos, se llevó a cabo un ensayo clínico utilizando *Facebook* a través del móvil para promover una intervención de actividad física moderada e intensa en 86 adultos jóvenes supervivientes de cáncer, con el que consiguieron demostrar el potencial de esta red social para este objetivo[92]. Utilizando la misma red social, en conjunto con un dispositivo portátil de seguimiento de actividad física (*Fitbit Flex*), con el objetivo de promover una intervención de actividad física, un estudio del *Seattle Children's Research Institute*, en Washington, demostró la fiabilidad y aceptabilidad de este tipo de intervenciones en niños supervivientes de

cáncer[93]. Sin embargo, a pesar de toda la evidencia científica disponible que afirma que las intervenciones *mHealth* son efectivas para la promoción de la actividad física y hábitos dietéticos saludables[94], son varios los estudios y revisiones sistemáticas recientes que ponen de manifiesto, por un lado, la dificultad para determinar el impacto específico de las estrategias *mHealth* destinadas a promover estilos de vida saludables en población oncológica y, por otro, la necesidad de desarrollar recursos específicos para esta población[95-98]. Además, desde nuestro conocimiento, ninguno de estos estudios hace hincapié en el equilibrio energético, ni especifica una monitorización de este, con un feedback instantáneo basado en la evidencia científica más actualizada. Las únicas referencias encontradas en este campo del equilibrio energético a través de *mHealth* han sido realizadas con población sana[80, 99, 100], niños y adolescentes[101], mujeres embarazadas[102], pacientes hospitalizados[103], pacientes con cirugía cardíaca[104] o diabetes[105]. Tan solo un estudio, realizado por Stubbins *et al.* y publicado en diciembre del 2018 desarrolló una aplicación móvil (denominada *MOCHA* por las siglas del hospital en el que se desarrolló: *Houston Methodist Hospital*) creada para el refuerzo personal de pacientes con cáncer para asumir patrones de vida más saludables en términos de contabilidad diaria de actividad física y nutrición. Sin embargo, tan solo utilizaron un periodo experimental de 14 días con 33 mujeres SCM[106] y sin resultados concluyentes.

Parece ser, por tanto, que las aplicaciones móviles se han instaurado en nuestro quehacer diario, habiéndose convertido en parte de nuestras vidas. Sus ventajas en el mundo de la salud digital son numerosas, y sus beneficios están siendo sostenidos por el crecimiento de publicaciones científicas de los últimos años. Sin embargo, existe un vacío en lo que se refiere a aplicaciones móviles destinadas a monitorizar el equilibrio energético en cáncer y promover una retroalimentación instantánea con recomendaciones basadas en las guías clínicas más actualizadas y reconocidas a nivel mundial.

Cáncer de Mama: secuelas y rehabilitación

Las cifras de supervivencia en el cáncer de mama son totalmente favorables. Sin embargo, esta ganancia en esperanza de vida no está exenta de un elevado coste, ya que las SCM tienen riesgo de presentar una amplia gama de posibles efectos a largo plazo, secundarios al tratamiento oncológico[107]. Éstos incluyen no solo riesgo de recidiva, aumento de morbilidad y mortalidad por enfermedades cardiovasculares, esqueléticas, etc., sino que también pueden aparecer innumerables efectos físicos como reducción de la amplitud del movimiento articular, principalmente en el brazo afectado, linfedema, fatiga, dolor, problemas psicosociales que pueden afectar a relaciones laborales, familiares y sociales o problemas cognitivos[108], pudiendo provocar limitaciones en las actividades de la vida

diaria, así como en la participación en actividades laborales, deportivas y de ocio[109]. Esperar que la calidad de vida vaya a mejorar tras el tratamiento oncológico puede, en muchos casos, no ser una suposición correcta, ya que más de la mitad de las SCM tienen síntomas persistentes que son similares a los que tuvieron durante el tratamiento activo, siendo la fatiga, el dolor y la depresión el *clúster* de síntomas más común[110, 111]. Un estudio realizado por Schmitz *et al.* (2012) en Australia demostró cómo más del 60% de las SCM experimentaban uno o más efectos secundarios al año tras el tratamiento oncológico, todos ellos susceptibles de recibir rehabilitación[112].

Secuelas funcionales

En cuanto a las limitaciones físicas; la cirugía y la radioterapia pueden provocar complicaciones en la pared torácica y senos, como fibrosis o necrosis de la piel y tejidos blandos, o reducción de la movilidad del brazo[113]. La radioterapia, además, puede agravar el dolor relacionado con la cirugía y la restricción motora, tanto a corto como a largo plazo. Los cambios musculo-esqueléticos posteriores a la cirugía, principalmente en los casos de mastectomía, suelen aparecer tanto en el lado afecto como en el no afecto[114]. Éstos, incluyen, entre otros, alteraciones en la inclinación y alineación en reposo de la escápula, que suelen conllevar una cascada de cambios en las articulaciones del hombro y zonas conlindantes, lo que aumenta el riesgo de pinzamiento y patología del manguito rotador[115]. Además, puede mostrarse falta de coordinación escapular y pérdida de fuerza muscular[115, 116] que pueden aparecer incluso 6 años tras la cirugía[117]. Todo este torrente de alteraciones se debe, en parte, al efecto directo de la cirugía sobre los tejidos, seguido de fibrosis, inflamación y cicatrización, como parte del proceso de curación normal; además, la angiogénesis secundaria a este proceso de curación se asocia con inflamación, lo que resulta en aumento del dolor local y regional con la consecuente restricción del movimiento de la zona afectada[118]; y por otro lado, la radioterapia provoca muerte celular con la consiguiente liberación de citocinas inflamatorias, daño tisular y fibrosis, lo que aumenta significativamente la disfunción y el dolor a largo plazo[119]. Otra de las complicaciones frecuentes es el linfedema, tanto de inicio temprano como tardío, que puede afectar al seno, el tórax y la extremidad ipsilateral[120]. La cirugía conservadora de seno o la mastectomía con disección de ganglios linfáticos axilares, así como la radioterapia ganglionar completa están relacionados con una tasa más alta de linfedema[121]. El daño del sistema linfático depende de la cantidad de ganglios linfáticos extirpados y se asocia con un mayor riesgo de alteración y disfunción en el hombro y brazo, linfedema y dolor[122, 123]. El daño a nivel nervioso, principalmente del nervio intercostobraquial, así como de otros del plexo braquial, puede ser una complicación de la cirugía, especialmente si se realiza disección de los ganglios linfáticos axilares, y puede verse empeorado

con la radioterapia[124]. Este daño provoca alteración de la sensibilidad en la pared torácica, axila, parte superior del brazo y, a veces, en la parte superior de la espalda, costado y mano[125, 126]. Tanto el linfedema, como el dolor y la restricción de movilidad del hombro y del brazo se han asociado significativamente con peor calidad de vida a largo plazo en mujeres SCM, por lo que estos problemas deberían ser diagnosticados y tratados con el objetivo de mejorar la calidad de vida de estas mujeres[125].

Secuelas cognitivas y emocionales

Si bien es cierto que el grado de alteración asociado con una posible disfunción cognitiva secundaria al tratamiento oncológico, principalmente a la quimioterapia, no está bien caracterizado, los datos sugieren que se trata de un problema real en las SCM[127-129]. Es el denominado deterioro cognitivo relacionado con el cáncer, y los pacientes lo describen como olvidos frecuentes (de nombres, fechas, números de teléfono, …), problemas para concentrarse o realizar tareas simultáneas, o dificultades a la hora de encontrar la palabra adecuada[130, 131]. Un estudio realizado por Schmidt *et al.* en 2016 con un amplio tamaño de muestra (n=3108 supervivientes de cáncer) puso de manifiesto que más de la mitad de las SCM manifestaban deterioro cognitivo[132]. Además, de acuerdo con varios estudios, hasta el 75% de las pacientes de cáncer de mama experimentaron deterioro cognitivo relacionado con el cáncer durante el tratamiento activo (como la quimioterapia o el tratamiento hormonal)[128, 133], y un estudio reciente publicado por Lange *et al.* de 2019 mostró que más del 70% de las SCM presentaban algún grado de deterioro cognitivo[134]. De entre todos los procesos cognitivos, los más frecuentemente afectados son la memoria (sobre todo la memoria de trabajo), fluidez verbal, velocidad de procesamiento, función ejecutiva y atención[135, 136]. En este sentido, estudios de neuroimagen sugieren que la terapia adyuvante contra el cáncer puede inducir una regulación anormal en los centros nerviosos del cerebro, principalmente el hipocampo y la corteza prefrontal[137-139]. Así encontramos, tanto en estudios con humanos como con animales, asociación entre el tratamiento quimioterapéutico y una variedad de cambios anormales en el hipocampo, incluida la pérdida de sustancia blanca y gris, disminución de la neurogénesis, aumento de muerte celular y daño en los vasos sanguíneos[140-142]. Además, un estudio reciente realizado por Apple *et al.* reveló una pérdida importante de volumen del hipocampo, vital en diversos procesos cognitivos como la memoria, en SCM sometidos a terapia adyuvante en comparación con controles sanos, y demostraron que el hipocampo es vulnerable al efecto del tratamiento contra el cáncer[143]. Otro estudio del mismo grupo de investigación publicado en 2018 reveló una mayor conectividad córtico-hipocampal relacionado con tareas funcionales en SCM en comparación con

controles sanos, lo que sugiere que esta conectividad puede ser un mecanismo compensatorio en el deterioro cognitivo relacionado con el cáncer[144]. Este deterioro suele ser invisible en la vida diaria de las mujeres, pero supone un gran impacto en su calidad de vida y su desempeño diario[145], lo que pone de manifiesto la necesidad de un soporte de apoyo rehabilitador y plantea el reto de generar protocolos de intervención adaptados a estas pacientes.

Desde el punto de vista psicológico, el cáncer de mama se asocia con una morbilidad psicológica significativa. Tras el tratamiento oncológico, la literatura científica revela que hasta el 90% de las mujeres tiene al menos una preocupación emocional, hasta el 80% miedo a la recurrencia del cáncer y hasta el 60% puede sentir pena, problemas de identidad e imagen corporal y angusta emocional[119, 146]. Además, la ansiedad y los trastornos depresivos son dos patologías psiquiátricas comunes en pacientes con cáncer de mama[147], y casi la mitad de las mujeres supervivientes experimentan algún trastorno de ansiedad o depresión tras el tratamiento oncológico[148]. Una revisión sistemática reciente sugiere, además, que al año tras el diagnóstico se experimenta un aumento de los síntomas de depresión en este tipo de pacientes, y que pueden ser persistentes hasta 5 o 10 años según la bibliografía consultada[149]. De hecho, en un estudio realizado en 2015 por Stanton *et al.* con 460 mujeres evaluadas a los 4 meses del diagnóstico de cáncer de mama y seguidas hasta un año tras el tratamiento oncológico con 7 evaluaciones en total, el 17% de las mismas cumplió criterios de diagnóstico de depresión mayor[150]. Diferentes factores de riesgo se han asociado con la aparición de este tipo de síntomas, como la presencia de comorbilidades previas, la cirugía y su afectación en la imagen corporal, problemas financieros, los dos primeros años de supervivencia, historia previa de depresión, soledad o estilos de vida sedentarios[151]. En este sentido, el apoyo social percibido adquiere un rol fundamental como moderador de la aparición de los denominados pensamientos intrusivos y angustia psicológica en mujeres SCM, así como en la aparición de algún síntoma o patología de carácter psicológico[152].

Secuelas sistémicas

Finalmente, en cuanto a los síntomas de carácter sistémico, el dolor, la fatiga y la disminución de la capacidad cardiorrespiratoria son muy frecuentes, especialmente en las mujeres tratadas con un inhibidor de la aromatasa[153]. La fatiga relacionada con el cáncer es uno de los efectos secundarios más comunes, definido por la *American Society of Clinical Oncology* (ASCO) como «una sensación angustiante, persistente y subjetiva de cansancio o agotamiento físico, emocional y/o cognitivo relacionado con el cáncer y/o el tratamiento del mismo, que no es proporcional a la actividad reciente e interfiere en el funcionamiento habitual»[154]. Aproximadamente una de cada cuatro SCM padece fatiga severa, y se ha relacionado su

aparición o empeoramiento con el estadio tumoral, así como con el tratamiento oncológico: quimioterapia y radioterapia con o sin tratamiento hormonal[155]. Debido a que la fatiga es un síntoma complejo que implica el aporte de varios sistemas fisiológicos, y su carácter subjetivo, no se conoce muy bien el mecanismo biológico para la aparición de la fatiga relacionada con el cáncer, habiéndose propuesto varios mecanismos como anemia, hipotiroidismo, insuficiencia suprarrenal, desregulación de serotonina, alteraciones en el metabolismo celular y disfunción neuroendocrina[156, 157]. Sin embargo, hasta la fecha, el mecanismo más ampliamente aceptado y apoyado empíricamente es la inflamación. Esta hipótesis se basa en la propuesta de que el cáncer y/o su tratamiento conducen a la liberación de citocinas proinflamatorias, que luego actúan sobre el cerebro para provocar una respuesta de *comportamiento de enfermedad*, incluídos los síntomas de fatiga[156, 158]. Estos niveles más elevados de fatiga se han asociado con peor calidad de vida, peor funcionamiento y capacidad de trabajo, con síntomas depresivos, ansiedad, trastornos del sueño, niveles más bajos de actividad física y el dolor[159]. Además, la fatiga provoca una interrupción significativa de las actividades ocupacionales, sociales y de ocio, lo que afecta a la capacidad de realizar las actividades diarias y al desempeño ocupacional[160].

En cuanto al dolor, el denominado síndrome de dolor crónico es otra de las complicaciones más experimentadas de las SCM, generalmente de origen neuropático[161]. Está definido como «un dolor crónico, no maligno y constante, inmediatamente después de la cirugía de cáncer de mama, que afecta al tórax, la axila y/o la parte medial del brazo»[126]. Debido a que no hay consenso sobre el tiempo durante el cual debe estar presente el dolor para considerarse crónico, la prevalencia tiene un rango del 4% al 100% de mujeres que padecen dolor poscirugía, según el criterio, el diseño del estudio y el marco temporal[126]. Entre los factores de riesgo para su desarrollo se incluyen la disección de los ganglios linfáticos axilares, cualquier procedimiento quirúrgico, la edad, el índice de masa corporal elevado y la radioterapia[119]. Finalmente, entre las complicaciones del cáncer de mama, el sistema cardiovascular puede verse afectado, principalmente por el tratamiento adyuvante, como la quimioterapia, que puede afectar a la fracción de eyección cardíaca a través del estrés oxidativo, dañando la membrana plasmática de las células cardíacas y promoviendo la apoptosis[162]. La definición más ampliamente aceptada sobre la alteración cardíaca relacionada con la terapia del cáncer es la propuesta por la *American Society of Echocardiography* y la *European Association of Cardiovascular Imaging* que la definen como «una disminución en la fracción de eyección del ventrículo izquierdo de más del 10% por debajo del límite inferior de la normalidad, que se considera de 53%» [163]. A pesar de que la prevalencia es del 10% entre supervivientes del cáncer[164], también se ha demostrado

que, aun sin presentar alteración cardiaca relacionada con la terapia del cáncer, es decir, con función cardiaca normal, las mujeres SCM tienen deficiencias significativas y marcadas en la función cardiopulmonar. Casi un tercio de las SCM tienen un consumo máximo de oxígeno (el *gold standard* de la aptitud cardiorrespiratoria) por debajo del umbral de independencia funcional (15.4 mL · kg –1 · min–1), por lo que, por definición, es poco probable que puedan realizar tareas domésticas pesadas o subir y bajar escaleras, viendo mermado su desempeño diario[165].

Por lo tanto, se ha demostrado que las SCM experimentan una serie de dificultades que pueden afectar a su calidad de vida general, a su desempeño ocupacional y a sus actividades de la vida diaria, lo que plantea la necesidad de intervenciones diseñadas y dirigicas específicamente a este tipo de pacientes, basándose en la más alta evidencia científica[166]. Sin embargo, la derivación a profesionales de rehabilitación en el proceso oncológico no está incluido en el soporte estándar a estos pacientes[167].

Rehabilitación oncológica

Los cuatro pilares de la atención en la supervivencia del cáncer son: el seguimiento y la prevención de recurrencia y segundos cánceres, la intervención en las consecuencias del tratamiento; la prevención de comorbilidades, y la coordinación del soporte entre la atención primaria, la oncología y otros especialistas y miembros del equipo rehabilitador[168]. Actualmente se está planteando la necesidad de definir un nuevo modelo de rehabilitación integral del cáncer, que involucre a un equipo multidisciplinar de profesionales que tenga como objetivo optimizar el funcionamiento físico, psicológico, vocacional, funcional y social de estas pacientes, debido a los límites impuestos por los efectos secundarios crónicos o tardíos del tratamiento y de la patología oncológica[169].

Es mucha la evidencia científica que apoya el beneficio de las diferentes técnicas y disciplinas en el proceso rehabilitador del cáncer y, en concreto en la fase de supervivencia, aunque, a su vez, también son muchas las limitaciones y controversias. En cuanto al ejercicio terapéutico y/o el entrenamiento de fuerza, son varias las revisiones sistemáticas con o sin metaanalisis que apoyan su eficiacia en la mejora de diferentes síntomas en la fase de supervivencia. Una revisión sistemática realizada por Hanson *et al.* en 2016 con el objetivo de examinar el efecto independiente de los programas de entrenamiento de resistencia para reducir o revertir los efectos del tratamiento oncológico concluyó que, a pesar de encontrar diferencias significativas en el grupo intervenido, el efecto independiente del entrenamiento de fuerza es todavía limitado, debido principalmente al bajo número de estudios disponibles en la literatura[170]. Más recientemente, una revisión sistemática realizada por Neil-Sztramko *et al.* en 2019 cuyo objetivo fue analizar la aplicación de los principios del

entrenamiento con ejercicios en la prescripción de ejercicio terapéutico en SCM, concluyó que es elevada la evidencia y los beneficios que aporta el ejercicio terapéutico, con 80 ensayos clínicos incluidos y un total de 6,878 mujeres[171]. Estos datos muestran una abrumadora evidencia sobre los beneficios del ejercicio durante y después del tratamiento y en fase de supervivencia en una variedad de secuelas psicosociales y relacionadas con la salud. Sin embargo, también ponen de manifiesto la necesidad de identificar la mejor dosis de prescipción de ejercicio para mejorar los resultados específicos en un determinado momento del tratamiento. En la misma línea, pero centrándose en el linfedema, Nelson publicó en 2016 una revisión sistemática sobre los beneficios del ejercicio de resistencia en la movilidad del brazo sin aumentar el riesgo de aparición o empeoramiento del linfedema[172]. Con seis ensayos clínicos incluidos corroboró la seguridad del entrenamiento de resistencia de alta intensidad para la ganancia de fuerza en mujeres SCM sin desencadenar cambios en el estado del linfedema.

Por otro lado, un metaanálisis realizado por Ye *et al.* en 2018 para examinar la eficacia de la terapia cognitivo-conductual en la mejora de la calidad de vida y la salud psicológica de SCM, concluyó que esta es razonablemente efectiva, con tamaños del efecto clínicamente significativos, pero con pocos estudios incluidos en el mismo[173]. En la misma línea, pero con el objetivo de valorar el efecto de las terapias de cambio de comportamiento a distancia para mejorar el nivel de actividad física en estas pacientes y secundariamente, su calidad de vida, Groen *et al.* publicaron una revisión sistemática con metaanálisis en 2018 en la que se incluyeron 29 ensayos clínicos, obteniendo un tamaño de muestra total de 5,218 participantes. Sus conclusiones fueron desafiantes, ya que el efecto de la intervención fue pequeño, planteando limitaciones de los ensayos como diseños metodológicos deficientes, tamaños de muestra pequeños, falta de poder estadístico u homogeneidad de las muestras; e instando a seguir investigando acerca del tema[79].

En 2017, la Organización Cochrane realizó una revisión sistemática sobre programas multidimensionales en domicilio para SCM, que incluyeran al menos terapia física, educativa y psicológica. En dicha revisión incluyeron 22 ensayos clínicos controlados y aleatorizados y cuatro cuasiexperimentales con 2,272 participantes. Concluyeron que estos programas parecen tener un efecto beneficioso a corto plazo en la mejora de la calidad de vida específica y global, así como parecen estar asociados con una reducción de la ansidad, la fatiga y el insomnio inmediatamente después de la intervención. Sin embargo, también ponen de manifiesto de nuevo la baja calidad científica de los artículos incluidos[174].

En cuanto al manejo de las secuelas cognitivas, la evidencia científica también plantea resultados contradictorios. Una revisión sistemática realizada por Chan *et al.* en 2015 con el objetivo de valorar la

efectividad de intervenciones farmacológicas y no farmacológicas para controlar las alteraciones cognitivas asociadas al tratamiento del cáncer de mama, en la que se incluyeron 13 estudios y 1,138 participantes, puso de manifiesto que, según la evidencia actual, el tratamiento farmacológico parece no estar indicado para el manejo de estas alteraciones cognitivas y que las intervenciones no farmacológicas, como el entrenamiento congitivo y la actividad física parecen prometedoras, pero con muchas deficiencias metodológicas. De hecho, de los 13 estudios incluidos en la revisión, 11 presentaron un riesgo de sesgos elevado y en dos no estaba claro[175]. Más recientemente, y mediante el uso de aplicaciones móviles, Vergani *et al.* publicaron en 2019 una revisión sistemática para comprobar si estas herramientas pudieran ser útiles para contrarrestar el deterioro cognitivo en estas pacientes. Incluyendo un total de 819 participantes procedentes de once estudios, destacan la falta de evidencia empírica sobre la eficacia de las aplicaciones disponibles para entrenar la función cognitiva[176].

También parece existir evidencia sobre el efecto de otras terapias complementarias, como el yoga[177] o el Taichi[178] en determinados síntomas secundarios al cáncer de mama en fase de supervivencia como la fatiga o, en términos generales, sobre la mejora de la calidad de vida. Sin embargo, las conclusiones de las revisiones sistemáticas analizadas son muy limitadas, con un tamaño de muestra pequeño, tamaños del efecto reducidos y resultados contradictorios.

En conclusión, son muchas las disciplinas o herramientas terapéuticas que han demostrado su eficacia tanto clínica como estadística en la rehabilitación de las secuelas del cáncer. A pesar del elevado número de referencias disponibles a nivel mundial, son muchas las controversias y queda claro el objetivo común: continuar investigando en la misma línea con el objetivo de delimitar las mejores intervenciones disponibles[179].

Terapia Ocupacional en oncología

La terapia ocupacional, está incluida dentro de las guías de práctica clínica de la rehabilitación del cáncer, en general y del cáncer de mama en particular, sin embargo, tanto su aprovechamiento como parte del equipo multidisciplinar de rehabilitación, así como su evidencia científica en el campo oncológico, es limitada[167, 180]. El campo de actuación de los terapeutas ocupacionales incluye centros oncológicos de rehabilitación, la comunidad o los cuidados paliativos, y su objetivo general va a ser mejorar la calidad de vida del paciente. La piedra angular de la terapia ocupacional es la ocupación, por lo que las intervenciones de estos profesionales utilizarán la ocupación como medio terapéutico para mejorar el desempeño ocupacional[181]. Además del entrenamiento en actividades básicas de la vida diaria cuyo desempeño se haya visto mermado tras el proceso de enfermedad, los terapeutas

ocupacionales pueden favorecer al paciente oncológico desde la educación en estilos de vida saludables, el fortalecimiento de las debilidades secundarias al tumor o su tratamiento, el control y paliación de los posibles síntomas cognitivos así como la mejora de la fatiga y la resistencia cardiorrespiratoria, siempre desde un punto de vista holístico e integral[182].

La evidencia científica sobre intervenciones o propuestas de intervención en población oncológica basadas en terapia ocupacional es muy limitada. Debido al amplio tamaño de muestra y su diseño metodológico, destaca la intervención propuesta por Sampedro Pilegaard et al, en 2018, denominada *Cancer Home-Life Intervention*, en la que llevaron a cabo una intervención de terapia ocupacional basada en la ocupación en personas con cáncer avanzado que tuviesen limitaciones funcionales. A pesar de que los resultados no obtuvieron diferencias significativas (debido principalmente a que la intervención solo planteaba una visita domiciliaria y un contacto telefónico) pudieron demostrar la factibilidad y coste-efectividad de realizar un programa domiciliario de terapia ocupacional en esta población y concluir que la mayoría de los participantes manifestaban la necesidad de una intervención de terapia ocupacional[183, 184]. De la misma manera, destaca el estudio realizado por Akel *et al.* y publicado en 2019 cuyo objetivo fue evaluar el efecto de un programa de rehablitación cognitiva funcional hospitalaria desde la terapia ocupacional en la percepción de fatiga y la independencia en cáncer pediátrico. En este caso sí que se encontraron mejoras estadísticamentes significativas tras el periodo experimental tanto en la disminución de la fatiga percibida como en la independencia funcional[185].

En cáncer de mama, tan solo se han podido identificar seis estudios publicados con un diseño experimental en el que se utilizase una intervención de terapia ocupacional, de los cuales, tres se realizaron con mujeres SCM.

En 2010, McClure *et al.*[186] llevaron a cabo un ensayo clínico controlado y aleatorizado con el objetivo de comprobar la mejora de síntomas físicos y emocionales de mujeres SCM (estadios I y II) con linfedema. Con un tamaño muestral global de 32 participantes divididos en dos grupos, y un periodo de seguimiento domiciliario de tres meses, la intervención del grupo experimental consistió en 10 sesiones de una hora de duración (dos sesiones a la semana), durante cinco semanas, mediante información audiovisual de ejercicios de movilidad del miembro superior y técnicas de relajación. El grupo control no recibió tratamiento o información alguna. Tras el periodo experimental, los resultados del estudio demostraron que el programa proporcionó un efecto significativo en la disminución del volumen del brazo afectado y mejoras en la movilidad del hombro, estado de ánimo y calidad de vida, aunque el efecto disminuyó con el seguimiento de tres meses.

En 2011, Hegel *et al.*[187] estudiaron la viabilidad de realizar un ensayo clínico controlado y aleatorizado en la mejora de secuelas funcionales en población rural (n=31), mediante una intervención telefónica de resolución de problemas y terapia ocupacional, mostrando la viabilidad del estudio. A pesar de la aclaración en el título del trabajo de mujeres SCM, no queda claro a lo largo del estudio si se consideró el criterio de supervivencia de haber finalizado el tratamiento activo, ya que parece intuirse que fueron participantes recibiendo quimioterapia durante la fase experimental del mismo. Posteriormente en 2015, el mismo grupo de investigación publicaba los resultados de este ensayo clínico, con el mismo tamaño muestral, pero con un diseño cuasiexperimental pre-post[188, 189]. La intervención consistió en nueve sesiones telefónicas de las que seis se realizaron una vez por semana durante seis semanas y tres fueron de seguimiento mensual. Estas sesiones siguieron la guía de resolución de problemas basada en el Modelo de Persona, Entorno y Ocupación, que incluye seis pasos: 1) identificiación de ocupaciones significativas, 2) establecimiento de metas, 3) lluvia de ideas de posibles soluciones, 4) análisis de soluciones y su viabilidad, 5) elección de soluciones y 6) implementación de las soluciones. Encontraron un efecto principal significativo en la mejora de la calidad de vida general, el afrontamiento activo, planificación y disminución del sentimiento de culpabilidad.

En conclusión, a pesar de que la terapia ocupacional ha demostrado eficacia en patologías o secuelas similares a las que puedan aparecer en las mujeres SCM mediante ensayos clínicos controlados y aleatorizados[190-194], en general, la evidencia científica existente sobre intervenciones de terapia ocupacional en esta población es escasa y no concluyente. Los estudios analizados carecían de poder estadístico, presentaban tamaños de muestra muy limitados o se centraban en pruebas de viabilidad en lugar de evaluar el efecto general de las intervenciones, y presentaban problemas de reclutamiento o pérdidas en el seguimiento. Sin embargo, también indican que es factible llevar a cabo intervenciones de rehabilitación basadas en esta disciplina en población con cáncer. Todo esto sugiere que la evidencia actual de la terapia ocupacional oncológica, en este caso centrada en el cáncer de mama, se encuentra aún en una fase de desarrollo muy prematura, planteando nuevos retos de investigación.

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OBJETIVOS
AIMS

OBJETIVOS

Los objetivos principales de esta Tesis Doctoral Internacional fueron: diseñar, desarollar, validar e implementar en un contexto clínico real un sistema móvil de salud de monitorización del balance energético (BENECA) en SCM (Sección 1); desarollar un programa presencial de rehabilitación de terapia ocupacional para mujeres supervivientes de cáncer de mama, y examinar la eficacia de una estrategia de soporte integral (programa de rehabilitación de terapia ocupacional junto con el uso del sistema móvil de salud) frente al uso del sistema móvil exclusivamente, para mejorar la calidad de vida de de supervivientes de cáncer de mama a corto y largo plazo (Sección 2).

Para responder a estos objetivos, esta Tesis está organizada en cinco estudios, basándose en los siguientes objetivos específicos:

Sección 1: Balance ENErgético en CAncer (BENECA).

1. Estudio I. Desarrollar y estudiar la fiabilidad del sistema móvil de salud BENECA, comprobando la capacidad del sistema en relación con pruebas *gold estándar* en dieta y actividad física.
2. Estudio II. Estudiar la factibilidad en una situación clínica real del sistema móvil de salud BENECA en términos de reclutamiento, aceptación, uso, adherencia y satisfacción; y examinar el efecto del uso de la aplicación en la calidad de vida, la composición corporal y la actividad física de mujeres supervivientes de cáncer de mama.
3. Estudio III. Explorar la posible relaciación entre el uso de una aplicación móvil de salud de monitorización del equilibrio energético y la reducción de la inflamación sistémica en mujeres supervivientes de cáncer de mama.

Sección 2: Programa integral de soporte a supervivientes de cáncer de mama.

4. Estudio IV: Diseñar la estrategia de soporte integral para mujeres supervivientes de cáncer de mama basada en la aplicación móvil de salud BENECA y un programa de rehabilitación presencial de terapia ocupacional.
5. Estudio V: Comparar la eficacia clínica de la aplicación móvil de salud BENECA frente a la estrategia integral de soporte que incluye también el programa de rehabilitación presencial de terapia ocupacional, en la mejora de la calidad de vida y la funcionalidad de mujeres supervivientes de cáncer de mama.

AIMS

The major aims of the present International Doctoral Thesis were: design, develop, validate and implement in a real clinical context a mobile health system for energy balance monitoring (BENECA mHealth) in breast cancer survivors (Section 1); develop a supervised occupational therapy rehabilitation program for breast cáncer survivors, and examine the effectiveness of an integral support strategy (occupational therapy rehabilitation program together with the use of the mobile health system) versus the use of the mobile system exclusively, to improve quality of life of breast cancer survivors in short and long term (Section 2).

To meet these aims, the present Thesis is organized in five studies, based on the following specific aims:

Section 1: Energy Balance on Cancer (BENECA):

1. Study I. To develop and study the reliability of the mobile health system BENECA, checking the capacity of the system in relation to *gold standard* tests in diet and physical activity.
2. Study II. To study the feasibility in a real clinical situation of the mobile health system BENECA in terms of recruitment, acceptance, use, adherence and satisfaction; and to examine the effect of using the application on quality of life, body composition and physical activity of breast cancer survivors.
3. Study III. To explore the possible relationship between the use of a mobile health application for energy balance monitoring and the reduction of systemic inflammation in breast cancer survivors.

Section 2: Integral support strategy for breast cancer survivors.

4. Study IV: To design the integral support strategy for breast cancer survivors based on the mobile health application BENECA and a supervised occupational therapy rehabilitation program.
5. Study V: To compare the clinical efficacy of the mobile health application BENECA versus the integral support strategy that also includes the supervised occupational therapy program, on improving the quality of life and functionality of breast cancer survivors.

MATERIAL Y MÉTODOS, RESULTADOS, DISCUSIÓN

METHODS, RESULTS, DISCUSSION

Table 1: Summary of the characteristics of the published articles included in the present International Doctoral Thesis.

Article	Design	Participants	Variable Studied
Section 1: Energy Balance on Cancer			
I. Monitoring Energy Balance in Breast Cancer Survivors Using a Mobile App: Reliability Study	Descriptive test-restest reliability study	20 BCS, 11 right breast affected side; age: 47.5±7.07 years; BMI: 26.51±3.06 kg/m^2.	Physical activity (accelerometry). Dietary Habits (24-hour dietary recalls and dietary records).
II. A Mobile System to Improve Quality of Life Via Energy Balance in Breast Cancer Survivors (BENECA mHealth): Prospective Test-Retest Quasiexperimental Feasibility Study	Prospective test-restest quasi-experimental study	80 BCS; age: 51.80±8.64 years; BMI: 29.11±4.77 kg/m^2.	Adoption, usage and Attrition rates Quality of BENECA mHealth (MARS). Barriers and Facilitatos if use Quality of life (EORT QLQ-C30). Self-Efficacy and Motivation in Relation to Physical Activity (EAF). Physical activity (accelerometry). Body Composition (DXA).
III. Mobile health strategy and biological changes in breast cancer survivors: a possible association?	Prospective test-restest quasi-experimental study	73 BCS; age: 51.35±8.58 years; BMI: 28.86±8.58 kg/m^2.	Salivary inflammatory markers (IL-6 and CRP). Quality of life (EORT QLQ-C30). Quality of BENECA mHealth (MARS). Physical activity (accelerometry) Weigh and Height

Section 2: Integral suport strategy in Breast Cancer Survivors

IV. Integral strategy to supportive care in breast cáncer survivors through occupational therapy and a m-Health system: design of a randomized clinical trial.	Protocol Study ClinicalTrials ID: NCT02817724	80 BCS; 40 in Integral group (BENECA + OT supervised rehabilitation program) and 40 in BENECA group.	Quality of life (EORT QLQ-C30 and BR23). Body Composition (DXA). Muscular strength (dynamometry). Upper body functionality (DASH). Active range of motion (goniometry). Cognitive function (WAIS-IV and TMT). Anxiety and depression (HADS). Physical fitness (VREM, EAF and Accelerometry). Lymphedema (upper body volume).
Mobile health and supervised rehabilitation versus mobile health alone in breast cancer survivors: randomized controlled trial	Assessor-blinded randomized controlled study	80 BCS; age: 51.80±8.64 years; BMI: 29.11±4.77 kg/m^2.	Quality of life (EORT QLQ-C30 and BR23). Upper body functionality (DASH). Active range of motion (goniometry). Muscular strength (dynamometry). Body Composition (DXA).

Abbreviations: BCS, breast cancer survivors; BMI, body mass index; CRP, C-reactive protein; DASH, Disabilities of the Arm, Shoulder and Hand questionnaire; DXA, dual-energy X-ray absorptiometry; EAF, Self Efficaty Scale for Physical Activity; EORT QLQ-C30/BR23, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 / Breast Cancer Module 23; HADS, Hospital Anxiety and Depression Scale; DIL-6, Interleukin 6; MARS, mobile app rating scale; mHealth, mobile health; TMT, trail making test VREM, short version of the Minnesota Leisure Time Physical Activity; WAIS-IV, Wechsler Adult Intelligence Scale.

Monitoring Energy Balance in Breast Cancer Survivors Using a Mobile App: Reliability Study

JMIR MHEALTH AND UHEALTH
2018

Journal Citation Report	
Impact Factor	4.301
Category	Medical Informatics
Rank	2/26 (94.231)

STUDY I

Study I. Monitoring Energy Balance in Breast Cancer Survivors Using a Mobile App: Reliability Study

Abstract

Background: The majority of breast cancer survivors do not meet recommendations in terms of diet and physical activity. To address this problem, we developed a mobile health (mHealth) app for assessing and monitoring healthy lifestyles in breast cancer survivors, called the Energy Balance on Cancer (BENECA) mHealth system. The BENECA mHealth system is a novel and interactive mHealth app, which allows breast cancer survivors to engage themselves in their energy balance monitoring. BENECA was designed to facilitate adherence to healthy lifestyles in an easy and intuitive way.

Objective: The objective of the study was to assess the concurrent validity and test-retest reliability between the BENECA mHealth system and the gold standard assessment methods for diet and physical activity.

Methods: A reliability study was conducted with 20 breast cancer survivors. In the study, tri-axial accelerometers (ActiGraphGT3X+) were used as gold standard for 8 consecutive days, in addition to 2, 24-hour dietary recalls, 4 dietary records, and sociodemographic questionnaires. Two-way random effect intraclass correlation coefficients, a linear regression-analysis, and a Passing-Bablok regression were calculated.

Results: The reliability estimates were very high for all variables (alpha≥.90). The lowest reliability was found in fruit and vegetable intakes (alpha=.94). The reliability between the accelerometer and the dietary assessment instruments against the BENECA system was very high (intraclass correlation coefficient=.90). We found a mean match rate of 93.51% between instruments and a mean phantom rate of 3.35%. The Passing-Bablok regression analysis did not show considerable bias in fat percentage, portions of fruits and vegetables, or minutes of moderate to vigorous physical activity.

Conclusions: The BENECA mHealth app could be a new tool to measure energy balance in breast cancer survivors in a reliable and simple way. Our results support the use of this technology to not only to encourage changes in breast cancer survivors' lifestyles, but also to remotely monitor energy balance.

Introduction

Although the relationship between diet, physical activity, and health is widely known, excess energy intakes (diet) and sedentary lifestyles are common negative habits in cancer survivors [1]. This energy imbalance may not only be highly associated with the increased risk of incidence of some of the most frequent types of cancer, but they may also be determinants in the appearance of new cancers, the increase of relapses, and even mortality due to cancer [2,3].

International guidelines for cancer survivors include maintaining a healthy weight, limiting the consumption of high-calorie foods, and engaging in physical activity [4,5], together known as energy balance. Unfortunately, only 20% to 32% of cancer survivors adhere to these standards [6,7]. Thus, the development of feasible, reliable, and accurate diet and physical activity assessment methods, as well as the promotion of cost-effective personalized behaviors are necessary to improve adherence to healthy lifestyles.

Currently, the gold standard instruments for measuring physical activity levels and diet in different populations include accelerometry and direct observation, daily records, and 24-hour dietary recall, respectively [8,9]. Despite their widespread use, new evaluation strategies are necessary to ensure that they (1) are less time consuming for patients and researchers; and (2) do not require the presence of a specialist.

Information and communication technologies are emerging as new methods to accurately and remotely evaluate different pathological processes [10-13], including oncology [14]. Literature has reported the use of electronic health (eHealth) tools that collect data on or that promote healthy lifestyles using the internet and Web-based programs [15-20]. Even though some eHealth programs were used in studies with patients with cancer [21-24], none of them quantified energy balance.

Mobile health (mHealth) apps offer many advantages over eHealth systems, including (1) instantaneous and personalized feedback; (2) self-directing data collection; (3) user-friendly interfaces; (4) evaluator bias reductions; and (5) lower costs by reducing face-to-face procedures [25]. To date, several mHealth apps have been developed to promote healthy lifestyles in the general population [26-30], and for some pathologies, such as cardiac rehabilitation [31], weigh loss interventions for endometrial carcinoma [32], and exercise and nutrition counseling for breast cancer survivors [33]. However, no mHealth app has been developed specifically for breast cancer survivors that simultaneously records energy balance (intake and physical activity) and provides immediate energy balance feedback.

The Energy Balance on Cancer (BENECA) mobile app, developed to help breast cancer survivors overcome energy balance challenges, aims to motivate and sensitize breast cancer survivors to adhere to fully

personalized physical exercise programs and nutritional plans in compliance with the international guidelines for cancer survivors. Here, we describe the development of the BENECA system, its test-retest reliability, and concurrent validity against the gold standard methods to assess diet and physical activity.

Methods

Overview

A descriptive reliability study was used to test inter- and intrarater responses for a novel mhealth assessment app for energy balance in breast cancer survivors. The app, BENECA mHealth system, was developed by the CUIDATE research group.

Participants, Sample, and Procedures

Breast cancer survivors were enrolled from the Complejo Hospitalario Universitario in Granada, Spain, following their oncologist's suggestion to join the test-retest reliability study between September 2016 and December 2016. Cancer survivors were eligible if (1) they had been diagnosed with breast cancer (estrogen-receptor-positive [ER+]); (2) had a body mass index (BMI) higher than 25 kg/m2; (3) were between 30 and 75 years old; (4) had basic abilities to use mobile apps; and (5) had completed their cancer treatment (adjuvant therapy) at least 6 months prior. The participants were excluded if they had chronic diseases or orthopedic issues that could interfere with their ability to walk. The project followed the Declaration of Helsinki guidelines and Law 14/2007 on biomedical research [34]. The study was approved by the local ethics committee of the Andalusian Health Service. All participants provided written informed consent.

A total of 20 patients was estimated to be necessary to achieve 90% power, to identify a correlation coefficient of 0.8 between the evaluation methods (gold standard versus the BENECA mHealth app), and to have an alpha error of 5%. Previous studies on the agreement between remote assessment methods had comparable sample sizes [12,14,35]. Taking into account potential study dropouts, 25 patients were invited to participate in this study. A pilot study was carried out with 10 healthy participants to develop, test, and improve the BENECA mHealth system. The data from the pilot study were not included in this study.

The participants attended the Sport and Health Center in Granada. A member of the research team downloaded the BENECA mHealth system app to the patient's mobile phone. The patients were asked to use the mHealth app at least once in the presence of a research team member to ensure the correct use of the system and ask questions if needed. Each participant was also equipped with a tri-axial accelerometer (ActiGraphGT3X+, Pensacola, FL, US). A specialized nutritionist with 3 years of experience with patients with cancer recorded the participant's sociodemographic data and their diet from the previous day using 24-hour dietary recalls. The participants also received 4

daily dietary record questionnaires, which they completed on 4 of the working days. When necessary, a member of the CUIDATE group telephoned participants if they were having difficulties with the BENECA mHealth system.

Gold Standard Methods

Physical Activity

An accelerometer was used to assess the level of physical activity of the participants following a previously published protocol [36]. The patients received a daily questionnaire and were equipped with pre-programmed accelerometers (tri-axial accelerometer, ActiGraphGT3X+, Pensacola, FL, US). They were instructed to wear the accelerometer for 24 hours for 8 consecutive days. Only records obtained from 4 or more days of use (excluding the first day) and at least 10 hours of recording (1-minute intervals) per day were analyzed. The accelerometer data were blinded to the participants.

Dietary Habits

The gold standard method for measuring diet is direct observation. However, in this study, direct observation of the participants' dietary habits was not feasible. Therefore, together with the diet information, 24-hour dietary recalls and dietary records were used as references [9]. With 4dietary records and 2, 24-hour dietary recalls, the intake of 6 days, with 5 eating occasions per day, could be collected.

Twenty Four-Hour Dietary Recalls

The 24-hour dietary recalls were obtained through interviews. The participants did not know in advance when they would be contacted. The specialized nutritionist asked, either in person or by phone [37], about their dietary intakes on the previous day. On the day of the evaluation, an interviewer (trained dietitian) systematically collected detailed information on the diet in the preceding 24 hours. The nutritional value (energy and macronutrients) was evaluated using the Alimentación y Salud software, version 2.0 (Instituto de Nutrición, Universidad de Granada, Spain).

Dietary Records

Due to their validity, dietary records are considered one of the best systems to evaluate dietary intake. These records are a kind of diary in which the patient must log all the food and beverages consumed during a full day [9]. Four dietary records were completed, coinciding with the accelerometer wearing time.

Description of the BENECA Mobile Health System

The BENECA system was developed by the CUIDATE group, which consists of physiotherapists, occupational therapists, physical activity professionals, nutritionists, and a sports physician. BENECA is a native-Android mobile app (Figure 1), with a commercial server and centralized data storage. Its internal

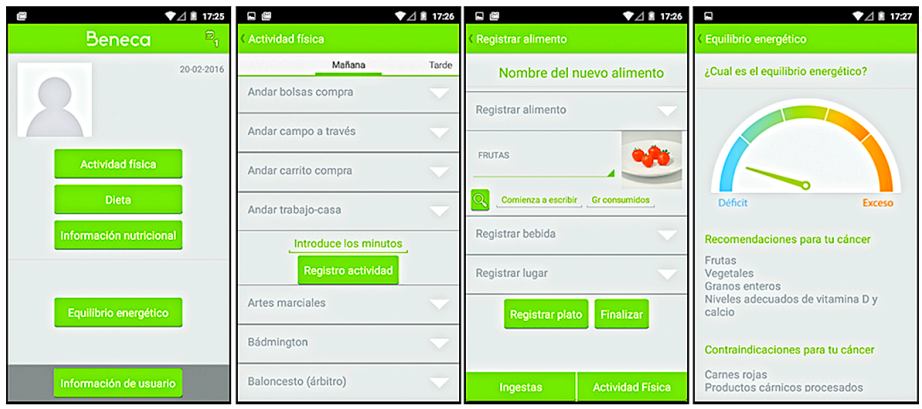
technological development has been described previously [38].

On first use, the users of the app record their personal and anthropometric data, such as weight, height, age, and type of cancer. They are then asked to record what they ate (every item) and what they did (in terms of physical activity) the day before. Regarding intake, BENECA uses a dietary record questionnaire, structured with 6 consumption times. On each day, for each period, users report all food and beverages taken. The app limits the food and drink options that can be selected, based on an internal, predefined list adjusted from the Spanish food database (Agencia Española de Seguridad Alimentaria y Nutrición/Base de Datos Española de Composición de Alimentos v1.0; 2010). The users are asked to record the most alike possibility offered if the food or drink is not on the predefined list.

The BENECA mHealth system was created from the validated Spanish version of the Minnesota Leisure-time Physical Activity Questionnaire [39]. The patients can record the activities completed during the day (intensity and duration), from 3 possible time periods (morning, afternoon, and evening). BENECA only records those activities that have a duration of at least 10 minutes. Internally, the app assigns a metabolic equivalent value (MET) to each activity based on the Compendium of Physical Activities [40].

Once the diet and physical activity are recorded, the users receive a daily straightforward notification about their energy balance, detecting if there has been an imbalance. Moreover, considering their individual profile and the information entered onto the BENECA mHealth app, the users can also obtain physical activity and dietary recommendations based on the guidelines of the World Cancer Research Fund International (WCRF), the strategies for physical activity and diet in patients with cancer from the American College of Sports Medicine [41], and the recommendations of the American Cancer Society [42]. A tutorial video of the BENECA mHealth app can be found in Multimedia Appendix 1.

Figure 1. Screenshots of the Energy Balance on Cancer (BENECA) mobile health system.



Statistical Analysis

For each outcome measure—minutes of moderate-to-vigorous physical activity, number of portions of fruits and vegetables, and percentage of fat—the agreement between gold standard assessment methods and the mHealth system was calculated. To evaluate a systematic change in the mean (bias) from test to retest, the mean difference with 95% CI was used. Moreover, we used 2-way random effect intraclass correlation coefficients (with their CIs) to the interrater reliably trials.

The agreement between diet (foods and drinks) recorded by BENECA and those reported in gold standard diet evaluation approaches were estimated based on the analysis reported previously by Hillier et al [10,11]. Match rates (food or drink items reported in gold standard methods that had also been recorded by the BENECA mHealth system), and phantom rates (items reported in gold standard methods that had not been recorded by the BENECA mHealth system), were calculated following the formulas described by Hillier et al [10].

Mean daily values of percentage of fat, portions of fruits and vegetables, and moderate-to-vigorous physical activity reported by BENECA were calculated for a concurrent validity analysis. The accuracy of the mHealth system was calculated using a linear regression analysis, and the correlation coefficient was determined. Finally, a Passing-Bablok regression was used to control bias [10]. IBM SPSS version 20 was used for all analyses (IBM Statistical Program for Social Sciences SPSS Statistic, Corp., Armonk, NY), and XLSTAT was used for Apple computers (2016 version, Addinsoft SARL).

Results

Test-Retest Reliability

The data obtained with each assessment method (gold standard versus BENECA mHealth system), and the mean differences are shown in Table 1. The mean difference of each outcome measure (gold standard versus BENECA mHealth system) and its alpha reliability estimate are also shown in Table 1. The reliability estimates in all analyses were high (alpha≥.90); portions of fruits and vegetables achieved the lowest reliability estimate with an alpha value of .94. The interrater intraclass correlation coefficients for each gold standard method and the BENECA mHealth system showed evidence of very good interrater reliability (intraclass correlation coefficient≥.90) (Table 1).

Concurrent Validity

A total of 21 breast cancer survivor participants were recruited for this study. Of the participants, 1 (1/21, 5%) could not be

Table 1. Cronbach alpha reliability estimates and interrater reliability between the gold standard measurement and the Energy Balance on Cancer (BENECA) mHealth system. ICC: intraclass correlation coefficient.

Variable	Mean difference between methods in units of measurement, 95% CI	Cronbach alpha reliability estimate interrater	Interrater reliability ICC	
			ρ^a	95% CI
Percentage of fat				
Total	0.15 (–1.44 to 1.74)	.956	.916	0.80 to 0.97
Dietary record	1.32 (0.23 to 2.4)	.957	.918	0.81 to 0.97
24-hour dietary recall	0.29 (–0.99 to 1.59)	.985	.971	0.93 to 0.99
Portions of fruits and vegetables				
Total	0.01 (–0.22 to 0.23)	.982	.964	0.91 to 0.99
Dietary record	–0.07 (–0.44 to –0.30)	.948	.901	0.77 to 0.96
24-hour dietary recall	0.26 (–0.11 to 0.63)	.970	.941	0.85 to 0.97
Minutes of moderate-to-vigorous physical activity	8.89 (6.16 to 11.64)	.991	.982	0.95 to 0.99

[a]ICC (ρ) was calculated using a 2-way mixed effect model.

included in the final sample because the Android version of her phone was not compatible with the BENECA system. Therefore, the final study sample consisted of 20 participants, with a mean age of 47.5 (SD 7.07) years.

The mean BMI of the sample was 26.51 (SD 3.06) kg/m2. Of the participants, 12 (12/20, 60%) had higher education, of which only 2 (2/20, 10%) had sick leave. The most commonly affected side was the right breast (11/20, 55%), and both breasts were affected in only 10% (2/20) of the survivors. Most of the participants were right-handed (18/20, 90%). Of the participants, 55% (11/20) had stage II breast cancer, and 20% (4/20) had stages I and IIIA.

A unilateral mastectomy and a lumpectomy had been performed on 40% (8/20) and 50% (10/20) of the participants, respectively. Only 2 (10%, 2/20) participants underwent a bilateral mastectomy. In addition, 75% (15/20) received postsurgical adjuvant radio-chemotherapy, and 75% (15/20) were also receiving hormonal therapy (the estrogen receptor antagonist tamoxifen).

Compliance with Methods

Paired data for the comparison between the BENECA mHealth system and the dietary records or accelerometer were collected for all participants. The compliance rates for all assessment methods were very high. All participants completed the BENECA system on the 6 requested days. In addition, 18 participants (90%, 18/20) completed the BENECA system on more days than requested. Similarly, compliance with the gold standard assessment methods was 100%. Breast cancer survivors completed the 4 dietary records and the 2, 24-hour dietary recalls; they also wore the accelerometer for the 8 requested days. Compliance with the accelerometer was very good; there were no incomplete sets of data, and the participants did not report any problems with the device (ie, allergic skin reactions).

The BENECA mHealth system showed excellent agreement with both dietary evaluation approaches (Table 2). The dietary records and 24-hour dietary recalls showed high match rates and low phantom

rates. There were 30 intake times and 1630 diet items recorded; only 106 items were not recalled in the BENECA system (omitted or forgotten). "Vegetables" was the most frequently ignored item, followed by biscuits and crisps. Of the total, there were 21 (1.29%, 21/1630) occasions in which the food was not available on the BENECA system. In most of these cases the food items were replaced by an appropriate alternative from the BENECA food option list. However, some food items, such as "couscous," were not replaced, and the choices were entered as "matches" for replaced items. Fifty nine "phantom" items were recorded in the BENECA system without being recorded in the gold standard dietary assessment methods, with biscuits and sweets being the most common "phantom" items.

No significant differences were found between the BENECA mHealth system and the gold standard assessment methods regarding percentage of fat compared to the 24-hour dietary recall (Table 3).

The linear regression analysis revealed coefficients of .93 (95% CI 0.88-1.34), .97 (95% CI 0.86-1.10), and .92 (95% CI 0.74-1.14), with respect to percentage of total fat, 24-hour dietary recalls, and dietary records, respectively. The coefficients for the portions of fruits and vegetables consumed were .97 (95% CI 0.95-1.22) for the total means, .94 (95% CI 0.82-1.19) for the 24-hour dietary recalls, and .93 (95% CI 0.59-0.86) for

Table 2. Food item agreement between the Energy Balance on Cancer (BENECA) app and the gold standard dietary instruments.

Day	Match rate	Phantom rate
Dietary record (%)		
1	94.41	5.63
2	88.87	2.53
3	89.04	2.02
4	94.01	19.10
Mean (SD)	91.58 (9.55)	7.32 (14.96)
24-hour dietary recall (%)		
1 (working day)	97.82	1.46
2 (holiday)	98.61	2.69
Mean (SD)	98.21 (2.68)	2.08 (2.88)
Global, mean (SD)	93.51 (6.36)	3.35 (4.33)

Table 3. Agreement between the Energy Balance on Cancer (BENECA) mHealth system and each gold standard assessment method.

Variable	BENECA mHealth System, mean (SD)	Gold standard method, mean (SD)	Difference of means	95% CI
Percentage of fat				
Total	38.46 (8.97)	38.61 (7.59)	−0.15	−1.74 to 1.44
Dietary record	37.44 (5.81)	38.76 (5.69)	−1.32	−2.41 to −0.23
24-hour dietary recall	38.17 (11.50)	38.47 (11.38)	−0.29	−1.59 to 0.99
Portions of fruits and vegetables				
Total	3.66 (1.91)	3.66 (1.71)	−0.01	−0.24 to 0.22
Dietary record	3.09 (1.56)	3.03 (1.96)	0.07	−0.30 to 0.44
24-hour dietary recall	3.89 (2.24)	4.15 (2.10)	−0.26	−0.63 to 0.11
Minutes of moderate-to-vigorous physical activity	85.51 (23.07)	86.91 (22.57)	−1.40	−3.34 to 0.55

Table 4. Passing-Bablok regression variables of the Energy Balance on Cancer (BENECA) mHealth system versus the 24-hour dietary recall, dietary records, and accelerometer.

Variable	Slope	95% CI	Intercept	95% CI
Percentage of fat				
Total	1.22	1.03 to 1.65	−7.85	−24.58 to −1.19
Dietary record	1.05	0.87 to 1.38	−2.84	−15.28 to 4.13
24-hour dietary recall	1.04	0.92 to 1.20	−1.17	−8.19 to 2.94
Portions of fruits and vegetables				
Total	1.11	0.98 to 1.20	−0.27	−0.58 to 0.02
Dietary record	0.84	0.70 to 1.05	0.61	−0.01 to 1.07
24-hour dietary recall	1.05	0.86 to 1.25	−0.19	−1.19 to 0.45
Minutes of moderate-to-vigorous physical activity	0.97	0.87 to 1.07	11.2	1.37 to 16.93

the dietary records. The model also showed a coefficient of .98 (95% CI 0.91-1.09) for the minutes of moderate-to-vigorous physical activity.

The Passing-Bablok regression analysis did not show considerable bias in percentage of fat (dietary record and 24-hour dietary recall), or portions of fruits and vegetables (Table 4). Only in terms of the percentage of total fat and minutes of moderate-to-vigorous physical activity did the analysis reveal a fixed bias without a substantial proportional bias. However, a substantial proportional bias, but not substantial fixed bias, was revealed when analyzing the percentage of total fat or moderate-to-vigorous physical activity in each assessment method (Table 4).

Discussion

Principal Results

The BENECA mHealth system can be used to assess the energy balance behaviors in breast cancer survivors. It is a straightforward, fast, and consistent assessment system, as shown by the results presented here. Although the BENECA mHealth system has been validated for use in breast cancer survivors, it could be used with other cancer survivors (ie, prostate or colon) because it is based on International Guidelines.

Comparison with Prior Work

The results of this study highlighted the positive agreement between the BENECA mHealth system and daily, 24-hour dietary recalls, as well as accelerometer data (high match rate, low phantom rate). Moreover, intraclass correlation coefficient data suggested satisfactory reliability, with high coefficients for the average of the measurements. To our knowledge, since this is the only strategy that has been developed to assess energy balance in cancer survivors, it is difficult to compare our results to other investigations. Hillier et al (2012) designed SNAPA, a Web-based computer platform that can evaluate the dietary and physical activity conducts in grown-ups. However, our results were not in agreement with this study, which had a match rate of over 75% and a phantom rate below 8.6%. Our results displayed greater a match rate and a lesser phantom rate than

other studies, which reported match rates between 51% and 73% [10,11,15], and phantom rates between 20% and 55% [15,43]. One possibility is that these women, who felt neglected after their medical intervention, adhered better to new technologies [44,45]. Nevertheless, the protocols and evaluation were not similar.

Similar to what has been observed with the SNAPA platform, the most commonly forgotten food in the BENECA mHealth system was "healthy" food, such as vegetables or fruits. It could be that fruits and vegetables were often forgotten because of how the dietary questionnaire in BENECA system was designed. The participants had to introduce each food separately making it easy to forget about fruit and vegetable accompaniments. In contract to our observations, there is a collective perception that people tend to record more "healthy" food and tend to forget "unhealthy" food [10]. Moreover, compared with other assessment methods that use communications and information technologies in different populations, the BENECA mHealth system shows equal or higher reliability [12-14].

Strengths and Limitations

One of the advantages of the BENECA mHealth system is making the main gold standard methods to assess diet and physical activity readily available to patients. Moreover, the BENECA mHealth system is simple to install, compatible with commonly-used Android systems (in the future BENECA will be developed for IOS), and ease of access (Google Play Store in the future). Importantly, an internet connection is not required for its use. Despite these advantages, participants found it difficult to introduce the diet data into the BENECA system, where the grams of each individual food had to be entered. Other disadvantages included: (1) a requirement for basic mobile phone capabilities; and (2) it is only available in Spanish. Our goal is to address these disadvantages and improve future versions of the app.

Given that one of the inclusion criteria to participate in the study was to be able to use mobile apps, the average age of the participants was relatively young. Technology capacity is more common in younger breast cancer survivors, so perhaps these results may not be generalizable to older breast cancer survivors. Future studies should be conducted to clarify this issue, including a population with a higher average age.

Clinical Implications

We believe it would be interesting to combine BENECA with some objective measurement instrument of physical activity, such as an automatic monitoring bracelet, in order to fully automate the recording of physical activity. BENECA is not only useful in clinical research to evaluate the instantaneous energy balance, but it could also be used as a tool to remotely evaluate the time change in this balance after different intervention procedures or surgical procedures.

Moreover, BENECA could be used to facilitate the incorporation of physical exercise programs and healthy diet into the care system of cancer survivors. It is possible that the triangulation generated between the methods used in this trial to monitor physical activity and diet (BENECA, accelerometers, professionals) could have an educational and motivational impact on the patient. However, due to the simplicity of the app, not having to combine it with other components could produce even better results by decreasing the time required to monitor physical activity with accelerometers. Moreover, it could promote patients' autonomy from health care professionals, lower sanitary costs, and supply motivational support through its real-time feedback system.

Conclusions

Our preliminary results showed that the mHealth app BENECA may be a new tool to measure physical activity and intake in breast cancer survivors, in a reliable and simple way. Not only will the real-time feedback system used in BENECA enable positive changes in the lifestyles of breast cancer survivors, it can be used to motivate them to maintain these changes over time.

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Conflicts of Interest

None declared.

Abbreviations

BENECA: Energy Balance on Cancer BMI: body mass index

eHealth: electronic health

mHealth: mobile health.

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A Mobile System to Improve Quality of Life Via Energy Balance in Breast Cancer Survivors (BENECA mHealth): Prospective Test-Retest Quasiexperimental Feasibility Study

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STUDY II

Study II. A Mobile System to Improve Quality of Life Via Energy Balance in Breast Cancer Survivors (BENECA mHealth): Prospective Test-Retest Quasiexperimental Feasibility Study

Abstract

Background: Energy balance is defined as the difference between energy expenditure and energy intake. The current state of knowledge supports the need to better integrate mechanistic approaches through effective studies of energy balance in the cancer population because of an observed significant lack of adherence to healthy lifestyle recommendations. To stimulate changes in breast cancer survivors' lifestyles based on energy balance, our group developed the BENECA (Energy Balance on Cancer) mHealth app. BENECA has been previously validated as a reliable energy balance monitoring system.

Objective: Based on our previous results, the goal of this study was to investigate the feasibility of BENECA mHealth in an ecological clinical setting with breast cancer survivors, by studying (1) its feasibility and (2) pretest-posttest differences with regard to breast cancer survivor lifestyles, quality of life (QoL), and physical activity (PA) motivation.

Methods: Eighty breast cancer survivors diagnosed with stage I to IIIA and with a body mass index over 25 kg/m2 were enrolled in this prospective test-retest quasi-experimental study. Patients used BENECA mHealth for 8 weeks and were assessed at baseline and the postintervention period. Feasibility main outcomes included percentage of adoption, usage, and attrition; user app quality perception measured with the Mobile App Rating Scale (MARS); satisfaction with the Net Promoter Score (NPS); and barriers and facilitators of its use. Clinical main outcomes included measuring QoL with the European Organization for Research and Treatment of Cancer QoL Questionnaire Core 30 (EORT QLQ-C30), PA assessment with accelerometry, PA motivation measure with a Spanish self-efficacy scale for physical activity (EAF), and body composition with dual-energy x-ray absorptiometry. Statistical tests (using paired-sample t tests) and Kaplan-Meier survival curves were analyzed.

Results: BENECA was considered feasible by the breast cancer survivors in terms of use (76%, 58/76), adoption (69%, 80/116), and satisfaction (positive NPS). The app quality score did not make it one of the best-rated apps (mean 3.71, SD 0.47 points out of 5). BENECA mHealth improved the QoL of participants (global health mean difference [MD] 12.83, 95% CI 8.95-16.71, P<.001), and EAF score (global MD 36.99, 95% CI 25.52-48.46, P<.001), daily moderate-to-vigorous PA (MD 7.38, 95% CI 0.39-14.37, P=.04), and reduced body weight (MD −1.42, 95% CI −1.97 to −0.87, P<.001). Conclusions: BENECA mHealth can be considered feasible in a real clinical context to promote behavioral changes in the lifestyles of

breast cancer survivors, but it needs to be enhanced to improve user satisfaction with use and functionality. This study highlights the importance of the use of mobile apps based on energy balance and how the QoL of breast cancer survivors can be improved via monitoring.

Introduction

There is a direct relationship between energy imbalance and an increased risk of not only multiple cancers but also cancer mortality, and a worsening of the effects of the disease [1-3]. Energy balance is defined as the difference between energy expenditure and energy intake [4]. Energy intake that exceeds energy expenditure is the main driver of weight gain; thus, balancing both helps weight maintenance [5].

A panel of experts from the International Agency for Research on Cancer and the World Cancer Research Fund agreed that 16 types of cancer are probably associated with one of the more relevant consequences of energy imbalance, excess fat accumulation in the body, making obesity the second leading cause of cancer worldwide [1,6]. Moreover, since the first decade of the 2000s, the scientific evidence on the benefits of physical activity (PA) in the quality of life (QoL) of cancer survivors (known as "oncological exercise") has grown exponentially, generating dozens of systematic reviews, several international guidelines, and the recommendation to include programs of exercise in cancer survivors care [7]. Dietary and exercise interventions can alter the energy imbalance associated with cancer and potentially decrease the QoL of cancer survivorship [5]. However, the literature shows that despite strong evidence of this association, an insurmountable barrier prevails between "what needs to be done" and "what patients really do," observing a significant lack of adherence to the preceding interventions [1].

In today's progressively technical world, the use of mobile apps in smart devices has become the norm. In the same way, patients increasingly use therapeutic mobile apps related to some form of cancer treatment [8]. More than 2500 mobile apps are defined as apps related to cancer, but this relationship is peripheral or based on unproven claims, such as apps for yoga and naturopathy that claim to help prevent or even cure cancer [9]. In 2017, 15% of studies conducted worldwide were aimed at digital health, with 75% of these studies being conducted in the United States [9]. Recently, 539 apps were considered in a systematic review, which concluded that the effectiveness of most of them had not been validated scientifically [8,10]. Duman-Lubberding and colleagues [11] have developed Oncokompas, an eHealth app to facilitate access to supportive cancer care and monitor cancer patients' QoL [12], specifically in the case of breast cancer [13]. Another study by Gietema and colleagues [14] assessed the feasibility of the Runkeeper app to improve the level of PA of cancer patients. They concluded that there is a need to increase research in the

area. Different studies and meta-analyses of cancer patients show the benefits of mHealth, which include reducing fatigue or pain [15,16], distance PA programs with inconclusive results for and against [17-19], the use of social networks by patients of some types of cancer to improve QoL [20], and monitoring of symptoms [21,22]. However, none of these studies refers to monitoring and providing high-quality research feedback to restore the energy balance in cancer patients. The only references found in this field were in healthy populations [23,24], children and adolescents [25], pregnant women [26], hospitalized patients [27], and cardiac surgery [28] and diabetes [29] patients. Furthermore, monitoring using globally extended systems, such as Fitbit wristbands, is being questioned [30]. A recent systematic review of 67 studies concluded that, except for the measurement of steps in adults, there are a limited number of situations in which these devices provide accurate measurement for use in research [30].

In an attempt to stimulate changes in breast cancer survivors' lifestyles based on energy balance, we developed the BENECA mHealth app: Energy Balance on Cancer [31,32]. BENECA mHealth aims to monitor the energy expenditure and energy intake of breast cancer survivors and provide instantaneous, simple, and clear feedback on the users' energy balance, along with recommendations on how to improve it. This strategy was based on a recent systematic review of behavior change techniques for increasing PA in cancer survivors [33], as well as another study carried out by Hillier et al [34], who developed a Web-based program to assess energy balance in healthy adults. The first essential step, to develop and validate our tool, was to ensure the reliability of the BENECA mHealth monitoring system. The results of our previous study showed that it is a direct, rapid, and consistent evaluation system [32]. Based on these results, the goal of this study was to investigate the feasibility of BENECA mHealth in an ecological setting with a population of cancer survivors after they are discharged from their oncology treatment.

This involved studying the adoption of the app, its usage, user app quality perception, and the barriers and facilitators of its use. In addition, we gained insight into pretest-posttest differences with regard to breast cancer survivors' lifestyles, QoL, and PA motivation. This investigation was based on the hypothesis that using the BENECA mHealth app for 8 weeks would help increase the motivation of breast cancer survivors to adhere to healthier lifestyles, thereby improving their QoL.

Methods

Study Design and Patient Recruitment

A prospective test-retest quasi-experimental study was carried out with 80 breast cancer survivors. The breast cancer survivors were selected based on the following eligibility criteria: (1) breast

cancer stage I, II, or IIIA, (2) 30 to 75 years old, (3) body mass index (BMI) over 25 kg/m2, (4) user-level skills for app management, and (5) completed the adjuvant treatment at least 6 months before being included in the study. Eligible participants were excluded if they had mental or physical health conditions that prevented them from walking and/or participating in the assessment or if they did not sign the informed consent form. In addition, participants had to have access to a mobile device or tablet with an internet connection and an Android operating system. The research team loaned out two devices in cases where this was not possible or the operating system was incompatible with the app. All participants were recruited through the oncology unit from the University Hospital Complex of Granada, Spain, after being informed about the study and being referred by their respective oncologist. All eligible participants were contacted via telephone, screened using the inclusion and exclusion criteria, and if they were interested in participating, cited for the baseline assessment.

This study was approved by the ethics committee of the Andalusian Health Service (FIS, PI14-01627; Granada, Spain) and it was performed in accordance with the Helsinki Declaration for biomedical research (14/2017) [35]. Participants completed informed consent forms before the assessment.

BENECA mHealth

The CUIDATE research group developed the Energy Balance on Cancer (BENECA) mHealth app to monitor and provide feedback to breast cancer survivors on healthy eating and PA. A description of the BENECA mHealth System [31,36] and a reliability study for the same [32] were previously published. After the baseline assessment was performed, a member of the research group downloaded the app on a patient's mobile phone and taught them how to use it. The patient then had to prove that she understood the instructions by using the app in the presence of the researcher. Patients had to use BENECA mHealth for 8 weeks during the study. Physical activity (duration and intensity) and diet (food and drink intake) data were recorded via the app (self-recorded). Intake was recorded using a dietary record questionnaire; BENECA is structured with six consumption times. On each day, for each period, users report all food and beverages consumed. For PA, BENECA incorporated the Minnesota Leisure-time Physical Activity Questionnaire. Patients had to record intensity and duration of activities each day; BENECA only recorded those activities with a duration of at least 10 minutes. Using this information, the app sent a notification to the user of their daily energy balance, offering recommendations on diet and PA, which were based on the guidelines of the World Cancer Research Fund International, the strategies for PA and diet in patients with cancer from the American College of Sports Medicine [37],

and the recommendations of the American Cancer Society [38]. Users receive a straightforward daily notification if there has been an energy imbalance; any difficulties in handling the app were resolved via calls and text messages between the researcher and patient (Multimedia Appendix 1). BENECA had been developed based on the theories of learning, Goal-Setting Theory, and Social Cognitive Theory to include techniques such as reinforcement, facilitation, self-monitoring, goal setting, feedback on performance, and reviewing goals, which have demonstrated to be promising in increasing PA in different populations [33,39]. A video tutorial was made available to the patients to review the use of the app.

Outcome Measures

Patient demographic and clinical data were obtained at the beginning of the study using a study-specific survey. Baseline data were gathered at the start of the study and again after 8 weeks of using BENECA mHealth. The outcomes measured are presented subsequently.

Feasibility of Main Outcomes

BENECA mHealth was considered feasible for use by breast cancer survivors as long as it met the following criteria, established based on previous studies with eHealth apps [11,13,40,41]: adoption and usage rate over 50%, a positive Net Promoter Score (NPS), and a Mobile App Rating Scale (MARS) score of up to 3.73 out of 5.

Adoption, Usage, and Attrition

The adoption rate was the percentage of the number of breast cancer survivors that agreed to participate in the study and completed the initial assessment, demonstrating the intention to use BENECA mHealth, out of the total number invited to participate in the study. The usage rate is the percentage of breast cancer survivors that used BENECA mHealth, which was determined through the logging data of the app. Both the adoption and usage rates were calculated based on the methods used in a previously published study [13]. The attrition rate is the percentage of breast cancer survivors that stopped using BENECA mHealth and did not use it again, as per Eysenbach's definition [42]. To assess the safety of the process, any adverse effects reported by the patients were recorded through a patient's daily diary.

BENECA mHealth Quality

The MARS was used to assess the quality of BENECA mHealth. The MARS is composed of 23 items grouped into different sections: engagement, functionality, aesthetics, and information quality (with which the overall average score of the scale is obtained). There are also two optional sections: subjective quality (with four items) and app-specific quality (with six items). Each item was assessed independently based on a Likert scale from 1 (inadequate) to 5 (excellent), and the mean score was calculated for each section. This scale has been validated and

has proven to be simple, objective, and reliable to assess the quality of mHealth apps [43]. Similarly, the NPS was used to measure satisfaction based on responses to the following question: How likely are you to recommend BENECA mHealth to other breast cancer survivors? The responses were recorded using an 11-point Likert scale in which 0 indicates "not likely" and 10 indicates "very likely." The percentage of detractors (those whose scores were from 0 to 6) and promoters (those whose scores were from 9 to 10) were calculated, and each group was given a score between –100 and 100. A positive score is considered good; a negative score is considered bad [44]. This methodology has been used as a predictor of growth and an indicator of customer satisfaction in for-profit industries, and it provides insight into the client experience in nonprofit health care settings [45].

Barriers and Facilitators

After the participants used BENECA mHealth for 8 weeks and completed the corresponding assessment, a trained member of the research team interviewed each participant using a standardized set of interview questions based on a previous study [13]. This interview focused on three main elements: overall experience with BENECA mHealth, congruence between expectations and reality with BENECA mHealth, and the perception and added value of BENECA mHealth. For cases in which the app was no longer used, the participants were asked about their reasons for not using the app and the preferences or needs that would prompt them to use it. Each interview was read several times and transcribed by the same researcher, and the barriers and facilitators reported by the breast cancer survivors were synthesized [46].

Main Clinical Outcomes

Quality of Life

The European Organization for Research and Treatment of Cancer QoL Questionnaire Core 30 (EORTC QLQ-C30) version 3.0 was used to assess the QoL of the participants. This questionnaire is intended to measure general aspects of QoL specific to cancer patients. It contains five functional scales (physical, role, cognitive, emotional, and social functioning), a global health status scale, and symptom scales of fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial problems. It is scored using a four-point Likert scale (from 1="not at all" to 4="very much") and the raw scores are transformed into a 0 to 100 scale. The higher the score on the functional scales, the better the QoL, but the higher the score on the symptom scales, the poorer the QoL [47,48].

Self-Efficacy and Motivation in Relation to Physical Activity

A Spanish self-efficacy scale for physical activity (EAF) was used to measure the self-efficacy and motivation of the participants to engage in PA and incorporate it into their daily activities. It consists of three domains: scheduled physical exercise, PA

in daily life activities, and walking, which determine a person's perception of their abilities to engage in PA (self-efficacy for PA) [49].

Physical Activity

Data on PA and the sedentary lifestyle of the breast cancer survivors were collected using accelerometry based on a previously published protocol of use and analysis [50]. A preprogrammed triaxial accelerometer (ActiGraph GT3X+, Pensacola, FL, USA) was used by each patient for eight consecutive days. The participants received a questionnaire diary and an instruction sheet on how to use the device. Only the records of more than 4 days and of at least 10 hours per day were included in the analysis.

Body Composition

Dual-energy x-ray absorptiometry densitometer from Hologic, QDR 4500W) was used for assessing BMI, the percentage of fat mass, and bone mineral density, as previously used for breast cancer patients [51] in accordance with protocol of use [52]. The height and weight of the participants were also measured at baseline as well as hip and waist circumferences.

Statistical Analysis

All analyses were performed using SPSS Statistics version 24 (IBM Corp, Armonk, NY, USA). Statistical significance was assumed when P<.05. The logging data from BENECA mHealth were obtained on request from the computer engineers responsible for the development of the app.

First, descriptive measures were used to report the data on adoption, use, attrition, and quality, as well as to report on the clinical and anthropometric variables of the participants. A Kaplan-Meier survival curve was used to visually examine the survival curve of the entire cohort to determine the attrition. In the analysis, an "app survivor" was defined as a breast cancer survivor that maintained logging practices using BENECA mHealth until at least 3 days before the last day of the experimental period. Those defined under "app death" were those who missed five consecutive daily loggings (based on a previous study [53]). A Kaplan-Meier estimator with right-censored data was used. This type of data was used because it best fit our study results. As most of the breast cancer survivors "survived" until the end of the experimental period, we do not know how long they would have continued using BENECA mHealth after this period. Then, a Cox proportional hazard model was used to examine if age, marital status, and employment had any effect on the attrition.

Second, to assess the pretest-posttest differences in the main outcomes, an analysis of paired-sample t tests was used and, when appropriate, Wilcoxon signed rank tests were conducted. Moreover, the effect size (ES) estimate was determined and interpreted using Cohen's guidelines of 0.1=small effect, 0.3=medium effect, and 0.5=large effect.

Table 1. Participant demographics (N=80).

Variables	Participants
Age (years), mean (SD)	51.80 (8.64)
Body mass index, mean (SD)	29.11 (4.77)
Marital status, n (%)	
Single	16 (20)
Married	50 (63)
Divorced	10 (13)
Other	4 (5)
Education, n (%)	
No education	1 (1)
Primary studies	23 (29)
Secondary studies	25 (31)
Higher education	31 (39)
Employment, n (%)	
Homemaker	18 (22)
Employee	32 (40)
Low	10 (13)
Unemployed by the disease	20 (25)
Cancer stage, n (%)	
I	10 (13)
II	40 (51)
IIIA	28 (36)
Surgery, n (%)	
Lumpectomy	24 (30)
Quadrantectomy	13 (16)
Unilateral mastectomy	27 (34)
Bilateral mastectomy	16 (20)
Medical treatment, n (%)	
None	6 (8)
Radiation therapy alone	10 (13)
Chemotherapy alone	6 (8)
Chemotherapy and radiation therapy	48 (60)
Adjuvant chemotherapy	7 (9)
Neoadjuvant chemotherapy	3 (4)

Third, to assess differences between "users" and "nonusers" and the patients' perception of BENECA mHealth quality, a Mann-Whitney test was used for categorizing the breast cancer survivors according to the cut-off used in the survival analysis. A simple linear regression was used to examine the influence of age on the perception of BENECA mHealth quality.

Our data contained a few missing values (5%, 4/80 of the total number of cases), but these can be considered random and inconsequential [54]. Hence, no multiple imputation method was necessary (casewise deletion was used).

Results

Demographic Characteristics

The baseline demographic and clinical characteristics of the participants (mean age 51.80, SD 8.64 years) are presented in

Table 1. Of the 80 breast cancer survivors, 50 (62%) were married, 31 (38%) had a higher education, and 40 (50%) were diagnosed with stage II breast cancer, followed in frequency by stage IIIA (28/80, 35%). All participants received instructions on how to use BENECA mHealth to monitor energy intake and expenditure. Four participants were unable to be assessed postintervention (dropouts); three were not assessed due to changes in their health status unrelated to the study, and one decided to discontinue.

Feasibility Outcomes

Adoption, Usage, and Attrition Rates

The study design is shown in Figure 1. The adoption rate of BENECA mHealth was 69%; 80 of 116 breast cancer survivors who were invited to participate intended to use BENECA mHealth, filled the informed consent form, and were assessed at baseline. The reasons for not participating in the study included lack of interest (too busy; n=14), incompatibility of the user's mobile operating system with BENECA mHealth (n=11), and failed initial contact (eg, wrong phone number or no answer; n=11).

The usage rate was 73% (58/80) including dropouts and 76% (58/76) excluding dropouts. The reasons for stopping using BENECA mHealth included technical issues, such as difficulty in finding specific foods (n=6), app blocks (n=4), difficulty in

Figure 1. Flow diagram of the study design. EAF: self-efficacy scale for physical activity; EORT QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire 30. *N=75 for accelerometry analyses (one broken device on preassessment).

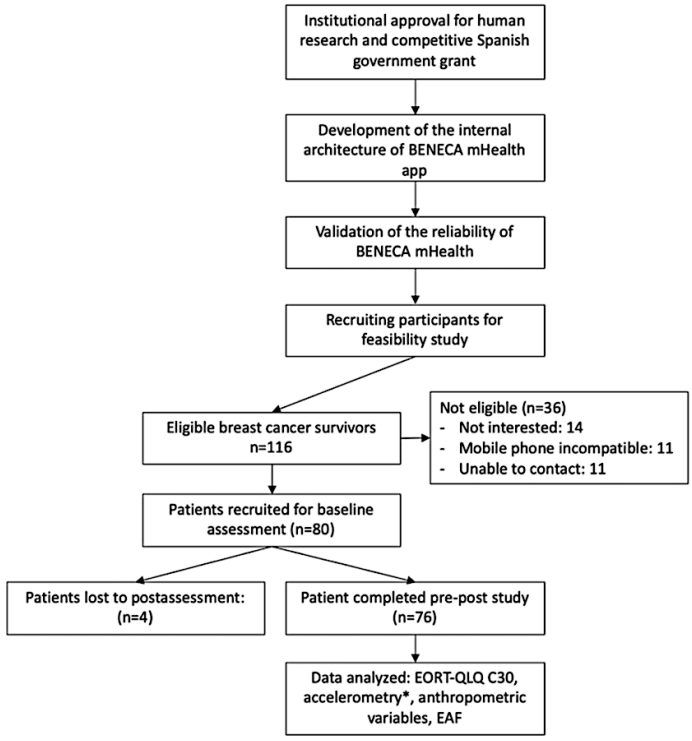


Figure 2. "Survival" of BENECA app participants as shown by a Kaplan-Meier survival curve with 95% CIs (dashed lines).

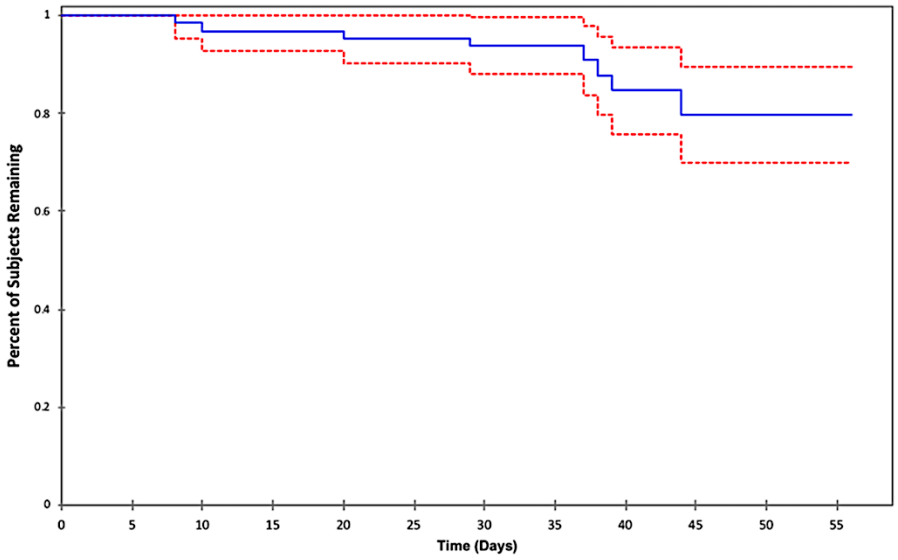


Table 2. Coefficients for the Cox proportional hazards model.

Coefficients	Coefficient estimate (95% CI)	*P* value
Age	1.12 (1.04-1.19)	.001
Marital status[a]		
Married	0.88 (0.25-3.18)	.85
Divorced	0.77 (0.15-4.04)	.76
Other	2.52 (0.35-18.26)	.36
Employment[b]		
Employee	0.46 (0.13-1.59)	.22
Low[c]	1.12 (0.27-4.62)	.87
Unemployed due to the disease	0.46 (0.12-1.67)	.24

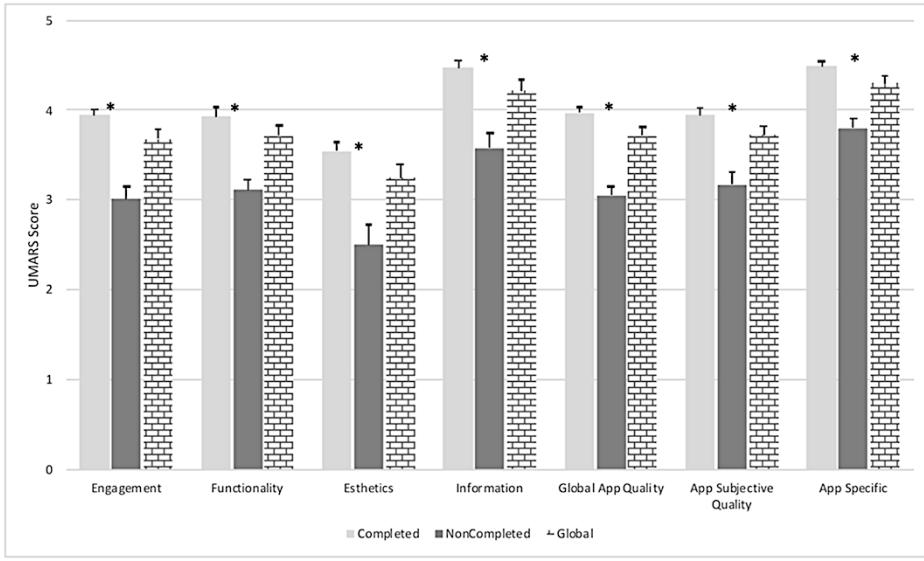
[a]Marital status reference category: single.
[b]Employment reference category: homemaker.
[c]Unemployed/on leave.

calculating proportions of diet registration (n=9), or lack of motivation (n=3). We examined attrition using the Kaplan-Meier survival curve and Cox proportional hazards model. Figure 2 illustrates the attrition curve of the study participants with their respective 95% CIs. The curve is flat at the beginning, begins to get steeper after the first month, and flattens again with time. The Cox proportional hazards model was used to assess the differences in the survival rate using covariables that could affect this rate from the clinical point of view based on a priori knowledge. The results obtained using this model with the covariates were significant at P=.02; the coefficients are shown in Table 2.

Patients' Perception of BENECA mHealth Quality

The mean MARS quality score for the app was 3.71 (SD 0.47) out of 5, and the NPS was positive (6.58 in range of −100 to 100),

Figure 3. Mobile App Rating Scale (MARS) mean scoring. Data show differences between completed and noncompleted users and global mean scoring. Completed users are defined as those who used the BENECA mHealth app until study completion (n=58). Noncompleted users are defined as those who stopped using the BENECA mHealth app study completion (n=22). *P<.001. UMARS: User Version of the Mobile Application Rating Scale.



consisting of 24% (19/80) detractors, 30% (24/80) promoters, and 46% (37/80) passives. On average, the best-rated MARS category was app-specific change (mean 4.30, SD 0.37), followed by information (mean 4.22, SD 0.51), app subjective quality (mean 3.73, SD 0.46), and functionality (mean 3.71, SD 0.52). The worst-rated section was aesthetics, with a mean of 3.25 (SD 0.63). The specific scores for each section of the MARS are illustrated in Figure 3. The participants were divided according to the cut-off used in the survival analysis. It shows how the participants who used BENECA until the end of the experimental period scored higher and were statistically significant in all sections (P<.001). Linear regression showed that the older the patient, the lower the app quality score (beta=–0.29, t75=–2.64, P=.01).

Barriers and Facilitators

In summary, seven barriers and five facilitators were quoted five times or more when the participants were interviewed. Among the barriers, the most common was "BENECA does not have some food items" followed by "difficulty at the time of introducing the intake." Among the facilitators, the most common was "BENECA provides relevant information to the patient" followed by "patient considers it important to know BENECA's feedback on energy balance." Table 3 summarizes the barriers and facilitators mentioned.

Main Clinical Outcomes

Quality of Life

The results of the main pre-post analyses of EORT QoL C30 are shown in Table 4. Statistically significant differences were observed after the experimental period with

Table 3. Barriers and facilitators toward the feasibility of the BENECA mHealth app (N=77).

Barriers and facilitators	n (%)
Barriers	
Extension of BENECA	29 (38)
BENECA does not have an added value for the patient	9 (12)
BENECA does not have some food items	59 (77)
BENECA does not have some physical activities	8 (10)
BENECA feedback is limited	17 (22)
Difficulty at the time of introducing the intake	42 (55)
The patient's perception of BENECA's contribution to her health is negative	2 (3)
Facilitators	
The usefulness of BENECA in general	32 (42)
Ease of introducing physical activity	27 (35)
Patient considers it important to know BENECA's feedback on energy balance	55 (71)
BENECA is easy to use	18 (23)
BENECA provides relevant information to the patient	51 (66)

moderate to large effects as follows: general QoL (t75=6.592, P<.001, d=0.87), physical functioning (t75=5.312, P<.001, d=0.63), emotional functioning (t75=2.981, P=.004, d=0.23), cognitive functioning (t75=5.575, P<.001, d=0.75), social functioning (t75=6.619, P<.001, d=0.82), fatigue (t75=−6.003, P<.001, d=0.85), pain (t75=−2.017, P=.047, d=0.23), dyspnea (t75=−5.190, P<.001, d=0.61), and insomnia (t75=−2.905, P=.005, d=0.32). An improvement in the scores of all these items, as well as a reduction in some symptoms, was observed after 2 months of using BENECA mHealth.

Self-Efficacy and Motivation for Physical Activity and Accelerometry

The results of the main pre-post analyses using the self-efficacy scale for PA and

Table 4. Within-group pre-post effects on mean quality of life scores on the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire 30 (EORTC QLQ-C30).

EORT QLQ-C30 variable	Study group, mean (SD)		Mean difference (95% CI)	*P* value[a]
	Pre (n=76)	Post (n=76)		
Global health	58.54 (14.40)	70.83 (11.26)	12.83 (8.95 to 16.71)	<.001
Physical functioning	75.25 (15.88)	85.35 (13.16)	10.88 (6.80 to 14.96)	<.001
Role functioning	66.45 (26.45)	70.83 (24.36)	5.26 (−1.99 to 12.52)	.15
Emotional functioning	59.06 (19.31)	64.04 (19.82)	5.59 (1.86 to 9.33)	.004
Cognitive functioning	62.5 (22.11)	80.26 (21.38)	17.98 (11.56 to 24.41)	<.001
Social functioning	66.88 (23.94)	86.62 (20.00)	20.17 (14.10 to 26.25)	<.001
Fatigue	42.5 (23.64)	23.68 (15.95)	−19.59 (−26.09 to −13.09)	<.001
Nausea	2.29 (6.35)	2.19 (5.67)	−0.22 (−1.54 to 1.10)	.95
Pain	44.58 (26.22)	38.6 (20.59)	−6.35 (−12.64 to −0.08)	.047
Dyspnea	27.92 (25.13)	12.72 (19.60)	−15.35 (−21.24 to −9.46)	<.001
Insomnia	46.25 (36.16)	35.09 (32.61)	−12.28 (−20.70 to −3.86)	.005
Appetite loss	9.58 (15.18)	7.46 (15.00)	−2.19 (−6.38 to 1.99)	.30
Constipation	21.67 (28.11)	19.74 (29.40)	−1.75 (−8.78 to 5.27)	.62
Diarrhea	10.83 (19.68)	12.72 (18.83)	1.31 (−1.85 to 4.47)	.41
Financial difficulties	19.17 (28.94)	16.67 (24.65)	−2.19 (−5.99 to 1.61)	.25

[a]Paired-sample *t* test or Wilcoxon signed rank test as appropriate. Analyses were performed on only those patients that followed-up.

accelerometry are shown in Table 5. There were significant statistical differences after the experimental period with a moderate ES on the EAF scale as follows: daily PA (t75=5.369, P<.001, d=0.56), walking (t75=6.228, P<.001, d=0.55), and total EAF score (t75=6.423, P<.001, d=0.67). For accelerometry, there were only significant differences in weekday moderate-to-vigorous physical activity (MVPA; t75=2.106, P=.04, d=0.26), observing trend in global MVPA (t75=1.917, P=.06), weekday steps (t75=1.779, P=.08), and global steps (t75=1.647, P=.10). Therefore, after using BENECA mHealth, the users felt more motivated to increase the levels of PA in their daily lives.

Body Composition

The results of the main pre-post analyses of the anthropometric variables are shown in Table 6. Statistically significant differences were observed after the experimental period with a moderate ES as follows: weight (t75=−5.050, P<.001, d=0.12) and BMI (t75=−4.804, P<.001, d=0.12). In addition, a

Table 5. Within-group pre-post effects on mean scores on the self-efficacy scale for physical activity (EAF) and accelerometry.

Variable	Study group, mean (SD)		Mean difference (95% CI)	*P* value[a]
	Pre (n=76[b])	Post (n=76)		
EAF				
Scheduled PA[c]	81.70 (33.08)	87.71 (19.22)	6.08 (−1.08, 13.24)	.10
Daily live PA	50.06 (22.67)	62.63 (17.64)	12.22 (7.69, 16.76)	<.001
Walking	15.20 (9.03)	20.34 (7.95)	5.12 (3.48, 6.76)	<.001
Total EAF score	146.96 (53.36)	184.61 (48.52)	36.99 (25.52, 48.46)	<.001
Accelerometry				
MVPA[d] weekday	50.68 (25.83)	58.07 (26.05)	7.38 (0.39, 14.37)	.04
MVPA weekend	41.77 (24.55)	42.77 (21.51)	0.99 (−4.62, 6.62)	.73
MVPA global	48.14 (24.31)	53.69 (21.85)	5.55 (−0.22, 11.34)	.06
Steps weekday	7488.97 (3142.34)	8268.41 (3230.87)	779.44 (−94.35, 1653.22)	.08
Steps weekend	6218.50 (3147.26)	6316.87 (2875.87)	98.37 (−678.14, 874.88)	.80
Steps global	7125.97 (2935.94)	7710.82 (2672.78)	584.85 (−123.09, 1292.78)	.10

[a]Paired-sample *t* test or Wilcoxon signed rank test as appropriate. Analyses were performed on only those patients that followed-up.
[b]Accelerometry analyses was perform on 75 participants because there was one more dropout on preassessment (broken device).
[c]PA: physical activity.
[d]MVPA: moderate-to-vigorous physical activity.

Table 6. Within-group pre-post differences on anthropometric and body composition variables.

Variable	Study group, mean (SD)		Mean difference (95% CI)	*P* value[a]
	Pre (n=76)	Post (n=76)		
Weight (kg)	73.09 (11.14)	71.67 (10.90)	−1.42 (−1.97, −0.86)	<.001
BMI[b] (kg/m^2)	29.11 (4.78)	28.51 (4.73)	−0.57 (−0.81, −0.34)	<.001
Waist circumference (cm)	87.45 (9.26)	86.97 (9.00)	−0.84 (−1.71, 0.04)	.06
Hip circumference (cm)	107.94 (14.23)	107.71 (13.11)	−0.64 (−1.93, 0.63)	.32
Body fat (%)	41.44 (6.23)	39.78 (7.34)	−1.57 (−3.18, 0.04)	.06
Bone mineral density (g/cm^2)	1.02 (0.11)	1.04 (0.14)	0.02 (−0.02, 0.05)	.31

[a]Paired-sample *t* test or Wilcoxon signed rank test as appropriate. Analyses were performed on only those patients that followed-up.
[b]BMI: body mass index.

trend was observed in waist circumference (t74=−1.900, P=.06) and body fat (t75=−1.946, P=.06). No differences were observed for hip circumference (t74=−1.007, P=.32) and bone mineral density (t75=−1.019, P=.31). After 2 months of using BENECA mHealth, a reduction in users' body weight was observed, which could lead to a reduction in the hip circumference and percentage of body fat.

Discussion

Principal Results

According to our initial hypothesis, after using BENECA mHealth for 8 weeks, the app was considered feasible by the breast cancer survivors in terms of use, adoption, and satisfaction, although the app quality score did not make it one of the best-rated apps. BENECA mHealth was associated with changes in the QoL of breast cancer survivors, as well as their self-perception of effectiveness and motivation for engaging in PA in their daily life.

Comparison with Prior Work

The adoption rate in this study was 69%, and the usage rate was 73% to 76%. These results can be explained by the technical characteristics of BENECA mHealth and its functionality, such as user-friendliness, the use of internationally accepted measures, and the visual feedback. The results of this study are comparable with those obtained by Melissant et al [13] for a supportive care app for breast cancer survivor, which had an adoption rate of 75% and usage rate of 75% to 84%. Another study of a lifestyle intervention with a mobile app for endometrial and breast cancer survivors recorded a 75% usage rate [55]. However, Duman-Lubberding et al [11] obtained an adoption rate of 64% and a usage rate of 75% to 91% for a similar app for head and neck cancer survivors. The somewhat lower rate of use in our study for the latter may be due to how these data were obtained (ie, by the number of log-ins—objective measure—instead of the self-reported data of those studies—subjective measure). With regard to "app survival," we found that in a study by Springer et al [53] to test an mHealth app targeting healthy eating behavior in the general population, they obtained a survival rate less than 60% using the Kaplan-Meier survival curve. The higher survival rate in our study (over 70%) can be explained by the type of population studied. In general, patients with some type of pathology will be more predisposed to be involved in this type of study than the general population [56]. In addition, experiencing cancer treatment may be a stimulus to use the app, as patients may feel the increased need to learn more about the treatment.

Taking into account the barriers perceived by the participants in the use of the app, the barriers reported by BENECA mHealth were in line with a recently published review on the adherence to online psychological interventions [57] as well as with those in a study by Melissant et al [13] with the Oncokompas app to monitor the QoL of breast cancer survivors (eg, "Oncokompas is too extensive"). The reported mean satisfaction score of the

quality of BENECA mHealth, although it may seem not very high, is in line with a recently published study on the quality of 18 mobile apps for pain management using the same MARS quality scale [41]. In addition, the low scores in some sections can be explained by the barriers reported by the patients, such as the difficulties in inputting the intake that makes it very extensive to fill in the app. This barrier was also reported in another feasibility study on head and neck cancer patients [11]. Considering that the minimum score to be considered a best-rated app based on the MARS scale is 3.73 (according to a previous study [41]), BENECA mHealth can be regarded as an app with average ratings. BENECA is currently being improved in an attempt to address the reported barriers.

The benefits of PA for cancer patients have been amply demonstrated [58], although a recent meta-analysis (2013-2018) of distance-based PA behavioral change interventions for cancer survivors concluded that the effects of interventions on PA were small [18]. In addition, although efficacy cannot be discussed in a study such as this, according to the literature, a difference of 8 points between assessments of QoL measured with the EORT QLQ-C30 is the minimum clinically significant difference required to discuss the clinical relevance of the findings [59]. The QoL findings in this study reinforce these preceding conclusions and are consistent with the results of the EAF scale and those observed via accelerometry. Changes are observed in the participants with more motivation to do PA, and it seems that using BENECA mHealth is associated with changes that lead to a positive feedback chain that improves physical and emotional functioning. The significant differences in cognitive functioning can be explained by the actual use of the mobile device, as there is evidence of the cognitive benefits of using electronic devices [60]. Our findings are in agreement with those reported by Pope et al [20], who used a mobile app and social media for 10 weeks to improve the QoL of breast cancer survivors, with a sample size much smaller than ours. However, they differ from the conclusions of McCarroll et al [55], who assessed the effectiveness of a public mobile app (LoseIT) for dietetic intervention for 4 weeks in breast and endometrial cancer survivors. They did not find significant changes in the QoL of the patients. It is possible that the experimental period of 4 weeks and lack of stratification of the type of cancer could explain these differences, despite the use of a powerful questionnaire to assess QoL. Lastly, we only found statistically significant differences in the MVPA of the data obtained via accelerometry, although we observed an improvement in other variables after the use of BENECA mHealth. These results are consistent with those of a clinical trial published in 2018 that used smartwatches and social media PA behavioral change over a 10-week intervention to determine the health outcomes for breast cancer survivors, in which no significant differences in the accelerometry variables were observed [61].

Finally, one of the main challenges not only with cancer patients but with the general population is the maintenance and reduction of body weight [5,62]. Different studies of lifestyle interventions have shown beneficial results, such as the one by von Gurenigen et al [63] in which they evaluated the effectiveness of a face-to-face intervention on diets in obese patients with endometrial cancer, achieving a reduction of approximately 5%. Similarly, McCarroll et al [55] achieved a reduction of approximately 6% from baseline weight. The literature indicates that a weight reduction of 5% is sufficient to reduce medical comorbidities [62]. In our study, an average weight loss of approximately 2% was achieved, which is below the recommendations. This may be because BENECA mHealth is not really a lifestyle intervention mobile app, but rather one that tries to incite behavioral change in users by monitoring their energy balance and making them aware of it. Therefore, we believe that the results obtained can be considered a first step, although future research should corroborate these results. The internal architecture of BENECA mHealth can also be extrapolated to suit patients with other types of cancer.

Strengths and Limitations

It is important to recognize some of the limitations of this study. The main one is its design. It is a nonrandomized, single-arm exploratory study; therefore, the results should be taken with caution. The ideal study would have been a randomized controlled trial (RCT); nevertheless, it was mandatory to develop a feasibility study for this sensitive population before carrying out an RCT. Moreover, due to the nature of the design of this study, the reported results must be confirmed in a larger RCT because the observed changes may not be attributable to the intervention. Secondly, BENECA was only developed for the Android operating system, but we are currently working on the next version of the BENECA app to solve this limitation. Thirdly, BENECA was designed to monitor energy balance and then propose recommendations based on international guidelines of clinical practice, systematic reviews, and meta-analysis to ensure the recommendations can be generalized. However, we believe that it is a good starting point, especially for very sedentary people. Finally, the generalization of results is limited due to the design of the study, the use of restrictive inclusion and exclusion criteria and the recruitment strategy (the participants were referred by their oncologists), which may involve a bias of the threat of regression to the mean. In addition, another added difficulty could refer to the use of the app by older people in southern Spain, who may not even have mobile phones adapted to the app. Therefore, future studies should be conducted with a larger sample size; a controlled and randomized clinical trial design comparing the use of BENECA with, for example, a face-to-face intervention; and including biomarker measurements such as those for

inflammation or development/ recurrence of breast cancer.

Despite these limitations, this study also has strengths. These include the wide range of ages of the participants, which makes it possible to generalize the results; the use of energy balance as a means of changing behavior, which has not been studied much; its ease of use; it has high adherence; and it has no adverse effect on the prior validation of BENECA mHealth [32], which guarantees its reliability.

Conclusions

BENECA mHealth can be considered feasible in a real clinical context and has been associated with behavioral changes in the lifestyles of breast cancer survivors, but it needs to be enhanced to improve user satisfaction with use and functionality. Having assumed that BENECA is usable and applicable in a real clinical context, as well as having the first data of its applicability and clinical efficacy, the next step will be to confirm these results through a larger study with a control group. In addition, efforts should focus on overcoming the barriers reported by the participants and developing a new version of BENECA mHealth in which these improvements will be implemented. Finally, future research could focus on its generalization for application to other oncological processes. This study highlights the importance of the use of mobile apps based on energy balance and how the QoL of breast cancer survivors can be improved via monitoring. The results of this study could garner support for the use of this type of strategy in the projected 29.5 million cancer patients in 2040 [64].

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Conflicts of Interest

None declared.

Abbreviations

BMI: body mass index

EAF: self-efficacy scale for physical activity (Spanish)

EORT QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

ES: effect size

MARS: Mobile App Rating Scale

MVPA: moderate-to-vigorous physical activity

NPS: Net Promoter Score

PA: physical activity

QoL: quality of life

RCT: randomized controlled trial

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Association Between the Use of a Mobile Health Strategy App and Biological Changes in Breast Cancer Survivors: Prospective Pre-Post Study

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STUDY III

Study III. Association Between the Use of a Mobile Health Strategy App and Biological Changes in Breast Cancer Survivors: Prospective Pre-Post Study

Abstract

Background: There is a bidirectional relationship between chronic low-grade inflammation and cancer. Inflammatory markers, such as interleukin-6 (IL-6), have been associated with both the malignant transformation of epithelial cells and tumor progression, thus linking low-grade inflammation with a higher risk of cancer and recurrence in the survival phase. Therefore, they are considered valuable prognostic biomarkers. Knowing and finding appropriate primary prevention strategies to modify these parameters is a major challenge in reducing the risk of cancer recurrence and increasing survival. Different therapeutic strategies have shown efficacy in the modification of these and other biological parameters, but with contradictory results. There are apparently no strategies in which telemedicine, and specifically mobile health (mHealth), are used as a means to potentially cause biological changes.

Objective: The objectives of this study were to: (1) check whether it is feasible to find changes in inflammation biomarkers through an mHealth strategy app as a delivery mechanism of an intervention to monitor energy balance; and (2) discover potential predictors of change of these markers in breast cancer survivors (BCSs).

Methods: A prospective quasi-experimental pre-post study was conducted through an mHealth energy balance monitoring app with 73 BCSs, defined as stage I-IIIA of breast cancer and at least six months from the completion of the adjuvant therapy. Measurements included were biological salivary markers (IL-6 and C-reactive protein [CRP]), self-completed questionnaires (the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, the user version of the Mobile Application Rating Scale [uMARS] and an ad hoc clinical and sociodemographic questionnaire) and physical objective measures (accelerometry, weight and height). In addition, using the logging data of the mHealth app, the rate of use (in days) was recorded during the entire experimental phase of the study. Using Stata software, a paired two-tailed t test, Pearson and Spearman correlations, and a stepwise multiple regression analysis were used to interpret the data.

Results: Analyzing changes in inflammatory biomarker concentrations after using the mHealth app, differences between preassessment CRP (4899.04 pg/ml; SD 1085.25) and IL-6 (87.15 pg/ml; SD 33.59) and postassessment CRP (4221.24 pg/ml; SD 911.55) and IL-6 (60.53 pg/ml; SD 36.31) showed a significant decrease in both markers, with a mean difference of –635.25

pg/ml (95% CI −935.65 to −334.85; P<.001) in CRP and −26.61 pg/ml (95% CI −42.51 to −10.71; P=.002) in IL-6. Stepwise regression analyses revealed that changes in global quality of life, as well as uMARS score and hormonal therapy, were possible predictors of change in CRP concentration after using the mHealth app. In the same way, the type of tumor removal surgery conducted, as well as changes in weight and pain score, were possible predictors of change in IL-6 concentration after using the app.

Conclusions: In conclusion, through the results of this study, we hypothesize that there is a possible association between an mHealth energy balance monitoring strategy and biological changes in BCSs. These changes could be explained by different biopsychosocial parameters, such as the use of the application itself, quality of life, pain, type of tumor removal surgery, hormonal treatment or obesity.

Keywords: mHealth; interleukin-6; C-reactive protein; breast cancer survivors; low-grade inflammatory.

Introduction

There is a bidirectional relationship between chronic low-grade inflammation and breast cancer, as a tumor can produce an inflammatory environment and therefore a systemic immune response, but chronic inflammation can also both precede and promote the development of cancer [1]. There is even talk of considering inflammation to be an enabling feature of breast cancer, or the seventh hallmark of the disease along with the six hallmarks already identified by Hanahan and Weinberg [2,3]. Inflammation is a process, or bodily response, secondary to infection or sudden injury, and it is associated with the activation of various molecular mechanisms [4]. This response can be local or systemic, depending on the severity, and both indicate an imbalance of the metabolism of the affected tissues. This metabolic imbalance in the lesion is produced by an increase of immune cells as well as inflammatory parameters of great clinical importance, such as C-reactive protein (CRP) and its inducer interleukin-6 (IL-6) [4,5].

Once the inflammatory response ends, tissue metabolism is normalized. If this process of remission is interrupted by some circumstance, such as pathogens, toxins or other stimuli, healthy tissue could be damaged and produce what is known as persistent low-grade inflammation, or chronic inflammation [6]. It is the result of an immune system that overreacts so that the concentrations of inflammatory factors are higher than in a healthy population [5]. This systemic and chronic inflammation is widely associated with chronic diseases [6] and even symptomatology, as there is a positive association between increased levels of CRP and excess of adipose mass (excess weight and obesity), which is a factor that could be potentially modified with physical activity and diet [4,7]. Moreover, inflammatory markers such as IL-6 have also been associated with the malignant transformation of epithelial cells and tumor progression, associating low-

grade inflammation with a higher risk of cancer and recurrence in the survival phase. Thus, these factors are considered valuable prognostic biomarkers in the population of those with cancer [1,8,9]. Therefore, knowing and finding appropriate primary prevention strategies to modify these parameters is a major challenge in the field, so as to reduce the risk of cancer recurrence and increase survival.

Different therapeutic strategies have shown efficacy in the modification of these and other biological parameters, but with contradictory results. The beneficial effects of physical exercise as a means of controlling low-grade inflammation have been amply demonstrated [10,11], even in breast cancer survivors (BCSs). A study conducted by Jones et al, in which they used a physical exercise program in BCSs, found a significant reduction of IL-6 [12]. Additional studies have evaluated other strategies, such as manual therapy [13], tai chi [14], mindfulness [15], or yoga [16], to reduce inflammation markers in different cancer populations. However, scientific evidence about strategies based on telemedicine are scarce, and they are practically nonexistent for cancer. A study conducted by Haggerty et al assessed two technology-based, 6-month, lifestyle interventions (telemedicine or text messaging) in obese women with endometrial hyperplasia, showing a reduction of some biomarkers such as IL-6 after the intervention [17]. Another study by Frank et al examined the effectiveness of telehealth coaching promoting nutrition and exercise in soldiers, evaluating biomarkers of bone health [18]. There are also some clinical trial protocols with no published results at present [19-21]. Therefore, at the moment there are no strategies in which telemedicine, and specifically mobile health (mHealth), are used as a delivery mechanism for interventions that could cause biological changes.

Low-grade inflammation is highly influenced by aspects such as obesity, fatigue or a sedentary lifestyle [22-24], and its relationship with chronic pathologies has been demonstrated. However, the issue of association, or the factors that influence its regulation through nonpharmacological and distance-based intervention strategies, remain unresolved [6]. In the biopsychosocial context that encompasses a subject with cancer, promoting changes through mHealth strategies in psychological, physical or social aspects is not entirely complicated (eg, quality of life) [25]. However, biological parameters have a high intersubject variability and are not usually addressed in these types of studies [24]. Therefore, understanding what factors can influence these parameters can help to develop mHealth-based strategies, thus increasing patient empowerment in regard to their health.

To the best of our knowledge, scientific evidence is scarce in regard to mHealth-based strategies related to tracking biomarkers of inflammation, and the importance of low-grade inflammation in cancer recurrence has already been

demonstrated. Thus, the objectives of this study were to:

1. Check whether it is feasible to find changes in inflammation biomarkers through an mHealth strategy as a delivery mechanism of an intervention to monitor energy balance.
2. Discover potential predictors of change of these markers in breast cancer survivors.

Methods

Study Design, Participants, and Description of the Mobile Health App

A prospective quasi-experimental pre-post study was conducted through an mHealth app to monitor energy balance (BENECA mHealth app) with 73 BCSs, defined as stage I-IIIA of breast cancer and at least six months from the completion of adjuvant therapy (only hormonal therapy was allowed). Participants were recruited from the oncology units of San Cecili University Hospital and Virgen de las Nieves University Hospital, both in Granada, Spain, through their reference oncologists. All participants received oral and written information about the assessment protocols, mHealth app characteristics, and risks and benefits of the study, and then written consent was obtained from all of them. The Ethics Committee on Human Research (CEIH) from Granada province, Spain, approved this study (FIS, PI14-01627), which was performed in accordance with the Declaration of Helsinki [26]. The inclusion and exclusion criteria for this study are shown in Textbox 1.

After the initial assessment, all participants were invited to use the mHealth app for two months. In summary, the mHealth app was developed to help breast cancer survivors overcome energy balance challenges and aimed to both motivate and sensitize breast cancer survivors to adhere to fully personalized physical exercise programs and nutritional plans, in compliance with the international guidelines for cancer survivors. On first use, the users of the app recorded their personal and anthropometric data such as weight, height, age, and type of cancer. They were then asked to record what they ate (every item) and what they did (in terms of physical activity) the day before. Regarding food intake, BENECA uses a dietary record questionnaire structured with 6 consumption times. Regarding physical activity, patients could record the activities they completed during the day (intensity and duration) from 3 possible time periods (morning, afternoon, and evening). BENECA only records those activities that have a duration of at least 10 minutes.

Based on all this information, the mHealth app provided automatic feedback about a person's energy balance or imbalance as well as nutritional information about what was ingested. In the presence of energy imbalance, it provided useful and simple tips to improve this imbalance. All these straightforward, daily notifications were based on the guidelines of the World

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Between 30 and 75 years of age.
- Body mass index >25 kg/m^2.
- Stage I-IIIA of breast cancer.

Exclusion criteria:

- No medical clearance to participate.
- Any physical health condition that prevents them from walking.
- Any physical or mental health condition that prevents them from participating in assessments.
- No access to any mobile device or tablet with an internet connection.

Cancer Research Fund International [27], the strategies for physical activity and diet in patients with cancer from the American College of Sports Medicine [28], and the recommendations of the American Cancer Society [29,30]. The mHealth app was developed based on the theory of Learning, on Goal-Setting Theory, and on Social Cognitive Theory so as to include techniques such as reinforcement, facilitation, self-monitoring, goal setting, feedback on performance and reviewing goals, which have proven to be promising in increasing physical activity in different populations [31,32]. The technical characteristics of the mobile application [33], as well as validation of the energy balance monitoring system [34] and its feasibility [35], have been previously published.

Participants were able to contact a researcher at any time via WhatsApp, in case of technical problems or to discuss any doubts they had. In addition, an online video tutorial was available at any time.

Outcomes Measures

To assess changes after use of the mHealth app, all measurements were taken at baseline and 8-weeks after having used it. Participants were called via phone for pre and postassessments and invited to Cuidate Support Unit for Oncology Patients, a clinical research center from the University of Granada, Spain. Measurements taken included biological markers, self-completed questionnaires, and both anthropometric and physical objective measures. In addition, using the logging data of the mHealth app, the rate of use (in days) was recorded during the entire experimental phase of the study.

Biological Markers: Main Outcomes

Two salivary inflammatory markers were obtained: IL-6 and CRP. Salivary biomarkers have previously demonstrated the potential to be used for screening and research purposes [36].

Sample Handling and Preparation: Salivary Interleukin-6 and C-reactive Protein Concentrations

On the day of sample collection, the participants were informed of the requirements: they were not allowed to eat, drink or brush their teeth during the two hours prior to the collection, and they were not allowed to visit the dentist 24 hours

before sampling, with the aim of reducing the risks of contamination. They were also not allowed to consume alcohol during the 12 hours prior to the collection of the sample, or to take acidic or high sugar foods. The saliva sample collection was done between 10:00 and 11:30 in the morning, and an attempt was made to match the time in the postassessment. Ten minutes before the collection of the sample, participants were asked to rinse their mouths with water. Saliva was collected by unstimulated passive drool for 3 minutes using a polypropylene vial. Participants were instructed to lean their heads forward, allowing the saliva to accumulate on the floor of the mouth. Immediately after collection, the sample was centrifuged at 3000-3500 rpm for 15 minutes (to remove mucins and other particles that might interfere with the results), and then the supernatant was stored in 200 µL tubes (total of 5 per participant). Finally, it was frozen and stored at –80°C for no longer than 3 months.

Sample Analysis (Enzyme Linked Immunosorbent Assay Procedures)

Once the sampling was completed, it was thawed completely until reaching room temperature prior to the completion of the solutions. The necessary sample was pipetted into dissolution tubes, and the residual saliva not analyzed was frozen again. The following enzyme linked immunosorbent assay (ELISA) kits were chosen: the Salimetrics C-Reactive Protein ELISA Kit (Kit number 1-3302, which is an enzyme-linked immunoassay specifically designed and validated for the quantitative measurement of salivary CRP), and the Salimetrics IL-6 ELISA Kit (Kit number 1-3602, which is a sandwich immunoassay specifically designed and validated for the quantitative measurement of salivary IL-6). Both have been designed and optimized for salivary research in humans. All analyses and calculations were performed following the manufacturer's protocol, as described by Salimetrics. A total of 15 µL and 60 µL of saliva were required for the analyses of CRP and IL-6, respectively.

Once the reagents were prepared, we designed the plate where 100 µl of the samples were added, as well as the successive dilutions of the standard of each marker that would be used for the design of the standard curve. The sample was covered with an adhesive and incubated for two hours at room temperature before mixing at the mix plate at 500 rpm. Then, the plate was washed 4 times with wash buffer by filling and emptying the wells to remove the solution by either aspiration or plate inversion. After washing, antibody conjugate solution was added (100 µL/well) and then diluted in blocking buffer in a series of twofold dilutions. Then the plate was sealed and incubated for 2 hours at room temperature. After the incubation, we repeated the washing as described above. Once the wash was completed, the substrate solution was added, and the plate was incubated in the dark at room temperature for 30 minutes before then mixing for 5 minutes on a plate rotator at 500 rpm. Then, we stopped the reaction by

adding the stop solution (50 µl). The solution was mixed at the plate rotator for 3 minutes at 500 rpm. The absorbance was then measured with a spectrophotometer (Biotek ELx800) at 450 nm, according to kit manufacturers. Results were compared with a standard curve that was previously designed. All standards, controls and samples were analyzed in duplicate.

Self-Completed Questionnaires

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORT QLQ-C30) version 3.0 was used to measure quality of life of the participants. It is a questionnaire specifically designed to evaluate general aspects of quality of life of patients with cancer. It is composed of a global scale of health status, five functional scales (in which the higher the score, the higher the quality of life reported) and eight symptom scales (in which the higher the score, the greater the symptoms reported). This instrument has shown adequate reliability [37,38].

The user version of the Mobile Application Rating Scale (uMARS) was used to measure the satisfaction and quality of usage of the mHealth app. This questionnaire is composed of 23 elements grouped into different sections, each of them evaluated independently through a Likert scale of 1 to 5 points (5 being excellent). Finally, the average score is calculated. This scale has been validated and has proven to be simple, objective and reliable [39].

An ad hoc questionnaire was used to collect clinical and sociodemographic characteristics of participants, including the stage of breast cancer, the type of tumor removal surgery, and the medical treatment and hormonal therapy. The stage of breast cancer could be I, II or III-A, the type of surgery was categorized in increasing order according to invasion of the surgery method (lumpectomy, quadrantectomy, unilateral mastectomy and bilateral mastectomy), the medical treatment was either a neoadjuvant or adjuvant treatment, and the hormonal therapy was registered as either taking or not taking hormonal treatment, as well as its typology.

Anthropometric and Physical Objective Measures

A preprogrammed triaxial accelerometer (ActiGraph GT3X+, Pensacola, Florida) was used to collect data on participants' physical activity over 8 consecutive days, together with a questionnaire diary based on a previously published protocol of use and analysis [40,41]. Only the records of more than 4 days, and of at least 10 hours per day, were included in the analysis. Minutes of vigorous-to-moderate physical activity (MVPA) were recorded.

Weight (kg) and height (cm) were measured with light clothing and without shoes. Weight was measured using an electronic scale (model SECA 869, Hamburg, Germany), and height was measured in the Frankfort plane using a stadiometer (model SECA 213).

Statistical Analysis

Measures of central tendency and dispersion were used for continuous variables with a normal distribution. Categorical variables were reported as proportions (%). The Kolmogorov-Smirnov test was used to check the normal distribution of the data. To evaluate the differences in the biological variables (CRP and IL-6) between baseline and after 8 weeks of use of the app, a paired two-tailed t test was used. To analyze the correlation between the different variables, Pearson and Spearman correlation were applied as appropriate. In this correlation analysis, the change variable (difference between postassessment and preassessment) was used with quantitative variables: biological variables, quality of life (EORT QLQ-C30 global score, fatigue and pain), satisfaction with the app (uMARS global score), use of the app (in days), MVPA (accelerometry) and weight. The change variable was also used to measure changes in clinical variables such as type of tumor removal surgery, stage of breast cancer, medical treatment and hormonal therapy. Dispersion diagrams were used to study the assumptions of normality, linearity and homoscedasticity. To determine which variables could explain the variation in CRP and IL-6 concentrations, a stepwise multiple regression analysis was used. For the regression model with the dependent variable of CRP, the score changes in general quality of life, hormonal treatment, quality and satisfaction were considered independent variables.

For the regression model with the dependent variable IL-6, type of tumor removal surgery, and score changes in both perceived pain and weight were considered independent variables. To be included in the multiple regression analysis, the independent variables had to have a correlation coefficient of $r>0.20$ between the dependent variable and the independent variable, and they had to be significant [42]. The possible collinearity between the independent variables was studied, and then the final model was validated using bootstrapping (the start-up method was carried out with repeated samples of the same size to replace the original samples). Two thousand repetitions were produced to estimate the confidence intervals accelerated and corrected for the starting bias. For statistical analyses, the level of significance was set at $P<.10$. All analyses were performed using the software Stata version 14 (Statacorp, College Station, Texas). At least two experiments were performed in all assays.

Results

User Statistics and Clinical Characteristics

Participants were, on average, 51.35 (SD 8.58) years of age, with a body mass index (BMI) of 28.86 (SD 8.58). A total of 64% of the BCSs listed their civil status as married and 21% as single, with 41% having an educational status of higher education and 31% having unfinished studies or primary school. Table 1 summarizes clinical and

sociodemographic participants' characteristics.

Participants showed moderate quality of satisfaction (score range=0-5) with the mHealth app (mean 3.71 points; SD 0.47 points), high app usage (mean 47.9 days; SD 10.40; max=56 days), and moderate to low scores (range 0-100) in general quality of life (mean 57.6; SD 14.07), fatigue (mean 23.14; SD 15.46), and pain (mean 45.66; SD 25.91). Finally, mean weight was 72.56 kg (SD 10.85 kg) and the mean MVPA was 47.27 (SD 23.41). Analyzing changes in inflammatory biomarker concentrations after using the mHealth app, differences between preassessment CRP (4899.04 pg/ml; SD 1085.25) and IL-6 (87.15 pg/ml; SD 33.59) and postassessment CRP (4221.24 pg/ml; SD 911.55) and IL-6 (60.53 pg/ml; SD 36.31) showed a significant decrease in both of them, with a mean difference of −635.25 pg/ml (95% CI −935.65 to −334.85; P<.001) in CRP and −26.61 pg/ml (95% CI; −42.51 to −10.71; P=.002) in IL-6.

Table 1. Participants' demographics (N=73).

Variables	Participants
Age (years), mean (SD)	51.35 (8.58)
Marital status, n (%)	
Single	15 (20.6)
Married	47 (64.4)
Divorced	7 (9.6)
Other	4 (5.5)
Education, n (%)	
No education	1 (1.4)
Primary studies	22 (30.1)
Secondary studies	20 (27.4)
Higher education	30 (41.1)
Employment, n (%)	
Housewife	18 (24.7)
Employee	28 (38.4)
Low	10 (13.7)
Unemployed by the disease	17 (23.3)
Cancer stage, n (%)	
I	8 (11.3)
II	37 (52.1)
IIIA	26 (36.6)
Surgery, n (%)	
Lumpectomy	24 (32.8)
Quadrantectomy	12 (16.4)
Unilateral mastectomy	26 (35.6)
Bilateral mastectomy	11 (15.1)
Medical treatment, n (%)	
None	5 (6.9)
Radiation therapy alone	6 (8.2)
Chemotherapy alone	5 (6.9)
Chemotherapy and radiation therapy	48 (65.8)
Adjuvant chemotherapy	6 (8.2)
Neoadjuvant chemotherapy	3 (4.1)

Correlation Analyses

Significant negative correlations were found between changes in CRP concentration and EORT QLQ C30 general quality of life (r=−0.281; P=.03), with hormonal therapy (r=−0.235; P=.07), with uMARS score (r=−0.284; P=.02) and with mHealth app usage (r=−0.263; P=.04). In addition, significant positive correlations were found between change in IL-6 concentration and EORT QLQ C30 pain (r=0.404; P=.01), with weight (r=0.301; P=.06) and with type of tumor removal surgery (r=0.311; P=.05).

In addition, significant correlations existed among the independent variables (Table 2) but was only high between uMARS score and mHealth usage (r=0.907; P<.001).

Table 2. Pearson product-moment correlation matrix for study variables.

Variable	Δ[a]CRP[b]	ΔIL-6[c]	ΔC30[d] QoL[e]	ΔC30 Fatigue	ΔC30 Pain	ΔWeight	ΔMV-PA[f]	Age	Stage BC[g]	Surgery type	Hormonal therapy	uMARS[h]	mHealth[i] use
ΔCRP	1.00	—[j]	—	—	—	—	—	—	—	—	—	—	—
ΔIL-6	0.191	1.00	—	—	—	—	—	—	—	—	—	—	—
P value	.28	—	—	—	—	—	—	—	—	—	—	—	—
ΔC30 QoL	−0.281	−0.168	1.00	—	—	—	—	—	—	—	—	—	—
P value	.03	.30	—	—	—	—	—	—	—	—	—	—	—
ΔC30 fatigue	0.054	0.208	−0.527	1.00	—	—	—	—	—	—	—	—	—
P value	.68	.20	<.001	—	—	—	—	—	—	—	—	—	—
ΔC30 pain	0.153	0.404	−0.35	0.678	1.00	—	—	—	—	—	—	—	—
P value	.24	.01	.002	<.001	—	—	—	—	—	—	—	—	—
ΔWeight	0.088	0.301	−0.183	0.088	0.04	1.00	—	—	—	—	—	—	—
P value	.50	.06	.12	.46	.73	—	—	—	—	—	—	—	—
ΔMVPA	0.099	0.011	−0.023	0.135	0.187	−0.116	1.00	—	—	—	—	—	—
P value	.47	.95	.85	.29	.14	.36	—	—	—	—	—	—	—
Age	−0.139	−0.04	0.259	−0.314	−0.301	0.20	−0.304	1.00	—	—	—	—	—
P value	.28	.8	.03	.01	.01	.09	.01	—	—	—	—	—	—
Stage BC	0.075	0.143	−0.055	0.079	−0.083	−0.045	−0.101	0.143	1.00	—	—	—	—
P value	.57	.38	.65	.51	.49	.71	.43	.23	—	—	—	—	—
Surgery type	−0.158	0.311	0.092	0.023	0.009	−0.023	−0.191	0.110	0.282	1.00	—	—	—
P value	.22	.05	.44	.84	.93	.85	.13	.35	.02	—	—	—	—
Hormonal therapy	−0.235	−0.001	0.142	−0.161	−0.161	0.088	0.018	0.285	0.052	0.247	1.00	—	—
P value	.07	>.99	.24	.18	.18	.46	.88	.02	.66	.04	—	—	—
uMARS	−0.284	−0.086	−0.105	0.09	0.188	−0.028	0.101	−0.309	−0.167	0.147	0.049	1.00	—
P value	.02	.57	.38	.45	.11	.81	.42	.01	.16	.23	.68	—	—
mHealth use	−0.263	−0.127	−0.101	0.112	0.184	−0.026	0.081	−0.402	−0.122	0.144	0.014	0.907	1.00
P value	.04	.43	.40	.35	.12	.82	.52	<.001	.31	.22	.91	<.001	—

[a]Δ: change between postassessment and preassessment.
[b]CRP: C-reactive protein.
[c]IL-6: interleukin-6.
[d]C30: EORT QLQ C-30 questionnaire.
[e]QoL: quality of life.
[f]MVPA: minutes of vigorous-to-moderate physical activity.
[g]BC: breast cancer.
[h]uMARS: user version of the Mobile Application Rating Scale.
[i]mHealth: mobile health.
[j]Not applicable.

Therefore, considering multicollinearity possible (defined as r>0.70), only uMARS score was included in the regression analyses.

Regression Analyses

Stepwise regression analyses revealed that changes in global quality of life, as well as uMARS score and hormonal therapy, were possible predictors of change in CRP concentration after using the app (Table 3). In the same way, the type of tumor removal surgery, as well as changes in weight and pain scores, were possible predictors of change in IL-6 concentration after using the app (Table 4). For both tables, r^2 denotes the variability of change in biomarker concentration by the predictors in percent.

Discussion

The objective of this study was to determine the preliminary results of the possible association between the use of an mHealth strategy app as a delivery mechanism to monitor energy balance in cancer and the reduction of systemic inflammation markers, as well as to suggest possible predictors of this change. Current findings suggest that after two months of use of the app, a significant reduction of these markers can be observed. Thus, there could be a possible association between the two. In addition, the change in weight, pain and quality of life, as well as the type of tumor removal surgery, hormone therapy and the uMARS score, can have a contribution in the changes found in the concentrations of CRP and IL-6.

Table 3. Summary of stepwise regression analyses to determine predictors of change in C-reactive protein concentration (r^2=19%).

Independent variables	Unstandardized coefficients, β[a]	95% CI for β	Bootstrap BCA[b], 95% CI	Bootstrap, β	Standardized coefficients, β	*t*	*P* value
Interceptil	2496.949	218.504-4775.395	4.641-4989.268	2496.949	_[c]	2.2	.03
Hormonal therapy	–110.304	–286.447 to 65.839	–272.774 to 52.166	–110.304	–0.155	–1.25	.22
uMARS[d] score	–728.786	–1338.675 to –118.898	–1396.04 to –61.533	–728.785	–0.289	–2.39	.02
Δ[e]Global QoL[f]	–18.601	–36.253 to –0.945	–37.022 to –0.177	–18.605	–0.261	–2.11	.04

[a]β: regression coefficient.
[b]BCA: bias-corrected and accelerated.
[c]Not applicable.
[d]uMARS: user version of the mobile application rating scale.
[e]Δ: change between postassessment and preassessment.
[f]QoL: quality of life.

Table 4. Summary of stepwise regression analyses to determine predictors of change in IL-6 concentration (r^2=26%).

Independent variables	Unstandardized coefficients, β[a]	95% CI for β	Bootstrap BCA[b], 95% CI	Bootstrap, β	Standardized coefficients, β	*t*	*P* value
Interceptil	–36.498	–68.898; –4.098	–71.773; –1.223	–36.498	_[c]	–2.28	.03
Type of surgery	8.219	–4.604; 21.04	–5.383; 21.821	8.22	0.194	1.3	.20
Δ[d]Weight	4.456	–1.263; 10.176	–0.582; 9.495	4.455	0.23	1.58	.08
ΔPain score	0.667	0.054; 1.279	0.003; 1.33	0.667	0.328	2.21	.03

[a]β: regression coefficient.
[b]BCA: bias-corrected and accelerated.
[c]Not applicable.
[d]Δ: change between postassessment and preassessment.

A system of monitoring energy balance through an mHealth app seems to reduce the biological parameters of systemic inflammation (CRP and IL-6). Our results suggest that after two months of use of the mHealth app, based on the monitoring of energy balance (in terms of diet and physical activity), the concentration of CRP and IL-6 are significantly reduced in BCSs. In fact, this change has a moderate effect size in CRP (Cohen d=−0.640; 95% CI −0.985 to −0.293) and a high effect size in IL-6 (Cohen d=−0.805; 95% CI −1.225 to −0.379). A study by Skogstad et al was the only one found with a design similar to ours, as it used a virtual internet physical activity motivation strategy in which some biological parameters were measured [43]. In this study, participants were included in a motivational physical activity program in which they measured their steps using a wrist-band accelerometer. However, unlike our study, no differences were found in CRP concentration after the intervention, perhaps because their study target population were healthy workers without pathology. The effect size reported for both our biomarkers supports the hypothesis that these changes are not due to time, but it is important to remark that the quasi-experimental pre-post design of our study does not allow us to affirm that the changes found are only attributable to the use of the app. Therefore, a controlled and randomized clinical trial should be carried out in the future.

Biological parameters of systemic inflammation can be mediated or modified by lifestyles changes such as physical activity and diet [4,6,7]. This study is the first to examine clinical and anthropometric factors that affect changes in these biological parameters, after using a mobile strategy to monitor energy balance in breast cancer survivors. Because rehabilitation strategies focus on face-to-face or distance physical activity and diet programs, understanding the potential determinants of reducing inflammation markers can help design more effective intervention strategies.

The results of our study show that possible moderators of a reduction in CRP concentration include not receiving hormonal therapy, as well as having higher satisfaction and changes in quality of life (the higher quality of life change, the lower the CRP concentration). The role of estrogen in inflammation is poorly understood, the mechanism is not well studied, and its relationship is very complex [44], and different studies show contradictory results depending on different pathologies, with some showing they are associated with an inflammatory activity, while others show a proinflammatory role [44]. The differences found in pre and postmenopausal women suggest that the peripheral production of estrogens plays an important role in these differences [44-47]. Our results provide new evidence in this regard, since not having received hormone therapy may be a predictor of a greater reduction in CRP concentration in female survivors of breast cancer. However, estrogen's relationship

with quality of life has been considered from another point of view. We understand that it is not that a higher perception of quality of life is a predictor of a reduction of proinflammatory markers but rather the other way around, that the diminished inflammatory state is associated with an increase in the quality of life [48,49]. Ultimately, our results suggest a higher score in uMARS as a predictor of the change in CRP concentration. In addition, there is a strong association between satisfaction and quality with the amount of time spent on the mHealth app. If women with the highest score in uMARS use the mHealth app more, then the reduction in inflammatory markers could be due to the direct relationship caused by a healthier lifestyle [6,50,51].

The results of our study also show possible moderators of the reduction in IL-6 include the type of tumor removal surgery (less invasive surgery), as well as changes in both weight and pain (the greater the reduction of these factors, the greater the reduction of IL-6). These results are consistent with the known bidirectional relationship between obesity and low-grade inflammation, which contributes to systemic metabolic dysfunction that is associated with obesity-linked disorders [4]. In the same way, an inflammatory reaction is also mediated by the classic cardinal signs of inflammation (eg, pain) [52].

Therefore, it is logical to think that a reduction in pain reported by breast cancer survivors can be a predictor of a reduction in IL-6 concentration such as that observed in our results. Finally, there is a lot of scientific evidence to support the use of minimally invasive surgical techniques since they don't raise inflammatory reactants as much, and these findings may support the relationship between IL-6 and the type of tumor removal surgery found in our results [53-56].

It is worth highlighting some strengths and limitations of the present study. The main strength lies in the nature of the study. To the best of our knowledge, this is the first study that proposes a mobile strategy to monitor energy balance as a mediator in the reduction of proinflammatory markers in BCSs. If future research supports our results, we will have found another support strategy for cancer survivors that is low cost and accessible to everyone and which could reduce markers highly related to the risk of recurrence. However, there are also many limitations to be noted. The main limitation lies in the design of the study, as well as the sample size, which prevents us from speaking in terms of causality and effectiveness. In addition, the r^2 obtained in the multiple regression models was low. However, we must not forget that we are trying to explain biological parameters with nonbiological variables. Our results may support the biopsychosocial model, since it shows how biology can be modified through these variables. Other biological parameters that can justify the rest of the variability that has remained to be explained should be taken into account in the future.

In conclusion, through the results of this study, we hypothesize that there is a possible association between an mHealth energy balance monitoring strategy app and biological changes in BCSs. These changes could be explained by different biopsychosocial parameters such as the use of the application itself, quality of life, pain, type of tumor removal surgery, hormonal treatment or obesity. Future studies should be carried out with a specific focus on all these biological parameters, and with an appropriate study design, to support these findings.

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Conflicts of Interest

None declared.

Abbreviations

BCS: breast cancer survivor

BMI: body mass index

CEIH: Ethics Committee on Human Research

CRP: C-reactive protein

ELISA: enzyme linked immunosorbent assay

EORT QLQ-C30: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

IL-6: interleukin-6

MVPA: minutes of vigorous-to-moderate physical activity

RCT: randomized controlled trial

uMARS: user version of the mobile application rating scale

WCRF: World Cancer Research Fund International

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Integral strategy to supportive care in breast cancer survivors through occupational therapy and a m-health system: design of a randomized clinical trial

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STUDY IV

Study IV. Integral strategy to supportive care in breast cancer survivors through occupational therapy and a m-health system: design of a randomized clinical trial

Abstract

Background: Technological support using e-health mobile applications (m-health) is a promising strategy to improve the adherence to healthy lifestyles in breast cancer survivors (excess in energy intake or low physical activity are determinants of the risk of recurrence, second cancers and cancer mortality). Moreover, cancer rehabilitation programs supervised by health professionals are needed due to the inherent characteristics of these breast cancer patients. Our main objective is to compare the clinical efficacy of a m-health lifestyle intervention system alone versus an integral strategy to improve Quality of Life in breast cancer survivors.

Methods: This therapeutic superiority study will use a two-arm, assessor blinded parallel RCT design. Women will be eligible if: they are diagnosed of stage I, II or III-A breast cancer; are between 25 and 75 years old; have a Body Mass Index > 25 kg/m2; they have basic ability to use mobile apps; they had completed adjuvant therapy except for hormone therapy; and they have some functional shoulder limitations. Participants will be randomized to one of the following groups: integral group will use a mobile application (BENECA APP) and will receive a face-to-face rehabilitation (8-weeks); m-health group will use the BENECA app for 2-months and will received usual care information. Study endpoints will be assessed after 8 weeks and 6 months. The primary outcome will be Quality of Life measured by The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core and breast module. The secondary outcomes: body composition; upper-body functionality (handgrip, Disability of the Arm, Shoulder and Hand questionnaire, goniometry); cognitive function (Wechsler Adult Intelligence Scale, Trail Making Test); anxiety and depression (Hospital Anxiety and Depression Scale); physical fitness (Short version of the Minnesota Leisure Time Physical Activity Questionnaire, Self-Efficacy Scale for Physical Activity); accelerometry and lymphedema.

Discussion: This study has been designed to seek to address the new needs for support and treatment of breast cancer survivors, reflecting the emerging need to merge new low-cost treatment options with much-needed involvement of health professionals in this type of patients.

Trial registration: ClinicalTrials.gov Identifier: NCT02817724 (date of registration: 22/06/2016).

Keywords: Breast, Neoplasms, Occupational therapy, Mobile applications, Quality of life.

Background

Cancer is one of the most incident diseases worldwide. Over 14 million new cancer cases occur every year but are projected to reach approximately 22 million by 2030 [1]. Among all cancer types, breast cancer is the most commonly diagnosed cancer in women, and approximately 4.4 million women worldwide live with a diagno- sis of breast cancer [2]. Fortunately, the survival rate is very encouraging; the estimated number of deaths from breast cancer is estimated to be less than one-third of new cases [1]. Developments in screening and improved treatments for breast cancer have led to improved sur- vival, and it is beginning to be regarded as a chronic disease [3, 4]. This new perspective of the disease has led to a growing need for long-term treatments [4] with an integrative strategy that takes into account the patients' lifestyles and physical, cognitive and emotional impairments [5–7].

Regarding the importance of the patients' lifestyles (in physical activity and diet), the literature highlights the importance of maintaining healthy lifestyles to reduce the risk of recurrence, secondary cancers or death. There is strong evidence about the efficacy and safety of exercise and healthy diet to improve the patients' quality of life (QoL) [8, 9] and reduce the effects of cancer [10, 11]. Recent research reveals that even when patients know the benefits of interventions aimed at pro- moting energy balance among cancer survivors (in terms of intake and physical activity), it is unrealistic to expect that most of them, who have a strong sedentary habit, will comply with the current good practice guidelines [10, 12]. In addition, survivors report difficulties in adhering to and maintaining an appropriate lifestyle [12]. Conse- quently, this energy imbalance increases the risk of cancer recurrence [13] and, along with the functional limitations and emotional/occupational imbalance, re- duces the QoL of breast cancer survivors (BCS) [14]. New strategies with a comprehensive approach of sup- port must be developed to improve the adherence and motivation of these patients and to reduce the high cost involved in creating individualized exercise programs and diets [15]. Currently, technological support is a promising strategy that could improve issues, such as barriers of distance, time, cost and motivational aspects [16]. Telehealth systems, which are based on computers and mobile applications (m-health), offer a promising approach for both dietary and physical activity assess- ments [17] and the patients' motivation can be signifi- cantly increased through the immediate feedback provided by these systems [18]. A recent study has developed a mobile application to simultaneously collect data on diet and physical activity in adults [17], but, to our knowledge, no programs exist that simultaneously col- lect data on diet and physical activity in cancer patients and provide immediate feedback with individualized recommendations.

In addition to the need to improve these patients' life- styles, the patients may experience physical, cognitive and

emotional impairments. The most common upper body symptoms reported by BCS are related to shoul- der impairments [19–21], although much research has supported the practice of performing early exercises to avoid limitations of range of motion (ROM) in the shoulder [22, 23]. Moreover, cognitive impairment oc- curs in 10%–50% of these women [24, 25], and the emotional distress caused by shifts in social support and the fear of recurrence and death has also impacted women's wellbeing [26, 27]. The performance of daily tasks (such as activities in daily living, work, and leisure tasks) are influence by all these complications and, along with unhealthy lifestyle habits, affect the overall QoL [22].

In this sense, occupational therapy is an effective inter- vention to improve the patients' QoL, ROM or distress in different conditions [28–30]. However, to our knowledge, the only published randomized controlled trial evaluating occupational therapy in BCS is an interven- tion aimed at reducing the limitations of rural patients in their daily activities [31]. The authors found that a telephone-based problem-solving occupational therapy intervention program was feasible and had positive effects on the patients' function, QoL and emotional state. However, the study had methodological limita- tions, such as a small simple size and intervention bias. Other previous studies with the aim of evaluating the effects of occupational therapy on cancer patients had several limitations, such as including any type of cancer [32–36], the use of a non-randomized controlled trial (RCT) approach [33–35, 37, 38], and pilot studies [31, 36] involving very few patients [31, 33, 36–38].

This study arises from the need to establish an integra- tive and multidisciplinary strategy to support BCS by taking advantage of the features of these two proposals: first, the functionality and independence provided by a mobile application that patients can use when and wher- ever they choose; secondly, the imperative need for a su- pervised face-to-face intervention by a health professional, due to the inherent characteristics of these patients. Our study aims to compare the clinical efficacy of an m-health lifestyle intervention system alone versus an integrative strategy that also includes a face-to-face intervention in BCS. In this manuscript, we describe the design and methods of the study.

Methods

Objectives

The main objective of this RCT is to assess if an integrated strategy that uses a m-health system in addition to a face-to-face treatment is better than the use of the m-health system alone to improve the immediate and long-term QoL of BCS. Second, we want to examine the effects of the interventions on the overall impact on functionality, body composition, anxiety and depression, physical measurement, lymphedema and cognitive func- tion. The integral group will use the m-health and re-ceive three occupational therapy sessions

each week for an 8-week period. We will also study the effect of a 24- week period without rehabilitation on the studied variables. We hypothesize that support care based on an Occupational Therapy-supervised rehabilitation program will promote functionality and the combination with the mobile system will improve the patients' lifestyles and QoL, reduce distress, and improve cognitive function and arm mobility.

Research design and methods

The present study is a parallel group, assessor-blind, su- periority RCT that will be conducted using assessments at baseline and immediately after the 8-weeks intervention. Follow-up measurements will be collected for 24 weeks after the end of the 8-week intervention period, resulting in a total trial data collection period of 32 weeks. We will use two separate assessment days to avoid fatigue in pa- tients. In Table 1 is shown the study assessment schedule.

Table 1 Study assessment schedule

Assessment	Baseline	Post-intervention (8 weeks)	Follow – up (24 weeks)
Informed Consent	x		
Day 1 testing			
Sociodemographic data	x		
Anthropometric data, pressure/rate heart	x	x	x
Accelerometry (1 week)	x	x	x
Body Composition (DEXA)	x	x	x
Minnesota	x	x	x
Self-efficacy Physical Activity questionnaire	x	x	x
EORTC QLQ-C30	x	x	x
EORT QLQ-BR23	x	x	x
Day 2 testing			
WAIS-IV[a](subtest)	x	x	x
Trail Making Test (TMT)	x	x	x
Handgrip strength	x	x	x
Lymphedema	x	x	x
Hospital Anxiety and Depression Scale	x	x	x
DASH	x	x	x
Goniometry	x	x	x

[a]Working memory and processing speed subtest

Participants

A total of 80 eligible (see inclusion criteria below) BCS will be randomized into the integral group (N=40) or the m-health group (N = 40). For feasibility, the study is conducted in three waves. During the first year of the study (from January to December 2016), we will prepare protocols, establish the measurement techniques, and enrol the first 25 women in the study. At the beginning of the second year of the study (between January and April 2017), we will enrol an additional 30 women, and in the third stage, we will enrol the remaining 25 women. In summary, the target sample size of 80 BCS will be achieved in these 3 waves.

The integral group will receive the m-health plus an 8-week occupational therapy onsite program , and the m-health group will only use the app. Participants will be enrolled in this study by oncologists from the Hospital Virgen de las Nieves (Breast Unit) and the Hospital Clínico San Cecilio, Granada (Spain). The Research Ethics Committee of the province of Granada approved this study.

Eligibility criteria

Eligible women require: 1) to be between 25.0 and 74.9 years-old, 2) to be diagnosed of stage I, II or IIIA breast cancer, 3) to have medical clearance of participation, 4) to be overweight or obese, according to the Spanish Society for the Study of Obesity

(SEEDO) [39], 5) to have basic ability to use mobile apps or living with someone who has this ability, 6) completion of ad- juvant therapy except for hormone therapy, 7) to have some functional or ROM limitations measures by goniometry and the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire, and 8) to have signed informed consent and have interest in improving lifestyle.

The exclusion criteria were defined as follows: history of cancer recurrence, to have had chronic disease or orthopaedic issues that would interfere with ability to participate in this rehabilitation program, or to have had uncontrolled hypertension (diastolic pressure > 95 mm Hg).

Outcome measures

The primary outcome measure is QoL. The secondary outcome variables include body composition, active range of motion (AROM), functionality, anxiety and depression, and cognitive function. Other variables of interest include muscular strength and free-living physicalactivity. Primary outcome measure

Quality of life: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) version 3.0 [40]: We will use the EORT QLQ-C30 to assess QoL. This question- naire is one of the most widely used instruments to measure QoL in cancer patients. The QLQ-C30 is composed of both multi-item scales and single-item mea- sures, as well as five functional scales, three symptom scales, a global health status/QoL scale, and six single items. The scores must be averaged and linearly trans- formed to obtain a range of scores from 0 to 100, with a higher score representing a greater response level. Thus, a high score for a functional scale represents a healthy level of functioning and a high score for the global health status represents a high QoL, but a high score for the symptom scale represents a high level of symptom- atology [41]. The test/retest reliability is high for all scales, ranging from 0.82 to 0.91 [40].

The European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Question- naire (EORT QLQ-BR23) [42]: This questionnaire is a breast cancer module of the EORTC QLQ-C30 that con- tains 23 items rated on a four-point scale ranging from 1 (not at all) to 4 (very much). The items assess the side effects of therapy, arm symptoms, breast symptoms, body image, and sexual function. Additionally, there are single items assessing sexual enjoyment, anxiety caused by hair loss, and future outlook. The scores range between 0–100 points. The procedure for scoring the breast cancer mod- ule is the same as the EORTC QLQ-C30 [41]. For scales evaluating function, a higher score represents a higher level of functioning. For scales evaluating symptoms, a higher score indicates more severe symptoms. The reli- ability has been shown to be high to moderate (Cronbach's α ranged between 0.46 – 0.94) [42].

Other outcome measures

Body composition

Height and weight will be measured. Body mass index, fat mass, lean body mass, abdominal adipose tissue and bone mineral density will also be assessed by conducting Dual-energy X-ray absorptiometry (DXA, Discover y densitometer from HOLOGIC, QDR 4500 W) using protocols reported in previous studies [43, 44]. This as- sessment tool has previously been used in breast cancer patients [45, 46].

Muscular strength

The handgrip strength test will be assessed using a digital dynamometer (TKK 5101 Grip-D; Takey, Tokyo, Japan). Following the protocol described by Ruiz-Ruiz *et al.* [47], the optimal grip span will be determined by a simple algorithm to adapt the dynamometer. Throughout the whole test, BCS will be in a bipedal position; they have to put their arm in complete extension without touching any part of their body [18], repeating the test three times with each hand, alternately. There will be a delay of one minute between each test. The mean of the three tests will be used for the main analysis. This measurement has been demonstrated to be valid and reliable [48].

Upper body functionality

The disability of the arm, shoulder and hand (DASH) questionnaire: the American Academy of Orthopedic Surgeons introduced the DASH questionnaire as a specific instrument to measure upper extremity functionality [49]. It is one of the most extensively used tools [50]. Of the 30-items that are included in the DASH questionnaire: 21 items ask about the degree of difficulty in physical ac- tivities; 5 items ask about the severity of some pain symptoms; and the final 4 items ask about other activi- ties such as social activities, sleep, work or self-image. The impact of the symptoms on each activity is also assessed. The scale score ranges from 0 to 100 points; the higher the score, the greater the disability [51]. The reliability of the Spanish version has a Cronbach's $\alpha = 0.96$ [52].

Active range of motion (AROM)

Shoulder AROM measurements will be obtained using a standard, two-armed goniometer, which is described as the clinical gold standard [53]. The patients will be asked to actively move their arms as much as they can to obtain measurements (in degrees) of flexion, extension, abduction, internal rotation and external rotation of the shoulder [23]. The movement will be validated by the interviewer and motion compensation will be limited to avoid overestimating the scores.

Cognitive function

Wechsler Adult Intelligence Scale (WAIS-IV): The WAIS-IV is an intelligence test designed to measure cognitive ability in adults and older adolescents and provides the most advanced adult measure of cognitive ability [54]. WAIS-IV subtests will be administered and scored according to standardized procedures [55]. For feasibility

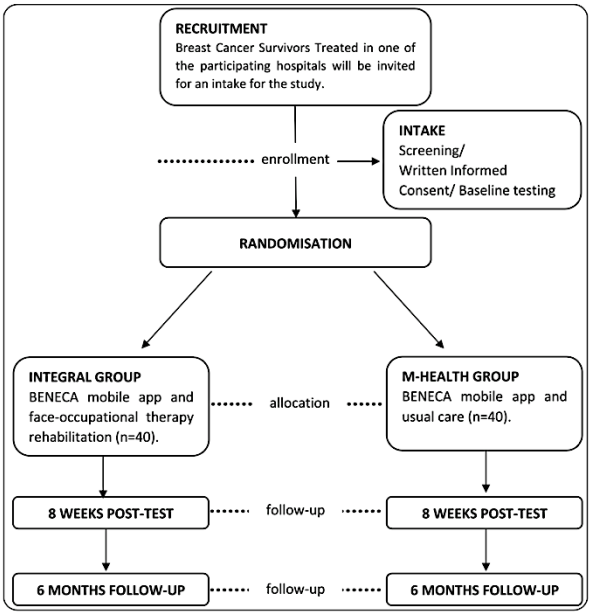

Fig. 1 Flow diagram showing the recruitment of patients

issues and because specific subtests provide information on a specific cognitive function (and can be used separately [55]), we will use two of the four index scores that compose the test: the Working Memory Index (WMI) and the Processing Speed Index (PSI). The WMI includes two subtests, Arithmetic and Digit Span, and the PSI also includes two subtests, Digit Symbol- Coding and Symbol Search.

The Trail Making Test (TMT) measures the flexibility of thinking using a visual-motor sequencing task and is one of the most important neuropsychological tests, providing information on speed of processing, visual search, mental flexibility, scanning and executive func- tions [56]. It is formed by two subtests. TMT-A requires the participant to draw lines that sequentially connect several encircled numbers (1 to 25) distributed on a sheet of paper. TMT-B is similar in requirements, but in this case, the participant must alternate between numbers and letters (e.g., 1, A, 2, B, 3, C, etc.). The score is based on the amount of time required to complete the task.

Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS): This scale consists of 14 items with two subscales (seven items for anxiety and seven for depression) and a score which ranges from 0 to 21 for each subscale. The ques- tionnaire contemplates a cutoff point of 11 or above to consider anxiety and depression conditions [57, 58].

Physical fitness

Short Version of the Minnesota Leisure Time Physical Activity Questionnaire (VREM) [59]: This questionnaire is a short version of the original Minnesota question- naire [60] and is composed of 5 items. It asks

for the period in a typical week that the participants perform routine housework activities (cleaning house and go shopping on foot). In addition, it asks about activities performed during the last month or in a typical month for the other items, such as walking, working in the garden, playing sports or dancing and climbing stairs. Finally, energy expenditure is calculated (in METS-min/ 14 days) and the participant is classified from sedentary to very active according to their energy expenditure [59].

Self-Efficacy Scale for Physical Activity (EAF): The EAF is a validated instrument that determines the participants' beliefs about their own abilities to perform physical activi- ties (self-efficacy for physical activity). It also allows us to identify the barriers and limitations that prevent the user from practicing this behaviour and the strength they require to perform regular physical activity. The EAF con- sists of three domains: scheduled physical exercise, physi- cal activity in daily activities and walking. A total of 39 items are rated from 0 to 10; the higher the score, the greater the ability to perform the activity [61, 62].

Accelerometry

Accelerometry will be used to obtain data about physical activity and sedentary time for each participant, fol- lowing a previously published protocol for usage and analysis [63]. A pre-programmed tri-axial accelero-meter (ActiGraph GT3X+, Pensacola, Fl., US) and a daily ques-tionnaire will be given to BCS. The participants will wear the accelerometer for 8 consecutive days. They will be instructed to wear the accelerometer on their lower back for the whole day (including when sleeping) but to take it off during aquatic activities. They will also receive an in-formation sheet with detailed instructions. Participants will be included in the main analysis if the device records data for at least 4 days over a period of at least 10 h each day. Data will be collected at intervals of 1 min. Nonwear periods (intervals of 60 consecutive minutes with zero counts) and the first day of wearing the device will be ex- cluded from analyses. Accelerometer data will be down- loaded to the same computer used to initialize them [18].

Lymphedema

We will measure changes in size or volume of the upper limbs to diagnose lymphedema. An inextensible flexible tape 0.5 cm wide x 2 m long with an accuracy of 0.1 cm will be used following the protocol using in some previ- ous studies [18, 64], which has been shown to be valid and reliable [65, 66].

Sample size

The sample size and power calculations for this trial were obtained through overall Health-Related QoL (HRQoL) using EORTC QLQ-C30 version 3.0 [40], and taking into account previously reported data [67] a mini- mally important difference from 5 to 10 points was con- sidered. Assuming that integral group increase HRQoL in BCS in compared with m-health

group [18] we can detect differences of at least 5% with a power of 90% and an α of 0.05 with two groups (Integral group and m-health group) of 36 participants assuming similar standard deviation (approximately 7 points). A maxi- mum loss at follow-up of 10% will be allowed to face a possible drop-out rate [9]. Hence, we will recruit 80 BCS (40 in each group). Fig. 1 shows the flow diagram of the study participants.

Randomization and blinding

To reduce the risk of bias during the assessment, after completion of the baseline assessment we will allocate eligible patients randomly either m-health or integral groups into three randomization waves, using computer- generated numbers (EPIDAT 3.1, Xunta de Galicia). An external member will introduce the sequence in sealed opaque envelopes. Assessment staff will be blinded to patients' randomization assignment and the staff respon- sible of the rehabilitation program will not be able to change any assignment. After the 6-month follow-up period, and because of ethical implications, once the last outcome variable has been measured, we will invite par- ticipants of the m-health group to participate into the face-to-face rehabilitation program.

Integral group

The intervention will be implemented by the CUIDATE research group. The supervised face-to-face program involves two parts (8 weeks in total). The participants will may use the BENECA System (mobile app) daily, which aims to recover a healthy lifestyle in BCS (in terms of energy balance: physical activity and dietary). On the second day of the assessment, staff will install the app on the participants' mobile phones and will train them to use it. Furthermore, the women will receive telephone calls and text messages (as required) to re- solve any questions and provide suggestions, and a video tutorial on how to use the application is also available on the web.

Moreover, participant will receive a supervised face- to-face rehabilitation program. This intervention con- sists of a supervised-occupational therapy rehabilitation program at the iMUDS centre (Mixed Institute University Sport and Health). Because there is no information about the ideal occupational therapy program for breast cancer patients, we have developed a compre- hensive program that covers most of the physical, cognitive and emotional needs of these patients after oncology treatment from the occupational therapy perspective.

The second part is based on the fact that this span has been used in previous RCTs that have similar outcomes and samples [9, 18]. The occupational therapy program includes 3 weekly sessions of 60 to 90 min each. The weekly sessions will be distributed as follows: 2 sessions/ week in a ROM-cognitive subprogram (approximately 50 min/session) using therapeutic workshops and individ- ualized treatment that focus on improving the ROM, muscle strength and endurance, and

manipulative skill and energy conservation as well as cognitive activities; 3 sessions/week of a psychomotricity program (approxi- mately 45 min/session) including activities to improve functional capacity and address fatigue and pain as well as a warm-up period and relaxation techniques; and fi- nally, 1 session/week of a psychosocial intervention (approximately 30 min/session), working on areas of ergonomics, techniques of energy conservation and fa- tigue management, job anxiety, coping techniques and occupational balance. All of these exercises will be assigned to women in the integral group according to their perceived needs at the baseline assessment. These needs will be established based on the fatigue levels, pain, functional capacity, ROM, and distress levels reported by the patients. Therefore, each participant will receive individual and progressive training (for example, the number and type of exercises, series, repetitions and so on). Efforts will be made to prevent the integral group from receiving additional physical care.

M-HEALT: BENECA APP system

BENECA asks users to register their food and drinks and the different activities performed during the previous day. With an open structure and four time periods, the application will take the form of a questionnaire on the diet (over the last 24 h) and a record of daily activities in terms of duration and intensity. Users also record their weight (kg) and height (cm). After entering the informa- tion, the system will provide the patient information about their energy balance and general recommendations on physical activity according to their individual profile, using the reference guide for exercise in cancer patients from the American College of Sports Medicine [68]. Addition- ally, it provides recommended substitutions for foods that are considered potentially carcinogenic with others that may have a protective capacity against cancer, according to the guidelines of the American Cancer Society [11, 69] and the recommendations of the WCRF about the consumption of food of plant and animal origins, food with low energy density, etc. Furthermore, the program also detects the presence of an energy imbalance.

Telephone calls

The CUIDATE group will make the telephone calls and send messages of encouragement. On the one hand, with these calls, participants will be able to solve any problems with the usage of BENECA app. Moreover, we will check the patients' improvement and satisfaction. On the other hand, the aim of messages will be to stimulate not only the adherence with BENECA app but also with the program.

M-Health group

Because it is a study of therapeutic superiority, the m- health group will use the BENECA app for 2 months and will receive some general recommendations about healthy lifestyle, stress management and occupational balance in paper format. After

completion of this study, the m-health participants will be given the opportunity to participate in the supervised face-to-face program due to the ethical concerns of the CUIDATE group. The data obtained will be not used in this study.

Data analysis

All analyses will be carried out using STATA/SE 14.0 StataCorp, College Station, TX, USA) or using Statistical Program for Social Sciences (IBM© SPSS© Statistic version 20, Corp., Armonk, NY). We will check the nor- mal distribution of variables with Kolmogorov-Smirnov and Shapiro-Wilk test, as appropriate, and the differences at baseline between groups with Chi-square test or Student t-test, as appropriate. The main analysis will be repeated measures analyses of the covariance (ANCOVA) with age, type of surgery, tumour stage and time since diagnosis as covariates. Intergroup effect sizes will be calculated to provide change magnitude information. We will use the intention-to-treat principle for all analyses.

Discussion

This RCT will investigate whether there are clinically relevant differences in improvements in the QoL of BCS between an integral strategy and the use of the m-health system alone. This study has been designed to address the new needs for support and treatment of breast cancer survivors, reflecting the emerging need to merge new, low cost treatment options with the much-needed involvement of health professionals in the treatment of this type of patients. The supervised program includes not only strengthening and range of motion exercises of the shoulder, which are necessary in these patients [9], but also features a cognitive [25] and psychosocial [27] approach in a single intervention program which, together with the use of the m-health application [17], provides the integral character of the project.

In addition, most studies in cancer patients have been conducted with a rehabilitation team comprising nurses, psychologists and physiotherapists [8, 27]. For this rea- son, we chose to use a supervised face-to-face rehabilita- tion program conducted by an occupational therapist, due to the holistic and integrative approach of the discipline. Although we expect to see improvements in the primary outcome in both groups, we hypothesize that the combination of the supervised program and the m-health system will cause significant differences in QoL compared with the m-health group. QoL improve- ment is considered an indicator of cancer rehabilitation success [70]. If this integral option is effective, it will highlight the need for health systems to include disci- plines such as occupational therapy in the supportive care of cancer patients during the survival period, as well as the potential advantage and cost reduction provided using a mobile app. Moreover, the results of this study could garner support for the use of this type of strategy in an increasing number of 17.8 million cancer patients in the European

Union [71], with a high proportion of them claiming adequate rehabilitation services.

Abbreviations

App: Mobile application; AROM: Active range of motion; BCS: Breast cancer survivors; DASH: Disabilities of the arm, shoulder and hand; EORT QLQ- BR23: European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core (30); HADS: Hospital anxiety and depression scale; HRQoL: Health-related quality of life; m-Health: Mobile health application; QoL: Quality of life; RCT: Randomized controlled trial; ROM: Range of motion; TMT: Trail making test; VREM: Short version of the Minnesota leisure time physical activity questionnaire; WAIS-IV: Wechsler adult intelligence scale

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Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Authors' contributions

MAM conceived the study, designed BENECA App, and drafted the manuscript. NGC, LMM, ICV, CFL, and MLL participated in the study design and planned the statistical analysis of data. NGC, LMM, FAS and MLL designed the diary sessions of supervised face-to-face intervention. ICV, CFL, and FAS give considerable facility to relation between hospital centres and university laboratories. CSS and MAM advised on the medical aspect of the protocol and participated in the enrolment of the patients to the study. All authors read and approved the final manuscript.

Authors' information

MLL is occupational therapist and is a lecturer at University of Granada and this project represents his PhD thesis topic. His particular interest has been the give support to breast cancer during rehabilitation phase. LMM is occupational therapist and NGC and CFL are physiotherapist and they are academic, working and researching the area of oncology rehabilitation. ICV is physical exercise specialists, physiotherapist and academic researching in the area of exercise in oncology patients. FAS is physiotherapist and PhD student, involves in research with breast cancer survivors. CSS is nurse and academic involves in research with cancer survivors. MAM is a sports physician and physiotherapist working as research leader in this project and supervisor of PhD thesis.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This trial was approved by Research Ethics Committee (Granada, Spain) and it was performed in accordance with the HELSINKLI Declaration (last modification in 2000) and The Biomedical Research (14/2007). All participants provided written informed consent.

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Mobile health and supervised rehabilitation versus mobile health alone in breast cancer survivors: randomized controlled trial

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STUDY V

Study V. Mobile health and supervised rehabilitation versus mobile health alone in breast cancer survivors: randomized controlled trial.

Abstract

Background. Survival rates in cancer are increasing exponentially, with a corresponding increase/influence in disability-adjusted life-years. Efforts should be made to explore the optimal balance between unsupervised/distance-based and supervised/onsite approaches to cancer care.

Objective. This study aimed to compare the clinical efficacy of the BENECA mobile Health (mHealth) lifestyle application combined with a supervised rehabilitation program (BENECA and rehabilitation) versus the BENECA mHealth lifestyle application alone on quality of life (QoL) and functional outcomes of breast cancer survivors.

Methods. This randomized controlled trial included 80 survivors of breast cancer diagnosed at stage I-IIIA, who completed adjuvant therapy and were overweight or obese at diagnosis. Participants were randomly allocated (ratio 1:1, 3 waves) to BENECA and rehabilitation for 2 months (n=40) or BENECA and usual care (BENECA alone; n=40). Participants completed a questionnaire at baseline (T1), 8-weeks post-intervention (T2) and 6-month follow-up (T3). The primary outcome was QoL assessed with the EORT QLQ-C30. Secondary outcomes included upper-limb functionality and body composition. Statistical (between-group analyses of covariance) and clinical effects were analyzed by intention to treat.

Results. Both groups showed improved outcomes, but global QoL was significantly better with BENECA and rehabilitation than BENECA alone (mean difference, 12.76; 95% confidence interval 4.85; 20.67; p=0.004), with a moderate-to-large effect size (d=72). The proportion of participants reporting reliable clinical improvement on global QoL at T2 was higher with BENECA and rehabilitation than BENECA alone (57.5% vs 26.3%, p=0.008). Improvement in subjective and objective upper-limb functionality was also higher with BENECA and rehabilitation.

Conclusions. The BENECA mHealth lifestyle application with a supervised rehabilitation program had a statistically and clinically significant effect on QoL and upper-limb functionality in breast cancer survivors and is a unique and important promising new approach.

Keywords: breast cancer, integral strategy, rehabilitation, mhealth, occupational therapy.

Introduction

Between 2006 and 2016, survival rates in some cancer types, especially breast cancer, exponentially increased (1), with a corresponding increase/influence in disability-adjusted life-years (DALYS) (2). DALYS secondary to cancer survival are associated with substantial medical expenses and loss of productivity in addition to long-term health effects (3). Specifically, breast cancer caused 15.1 million DALYs (95% confidence interval [CI] 14.3–16.2) (1). The annual economic burden of cancer survivors > 65 years old exceeds USD $15,500 (3). In fact, even the economic burden of breast cancer in the survival phase has been associated with loss of quality of life (QoL) (4). The number of cancer survivors is estimated to be 18 million by 2022 (2). Multifaceted intervention and rehabilitation strategies should be key points of research, with the aim of reducing the economic, social, and disability impact of cancer (3).

Cancer rehabilitation may improve functional, physical, cognitive, and psychological outcomes during and after treatment; all are affected aspects in most breast cancer survivors. (5–7). Although the need for personalized treatments has been studied (8) and the preference of patients for face-to-face treatments demonstrated (9), this care is under-utilized (5). Moreover, a high number of breast cancer survivors do not adhere to international clinical practice guidelines in terms of healthy lifestyles, so the best rehabilitation model needs to be determined to promote lifestyle behavior changes (10).

Our group previously validated a mobile health (mHealth) tool (BENECA mHealth) to incorporate highly validated nutrition and exercise recommendations in cancer survivors (11), with the intention of improving energy balance, which aids in avoiding recurrence and loss of QoL (12). The World Health Organization defines eHealth as a transfer of health care through electronic devices, including mobile platforms (13). The number of applications for cancer is small (14,15), and only a few are aimed at prevention (2.0%) or management (3.7%) (14). Integrating mHealth into the oncology care continuum may be a successful approach to offer low-cost, real-time ways to encourage preventive strategies or monitor different behaviors, symptoms, and physiological indicators of disease as well as provide interventions (14,16). The scientific evidence seems to indicate the benefits of these strategies in different populations with and without pathology, especially in breast cancer, as well as in different outcomes, such as physical activity, nutrition, and fatigue (16–18). However, there are some limitations, such as validation of data collection methods, adherence, and maintenance of long-term results (16–18). Studies also agree on the complementary and non-substituting nature of these tools in terms of face-to-face intervention strategies and the need for professional supervision.

Although benefits and effect size (ES) values are greater with supervised/face-to-

face than unsupervised/distance-based rehabilitation programs for cancer survivors, unsupervised programs have some advantages (e.g., fewer barriers, lower cost, and instant feedback) (19). Efforts should be made to explore the optimal balance between unsupervised/distance-based and supervised/face-to-face approaches to cancer care. Starting from the hypothesis that a mixed approach may be ideal, with a transition to a more self-directed approach, the aim of the current study was to compare the clinical efficacy of an mHealth lifestyle app (BENECA mHealth) used alone versus an integral approach combining BENECA mHealth with a supervised rehabilitation program (BENECA and rehabilitation) in terms of QoL and functional outcomes of breast cancer survivors. We hypothesized that both strategies would improve outcomes, but BENECA and rehabilitation would be superior to BENECA mHealth alone.

Methods

Study design

An assessor-blinded, randomized, controlled, parallel-group design was approved by the Research Ethics Committee of the province of Granada, Spain (FIS PI14-01627). The trial was registered (ClinicalTrials.gov NCT02817724), and the study protocol was published (20). Participants were randomly assigned to receive BENECA and rehabilitation or BENECA mHealth and usual care. This trial adheres to the CONSORT 2010 statements (21) for parallel-group randomized controlled trials and the TIDieR Checklist (22) for intervention description and replication. All participants provided written informed consent.

Participants

A total of 80 breast cancer survivors were randomly allocated to BENECA and rehabilitation (n = 40) or BENECA and usual care (n = 40). The recruitment was conducted in 2 hospitals, the Hospital Virgen de las Nieves (Breast Unit) and the Hospital Clinico San Cecilio, Granada (Spain). The inclusion criteria were age 25 to 75 years, diagnosis of stage I-IIIA breast cancer, some range of motion (ROM) limitation measures by goniometry, overweight or obese according to the Spanish SEEDO guidelines (23), able to access mobile apps or living with someone who has this ability, medical clearance for participation, completed adjuvant therapy except hormonal therapy, and signed informed consent. According to Spanish SEEDO guidelines (23), people with a body mass index (BMI) > 25 kg/m2 are considered overweight. This criterion was chosen because of the high risk of second cancers and recurrence in overweight people (24). Exclusion criteria were cancer recurrence, chronic disease or orthopedic issues that would interfere with study participation, and uncontrolled hypertension (diastolic pressure > 95 mmHg).

Randomization and blinding process

The randomized process consisted of 3 waves (25:30:25) from 2016 to 2018 (using the epidemiological data analysis program Epidat v4.2, 2016. Consellería de Sanidade, Xunta de Galicia, España; Organización Panamericana de la salud; Universidad CES, Colombia). Treatment allocation was performed by an external member who was blinded to the study. The allocation sequence was based on sealed, sequentially numbered, opaque envelopes that were opened after baseline assessment so that the assessor member (NGC) was blinded to the random process, limiting risk of bias during assessments. The assessor member was different from the therapist who performed the supervised program for the BENECA and rehabilitation group.

Interventions

The study protocol was published and both intervention groups were described in detail (20). Briefly, all participants used BENECA mHealth for 8 weeks. The BENECA and rehabilitation group also underwent an 8-week supervised program (3 sessions/week) led by the CUIDATE research group at the "Cuídate" Support and Research Unit for Oncology Patients (University of Granada, Spain). The program focuses on symptoms, therapeutic exercises, and group sessions of psychomotricity. The supervised program was in a group, but each activity was personalized to each patient. In addition, participants were guided to extrapolate the exercises to their daily activities (Supplementary Table 1). The supervised program was conducted by an expert occupational therapist (always the same one for the 3 waves). The BENECA and usual care group also received usual care. For ethical reasons and once the study ended, participants from the BENECA and usual care group were invited to receive the supervised program; however, the data were not analyzed.

The BENECA app used in both groups allows for recording dietary and physical activity habits daily to obtain energy feedback, which helps participants adapt their lifestyle habits. More information related to the installation, management, and reliability of the BENECA mHealth app can be found elsewhere (20,25).

Outcome measures

Data were collected at baseline (T1), 8 weeks post-intervention (T2), and 6-month follow-up (T3).

Primary endpoint: QoL

QoL was assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORT QLQ-C30) v3.0 (26) and its breast cancer module Breast Cancer-Specific Quality of Life Questionnaire (EORT QLQ-BR23) (27). The EORT QLQ-C30 includes global health status, 5 functional scales (physical, role, emotional, cognitive and social functioning) and 9 symptom items (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial

difficulties. The EORT QLQ-BR23 includes 4 functional scales (body image, sexual functioning, sexual enjoyment and future perspective) and 4 symptom items (systemic therapy side effects, breast symptoms, arm symptoms and upset by hair loss; the latter was not evaluated because of the cancer stage of our participants). These instruments have shown adequate reliability (26,27).

Secondary endpoints: functional assessment

Disability was assessed by the Disabilities of the Arm, Shoulder and Hand (DASH), a self-reported questionnaire that measures symptoms and physical function (disability) for any upper-limb region (28). A Spanish version (Cronbach's alpha 0.96) (29) has been used in breast cancer (30).

The active range of motion (AROM) of the shoulder was assessed bilaterally by using a plastic universal goniometer with the Norking and White approach (31). The intra-rater reliability of the goniometer has been reported for shoulder AROM with an intraclass correlation coefficient of >0.94 for main assessed movements (32).

Upper-body muscular strength was measured by using a digital handgrip (TKK 5101 Grip-D; Tokyo, Japan). Patients maintained a standing position with the elbow extended (33) and the grip adjusted to the patient's hand size (34). Three repetitions were recorded for each hand, with a 1-min rest period between repetitions. The average score for each hand was recorded (35).

Body mass index, percentage fat mass, and bone mineral density were measured by dual-energy X-ray absorptiometry (QDR 4500 W, HOLOGIC) as described (36) (37). Height and weight were measured at baseline.

Sample size calculations

The primary outcome EORTC QLQ-C30 v3.0 (26) with overall health-related QoL (HRQoL) was used based on an expected increase in HRQoL with BENECA and rehabilitation versus BENECA and usual care, and from our previous study in a similar population (38), we considered 5-10 points to be a minimally important difference (39). With differences of at least 5%, power of 0.90 and p=0.05 level of significance between 2 groups of 36 participants assuming similar standard deviation (approximately 7 points), assuming a maximum follow-up loss of 10% (40), we needed 80 participants (40 in each group).

Statistical analysis

Descriptive statistics are expressed as mean (SD) with 95% CIs and frequency (%). The Kolmogorov–Smirnov test was used to test the normal distribution of the data ($P > 0.05$), and Student t or chi-squared test was used to analyze between-group differences at baseline, as appropriate.

The main analysis included all participants who were randomly assigned and all available in-trial data at the end of study in accordance with the intention-to-treat (ITT) principle. Our data had few missing

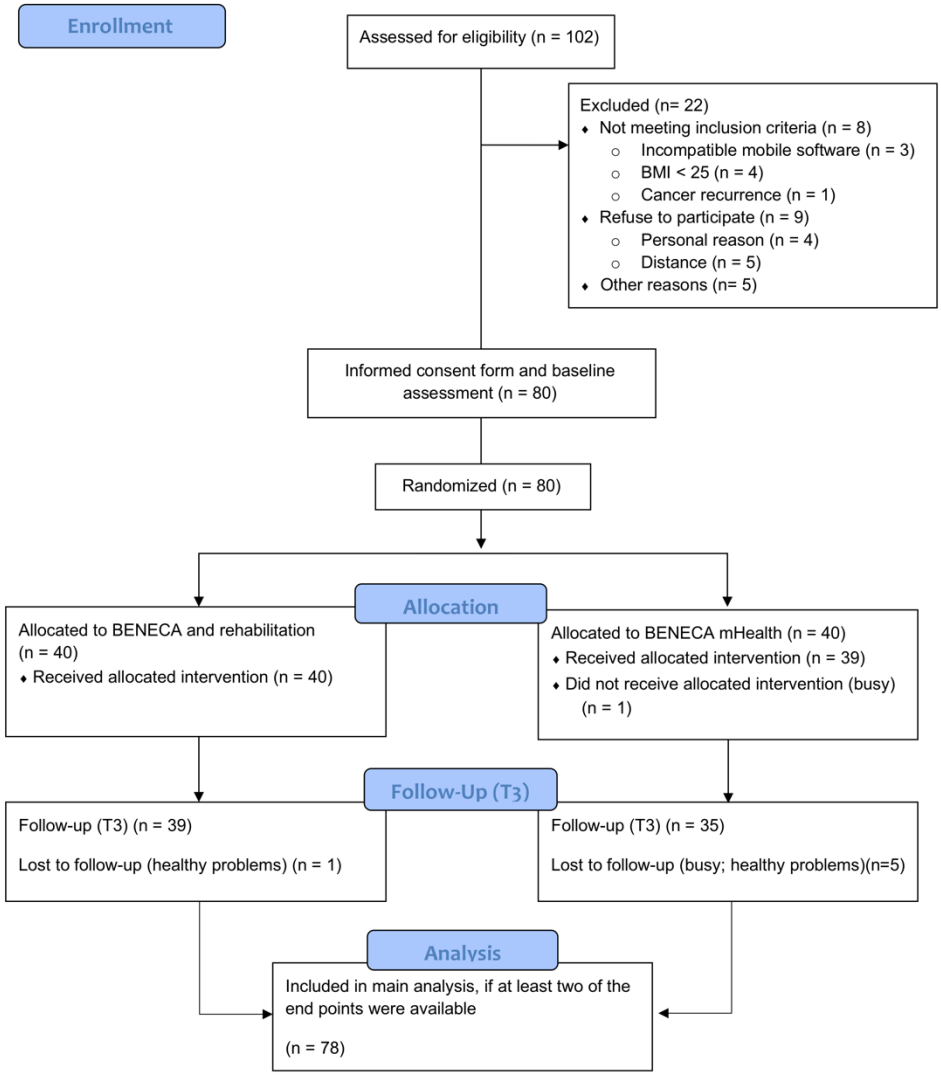

Figure 1: Flow of participants in the trial. BMI, body mass index; T3, 6-month follow-up

values (<5% of the total number of cases), which can be considered to be missing at random and inconsequential (41). Hence, no multiple imputation method was necessary, and the ITT principle was used (with the worst value carried forward in patients with missing data). This analysis was performed by repeated measures of analysis of covariance (ANCOVA) followed by post-hoc analysis with Bonferroni adjustment for multiple comparisons. The ANCOVA analysis also adjusted for covariate effects (age, type of surgery, stage, time since diagnosis, and marital status). We analyzed intervention effects and maintenance of effects on study variables. In addition, ES values were estimated with Cohen d values (42), considering 0–0.19 negligible, 0.2–0.49 small, 0.5–0.79 moderate, and ≥ 0.8 large.

The reliable change index (RCI) was analyzed to determine whether statistically significant changes had occurred in QoL with a significant interaction × group effect. The RCI indicates the change between an individual's pre- and post-intervention scores divided by the standard error of difference between the scores. The possible outcomes were reliable improvement (RCI > 1.96), no reliable change (RCI 1.96 to -1.96), and reliable deterioration (RCI < -1.96) (43). Fisher exact test was used to compared proportions between groups.

We used STATA/SE 14.0 (StataCorp, College Station, TX, USA) or SPSS (IBM SPSS v20, Corp., Armonk, NY, USA) for analyses, with $p < 0.05$ considered statistically significant.

Results

Between September 2016 and December 2017, 102 women were assessed for eligibility. The CONSORT diagram indicates the number of breast cancer survivors approached, screened, randomly assigned, and retained, as well as the availability of the data at each endpoint (Figure 1).

Supplementary Table 2 provides the demographic and medical characteristics of participants. Baseline characteristics of the 2 groups were well balanced (significant differences were observed only in marital status, so this variable was included as a covariate in the main analysis).

Differences between baseline outcome scores were studied, without significance, except for the baseline DASH score ($t = -2.165$; $p = 0.034$), so it was included as a covariate in the analysis.

Primary outcome: QoL

The ANCOVA main analyses showed significant interaction time × group effects for global health status ($F = 5.82$; $p = 0.004$); all functional subscales of the QLQ C-30: physical ($F = 14.31$; $p < 0.001$), role ($F = 18.37$; $p < 0.001$), emotional ($F = 6.31$; $p = 0.003$), cognitive ($F = 27.20$; $p < 0.001$), and social functioning ($F = 7.65$; $p = 0.001$) (Table 1); and some symptom subscales (Supplementary Table 3). Significant effects were also found for body image ($F = 13.24$; $p < 0.001$), future perspectives ($F = 8.08$; $p < 0.001$), systemic therapy side effects ($F = 3.70$; $p = 0.03$), breast symptoms ($F = 5.50$; $p = 0.006$), and arm symptoms ($F = 17.71$; $p < 0.001$) (Table 1). At T2, statistically significant differences favour BENECA and rehabilitation, with better scores as compared with BENECA and usual care in global health status ($p = 0.002$); functional subscales: physical ($p < 0.001$), role ($p < 0.001$), emotional ($p < 0.001$), cognitive ($p < 0.001$), and social functioning ($p < 0.001$); body image ($p < 0.001$); future perspectives ($p < 0.001$); systemic therapy side effects ($p = 0.025$); breast symptoms ($p=0.002$); and arm symptoms ($p < 0.001$). At T3, the effects were maintained (all $p < 0.05$) except for emotional functioning ($p = 0.06$), social functioning ($p = 0.05$), systemic therapy side effects ($p = 0.21$), and breast symptoms ($p =$

0.05) (Table 1 and Supplementary Table 3). Figure 2 shows the ES values for significant between-group differences at T2 and T3, showing moderate-to-large ES for most variables. After including covariates, results did not differ.

Table 1. Within-group and between-group effects for mean quality of life scores on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and breast module (EORT QLQ-BR23) at T1, T2 and T3.

EORT QLQ-C30	BENECA and usual care (n = 38)	BENECA and rehabilitation (n = 40)	Between-group effects
Global health			
Within-group effects			
T1 to T2	11.40 (5.74; 17.07)	24.17 (18.65; 29.69)	12.76 (4.85; 20.67)[b]
T1 to T3	12.50 (5.56; 19.44)	27.92 (21.15; 34.68)	15.41 (5.72; 25.11)[b]
Physical functioning			
Within-group effects			
T1 to T2	2.11 (-2.04; 6.25)	17.50 (13.46; 21.54)	15.40 (9.61; 21.18)[c]
T1 to T3	2.11 (-3.06; 7.27)	18.67 (13.64; 23.70)	16.56 (9.35; 23.77)[c]
Role functioning			
Within-group effects			
T1 to T2	-1.75 (-9.09; 5.58)	29.16 (22.02; 36.32)	30.92 (20.68; 41.17)[c]
T1 to T3	5.70 (-2.78; 5.58)	28.75 (20.48; 37.02)	23.05 (11.21; 34.89)[c]
Emotional functioning			
Within-group effects			
T1 to T2	12.28 (6.14; 18.42)	27.08 (21.10; 33.06)	14.80 (6.23; 23.37)[b]
T1 to T3	15.35 (9.38; 21.32)	23.13 (17.30; 28.94)	7.77 (-0.56; 16.11)
Cognitive functioning			
Within-group effects			
T1 to T2	-2.19 (-7.90; 3.52)	27.50 (21.93; 33.06)	29.69 (21.72; 37.66)[c]
T1 to T3	1.32 (-6.61; 9.24)	25.00 (17.27; 32.73)	23.68 (12.61; 34.76)[c]
Social functioning			
Within-group effects			
T1 to T2	8.77 (0.98; 16.56)	29.17 (21.58; 36.76)	20.39 (5.46; 31.27)[c]
T1 to T3	11.40 (2.72; 20.09)	23.33 (14.87; 31.80)	11.93 (-0.20; 24.06)
EORT QLQ-BR23			
Body image			
Within-group effects			
T1 to T2	9.26 (2.84; 15.69)	32.31 (26.05; 38.58)	23.05 (14.08; 32.03)[c]
T1 to T3	13.60 (4.69; 22.50)	27.29 (18.62; 35.97)	13.70 (1.26; 26.13)[b]
Sexual functioning			
Within-group effects			
T1 to T2	1.75 (-2.68; 6.19)	7.50 (3.18; 11.82)	5.75 (-0.44; 11.93)
T1 to T3	1.32 (-5.06; 7.69)	7.08 (0.87; 13.30)	5.77 (-3.14; 14.67)
Sexual enjoyment			
Within-group effects			
T1 to T2	2.25 (-5.96; 10.47)	10.76 (2.77; 18.78)	8.52 (-15.89; 23.37)
T1 to T3	5.41 (-8.66; 19.47)	1.67 (-12.03; 15.36)	-3.74 (-23.37; 15.89)
Future perspectives			
Within-group effects			
T1 to T2	7.21 (-1.82; 16.23)	32.03 (23.35; 40.71)	24.82 (12.30; 37.35)[c]
T1 to T3	9.46 (-3.41; 22.33)	31.67 (19.29; 44.04)	22.21 (4.36; 40.06)[b]
Systemic therapy side effects			
Within-group effects			
T1 to T2	-7.16 (-11.01; -3.31)	-13.31 (-17.06; -9.56)	-6.15 (-11.52; -0.78)[b]
T1 to T3	-8.02 (-12.46; -3.58)	-11.92 (-16.25; -7.59)	-3.90 (-10.09; 2.30)
Breast symptoms			
Within-group effects			
T1 to T2	-5.32 (-11.48; 0.83)	-19.40 (-25.39; -13.40)	-14.07 (-22.67; -5.48)[b]
T1 to T3	-8.96 (-16.95; -1.57)	-19.13 (-26.34; 11.93)	-10.18 (-20.50; 0.14)[b]
Arm symptoms			
Within-group effects			
T1 to T2	-0.48 (-6.20; 5.24)	-24.45 (-30.02; -18.89)	-23.97 (-31.95; -15.97)[c]
T1 to T3	-4.66 (-12.52; 3.20)	-26.38 (-34.04; -18.71)	-21.72 (-32.69; -18.71)[c]

Data are mean (SD) (95% confidence interval [CI] for the mean) values at T1, T2 and T3, and mean differences (95% CI for the difference) for within-group and between-group effects. Bonferroni adjustment was used for pairwise comparisons.

T1, baseline; T2, 8-weeks post-intervention; T3, 6-month follow-up

[b] = $P<0.05$ (significant between-groups effect).

[C] = $P<0.001$ (significant between-groups effect).

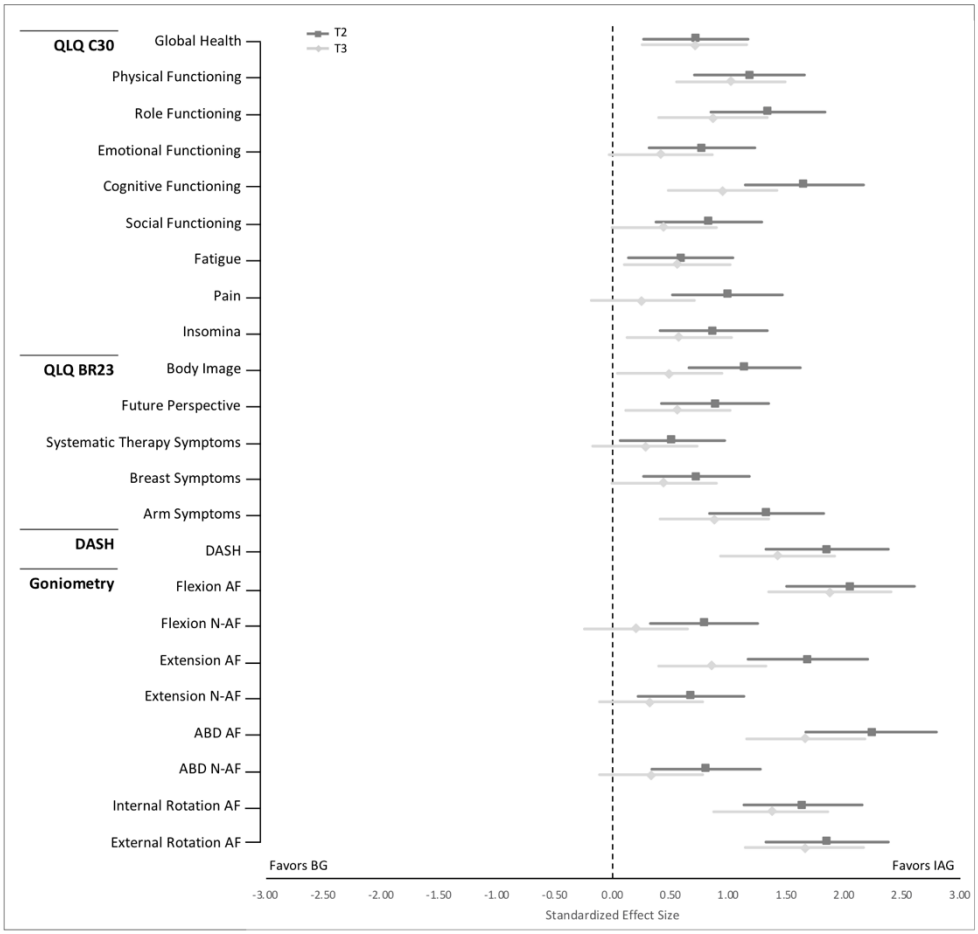

Figure 2. Standardized effect sizes (and 95% CIs) of the difference between treatment groups in quality of life and functionality outcomes. Standardized effect sizes < 0.2 are not likely to be clinically important. Abbreviations: DASH, Disability of the Arm, Shoulder and Arm questionnaire; AF, affected side; N-AF, non-affected side.

Secondary outcomes

The major secondary outcome was upper-limb functionality. We observed significant interaction effects for the DASH score ($F = 12.98$; $p < 0.001$)(Supplementary Table 4) and all AROM objective measures for the affected side (all $p < 0.001$)(Figure 3). At T2, the BENECA and rehabilitation group showed higher DASH scores ($p < 0.001$) (Supplementary Table 4) and higher AROM (all $p < 0.001$ on the affected side) (Figure 3). These results were maintained at T3 (all $p < 0.001$) (Figure 3), with moderate-to-large ES values at both T2 and T3 (Figure 2). After including covariates (including baseline DASH score), results did not differ.

The other secondary outcomes were upper-limb strength and anthropometric measures, and at T2 and T3, we found no significant between-group interaction in any variable (Supplementary Tables 5 and 6).

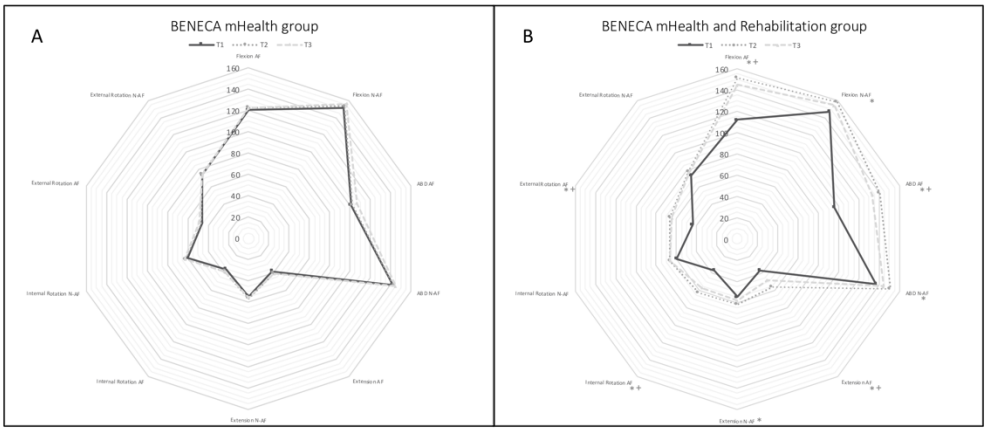

Figure 3. Changes in shoulder active range of motion (T1, T2, T3) between BENECA and usual care (A) and BENECA and rehabilitation (B), measured by goniometry. Data are mean scores over time. Main analyses performed by repeated measures of analysis of covariance. With significant interaction, between-group effects are shown with Bonferroni adjustment for pairwise comparisons as follows: * T1/T2 and + T1/ T3 ($p < 0.01$ significance in all between-group effects). AF, affected side; N-AF, non-affected side; ABD, abduction.

Reliable clinical improvement

Figure 4 shows the proportion of participants reporting reliable clinical improvement in QoL at T2, which was higher with BENECA and rehabilitation than BENECA and usual care in global QoL (57.5% vs 26.3%, $p = 0.008$) and functional subscales: physical (47.5% vs 13.2%, $p = 0.001$), role (62.5% vs 15.8%, $p < 0.001$), emotional (52.5% vs 18.4%, $p = 0.003$), cognitive (55.0% vs 2.6%, $p < 0.001$), and social (55.0% vs 21.1%, $p = 0.002$) functioning.

Implementation of the protocol: adherence rate and adversity

The adherence rate for BENECA was higher with BENECA and rehabilitation than BENECA and usual care (94.32% vs 79.6%) at a mean (SD) of 52.82 (5.19) versus 44.55 (7.33) of 56 possible registration days (mean difference 8.27, 95% CI 11.13 ; 5.42, $p < 0.001$). The adherence rate for the supervised program with BENECA and rehabilitation was high (98.75%), at a mean (SD) of 23.7 (1.04) of 24 scheduled sessions, and no remarkable health problems or technical issues were recorded.

Discussion

The benefits of distance-based strategies (44,45) as well as on-site rehabilitation programs (46,47) in cancer have been demonstrated and validated versus usual care. Thus, the aim of this study was to compare the efficacy of an integral approach combining mHealth (our BENECA app) and rehabilitation as compared with mHealth alone to improve QoL of breast cancer survivors. Consistent with our hypotheses, we observed improvement in both groups in the main subscales of QoL (both C30 and BR23), but BENECA and rehabilitation significantly improved QoL, and AROM and upper-limb functionality were better with BENECA and rehabilitation than BENECA and usual care. In addition, most of the benefits were maintained after 6 months. Importantly, approximately two-thirds of the BENECA

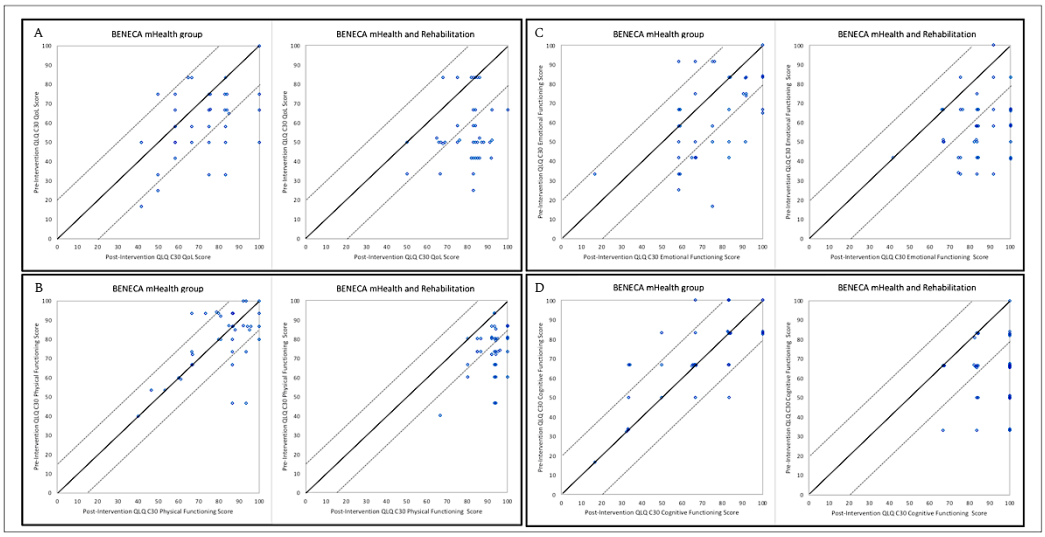

Figure 4. Reliable change index for the QLQ-C30. Change in (A) general quality of life (QoL), (B) physical functioning, (C) emotional functioning, (D) cognitive functioning, between T1 and T2 assessment with BENECA and usual care (left, n = 38) and BENECA and rehabilitation (right, n = 40). The diagonal line indicates no change; the dashed upper and lower lines indicate the 95% CIs for the Jacobson-Truax reliable change index. Bookmarks indicate improvement (below the diagonal line) or deterioration (above the diagonal line). Figure inspired by van de Wal et al. (2017).

and rehabilitation group showed reliable clinical improvement, as compared with less than one-third of the BENECA and usual care group. To the best of our knowledge, this study is the first to investigate the effect of an integral approach (with mHealth and a supervised rehabilitation program) in breast cancer survivors.

Our results show that use of the BENECA mHealth app alone conferred improvements in some QoL scores (48). Nonetheless, in the most functional variables, the integral approach obtained better results. The between-group ES values for QoL after the intervention were moderate to large in favor of BENECA and rehabilitation. A meta-analysis of the effect of digital technologies on some outcomes, such as behavior change for diet and physical activity, found ES values for QoL ranging from 0.20 to 2.64. The overall ES value was 0.06 for randomized controlled trials (49), which suggests that non-digital interventions can obtain a larger ES because of human supervision or interaction and could encourage higher levels of engagement and adherence. Other recent meta-analyses of onsite interventions for breast cancer patients (6) or survivors (7) found ES values between 0.22 and 0.59, with an overall EF of 0.40 and 0.45, respectively. Therefore, the combination of a supervised rehabilitation program and mHealth seems to double or triple the EF. The integral approach seems to be a promising strategy.

Similarly, our results regarding upper-limb functionality (both subjective and objective) show large ES values in favor of BENECA and rehabilitation (all $d > 1.50$), with improvement in AROM of both upper limbs. The mean differences for all measures exceeded the minimal clinical difference for goniometry (50). Furthermore, the improvement in the

breast and arm symptom subscales of the QLQ-BR23 reinforce these findings. One of the main consequences of oncological treatment is the cardiotoxic systemic effects. Our study managed to reduce their perception with a moderate ES (d = 0.51).

Uhm et al. compared an innovative mHealth with a pedometer versus a conventional program and found significant intra-group but not inter-group improvement (51). Unlike our study, their study involved resistance exercises to improve upper-limb functionality. By using the same intervention strategy but different transmission methods, the authors concluded that both strategies were equally valid. We believe that these findings reinforce our results, because we combined both strategies. Egbring et al. found that supervision has beneficial effects on patient functionality. Unlike our study, Pope et al. demonstrated a behavioral change and improved QoL after a 12-week mHealth program. However, the authors pointed to the need to consider the exclusive use of an mHealth system compared to a conventional one, because the experimental group did not show significantly different improvements over time (52). Our results for the objective and subjective functionality of the upper limb as well as in reduction of breast and arm symptoms may be due to the focality of the proposed exercises, designed for each patient to gain articular amplitude and promote the generalization of movements through daily activities. Similarly, we observed no significant differences in upper-limb strength, probably because resistance exercises were not used. Therefore, BENECA mHealth could result in benefits for patients in some of the variables studied, although it obtained better results in more variables when combined with the supervised rehabilitation program.

Our study has several limitations. The BENECA and usual care group did not have the active presence of a therapist, so we cannot rule out the impact of the therapist's attention. Therefore, the effect of the treatment may have been overestimated. The sample sizes do not allow comparisons between patients and groups to identify moderators of the treatment effect, such as complexity of treatment, type of surgery, disease staging, time since diagnosis, survival time or even potential anxiety biomarkers. However, the study shows new knowledge about the effectiveness of the integral comprehensive strategy for breast cancer survivors. Unfortunately, the integral approach can be not cost-effective, because it requires rehabilitation staff. Finally, we recognize that the ideal design for this study would have been to include a randomly assigned control group without any intervention. However, this was not feasible mainly because the objective was to show differences between an app and an integral approach. In addition, already knowing the benefits of intervention in these patients, it did not seem ethical to include this group. However, the placebo effect of the expectation of benefit has been demonstrated, and some variables could be

influenced in this sense. All these aspects raise questions and hypotheses that should be answered in future investigations.

Our study's strengths include an innovative approach taking advantage of the benefits of supervised rehabilitation and mHealth, an adequate overall sample size, excellent adherence, the use of validated measures and an in-depth assessment of outcomes, ITT analysis, minimal loss to follow-up, and statistically and clinically meaningful effects on outcomes. We also consider the reduced intervention time as another strength of the study. We believe that the program is successful because it is a comprehensive strategy adjusted to the level of each patient. Because of the limited specific material used, this comprehensive treatment strategy could be implemented at any cancer center or community-based center under the supervision of qualified staff.

In summary, previous research showed the benefits of supervised rehabilitation programs or the use of mHealth on outcomes of cancer survivors, without combining the strategies. The current trend in medicine is personalized treatment. Similarly, in rehabilitation, we must increasingly use techniques focused on the personal profile of patients, to reduce their DALYS. Our trial provides a unique and important mechanism to do so and is the first compelling evidence of the effectiveness of this integral approach in the physical and functional aspects of QoL in breast cancer survivors.

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Conflict of interest

None declared

Legends

Figure 1. Flow of participants in the trial. BMI, body mass index; T3, 6-month follow-up

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Supplementary table 1. Scheduled structure for supervised rehabilitation program.

SUPERVISED REHABILITATION PROGRAM
(tailored program according needs perceived at baseline)

Sessions	*Main objective*	*Progression*					*Materials*	*Frequency & duration*
		Phase 1 (1–2 weeks)	Phase 2 (3–4 weeks)	Phase 3 (5–6 weeks)	Phase 4 (7–8 weeks)	Extra phase		
Individualized AROM session	Active ROM	Control of pain and inflammation Flx and ABD ROM: 0º–45º. Technical-therapeutic activities in sagittal and frontal planes.	Control of pain and inflammation Flx and ABD ROM: 0–90º. Technical-therapeutic activities in sagittal and frontal planes (combined).	Control of pain and inflammation Flx and ABD ROM: 0–135º. Rot ROM: 0–30º ext. and int. Ext ROM: Introduction Technical-therapeutic activities in sagittal, frontal and transverse planes.	Control of pain and inflammation. Flx and ABD ROM: 0–150º. Rot ROM: 0–45º ext. and int. Ext ROM: Introduction Technical-therapeutic activities in every planes, combined. Optimizing muscle endurance.	Maintain full ROM without pain Technical-therapeutic activities in every plane, combined Optimizing muscle endurance. Normalize movement patterns.	Different materials were used depending on the objective of the week. Namely: Balls. Hoops. Spades. Strings Therapeutic putty Therapeutic tree Rehabilitation tree of the shoulder. Scarves Towels Marbles Balloons Therapeutic parachute Mattresses Psychomotricity trolley	2 sessions/week 50 min/session
Group psychomotricity sessions	Active ROM, coordination reduction of fatigue, improvement of cognitive elements (processing speed, working memory, attention).	Each psychomotricity session was divided into 3 parts: warm-up, central part, and return to calm. Psychomotricity sessions was progressively increased by weeks, according to patient's progression. We increased the difficulty and requirements of the sessions by increasing the number of exercises repetitions, the inclusion of a greater number of stimuli, etc.; with the following exercises: Cognitive and symbolic processes functional activities. General dynamic coordination and aerobic exercises. Upper extremity mobility exercise, body image and scheme, bilateral coordination exercises. Relaxation, reduction of pain, fatigue and anxiety.						3 sessions/week 45 min/session
***Group* psychosocial sessions**	Know and share difficulties expressed by the participants in their management and daily occupational performance.	Occupational Balance I	ADL: fatigue and ergonomics	Stress management	Occupational Balance II / Return to work	--	Slate and audiovisual material prepared.	1 session/week 30 min/session

ABD, abduction; ADL, activities of daily living; AROM, active range of motion; Flx, flexion; Ext, extension
Starting with 8 repetitions/series, and 2 series/exercise, the progression was performed every day/week depending on the patient's abilities individually, based on their perceived pain and fatigue (by a visual analog scale). The proposed progression was adapted to each participant, so that one participant could start directly with the objectives of weeks 3-4 while another participant could start with the objectives of week 1-2. Hence, an extra phase was proposed. Program developed by the CUIDATE research team with extensive experience in oncological rehabilitation (composed of physiotherapists, occupational therapists, graduates in physical activity and sport and sports doctors). Sessions developed by an expert and trained therapist, and with 5 years of experience in oncological rehabilitation.

Supplementary Table 2. Sociodemographic and clinical characteristics of the participants by study group.

Variable	BENECA and usual care (n = 40)	BENECA and rehabilitation (n = 40)	p-Value*
Age	49.76 ± 8.42	53.40 ± 8.66	0.098
Marital status			0.044
Single	8 (20.0)	8 (20.0)	
Married	22 (55.0)	28 (70.0)	
Divorced/widowed	9 (22.5)	1 (2.5)	
Other	1 (2.5)	3 (7.5)	
Time since surgery (months)			0.317
≤ 12	9 (22.5)	13 (32.5)	
>12	31 (77.5)	27 (67.5)	
Educational level			0.402
No education	0 (0.0)	1 (2.5)	
Basic	9 (22.5)	14 (35.0)	
Medium	13 (32.5)	12 (30.0)	
High	18 (45.0)	13 (32.5)	
Employment status			0.104
Housewife	5 (12.5)	13 (32.5)	
Employed	20 (50.0)	12 (30.0)	
Medical leave	4 (10.0)	6 (15)	
Unemployed (because of illness)	11 (27.5)	9 (22.5)	
Breast cancer stage			0.371
I	7 (17.5)	3 (7.5)	
II	19 (47.5)	23 (57.5)	
IIIA	14 (35.0)	14 (35.0)	
Type of surgery			0.129
Lumpectomy	10 (25.0)	14 (35.0)	
Quadrantectomy	7 (17.5)	6 (15.0)	
Unilateral mastectomy	11 (27.5)	16 (40.0)	
Bilateral mastectomy	12 (30.0)	4 (10.0)	
Medical treatment			0.204
None	2 (5.0)	4 (10.0)	
Radiotherapy	8 (20.0)	2 (5.0)	
Chemotherapy	7 (17.5)	9 (22.5)	
Radiotherapy and chemotherapy	23 (57.5)	25 (62.5)	
Menopausal status			0.305
Premenopausal	3 (7.5)	1 (2.5)	
Postmenopausal	37 (92.5)	39 (97.5)	

Data are as mean (SD) or n (%) as appropriate.
*Student *t* test for independent samples and chi-square analysis were used for continuous and categorical variables, respectively.

Supplementary Table 3. Within-group and between-group effects for mean quality of life (QoL) scores on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) symptom subscales at T1, T2 and T3.

EORT QLQ-C30 subscales	BENECA and usual care (n = 38)	BENECA and rehabilitation (n = 40)	Between-group effects
Fatigue			
T1	35.38 (23.08) (27.79; 42.97)	42.22 (15.75) (37.18; 47.26)	
T2	27.49 (17.66) (21.68; 33.29)	20.28 (13.52) (15.95; 24.60)	
T3	26.90 (17.06) (21.29; 32.51)	20.00 (8.79) (17.19; 22.81)	
Within-group effects			
T1 to T2	-7.89 (-15.45; -0.34)	-21.94 (-29.31; -14.57)	-14.05 (-24.60; -3.49)[b]
T1 to T3	-8.48 (-16.32; -0.64)	-22.22 (-29.86; -14.57)	-13.74 (-24.69; -2.78)[c]
Nausea			
T1	2.63 (7.27) (0.24; 5.02)	1.67 (5.06) (0.05; 3.29)	
T2	3.07 (6.55) (0.92; 5.22)	1.25 (4.45) (-0.17; 2.67)	
T3	1.32 (4.55) (-0.18; 2.81)	0.83 (3.68) (-0.34; 2.01)	
Within-group effects			
T1 to T2	0.44 (-1.51; 2.39)	-0.42 (-2.32; 1.48)	-0.86 (-3.58; 1.87)
T1 to T3	-1.31 (-3.33; 0.70)	-0.83 (-2.80; 1.13)	0.48 (-2.33; 3.29)
Pain			
T1	36.84 (26.33) (28.19; 45.49)	40.83 (16.43) (35.58; 46.09)	
T2	32.45 (24.79) (24.31; 40.61)	17.50 (15.07) (12.68; 22.32)	
T3	27.63 (16.57) (22.19; 33.08)	25.42 (13.60) (21.07; 29.77)	
Within-group effects			
T1 to T2	-4.39 (-10.47; 1.69)	-23.33 (-29.26; -17.41)	-18.95 (-27.44; -10.45)[c]
T1 to T3	-9.21 (-16.97; -1.42)	-15.42 (-22.99; -7.85)	-6.21 (-17.05; 4.64)
Dyspnonea			
T1	24.56 (22.84) (17.05; 32.07)	31.66 (27.16) (22.98; 40.35)	
T2	14.04 (22.77) (6.55; 21.52)	10.83 (15.81) (5.78; 15.89)	
T3	6.14 (13.09) (1.84; 10.44)	3.33 (10.13) (0.09; 6.57)	
Within-group effects			
T1 to T2	-10.53 (-18.68; -2.37)	-20.83 (-28.78; -12.88)	-10.31 (-21.69; 1.08)
T1 to T3	-18.42 (-26.85; -9.99)	-28.33 (-36.54; -20.12)	-9.91 (-21.68; 1.85)
Insomnia			
T1	42.98 (37.09) (30.79; 55.17)	50.83 (35.40) (39.51; 62.15)	
T2	46.49 (35.12) (34.94; 58.04)	25.83 (24.44) (18.02; 33.65)	
T3	38.60 (25.14) (30.33; 46.86)	22.50 (23.13) (15.10; 29.89)	
Within-group effects			
T1 to T2	3.51 (-6.91; 13-92)	-25.00 (-35.15; -14.85)	-28.51 (-43.05; -13.97)[c]
T1 to T3	-4.39 (-17.77; 9.00)	-28.33 (-41.38; -15.28)	-23.95 (-42.64; -5.25)[b]
Appetite loss			
T1	8.77 (14.88) (3.88; 13.66)	10.00 (15.46) (5.05; 14.95)	
T2	10.52 (15.70) (5.36; 15.69)	4.16 (13.48) (-0.14; 8.47)	
T3	4.38 (11.42) (0.63; 8.14)	2.50 (8.89) (-0.34; 5.35)	
Within-group effects			
T1 to T2	1.75 (-3.99; 7.51)	-5.83 (-11.44; -0.23)	-7.59 (-15.62; 0.44)
T1 to T3	-4.39 (-10.09; 1.31)	-7.50 (-13.06; -1.94)	-3.11 (-11.08; 4.85)
Constipation			
T1	25.44 (29.44) (15.76; 35.11)	17.50 (26.13) (9.14; 25.86)	
T2	29.82 (28.77) (20.36; 39.28)	16.66 (26.15) (8.30; 25.03)	
T3	15.79 (21.56) (8.70; 22.87)	11.66 (17.78) (5.98; 17.35)	
Within-group effects			
T1 to T2	4.39 (-3.75; 12.52)	-0.83 (-8.76; 7.09)	-5.21 (-16.57; 6-14)
T1 to T3	-9.65 (-17.02; -2.28)	-5.83 (-13.02; 1.35)	3.82 (-6.48; 14.11)
Diarrhea			
T1	13.16 (21.28) (6.16; 20.15)	9.17 (18.47) (3.26; 15.07)	
T2	8.77 (20.04) (2.19; 15.36)	5.00 (12.05) (1.14; 8.86)	
T3	5.26 (14.55) (0.48; 10.05)	0.83 (5.27) (-0.85; 2.52)	
Within-group effects			
T1 to T2	-4.39 (-11.07; 2.23)	-4.16 (-10.62; 2.29)	0.22 (-9.03; 9.47)
T1 to T3	-7.89 (-14.48; -1.32)	-8.33 (-14.75; -1.92)	-0.44 (-9.62; 8.75)
Financial difficulties			
T1	18.42 (27.62) (9.34; 27.49)	20.83 (30.84) (10.97; 30.70)	
T2	14.03 (26.43) (5.35; 22.72)	10.83 (17.52) (5.23; 16.44)	
T3	7.89 (16.32) (2.53; 13.26)	7.50 (14.09) (2.99; 12.01)	
Within-group effects			
T1 to T2	-4.39 (-11.24; 2.46)	-10.00 (-16.68; -3-32)	-5.61 (-15.18; 3.95)
T1 to T3	-10.53 (-18.12; -2.93)	-13.33 (-20.74; -5.93)	-2.81 (-13.42; 7.80)

Data are mean (SD) (95% confidence interval [CI] for the mean) values at T1, T2 and T3 and mean differences (95% CI for the difference) for within-group and between-group effects. Bonferroni adjustment was used for pairwise comparisons.

T1, baseline; T2, 8-weeks post-intervention; T3, 6-month follow-up

[b] = $P<0.05$ (significant between-groups effect).

[C] = $P<0.001$ (significant between-groups effect).

Supplementary Table 4. Within-group and between-group effects for mean Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire at T1, T2 and T3.

DASH Questionnaire	BENECA and usual care (n = 38)	BENECA and rehabilitation (n = 40)	Between-group effects
T1	30.78 (13.85) (26.24; 35.34)	37.29 (12.67) (33.24; 41.34)	
T2	27.54 (13.10) (23.24; 31.85)	12.84 (8.05) (10.27; 15.42)	
T3	27.57 (11.44) (23.81; 31.33)	17.48 (7.04) (15.23; 19.73)	
Within-group effects			
T1 to T2	-3.25 (-6.88; 0.39)	-24.45 (-27.99; -20.91)	-21.20 (-26.28; -16.12) [c]
T1 to T3	-3.21 (-6.93; 0.49)	-19.81 (-23.42; -16.20)	-16.59 (-21.76; -11.41) [c]

Data are mean (SD) (95% CI for the mean) values at T1, T2 and T3 and as mean differences (95% CI for the difference) for within-group and between-group effects.
T1, baseline; T2, 8-weeks post-intervention; T3, 6-month follow-up
Bonferroni adjustment was used for pairwise comparisons.
[C] = $P<0.001$ (significant between-groups effect).

Supplementary Table 5. Within-group and between-group effects for mean upper body strength scores at T1, T2 and T3.

Upper body strength	BENECA and usual care (n = 38)	BENECA and rehabilitation (n = 40)	Between-group effects
Handgrip affected			
T1	19.58 (5.49) (17.77; 21.38)	21.54 (5.33) (19.84; 23.25)	
T2	20.39 (5.59) (18.59; 22.23)	23.27 (4.71) (21.77; 24.78)	
T3	20.73 (4.97) (19.10; 22.36)	23.81 (5.01) (22.21; 25.42)	
Within-group effects			
T1 to T2	0.82 (0.20; 1.45)	1.70 (1.09; 2.31)	0.88 (0.01; 1.75)
T1 to T3	1.15 (0.18; 2.13)	2.24 (1.29; 3.19)	1.08 (-0.28; 2.44)
Handgrip not affected			
T1	22.57 (6.28) (20.50; 24.63)	25.11 (5.71) (23.28; 26.94)	
T2	23.01 (6.03) (21.03; 24.99)	26.18 (5.09) (24.55; 27.81)	
T3	23.69 (6.22) (21.65; 25.74)	25.79 (4.81) (24.26; 27.33)	
Within-group effects			
T1 to T2	0.44 (-0.11; 0.99)	1.07 (0.54; 1.61)	0.63 (-0.39; 1.27)
T1 to T3	1.12 (0.53; 1.72)	0.68 (0.11; 1.26)	-0.44 (-1.27; 0.39)

Data are mean (SD) (95% CI for the mean) values at T1, T2 and T3, and as mean differences (95% CI for the difference) for within-group and between-group effects.
T1, baseline; T2, 8-weeks post-intervention; T3, 6-month follow-up

Supplementary Table 6. Within-group and between-group effects for mean anthropometric outcomes at T1, T2 and T3.

Anthropometric outcomes	BENECA and usual care (n = 38)	BENECA and rehabilitation (n = 40)	Between-group effects
Weight (kg)			
T1	72.03 (9.14) (69.02; 75.03)	73.32 (10.04) (70.07; 76.57)	
T2	71.14 (9.28) (68.09; 74.19)	71.53 (9.51) (68.45; 74.62)	
T3	70.95 (9.08) (67.97; 73.93)	71.93 (9.49) (68.87; 75.03)	
Within-group effects			
T1 to T2	-0.89 (-1.66; -1.12)	-1.79 (-2.55; -1.02)	-0.90 (-1.99; 0.19)
T1 to T3	-1.08 (-1.86; -0.29)	-1.37 (-2.14; -0.59)	-0.29 (-1.39; 0.82)
BMI (kg/m2)			
T1	28.55 (4.07) (27.21; 29.88)	29.29 (4.28) (27.90; 30.68)	
T2	28.21 (4.22) (26.82; 29.60)	28.55 (4.09) (27.22; 29.87)	
T3	28.05 (4.15) (26.69; 29.42)	28.66 (4.14) (27.31; 29.99)	
Within-group effects			
T1 to T2	-0.34 (-0.67; -0.01)	-0.74 (-1.07; -0.42)	-0.41 (-0.87; -0.06)
T1 to T3	-0.49 (-0.83; -0.16)	-0.64 (-0.97; -0.31)	-0.15 (-0.61; 0.33)
Waist circumference (cm)			
T1	84.79 (6.83) (82.55; 87.04)	89.46 (10.61) (86.03; 92.91)	
T2	84.46 (6.60) (82.30; 86.63)	89.37 (9.88) (86.17; 92.57)	
T3	83.82 (6.84) (81.57; 86.07)	88.99 (9.00) (85.75; 92.23)	
Within-group effects			
T1 to T2	-0.33 (-1.77; 1.10)	-0.10 (-1.51; 1.33)	0.24 (-1.78; 2.26)
T1 to T3	-0.98 (-1.89; -0.07)	-0.47 (-1.37; 0.43)	0.50 (-0.78; 1.78)
Hip circumference (cm)			
T1	106.58 (12.69) (102.40; 110.75)	108.27 (13.48) (103.90; 112.64)	
T2	106.27 (12.58) (102.13; 110.40)	108.55 (10.79) (105.05; 112.05)	
T3	106.19 (11.79) (102.31; 110.07)	107.03 (12.49) (102.98; 110.07)	
Within-group effects			
T1 to T2	-0.31 (-2.13; 1.51)	0.28 (-1.51; 2.08)	0.59 (-0.84; 2.56)
T1 to T3	-0.38 (-1.59; 0.83)	-1.24 (-2.44; -0.05)	-0.86 (-2.56; 0.84)
BMD (g/cm2)			
T1	1.04 (0.10) (1.01; 1.07)	1.04 (0.09) (1.01; 1.06)	
T2	1.01 (0.16) (0.96; 1.06)	1.03 (0.15) (0.98; 1.08)	
T3	0.98 (0.09) (0.96; 1.02)	1.03 (0.10) (1.00 (1.06)	
Within-group effects			
T1 to T2	-0.03 (-0.08; 0.03)	-0.01 (-0.06; 0.04)	0.02 (-0.06; 0.09)
T1 to T3	-0.05 (-0.08; -0.02)	-0.01 (-0.04; 0.02)	0.04 (-0.01; 0.08)
Body fat (%)			
T1	41.40 (4.39) (39.96; 42.84)	41.78 (6.25) (39.75; 43.81)	
T2	41.37 (5.49) (39.57; 43.18)	39.63 (5.06) (37.99; 41.27)	
T3	40.79 (6.19) (38.75; 42.82)	39.97 (6.62) (37.82; 42.12)	
Within-group effects			
T1 to T2	-0.03 (-1.60; 1.55)	-2.15 (-3.70; -0.60)	-2.12 (-4.34; 0.09)
T1 to T3	-0.62 (-2.87; 1.64)	-1.81 (-4.04; 0.42)	-1.20 (-4.37; 1.97)

BMI, body mass index; BMD, bone mineral density.

Data are mean (SD) (95% CI for the mean) values at T1, T2 and T3 and as mean differences (95% CI for the difference) for within-group and between-group effects.

T1, baseline; T2, 8-weeks post-intervention; T3, 6-month follow-up

LIMITACIONES GLOBALES
GLOBAL LIMITATIONS

LIMITACIONES GLOBALES

Esta Tesis Doctoral Internacional presenta una serie de limitaciones que se han ido planteando a lo largo de los diferentes estudios expuestos, pero que es preciso resumir en este apartado, para que los resultados sean considerados en este contexto.

La principal limitación de esta tesis radica en el diseño y uso de la herramienta mHealth desarrollada, BENECA. En primer lugar, la versión original de BENECA se desarrolló exclusivamente para un entorno móvil basado en Android, por lo que se excluirían a todos los participantes que tuvieran dispositivos móviles de otras plataformas. Por otro lado, las dificultades a la hora de introducir la ingesta hacen que sea tedioso, tal y como nos refirieron algunas de las participantes y puede reducir la adherencia del uso de la aplicación. Además, la necesidad de los participantes de tener conocimientos básicos en el manejo y uso de aplicaciones móviles podría haber hecho que algunos participantes no hubieran sido incluídos. Por último, solo se encuentra disponible en castellano, lo que impide la replicabilidad de los estudios en otros países de habla no hispana. Sin embargo, creemos que con versiones posteriores de BENECA estamos solventando todas estas limitaciones, (véase apartado de Futuras Líneas de Investigación).

Por otro lado, el diseño metodológico utilizado para los estudios II y III pre-post cuasiexperimental de un solo brazo plantea la necesidad de leer sus resultados con cautela, ya que no es posible establecer una relación de causalidad.

En el estudio V, no se ha realizado un estudio de coste-efectividad, el cual podría haber sido interesante dada la necesidad de la presencialidad de un terapeuta ocupacional para llevar a cabo las sesiones de intervención. Por último, el diseño ideal del estudio habría incluído un grupo control sin intervención, con el objetivo de valorar el efecto independiente de cada una de las estrategias de intervención propuestas. Sin embargo, desde el punto de vista ético, conociendo las ventajas del uso de la aplicación móvil BENECA, no se planteó la posibilidad de de incluir un grupo de tales características.

FUTURAS LÍNEAS INVESTIGACIÓN

FUTURE DIRECTIONS

FUTURAS LINEAS DE INVESTIGACIÓN

A partir de los resultados obtenidos en esta Tesis Doctoral Internacional, y conociendo la reducida evidencia científica sobre la terapia ocupacional y sobre esta y otras poblaciónes, se plantean diferentes líneas de investigación futuras, sobre las que profundizar y trabajar. Por un lado, desde el punto de vista de la mHealth aplicada a oncología:

- El desarrollo de BENECA ha permitido implementar una estrategia móvil de salud factible y viable en supervivientes de cáncer de mama. Sin embargo, nuevas formas de introducción de ingesta y actividad física deberían ser exploradas, así como la integración con los nuevos dispositivos de monitorización (los denominados *wearables*), con el objetivo de facilitar su uso y maximizar su funcionalidad en versiones futuras de la aplicación.
- Se pretende desarrollar la aplicación en un lenguaje de programación universal, de manera que pueda ser accesible desde cualquier dispositivo móvil.
- Ampliar las recomendaciones de dieta y actividad física que envía la aplicación, y personalizar al máximo las mismas, utilizando una gran cantidad de información recolectada de diferentes fuentes, empleando el denominado *Big Data*, de manera que pueda ir aprendiendo y expandiéndose con el tiempo.
- Ampliar las funcionalidades de la aplicación, incluyendo no solo balance energético, sino también rehabilitación oncológica.
- Expandir el uso de la aplicación en todos los tipos de cáncer, o en los cánceres más frecuentes.
- Un estudio mayor, con grupo control, podrá apoyar los resultados de esta tesis, incluyendo los cambios biológicos, haciendo un esfuerzo por controlar todas los posibles confusores.

En cuanto al campo de rehabilitación, y en concreto, a la terapia ocupacional oncológica:

- Como ha quedado evidente, la evidencia científica es escasa y muchas veces inconcluyente. A partir de los resultados de esta tesis, realizar un estudio mayor, comparando diferentes técnicas de intervención en diferentes fases del proceso oncológico del cáncer de mama y no solo en la fase de supervivencia.
- En este sentido, desarrollar un programa de rehabilitación oncológica paliativa en mujeres con cáncer de mama y metástasis, campo que está actualmente en expansión, por las graves consecuencias que conlleva, sobre todo las metástasis óseas.

CONCLUSIONES
CONCLUSIONS

CONCLUSIONES

Conclusiones Generales

Esta Tesis Doctoral Internacional presenta una nueva herramienta de salud móvil, válida y fiable, con la que realizar una monitorización del balance energético en supervivientes de cancer de mama. De la misma manera, nuestros resultados sugieren que el uso de la aplicación puede tener efectos positivos en la calidad de vida de estas mujeres. Por otro lado, se ha desarrollado e implementado un programa de rehabilitación presencial para mujeres supervivientes de cáncer de mama basado en terapia ocupacional. Los resultados muestran que dicho programa es beneficioso para las secuelas que presentan las supervivientes de cáncer de mama, tanto clínica como estadísticamente.

Conclusiones Específicas

Las principales conclusiones de esta Tesis Doctoral Internacional son:

Sección 1: Balance ENErgético en CAncer (BENECA).

1. El sistema móvil de salud BENECA es fiable y preciso en la monitorización del balance energético en supervivientes de cáncer de mama, en comparación con las pruebas *gold estándar* de dieta y actividad física.
2. BENECA mHealth puede considerarse factible en un contexto clínico real y se ha asociado con cambios de comportamiento en los estilos de vida de las sobrevivientes de cáncer de mama, debiendo mejorar en futuras versiones de la aplicación su funcionalidad. Además, los resultados sugieren su eficacia clínica en la mejora de la calidad de vida de estas mujeres y en la composición corporal.
3. Existe una posible asociación entre el uso de una aplicación móvil de salud de monitorización del balance energético y cambios biológicos en supervivientes de cáncer de mama. A partir de los resultados de esta tesis, nos planteamos una hipótesis, como punto de partida de futuras investigaciones, apoyando el modelo biopsicosocial, ya que variables no biológicas podrían explicar comportamientos biológicos.

Sección 2: Programa integral de soporte a supervivientes de cáncer de mama.

4. Una estrategia de soporte integral se ha diseñado, mediante el uso de la mHealth BENECA y un programa presencial de rehabilitación oncológica de terapia ocupacional.
5. Los resultados de esta tesis apoyan la hipótesis de que ambas estrategias pueden mejorar la calidad de vida de estas mujeres, pero la estrategia de soporte integral obtuvo resultados significativos clínica y estadísticamente superiores en la mejora de la calidad de vida, y la funcionalidad del miembro superior, manteniendo el

efecto a largo plazo. Desde nuestro conocimiento, se trata de la primera evidencia convincente de la efectividad de este enfoque integral en los aspectos físicos y funcionales de la calidad de vida en las sobrevivientes de cáncer de mama.

CONCLUSIONS

General Conclusions

This International Doctoral Thesis propose a new mobile health tool, valid and reliable, with which to perform an energy balance monitoring in breast cancer survivors. In the same way, our results suggest the use of the application can have positive effects on the quality of life of these women. On the other hand, a face-to-face rehabilitation program has been developed and implemented for women survivors of breast cancer based on occupational therapy. The results suggest that this program is beneficial for the sequelae presented by breast cancer survivors, both clinically and statistically.

Specific Conclusions

The main conclusions of this International Doctoral Thesis are:

Section 1: ENERGY Balance in Cancer (BENECA).

1. BENECA mobile health system is reliable and accurate in monitoring the energy balance in breast cancer survivors, compared to the *gold standard* tests of diet and physical activity.
2. BENECA mHealth can be considered feasible in a real clinical context and has been associated with behavioral changes in the lifestyles of breast cancer survivors, but its functionality should be improved in future versions of the application. In addition, the results suggest their clinical efficacy in improving quality of life of these women and in body composition.
3. There is a possible association between the use of a mobile health application for monitoring energy balance and biological changes in breast cancer survivors. The results of this thesis raise a hypothesis, as a starting point for future research, supporting the biopsychosocial model, since non-biological variables could explain biological behaviors.

Section 2: Integral support program for breast cancer survivors.

4. An integral support strategy has been designed, through the use of mHealth BENECA and a face-to-face occupational therapy oncology rehabilitation program.
5. The results of this thesis support the hypothesis that both strategies can improve the quality of life of these women, but the integral strategy showed significant results clinically and statistically superior in improving quality of life, and functionality of the upper body, maintaining the long-term effect. To our knowledge, this is the first convincing evidence of the effectiveness of this comprehensive approach in the physical and functional aspects of the quality of life in breast cancer survivors.

ANEXOS
ANEXES

Artículos derivados de la Tesis Doctoral Internacional

A continuación, se enumeran y presentan (portada y última página) las publicaciones derivadas de esta Tesis Doctoral Internacional, ya incluídas en el manuscrito en la sección de material y métodos, resultados y discusión. De la misma manera, se enumeran las publicaciones derivadas de la misma que se encuentran en fase de preparación/envío.

1. Lozano-Lozano M, Martin-Martin L, Galiano-Castillo N, Alvarez-Salvago F, Cantarero-Villanueva I, Fernandez-Lao C, et al. Integral strategy to supportive care in breast cancer survivors through occupational therapy and a m-health system: design of a randomized clinical trial. BMC medical informatics and decision making. 2016;16(1):150.
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BMC Medical Informatics and Decision Making

STUDY PROTOCOL Open Access

Integral strategy to supportive care in breast cancer survivors through occupational therapy and a m-health system: design of a randomized clinical trial

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Abstract

Background: Technological support using e-health mobile applications (m-health) is a promising strategy to improve the adherence to healthy lifestyles in breast cancer survivors (excess in energy intake or low physical activity are determinants of the risk of recurrence, second cancers and cancer mortality). Moreover, cancer rehabilitation programs supervised by health professionals are needed due to the inherent characteristics of these breast cancer patients. Our main objective is to compare the clinical efficacy of a m-health lifestyle intervention system alone versus an integral strategy to improve Quality of Life in breast cancer survivors.

Methods: This therapeutic superiority study will use a two-arm, assessor blinded parallel RCT design. Women will be eligible if: they are diagnosed of stage I, II or III-A breast cancer; are between 25 and 75 years old; have a Body Mass Index > 25 kg/m^2; they have basic ability to use mobile apps; they had completed adjuvant therapy except for hormone therapy; and they have some functional shoulder limitations. Participants will be randomized to one of the following groups: integral group will use a mobile application (BENECA APP) and will receive a face-to-face rehabilitation (8-weeks); m-health group will use the BENECA app for 2-months and will received usual care information. Study endpoints will be assessed after 8 weeks and 6 months. The primary outcome will be Quality of Life measured by The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core and breast module. The secondary outcomes: body composition; upper-body functionality (handgrip, Disability of the Arm, Shoulder and Hand questionnaire, goniometry); cognitive function (Wechsler Adult Intelligence Scale, Trail Making Test); anxiety and depression (Hospital Anxiety and Depression Scale); physical fitness (Short version of the Minnesota Leisure Time Physical Activity Questionnaire, Self-Efficacy Scale for Physical Activity); accelerometry and lymphedema.

Discussion: This study has been designed to seek to address the new needs for support and treatment of breast cancer survivors, reflecting the emerging need to merge new low cost treatment options with much-needed involvement of health professionals in this type of patients.

Trial registration: ClinicalTrials.gov Identifier: NCT02817724 (date of registration: 22/06/2016).

Keywords: Breast, Neoplasms, Occupational therapy, Mobile applications, Quality of life

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JMIR MHEALTH AND UHEALTH Lozano-Lozano et al

Original Paper

Monitoring Energy Balance in Breast Cancer Survivors Using a Mobile App: Reliability Study

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Abstract

Background: The majority of breast cancer survivors do not meet recommendations in terms of diet and physical activity. To address this problem, we developed a mobile health (mHealth) app for assessing and monitoring healthy lifestyles in breast cancer survivors, called the Energy Balance on Cancer (BENECA) mHealth system. The BENECA mHealth system is a novel and interactive mHealth app, which allows breast cancer survivors to engage themselves in their energy balance monitoring. BENECA was designed to facilitate adherence to healthy lifestyles in an easy and intuitive way.

Objective: The objective of the study was to assess the concurrent validity and test-retest reliability between the BENECA mHealth system and the gold standard assessment methods for diet and physical activity.

Methods: A reliability study was conducted with 20 breast cancer survivors. In the study, tri-axial accelerometers (ActiGraphGT3X+) were used as gold standard for 8 consecutive days, in addition to 2, 24-hour dietary recalls, 4 dietary records, and sociodemographic questionnaires. Two-way random effect intraclass correlation coefficients, a linear regression-analysis, and a Passing-Bablok regression were calculated.

Results: The reliability estimates were very high for all variables (alpha≥.90). The lowest reliability was found in fruit and vegetable intakes (alpha=.94). The reliability between the accelerometer and the dietary assessment instruments against the BENECA system was very high (intraclass correlation coefficient=.90). We found a mean match rate of 93.51% between instruments and a mean phantom rate of 3.35%. The Passing-Bablok regression analysis did not show considerable bias in fat percentage, portions of fruits and vegetables, or minutes of moderate to vigorous physical activity.

Conclusions: The BENECA mHealth app could be a new tool to measure energy balance in breast cancer survivors in a reliable and simple way. Our results support the use of this technology to not only to encourage changes in breast cancer survivors' lifestyles, but also to remotely monitor energy balance.

Trial Registration: ClinicalTrials.gov NCT02817724; https://clinicaltrials.gov/ct2/show/NCT02817724 (Archived by WebCite at http://www.webcitation.org/6xVY1buCc)

(JMIR Mhealth Uhealth 2018;6(3):e67) doi:10.2196/mhealth.9669

KEYWORDS

telemedicine; breast neoplasms; survivors; life style; exercise; diet; mhealth

Abbreviations

BENECA: Energy Balance on Cancer
BMI: body mass index
eHealth: electronic health
mHealth: mobile health

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JMIR MHEALTH AND UHEALTH Lozano-Lozano et al

Original Paper

A Mobile System to Improve Quality of Life Via Energy Balance in Breast Cancer Survivors (BENECA mHealth): Prospective Test-Retest Quasiexperimental Feasibility Study

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Abstract

Background: Energy balance is defined as the difference between energy expenditure and energy intake. The current state of knowledge supports the need to better integrate mechanistic approaches through effective studies of energy balance in the cancer population because of an observed significant lack of adherence to healthy lifestyle recommendations. To stimulate changes in breast cancer survivors' lifestyles based on energy balance, our group developed the BENECA (Energy Balance on Cancer) mHealth app. BENECA has been previously validated as a reliable energy balance monitoring system.

Objective: Based on our previous results, the goal of this study was to investigate the feasibility of BENECA mHealth in an ecological clinical setting with breast cancer survivors, by studying (1) its feasibility and (2) pretest-posttest differences with regard to breast cancer survivor lifestyles, quality of life (QoL), and physical activity (PA) motivation.

Methods: Eighty breast cancer survivors diagnosed with stage I to IIIA and with a body mass index over 25 kg/m2 were enrolled in this prospective test-retest quasi-experimental study. Patients used BENECA mHealth for 8 weeks and were assessed at baseline and the postintervention period. Feasibility main outcomes included percentage of adoption, usage, and attrition; user app quality perception measured with the Mobile App Rating Scale (MARS); satisfaction with the Net Promoter Score (NPS); and barriers and facilitators of its use. Clinical main outcomes included measuring QoL with the European Organization for Research and Treatment of Cancer QoL Questionnaire Core 30 (EORT QLQ-C30), PA assessment with accelerometry, PA motivation measure with a Spanish self-efficacy scale for physical activity (EAF), and body composition with dual-energy x-ray absorptiometry. Statistical tests (using paired-sample t tests) and Kaplan-Meier survival curves were analyzed.

Results: BENECA was considered feasible by the breast cancer survivors in terms of use (76%, 58/76), adoption (69%, 80/116), and satisfaction (positive NPS). The app quality score did not make it one of the best-rated apps (mean 3.71, SD 0.47 points out of 5). BENECA mHealth improved the QoL of participants (global health mean difference [MD] 12.83, 95% CI 8.95-16.71, P<.001), and EAF score (global MD 36.99, 95% CI 25.52-48.46, P<.001), daily moderate-to-vigorous PA (MD 7.38, 95% CI 0.39-14.37, P=.04), and reduced body weight (MD −1.42, 95% CI −1.97 to −0.87, P<.001).

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JOURNAL OF MEDICAL INTERNET RESEARCH Lozano-Lozano et al

Original Paper

Association Between the Use of a Mobile Health Strategy App and Biological Changes in Breast Cancer Survivors: Prospective Pre-Post Study

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Abstract

Background: There is a bidirectional relationship between chronic low-grade inflammation and cancer. Inflammatory markers, such as interleukin-6 (IL-6), have been associated with both the malignant transformation of epithelial cells and tumor progression, thus linking low-grade inflammation with a higher risk of cancer and recurrence in the survival phase. Therefore, they are considered valuable prognostic biomarkers. Knowing and finding appropriate primary prevention strategies to modify these parameters is a major challenge in reducing the risk of cancer recurrence and increasing survival. Different therapeutic strategies have shown efficacy in the modification of these and other biological parameters, but with contradictory results. There are apparently no strategies in which telemedicine, and specifically mobile health (mHealth), are used as a means to potentially cause biological changes.

Objective: The objectives of this study were to: (1) check whether it is feasible to find changes in inflammation biomarkers through an mHealth strategy app as a delivery mechanism of an intervention to monitor energy balance; and (2) discover potential predictors of change of these markers in breast cancer survivors (BCSs).

Methods: A prospective quasi-experimental pre-post study was conducted through an mHealth energy balance monitoring app with 73 BCSs, defined as stage I-IIIA of breast cancer and at least six months from the completion of the adjuvant therapy. Measurements included were biological salivary markers (IL-6 and C-reactive protein [CRP]), self-completed questionnaires (the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, the user version of the Mobile Application Rating Scale [uMARS] and an ad hoc clinical and sociodemographic questionnaire) and physical objective measures (accelerometry, weight and height). In addition, using the logging data of the mHealth app, the rate of use (in days) was recorded during the entire experimental phase of the study. Using Stata software, a paired two-tailed t test, Pearson and Spearman correlations, and a stepwise multiple regression analysis were used to interpret the data.

Results: Analyzing changes in inflammatory biomarker concentrations after using the mHealth app, differences between preassessment CRP (4899.04 pg/ml; SD 1085.25) and IL-6 (87.15 pg/ml; SD 33.59) and postassessment CRP (4221.24 pg/ml; SD 911.55) and IL-6 (60.53 pg/ml; SD 36.31) showed a significant decrease in both markers, with a mean difference of –635.25 pg/ml (95% CI –935.65 to –334.85; P<.001) in CRP and –26.61 pg/ml (95% CI –42.51 to –10.71; P=.002) in IL-6. Stepwise regression analyses revealed that changes in global quality of life, as well as uMARS score and hormonal therapy, were possible

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Original article

Mobile health and supervised rehabilitation versus mobile health alone in breast cancer survivors: Randomized controlled trial

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ABSTRACT

Background: Survival rates in cancer are increasing exponentially, with a corresponding increase/influence in disability-adjusted life-years. Efforts should be made to explore the optimal balance between unsupervised/distance-based and supervised/onsite approaches to cancer care.
Objective: This study aimed to compare the clinical efficacy of the BENECA mobile Health (mHealth) lifestyle application combined with a supervised rehabilitation program (BENECA and supervised rehabilitation) versus the BENECA mHealth lifestyle application alone on quality of life (QoL) and functional outcomes of breast cancer survivors.
Methods: This randomized controlled trial included 80 survivors of breast cancer diagnosed at stage I–IIIA, who completed adjuvant therapy and were overweight or obese at diagnosis. Participants were randomly allocated (ratio 1:1, 3 waves) to BENECA mHealth and rehabilitation for 2 months ($n = 40$) or BENECA mHealth and usual care (BENECA mHealth alone; $n = 40$). Participants completed a questionnaire at baseline (T1), 8-weeks post-intervention (T2) and 6-month follow-up (T3). The primary outcome was QoL assessed with the EORT QLQ-C30. Secondary outcomes included upper-limb functionality and body composition. Statistical (between-group analyses of covariance) and clinical effects were analyzed by intention to treat.
Results: Both groups showed improved outcomes, but global QoL was significantly better with BENECA mHealth and rehabilitation than BENECA mHealth alone (mean difference, 12.76; 95% confidence interval 4.85; 20.67; $P = 0.004$), with a moderate-to-large effect size ($d = 72$). The proportion of participants reporting reliable clinical improvement on global QoL at T2 was higher with BENECA mHealth and rehabilitation than BENECA mHealth alone (57.5% vs 26.3%, $P = 0.008$). Improvement in subjective and objective upper-limb functionality was also higher with BENECA mHealth and rehabilitation.
Conclusions: The BENECA mHealth lifestyle application with a supervised rehabilitation program had a statistically and clinically significant effect on QoL and upper-limb functionality in breast cancer survivors and is a unique and important promising new approach.

1. Introduction

Between 2006 and 2016, survival rates in some cancer types, especially breast cancer, exponentially increased [1], with a corresponding increase/influence in disability-adjusted life-years (DALYS) [2]. DALYS secondary to cancer survival are associated with substantial medical expenses and loss of productivity in

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Short Curriculum Vitae

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Education

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Grants

2013-2014	Starting-up research grant. University of Granada, Spain.
2014-2015	Research Fellowship: Colaboración en departamentos. Deparment of Physical Therapy. University of Granada, Spain. Spanish Ministry of Education, Culture and Sports, Spanish Gobernment, Spain.
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2017	International Research Intership Fellowship: Movilidad de Formación de Profesorado Universitario (FPU Movilidad). Spanish Ministry of Education, Culture and Sports, Spanish Gobernment, Spain.

Supervision

2016-2019	Supervisor for eight graduate Thesis (Graduate Degree in occupational Therapy, University of Granada, Spain).
2016-2019	Supervisor for nine master Thesis (Master's degree in Manual and Invasive Physiotherapy, University of Granada, Spain).
2018-2019	Supervisor for one master Thesis (Master's degree in Intervention in Functional Diversity, University of Granada, Spain).

International Internships

2017	School of Applied Sciences, Napier Edinburgh University, Edinmburgh, United Kingdom. Prof. Anne Campbel.

Research Projects

2016-2018 Effect of backpack weight on biomechanical parameters of locomotion in infantrymen and its relation to fatigue, body composition and physical condition. Funded by the Centro Mixto UGR-MADOC.

2015-2019 BENECA: Balance Energético en Cáncer. Funded by Spanish Ministry of Economy and competitiveness among others.

2018-curr. Efectos sobre la aparición de la toxicidad producida por el tratamiento oncológico mediante un programa de ejercicio terapéutico adaptado (ATOPE): ensayo clínico controlado, aleatorizado en mujeres con cáncer de mama. Funded by Spanish Ministry of Economy and competitiveness among others.

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Congress Communications

The PhD Student has presented more than 75 congress communitations, of which it stands out, for their relationship with the thesis:

1. Lozano-Lozano M, et al. Efectividad de una estrategia integral de rehabilitación de terapia ocupacional y mHealth en la mejora de la calidad de vida general autopercibida en supervivientes de cáncer de mama: resultados principales de un ensayo clínico controlado y aleatorizado. V Congreso Internacional de Terapia Ocupacional. May, 2019.
2. Lozano-Lozano M, et al. Efecto de un programa presencial de terapia ocupacional sobre las secuelas psicológicas en supervivientes de cáncer de mama: estudio preliminar. V Congreso Internacional en contextos psicológicos, educativos y de la salud. November, 2018.
3. Lozano-Lozano M, et al. Pérdida de roles e intereses en supervivientes de cáncer de mama: estudio descriptivo. V Congreso Internacional de Investigación en salud y Envejecimiento & III Congreso Internacional de Investigación en Salud. June, 2018.
4. Lozano-Lozano M, et al. Efecto de un programa presencial de terapia ocupacional sobre la capacidad funcional subjetiva y objetiva del miembro superior afecto en supervivientes de cáncer de mama: estudio preliminar. V Congreso Internacional de Investigación en salud y Envejecimiento & III Congreso Internacional de Investigación en Salud. June, 2018.
5. Arroyo-Morales M, Lozano-Lozano M, et al. Implicating breast cáncer survivors in its energy balance regulation: BENECA mHealth app. International Conference on Physical Therapy in Oncology. June 2018.
6. Lozano-Lozano M, et al. Prevalencia del desempeño ocupacional enmuejres supervivientes de cáncer de mama. II Congreso Internacional y VII Encuentros Hispano-Cubanos en Ciencias de la Salud. May, 2018.
7. Lozano-Lozano M, et al. BENECA mHealth APP como recurso para la mejora de la percepción de capacidad para la realización de actividad física regular en cáncer de mama. 3 Congreso Español de la Mama, XXXVI Congreso SESPM, XV Congreso Sedim y XII Reunión SETS. October, 2017.
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9. Lozano-Lozano M, et al. Evaluación de la dieta en supervivientes de cáncer de mama: validación de concordancia del sistema móvil BENECA. IV Congreso Internacional de Investigación en Salud y Envejecimiento & II Congreso Internacional de Investigación en Salud. June, 2017.
10. Lozano-Lozano M, et al. Designing BENECA, a mHealth app to Monitor Diet and Physical Activity in Cancer Survivors. 14th International Work-Conference on Artificial Neural Networks. June, 2017.
11. Lozano-Lozano M, et al. Influence of the level of self-confidence on the real physical activity practice in breast cancer survivors: a cross sectional study. III Congreso Internacional en Contextos Clínicos y de la Salud. March, 2017.

12. Lozano-Lozano M, et al. Programa combinado de rehabilitación de terapia ocupacional y el sistema BENECA ("Cancer OTAPP Program") para mejorar la calidad de vida de supervivientes de cáncer de mama: justificación y protocolo de un estudio para un ensayo clínico aleatorizado. III Congreso Internacional de Investigación en Salud y Envejecimiento & I Congreso Internacional de Investigación en Salud. July, 2016.
13. Lozano-Lozano M, et al. BENECA Project: Energy Balance on Cancer. Feasibility of a m-Health system in patients with cáncer. First International Online BioMedical Conference. September, 2015.

Other research merits

- 34 teacher and research training courses.
- Reviewer for 9 JCR-journals.
- Member of the research group (BIO-277), in the line of Physical Exercise and Cancer research, University of Granada, Spain.
- Member of the "Sports and Health Research Center", University of Granada, Spain.
- Member of the organizing and / or scientific committee of eight international conferences.

Other merits

2014	University of Granada Final Degree Award.
2015-	Lecturer in the degree of Occupational Therapy, University of Granada, Spain.
2015-	Lecturer in the master's degree in Manual and Invasive Physiotherapy, University of Granada, Spain.
2018-	Lecturer in the master's degree in Intervention in Functional Diversity, University of Granada, Spain.
2016	Teaching stay at University of Valparaiso, Chile.
2019	Teaching stay at University of Florence, Italy.

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