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Psychobiological Characterization of Resilience: Study of the Effectiveness of a Peer Support Intervention in Breast Cancer Patients

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DOCTORAL THESIS

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Para Carmen

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ACRONYMS

AECC	Asociación Española contra el Cáncer
AIs	Aromatase Inhibitors
ALLO	Allopregnanolone
AUCg	Area Under the Curve With Respect To The Ground
BC	Breast Cancer
BM	Bularreko Minbizia
BRCA 1/2	Breast Cancer 1/2
CBT	Cognitive Behavioral Therapy
CM	Cander de Mama
CRP	C-Reactive Protein
CT	Chemotherapy
DHEA-S	Dehydroepiandrosterone Sulfate
DFS	Disease-Free Survival
ER	Estrogen Receptor
ERα	Estrogen Receptor Alpha
$GABA_A$	γ-Aminobutyric acid type A
HER2	Human Epidermal Growth Factor 2
HPA	Hypothalamic-Pituitary-Adrenocortical
HRQoL	Health-related Quality of Life
IL-6	Interleukin-6
MBSR	Mindfulness-Based Stress Reduction
mHealth	mobile Health
NCI	National Cancer Institute
NPY	Neuropeptide Y
OS	Disease Overall Survival
PD-L1	Programmed Death-Ligand 1
PIK3CA	Phosphatidylinositol-4,5-Isphosphate 3-Kinase Alpha Catalytic Subunit
PR	Progesterone Receptor

QoL	Quality of Life
RS	Relative Survival
RCT	Randomized Controlled Trial
SEGT	Supportive-Expressive Group Therapy
SERMs	Selective Estrogen Modulators
SEOM	Sociedad Española de Oncología Médica
SNS	Sympathetic Nervous System
SMIs	Stress Management Interventions
SNS	Sympathetic Nervous System
TAU	Treatment As Usual
TILs	Tumor-Infiltrating Lymphocytes
TNM	Tumor, Node, Metastasis system

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ABSTRACT

As breast cancer (BC) continues to be a leading cause of death among women worldwide, understanding the factors contributing to disease adjustment is essential. Psychological resilience, defined as the ability to maintain or recover stable psychophysiological functioning during or after exposure to stressful life-events, has recently been proposed as a key factor enabling effective adaptation to cancer-related adversity. Recognizing the shortcomings of the still limited number of studies exploring resilience in BC care, including the variability in methods for measuring resilience, small sample sizes, and the lack of research on key biomarkers linked to cancer adaptation and survival, the present doctoral thesis sought to bridge these gaps by examining the multifaceted dimensions of psychological resilience in BC. To this end, four studies were conducted, which aimed to clarify the dynamic interplay of resilience with biopsychosocial factors and assess interventions to enhance it among women with BC. In Study #1, a systematic review was conducted with the aim of synthesizing evidence regarding biopsychosocial factors and psychosocial interventions associated with BC resilience. The results indicated significant associations between resilience and an extensive array of clinical, sociodemographic, psychosocial, and physiological variables, with psychosocial factors playing the most pivotal role in the enhancement of resilience. The findings also showed that interventions aimed at enhancing resilience were effective in improving psychological and physical well-being across the BC continuum. The lack of studies on potential immune and/or endocrine correlates of resilience identified in Study #1 guided Study #2, which attempted to address part of this gap by systematically reviewing current

literature on the link between resilience and cortisol in adult populations. Their results revealed a significant relationship between resilience and cortisol levels indicative of acute and chronic stress, among which a single study conducted in cancer patients was identified. However, significant methodological variability across the studies hindered the ability to make conclusive statements regarding the direction of the results. These considerations prompted Study #3, which cross-sectionally examined the predictive value of social support and diurnal cortisol levels (AUCg) on resilience in recently diagnosed women with BC. Its results indicated that emotional support, specifically in patients with medium and low AUCg levels, acted as a significant predictor of enhanced resilience. Study #4, in turn, intended to go beyond the theoretical insights gleaned by the previous studies through the implementation of a RCT to evaluate the influence of a peer support intervention on resilience, social support, and AUCg in women newly diagnosed with BC. Findings revealed the intervention's potential to enhance resilience in patients undergoing chemotherapy, predicted by changes in emotional support, affective support, and AUCg post-intervention. It also highlighted that the non-administration of the intervention in radiotherapy patients could potentially hinder resilience development. The evidence extracted from the four studies of this doctoral thesis accentuates the need for comprehensive and individualized BC management strategies that recognize the importance of psychobiological factors in the resilience-building process. Peer support is identified as an integrative and potentially beneficial strategy for enhancing psychological adjustment to BC via its influences on patients' psychobiological profiles, thus laying the groundwork for future research designing holistic interventions across the spectrum of BC care.

RESUMEN

Dado que el cáncer de mama (CM) continúa siendo una de las principales causas de mortalidad entre mujeres a nivel mundial, es esencial comprender los factores que contribuyen al ajuste de esta enfermedad. La resiliencia psicológica, definida como la capacidad de mantener o recuperar un funcionamiento psicofisiológico estable durante o después a la exposición de eventos vitales estresantes, ha sido recientemente identificada como un factor clave para la adaptación efectiva a las adversidades relacionadas con el cáncer. Reconociendo las limitaciones del aún escaso número de investigaciones que han explorado la resiliencia en el cuidado del CM, incluyendo la variabilidad en los métodos para medir la resiliencia, los reducidos tamaños muestrales, y la falta de estudios sobre biomarcadores clave vinculados a la adaptación y supervivencia al cáncer, la presente tesis doctoral buscó superar estas deficiencias mediante el análisis exhaustivo de las dimensiones multifacéticas de la resiliencia psicológica en el CM. Con este fin, se llevaron a cabo cuatro investigaciones, las cuales pretendieron esclarecer la dinámica interacción entre la resiliencia y distintos factores biopsicosociales, además de evaluar intervenciones destinadas a reforzarla en mujeres con CM. En el Estudio #1, se realizó una revisión sistemática con el fin de sintetizar la evidencia sobre los factores biopsicosociales e intervenciones psicosociales asociadas con la resiliencia al CM. Los resultados demostraron asociaciones significativas entre la resiliencia y un extenso espectro de variables clínicas, sociodemográficas, psicosociales y fisiológicas, siendo los factores psicosociales los más influyentes en el fortalecimiento de la resiliencia. Asimismo, se observó que las intervenciones

dirigidas a mejorar la resiliencia resultaron efectivas para potencial el bienestar psicológico y físico a lo largo del continuum del CM. La ausencia de investigaciones identificadas en el Estudio #1 centradas en explorar los posibles correlatos inmunológicos y/o endocrinos de la resiliencia motivó el Estudio #2, que se propuso abordar parte de esta laguna mediante una revisión sistemática de la literatura actual sobre la asociación entre la resiliencia y el cortisol en poblaciones adultas. Los resultados revelaron una relación significativa entre la resiliencia y niveles de cortisol indicativos de estrés agudo y crónico, entre los cuales se identificó un único estudio llevado a cabo en pacientes con cáncer. No obstante, la considerable variabilidad metodológica de los estudios impidió extraer conclusiones definitivas sobre la dirección de estos resultados. Estas consideraciones impulsaron el Estudio #3, el cuál examinó de manera transversal el valor predictivo del apoyo social y los niveles de cortisol diurno (AUCg) en la resiliencia de mujeres recién diagnosticadas con CM. Los resultados indicaron que, específicamente en aquellas pacientes con niveles medios y bajos de AUCg, el apoyo emocional actuó como predictor significativo de una mayor resiliencia. Finalmente, el Estudio #4, buscó extender los planteamientos teóricos de los estudios previos mediante la implementación de un ensayo clínico aleatorizado para valorar el impacto de una intervención de apoyo entre pares en la resiliencia, el apoyo social y el AUCg de mujeres recién diagnosticadas con CM. Los hallazgos revelaron el potencial de la intervención para mejorar la resiliencia de las pacientes sometidas a quimioterapia, cuyo efecto fue predicho por cambios en el apoyo emocional, el apoyo afectivo y el AUCg post-intervención. También sugirieron que la no administración de la intervención en pacientes en tratamiento de radioterapia podría limitar el

desarrollo de la resiliencia. Las evidencias extraídas de estos cuatro estudios subrayan la necesidad de implementar estrategias integrales e individualizadas para manejo del CM que reconozcan el rol de los factores psicobiológicos en el proceso de construcción de la resiliencia. El apoyo entre pares emerge como una estrategia integradora y prometedora para mejorar el ajuste psicológico al CM a través de su influencia en los perfiles psicobiológicos de las pacientes, sentando así las bases para futuras investigaciones orientadas al diseño de intervenciones holísticas a lo largo del espectro del cuidado del CM.

LABURPENA

Bularreko minbizia (BM) emakumeen artean heriotza-kausa nagusietako bat izaten jarraitzen duen heinean, gaixotasunaren egokitzapenean eragiten duten faktoreak ulertzea ezinbestekoa da. Erresilientzia psikologikoa, bizi-gertaera estresagarrien aurrean edo ondoren funtzionamendu psikofisiologiko egonkorra mantentzeko edo berreskuratzeko gaitasun gisa definitua, minbiziarekiko egokitzapen eraginkorrean funtsezko papera jokatzen duela proposatu da berriki. BM-aren zaintzan erresilientzia aztertu duten azterlanen kopuru oraindik mugatuaren gabeziak aintzat hartuta, erresilientzia neurtzeko metodoen aldakortasuna, lagin-tamaina txikiak eta minbiziaren egokitzapenari eta biziraupenari lotutako funtsezko biomarkatzaileei buruzko ikerketarik eza barne, doktoretza-tesi honek gabezia horiek gainditzea bilatu zuen, erresilientzia psikologikoak BM-an dituen dimentsio anitzak osorik aztertuz. Horretarako, lau ikerketa burutu ziren, erresilientziaren eta faktore biopsikosozialen arteko elkarrekintza dinamikoa argitzea eta BM-dun emakumetan erresilientzia indartzeko esku-hartzeak ebaluatzea helburu zutelarik. #1 Azterlanean, berrikuspen sistematiko bat gauzatu zen, BM-aren erresilientziarekin lotutako faktore biopsikosozialei eta esku-hartze psikosozialei buruzko ebidentziak sintetizatzeko asmoz. Emaitzek erresilientziaren eta aldagai kliniko, soziodemografiko, psikosozial, eta fisiologikoen arteko erlazio garrantzitsuak adierazi zituzten, faktore psikosozialak erresilientziaren hobekuntzan paper garrantzitsuenetarikoa betetzen zutela erakutsiz. Aurkikuntzek ere erakutsi zuten erresilientzia hobetzeko esku-hartzeak eraginkorrak izan zirela ongizate psikologikoa eta fisikoa hobetzeko BM-aren continuumean zehar. # 1

Azterlanean erresilientziaren balizko korrelatu immunologikoei eta/edo endokrinoei buruz aurkitutako ikerketen faltak # 2 Azterlana bultzatu zuen, non erresilientziaren eta kortisolaren arteko loturari buruzko egungo literaturaren berrikuspen sistematiko baten bidez hutsune hori partzialki betetzea bitatu zuen. Emaitzek erresilientzia eta estres akutu eta kronikoaren adierazgarri diren kortisol mailen arteko erlazio esanguratsua erakutsi zuten, horien artean minbizidun pazienteetan egindako ikerketa bakarra identifikatu zelarik. Hala ere, ikerketen arteko aldakortasun metodologiko nabarmenak emaitzen norabidea zehazki adierazteko gaitasuna mugatu zuen. Gogoeta horiek #3 Azterlana bultzatu zuten, zeinak zeharka aztertu zuen gizarte laguntzaren eta eguneko kortisol- mailen (AUCg) balio aurreikuslea berriki diagnostikatutako BM-dun emakumeen erresilientzian. Emaitzek laguntza emozionalak, batez ere AUCg maila ertain eta baxuetan duten pazienteetan, erresilientzia handiagoaren iragarle esanguratsua dela adierazi zuten. #4 Azterlanak, berriz, aurreko azterlanen planteamendu teorikoetatik haratago joan nahi izan zuen, saiakuntza kliniko bat inplementatuz, BM-az berriki diagnostikatutako emakumeen erresilientzian, gizarte laguntzan eta AUCg-ean berdinen arteko gizarte laguntza esku-hartze baten eragina ebaluatuz. Aurkikuntzek esku-hartzeak kimioterapiapeko pazienteen erresilientzia hobetzeko ahalmena erakutsi zuten, honek laguntza emozionalean, laguntza afektiboan eta AUCg mailetan eragindako aldaketek aurreikusita. Halaber, esku-hartzea ez aplikatzeak radioterapiapeko pazienteen erresilientziaren garapena oztopa zezakeela iradoki zuten. Doktorego-tesi honetako lau azterlanetatik ateratako frogek BMren kudeaketan estrategia integral eta indibidualizatuen beharra azpimarratzen dute, faktore psikobiologikoek erresilientzia eraikitzeko prozesuan duten garrantzia aldi

berean aitortuz. Berdinen arteko gizarte laguntza estrategia integratzaile eta itxaropentsu gisa identifikatzen da. Estrategia honek BM-aren egokitzapen psikologikoa hobetzen lagundu dezake pazienteen profil psikobiologikoetan duen eraginaren bidez, bidebatez BM-aren zaintzaren eremuan esku-hartze holistikoak diseinatuko dituzten etorkizuneko ikerketetarako oinarriak ezartzen lagunduz.

SECTION I. INITIAL OVERVIEW

Introduction, Theoretical Framework, Objectives and

Hypotheses, Methods, Results and Discussion, References

INTRODUCTION

Resilience, a concept traditionally rooted in psychological studies, has recently gained prominence in the realm of oncology, especially in understanding how individuals cope with cancer diagnoses. Conceptualized as a continuous, interactive, and dynamic process of modifiable nature, the significance of resilience in the context of cancer has been underscored by its critical role in facilitating successful adaptation to disease-related adversity (Eicher et al., 2015). Thus, in addition to contributing to diminishing distress symptoms and bolstering cognitive flexibility and well-being (Seiler et al., 2019, Min et al., 2013), resilience also appears to play a role in mitigating cancer-related physical symptoms such as pain and fatigue, among others (Eicher et al., 2015). In the realm of breast cancer, albeit to a limited extent, there is evidence of increased use of adaptive coping strategies, greater self-efficacy and emotional management of cancer-associated challenges, and a lower treatment-related symptom burden among highly resilient patients (Huang et al., 2019; Alarcon et al., 2020; Fradelos et al., 2018). The current landscape of resilience literature in BC, although expanding, reveals conspicuous gaps, particularly in the variability of methodological approaches used to measure resilience and in understanding its biological underpinnings. These gaps are significant considering the diverse trajectories observed in patients' resilience development – while some are able to adapt flexibly to their new reality and develop resilience, many others develop stress-related mental health problems at some point in the oncology process that can generate significant repercussions on their disease prognosis and quality of life (QoL) (Seib et al., 2018). This fact highlights the need for comprehensive

research into psychobiological factors that may underlie the development and strengthening of resilience. Understanding the complex interrelationships between these factors is crucial for the potential design of early interventions aimed at enhancing resilience, which could significantly improve patients' adjustment to the oncological process

The present doctoral thesis doctoral represents the culmination of 4.5 years of dedicated research, which, framed in the context of a longitudinal clinical trial, has required a collaborative effort between the researchers of the Psychobiology Team of the UPV/EHU and both the research and health personnel of the Onkologikoa Hospital of Gipuzkoa. The thesis was guided by two primary objectives: (1) to explore the intricate interactions between resilience and biopsychosocial determinants, aiming to broaden the current understanding of psychological resilience in the context of cancer and enhance its psychobiological characterization; and (2) to implement and assess the efficacy of a peer support-based resilience-enhancing intervention in breast cancer patients at the Onkologikoa Hospital of Gipuzkoa. The fruition of these objectives is reflected in the publication of three scientific articles and a fourth currently under review, where two are systematic reviews, one a cross-sectional study and the last a longitudinal study. Hereafter these studies will be referred to as Study #1, #2, #3, and #4:

Study #1:

Aizpurua-Perez, I., & Perez-Tejada, J. (2020). Resilience in women with breast cancer: A systematic review. *European journal of oncology nursing*, *49*, 101854. https://doi.org/10.1016/j.ejon.2020.101854

Study #2:

Aizpurua-Perez, I., Arregi, A., Labaka, A., Martinez-Villar, A., & Perez-Tejada, J. (2023a). Psychological resilience and cortisol levels in adults: A systematic review. *American journal of human biology*, *35*(12), e23954. https://doi.org/10.1002/ajhb.23954

Study #3:

Aizpurua-Perez, I., Arregi, A., Gonzalez, D., Macia, P., Ugartemendia, G., Labaka, A., Zabalza, N., & Perez-Tejada, J. (2023b). Resilience in Newly Diagnosed Breast Cancer Women: The Predictive Role of Diurnal Cortisol and Social Support. *Biological research for nursing*, *26*(1), 68–77. https://doi.org/10.1177/10998004231190074

Study #4:

Aizpurua-Perez, I., Arregi, A., Gonzalez, D., Urruticoechea, A., Labaka, A., Minguez, X., Ugartemendia, G., Pascual-Sagastizabal, E., Echeverria, R., & Perez-Tejada, J. (under review). Elkar-laguntza study, a randomized controlled trial on the effectiveness of a one-to-one peer support intervention on resilience, social support, and salivary cortisol in recently diagnosed women with breast cancer

This research endeavor was made possible by a pre-doctoral grant from the Education Department of the Basque Government (reference code: PRE_2019_1_0041), which not only provided financial support but also symbolized the academic and scientific community's recognition of the importance of this research. The PhD candidate was also awarded a grant for an

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THEORETICAL FRAMEWORK

1. BREAST CANCER

1. Epidemiology

Breast cancer (BC) is the most prevalent malignancy among women, with approximately 2.3 million new cases identified globally each year which is expected to reach 2.7 million by 2030 (Ferlay et al., 2020). Recognized as a leading cause of female cancer mortality and the 5th leading cause of cancer death, it accounted for 685,000 deaths worldwide in 2020 (World Health Organization, WHO, 2022).

In Spain, approximately ninety-five women are diagnosed with BC every day, equating to about 35,000 cases annually (Red Española de Registros del Cáncer, REDECAN, 2023). Men, in contrast, represents less than 1% of all new diagnoses of this disease (Sociedad Española de Oncología Médica, SEOM, 2023). According to the SEOM (2023), the highest incidence of the disease is between 45-65 years of age, coinciding with the time when hormonal changes occur in the peri- and post-menopausal periods. This incidence curve continues to increase as women grow older. Thus, the incidence rate of BC in Spain is rising, increasing by 11% over the last decade (Asociación Española Contra el Cáncer, AECC, 2022). These data, however, contrast with the marked improvement in the BC survival rate recorded during the last 20 years, which can be explained by the advance of early detection techniques and improvements in the treatment (AECC, 2022). Indeed, the Spanish Network of Cancer Registries has recently confirmed the increase in BC survival, reporting an absolute rise of

+2.3 percentage points in 5-year net survival rates between 2002-07 and 2008-13 (Guevara et al., 2022). Specifically, the 5-year relative survival (RS) rate for BC in Spain turned out to be 82.8% for the period 2000-07 according to EUROCARE-5, somewhat higher than the average in Europe (81.8%) (Sant et al., 2015). When the stage of the patients at the time of diagnosis is taken into account, national survival rates for BC vary considerably, with a 5-year RS rate of 62.5% for stage III (when the tumor has spread to lymph nodes near the breast) and 23.3% for stage IV (when the tumor has spread to other parts of the body) according to the Granada Registry (Baeyens-Fernández et al., 2018). Notably, only 6.1% of BCs in Spain are metastatic at the time of diagnosis (stage IV) (AECC, 2020), defined as the state in which cancer cells have spread (metastasized) to distant locations of the breast and its regional lymph nodes.

2. Diagnosis and staging

The diagnosis of BC is determined by histological evaluation in accordance with standardized pathological criteria. The most prevalent histopathological subtypes include invasive ductal carcinoma (accounting for 55%-75% of patients, marked by an abnormal cellular proliferation in the breast's milk duct lining that extends to adjacent breast tissue), succeeded by invasive lobular carcinoma (manifesting in 5%-15% of cases, characterized an abnormal cellular proliferation in the breast's lobules that extends to adjacent breast tissue) (Dillon et al., 2014; Makki, 2015; Waks & Winer, 2019). Mixed ductal/lobular carcinomas and other histological variations are observed less frequently in the remaining patient population (Waks & Winer, 2019). Moreover, BC is divided into 3 subtypes according to the presence or absence of molecular markers for

estrogen or progesterone receptors (ER and PR, respectively) and human epidermal growth factor 2 (HER2). The first of these subtypes, the ER-positive or PR-positive, is expressed in approximately 70% of invasive BCs. The molecular pathogenesis of this subtype is mediated by estrogen receptor alpha (ERα), identified as activating oncogenic growth pathways in BC cells, with intimately related PR expression serving as an indicator of ERα activity (Waks & Winer, 2019). The HER2-positive subtype, which is present in 15-20% of BCs, is mediated by the over-activation of the Her2 oncogene, which encodes Her2, a receptor tyrosine kinase present on mammary cells involved in the regulation of cell proliferation and apoptosis, among others (Piccart-Gebhart et al., 2005). Evidence has associated overexpression of the Her2 protein with a worse prognosis when systemic treatment is not available (Piccart-Gebhart et al., 2005). The triple-negative subtype, whose name refers to the lack of expression of the molecular markers ER, PR, and Her2, is present in 15% of breast tumors (Denkert et al., 2017). The specific molecular pathophysiology of this subtype is still poorly understood and its presence is associated with an increased risk of distant relapse in the first 3 to 5 years after diagnosis (Foulkes et al., 2010; Waks & Winer, 2019).

BC is staged according to the characteristics of the primary tumor and its extension, the former being one of the factors that together with age, general health, and the hormonal subtype of the tumor have a significant impact on the patient's prognosis (National Cancer Institute, NCI, 2019). Particularly, stage (also described by the Tumor, Node, Metastasis [TNM] system) refers to how widespread the cancer is in the breast tissue and is usually expressed as a

number on a scale from 0 to IV, which depends on the size and grade of the primary tumor, the spread to lymph nodes or other parts of the body, and the presence or absence of ER, PR and HER2 biomarkers (NCI, 2019). While early-stage BC (Stage I or II) is highly treatable even if it requires immediate treatment, advanced-stage (Stage III) or metastatic (Stage IV) BC makes tumor removal increasingly challenging and has a significant effect on patients' survival rate (NCI, 2019). Thus, unlike stage I BCs which have a 5-year BC-specific survival ranging from 85% to 99% depending on the hormonal subtype, stage IV BCs exhibit a median overall survival of 1 year for triple negatives and about 5 years for ER, PR or HER2-positive subtypes (Waks & Winer, 2019). Generally, the more advanced the stage the more treatment is likely to be needed (American Cancer Society, 2019).

3. Treatment

BC is characterized by being highly heterogeneous, and treatment strategies differ depending on the molecular features of the tumor, such as activation of the HER2 protein and the ER and PR hormone receptors, expression of different markers of the tumor microenvironment (such as tumor-infiltrating lymphocytes [TILs] and programmed death-ligand 1 [PD-L1]) and genetic mutations (such as breast cancer 1/2 [BRCA 1/2] and phosphatidylinositol-4,5-bisphosphate 3-kinase alpha catalytic subunit [PIK3CA]) (Hong & Xu, 2022). In patients with non-metastatic, operable BC, multidisciplinary treatments combine loco-regional therapies such as surgical and radiation therapies, with systemic treatments that include a broader spectrum of drugs. Thus, while surgery and radiotherapy promote local control of cancer, systemic therapy is especially

important to improve disease-free (DFS) and overall survival (OS) by eradicating micrometastatic foci of disease (Teven et al., 2017). The timing of systemic therapies for non-metastatic, operable BC comprises adjuvant therapy after surgery and preoperative or neoadjuvant therapy before surgery (Shien & Iwata, 2020), whose long-term efficacy has been shown to be the same through different randomized clinical trials (Mauri et al., 2005; Rastogi et al., 2008). Systemic forms of therapy include hormonal therapy, chemotherapy, and targeted/molecular therapy, which can be administered alone or in multiple-drug regimens. In this regard, categorizing the molecular subtype of BC according to the expression of the aforementioned biomarkers ER, PR, and HER2, among other features, proves highly useful for ascertaining the optimal systemic therapeutic approach (Shien & Iwata, 2020).

Eradicating or delaying the appearance of hidden micrometastatic disease, which is considered responsible for distant recurrence treatment failures after local therapy, is the main goal of adjuvant treatment (Fishman & Verma, 2006). Thus, the use of endocrine therapy (through selective estrogen modulators (SERMs) in premenopausal patients [e.g., Tamoxifen] and aromatase inhibitors (AIs) in postmenopausal patients [e.g., Anastrozole, Letrozole, and Exemestane]), chemotherapy (usually through anthracycline-, taxane-, cyclophosphamide- or carboplatin-containing regimens, among others) and anti-Her2 molecular target therapy (often in combination with adjuvant chemotherapy via monoclonal antibody conjugates, such as trastuzumab or pertuzumab) (American Cancer Society, 2021; NCI, 2022) contribute to improving both DFS and OS (Shien & Iwata, 2020). The selection and magnitude of benefit derived

from each of these pharmaceutical agents depends on baseline risk, which may be gauged from both the quantity of lymph node metastases and the biological and clinical features of the invasive tumor (Shien & Iwata, 2020).

As for neoadjuvant systemic therapy, recent years have seen a shift from the dominance of chemotherapy to further exploration of hormonal and targeted therapies, administered either concurrently with or as alternatives to chemotherapy. Classical clinical benefits from neoadjuvant systemic therapy include tumor shrinkage and downstaging, leading to improved surgical outcomes and breast conservation by turning inoperable tumors into operable ones (Hong & Xu, 2022). Thus, there is evidence that about 40% of HER2-positive and triple-negative tumors suitable for mastectomy may become candidates for breast-conserving surgery by neoadjuvant systemic treatment (Golshan et al., 2016; Hong & Xu, 2022). Beyond surgical advantages, the latter is also known to provide valuable prognostic information based on the degree of response to treatment, thus allowing to guide postoperative systemic treatment decisions (Globus et al., 2022). Moreover, pathological complete response after neoadjuvant chemotherapy has been shown to be associated with higher DFS and OS in early BC, with a significantly stronger association in HER2-positive and triple-negative tumor patients compared to those positive for hormone receptors (Cortazar et al., 2014; Globus et al., 2022; Hong & Xu, 2022). This and other available evidence (Masuda et al., 2017; von Minckwitz et al., 2019) make neoadjuvant therapy the gold standard treatment approach for patients with stage II or III triple-negative or HER2-positive tumors (Hong & Xu, 2022).

4. Psychological impact of cancer diagnosis

Life-threatening events, such as the diagnosis of BC, can significantly affect patients' well-being due to its consequences in the physical, psychological, social, economic, and spiritual domains (Aizpurua-Perez & Perez-Tejada, 2020). Frequently, the news of the diagnosis forces the patient to confront a perceived lack of control on the outcome of the disease, which coupled with the assimilation of new information and the need for prompt treatment-related decisions, represents a particularly complex challenge. Thus, for many women coping with disease-related demands constitutes an extremely stressful experience that can lead to several long-lasting negative emotional outcomes and mental health problems (Aizpurua-Perez & Perez-Tejada, 2020; Hernández Blázquez & Cruzado, 2016; Seib et al., 2018). The existing literature groups the impact of BC into three distinct areas related to possible psychiatric disorders: (1) mood disturbances (including depression and anxiety), (2) lifestyle changes associated with pain, decreased activity and/or sexual problems, and (3) fear associated with mastectomy and its effect on body image, recurrence and/or death (Meyerowitz, 1980; Valderrama Rios & Sánchez Pedraza, 2018). Of these, anxiety and depression symptoms stand out for their high prevalence, identifying that approximately 50% of patients with early BC develop depression, anxiety, or both during the year following diagnosis, which can persist for many years post-diagnosis (Burgess et al., 2005; Carreira et al., 2018; Lopes et al., 2022).Such alterations can range from mild to totally incapacitating and manifest in a variety of ways. Specifically, evidence points to an increased risk of developing anxiety and depression shortly after BC diagnosis, suggesting that diagnosis-specific

stress is qualitatively distinct from the stress experienced during treatment and the overall oncologic process (Yang et al., 2017). The putative time-dependent risk of stress-related mental health symptoms underscores the need to study each of the periods separately (Fortin et al., 2021), yet many existing studies do not distinguish between the emotional reactions experienced in response to each of the phases (Holland et al., 2013).

Either during the treatment period and/or post-treatment, these stress-related mental health problems have important repercussions for the prognosis of the disease, significantly affecting the course and effectiveness of medical treatment, and consequently, QoL (Aizpurua-Perez & Perez-Tejada, 2020; Seib et al., 2018). A recent longitudinal investigation identified worse levels of QoL across all examined domains (i.e., functional capacity, physical limitations, bodily pain, general health status, vitality, socio-emotional aspects, and mental health) in BC patients enduring persistent depression, both at baseline and during follow-up, in comparison to their non-depressed counterparts (Ribeiro et al., 2023). Psychological distress was also identified as one of the main predictors of relatively low health-related QoL (HRQoL) in early-stage BC survivors at 1 to 3 years following chemotherapy (Syed Alwi et al., 2022). These results highlight the importance of closely monitoring mood disturbances and/or psychological disorders in these patients. However, whereas some women find it especially difficult to cope with illness-related adversity, many others are able to adapt flexibly to the changing demands of this stressful experience. Psychological resilience has been proposed to explain the reasons for this variability (Mikolajczak et al., 2008).

2. RESILIENCE AND REAST CANCER

1. Resilience and its relationships with psychological variables

Resilience is a variable that, despite its significant influence on human life, was not studied in detail until the emergence of positive psychology in the 1990s (Cerezo et al., 2022; Garmezy, 1991). Resilience refers to an individual's ability to maintain or recover relatively stable psychophysiological functioning during or after exposure to stressful life events of a traumatic nature (Bonanno, 2012). In cancer patients, resilience represents a continuous, fluid, and dynamic process that enables effective adaptation to disease-related adversity (Eicher et al., 2015). This conceptualization emphasizes the context- and time-specific nature of the resilience building-process, also understood as the ability to seek out and develop resources that allow an individual to flexibly manage adversity with positive health outcomes (Haase, 2009). Several studies have related high levels of resilience to better mental and physical health results in cancer patients. Thus, apart from facilitating the reduction of anxiety and depressive symptoms and improving both QoL and cognitive flexibility (Min et al., 2013; Seiler & Jenewein, 2019), psychological resilience also seems to contribute to the reduction of cancer-related physical symptoms such as fatigue, nausea or pain, among others (Eicher et al., 2015). In the context of BC, research shows that highly resilient patients exhibit personal protective attributes including greater self-efficacy (Huang et al., 2019; Ye et al., 2018), self-compassion (Alizadeh et al., 2018), emotional intelligence (Alarcón et al., 2020), and positive affect (Alarcón et al., 2020; Markovitz et al., 2015). Highly resilient patients also demonstrate a higher use of adaptive coping strategies such as active coping (Lai et al., 2020) or

positive acceptance coping (Tu et al., 2020); these strengths lead to more favorable outcomes when dealing with disease-related challenges. In this sense, evidence also points to higher symptom burden and physical distress among less resilient BC patients (Fradelos et al., 2018; Ye et al., 2018). Moreover, in a study by Ristevska-Dimitrovska et al (2015), the authors identified a more pessimistic attitude, increased physical impairment, and more severe treatment-related side effects among those patients reporting lower resilience scores. Although still limited, these results are of practical importance since, in addition to highlighting resilience as a valuable resource for coping with cancer-related adversity, they offer a tentative insight into features of the resilience process that might be targeted throughout the BC continuum.

2. Resilience and social support

Among the various protective factors presumably necessary for the development of resilience (Eicher et al., 2015), social support emerges as one of the most relevant in the literature (Zhang et al., 2017). Notwithstanding the considerable variability in the definition of social support, it generally refers to an individual´s appraisal of the availability of emotional, affectionate, or tangible resources provided by support networks (Sherbourne & Stewart, 1991). The perception of the availability of social support has shown to be especially important at times of traumatic life experiences, such as a cancer diagnosis. Thus, there is evidence indicating that social support can help patients cope with the adverse impact of cancer-related stress by helping them process trauma, foster adaptive coping, and draw positive meaning from the experience, among others (Aizpurua-Perez & Perez-Tejada, 2020; Greup et al., 2018; Huang et al.,

2019; Leung et al., 2014). Notably, social support is thought to be a pivotal factor in enhancing psychological resilience, with several studies having found positive relationships between the two variables in women with BC (Aizpurua-Perez et al., 2023b; Alizadeh et al., 2018; Bazzi et al., 2018; Huang et al., 2019; Kamen et al., 2017; Tao et al., 2022; Wu et al., 2016; Ye et al., 2018; Zhang et al., 2017; Zhou et al., 2022a; Zhou et al., 2022b). These results highlight the strong link that appears to exist between social support and resilience (Çakir et al., 2021) and indicate that the latter should be bolstered through an increase availability of social support (T. Hu et al., 2018). Moreover, social support and psychological resilience have been shown to buffer the negative impact of stress and improve QoL by reducing patients' levels of distress (Min et al., 2013; Zhang, H., Zhao, Q., Cao, P., & Ren, 2017). In the study by Zhou et al (2022b), social support was found to act as a mediator in the relationship between psychological resilience and cancer-related QoL in women with newly diagnosed BC. Specifically, the authors identified that higher levels of social support served to reinforce the positive influence of resilience on HRQoL, thus suggesting that effective and holistic interventions for quality of life improvement should take into account both resilience status and perceived social support in BC patients. However, due to the great methodological variability (e.g., use of different scales, low sample heterogeneity, cross-sectional design, among others) of studies analyzing both resilience and social support in this population (Aizpurua-Perez & Perez-Tejada, 2020), more research is needed to extract clear conclusions and to further investigate the relationships with other psychophysiological variables.

3. Resilience and biological variables

While resilience has been mainly defined by its relationship with psychological factors, there are a limited number of studies that have investigated its biological correlates, whose findings may account for the biological basis of this construct. On the one hand, literature suggests that peripheral biomarkers including the anxiolytic neuromodulators neuropeptide Y (NPY) and oxytocin, the circulating plasma C-reactive protein (CRP), as well as the neurosteroidogenic enzyme allopregnanolone (ALLO), among others, are potentially related to both psychological and stress resilience (Berg et al., 2017; Gundogmus et al., 2022; Osório et al., 2017; Petros et al., 2013). The consideration of NPY and oxytocin as biological correlates of resilience/stress resilience comes from human and animal studies, which have highlighted the anti-anxiogenic and stress-regulatory properties of these biomarkers in addition to their role in building and/or maintaining resilience (Morales-Medina et al., 2010; Ozbay et al., 2008; Yehuda et al., 2006). CRP, shown to be negatively related to resilience in adult humans (Berg et al., 2017), is considered a biomarker for the risk of developing both depression and anxiety (Naudé et al., 2018). ALLO, for its part, primarily acting on γ-Aminobutyric acid type A ($GABA_A$) receptors (Bali et al., 2014), has been found to play an important role in regulating hypothalamic-pituitary-adrenocortical (HPA) axis hyperactivity in acute stress and has been proposed to play a role in promoting resilience (Drugan et al., 2013; Gundogmus et al., 2022; Osório et al., 2017).

Continuing this focus on the HPA axis, research has also suggested that the neuroendocrine response to stress via the HPA axis, and with it the

glucocorticoid hormones implicated in stress such as dehydroepiandrosterone sulfate (DHEA-S) and cortisol, are associated with psychological resilience (Osório et al., 2017; Petros et al., 2013; Russo et al., 2012). It is particularly through the regulation of daily cortisol patterns that resilience has been proposed to play a key role in the physiological response to stress, enhancing adaptation by its modulatory action on the relationship between cortisol and health (Aizpurua-Perez et al., 2023a; Gaffey et al., 2016). Thus, some authors have identified the existence of an inverse relationship between resilience and cortisol (Krisor et al., 2015; Ruiz-Robledillo et al., 2014; Sun et al., 2014), and it has been theorized that resilient individuals may exhibit better regulated cortisol levels than their non-resilient homologs (Nishimi et al., 2022; Petros et al., 2013). However, the mixed results found by a recent systematic review on the resilience-cortisol relationship, which according to the authors may have been largely influenced by the methodological heterogeneity identified among the studies measuring both variables (Aizpurua-Perez et al., 2023a), emphasize the need for further investigations to clarify this bidirectional relationship. It is noteworthy that only one of the studies included in the systematic review was conducted in cancer patients (Sharpley et al., 2018), which, after analyzing the basal salivary cortisol response of prostate cancer patients found no significant associations with resilience. Furthermore, the only two studies that, to the author's knowledge, have so far analyzed the relationship between resilience and cortisol in BC patients (Aizpurua-Perez et al., 2023b; Gundogmus et al., 2022) found no significant direct relationship between the two variables. Given the potential of resilience to attenuate pathological states that often arise after exposure to adverse events such as cancer diagnosis, and which are related to alterations in

circulating cortisol, additional research is needed to discern the conditions under which the relationship between the two variables occurs in BC patients.

3. RESILIENCE-ENHANCING INTERVENTIONS IN CANCER CARE

1. Rationale and main effects

Because of the current conceptualization of resilience as a dynamic and variable process of adaptation resulting from individual-environment interaction, both personal factors (e.g., optimism) and environmental factors (e.g., social support) can influence its development (Chmitorz et al., 2018; Helmreich et al., 2017). This process-oriented approach emphasizes the modifiability of resilience, which can be trained and enhanced through interventions (Bonanno & Diminich, 2013; Helmreich et al., 2017). Resilience-enhancing interventions aim to promote resilience in the context of potentially stressful situations such as cancer, taking place either immediately after exposure to the news of the initial diagnosis or recurrence or also during (over the course of the disease) or after the end of the medical treatment (survivorship), as resilience can only be determined with respect to stressors (Helmreich et al., 2017; Ludolph et al., 2019). Furthermore, resilience as an outcome of adaptation to stress is presumed to be influenced by multiple resilience factors (i.e., psychosocial and socio-contextual resources associated with resilience), which is why resilience interventions are typically resource-oriented and aim to potentiate one or more resilience factors, including self-concept, optimism, social support or adaptive coping strategies (Helmreich et al., 2017; Ludolph et al., 2019; Seiler & Jenewein, 2019). To date, several interventions have been developed to improve resilience in cancer patients (Ludolph et al., 2019; Molina et al., 2014; Seiler & Jenewein, 2019; Sihvola et al.,

2023; Tan et al., 2019). These programs have employed various modalities, including online, telephone, or face-to-face, combining methods such as discussions, role-playing, and/or practical exercises, and being delivered in group or individual formats. Their effectiveness in improving resilience, mainly assessed using the Connor–Davidson Resilience Scale (Connor & Davidson, 2003; CD-RISC), and Wagnild and Young's Resilience Scale (Wagnild & Young, 1993; RS), has been largely demonstrated, particularly for those programs provided in the period immediately following diagnosis (Ludolph et al., 2019; Seiler & Jenewein, 2019; Sihvola et al., 2023). In addition to resilience itself, resilience-enhancing interventions have also been found to improve QoL (Wu et al., 2018; Ye et al., 2016; Zhang et al., 2020), perceptions of social support and hope toward the future (Ye et al., 2016), and self-efficacy (Yi & Ryu, 2017), as well as reduce symptoms of distress (Ye et al., 2016, 2017; Zhou & Kong, 2019), and uncertainty about the disease (Ye et al., 2016).

2. Current resilience-enhancing interventions in breast cancer

In the context of BC, the effects of resilience-enhancing interventions have been evaluated so far by only two systematic reviews, of which one circumscribed its results to resilience as the only outcome variable (Wang et al., 2021) and the other provided integrated evidence of the variables influenced by these interventions (Aizpurua-Perez & Perez-Tejada, 2020). Both studies, which included patients in active treatment and BC survivors, confirmed the ability of the majority of the interventions to improve participants' resilience. In addition, the study by Aizpurua-Perez and Perez-Tejada (2020) also reported significant post-intervention improvements along a spectrum of variables, encompassing

affect, optimism and happiness, anxiety and depression, body image and self-esteem, self-efficacy, future perspective and hope, perception of social support, QoL-related cognitive, emotional and physical functions, while also ameliorating the management of symptoms associated with BC treatment (including fatigue, nausea, vomiting, and constipation). However, despite the apparent advantageous effects of resilience-promoting interventions, the evidence for such programs is still limited in the oncological setting (Tan et al., 2019). This, together with the great variability in the instruments used to measure resilience, small sample sizes, variations in the duration of interventions, and possible cultural biases derived from the large geographic variability (Aizpurua-Perez & Perez-Tejada, 2020; Wang et al., 2021), among other factors, may limit the generalizability of the results. Furthermore, to the best of the authors' knowledge, none of the resilience interventions conducted so far in women with BC have measured effects on biomarkers related to cancer adaptation and survival (neuroendocrine and/or immune system variables). In this regard, there is evidence that some Stress Management Interventions (SMIs), including Cognitive Behavioral Therapy (CBT)-based interventions, have demonstrated efficacy in reducing serum cortisol levels (Phillips et al., 2008), enhancing cellular immune functionality (Antoni et al., 2009; McGregor et al., 2004) and attenuating the expression of proinflammatory genes in leukocytes (Antoni et al., 2012, 2016) in BC patients during the first year of their medical treatment, in parallel to promoting psychological adjustment. Given that studies showing intervention effects on psychological adaptation in cancer patients often show concurrent effects on their physiological adaptation (McGregor & Antoni, 2009), further studies are needed to explore the possible biopsychosocial effects of resilience-

enhancing interventions in order to develop a more integrative approach to BC care.

With respect to their theoretical basis, resilience training programs tend to diverge considerably in terms of their main components and design due to variations in their underlying frameworks (Joyce et al., 2018). Notwithstanding that some authors have rightly pointed out as a major limitation in the resilience literature the lack of consensus regarding the best-suited theoretical framework to guide the development of these programs (Leppin et al., 2014), a remarkable emergence of new studies in the context of BC has supported the benefits of resilience training at different stages of the oncologic journey ((Aizpurua-Perez & Perez-Tejada, 2020; Wang et al., 2021). In this sense, from the available literature on resilience-promoting interventions, it can be concluded that programs whose theoretical foundations have been mainly based on CBT (Loprinzi et al., 2011), Mindfulness-Based Stress Reduction (MBSR) therapy in combination with CBT (Cui & Wang, 2020; May, 2016), Supportive-Expressive Group Therapy (SEGT) (Ye et al., 2016, 2017) as well as positive psychology (Cerezo et al., 2014) and psychoeducation (Wang & Wang, 2020; Wu et al., 2018; Yi & Ryu, 2017; Zhou & Kong, 2019) have been shown to benefit BC patients' and survivors' resilience. These interventions have been mainly delivered in face-to-face and group modalities, except the psychoeducational approach, where a growing trend has been observed towards the use of mobile health (mHealth)-based interventions, such as the WeChat platform in China, to provide health education on BC treatment (Wang & Wang, 2020; Zhou & Kong, 2019). In addition to the above approaches, interventions focusing on social interaction,

such as peer support, have also emerged during the last years to promote resilience (Chmitorz et al., 2018). Building on Festinger's Social Comparison Theory (1954) and Bandura's Social Learning Theory (1977), resilience-enhancing interventions based on peer support are founded on the premise that sharing personal experiences with individuals who have experienced complexities of similar challenges not only normalizes and dignifies patients' experience, but also promotes their psychological adjustment. Although the evidence for these interventions is still scarce in BC, evidence points to their effectiveness in promoting patient resilience (Wang et al., 2021).

4. PEER SUPPORT INTERVENTIONS IN CANCER CARE

1. Definition and rationale

Peer support represents an inclusive paradigm of reciprocal empowerment, wherein empathetically grounded relationships, anchored in shared experiences, offer the appropriate spaces for the construction of self-meaning. Grounded in principles of reciprocal respect, responsibility, and agreement, peer support involves understanding the other person's situation via the mutual experience of emotional and psychological pain (Mead et al., 2001). Thus, it can be understood as an informal and unstructured form of social support facilitated by people who have navigated similar adversities or conditions (Ramchand et al., 2017; Zhang et al., 2022). Unlike professional help, peer support relies on an egalitarian and non-hierarchical relational framework wherein individuals facing the same problem come together to share personal experiences, exchange information, and provide mutual encouragement to

overcome difficulties (Aizpurua-Perez et al., 2023c; Munce et al., 2017; Park et al., 2019).

In the context of cancer, the psychosocial challenges associated with diagnosis and treatment are multifaceted and evidence suggests that some of the emotional needs of patients are not fulfilled by typical sources of social support such as partners, family, or friends (Kowitt et al., 2019; Park et al., 2019; Ussher et al., 2006). These emotional needs may encompass managing guilt or anger associated with the diagnosis, alleviating social isolation, addressing concerns about quality of life and lack of information regarding treatment decisions, as well as mitigating the fear of recurrence (American Cancer Society, 2020; Ussher et al., 2006). Peers who have faced comparable life experiences (i.e., cancer survivors who have recovered from cancer) may be ideally suited to complement the formal and/or affective support rendered to patients by institutions and/or close relatives and friends, providing them with practical information, emotional support, assistance with combating isolation and overall, contributing to improved coping with the disease (Meyer et al., 2015). Because of their authentic and experiential knowledge, peers possess a unique ability to comprehend the challenges others are confronting, which may be more difficult to grasp for individuals who have not been personally affected by the same condition (Kirkegaard, 2022; Meyer et al., 2015; Pistrang et al., 2013). This understanding enables them to engage in sincere and reciprocal emotional relationships with others (Aizpurua-Perez et al., 2023c).

In addition to providing patients with a safe space for expressing practical and emotional concerns to help them cope with disease-related difficulties

(Pistrang et al., 2013), peers can efficiently address the various health needs of patients by improving their linkage to care (Kowitt et al., 2019). Hence, peer support can also be regarded as a compelling strategy for disease prevention and management that facilitates connections to clinical and community resources (Kowitt et al., 2019). Prior research points to peer support as an effective strategy for surmounting numerous obstacles at different phases of the cancer care continuum, such as primary and secondary prevention (Ancker et al., 2009), early detection and diagnostic follow-up (Maxwell et al., 2010; Whop et al., 2012), medical treatment (Hoey et al., 2008; Meyer et al., 2015), and survivorship (Hoey et al., 2008; Meyer et al., 2015). By collaborating with patients and/or care providers, peers can assist in tackling system-level barriers and practical challenges (Kowitt et al., 2019), making it easier to navigate health and community care systems.

However, providing support to individuals in emotional pain presents a paradoxical scenario, entailing a complex interplay of burdens and rewards (Pistrang et al., 2012). Within the context of cancer-related peer support, a prominent risk emerges when exposure to patients' emotional distress intensifies or rekindles the personal fears and vulnerabilities of the supporters, potentially leading to re-traumatization. Acknowledging this risk of negative repercussions, existing research emphasizes the critical need to conduct comprehensive assessments to track both the positive and potentially adverse effects of peer support provision on the psychological health of peer supporters (Clougher et al., 2023; Embuldeniya et al., 2013; Giese-Davis et al., 2006; Meyer et al., 2015; Pistrang et al., 2013).

Additionally, it is common for professionals to train peer supporters by providing them with a basic theoretical framework that facilitates their comprehension of the fundamental aspects of supportive interactions, as well as by training them in communication skills (e.g. practicing active listening or using self-disclosure) (Pistrang et al., 2012), educational skills (e.g. by providing up-to-date information on disease management and treatment options) (Kiemen et al., 2023), and/or leadership skills (e.g. learning to navigate interpersonal conflicts) (Ziegler et al., 2022). The aim of this training is usually to equip peers with the necessary tools to ensure effective session management and comprehensive patient follow-up (Aizpurua-Perez et al., 2023c). This trained peer support is not generally regarded as professional support (Kiemen et al., 2023). Moreover, with the focus on fostering a “natural” conversation flow characterized by two-way dialogue (Pistrang et al., 2012), peer support interventions are primarily intended to complement, not replace, professionally rendered psychological support (Zhang et al., 2022), since they alone may not adequately address the psychosocial and emotional needs of patients throughout the oncological process (Aizpurua-Perez et al., 2023c).

2. Types and main effects

Peer support interventions can be administered in a diverse array of modalities and/or formats. These range from one-to-one modalities involving one patient and one peer supporter, to group modalities that include multiple patients and one or more peer supporters. Moreover, these interventions can be facilitated in face-to-face, online (e.g. via chat rooms), or via telephone. The settings may vary significantly, ranging from groups for patients sharing a specific diagnosis or

diverse types of cancer, to the inclusion, albeit less frequently, of family members or partners in the sessions (Kiemen et al., 2023; Luu et al., 2022). Accessibility of these programs extends to patients at every stage of their oncological process, from the initial diagnosis to the long-term post-cancer survival phase (Kiemen et al., 2023). Regardless of the form of peer support administration, a universal characteristic of all interactions is the reciprocity of support exchanged between patients, which becomes a natural extension and expansion of the community that does not attempt to model professionalized psychosocial care (Mead et al., 2001).

Within the spectrum of peer support, literature predominantly converges upon the examination of the effects of interventions delivered through the one-to-one modality via telephone and face-to-face formats, as well as through the group modality in both online and face-to-face formats (Kiemen et al., 2023; Ziegler et al., 2022). Early research studies in this field highlighted the importance of prioritizing one-to-one face-to-face and Internet-based group modalities when considering different ways of providing peer support to cancer patients (Hoey et al., 2008). Similarly, some authors noted that, in particular, the one-to-one modality might be preferred by some patients, as participants in group modalities are often at different stages of the cancer trajectory, making it particularly difficult for some to meet their specific individual needs (Yaskowich & Stam, 2003). Subsequently, other studies revealed that patients' preference for the one-to-one setting could be based on the greater ease offered by this modality in establishing harmonious relationships with peers (Boyes et al., 2018; Salzer et al., 2010). Thus, one-to-one interactions may allow for personalized attention and the

development of a closer, more individualized supportive relationship, although they may not provide the same sense of shared community that a group setting can offer (Cuesta-Briand et al., 2015; Ussher et al., 2006). Currently, there is no definitive consensus on which modality is universally most effective (Kiemen et al., 2023; Meyer et al., 2015; Ziegler et al., 2022), with effectiveness depending on the individual preferences and needs of the cancer patient, as well as the quality of peer support provided, which to a large extent depends on the training received by peer supporters (Hu et al., 2019). Regarding the different formats for conducting peer support, it has recently been suggested that blended formats, which incorporate face-to-face and telephone modalities, can enhance patient health outcomes by capitalizing on the strengths of nonverbal communication alongside the flexibility of the telephone (Zhang et al., 2022). On the other hand, the timing of the interventions constitutes a factor exhibiting considerable variation across studies, with durations ranging from a single session to multiple sessions within a 12-month period (Ziegler et al., 2022), and intervals between each session ranging from weeks to months (Zhang et al., 2022). Although some studies have suggested that patients prefer longer durations (Nápoles et al., 2018), recent evidence indicated that the benefits of peer support can be observable regardless of the duration of intervention (Ziegler et al., 2022). Moreover, recent research is more inclined to emphasize that it is especially the non-hierarchical and reciprocal nature of the patient-peer relationship that makes peer support a suitable complement to professional psychosocial support (Kiemen et al., 2023; Kowitt et al., 2019).

Although the emergence of peer support interventions has been relatively recent in the field of oncology, over the last few years a growing body of evidence has documented their role in improving the QoL of patients undergoing or recovering from cancer treatment, making these interventions a significant component of comprehensive cancer care. Thus, these interventions have been shown to exert substantial effects on the psychological dimension of patients' well-being, with some emerging evidence from the field of social support suggesting that their benefits may also extend to the biological domain. Concerning their psychological benefits, peer support interventions have been shown to be effective in mitigating symptoms of depression, anxiety, and profound emotional distress that often dampen the psychological outlook of cancer patients (Lee et al., 2013; Weber et al., 2007; White et al., 2014; Zhang et al., 2022). By fostering a sense of community and shared understanding, these programs have been found to alleviate feelings of isolation (Kosugi et al., 2021), fostering both psychological resilience (Mollaei et al., 2022) and adaptive coping strategies (Skirbekk et al., 2018). They have also been found to promote empowerment through the enhancement of self-efficacy, self-perceived cancer-related information and knowledge, and active coping-based strategies to manage their disease (Ziegler et al., 2022). In terms of cancer-specific QoL and psychological challenges, peer support interventions have been shown to successfully address the psychological (e.g., life satisfaction, body image, or future outlook) and physical (e.g. fatigue, pain, insomnia, sexual functioning or loss of appetite) domains of QoL, and the complexities of transitioning to survivorship (e.g., fear of recurrence) (Kiemen et al., 2023). In addition to these benefits, in the context of BC, these interventions have been demonstrated to be

effective in improving the management of reproductive issues, as well as cultivating a sense of being well-informed about disease-related aspects such as post-surgical recovery and its implications on femininity, body image, and sexual functioning, among others (Hu et al., 2019; St-Pierre et al., 2018). Furthermore, they have played a significant role in encouraging adherence to treatment protocols and helping women undergoing bilateral prophylactic mastectomy to make more informed decisions about their treatment options (St-Pierre et al., 2018). The effects of peer support have shown to be especially evident in women carrying the BRCA1/2 mutation, resulting in sustained improvements in their cancer-specific QoL between the 4 weeks to 3 months following the end of interventions (Kiemen et al., 2023).

However, it is important to acknowledge the presence of contradictory data on the effects of peer support interventions, which challenge the generally positive narrative of their substantial benefits. Several studies have reported mixed (Klemm, 2012; Salzer et al., 2010) or inconclusive results (Chambers et al., 2015; Gotay et al., 2007; Høybye et al., 2010; Nápoles et al., 2020) concerning the efficacy of these interventions in addressing psychological aspects of cancer adaptation. A recent meta-analysis by Zhang et al (2022) identified in two studies (Lee et al., 2013; Nápoles et al., 2015) that peer support provided within the first year of diagnosis demonstrated no significant impact on anxiety and depression in BC patients, attributing this lack of effect to the timing of the interventions. The authors posited that the heightened levels of distress characterizing this period might necessitate personalized support from health professionals (Lee et al., 2013; Zhang et al., 2022). Additionally, it has been

observed that unmoderated and unstructured peer support interventions in the context of BC not only fail to reduce the incidence of depressive symptoms but also potentially exert detrimental effects on variables such as quality of life and distress (Hu et al., 2019). These findings suggest that unmoderated web-based group peer support programs may not be ideally suited for women with BC (Hu et al., 2019). The limited evidence for these interventions, coupled with a notable lack of randomized controlled trials (RCTs) with control groups, which are essential to establish causal relationships, and a dearth of longitudinal studies to understand their long-term impact, significantly limits the robustness of the findings on their effects to date. This methodological gap underscores the need for more rigorous and comprehensive studies to better understand and substantiate the role of peer support programs in cancer care, particularly in areas where results have been mixed or contradictory, as emphasized in recent systematic reviews of the field (Clougher et al., 2023; Hu et al., 2019; Kiemen et al., 2023).

On the other hand, although the investigation into the direct biological effects of peer support interventions is another area that requires further exploration, there is a growing body of research suggesting that social support influences physiological outcomes in cancer patients (Kroenke, 2018). Some studies point to low perceived social support as a key factor contributing to increased cancer mortality and reduced survival time in several different cancer types (Chida et al., 2008; Kroenke, 2018). Within the realm of BC research, associations have been established between elevated mortality rates and low perceived social support (Beasley et al., 2010), impoverished social networks

(Kroenke et al., 2006), and reduced social well-being (Epplein et al., 2011), with Kroenke et al.'s (2013) research specifically highlighting that it is the absence of supportive relationships, rather than the lack of extensive social networks, that is associated with a heightened mortality risk among affected women. Alteration of the physiological response to stress through dysregulation of the sympathetic nervous system (SNS) and HPA axis hormones is one of the mechanisms by which low social support may influence tumor progression and worse clinical outcomes (Lutgendorf et al., 2010). A potential conduit for these interactions is the inflammatory signaling orchestrated by leukocytes, which have demonstrated their ability to interact with neoplastic cells, facilitating angiogenic and tissue invasive processes associated with metastatic spread (Cohen et al., 2015; Jutagir et al., 2017). In addition, the elevated glucocorticoid production that accompanies chronic social isolation is often related to increased inflammation in which leukocytes exhibit desensitization to prolonged cortisol release, resulting in uninhibited transcription of genes responsible for inflammatory cytokine production (Jutagir et al., 2017; Miller et al., 2008). Thus, some studies have found higher levels of the proinflammatory cytokine interleukin-6 (IL-6) and cortisol among non-metastatic BC patients with reduced levels of perceived support (Chang et al., 2022; Hughes et al., 2014). Moreover, Jutagir et al (2017) found higher levels of social well-being associated with lower proinflammatory and prometastatic leukocyte gene expression in post-surgical non-metastatic BC patients prior to the initiation of adjuvant therapy. This evidence suggests that supportive social resources may help buffer cancer-promoting biological processes, and underscores the importance of measuring cancer adaptation and survival-related neuroendocrine and immune biomarkers in future peer support-

based psychosocial interventions. Given the documented preventative effects of participation in peer support groups at both the secondary (preventing disease recurrence) and tertiary (mitigating disease progression) levels (Kiemen et al., 2023; Straka, 2007), there is a need for further research to elucidate the physiological impacts of these interventions on individuals diagnosed with cancer.

3. Current challenges and future directions

The contemporary research landscape investigating peer support interventions for cancer patients presents a myriad of challenges that must be tackled to optimize their effectiveness and accessibility. One of the principal issues is the heterogeneity in the implementation of these programs, leading to a lack of standardization across different settings. In the recent systematic review by Kiemen et al (2023), the authors also underscored the challenges encountered in peer support research when devising rigorous randomized controlled trials, pinpointing the unfeasibility of implementing blinding procedures, a critical factor that potentially introduces biases during the allocation of participants to either the intervention or the control groups. Another important element required to consolidate the peer support paradigm is the proper recruitment and training of peer supporters, as it is crucial that they possess the necessary skills, knowledge, and empathy to offer quality support. In this regard, a host of studies highlight the need to provide quality training to peer supporters on how to provide support and to understand what to expect from it (Clougher et al., 2023). Furthermore, a more comprehensive understanding of the diverse needs of cancer patients is needed, as these can vary significantly based on factors such as individual preferences,

clinical factors, and cultural backgrounds, among others (Clougher et al., 2023; Meyer et al., 2015; S. Zhang et al., 2022). Addressing these diverse needs and ensuring that potential barriers to the experience of peer support are adequately managed requires a tailored approach to peer support interventions. In addition, given that the absence of shared characteristics related to specific aspects of disease, age, lifestyle, or concerns about mortality has been found to hinder connection among program participants, it becomes imperative to pursue further investigation into the creation of innovative approaches that enhance conventional matching techniques (Clougher et al., 2023; Ono et al., 2017). Finally, there is a need for robust assessment frameworks capable of capturing the biopsychosocial impact of peer support interventions, which are indispensable for the development of holistic and tailored programs aimed at improving the long-term clinical outcomes of cancer patients. A patient-centered approach that adapts patients' changing needs and fosters synergies between healthcare practitioners, research community, and patient support networks is essential for the long-term feasibility of peer support interventions (Clougher et al., 2023; Meyer et al., 2015).

HYPOTHESES AND OBJECTIVES

Table 1: *General and Specific Hypotheses and Objectives of the Studies Included in the Doctoral Thesis*

STUDY	HYPOTHESIS	OBJECTIVES
	General	General
Study #1	G.H.1 Psychological resilience as a dynamic process that promotes cancer-related adaptation will be susceptible to numerous personal and environmental factors in addition to be trainable through psychosocial interventions.	G.O.1 Integrate evidence on quantitative studies that have investigated the factors involved in the resilience of women with BC as well as psychosocial interventions that can significantly contribute to its improvement.
	Specific	Specific
	S.H.1. Several quantitative studies will be identified that examine biopsychosocial factors associated with psychological resilience in women with BC. S.H.2 These studies will vary in terms of design, sample characteristics, the instruments used for measuring resilience, and the biopsychosocial variables studied in relation to resilience S.H.3 Studies will more frequently identify significant relationships between resilience and sociodemographic, clinical, and psychosocial variables, and less frequently between resilience and biological variables S.H.4 A positive relationship between resilience and protective variables such as social support, QoL, and adaptive coping will be identified. S.H.5 4 A negative relationship between resilience and detrimental variables such as anxiety and depressive symptoms will be identified.	S.O.1 Identify cross-sectional and longitudinal design studies that examine the relationships between resilience and any biopsychosocial variables in BC patients and survivors through quantitative methods. S.O.2 Synthesize information on the study design, sample characteristics, scales used for assessing resilience and biopsychosocial variables studied in relation to resilience identified in the studies. S.O.3 Sort the results of the studies and, with it, the variables related to resilience according to their sociodemographic, clinical, psychosocial, and physiological nature. S.O.4 y S.O.5 Explore the nature of the relationships between resilience and the diverse biopsychosocial variables identified by the studies.
	S.H.6 A limited number of quantitative studies will be identified that examine the effects of targeted psychosocial interventions to enhance resilience in women with BC. S.H.7 These studies will vary in terms of the characteristics of the intervention programs, study design, sample characteristics, and the instruments used for measuring resilience. S.H.8 The majority of studies will point to the significant effects of the interventions on participants' resilience. S.H.9 Most studies will provide evidence of the positive effects of the interventions on the development of participants' resilience.	S.O.6 Identify RCTs, non-RCTs, quasi-experimental, and non-experimental intervention design studies that use quantitative methods to examine the effects of resilience-enhancing interventions on the resilience of BC patients and survivors. S.O.7 Synthesize information on the characteristics of the intervention programs, study design, sample characteristics, and scales for assessing resilience identified in the studies. S.O.8 y S.O.9 Examine the nature of the effects of these interventions on participants' resilience.

	S.H.10 Resilience-enhancing psychosocial interventions will significantly influence biopsychosocial variables beyond resilience in women with BC. S.H.11 Specifically, these interventions will positively impact variables other than resilience, leading to favorable health outcomes for the patients.	S.O.10 and S.H.11 Examine the nature of the effects of resilience-enhancing interventions on biopsychosocial variables beyond resilience.
Study #2	General	General
	G.H.2 Psychological resilience as a potential key factor in modulating the physiological response to stress, will be significantly associated with cortisol.	G.O.2 Gather evidence on quantitative studies that have investigated the relationship between psychological resilience and cortisol levels in clinical and non-clinical adult populations.
	Specific	Specific
	S.H.12 Several quantitative studies that explore the relationships between psychological resilience and cortisol levels in adults will be identified. S.H.13 These studies will vary in their design, sample characteristics, and the instruments and methods used for measuring resilience and cortisol. S.H.14 A minority will study the relationship between psychological resilience and cortisol in cancer populations. S.H.15 Studies will identify significant relationships, rather than null or non-significant ones, between psychological resilience and participants' cortisol levels. S.H.16 Studies will largely report that psychological resilience serves as a protective resource to ward off stress-related pathological states associated with alterations in circulating cortisol.	S.O.12 Identify cross-sectional, longitudinal, and intervention-design studies that examine the relationships between resilience and cortisol levels in adults through quantitative methods. S.O.13 Synthesize information on the study design, sample characteristics, scales used to assess resilience, and cortisol parameters and measurement methods identified in the studies. S.O.14 Identify the number of studies conducted within cancer populations and potentially examine the relationships described therein between resilience and cortisol S.O.15 and S.O.16 Describe the nature of the relationships between resilience and cortisol levels in the selected studies.
	S.H.17 The relationships between psychological resilience and cortisol will be uniquely influenced by the different periods covered by the cortisol matrices selected in the studies, as well as by the specific components of HPA output they refer to.	S.O.17 Examine and sort the relationships between resilience and cortisol based on (1) the short and long-term secretion span encompassed by the cortisol matrices chosen in studies, and (2) the differentiated diurnal, phasic (acute), and tonic (basal) elements of the HPA output they address.
Study #3	General	General
	G.H.3 Psychological resilience in newly diagnosed BC patients will be partially determined by their levels of perceived social support and their physiological response to stress.	G.O.3 Investigate the predictive role of perceived social support and salivary cortisol in the resilience levels of recently diagnosed women with early-stage (I-III) BC.
	Specific	Specific
	S.H.18 Psychological resilience will be significantly related to both the total score and subscales of social support (affective, emotional and instrumental support), as well as to diurnal cortisol levels in newly diagnosed women with BC.	S.0.18 Analyze, using a cross-sectional and quantitative approach, the potential associations between resilience, perception of social support, and diurnal salivary cortisol levels in a group of women newly diagnosed with early BC.

	S.H.19 The availability of social support at the time of diagnosis will function as a protective factor, leading to greater levels of resilience among BC patients. S.H.20 The dysregulation of cortisol levels at the time of diagnosis will serve as a risk factor, leading to diminished levels of resilience among BC patients.	S.O.19 Explore the nature of the potential associations between resilience and the perception of different types of social support (i.e. emotional, affective, and instrumental) among BC patients. S.H.20 Explore the nature of the possible associations between resilience and diurnal cortisol profiles among BC patients.
	S.H.21 The potential protective effect of social support on patients' psychological resilience will be mediated by their diurnal cortisol profiles.	S.O.21 Investigate whether diurnal cortisol levels at diagnosis moderate the assumed relationship between social support and resilience in BC patients
Study #4	General	General
	G.H.4 Peer support will be an effective strategy to promote psychological resilience, social support, and physiological adaptation to the disease among newly diagnosed BC patients.	G.O.4 Analyze the effectiveness of a RCT assessing the impact of a one-to-one peer support intervention on the resilience, perceived social support, and salivary cortisol levels of women newly diagnosed with early-stage (I-III) BC.
	Specific	Specific
	S.H.22 The one-to-one peer support intervention will have a significant effect on the target biopsychosocial variables immediately after its application, regardless of the type of medical treatment received by the patients. S.H.23 The intervention's effects will lead to significant differences in the target variables between the different study conditions after its implementation.	S.O.22 and S.H.23 Evaluate potential group variations in resilience, perceived social support, and salivary cortisol due to the intervention, based on the study condition (control = treatment as usual or experimental = peer support intervention) and the type of medical treatment of the patients (prescription or absence of CT treatment), within each study assessment (Baseline or Time 1, and Post-intervention or Time 2).
	S.H.24 Participants in the experimental condition will exhibit significantly higher levels of psychological resilience over time immediately following the application of the intervention compared to those in the control condition.	S.O.24 Evaluate the potential differential change by study condition in resilience before (T1) and immediately after (T2) the application of the intervention.
	S.H.25 The expected improvements in the resilience of participants in the experimental condition will be influenced by the benefits of the intervention on their levels of social support and diurnal cortisol profiles.	S.H.25 To study the predictive value of potential changes in social support and diurnal cortisol levels by study condition, occurring between the time before (T1) and immediately after (T2) the application of the intervention, on the expected increases in resilience.

Note. G.H. = General Hypothesis; S.H. = General Hypothesis; G.O. = General Objective; S.O. = Specific Objective

METHODS

A summarized description of the methodologies employed in each study included in this thesis is provided below.

Study #1

1. PROCEDURE

Study 1 was founded on the development of a systematic review, the steps of which adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This approach was instrumental in ensuring the comprehensive and accurate reporting of the essential, evidence-based items (Liberati et al., 2009).

1. Information Sources and Search Strategy

Three electronic databases, namely, PubMed, PsycINFO, and Web of Science were searched from their inception up until March 27, 2020. Existing literature on psychological resilience in BC patients and survivors was captured using the following keyword combinations: resilien* AND breast cancer. Reference lists of all pertinent articles were diligently examined to identify additional relevant studies. Gray literature searches for the identification of non-indexed research were not conducted. For optimal organization and management, the retrieved articles were systematically cataloged using the Mendeley Reference Manager.

2. Eligibility Criteria

Quantitative studies were considered eligible for initial review if they met the following criteria: (1) participants were adult (≥18 years) BC patients or/and survivors at any stage of cancer (I-IV) or time point since diagnosis; (2) assessment of participants' psychological resilience was conducted using quantitative procedures; (3) studies were original articles published in either English or Spanish. They were excluded if: (1) merely mentioned resilience without empirical quantification; (2) participants were diagnosed with non-BC related illnesses or cancer types; (3) utilized qualitative methodologies for resilience evaluation; (4) were not published in English or Spanish; (5) were in the form of non-original publications (such as review papers, book chapters, editorials, abstracts, case reports, or dissertations).

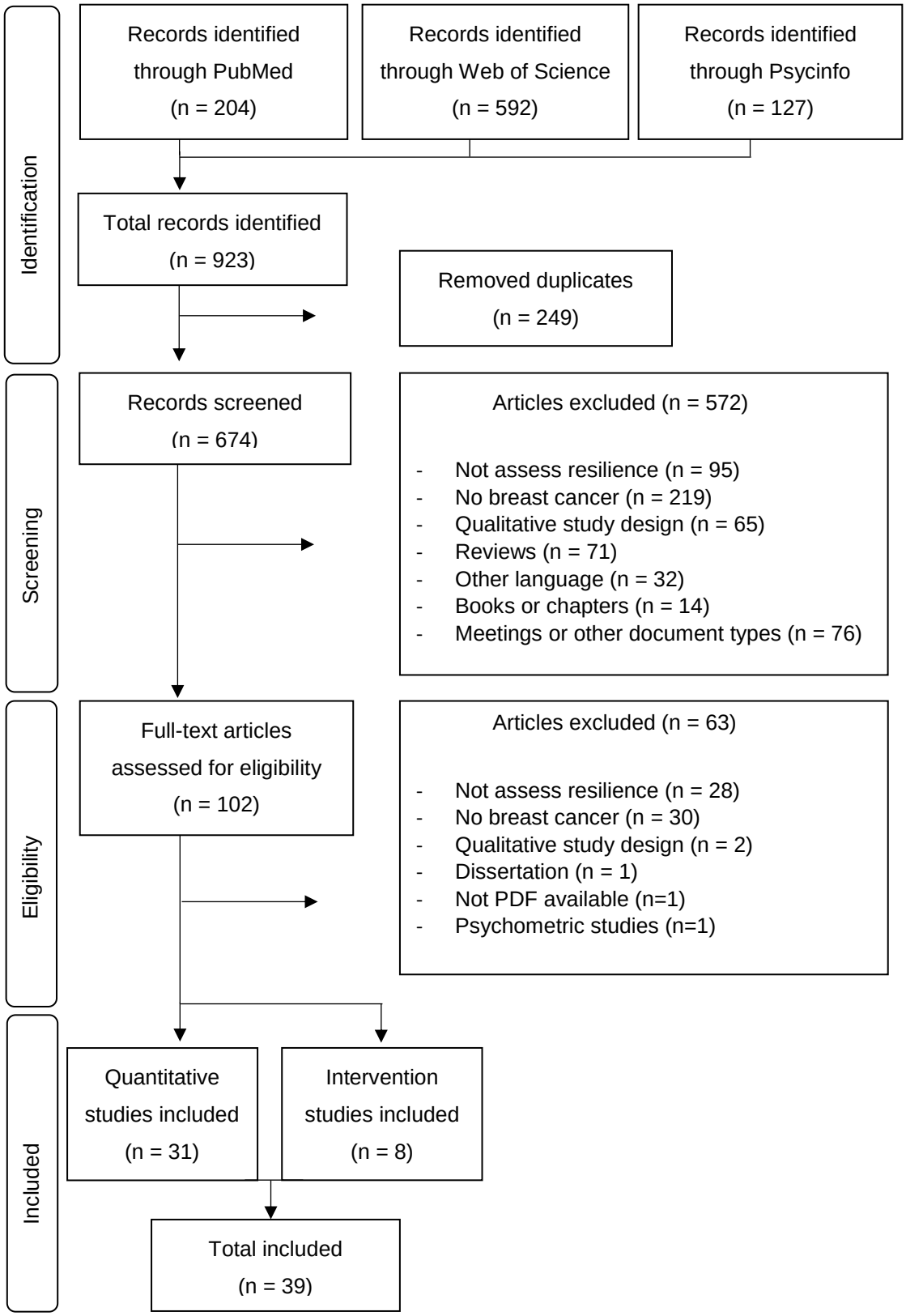
On the other hand, intervention studies were deemed eligible for initial review if they met the following criteria: (1) participants were adult (≥18 years) BC patients or/and survivors at any stage of cancer (I-IV) or time point since diagnosis; (2) resilience, as the primary outcome, was quantitatively assessed (3) studies included RCTs, non-RCTs, quasi-experimental or non-experimental designs; (4) studies were published in English or Spanish. They were excluded if: (1) participants were diagnosed with non-BC related illnesses or cancer types; (3) employed qualitative methodologies for resilience evaluation; (3) were published in languages other than English or Spanish.

2. STUDY SELECTION AND EXTRACTION PROCEDURE

Data were initially screened based on the predetermined eligibility criteria through a procedure mutually agreed upon by two independent reviewers – the author and one of the thesis supervisors. After the primary database search, 923 articles were identified (see Figure 1: PRISMA flowchart). Following the removal of duplicates, the titles and abstracts of the remaining studies were methodically examined to select those conforming to the eligibility requirements. A second-stage screening was independently conducted by the reviewers only when the inclusion criteria were met, involving a comprehensive review of the full documents. Any disagreements regarding inclusion were resolved through consensus.

For data organization, two distinct extraction templates were created for quantitative and intervention studies. For quantitative studies, extracted data encompassed authorship details, publication year, study design, sample size, participant characteristics, scales used to measure resilience, variables assessed in relation to resilience, and key findings. For intervention studies, the framework additionally captured intervention frequency, duration, and resultant outcomes, alongside the aforementioned details.

Figure 1: *PRISMA Flow Chart For Study #1: Study Selection.*



Study #2

1. PROCEDURE

Study 2 was based on the elaboration of a second systematic review that, as with the first, adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This approach ensured the thorough and evidence-based reporting of key items (Liberati et al., 2009).

1. Information Sources and Search Strategy

A comprehensive systematic review of existing literature examining the relationship between psychological resilience and cortisol was undertaken in the PubMed and Web of Science databases, spanning from their inception to January 11, 2022. The search strategy included the specific set of keywords 'resilienc*' and 'cortisol', linked by the Boolean operator “AND”. Eligible for inclusion in this review were peer-reviewed published articles and in-press manuscripts to ensure broad coverage of the latest research. Additionally, a thorough review of references from these articles helped identify studies potentially missed in the initial search. Grey literature was excluded to ensure the scientific validity of the sources. The selected articles were systematically organized in the Mendeley Reference Manager for effective analysis.

2. Eligibility Criteria

In the initial review phase, studies were considered eligible if they met the following criteria: (1) involvement of adult participants (≥18 years); (2) use of quantitative procedures to assess psychological resilience and cortisol; (3) a

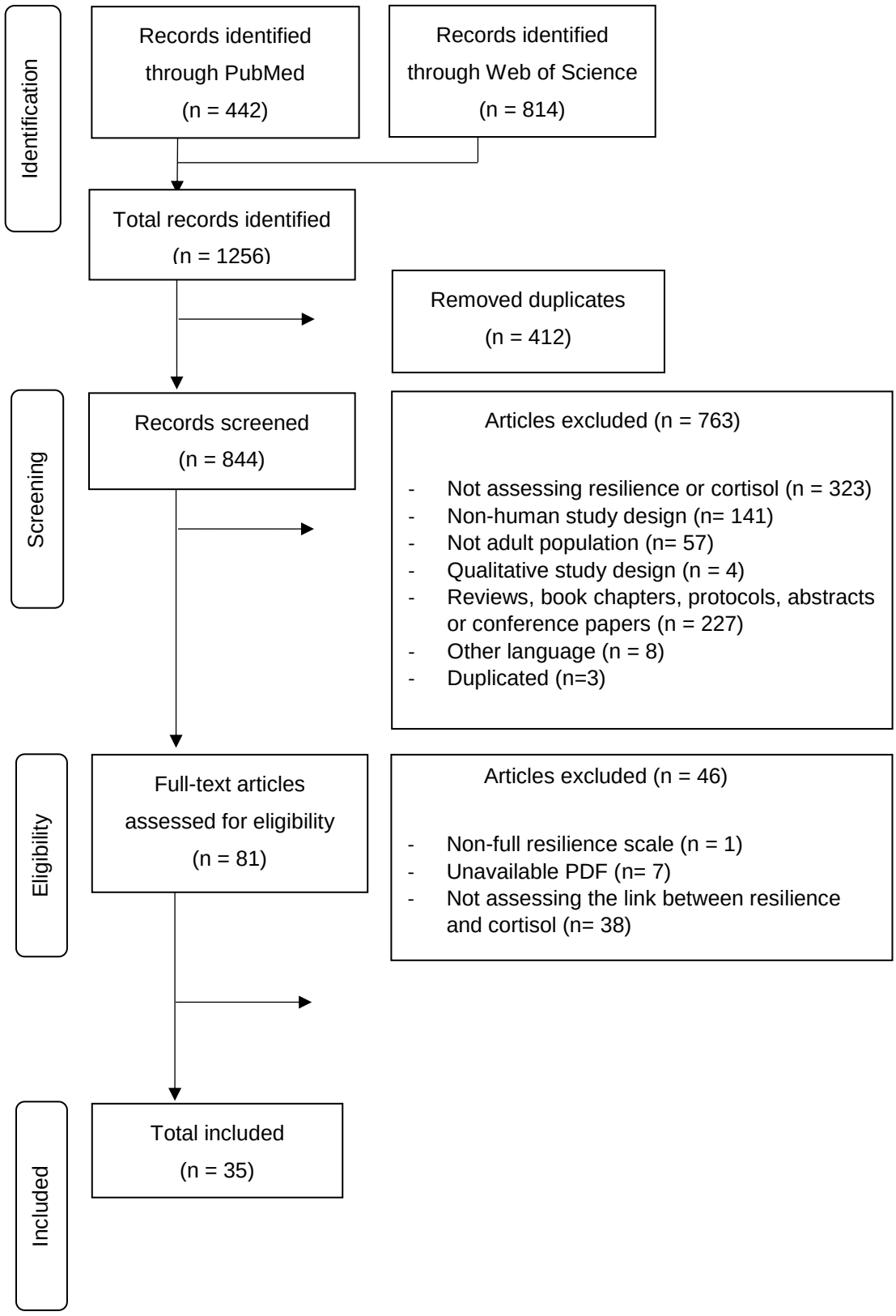
focus on exploring the link between resilience and cortisol; and (4) studies were original articles published in either English or Spanish.

While there were no constraints on the publication year, exclusions were made for quantitative studies that (1) did not involve human subjects; (2) only referenced resilience or cortisol without their empirical measurement; (3) relied on qualitative methods for evaluating participants' resilience; (4) were published in languages other than English or Spanish; and (5) were in forms such as review articles, books, chapters, commentaries, protocols, editorials, abstracts, case reports, or dissertations.

2. STUDY SELECTION AND DATA EXTRACTION PROCEDURE

In the initial database search, a total of 1256 articles were identified (see Figure 2: PRISMA flowchart). Three independent evaluators (the author, a thesis supervisor, and a co-author) screened the data, adhering to pre-established eligibility criteria and a mutually agreed-upon screening procedure. Following the initial removal of duplicates, 763 articles were excluded based on titles and abstracts for reasons like irrelevant content and language barriers. The second-stage screening of the remaining 81 articles, conducted independently by the reviewers, resulted in 35 articles meeting the inclusion criteria. Any possible discrepancies regarding study inclusion were harmonized via consensus discussions. The data extracted from the qualifying articles included study design, sample characteristics, instruments for measuring resilience, parameters and methods used for cortisol analysis, and key findings.

Figure 2: *PRISMA Flow Chart For Study #2: Study Selection.*



Study #3

1. STUDY DESIGN

Study 3 utilized a descriptive cross-sectional design to investigate the impact of perceived social support and salivary cortisol on psychological resilience among newly diagnosed women with BC. All research procedures were conducted in compliance with pertinent national legislation and received approval from the appropriate Ethics Committee.

2. DESCRIPTION OF THE SAMPLE

Participants in this study consisted of 132 women who had recently been diagnosed with BC. Recruitment took place between June 2019 and August 2022 at Onkologikoa hospital, an oncological hospital located in the Basque Country (Spain). The sample was focused on women receiving their first-time cancer diagnosis, as it was believed that a prior cancer diagnosis could potentially influence their psychological state. Thus, the inclusion criteria for this study were as follows: (1) non-pregnant women aged between 18 and 70 years with stage I-III BC; (2) a first-time diagnosis of cancer received within the last two months; and (3) without a history of known mental disorders. Exclusion criteria included women with metastases. Eligible participants were informed about the study procedures and were offered a thorough informed consent form, allowing them sufficient time for thoughtful consideration before deciding whether to participate.

3. DATA COLLECTION

1. Procedure for salivary cortisol collection

After obtaining signed informed consent, participants were provided with four saliva sample collection tubes, with instructions to collect the samples at four specific times on the same day they were to complete the questionnaires. The stipulated moments included the moment immediately after waking up, 30 minutes after getting up, the period between 13:00 and 13:30 hours, and the span between 20:00 and 20:30 hours, all within the course of a single day. To ensure the purity of the saliva samples and minimize the risk of contamination from particulate matter or any potential interfering substances, participants were specifically advised to refrain from eating, drinking, or brushing their teeth for at least 30 minutes before each sample collection. Following the cortisol self-collection, participants were responsible for storing the saliva samples in their home freezers at a temperature of 4°C. The following day, they were required to deliver both the frozen saliva samples and the completed questionnaires to the research team.

2. Psychological and physiological variables

In the realm of psychological assessments, the study incorporated the Medical Outcomes Study-Social Support Survey (MOS-SSS) and the Resilience Scale Short Version (RS-14). The MOS-SSS, developed by Sherbourne and Stewart in 1991, serves as a self-administered, multidimensional indicator of social support. It evaluates the presence of various support dimensions through a set of 19 items employing a 5-point Likert scale, spanning from 'never' (1) to

'constantly' (5). In the Spanish adaptation of the questionnaire for the oncology population (Costa Requena et al., 2007), researchers identified that the MOS-SSS is grouped into three main factors: (a) emotional/informational support and positive social interaction, (b) affective support, and (c) instrumental support. The total scale score is calculated by summing all the items (range 19-95). In this study, Cronbach's Alpha coefficient for the total scale and the subscales of affective support, emotional support, and instrumental support was calculated at .949, .783, .948, and .817, respectively, indicating acceptable to high internal consistency.

The RS-14, a concise 14-item Spanish adaptation of Wagnild and Young's resilience scale originally formulated in 1993, was employed to measure the participants' resilience levels (Sánchez-Teruel & Robles-Bello, 2015). In this context, resilience is regarded as the degree of competence and self-acceptance perceived by the patients. Each of the 14 items in the RS-14 questionnaire elicits responses on a 7-point Likert-type scale, ranging from '1' (strongly disagree) to '7' (strongly agree), resulting in a cumulative score range of 14 to 98. Specifically, scores below 65 are indicative of low resilience, those failing within the range of 65 to 81 reflect moderate resilience, while exceeding 81 represents high levels of resilience (Miroševič et al., 2019). In this study, the reliability coefficient for psychological resilience was 0.897, demonstrating strong internal consistency.

Saliva samples were centrifuged at 3000 rpm for 15 minutes to eliminate mucins and were subsequently stored at -80°C. Cortisol concentrations were determined using an enzyme immunoassay kit (Salimetrics, Stratech Scientific, UK), with measurements performed at 450 nm utilizing a Synergy™ HT plate

reader (Bio-Tek Instruments, Inc., VT, USA). The cortisol assay exhibited a sensitivity of .007 µg/dL, with average coefficients of variation for both intra-assay and inter-assay precision at 1.8% and 1.97%, respectively. Lastly, the Area Under the Curve with respect to the ground (AUCg) was computed to evaluate participants' diurnal cortisol production based on the cortisol data obtained.

4. DATA ANALISYS

Data were analyzed with IBM SPSS Statistics version 28, for which a first screening search for outliers and assumptions of normality was conducted. For variables that did not follow a normal distribution, Bloom's transformation was applied. Spearman correlation analyses were employed to explore potential relationships among the diverse study variables. Regression analyses were used to assess the effects of AUCg, the different dimensions of social support, and their interactions on resilience, while adjusting for the following variables: type of initial treatment (chemotherapy or surgery), type of surgery (mastectomy or lumpectomy), and use of psychotropic drugs. To assess significant interactions, moderation analyses with the Johnson–Neyman technique were utilized (Hayes, 2013).

Study #4

1. STUDY DESIGN

Study 4 was based on the implementation of a RCT to investigate the biopsychosocial impact of a one-to-one peer support-based psychosocial intervention in a sample of women with BC (National Institutes of Health Clinical Trial NCT05077371). The procedures performed in this study were in strict compliance with the ethical standards set forth in the Declaration of Helsinki, aligned with pertinent national regulations, and received approval from the respective Ethics Committee (registration number PI2018068). In conducting this research, the Consolidated Standards of Reporting Trials (CONSORT) guidelines were meticulously followed. All participants provided written consent prior to their involvement in the study.

2. DESCRIPTION OF THE SAMPLE

The study involved 121 newly diagnosed BC patients recruited from Onkologikoa hospital, an oncology hospital located in the Basque Country (Spain) by two researchers (the author and one thesis supervisor) from June 2019 to August 2022 (see Figure 3). Patients were approached following their consultations for diagnosis and treatment plan consultations, and were stratified based on primary treatment, which was either surgery or neoadjuvant chemotherapy. Recruitment took place within two weeks before primary treatment or after the first chemotherapy session. Out of 247 potential participants, those eligible were informed individually about the study, presenting it as an opportunity to share concerns with others who had undergone similar

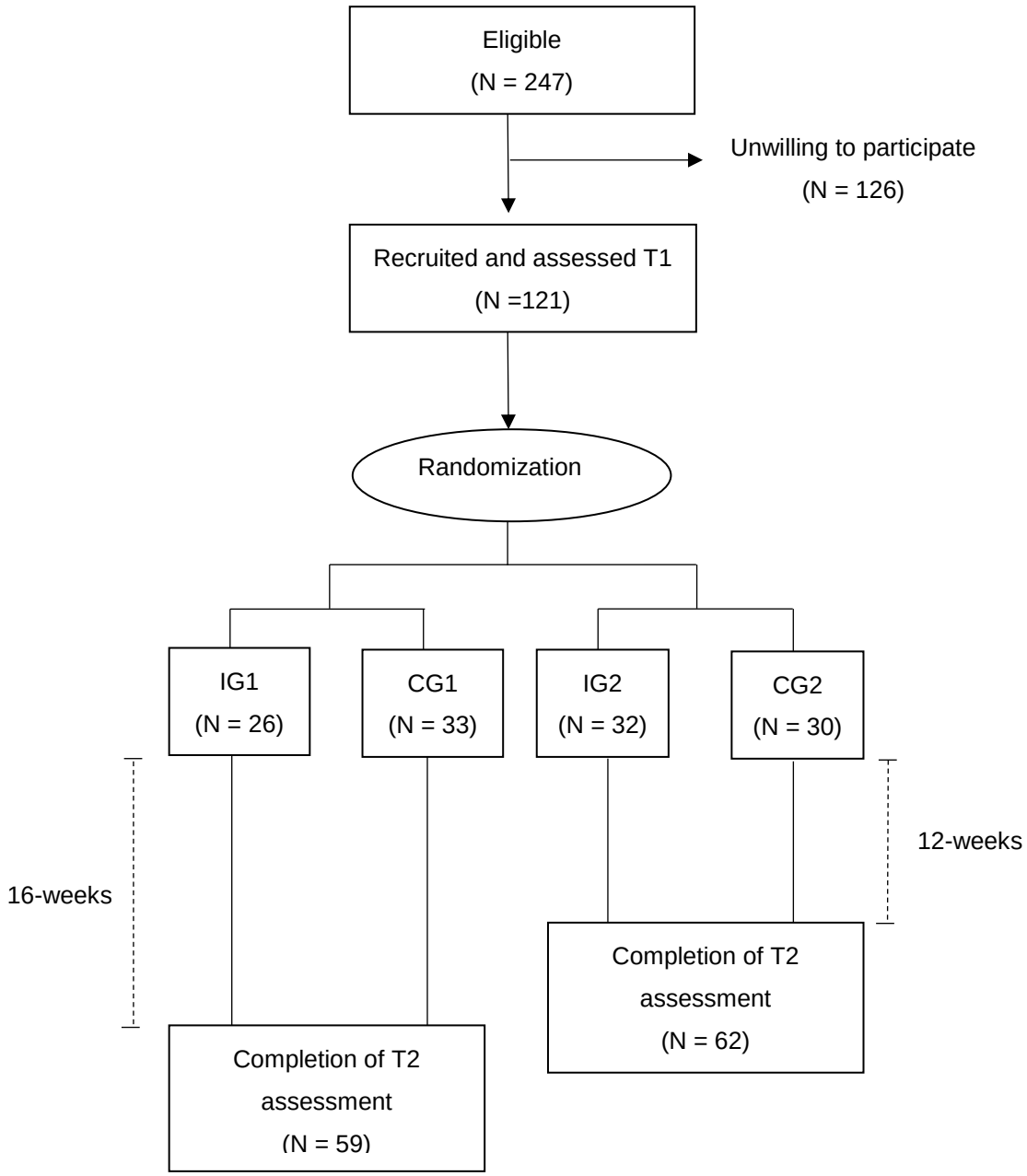
experiences. Participants were also notified that their involvement in the study was voluntary and would not be subject to any form of remuneration. The inclusion criteria for participants were (1) women aged 30-70 with stage I-III BC, (2) diagnosed within the past two months, (3) not having major psychiatric conditions (DSM-V criteria), and (4) Spanish-speaking. The exclusion criteria included (1) a prior history of cancer (excluding minor skin cancer) and (2) metastasis. After providing informed consent, participants were given psychosocial self-report measures and instructed to collect four salivary cortisol samples at specific times on a single day (upon awakening, 30 minutes after, at 1:00-1:30 pm, and 8:00-8:30 pm). They were advised to avoid eating, drinking, or brushing their teeth 30 minutes before sample collection and to store samples at 4º C. Baseline data collection (Time 1; T1) and a follow-up after 12-16 weeks post-intervention (Time 2; T2) were conducted at the hospital.

3. DESCRIPTION OF SUPPORT PROVIDERS

Peer support providers (hereinafter referred to as volunteers) consisted of 14 disease-free BC survivors recruited between June and November 2017 from Onkologikoa hospital, from “Active Patient” program from Osakidetza, a self-care education program of the territorial health system, and from Katxalin, a BC association in the Basque Country (Spain). The recruitment process involved the participation of oncologists and nurses, public talks, and the distribution of informative letters. The inclusion criteria for volunteers were (1) being women aged 18 or older, (2) having completed cancer treatment at least one year prior to recruitment (including surgery, chemotherapy, and radiation therapy), and (2)

having no diagnosis of major psychiatric disorders (DSM-V criteria). The sole exclusion criterion was the presence of metastasis.

Figure 3: *Experimental Design and CONSORT Flow Diagram of Participation in Study #4*



Note. IG1 = Intervention Group I; IG2 = Intervention Group II; CG1 = Control Group I; CG2 = Control Group II.

Interested women contacted one of the study researchers (one of the author's thesis supervisors) to confirm their eligibility. They then underwent an individual semi-structured psychological interview to evaluate their mental and physical recovery, ensuring minimal psychological impact from participation in the program. This interview included the completion of a battery of psychological measures, as detailed in Table 2.

Table 2. *Psychological Variables Assessed in the Initial Interview of Volunteers Prior to Their Participation in the Study*

Variable	Measures
Personality	The Big-5 Inventory (BFI) (Benet-Martínez & John, 1998; John, 1990)
Coping	Brief Coping Orientation to Problems Experienced Questionnaire (COPE-28) (Carver, 1997; Morán et al., 2009)
Anxiety and Depressive Symptoms	Hospital Anxiety and Depression Scale (HADS) (López-Roig et al., 2000; Zigmond & Snaith, 1983)
Resilience	Brief Resilience Scale (RS-14) (Sánchez-Teruel & Robles-Bello, 2015; Wagnild & Young, 1993)
Emotional Regulation	Emotion Regulation Questionnaire (ERQ) (Cabello et al., 2012; Gross & John, 2003)

Selected volunteers engaged then in a 3-month Psychoeducational and Emotional Intelligence-based training supervised by two study researchers (the author and one thesis supervisor) aimed to equip them with the necessary skills for effective session management and patient follow-up. This training encompassed six 3-hour workshops (18 hours total) conducted by psychology professionals, covering topics such as BC, healthy habits, components of

emotional intelligence, communication skills, and the importance of confidentiality.

Throughout the study, the volunteers attended sixteen 3-hour quarterly supervision meetings (48 hours total) led by the two study researchers. These sessions were designed to assess the intervention, pinpoint training gaps, and address the challenges faced during sessions. Additionally, they also sought to foster group cohesion and emotional support among volunteers by facilitating the sharing of personal experiences related to patient support. Volunteers were also encouraged to document the challenges encountered during the support sessions with patients for subsequent analysis.

4. PROCEDURE

Upon recruitment, participants underwent an initial assessment (T1) and were randomly assigned to the intervention [Intervention Group I (IG1); Intervention Group II (IG2)] or control groups [Control Group I (CG1); Control Group II (CG2)], based on their specific of medical treatments. This allocation, done via balanced block randomization, remained undisclosed until after T1. The assignment was executed in a 1:1 ratio across four groups, randomized by one study researcher (one of the author's thesis supervisors) using Microsoft Excel (2016 version).

Allocation of participants to intervention groups was contingent on their particular treatment regimen: IG1 (n=27) included patients scheduled for chemotherapy treatment (adjuvant or neoadjuvant), whereas IG2 (n=32) comprised patients undergoing shorter adjuvant radiotherapy treatment without

chemotherapy. Control groups were similarly aligned: CG1 (n=32) for those receiving chemotherapy and CG2 (n=30) for patients with shorter adjuvant radiotherapy treatment.

The intervention for IG1 spanned 16 weeks and 12 weeks for IG2, in alignment with their respective treatment durations. Control groups received TAU. The second assessment (T2) occurred at the intervention's end, 16 weeks after T1 for IG1 and CG1, and 12 weeks for IG2 and CG2, resulting in 4-month and 3-month follow-up periods for these groups respectively.

1. Peer Support Intervention

The one-to-one peer support program was designed to provide newly diagnosed BC patients with a space in which to communicate their concerns, obtain practical information, and receive social support from survivors who faced the same challenge. Specifically, the program was built on the premise that exchanging personal experiences with individuals who have successfully navigated similar difficulties normalizes patient experiences and facilitates their psychological adjustment to the oncological process. The intervention comprised 6 to 8 biweekly sessions, either in-person, by phone, or virtually, tailored to the patient’s treatment schedule — 8 for patients prescribed chemotherapy treatment and 6 for those undergoing a shorter radiotherapy treatment. These sessions, flexible in duration and format, focused on fostering a supportive and open environment without predefined discussion topics. Patients were matched with volunteers by two researchers (the author and one thesis supervisor), considering factors such as diagnosis and medical treatment, age, household

composition, and personality. This matching process started with an initial exchange of information while respecting confidentiality. Volunteers, who often supported multiple patients, received individual psychological supervision post-sessions from the aforementioned researchers to discuss their experiences and address any potential risk of retraumatization. During these debriefing sessions, volunteers were also asked about the format and duration of their sessions with patients for data recording (average duration of sessions = 47.07 minutes).

2. TAU

Women in the control group received TAU, which included detailed information about the psycho-oncology services available at the hospital, highlighting the significance of consulting these specialists as needed. Ethically, control group participants were not dissuaded from pursuing peer support if required.

5. PSYCHOLOGICAL AND PHYSIOLOGICAL VARIABLES

1. Resilience

The Spanish version of the 14-item Wagnild Resilience Scale (RS-14) was employed to evaluate participant resilience levels (Sánchez-Teruel & Robles-Bello, 2015). The RS-14 presents a 7-point Likert scale, ranging from "1" (strongly disagree) to "7" (strongly agree), resulting in a possible total score between 14 and 98. Scores below 65 reflect low resilience, 65-81 denote moderate resilience, and scores exceeding 81 are indicative of high resilience (Miroševič et al., 2019). The scale's reliability coefficient was established at 0.895 and .932 at T1 and T2, respectively.

2. Social Support

The Spanish adaptation of the Medical Outcomes Study-Social Support Survey (MOS-SSS) for cancer patients was used to measure patients' perceived availability of social support (Costa Requena et al., 2007; Sherbourne & Stewart, 1991). This adaptation of the survey, which consists of 19 items rated on a 5-point Likert scale (from "never" = 1 to "all the time" = 5), classifies social support into three factors: groups social support into three factors: a) emotional/informational support and positive social interaction, b) affective support, and c) instrumental support. The total score, ranging from 19 to 95, is obtained by summing all item responses. Cronbach's alpha coefficients for the total scale and the subscales of affective support, emotional support, and instrumental support were calculated to be .950, .779, .949, and .826, respectively, at T1, and .967, .895, .961, and .897, respectively, at T2.

3. Salivary Cortisol

Saliva samples were initially centrifuged (at 3000 rpm for 15 minutes) to eliminate mucins and then frozen at -80ºC. Once thawed and agitated, samples were analyzed using the Salimetrics high-precision enzyme immunoassay kit (Stratech Scientific, UK). Measurements were taken at 450 nm with the Synergy™ HT reader (Bio-Tek Instruments, USA). The assay's sensitivity was noted as 0.007 µg/dL, with average intra-assay and inter-assay variances of 1.8% and 1.97%, respectively. AUCg was finally calculated to quantify the total daily cortisol production for each participant in the study.

6. DATA ANALISYS

Data were analyzed with IBM SPSS Statistics version 28. An initial screening for outliers and assumptions of normality was performed, applying Bloom's transformation for variables that did not follow a normal distribution. Analysis of Variance (ANOVA) was employed to evaluate group differences at each study checkpoint (T1, T2), with repeated measures ANOVA particularly focused on analyzing the varied resilience shifts among groups from T1 to T2. The initial sample size was determined using G*Power, accounting for interaction effects in repeated-measures ANOVA and adopting an effect size criterion suggested by Cohen (1988). To explore whether variations in cortisol and social support between T1 and T2 could predict shifts in resilience, a Multiple Linear Regression analysis was performed.

RESULTS AND DISCUSSION

This section begins with a summary of the results obtained from each of the four studies framed within this doctoral thesis, accompanied by a brief and updated discussion of each case. To ensure coherence, these summaries have been organized according to the study hypotheses. For an in-depth and exhaustive examination of both the results and their corresponding discussions, the reader is referred to Section III (Appendices: Published Manuscripts and Manuscripts Under Review). This section concludes a general discussion aimed at connecting the findings and the practical implications of each study.

1. SUMMARY OF RESULTS AND DISCUSSION

Study #1

The first article of this doctoral thesis aimed to systematically review the available literature on studies conducted on psychological resilience in BC care (G.O.1). Its objectives were twofold: firstly, to identify the biopsychosocial factors that contribute to the development of resilience in women with BC, and secondly, to compile and integrate evidence on interventions that might significantly strengthen it.

The systematic search culminated in the identification of 39 quantitative articles, comprising 31 cross-sectional and longitudinal studies, and 8 intervention studies, all incorporated into the study after their compliance with the defined eligibility criteria was confirmed (S.H.1; S.H.6). Regarding the design, sample characteristics, measures for assessing resilience, variables related to it,

and features of the intervention programs, the studies exhibited significant variability and heterogeneity (S.H.2; S.H.7).

Consistent with a segment of the overall hypothesis (G.H.1), findings drawn from cross-sectional and longitudinal investigations (n = 31) indicated that the resilience of women diagnosed with BC was influenced by a confluence of multiple variables: clinical, sociodemographic, psychosocial, and physiological. Notably, psychosocial determinants emerged as the predominant factors influencing resilience development (S.H.3). Thus, protective factors such as social support, various dimensions of QoL (i.e. physical, cognitive, social, and emotional), and adaptive coping strategies were found to be relevant contributors in facilitating resilience in both BC patients and survivors (S.H.4). In terms of adaptive coping, strategies predominantly based on active coping and positive acceptance were found to be most commonly linked to higher resilience levels among these women. These findings echo the trajectory of previous research conducted in cancer populations (Dong et al., 2022; Llewellyn et al., 2013), suggesting that the adoption of both proactive and problem-focused strategies which involve taking direct action on the situation, alongside those aimed at acknowledging and accepting the unchangeable reality of the diagnosis, may facilitate women's psychological resilience to the disease throughout the BC continuum (Lai et al., 2020; Tu et al., 2020). Likewise, evidence indicates that these strategies may facilitate more effective social support seeking and utilization (Manne et al., 2018; Siquiera-Costa et al., 2017; Somasundaram & Devamani, 2016), with social support serving as a mediating factor in the

relationship between health-related QoL and resilience in newly diagnosed BC patients (Zhou et al., 2022a).

On the other hand, the study also identified depressive and anxious symptoms, in addition to non-adaptive coping strategies (e.g., anxious preoccupation, negative affect, or cognitive avoidance), as the predominant adverse variables inversely affecting participants' resilience. Anxiety and depression symptoms are prevalent medical health conditions throughout the continuum of cancer (Grassi et al., 2023), being psychological manifestations that beyond their association with diminished OS and QoL (Antoni et al., 2023), may exacerbate the challenges faced in navigating and effectively managing cancer-related adversities (Brunault et al., 2016; Gold et al., 2016). While the use of non-adaptive strategies can often offer short-term relief, they can also impede the development of effective coping skills, and, with it, the opportunities for adequate emotional processing of the situation (Nipp et al., 2016). These results, in line with the hypothesis (S.H.5), point to the enhancement of resilience as a promising factor for the development of adaptive competencies and the prevention of psychological distress. Moreover, the fact that resilience was also, albeit to a lesser extent, associated with clinical and physiological variables indicative of better physical and functional adaptation, confirms prior (Ristevska-Dimitrovska et al., 2015) and subsequent evidence (Faroughi et al., 2023) to the publication of the present study regarding its inherent potential to improve the health status of patients undergoing the oncological process.

In line with the remaining segment of the general hypothesis (G.H.1), evidence derived from intervention studies (n = 8), which focused on examining

the effect of resilience-enhancing interventions, predominantly reported significant effects on the resilience of women with BC (S.H.8). Besides incorporating resilience itself as a fundamental component of their training programs, the resilience-enhancing interventions also promoted resilience factors through the facilitation of adaptive coping strategies, self-esteem, optimism, and increased perception of social support, among others. These interventions often included psychoeducational components aimed at improving self-perceived awareness and mastery over mental health and emotional intelligence-related issues. The majority of the intervention studies were found to be effective in promoting resilience among BC patients and survivors, with significant improvements identified in 6 of the 8 studies included in this work (S.H.9). While these findings align with those reported from prior investigations on resilience-enhancing interventions in other cancer populations (Ludolph et al., 2019; Seiler & Jenewein, 2019; Sihvola et al., 2023), the high variability identified in terms of size and characteristics of the samples, along with the considerable divergence in the theoretical frameworks underpinning the various components and designs of the intervention programs, posed challenges to draw valid conclusions regarding their effectiveness. The latter aspect, which according to Leppin et al (2014) remains a major limitation in the resilience literature, justifies the need to investigate the most suitable theoretical framework to guide the development of these programs. This should be coupled with the use of standardized methods that allow for the extraction of reliable conclusions about their efficacy at different stages of the BC continuum. Beyond improvements in resilience, studies also reported significant post-intervention benefits across a wide range of psychosocial variables (e.g., distress symptoms, body image, self-

esteem, self-efficacy, future perspective, and hope, perceived social support, and QoL-related cognitive and emotional functions) and BC treatment-related clinical variables (e.g., fatigue, nausea, vomiting, constipation, and QoL-related physical functions). These results, which support the hypotheses (S.H.10; S.H.11), provide evidence of the potential of resilience-enhancing interventions to promote the psychological and physical well-being of women with BC, and highlight the need for further research due to the still limited reliable evidence of their biopsychosocial effects in the oncology setting (Tan et al., 2019). Furthermore, it should be noted that apart from physiological variables such as sleep quality and physical exercise status, no interventional, cross-sectional, or longitudinal research was identified in this study exploring the relationship between resilience and immune and neuroendocrine biomarkers related to cancer adaptation and survival. In this regard, although still limited, there is evidence suggesting that, aside from its potential influence on the immune response via inflammatory markers (Berg et al., 2017), resilience may also exert regulatory actions on the neuroendocrine response to stress through the HPA axis (Osório et al., 2017; Petros et al., 2013; Russo et al., 2012). As such, it has been proposed that it is specifically through the mechanism of cortisol, the primary glucocorticoid hormone secreted by the adrenal cortex that serves as a peripheral marker of hypothalamic activity (Dubey & Boujoukos, 2004), that resilience mitigates the anti-salutogenic effects of the physiological stress response (Gaffey et al., 2016). This fact underscores the imperative that future studies incorporate in their designs the exploration of both the biological correlates of resilience and the physiological effects of resilience-enhancing interventions for the development of a more integrative approach to BC care.

Study #2

With the aim of addressing part of the previously exposed underexplored research gap on the putative modulatory effect of resilience on the physiological response to stress, the second study of this doctoral thesis aimed to systematically review the current literature on investigations exploring the relationship between resilience and cortisol in adult populations (G.O.2). Specifically, the study intended to provide evidence to discern the particular methodological conditions under which the relationship between resilience and cortisol occurred, distinguishing among the different 1) scales for measuring resilience, 2) cortisol measurement matrices (i.e., hair, saliva, serum, or urine), and 3) strategies for quantifying cortisol [e.g., cortisol awakening response (CAR), 24-hour integrated cortisol levels, or a single time-point mean net cortisol levels, among others] employed by the studies. Due to the limited prior research on the topic and its novelty, the systematic search extended beyond oncologic populations to include both clinical and non-clinical populations for a comprehensive perspective of the matter in question.

The extensive systematic search resulted in the inclusion of 35 articles, meticulously selected after confirming their compliance with the study's eligibility criteria (S.H.12). All articles employed a quantitative methodology, and mostly followed a cross-sectional design (n = 21), with the remaining studies having either an intervention (n = 9) or a longitudinal design (n = 5). Besides the study design, elements that displayed notable variability among the selected studies included sample size, its characteristics, the instruments utilized for measuring resilience, and the methods employed for cortisol analysis (S.H.13).

The results of this study were systematically categorized based on (1) the secretion period (short and long-term) encompassed by the cortisol matrices employed in the studies, and (2) the specific diurnal, phasic (acute), and tonic (basal) elements of the HPA production to which they alluded and their interconnections with resilience. This classification responded to the evidence suggesting that cortisol can reflect differentiated physiological mechanisms within the HPA axis, dependent on their collection timing and the particular measurement parameters used (Dobler et al., 2019; Epstein et al., 2021; Y. Jiang et al., 2019; Short et al., 2016). In partial fulfillment of the general hypothesis (G.H.2), studies revealed significant positive and negative correlations between resilience and cortisol levels, in addition to instances of non-significant or null associations between these variables. Notably, a majority of the studies (N = 19 out of 35) (S.H.15) reported significant correlations between resilience and cortisol, which were discerned across the various diurnal, acute, and basal components of the HPA axis response, as indicated by the short- and long-term secretion intervals of the cortisol biospecimens utilized in the investigations. Furthermore, in contrast to cross-sectional and longitudinal design studies, which discerned notable associations between resilience and cortisol in approximately 40-50% of instances, a predominant proportion of intervention-based studies (80%) established significant correlations between these variables. These findings underscore the potential role of resilience as a modifiable, and thus, trainable factor in modulating the physiological response to stress, a notion that has gained substantial validation from recent research (Bergquist et al., 2021; Harvanek et al., 2021). Surprisingly, according to the author's knowledge, only a single study thus far has delved into the influence of a resilience-enhancing

intervention on cortisol concentrations in adult subjects (Arch et al., 2014), following the implementation of a brief training course in self-compassion (a well-known resilience factor), without finding significant changes in salivary cortisol among female undergraduates. Given the recognized potential of resilience in regulating the stress response, it is imperative that future resilience-enhancing interventions assess their effects on the cortisol levels of adult populations in clinical and non-clinical settings.

Contrary to the hypothesis (S.H.16), a lack of clear directionality was identified in the results of both the intervention studies and the cross-sectional and longitudinal studies. This absence of a definite trend precluded confirmation of the previously suggested protective effect of resilience in warding off alterations in circulating cortisol, which is often associated with psychopathological states resulting from sustained stress (Zapater-Fajarí et al., 2021; Zautra et al., 2010). It is believed that the inability to discern the nature of the interaction between the two variables was attributable, on the one hand, to the presence of unaccounted third variables that might be modulating this relationship. For instance, in the studies by Zapater Fajarí et al (2021) and Ruiz-Robledillo et al (2017), the authors found that variables such as coping strategies and anger, respectively, mediated the relationship between resilience and the acute cortisol response to a psychosocial laboratory stressor in both healthy adults and caregivers of children with autism spectrum disorder. Their results, which pointed to active coping strategies and decreased feelings of anger as mechanisms through which resilient individuals bounce back from stressful life experiences, underscored the need to incorporate third variables into studies that

explore resilience to elucidate potential mechanisms that underlie variations in stress regulation among individuals (Wu et al., 2013). On the other hand, another reason that is considered to have hindered the establishment of a clear direction indicated by the results is the significant heterogeneity observed regarding the backgrounds of the populations included in the studies, the questionnaires employed to measure resilience, and the biological matrices, measurements, and time points used for both cortisol recording and sampling, among other variables. Specifically, the latter aspect may have distinctively influenced the findings of the present study, given that the majority of studies (6 out of 7) failing to discern associations between resilience and short-term basal tonic cortisol levels relied exclusively on a single morning saliva or plasma sample to evaluate HPA axis activity. Due to the notable day-to-day variability in plasma and salivary cortisol levels previously documented (El-Farhan et al., 2017; Matsuda et al., 2012), this chosen methodological approach may have given rise to false negatives, aligning with the hypothesis (S.H.17).

Another noteworthy aspect of the studies included in this systematic review is that only one of them was conducted in cancer patients (Sharpley et al., 2018), which, after assessing the basal salivary cortisol response of prostate cancer patients, found no significant associations between resilience and the former. This fact, which aligns with our hypothesis (S.H.14), further underscores the ongoing necessity for additional studies that assess the relationship between both variables in oncology populations. This need arises from the proven beneficial effects of resilience on mental and physical health outcomes closely

associated with diurnal cortisol secretion (Caulfield & Cavigelli, 2020; McGowan et al., 2018).

Although the substantial methodological heterogeneity characterizing the studies included in the present systematic review eluded the possibility of reaching definitive conclusions about the direction of their results, the data collected therein did indicate a consistent association between resilience and cortisol levels. This observation underscores the need for further research in a broader set of clinical and nonclinical populations, focusing on specific mechanisms and potential confounders that may comprehensively elucidate this relationship. Considering the well-established health-promoting properties of resilience (Chmitorz et al., 2018; Dulin et al., 2018), future research should focus on examining the impact of resilience-enhancing interventions on cortisol as a key stress marker, to expedite their integration into early health strategies.

Study #3

The substantial relationship established in Study #2 between resilience and cortisol underpinned the motivation for the third study of this doctoral thesis. Addressing the need to explore the connection between the two variables in cancer patients, and informed by literature that recognizes social support as a critical protective factor in resilience (Zhang et al., 2017), Study #3 aimed to transversely investigate the predictive role of perceived social support and AUCg in the resilience levels of women with early BC (G.O.3).

The participants in this study consisted of 132 middle-aged women (M_{age} = 54.51 ± 8.29 years) who had recently been diagnosed with early-stage (I-III) BC. The majority underwent surgery as their primary treatment (surgery: n = 93; 70.5% vs. neoadjuvant chemotherapy: n = 39; 29.5%). The average resilience and social support scores observed among participants were moderate ($M_{Resilience}$ = 73.93 ± 14.14 and $M_{S.SupportTotal}$ = 13.67 ± 1.91, respectively), and the mean AUCg values (M_{AUCg} = 3.09 ± 2.48) turned out to be lower than those reported in previous studies conducted with early-stage BC patients (Kuhlman et al., 2017; Samayoa et al., 2022). The relationship between the study variables was explored through Spearman's correlation analysis, which revealed significant associations between resilience and both the overall score ($r = .38$, $p < .001$) and the affective, emotional, and instrumental subscales of social support ($r = .31$, $p < .001$; $r = .39$, $p < .001$; $r = .29$, $p < .001$, respectively), as well as non-significant associations between resilience and AUCg ($r = - .158$, $p = .07$). While the lack of statistical significance in the relationship between AUCg and resilience allowed for only partial fulfillment of the study hypothesis (S.H.18), the noted negative trend between these variables aligned with evidence suggesting enhanced cortisol regulation among highly resilient individuals (Nishimi et al., 2022; Petros et al., 2013). The observed trend thus contributes to supporting the hypotheses of previous studies that point to resilience as a potential buffer against the deleterious effects of diurnal cortisol alterations on health (Gaffey et al., 2016; Ruiz-Robledillo et al., 2017). These alterations might arise from distress and/or mood changes triggered by the news of the diagnosis, as has been uniquely observed in a yet-to-be-published work by the author on the afternoon-evening serum cortisol levels of women with early-stage (I-III) BC (Aizpurua-Perez et al.,

2024) (S.H.20). For its part, social support demonstrated a significant and positive association with resilience, interacting with the latter through its affective, emotional, and instrumental dimensions, as well as its overall score. These results, consistent with the hypothesis (S.H.19), indicate that the availability of social support at the time of diagnosis functions as an enhancer of resilience in BC patients, thereby reinforcing the findings of Study #1 and those subsequently published by various authors (Tao et al., 2022; Zhou et al., 2022a; Zhou et al., 2022b).

Moreover, the regression analyses aimed at determining the predictive value of the study variables on resilience, revealed that both the main effects of emotional support and its interaction with AUCg significantly predicted the resilience levels of participants, accounting for 28% of the latter's variance (R^2 = .283, $F_{(10, 117)}$ = 4,6091, $p < .001$). Specifically, moderation analyses conducted to explore the interaction between emotional support and AUCg showed that moderate (M = 3.08; $p < .05$) and low levels (M = .59; $p < .001$) of AUCg, unlike high levels (M = 5.55; p = .75), strengthened the positive contribution of emotional support to resilience. These results, which remained consistent regardless of the type of primary treatment (i.e. surgery or neoadjuvant chemotherapy), surgery procedure type (i.e. conservative surgery or mastectomy), and the use of anxiolytics and antidepressants, indicated that the protective and enhancing effect of emotional support on resilience was mediated by diurnal cortisol profiles in patients with medium and low levels of this hormone, in line with the study hypothesis (S.H.21). Drawing from these findings, it is proposed that this specific group of women could particularly benefit from interventions focused on

increasing the availability of emotional support at the time of diagnosis. Such interventions may be a valuable strategy for improving their resilience levels, contrasting with the assumptions of previous studies involving newly diagnosed BC patients which investigated the relationship between resilience and social support without considering the impact of cortisol levels (Gálvez-Hernández et al., 2018; Z. Wu et al., 2016). In turn, the lack of effectiveness of emotional support in stimulating the resilience of CB patients with high levels of AUCg suggests the need for more personalized and qualitatively distinct support beyond the standard to address their emotional needs. The literature's documented close relationship between elevated AUCg levels and the occurrence of anxious-depressive symptoms and stress (Baliyan et al., 2021; Merswolken et al., 2013) implies that these women might be particularly susceptible to the adverse effects of the diagnosis, thereby increasing their likelihood of developing stress-related psychological disorders throughout their treatment and ongoing survival period. These findings, therefore, point to the assessment of resilience and diurnal salivary cortisol at diagnosis as strategies of high informative value. They are believed to contribute to improving decision-making regarding the design of psychotherapeutic interventions that, in addition to preventing the onset of distress, optimize patients' adjustment to the oncologic process.

The current study, in alignment with the general study hypothesis (G.H.3), demonstrated that the resilience of newly diagnosed BC patients is partially influenced by social support and diurnal cortisol secretion. By being the first article, to the best of the author's knowledge, to simultaneously assess resilience,

cortisol, and social support in BC patients, it establishes a comprehensive framework for evaluating psychobiological markers and pinpointing patients at risk before the emergence of stress-related disorders.

Study #4

The findings of the Study #3 underscored the pivotal role of emotional support in reinforcing resilience among newly diagnosed BC patients, thus pointing to the potential of emotional support based resilience-enhancing interventions, such as peer support, to alleviate the adverse psychological impact of the oncological process. Building upon the identified need in the previous study for personalized care delivery programs tailored to women with different diurnal cortisol profiles, the fourth study of the present doctoral thesis sought to analyze the efficacy of a RCT assessing the impact of a one-to-one peer support intervention on the psychological resilience, perceived social support, and AUCg levels of women with early BC (G.O.4).

Participants were 121 women newly diagnosed women with early-stage (I-III) BC (M_{age} = 54.29 ± 8.47), most of whom received surgery as primary treatment (surgery: n = 84; 69.42% v. neoadjuvant chemotherapy: n = 37; 30.57%). The average resilience and social support scores observed at T1 among women belonging to IG1, CG1, IG2, and CG2 were found to be moderate ($IG1_{Resilience}$ = 71.60 ± 16.33 and $IG1_{S.SupportTotal}$ = 13.4 ± 1.87; $CG1_{Resilience}$ = 78.03 ± 8.35 and $CG1_{S.SupportTotal}$ = 13.52 ± 3.32; $IG2_{Resilience}$ = 74.12 ± 13.23 and $IG2_{S.SupportTotal}$ = 13.69 ± 1.98; $CG2_{Resilience}$ = 76.88 ± 10.52 and $CG2_{S.SupportTotal}$ = 14.01 ± 1.23),

and their mean AUCg values instead lower than those reported in previous studies in early-stage BC patients ($IG1_{AUCg}$ = 2.31 ± 0.90; $CG1_{AUCg}$ = 2.91 ± 1.79; $IG2_{AUCg}$ = 2.79 ± 1.70; $CG2_{AUCg}$ = 2.94 ± 1.51) (Kuhlman et al., 2017; Samayoa et al., 2022). No significant differences were observed at T1 with respect to the study variables, age, clinical stage (i.e. I-III), primary treatment (i.e. surgery or neoadjuvant chemotherapy), type of surgery (i.e. conservative surgery or mastectomy), and consumption of anxiolytics and antidepressants between IG1 and CG1 patients, and those of IG2 and CG2. The ANOVA analyses, conducted to assess group variations within each study assessment (T1, T2), revealed no significant differences in resilience, cortisol, or on the affective, instrumental, and emotional subscales of social support, either between the IG1 and CG1 or the IG2 and CG2 (S.H.22), nor among all four groups—IG1, CG1, IG2, CG2 (S.H.23) immediately post-intervention (T2). Contrary to the hypotheses (S.H.22 and 23), these results suggest that the intervention did not produce significant changes in the target biopsychosocial variables between groups at T2, regardless of the primary treatment received by participants or when comparing patients across all four study conditions. However, because the simple ANOVA test primarily focuses on elucidating between-group differences, without separately analyzing within-group changes, this approach may have overlooked significant within-group changes resulting from the intervention (Drummond & Vowler, 2012). With this in mind, a mixed ANOVA analysis was employed to uncover significant changes within each group over time (from T1 to T2), changes that were not evident in the between-group comparisons. Thus, the results of the mixed ANOVA test showed a statistically significant interaction effect for resilience ($F_{(1,116)}$ = 3.368; p = 0.021; ω_P^2 = 0.047), with pairwise comparisons revealing

significant reductions in resilience from T1 to T2 for CG2 ($F_{(1,29)}$ = 9.317; p = 0.003; dDc = 0.88), and non-significant but moderate effect size increases for IG1 ($F_{(1,25)}$ = 1.362; p = 0.246; dDc = 0.47). As the reader will have noticed, a key difference between CG2 and IG1, apart from their experimental condition, was the type of treatment prescribed to their participants, which turned out to be adjuvant radiotherapy for CG2 and adjuvant or neoadjuvant chemotherapy for IG1. Due to the impact of side effects on the physical and emotional dimensions of their quality of life, chemotherapy is today widely conceived as a significant factor in exacerbating the well-being deterioration of BC patients (Velickovic et al., 2022; Zhao et al., 2022). However, it is noteworthy that, in addition to observing a temporal increase in resilience levels in IG1, the results also identified significant decreases in resilience levels in CG2 at T2 compared to T1, in partial alignment with the hypothesis (S.H.24). It is believed that this fact underscores the dual health and resilience fostering effect that the peer support intervention may have exerted in participants, helping them to demystify and normalize their experiences while improving psychological adjustment to cancer-related challenges, as captured in previous research (Pistrang et al., 2013; Zhang et al., 2022). These findings also indicate that the absence of opportunities for mutual emotional exchange during ongoing treatment may not only fail to promote, but also potentially impede patient resilience development, which according to some authors may be due to paternalistic tendencies in oncology care that overlook patient preferences and feelings (Taleghani et al., 2022).

Furthermore, the study also wanted to investigate which variable(s) (i.e. change in cortisol, change in affective support, change in emotional support,

and/or change in instrumental support) could predict the change in resilience levels experienced between T1 and T2 by IG1 and CG2 participants. As for IG1, the results of the regression analysis, in agreement with the hypothesis (S.H.25), showed that increases in their resilience scores from T1 to T2 were driven by larger increases in emotional support (β = .936, p = .006), as well as by steeper declines and shorter increases in affective support (β = -.997, p = .011) and AUCg (β = -.654, p = .008), respectively (R^2 = 0.548; $F_{[4, 18]}$ = 4.238, p = 0.019). The positive relationship identified between emotional support — which referred in this study to the possibility of receiving empathic understanding and practical guidance from others (Costa Requena et al., 2007) — and resilience reinforces its vital role in enhancing the psychological resilience of women with BC, consistent with the findings of Study #3. The intervention's focus on fostering meaningful emotional connections likely offered patients a robust psychological anchor, which not only assisted them in managing the complexities of their oncologic journey but also simultaneously propelled greater satisfaction of their emotional needs. These data shed light on one of the mechanisms through which peer support interventions can improve participants' psychological adjustment and demonstrate their effectiveness in increasing the resilience of newly diagnosed BC patients. On the other hand, the negative relationship identified between changes in affective support —defined as genuine expressions of love or affection by the close social network (Costa Requena et al., 2007) — and improvements in resilience suggests that participants might have perceived the demonstrations received from their environment as non-beneficial. Evidence points to the common use of overprotective or undermining attitudes toward patients' concerns by the surrounding community (Manne et al., 2019; Peters-

Golden, 1982; Woźniak & Iżycki, 2014), which in view of our results could interfere with the psychological adjustment of the patients. The peer support intervention may have fulfilled emotional needs more effectively, reducing the demand for external affective support. Finally, the inverse relationship identified between changes in AUCg and resilience suggests that influencing the physiological stress response is another mechanism through which the intervention may have improved resilience. These findings, supporting previous research on the negative correlation between resilience and cortisol (Krisor et al., 2015; Ruiz-Robledillo et al., 2014; Sun et al., 2014) and mirroring Study #3's insights on decreased AUCg levels facilitating resilience through emotional support, indicate that peer support interventions may be particularly effective in modulating the physiological stress responses of women with BC in ways that lead to an enhancement of their resilience.

The regression analysis results for CG2 revealed that neither the change in cortisol (β = -,267, p= .758) nor the changes in any social support subscales (affective support: β = ,586, p= .094; emotional support: β = -,171, p= .595; instrumental support: β = -,282, p= .228) accounted for the decrease in resilience among participants who, in addition to not undergoing chemotherapy, did not receive the peer support intervention (R^2= 0.184; $F_{[4, 25]}$= 1.184, p= 0.346). These data are considered to point toward the existence of additional, unexplored variables that might more comprehensively explain the reduction in resilience, such as diminished hope, a factor previously shown to mediate the link between shifts in perceived social support and resilience among BC patients (Hsu et al., 2021). Although social support and cortisol did not explain women's susceptibility

to reduced resilience, it is believed that timely administration of peer support could be beneficial due to its distress-preventive (Manigault et al., 2022) and quality-of-life facilitating effects (Velickovic et al., 2022) through resilience in BC patients.

The findings of this study, in line with the general hypothesis (G.H.4), underscore the effectiveness of peer support interventions in fostering the psychological adjustment of BC patients through its benefits on resilience, wherein social support and the diurnal response to cortisol play a pivotal role. Furthermore, it was also observed that the non-administration of the intervention in patients without chemotherapy might not only fail to promote, but also potentially hinder their resilience development. As the first RTC to examine the impact of a one-to-one peer support intervention on both psychosocial and physiological variables in newly diagnosed women with early BC, it presents a promising avenue for future research to develop comprehensive interventions across the BC care continuum.

2. GENERAL DISCUSSION

The four studies presented in this doctoral thesis painted a comprehensive picture of psychological resilience in BC care. Aiming to shed light on the intricate relationship between resilience and biopsychosocial determinants, the four studies collectively addressed this dynamic interplay, each responding to a distinct yet interconnected aspect of this broad research area. Beginning with the desire to unravel the unexplored literature on resilience in BC, Study #1 of this thesis embarked on a journey of systematically integrating the evidence on

biopsychosocial factors and psychosocial interventions associated with BC resilience. Offering evidence of the multiple clinical, sociodemographic, psychosocial, and physiological variables associated with the latter, in addition to interventions that sought to facilitate it, its findings laid the groundwork for a better understanding of the biopsychosocial mechanisms and programs that contribute to the psychological adjustment of women with BC across the cancer continuum. These findings are of high practical importance, especially in light of emerging evidence on the putative relationship between resilience and immune and neuroendocrine biomarkers related to cancer adaptation and survival (Berg et al., 2017; Osório et al., 2017; Petros et al., 2013; Russo et al., 2012), including the physiological response to stress through cortisol. The lack of research identified in Study #1 concerning the exploration of possible biological correlates of resilience in BC patients motivated Study #2, which by systematically analyzing the interconnection between resilience and cortisol sought to address part of the previously identified gap in the resilience literature. Responding to the evidence suggesting that cortisol reflects differentiated physiological mechanisms within the HPA axis (Dobler et al., 2019; Epstein et al., 2021; S. Jiang et al., 2019; Short et al., 2016), this second study categorized cortisol measures according to their secretion period and HPA components, providing evidence for a significant relationship between resilience and cortisol levels indicative of acute and chronic stress in both clinical and non-clinical adults. However, in addition to the drawback of only one study in the review being conducted on cancer patients, the substantial methodological variability among the investigations also precluded the possibility of drawing definitive conclusions about the direction of their results. These latter considerations, coupled with the association between

cortisol and resilience found in Study #2, and the well-validated salutogenic properties of resilience (Chmitorz et al., 2018; Dulin et al., 2018), underpinned the execution of Study #3. Informed by research establishing social support as a critical protective factor in resilience (Zhang et al., 2017), the third study cross-sectionally examined the predictive value of social support and AUCg on resilience in newly diagnosed BC patients, identifying significant effects of both variables on the latter's development. In addition to emphasizing the importance of emotional support as a direct driver of patients' resilience, thus corroborating the results obtained in Study #1, the findings of the third study also pointed to the moderating role of medium and low AUCg profiles in the resilience-enhancing effect produced by emotional support. In line with evidence from previous studies on the negative interrelationship between resilience and cortisol (Krisor et al., 2015; Ruiz-Robledillo et al., 2014; Sun et al., 2014), these results suggested that emotional support-based resilience-enhancing interventions at diagnosis might be more beneficial for patients with decreased diurnal cortisol profiles, compared to those with elevated levels, who may require more tailored and qualitatively different psychological support therapies beyond purely emotional support. Highlighting the need for personalized care models for BC patients with different biological profiles, these findings established a framework for the early identification of patients at risk to prevent the onset of stress-related disorders. Directly informed by its predecessor study's findings on the potential of emotional support-based interventions for BC patients with varying cortisol profiles, Study #4 introduced a practical dimension to previously drawn theoretical insights by assessing the efficacy of a RCT on the impact of a peer support intervention on the resilience, social support, and AUCg in newly diagnosed BC patients. Its

results revealed the potential of the intervention to promote the resilience of patients undergoing chemotherapy, whose improvements were significantly influenced by changes in levels of emotional support, affective support, and AUCg following the intervention's application. Furthermore, findings from this fourth study also revealed that the absence of opportunities for mutual emotional exchange during ongoing radiotherapy treatment may not only fail to promote but could also potentially hinder the enhancement of patient resilience. Supporting through its data the observations from Study #3 on the resilience-promoting role of emotional support and lower AUCg in BC patients, the results of Study #4 are of elevated clinical significance due to the described crucial role of resilience in mitigating the effects of stress on inflammation-associated depressive symptoms in these patients (Manigault et al., 2022), as well as in improving their quality of life (Velickovic et al., 2022). By providing a comprehensive approach to enhancing resilience, the findings of this study offered a promising avenue for future research aimed at developing integrative interventions across the BC care continuum.

The evidence presented in these four studies highlights the need for holistic, personalized, and contextually sensitive approaches that encompass both the psychological and physiological aspects of the resilience-building process, ultimately aiming to improve the psychological well-being and adjustment to cancer-related health challenges of women with BC

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SECTION II. CONCLUSIONS

Study #1

- Resilience in women with BC is influenced by an array of clinical, sociodemographic, psychosocial, and physiological variables throughout the disease continuum.
- Among these factors, psychosocial factors are most frequently associated with resilience, and play a significant role in its development.
- Significant contributors to the development and enhancement of resilience include protective psychosocial factors such as social support, and the physical, social, and emotional dimensions QoL, as well as adaptive coping strategies like active coping and positive acceptance.
- Conversely, adverse psychosocial factors, including symptoms of anxiety and depression, along with non-adaptive coping strategies such as anxious preoccupation, negative affect, and cognitive avoidance, are often identified as key determinants of diminished and weakened resilience.
- Interventions aimed at enhancing resilience have been predominantly effective not only in bolstering resilience itself but also in improving a broad range of psychosocial and BC treatment-related clinical variables. This underscores their potential to foster the psychological and physical well-being of women with BC.
- The significant variability in resilience measurement tools, combined with the substantial heterogeneity and limited sample size of the studies, limits the generalizability of the present findings and emphasizes the need for additional research to draw more definite conclusions regarding these aspects.

Study #2

- Resilience and cortisol display a markedly variable relationship, with evidence revealing both positive and inverse associations, alongside instances of non-significant or null interactions between these variables in both clinical and non-clinical adult populations.
- Importantly, a majority of studies underscore the presence of significant correlations between resilience and both short-term and long-term cortisol secretion patterns, reflective of the diverse diurnal, acute, and basal elements of the HPA axis response.
- The predominant proportion of research linking resilience and cortisol uses an intervention design, in contrast to cross-sectional or longitudinal studies. These findings emphasize the malleable and thus trainable nature of resilience, accentuating its potential as a modulator of the physiological response to stress.
- Regardless of research design, a notable lack of directional clarity is evident in the relationship between the two variables under study. This ambiguity is attributed to the substantial methodological heterogeneity among the studies and the presence of overlooked third variables that could more accurately elucidate this connection.
- Despite these methodological limitations, the significant association found between resilience and cortisol underscores the need for future research to consistently explore their relationship, thereby paving the way for the development of interventions aimed at fostering resilience as a crucial constituent of health promotion.

Study #3

- The resilience of women recently diagnosed with BC is significantly and positively correlated with their perceived levels of social support across the affective, emotional, and instrumental dimensions, and also exhibits a tentative negative correlation with their AUCg levels.
- Furthermore, it is observed that the main effects of the emotional support dimension, along with its interaction with AUCg, significantly account for 28% of the total variance of resilience. The examination of the latter interaction further reveals that, unlike high levels of AUCg, only middle and low levels of AUCg amplify the beneficial influence of emotional support on resilience.
- Drawing from these findings, it is proposed that women with middle and low levels of AUCg could particularly benefit from emotional support-based interventions early in the oncological process, due to the distinct protective and resilience-enhancing effects shown by this type of support at diagnosis.
- Conversely, women with high AUCg levels may be more susceptible to the adverse effects of diagnosis, owing to the limited effectiveness of emotional support in enhancing their resilience. This indicates that such patients may need more personalized psychological support therapies, distinct from conventional emotional support, to address their unique emotional needs.
- The explanatory function of social support and AUCg in enhancing the resilience of women recently diagnosed with BC reveals that specific psychobiological profiles impact susceptibility to new life challenges, and emphasizes the need for personalized support delivery programs aimed at promoting their successful adaptation to the disease.

Study #4

- A peer support intervention, based on the provision of emotional support by peers who have undergone the same experience, shows the potential to enhance resilience among women recently diagnosed with BC.
- Results point to greater increases in emotional support, as well as steeper declines and shorter increases in affective support and AUCg, respectively, as the underlying mechanisms through which the intervention may have enhanced the resilience of patients undergoing chemotherapy.
- Findings also indicate that a lack of reciprocal emotional exchange during ongoing treatment may not only fail to nurture but could also impede the development of participant's resilience. This is evidenced by the significant decline in resilience levels among women who, while not receiving chemotherapy, also did not receive the intervention.
- The lack of predictive value of changes in social support and cortisol levels for the latter's reduced resilience states suggests that peer support's effect may depend on the type of treatment received by the patients. This highlights the need for future research to gather longitudinal data on the interplay between resilience, social support, and cortisol, while considering the unique influences of the various BC treatments.
- In addition to emphasizing the potential benefits of non-hierarchical, experience-based emotional support from peers, this study's findings offer a comprehensive framework for enhancing the resilience of women with BC and open avenues for future research to develop holistic interventions across the entire spectrum of BC care.

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SECTION III. APPENDICES

PUBLISHED MANUSCRIPTS

This section outlines the published or under-review papers that have emerged from the four studies conducted for this doctoral thesis. For the convenience of the reader, the quality metrics of the respective journals are provided below:

1. Study #1

Aizpurua-Perez, I., & Perez-Tejada, J. (2020). Resilience in women with breast cancer: A systematic review. *European journal of oncology nursing*, *49*, 101854. https://doi.org/10.1016/j.ejon.2020.101854

- Quality Indicators (2020):
    - Journal Impact Factor: 2.398
    - Category: Nursing
        - Quartile: Q1
        - Rank: 45/122

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Resilience in women with breast cancer: A systematic review

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ABSTRACT

Purpose: Resilience refers to a dynamic process that promotes a successful adaptation to cancer-related adversity. The aim of this systematic review was to identify the biopsychosocial factors involved in the resilience of women with breast cancer and to integrate evidence on the interventions that can contribute to significantly enhancing it.

Method: Three databases were searched. In all, 923 articles were identified and, of these, 39 peer-reviewed articles were included.

Results: Resilience was associated with multiple clinical, sociodemographic, social, psychological and physiological variables, with psychological factors being the most important contributors to the development of resilience. Some protective factors were identified, such as social support, several dimensions of quality of life (QOL) and adaptive coping strategies. Psychological distress was the variable most frequently linked to reductions in resilience, finding a bidirectional relationship between them. Resilience-promoting interventions were found to be effective in improving participants' psychological well-being.

Conclusion: Resilience is a relevant factor related with several sociodemographic, clinical, psychosocial and physiological variables in women with breast cancer. However, limitations such as the wide variability of instruments used together with the heterogeneity and small size of the samples restrict the generalizability of our conclusions.

1. Introduction

Breast cancer is the most common cancer among women worldwide, with 1.4 million new cases detected each year (Torre et al., 2015). The diagnosis and treatment of breast cancer impact all aspects of women's health, affecting physical, psychological, social, economic, and spiritual aspects. Thus, for many women coping with disease-related demands represents an extremely stressful process that can trigger a variety of long-lasting negative outcomes, including symptoms of depression, anxiety, fatigue, and exacerbations of premorbid and/or latent psychiatric conditions (Hill et al., 2011; Phillips-Salimi and Andrykowski, 2013; Saboonchi et al., 2014). In particular, studies indicate that one-fourth to one-third of breast cancer patients will develop anxiety and/or depression at some point in the process (Linden et al., 2012; Naik et al., 2020) and those aged younger than 50 years are especially likely to report psychological distress (Champion et al., 2014; Howard-Anderson et al., 2012). These stress-related mental health problems exerts a negative impact on the course and effectiveness of the patient's treatment, affecting cancer-related morbidity and mortality, as well as quality of life (QOL) (Adler and Page, 2008). Interestingly, not everyone copes adversities in the same manner, finding that many breast cancer patients develop resilience in the face of illness.

Resilience can be defined as an individual's ability to maintain or recover relatively stable psychological and physical functioning during or after exposure to significant stressful life events (Bonanno et al., 2011). It is important to note that although resilience and post-traumatic growth are closely related concepts, these terms should be viewed as two independent constructs (Westphal and Bonanno, 2007). While resilience indicates the ability to cope with negative emotions and means a return to the normal capacity after difficulty, post-traumatic growth involves a positive change exceeding the earlier level of psychological functioning (Carver, 1998; Layne et al., 2014). In other words, to develop post-traumatic growth, a cancer patient has to return to higher and more efficient mental health outcomes than previous levels of functioning (Greup et al., 2018). Hence, only a few percent of resilient patients will be able to develop post-traumatic growth. Despite these important

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differences, many studies have explicitly or implicitly equated post-traumatic growth with resilience (Westphal and Bonanno, 2007).

In cancer patients, resilience refers to a dynamic process in which successful adaptation to cancer-related adversity is promoted (Eicher et al., 2015). Further, resilience is presumably influenced to some personal characteristics and protective factors, such as optimism, positive emotions, self-esteem, coping or social support (Eicher et al., 2015). These factors can be modifiable through specific interventions, which can have a positive effect not only on the development of resilience, but also on other favorable clinical outcomes, including enhancements in anxiety and depressive symptomatology and QOL (Hou et al., 2010; Tian and Hong, 2014; Wu et al., 2015). Identifying resilience as a psychological indicator of resistance to adversities may provide an opportunity for improving psychological outcomes in breast cancer care. By enhancing resilience, women with breast cancer can alleviate the negative impact of physical, psychological, and social changes experienced during the course of the illness, as well as to establish health-promoting behaviors that enable them to positively integrate those changes in their lives. Therefore, improving resilience through the promotion of specific adaptive interventions should be an essential component to optimize breast cancer care, but a better understanding of factors involved at each stage of the breast cancer continuum is necessary in order to advance in such interventions. Thus, the aim of the present study was, on the one hand, to identify which biopsychosocial factors are involved in the resilience of women with breast cancer, and, on the other hand, to integrate evidence on the interventions that may significantly improve it. To accomplish this objective, we conducted a systematic review of the literature to address the following research questions:

1. What factors can significantly influence the resilience of women with breast cancer?
2. What interventions have been used so far to promote the resilience in women with breast cancer?

2. Methods

This systematic review used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow sheet and checklist to ensure complete reporting of the evidence-based minimum reporting items (Liberati et al., 2009).

2.1. Search strategy

A total of 3 databases were searched – PubMed, Psycinfo and Web of Science – from inception up until March 27, 2020. In order to capture the existing literature on resilience in both breast cancer patients and survivors, the following key word combinations were searched: resilien* AND breast cancer. Reference lists of all eligible articles were also hand-searched for further studies. Grey literature was not searched. The identified articles were exported to Mendeley Reference Manager for management.

2. Eligibiliy criteria

Quantitative studies were eligible for initial review if they met the following criteria:

(1) The participants were breast cancer patients or/and survivors of any cancer stage, at any time point since breast cancer diagnosis and were adults aged 18 years or older.
(2) Participant's resilience was assessed through quantitative procedures.
(3) Studies were published in English or Spanish.

Quantitative studies were excluded if (1) they only mentioned resilience without objectively assessing it; (2) the participants were diagnosed with other illnesses or cancer type; (3) measured resilience through qualitative procedures (studies that based their analyses on qualitative interpretations of the data obtained from the participants were not included in order to ensure generalizability of the results and compare their findings with each other); (4) were not published in English or Spanish; (5) were review articles, books or chapters, commentaries, editorials, poster abstracts, case reports and dissertations.

On the other hand, the inclusion criteria for intervention studies were as follows:

(1) The participants were adult breast cancer patients or/and survivors of any cancer stage and at any time point since breast cancer diagnosis.
(2) Resilience was the dependent variable and was assessed through quantitative procedures.
(3) Studies employed randomized controlled trials, non-randomized controlled trials, quasi-experimental or non-experimental designs.
(4) Studies were published in English or Spanish.

Intervention studies were excluded if (1) participants were diagnosed with other illnesses or cancer type; (2) they employed qualitative procedures to assess participant's resilience; (3) they were not published in English or Spanish.

2.3. Study selection and data extraction procedure

We identified 923 articles in our initial database search (Fig. 1: PRISMA flowchart). After removing duplicates, the titles and abstracts of the remaining articles were screened by two independent reviewers (author JPT and author IAP) to select only those that met the eligibility criteria. When the inclusion criteria were met, a second-stage screening was independently conducted by JPT and IAP where the full-documents were reviewed. Any disagreements regarding the inclusion of a study were resolved by consensus.

In order to organize the data from quantitative and intervention studies, two forms of data extraction were developed. Data extracted from quantitative studies included: authors and year of publication, study design and sample size, participant's characteristics, scale used to measure resilience, variables studied in relation to resilience and findings. On the other hand, the information extracted for the intervention studies included: authors and year of publication, study design and sample size, participant's characteristics, frequency and duration of intervention, scale used to measure resilience, variables studied in relation to resilience and results.

3. Results

31. Research design of the reviewed studies

Thirty-nine studies met the inclusion criteria and were included in the final review (Tables 1 and 2). All the articles followed a quantitative methodology and convenience sampling was used in most of them. Most studies were written in English (n = 34) and to a lesser extent in Spanish (n = 5), and were conducted in Asia (n = 16), Europe (n = 14), America (n = 8) and Oceania (n = 1). Cross-sectional design was identified in thirty studies, followed by eight intervention design and one longitudinal design study.

3.2. Study participants

The sample sizes of the reviewed studies ranged from 10 to 540 participants, and the ages ranged from 18 to 90 years. Participants were recruited mainly from hospitals and cancer centers (n = 27), and in some cases via online recruiting platforms (n = 3) and breast cancer

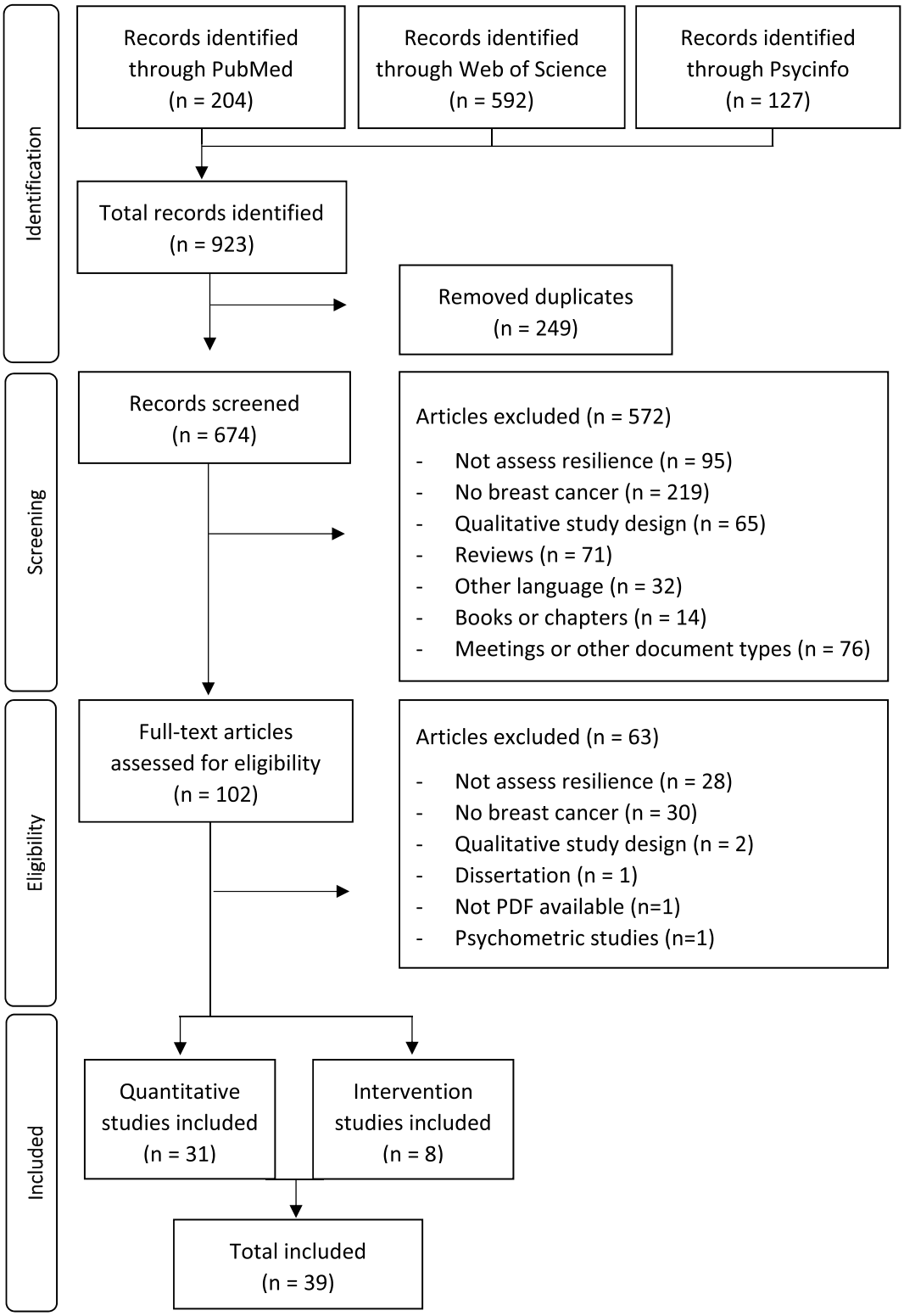

Fig. 1. PRISMA flowchart of study selection.

associations (n = 6). One study recruited women who were enrolled in a weekend therapeutic retreat program and two studies did not report information about the recruitment process. Twenty-two studies included breast cancer patients who in most cases were in active treatment, followed by twelve involving breast cancer survivors and five studies comprising both patients and survivors. Participants from sixteen studies received a primary breast cancer diagnosis between stages I-III, while the remaining studies recruited patients in advanced (n = 1) or mixed cancer-stages (n = 12). Patients cancer-stage was not reported in ten studies. Most studies excluded participants with prior psychiatric comorbidities, advanced cancer-stage or a history of cancer recurrence.

Table 1
Descriptive summary of cross-sectional and longitudinal design-studies.

Authors (year)	Study design (sample size)	Participants: 1) BCP, BCS, CG; 2) Age in years (SD); 3) Stage; 4) Mean time since diagnosis in years (SD)	Scale to assess resilience	Variables studied in relation to resilience	Results
Al Eid et al. (2020)	Cross-sectional **n = 329**	1. BCP and BCS	**RS-14**	**Alternative therapeutic interventions currently used**	- **Positive correlations**: resilience (subscales and the global score) with virtues, worship and creed dimensions, as well as with alternative therapeutic interventions currently used.
	BCP: n = 150	2. Nor reported	*Subscales: Self-reliance, Meaningfulness, Balance, Perseverance, Existential Aloneness*	**Future alternative therapeutic interventions**	- **Regression**:
	BCS: n = 179	3. Not reported		**Religiosity** (Islamic Religiosity Attitude scale*: virtues, worship, creed, forbidden)*	o Self-reliance and balance domains of resilience predicted anxiety.
		4. Not reported		**Anxiety/depressive symptoms** (HADS)	o Resilience did not predict depression
Alarcón et al. (2020)	Cross-sectional **n = 169**	1. BCP and BCS	**CD-RISC-10**	**Satisfaction with life** (SWLS)	- Mean of resilience: μ = 25.35 (7.36)
		2. μ = 51.62 (10.57)		**Emotional intelligence** (TMMS-24: *attention, clarity, repair)*	- **Positive correlations:** resilience with life satisfaction, self-esteem, positive affect, and clarity and repair subscales.
		3. Stage 0: 5.3%; Stage I: 8.9%; Stage II: 55%; Stage III: 29.6%; Stage IV: 1.2%		**Self-esteem** (RSS)	- **Negative correlation**: resilience with negative affect
		4. μ = 3.77 (3.85)		**Positive and negative affect** (PANAS)	
Alizadeh et al. (2018)	Cross-sectional **n = 150**	1. BCP	**CD-RISC-25**	**Self-compassion** (Self-compassion Scale)	- Mean of resilience: μ = 67.54 (17.42)
		2. Not reported		**Social support** (MSPSS)	- **Positive correlations:** resilience with self-compassion, social support and sense of belonging.
		3. Stage I: 20,7%; Stage II: 47.3%; Stage III: 32%		**Sense of belonging** (SOBI)	
		4. Not reported			
Bazzi et al. (2018)	Cross-sectional **n = 540**	1. BCS	**RS-14**	**Sociodemographic variables** (age, race, Hispanic ethnicity, educational attainment, employment, health insurance status, income, partnership status, living with partner/spouse, spouse/partner is female, marital status)	- Mean of resilience: μ = 86.0 (9.2). HSW: μ = 86.0 (9.4); SMW: μ = 85.9 (8.8).
	HSW (heterosexual) = **339**	2. μ = 54.4 (8.7). HSW: μ = 55.1 (8.8); SMW: μ = 53.4 (8.5)		**Clinical variables** (cancer grouping, years since first BC diagnosis, clinical stage, treatment type, number of comorbidities, BMI)	- **Regression**:
	SMW (sexual minority) = **201**	3. Stage 0: 14,3%; Stage I: 34,8%; Stage II: 29,9%; Stage III: 8,9%; Stage IV: 12,1%		**Psychosocial factors** (cancer support group attendance, mental health counseling before BC diagnosis, discrimination experiences)	o Social support as well as fighting spirit combined with helplessness/hopelessness and fatalism dimensions positively predicted resilience.
		4. μ = 4.9 (5,7)		**Social support** (ISEL)	o Mental health counseling before breast cancer diagnosis and the anxious preoccupation dimension negatively predicted resilience.
				Cancer coping (Mini-MAC: *fighting spirit; anxious preoccupation; helplessness/*	o Sexual orientation was not independently associated with resilience; however, the interaction between sexual

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Table 1 (*continued*)

Authors (year)	Study design (sample size)	Participants: 1) BCP, BCS, CG; 2) Age in years (SD); 3) Stage; 4) Mean time since diagnosis in years (SD)	Scale to assess resilience	Variables studied in relation to resilience	Results
				hopelessness; fatalism; cognitive avoidance)	orientation and employment negatively predicted resilience, revealing that SMW had lower resilience than employed SMW.
Burgos-Felix et al. (2014)	Cross-sectional **n = 10**	1. BCS 2. μ = 57.10 (8.29) 3. Stage I: 20%; Stage II: 30%; Stage III: 40%; Stage IV: 10% 4. Not reported	**EFIR**	**Clinical variables** (breast reconstruction, time since breast reconstruction)	- No significant differences in resilience depending on the breast reconstruction or time since breast reconstruction.
Dubey et al. (2015)	Cross-sectional **n = 10**	1. BCP 2. Not reported 3. Not reported 4. Not reported	**CD-RISC-25**		- Mean of resilience: μ = 81.2 (9.4).
Edward et al. (2019)	Longitudinal study. Follow-up at baseline, 6 and 12 months postoperatively. **n = 49**	1. BCP 2. μ = 56.6 years (11.6) 3. Stage I: 43.1%; Stage II: 41.2%; Stage III: 15.7% 4. Not reported	**CD-RISC-25**	**Clinical variables** (time after diagnosis)	- Mean of resilience: Baseline: μ = 76.8 (15.2); 6 months: μ = 72.8 (15.7); 12 months: μ = 72.8 (14.6) - Resilience did not vary significantly between the baseline and following 12 months.
Fradelos et al. (2017)	Cross-sectional **n = 144**	1. BCS 2. μ = 53.5 (11.7) 3. Stage I: 48.6%; Stage III-IV: 50.7% 4. Not reported	**CD-RISC-25**	**Sociodemographic variables** (age) **Clinical variables** (clinical stage, type of surgery, symptom burden) **Anxiety** (GAD-2) **Depression** (PHQ-2)	- Mean of resilience: μ = 65.3 (17.9). - Older women showed lower levels of resilience than younger women. - Participants reporting higher symptom burden were more likely to be less resilient. - **Negative correlations**: resilience with depression and anxiety - **Regression**: each 1-point increase in psychological resilience implied a 3.4% reduction in depression levels.
Fradelos et al. (2018)	Cross-sectional **n = 152**	1. BCP 2. μ = 53.2 (12) 3. Not reported 4. Not reported	**CD-RISC-25**	**Clinical variables** (symptom burden) **Anxiety** (GAD-2) **Depression** (PHQ-2) **Religiosity** (CRS-15: *religious beliefs, religious practices)*	- Mean of resilience: μ = 65.5 (19). - **Positive correlation:** resilience with religious beliefs and practices. - **Negative correlations**: resilience with depression, anxiety and symptom burden. - **Regression**: o Symptom burden and religious beliefs predicted resilience o Each 1-point increase in psychological resilience implied a 0.9% reduction in depression levels.
Franco et al. (2019)	Cross-sectional **n = 50**	1. BCP.	**CD-RISC-10**	**QOL** (MOS-SF36*: physical function, physical role, body pain, general health, vitality, social function, emotional role, mental*	- Mean of resilience: μ = 32.88 (5.54).

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Table 1 (*continued*)

Authors (year)	Study design (sample size)	Participants: 1) BCP, BCS, CG; 2) Age in years (SD); 3) Stage; 4) Mean time since diagnosis in years (SD)	Scale to assess resilience	Variables studied in relation to resilience	Results
				health, physical health sum index, mental health sum index)	
		2. μ = 50,42 (11,28)			- **Positive correlations:** resilience with physical function, body pain, general health, vitality, social function, emotional role, mental health, physical health summary index and mental health summary of QOL.
		3. Stage I: 2%; Stage II: 58%; Stage III: 40% 4. Not reported			
Gálvez-Hernández et al. (2018)	Cross-sectional **n = 150** **BCP: n = 75** **BCS: n = 75**	1. BCP and BCS 2. μ = 35,27 (4,22). BCP: μ = 34,26 (4,82); BCS: μ = 36,28 (3,26) 3. Stage I: BCP 9,3%, BCS 8%; Stage II: BCP 41,3%, BCS 46,7%; Stage III: BCP 45,3%, BCS 45,3%; Stage IV: BCP 4% 4. BCP: μ = 0,63 (0,40); BCS: μ = 3,06 (2,38)	**RESI-M** *Subscales: Strength and Self-confidence, Social Competence, Family Support, Social Support, Structure.*	**Sociodemographic variables** (marital status, educational level, employment) **Clinical variables** (time since diagnosis, clinical stage, treatment type) **Perceived unmet supportive care needs** (SCNS-SF32 M*: health and information system needs, psychological needs, physical needs; two indicators: sexuality and patient care and support needs)*	- Mean of resilience: μ = 70.54. BCP: μ = 70,98; BCS: μ = 80,02. - BCP scored significantly lower in social competence domain than BCS. - **Positive correlations:** strength and self-confidence domains with educational level and social competence domain with time since diagnosis. o BCP: strength and self-confidence domains and the global score with educational level. o BCS: social support domain with educational level. - **Negative correlations:** structure domain with global score of perceived unmet supportive care needs o BCP**:** strength and self-confidence domain with psychological needs domain; social support and familiar support domains with marital status. o BCS: structure domain with global score of perceived unmet supportive care needs, health and information system needs domain and patient care and support needs indicator; family support, social support, strength and self-confidence domains and the global score of resilience with the patient care domain and the support needs indicator.
García-Maroto et al. (2015)	Cross-sectional n = **300** **EG: n = 150** **CG: n = 150**	1. BCP 2. EG: μ = 54,71 (9,16); CG: μ = 55,51 (10,76) 3. Not reported 4. Not reported	**RS-14**	**Anxiety** (STAI)	- Mean of resilience: EG: μ = 137,93 (12,06); CG: μ = 121,71 (15,58). - EG reported significantly higher resilience than CG. - **Regression**: resilience did not predict participants' anxiety levels.
Huang et al. (2019)	Cross sectional **n = 208**	1. BCP 2. μ = 48.73 (8.72)	**CD-RISC-25**	**Clinical variables** *(courses of adjuvant therapy, clinical stage)* **Self-efficacy** (GSES)	- Mean of resilience: μ = 65.18 (13.16) - Post-operative physical exercise status, courses of

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Table 1 (*continued*)

Authors (year)	Study design (sample size)	Participants: 1) BCP, BCS, CG; 2) Age in years (SD); 3) Stage; 4) Mean time since diagnosis in years (SD)	Scale to assess resilience	Variables studied in relation to resilience	Results
					adjuvant therapy and clinical stage significantly affected psychological resilience.
		3. Stage I: 20.2%; Stage II: 42.8%; Stage III: 37.0%		**Family hardiness** (FHI: *commitment, challenge, control)*	- **Positive correlations:** resilience with the global score of self-efficacy, family hardiness (all the dimensions and the global score) and social support (all the dimensions and the global score).
		4. Not reported		**Social support** (SSRS: *objective support, subjective support, availability of support)*	- **Regression**:
				Physical exercise status *(high-, moderate- or low-intensity exercise)*	o Clinical stage of breast cancer and courses of adjuvant therapy negatively contributed to psychological resilience. o Moderate postoperative physical exercise status, family commitment domain, control domain and subjective support domain positively contributed to psychological resilience.
Izydorczyk et al. (2018)	Cross sectional **n = 120**	1. Post-mastectomy BCP and BCS	**SPP-25**	**Body Image** (1. BAT*: dissatisfaction with the body, control over the body, perception of the body;* 2. BSQ*: self-assessment of the body, intimate relations, physical activity, eating attitude and weight control, physical attractiveness)*	- Mean of resilience: EG1: μ = 73,33 (13,07); EG2: μ = 67,89 (14,48).
	EG1 (up to 2 years after mastectomy): **n = 64**	2. μ = 54.0	*Subscales: 1. Capacity to evoke positive emotions: a) Optimism and Capacity to Mobilize oneself (OCM), b) Openness to New Experiences and Humor (ONEH); 2. Capacity to bounce back from difficult situations: a) Consistency and Determination (CD), b) Coping with Negative Emotions (CNE), c) Failure Tolerance (FT)*		- EG1 showed significantly higher general psychological resilience and capacity to bounce back from difficult situations than EG2.
	EG2 (over 2 years): **n = 56**	3. Not reported			- **Regression**:
		4. Not reported			o Resilience (global score) positively predicted self-assessment of the body and physical attractiveness, and negatively control over the body and dissatisfaction with the body. ONEH positively predicted intimate relationships. FT positively predicted weight control and CNE negatively predicted perception of the body. o EG1: resilience (global score) negatively predicted control over the body and dissatisfaction with the body. ONEH and OCM positively predicted intimate relationships and self-acceptance, respectively. Weight control was positively predicted by FT and negatively by CD. FT also predicted negatively the

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Table 1 (*continued*)

Authors (year)	Study design (sample size)	Participants: 1) BCP, BCS, CG; 2) Age in years (SD); 3) Stage; 4) Mean time since diagnosis in years (SD)	Scale to assess resilience	Variables studied in relation to resilience	Results
					perception of the body domain. o EG2: resilience (global score) negatively predicted control over the body and dissatisfaction with the body. ONEH positively predicted the intimate relationships. CNE positively predicted self-acceptance and weight control and negatively perception of the body. CD positively predicted physical attractiveness.
Izydorczyk et al. (2019)	Cross sectional **n = 219**	1. Post-mastectomy BCP and BCS and CG	**SPP-25**	**Body Image** (1. BAT: *dissatisfaction with the body, control over the body, perception of the body;* 2. BSQ*: self-assessment of the body, intimate relations, physical activity, eating attitude and weight control, physical attractiveness)*	- Mean of resilience: EG1: μ = 74,50 (13,07); EG2: μ = 69,50 (14,49); CG: μ = 70 (12,09).
	EG: n = 120	2. EG: μ = 55.90 (11,74); CG: μ = 54.40 (12,07)	*Subscales: 1. Capacity to evoke positive emotions: a) Optimism and Capacity to Mobilize oneself (OCM), b) Openness to New Experiences and Humor (ONEH); 2. Capacity to bounce back from difficult situations: a) Consistency and Determination (CD), b) Coping with Negative Emotions (CNE), c) Failure Tolerance (FT)*		- CD, CNE and the global score of resilience were significantly higher in EG1 than in the CG.
	EG1 (up to 2 years after mastectomy): n = 64	3. Not reported			- The global score of resilience, CD, CNE and FT were significantly higher in EG1 than in EG2.
	EG2 (over 2 years): n = 56	4. Not reported			
	CG: n = 99				
Kaczmarek et al. (2012)	Cross sectional **n = 30**	1. BCP.	**ERS**	**Coping** (Mini-MAC*: anxious preoccupation, fighting spirit, helplessness/hopelessness, positive reframing)*	- Mean of resilience: μ = 43.68 (6.02)
		2. μ = 53.23 (9)		**Satisfaction with life** (SWLS)	- **Positive correlation:** resiliency with positive reframing
		3. Not reported			- **Negative correlations:** resiliency with helplessness/ hopelessness and anxious preoccupation.
		4. Not reported			- **Regression:** the positive indirect effect of resiliency on satisfaction with life was positively mediated by positive reframing and negatively by helplessness/ hopelessness and anxious preoccupation.
Kamen et al. (2017)	Cross sectional **n = 201**	1. BCP and BCS	**RS-14**	**Discrimination** (asking participants if they have ever felt discriminated)	- Mean of resilience: μ = 84, 94 (8,78)
		2. μ = 53 (8.48)		**Negative Identity** (LGB)	- **Positive correlation:** resiliency with social support
		3. Stage 0: 18.9%; Stage I: 31,3%; Stage II: 31,8%; Stage III: 7,5%; Stage IV: 8%		**Outness** (OI)	- **Negative correlations:** resiliency with anxiety/ depressive symptoms and discrimination
		4. μ = 4.56		**Social support** (ISEL)	- **Regression**: Resilience significantly mediated the positive relationship

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Table 1 (*continued*)

Authors (year)	Study design (sample size)	Participants: 1) BCP, BCS, CG; 2) Age in years (SD); 3) Stage; 4) Mean time since diagnosis in years (SD)	Scale to assess resilience	Variables studied in relation to resilience	Results
					between discrimination and psychological distress.
				Anxiety/depressive symptoms (HADS)	
Kokofu (2012)	Cross-sectional **n = 64**	1. BCP	**PRS**	**Decisional conflict** (DCS: *uncertainty, feeling uninformed, feeling unsupported by others, lack of advice, perception of the quality of the decision made)*	- Mean of resilience: μ = 71.59 (10.37**)**
		2. μ = 53.4 (10.8)	*Subscales: Novelty Seeking, Emotional Regulation, Positive Future*		- **Negative correlations:** the positive future orientation domain with feeling unsupported by others and lack of advice domains.
		3. Stage I: 40,7%; Stage II: 35,9%; Stage III-IV: 10,9%; Unknown: 12,5%	*Orientation*		
		4. Not reported			
Lai et al. (2019)	Cross-sectional **n = 175**	1. BCP	**ORS**	**Sociodemographic variables** (age, education, income, marital satisfaction)	- **Positive correlations:** resilience with marital satisfaction, active coping and minimizing the situation domains.
		2. μ = 52.2 (8.9)		**Clinical variables** (time since diagnosis, clinical stage)	- **Negative correlations:** resilience with anxiety and depressive symptoms
		3. Stage I: 32,6%; Stage II: 38,3%; Stage III: 22,2%; Stage IV: 6,9%		**Coping** (WOC: *avoidance coping, active coping, minimizing the situation)*	- **Regression**:
		4. μ = 1.83		**Anxiety/depressive symptoms** (HADS)	o Resilience had direct negative effects on anxiety/ depressive symptoms, and sleep disorders.
				Sleep disorders (PSQI)	o Active coping and marital satisfaction had a significant direct positive effect on resilience.
					o A mediating effect of resilience was observed between marital satisfaction and depressive symptoms.
Lee et al. (2018)	Cross-sectional **n = 209**	1. BCS	**CD-RISC-10**	**Symptom distress** (MSAS-SF)	- Mean of resilience: μ = 35.9 (6.5)
		2. μ = 39.90 (4.12)		**Coping** (CCQ)	- **Regression:**
		3. Stage I: 48.8%; Stage II: 38.8%; Stage III: 12.4%			o Symptom distress had direct effects on resilience.
		4. Not reported			o Symptom distress had a significant indirect effect on coping through resilience as a mediating variable.
					o Resilience had direct effects on coping.
Li et al. (2018)	Cross-sectional **n = 108**	1. BCS	**CD-RISC-10**	**Family resilience** (FRAS-C: *family communication and problem solving (FCPS), utilizing social resources (USR), maintaining a positive outlook (MPO))*	- Mean of resilience: μ = 27.6 (7.4)
		2. μ = 49 (9)		**Caregiver burden** (CZBI)	- **Positive correlation:** individual resilience with family resilience.
		3. Stage I: 51,9%; Stage II: 28,7%; Stage III: 19,4%			- **Negative correlations:** individual resilience with caregiver burden.
		4. μ = 0,96 (1.1)			- **Regression:**
					o Family resilience positively predicted individual resilience

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Table 1 (*continued*)

Authors (year)	Study design (sample size)	Participants: 1) BCP, BCS, CG; 2) Age in years (SD); 3) Stage; 4) Mean time since diagnosis in years (SD)	Scale to assess resilience	Variables studied in relation to resilience	Results
					o Individual resilience negatively predicted caregiver burden. o Individual resilience was a partial mediator of the relationship between family resilience and caregiver burden.
Markovitz et al. (2015)	Cross-sectional **n = 464** EG: n = 253 CG: n = 211	1. BCP and CG 2. BCP: μ = 53.9 (10.5); CG: μ = 45.7 (12.3) 3. Stage I or II 4. Not reported	**CD-RISC-25**	**Anxiety/depressive symptoms** (HADS) **Positive and negative affect** (Short PANAS) **Happiness** (WDH: *general happiness, current happiness)*	- Mean of resilience: EG: μ = 93.8 (14.6); CG: μ = 93 (11.9). - No differences between EG and CG in the levels of resilience. - **Regression:** o Resilience positively predicted current happiness and positive affect, and negatively anxiety, depression and negative affect in both EG and CG. o The interaction between resilience and group (EG or CG) negatively predicted anxiety, depression and negative affect, and positively current happiness. EG with low (-2SD) and mean levels of resilience reported significantly more anxiety, depression and less current happiness than CG. However, EG participants with higher (+2SD) levels of resilience not differed in anxiety/depressive symptoms and current happiness from CG. For negative affect, the difference between EG and CG was significant at all levels of resilience, indicating that EG reported higher negative affect than CG.
Ocampo et al. (2011)	Cross-sectional **n = 50**	1. BCP and BCS 2. μ = 46 (9,8) 3. Not reported 4. Not reported	**SV-RES** *Subscales: Identity, Learning, Satisfaction, Pragmatism, Social Support, Autonomy, Personal Strength, Goals, Sense of life, Bonds, Self-esteem and Affectivity.*	**QOL** (QOLHI)	- **Positive correlation:** social support, personal strength, sense of life and identity subscales with QOL. - **Regression**: personal strength positively predicted QOL.
Padilla-Ruiz et al. (2019)	Cross-sectional **n = 59**	1. BCS 2. μ = 60 3. Stage I: 45.5%; Stage II: 34,5%; Stage III: 20%	**CD-RISC-25** *Factors: Persistence-Tenacity-Self efficacy, Control Under Pressure, Adaptability, Control and Purpose,* *Spirituality*	**Sociodemographic variables** (age, educational level, employment status, marital status, household situation) **Clinical variables** (time since diagnosis, clinical stage, type of surgery, lymphadenectomy, chemotherapy, radiotherapy, hormonotherapy)	- Mean of resilience: μ = 77 - Adaptability and control domains, as well as the global score of resilience were significantly higher among participants with higher levels of education. - Control under pressure and adaptability domains, as well as the global score of

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Table 1 (*continued*)

Authors (year)	Study design (sample size)	Participants: 1) BCP, BCS, CG; 2) Age in years (SD); 3) Stage; 4) Mean time since diagnosis in years (SD)	Scale to assess resilience	Variables studied in relation to resilience	Results
		4. μ = 6			resilience were significantly higher among participants in whom a shorter period of time had elapsed since diagnosis. - Persistence-tenacity-self-efficacy and control under pressure domains, as well as the global score of resilience were significantly higher among participants who had received chemotherapy.
Ristevska-Dimitrovska et al. (2015a)	Cross-sectional **n = 218**	1. BCS	**CD-RISC-25**	**QOL** (EORTC QLQ-C30: *1. Functional Scales: physical, role, cognitive, social, emotional; 2. Symptom Severity Scales: nausea, pain, fatigue, dyspnea, diarrhea, constipation, insomnia, appetite loss, financial difficulties; 3. Global Health Scale.* EORTC QLQ-BR23: *1. Functional scales: body image, sexual function, sexual enjoyment, future perspective; 2. Symptom Scales: systemic therapy side effects, arm and breast symptoms, upset by hair loss)*	- **Positive correlation:** resilience with all the functional scales, the body image domain and the future perspective domain of QOL.
		2. μ = 60.2			- **Negative correlation:** resilience with all the symptom severity scales, the systemic therapy symptoms domain and arm/breast symptoms domain of QOL.
		3. Stage I: 27.9%; Stage II: 39,8%; Stage III: 32,3%			
		4. Not reported			
Ristevska-Dimitrovska et al. (2015b)	Cross-sectional **n = 218**	1. BCS	**CD-RISC-25**	**Anxiety/depressive symptoms** (HADS)	- Mean of resilience: μ = 74.7 (17.0). Not depressed group (NDG): μ = 79.1 (14.6); Subthreshold group (SG): μ = 68.2 (14.3); Depressed group (DG): μ = 56.4 (18.7)
		2. μ = 60.2			- **Negative correlation:** resilience with depressive symptoms.
		3. Stage I: 27.9%; Stage II: 39,8%; Stage III: 32,3%			- **S**ignificant differences in resilience between groups. NDG reported significantly higher levels of resilience than SG and DG.
		4. Not reported			
Tadayon et al. (2018)	Cross-sectional **n = 114**	1. BCP	**CD-RISC-25**	**Depression** (BDI-II)	- Significant differences in resilience depending on depression levels (non, mild, moderate, severe).
		2. Not reported			- **Negative correlation:** resilience with depressive symptoms.
		3. Not reported			
		4. Not reported			
Tu et al. (2019)	Cross-sectional **n = 201**	1. BCP and BCS	**CD-RISC-25**	**Coping style** (Mini-MAC: *Positive-Acceptance (PA), Negative-Affect (NA), Cognitive-Avoidant (CA) coping)*	- **Positive correlations:** resilience with QOL, perceived growth and PA coping.
		2. μ = 51.54 (9.7)		**Perceived Growth** (PTGI)	- **Negative correlations:** resilience with NA coping and CA coping.
		3. Stage I: 36.3%; Stage II: 48.3%; Stage III: 14.9%; Stage IV: 0.5%		**QOL** (FACT-B)	- **Regression**:

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Table 1 (*continued*)

Authors (year)	Study design (sample size)	Participants: 1) BCP, BCS, CG; 2) Age in years (SD); 3) Stage; 4) Mean time since diagnosis in years (SD)	Scale to assess resilience	Variables studied in relation to resilience	Results
		4. μ = 2,84 (1,54)			o Resilience positively predicted QOL and perceived growth, and this effect was moderated by PA coping.
Wu et al. (2016)	Cross-sectional **n = 213**	1. BCP	**CD-RISC-25**	**Sociodemographic variables** *(age, BMI, marital status, educational level, monthly family income, family history of BC, religion)*	- Mean of resilience: μ = 60.97 (12.30)
		2. μ = 47.30 (7.87)		**Clinical variables** *(clinical stage, surgery type, time span after diagnosis)*	- Participants with 44 years old or younger, whose BMI was less than 24, with education level of high school, junior college or above, with higher monthly family income, and receiving conservative surgery reported a higher level of resilience.
		3. Stage 0 or I: 23.48%; Stage II: 65.25%; Stage III: 11.27%		**Social Support** (SSRS)	- **Positive correlations:** resilience with time span after diagnosis, social support, confrontation coping, avoidance coping, and hope.
		4. μ = 85 days		**Coping** (MCMQ**:** *confrontation, avoidance, acceptance-resignation)*	- **Negative correlations:** resilience with age, BMI, and acceptance-resignation coping.
				Hope (HHI)	- **Regression**: hope, educational level of junior college or above, educational level of high school, avoidance coping, confrontation coping, and age were predictors of resilience.
Ye et al. (2018)	Cross-sectional **n = 342**	1. BCP	**CD-RISC-10**	**Emotional distress** (HADS)	- Mean of resilience: μ = 18,96 (7,89).
		2. Not reported		**Physical distress** (EORTC QLQ-C30)	- **Positive correlations:** resilience with social support, hope for the future, courage-related strategy and self-efficacy.
		3. Stage 0: 16.7%; Stage I: 36.0%; Stage II: 28.9%; Stage III: 11.1%; Stage IV: 7.3%		**Intrusive Thoughts** (IES)	- **Negative correlations**: resilience with emotional distress, physical distress, and intrusive thoughts.
		4. Not reported		**Social Support** (SSS) **Hope for the future** (HS)	- **Regression**: o Emotional distress, physical distress and social support were independent predictors of resilience by adjusting four moderating variables of self-efficacy, courage-related strategy, intrusive thoughts and hope for the future.
				Courage-related strategy (JCS) *(direct, optimistic, and supportive coping)*	o Courage-related strategy, self-efficacy and hope positively predicted resilience. Intrusive thoughts was an intermediate variable negatively related with courage-related strategy and self-efficacy that affected resilience in an indirect way.
				Self-efficacy (GSES)	
Zhang et al. (2017)	Cross-sectional **n = 98**	1. BCP	**CD-RISC-25**	**Social Support** (MOS-SSS) *(emotional-informational support*	- Mean of resilience: μ = 54.68 (16.83**)**

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Table 1 (*continued*)

Authors (year)	Study design (sample size)	Participants: 1) BCP, BCS, CG; 2) Age in years (SD); 3) Stage; 4) Mean time since diagnosis in years (SD)	Scale to assess resilience	Variables studied in relation to resilience	Results
				(ES), tangible support (TS), affectionate support (AS), positive social interaction (PS))	
		2. μ = 47.02 (9.59)		**QOL** (FACT-B)	- **Positive correlations:** resilience with ES, TS, AS and PS domains, global score of social support and QOL.
		3. Stage 0: 6,1%; Stage I: 19,4%; Stage II: 40,8%; Stage III: 25,5%; Stage IV: 8,2%			- **Regression**: Social support played a partial mediator role in the relationship between resilience and QOL. The mediation effect ratio was 28.0%
		4. Not reported			

Note. BAT = Body Attitude Test; BCP = Breast cancer patients; BCS = Breast cancer survivors; BDI-II= Beck Depression Inventory; BSQ= Body-Self Questionnaire; CCQ = Cancer Coping Questionnaire; CD-RISC-10 = Connor-Davidson Resilience Scale 10; CD-RISC-25 = Connor-Davidson Resilience Scale 25; CG = Control group; EFIR = Internal Resilience Factor Scale; CRS-15 = Centrality of Religiosity Scale-15; CZBI = Zarit Caregiver Burden Interview; DCS = Decisional Conflict Scale; EG = Experimental group; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-BR23 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-breast cancer module 23; ERS = Ego Resiliency Scale; FACT-B = Functional Assessment of Cancer Therapy-Breast; FHI = Family Hardiness Index; FRAS-C = Family Resilience Assessment Scale; GAD-2 = Generalized Anxiety Disorder Questionnaire-2 short version; GSES = General Self-Efficacy Scale; HADS = Hospital Anxiety and Depression Scale; HHI = Herth Hope Index; HS = 8-item Hope Scale; IES = Impact of Event Scale; ISEL= Interpersonal Support Evaluation List-6 short form; IUSP = Illness Uncertainty Scale for Patients-5; JCS = Jalowiec Coping Scale; LGB = LGB Identity Scale; MCMQ = Medical Coping Modes Questionnaire; Mini-MAC = Mental Adjustment to Cancer Scale-29; MSAS-SF = Memorial Symptom Assessment Scale-Short Form; MSPSS = Multidimensional Scale of Perceived Social Support; MOS-SF36 = Medical Outcomes Study-Short Form 36; MOS-SSS = Medical Outcomes Study-19; OI = Outness Inventory; ORS = Original resilience scale; PANAS = Positive and Negative Affect Schedule; PHQ-2 = Patient Health Questionnaire Two-Item Depression Scale; PRS = Psychological Resilience Scale; PSQI = Pittsburgh Sleep Quality Index; PTGI = Posttraumatic Growth Inventory; QOL = Quality of life; QOLHI = Quality of Life and Health Inventory; RESI-M = Mexican Resilience Scale; RSS = Rosenberg Self-Esteem Scale; RS-14 = 14-Item Resilience Scale; SCNS-SF32 M = Supportive Care Needs Survey-Short Form 32 Mexican Version; Self-Compassion Scale; Short PANAS = Short Version of Positive and Negative Affect Schedule; SOBI = Sense of Belonging Instrument; SPP-25 = Resilience Measurement Scale; SSRS = Social Support Rate Scale; SSS = Social Support Scale; STAI = State-Trait Anxiety Inventory; SV-RES = Resiliency Scale SV-RES; SWLS = Satisfaction with Life Scale; TMMS-24 = Trait Meta-Mood Scale-24; WDH = Two-single item questions from World Database of Happiness; WOC = Ways of Coping Checklist.

4. Cross-sectional and longitudinal studies

4.1. General features

Thirty studies followed a cross-sectional design and only one longitudinal study was identified (Edward et al., 2019) (Table 1). Age- and sex-matched controls were included in two studies (García-Maroto et al., 2015; Izydorczyk et al., 2019), one study involved sex- but not age-matched controls (Markovitz et al., 2015) and the remaining studies did not incorporated healthy controls.

Most of the studies used various forms of the Connor-Davidson Resilience Scale to assess participant's resilience (CD-RISC) (n = 20). Specifically, fourteen studies employed the original 25-Item version of the CD-RISC (Connor and Davidson, 2003) and five studies used the reduced 10-Item version of Campbell-Sills and Stein (2007). Instruments used by the rest of studies included the 14-Item Resilience Scale (RS-14) designed by Wagnild and Young (1993) (n = 4), the Resilience Measurement Scale (SPP-25, Ogińska-Bulik and Juczyński, 2008) (n = 2), the Ego Resiliency Scale (Block and Kremen, 1996) (n = 1), the Psychological Resilience Scale (PRS, Oshio et al., 2002) (n = 1), the Original Resilience Scale (Friborg et al., 2006) (n = 1), the Resilience Scale SV-RES (SV-RES, Saavedra-Guajardo and Villalta-Paucar, 2008) (n = 1), the Mexican Resilience Scale (RESI-M, Palomar-Lever and Gómez-Valdez, 2010) (n = 1) and the Internal Resilience Factor Scale EFIR (EFIR, García-Robles and Sayers-Montalvo, 2010) (n = 1).

4.2. Variables associated with resilience

We identified significant correlations between resilience and multiple biopsychosocial variables analyzed in the studies. Specifically, clinical variables (Fradelos et al., 2018, 2017; Gálvez-Hernández et al., 2018; Huang et al., 2019; Izydorczyk et al., 2018, 2019; Lee and Kim, 2018; Padilla-Ruiz et al., 2019; Ristevska-Dimitrovska et al., 2015a; Wu et al., 2016; Ye et al., 2018), sociodemographic variables (Bazzi et al., 2018; Fradelos et al., 2017; Gálvez-Hernández et al., 2018; Padilla-Ruiz et al., 2019; Wu et al., 2016), social variables (Al Eid et al., 2020; Alizadeh et al., 2018; Bazzi et al., 2018; Fradelos et al., 2018; Gálvez-Hernández et al., 2018; Huang et al., 2019; Kamen et al., 2017; Kokufu, 2012; Lai et al., 2019; Li et al., 2018; Wu et al., 2016; Ye et al., 2018; Zhang et al., 2017), psychological variables (Al Eid et al., 2020; Alarcon et al., 2020; Alizadeh et al., 2018; Bazzi et al., 2018; Fradelos et al., 2018, 2017; Fraanco et al., 2019; Huang et al., 2019; Izydorczyk et al., 2018; Kaczmarek et al., 2012; Kamen et al., 2017; Lai et al., 2019; Lee and Kim, 2018; Markovitz et al., 2015; Ocampo et al., 2011; Ristevska-Dimitrovska et al., 2015a, 2015b; Tadayon et al., 2018; Tu et al., 2019; Wu et al., 2016; Ye et al., 2018; Zhang et al., 2017) and physiological variables (Huang et al., 2019; Lai et al., 2019) were significantly associated to participants' resilience levels. Some authors did not find significant relationships between resilience and the other variables studied (Burgos-Félix et al., 2014; Edward et al., 2019) or did not analyze such associations (Dubey et al., 2015).

In relation to clinical variables, time elapsed since diagnosis or surgery, treatment type, clinical stage, symptom burden or severity and physical symptom distress appeared to impact participants' resilience. In the studies of Wu et al. (2016) and Gálvez-Hernández et al. (2018), a positive relationship between resilience and time span since breast cancer diagnosis was identified. In contrast, an inverse relationship was observed by Padilla-Ruiz et al. (2019), as they found higher levels of resilience among women in which a shorter period of time had passed since diagnosis. Likewise, Izydorczyk et al. (2018, 2019) found that

Table 2
Descriptive summary of intervention design-studies.

First author (year)	Design (sample size)	Participants: 1) BCP, BCS, CG; 2) Age in years (SD); 3) Stage; 4) Mean time since diagnosis in years (SD)	Intervention program: session frequency and duration	Scale to assess resilience	Variables studied in relation to resilience	Results
Cerezo et al. (2014)	RCT	1. BCP and CG	Positive psychology group intervention	**CD-RISC-25**	**Cognitive well-being** (SWLS)	Participants from EG reported improvements in all studied variables after the intervention.
	EG: **n = 101**	2. EG: μ = 50.71 (9.44); CG: μ = 49.35 (9.85)	14 × 120 min, 1 × /week		**Positive and negative affect** (AF-6)	
	CG: **n = 106**	3. Stage I-III			**Happiness** (SWLS)	
		4. Not reported			**Optimism** (LOT-R)	
					Emotional intelligence (TMMS-24)	
					Self-esteem (RSS)	
Henry (2017)	Cohort study **n = 26**	1. BCS	The Casting for Recovery therapeutic intervention	**CD-RISC-25**	**QOL** (QOL-BC)	Resilience and QOL did not improve after intervention.
		2. Not reported	3 days (the duration of session was not provided)		**Perceptions about the value of the intervention** *(qualitative data)*	
		3. Any disease stage				
		4. Not reported				
Lopprinzi et al. (2011)	RCT	1. BCS and CG	Stress Management and Resilience Training	**CD-RISC-25**	**Anxiety** (SAS)	Participants from EG reported significant improvements in resilience, anxiety, QOL and perceived stress after intervention. Fatigue did not improve.
	EG: **n = 12**	2. EG: μ = 61; CG: μ = 61	3 × 90 min, 3 × follow up phone call		**QOL** (LASA)	
	CG: **n = 12**	3. Stage 0: CG 8.3%; Stage 1: EG 41.6%, CG 33.3%; Stage 2: EG 41.6%, CG 16.6%; Stage 3: EG 8.3%; Unknown: EG 8.3%, CG 41.6%			**Fatigue** (VAS-Fatigue)	
		4. Not reported			**Perceived stress** (PSS)	
Swainston & Derakshan (2018)	Non-RCT. Follow-up at 1 and 15 months	1. BCS and CG	Adaptive Dual n-back Cognitive Training	**CD-RISC-25**		Participants resilience did not improve.
	EG: **n = 39**	2. EG: μ = 51 (6.0); CG: μ = 48 (5.52)	12 × 30min			
	CG: **n = 40**	3. Not reported				
		4. Not reported				
Wu et al. (2018)	RCT. Follow-up at 3rd and 5th CT sessions and 2 weeks after the final CT	1. BCP and CG	Psychoeducational Intervention	**RS-14**	**Anxiety/depressive symptoms** (HADS)	Participants from EG reported significant improvements in resilience, anxiety, depression and QOL (physical function, cognitive function, nausea, constipation, body image, future perspective and breast symptoms) 2 weeks after CT. They also showed higher disease-specific care knowledge and self-efficacy during the 3rd and 5th CT session, respectively.
	EG: **n = 20**	2. EG: μ = 51.2 (9.18); CG: μ = 51.2 (10,71)	6 × 60 min		**QOL** *(*EORTC QLQ-C30*: 1. Functional Scales: physical, role, cognitive, social, emotional; 2. Symptom Severity Scales: nausea, pain, fatigue, dyspnea, diarrhea, constipation, insomnia, appetite loss, financial difficulties; 3. Global Health Scale.* EORTC QLQ-BR23*: 1. Functional scales: body image, sexual function, sexual enjoyment, future perspective; 2. Symptom Scales: systemic therapy side effects, arm and breast symptoms, upset by hair loss)*	
	CG: **n = 20**	3. Stage I: EG 35%, CG 10%; Stage II: EG 40%, CG 30%; Stage III: EG 15%, CG 35%; Stage IV: EG 10%, CG 25%			**Self-efficacy** (SES)	

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Table 2 (*continued*)

First author (year)	Design (sample size)	Participants: 1) BCP, BCS, CG; 2) Age in years (SD); 3) Stage; 4) Mean time since diagnosis in years (SD)	Intervention program: session frequency and duration	Scale to assess resilience	Variables studied in relation to resilience	Results
		4. Not reported			**Disease-specific care knowledge** (DSCKS)	
Ye et al. (2016)	RTC. Follow-up at 2, 6 and 12 months	1. BCP and CG	Be Resilient to Breast Cancer	**CD-RISC-10**	**Anxiety/depressive symptoms** (HADS) **illness uncertainty** (IUSP)	Participants from EG reported significantly lower depression and illness uncertainty as well as better hope and QOL (emotional function, role function and global score) at 2 months. They also showed greater resilience, social support and transcendence as well as lower anxiety and physical distress (fatigue, nausea and vomit) at 6 months.
	EG: **n = 101**	2. Not reported	8 × 180min, 1 × /week		**Physical distress** (EORTC QLQ-C30: *pain, nausea, fatigue*)	
	CG: **n = 103**	3. Stage 0: EG 22.6%, CG 18.3%; Stage I: EG 44.1%, CG 41.5%; Stage II: EG 33.3%, CG 40.2%	3 additional sessions in following 10 months		**QOL** (EORTC QLQ-C30: *Physical Function, Emotional Function, Role Function, Cognitive Function, Social Function*)	
		4. Not reported			**Hope** (HS)	
					Transcendence (CSTS)	
					Social support (SSS)	
Ye et al. (2017)	RCT. Follow-up at 2, 6 and 12 months.	1. Metastatic BCP and CG	Be Resilient to Breast Cancer	**CD-RISC-10**	**Clinical variables** *(3- and 5-year cancer-specific survival)*	Participants from EG reported significant improvements in resilience, anxiety, depression, QOL (global score and its dimensions) and allostatic load index after 2 months. Cancer-specific survival did not improve.
	EG: **n = 113**	2. Not reported	53 × 120 min, 1 × /week		**Anxiety/depressive symptoms** (HADS)	
	CG: **n = 113**	3. Not reported			**QOL** (EORTC QLQ-C30: *Physical Function, Emotional Function, Role Function, Cognitive Function, Social Function, Pain, Fatigue, Nausea and Vomiting*)	
		4. Not reported			**Allostatic load index**	
Zhou et al. (2019)	RCT. Follow-up at 4, 8, and 12 weeks	1. BCP and CG	Cyclic Adjustment Training intervention	**CD-RISC-25**	**Anxiety** (SRAS)	Participants from EG reported significant improvements in resilience, anxiety and depression at 3 follow-ups.
	EG: **n = 66**	2. EG: μ = 44.62 (7.89); CG: μ = 44.37 (7.32).	Not reported		**Depression** (SDS)	
	CG: **n = 66**	3. Stage I: EG 43.9%, CG 47%; Stage II: EG 45.5%, CG 40.9%; Stage III: EG 10.6%, CG 12.1%				
		4. Not reported				

Note. AF-6 = Affectivity Scale-6; BCP=Breast cancer patients; BCS = breast cancer survivors; CD-RISC-10 = Connor-Davidson Resilience Scale 10; CD-RISC-25 = Connor-Davidson Resilience Scale 25; CG=Control group; CI= Resilience as a component of the intervention; CSTS = Self-Transcendence Scale; CT=Chemotherapy; DSCKS = Disease-Specific Care Knowledge Scale; DV = Resilience only as a dependent variable; EG = Experimental group; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HADS = Hospital Anxiety and Depression Scale; HS = 8-item Hope Scale; LASA = Linear Analog Self-Assessment Scale; LOT-R = Life Orientation Test–Revised; MO = Resilience as the main objective of intervention; PSS = Perceived Stress Scale; QOL = Quality of life; QOL-BC = Quality of life instrument–Breast cancer patient version; RCT = Randomized controlled trial; RSS = Rosenberg Self-Esteem Scale; RS-14 = 14-Item Resilience Scale; SWLS = Satisfaction with Life Scale; SAS = Smith Anxiety Scale; SDS = Self-Rating Depression Scale; SES = Self-Efficacy Scale; SRAS = Self-Rating Anxiety Scale; SSS = Social Support Scale; TMMS-24 = Trait Meta-Mood Scale-24; VAS-Fatigue = Visual Analog Scale-Fatigue.

breast cancer patients differed in the level of resilience experienced depending on the time elapsed since mastectomy, manifesting higher resilience in the short period of time after the procedure (up to 2 years). Regarding the treatment type, conservative surgery (Wu et al., 2016) and chemotherapy (Padilla-Ruiz et al., 2019) generated the greatest impact in terms of increasing participants resilience levels, while the number of courses of adjuvant-therapy (including chemotherapy, radiotherapy, or endocrine therapy) contributed to significantly decreasing it (Huang et al., 2019). Clinical stage was also found to be inversely related to resilience, since the earlier the clinical stage, the greater the resilience obtained by the patients (Huang et al., 2019). Other studies identified variables such as symptom burden, symptom severity and physical symptom distress significantly correlated with lower resilience scores (Fradelos et al., 2018, 2017; Lee and Kim, 2018; Ristevska-Dimitrovska et al., 2015a; Ye et al., 2018).

Regarding sociodemographic variables, Wu et al. (2016) found greater levels of resilience among younger and highly educated breast cancer patients who showed a higher monthly family income and whose BMI was less than 24. Similarly, increased resilience was observed by Fradelos et al. (2017) among younger breast cancer survivors as well as by Gálvez-Hernández et al. (2018) and Padilla-Ruiz et al. (2019) among participants showing higher levels of education. Gálvez-Hernández et al.

(2018) also found a negative association between resilience and marital status. Employment status probed to be another sociodemographic variable related to women resilience levels. In such study, Bazzi et al. (2018) compared two groups of breast cancer survivors, heterosexual and sexual minority (lesbian or bisexual women), and found that, although there was no relationship between employment and resilience among the former, unemployed sexual minority women showed lower levels of resilience than employed ones.

Additionally, many studies found that participants perceiving the availability of social support seemed to be more likely to display higher levels of resilience (Alizadeh et al., 2018; Bazzi et al., 2018; Huang et al., 2019; Kamen et al., 2017; Wu et al., 2016; Ye et al., 2018; Zhang et al., 2017). Likewise, some authors highlighted the important function that family plays in women with breast cancer, since family hardiness, family resilience and marital satisfaction have been identified as factors positively related to improvements in resilience (Huang et al., 2019; Lai et al., 2019; Li et al., 2018). The role of religiosity in fostering participants resilience has also been acknowledged by Al Eid et al. (2020) and Fradelos et al. (2018), just as sense of belonging to a group, which showed to positively influence patients levels of resilience (Alizadeh et al., 2018). In a study conducted with sexual minority breast cancer survivors, Kamen et al. (2017) found that resilience mediated the relationship between the exposure to discrimination and higher rates of distress. Other studies reported that variables such as unmet supportive care needs (Gálvez-Hernández et al., 2018), caregiver burden (Li et al., 2018) and decisional conflict in the context of the choice of the initial treatment (Kokufu, 2012), had a negative impact on participants resilience. The relationship between resilience and mental health needs was also analyzed by Bazzi et al. (2018), who showed that psychological counseling prior to diagnosis was significantly associated with reduced levels of resilience among breast cancer survivors.

A number of studies have identified different psychological variables as relevant contributors in both facilitating and reducing participants' resilience. Among others, self-esteem (Alarcon et al., 2020), self-compassion (Alizadeh et al., 2018), self-efficacy (Huang et al., 2019; Ye et al., 2018), body image (Izydorczyk et al., 2018), posttraumatic growth (Tu et al., 2019), QOL (Franco et al., 2019; Ocampo et al., 2011; Ristevska-Dimitrovska et al., 2015b; Tu et al., 2019; Zhang et al., 2017), life satisfaction (Alarcon et al., 2020; Kaczmarek et al., 2012), hope (Wu et al., 2016; Ye et al., 2018), positive affect (Alarcon et al., 2020; Markovitz et al., 2015), emotional intelligence (Alarcon et al., 2020), current happiness (Markovitz et al., 2015) and coping (Bazzi et al., 2018; Kaczmarek et al., 2012; Lai et al., 2019; Lee and Kim, 2018; Tu et al., 2019; Wu et al., 2016; Ye et al., 2018) have been recognized as being important cognitive and emotional factors linked to increased levels of resilience. In terms of coping, studies showed that those strategies oriented to positively interpret adverse situations such as minimizing the situation and active coping (Lai et al., 2019) and positive acceptance (Tu et al., 2019) were significantly related to higher resilience levels. Moreover, courage-related coping, understood as a direct, supportive and optimistic strategy (Ye et al., 2018), confrontation and avoidance coping (Wu et al., 2016) and both fighting spirit combined with helplessness/hopelessness and fatalism (Bazzi et al., 2018) were found to be positively associated with resilience. In the study of Kaczmarek et al. (2012), resiliency showed to have an indirect positive effect on patients life satisfaction through coping strategies. Specifically, higher use of adaptive strategies such as positive reframing, as well as less utilization of maladaptive ones such as helplessness/hopelessness and anxious preoccupation proved to be significantly associated with greater resilience levels. On the other hand, anxious preoccupation, acceptance-resignation, cognitive-avoidance and negative-affect coping have been identified as strategies linked to significant reductions in resilience (Bazzi et al., 2018; Tu et al., 2019; Wu et al., 2016). Frequently, psychological distress, including anxiety and depressive symptoms, as well as QOL were negatively associated with resilience (Al Eid et al., 2020; Fradelos et al., 2018, 2017; Franco et al., 2019; Kamen et al., 2017; Lai et al., 2019; Lee and Kim, 2018; Markovitz et al., 2015; Ocampo et al., 2011; Ristevska-Dimitrovska et al., 2015a, 2015b; Tadayon et al., 2018; Tu et al., 2019; Ye et al., 2018; Zhang et al., 2017). In the study of Ye et al. (2018), the amount of intrusive thoughts reported by patients during breast cancer treatment was found to be an important factor related to reductions in participants resilience levels. An inverse relationship was also observed in the studies of Alarcon et al. (2020) and Markovitz et al. (2015) between resilience and the levels of negative affect exhibited by participants.

Authors also studied the influence of some physiological variables on participants' resilience. In this regard, Huang et al. (2019) found that moderate physical exercise after breast cancer contributed to significantly increase patients levels of resilience. Additionally, Lai et al. (2019) observed fewer sleep disorders among participants displaying higher resilience scores.

5. Intervention studies

5.1. General features

A total of eight intervention studies were identified, of which six were randomized controlled trials (RCT) and two quasi-experimental (non-randomized controlled trial) and non-experimental (cohort study) research designs, respectively (Table 2). Most studies provided face-to-face interventions and one study conducted an online intervention. Group intervention approach was used in a half of studies while the other half used an individual intervention approach. A waiting-list or an usual treatment control group was incorporated in the majority of the studies and only one study included an active control group.

Among all the intervention programs, seven studies used resilience in both their intervention programs as well as a dependent variable, and one study used resilience only as a dependent variable. In the first case, two studies included resilience as a component of their training programs (Cerezo et al., 2014; Wu et al., 2018), while the remaining five were focused on enhancing and strengthening the resilience of participants (Henry, 2017; Loprinzi et al., 2011; Ye et al., 2017, 2016; Zhou et al., 2019). The number of sessions of the intervention programs that included resilience was highly variable, from a minimum of two sessions to a maximum of 53 sessions, lasting from 20 to 180 min. In one of the studies, the intervention program lasted a total of 3 days (Henry, 2017) and another study did not provide information about the total number of sessions included in the program (Zhou et al., 2019). The only intervention study that used resilience as a dependent variable and not as part of the intervention program consisted of 12 30-min sessions (Swainston and Derakshan, 2018). While the majority of the studies used a controlled pre and post-test design (Cerezo et al., 2014; Loprinzi et al., 2011; Wu et al., 2018; Ye et al., 2016, 2017; Zhou et al., 2019), one study did not fully randomly allocate participants to each intervention and control group (Swainston and Derakshan, 2018) and another study did not use a comparison group to measure outcomes before and after the program occurred (Henry, 2017).

According to the instruments used for assessing resilience, most studies employed the original 25-item (Connor and Davidson, 2003) and the reduced 10-item version of CD-RISC (Campbell-Sills and Stein, 2007) and only one study used RS-14 (Wagnild and Young, 1993).

5.2. Effect of interventions on participants' resilience

Most of the intervention programs were found to be effective for improving participants resilience (Cerezo et al., 2014; Loprinzi et al., 2011; Wu et al., 2018; Ye et al., 2016, 2017; Zhou et al., 2019). Cerezo et al. (2014) found significantly higher levels of resilience in addition to other health-related psychological factors (i.e., well-being, emotional intelligence, optimism, self-esteem) in participants who received a positive-psychology based group intervention. Ye et al. (2016, 2017) tested the effect of a 12 months mentor-based and educational program

in early-stage and metastatic breast cancer patients, respectively, and found that the intervention had a positive impact on patient resilience levels. In the study of Wu et al. (2018), the administration of a psychoeducational intervention was shown to be effective in improving perceived knowledge, QOL and resilience in a sample of breast cancer patients during and after chemotherapy. Similarly, brief resilience training by using the stress management and resilience training program proved to increase resilience and QOL as well as decrease stress, anxiety and fatigue in a small group of breast cancer survivors (Loprinzi et al., 2011). Greater resilience levels were also observed by Zhou et al. (2019) in post-surgical breast cancer patients who had received a cyclic adjustment training intervention through a mobile phone application. In contrast, two studies reported not having found significant differences in participants resilience levels following the administration of the intervention program (Henry, 2017; Swainston and Derakshan, 2018). In this regard, Swainston and Derakshan (2018) found that although the participation in a course of adaptive dual n-back cognitive training significantly reduced breast cancer survivors anxiety and rumination, it did not serve to improve their resilience levels. Henry (2017), for its part, observed that while the participation in a fly-fishing weekend therapeutic retreat program resulted highly satisfactory for breast cancer survivors, it also did not contribute to increasing their resilience and QOL.

6. Discussion

This systematic review aimed to provide an overview of the studies conducted on resilience in breast cancer care. We have summarized the available evidence on different sociodemographic, clinical and psychosocial variables related to resilience in women with breast cancer. However, the lack of consistency in the measures used, the heterogeneity of the included populations (different stages, age of participants, etc.), together with the cultural bias derived from the variability of geographic and cultural contexts (Ungar, 2012), the small sample size of some researches and the fact that most of them did not include healthy controls could limit the generalizability of our conclusions. It should be noted that some studies have included newly diagnosed patients in the sample, along with women whose treatments have long since ended. In fact, many authors did not indicate the period of time elapsed after the breast cancer diagnosis. Undoubtedly, the cancer experience is a highly complex time-dependent process, and, therefore, as a dynamic entity, the psychosocial repercussions of each of these moments are extremely different (Deckx et al., 2015; Kypriotakis et al., 2016; Molina et al., 2014), which does not allow patients from different phases to be grouped together.

Overall, results suggest important differences in prevalence rates of resilience scores in women with breast cancer, finding both lower and higher values than in the general population. This inconsistence could be due to the heterogeneity of the samples and by the fact that different resilience assessment tools were used. With regard to sociodemographic and clinical variables, some authors found that age, education level, employment, marital satisfaction and status, body mass index, monthly family income, religion, time span after diagnosis, clinical stage of breast cancer, treatment type (chemotherapy, conservative surgery), number of courses of adjuvant therapy, symptom burden or severity and physical symptom distress were related to resilience (Al Eid et al., 2020; Bazzi et al., 2018; Fradelos et al., 2018, 2017; Gálvez-Hernández et al., 2018; Huang et al., 2019; Izydorczyk et al., 2018, 2019; Lai et al., 2019; Lee and Kim, 2018; Padilla-Ruiz et al., 2019; Ristevska-Dimitrovska et al., 2015a; Wu et al., 2016; Ye et al., 2018). However, the use of a particular questionnaire may have conditioned the emergence of specific variables that are better adjusted with the tool itself, giving rise to a significant risk of outcome bias (Casellas-Grau et al., 2017). More studies must be conducted to identify sociodemographic and clinical variables related to resilience.

Although there is a wide variability in the psychosocial variables studied (such as emotional intelligence, self-esteem, self-efficacy, happiness and hope, between others), in general, the authors have focused on aspects related to anxiety, depression, QOL, coping styles and perceived social support. Resilience was strongly associated with indicators of psychological well-being, with a negative association with anxiety and depression in both BCP (Fradelos et al., 2018; Lai et al., 2019; Markovitz et al., 2015; Tadayon et al., 2018; Ye et al., 2018) and BCS (Fradelos et al., 2018; Ristevska-Dimitrovska et al., 2015b). In addition, despite the absence of results found by García-Maroto et al. (2015), the regression analyses carried out support the existence of a bidirectional relationship between anxiety/depressive symptoms and resilience, in which resilience could lead to a reduction of emotional problems and vice versa in both BCP and BCS (Al Eid et al., 2020; Fradelos et al., 2018, 2017; Lai et al., 2019; Lee and Kim, 2018; Ye et al., 2018). Anxiety/depressive symptoms are common in the continuum of treatment and survivorship (National Comprehensive Cancer Network, 2019), and these psychological symptoms also contribute to reduced QOL and cancer survival and influence women with breast cancer to have more difficulty in coping with cancer (Brunault et al., 2016; Gold et al., 2016; Shim et al., 2006). Despite the fact that the use of different scales makes it difficult to clearly compare results, in general coping has been often found to be related to resilience. Thus, an adaptive coping strategies (characterized by subscales such as active coping or positive acceptance) were associated with higher levels of resilience among BCP and BCS, whilst non-adaptive ways of coping (e.g. anxious preoccupation, negative-affect or cognitive-avoidance) were negatively correlated with resilience (Bazzi et al., 2018; Kaczmarek et al., 2012; Lai et al., 2019; Tu et al., 2019; Wu et al., 2016), consistently with previous studies with other cancer populations (Llewellyn et al., 2013; Wu et al., 2013). Some authors have even found that coping was able to predict the psychological resilience of BCP and BCS (Lai et al., 2019; Lee and Kim, 2018; Wu et al., 2016). These results suggest that the ability to cope with an adversity, develop adaptive competences and transform it into a more protective situation diminish the impact of cancer and its treatment. Patients who adopt appropriate coping strategies may be able to effectively reduce their psychosocial distress, increase their levels of resilience and thereby improve their QOL (Elsheshtawy et al., 2014; Kvillemo and Bränström, 2014; Lim, 2014; Llewellyn et al., 2013). Consistently, the results suggest a positive association between resilience and several dimensions of QOL (Franco et al., 2019; Ocampo et al., 2011; Ristevska-Dimitrovska et al., 2015a; Tu et al., 2019; Zhang et al., 2017). On the other hand, highly resilient patients using active coping styles also seem to use social support more efficiently (Siqueira-Costa et al., 2017; Somasundaram and Devamani, 2016). Based on these results, social support may act as a protective factor in developing resilience in both BCP and BCS (Alizadeh et al., 2018; Bazzi et al., 2018; Huang et al., 2019; Kamen et al., 2017; Wu et al., 2016; Ye et al., 2018; Zhang et al., 2017). Social support can help cancer patients to process their trauma, facilitate coping and increase adjustment (Greup et al., 2018). Therefore, all of these results indicate that there is a close relationship between resilience, anxiety-depressive symptoms, QOL, coping and social support within breast cancer care continuum, which reflects many potential targets for improving resilience in both BCP and BCS.

In the present review, we found that interventions among BCP and BCS comprised issues that enhanced psychological resilience, such as improved coping strategies, psychosocial support groups or education and counseling for stress management. Notwithstanding the lack of effectiveness shown by Henry (2017) and Swainston and Derakshan (2018), in general intervention studies have been effective in improving psychological factors, such as resilience, anxiety, depression and QOL, among others. Despite the fact that these conclusions are consistent with those reported from previous studies on resilience-enhancing interventions with other populations (Joyce et al., 2018; Leppin et al., 2014; Ludolph et al., 2019), it is difficult to draw concrete conclusions because the characteristics of the sample and the type and length of the intervention programs varied widely. Some authors affirm that in

patients with chronic diseases, such as breast cancer, resilience could help patients to identify changes in their lives, to accept modifications in their physical and social states and to motivate them to actively participate in treatment, which can ultimately lead to a healthier life (Kim et al., 2019). Therefore, future research should employ standardized methods in resilience-promoting interventions to elucidate clear conclusions about the efficacy of this type of intervention in breast cancer care.

Nevertheless, this systematic review does have some limitations which should not be overlooked. It is important to note that the heterogeneity of study samples and designs make it impossible to draw definitive conclusions. In addition, different instruments used to assess resilience and other variables related could explain the contradictory study findings. Finally, there is a lack of unification in the characteristics of the interventions conducted.

In conclusion, this study provides evidence about multiple clinical, sociodemographic, social, psychological and physiological variables related to resilience of women with breast cancer. These results have practical importance since they provide tentative insight of the targets that contribute to the promotion of positive outcomes during breast cancer care continuum. In addition, the results found in this review suggested the existence of different interventions that could improve resilience in women with breast cancer. However, due to the significant variability, more research is needed in order to extrapolate clear conclusions and to deepen in the associations with other variables. Given the pronounced individuality of the breast cancer experience, a better understanding of biopsychosocial factors related to healthier life is critical to develop an integrative praxis on breast cancer care-giving. Therefore, an opportunity exists for nursing scientists to explore these factors across every stage of breast cancer continuum, identifying those women who could probably benefit from a resilience-enhancing intervention. Once identified, successful nursing interventions should be addressed to promote resilience as an essential component of breast cancer care.

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2. Study #2

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REVIEW

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Psychological resilience and cortisol levels in adults: A systematic review

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Abstract

Resilience or the capacity to "bend but not break" refers to the ability to maintain or regain psychobiological equilibrium during or after exposure to stressful life events. Specifically, resilience has been proposed as a potential resource for staving off pathological states that often emerge after exposure to repeated stress and that are related to alterations in circulating cortisol.

The aim of this systematic review of the literature was to gather evidence related to the relationship between psychological resilience and cortisol levels in adult humans.

An extensive systematic search was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method in the PubMed and Web of Science databases. In total, 1256 articles were identified and, of these, 35 peer-reviewed articles were included in the systematic review.

We categorized findings according to (1) the short and long-term secretion period covered by the cortisol matrices selected by studies and also according to (2) the differentiated diurnal, phasic (acute), and tonic (basal) components of the HPA output to which they refer and their relationships with resilience. Reported relationships between psychological resilience and distinct cortisol output parameters varied widely across studies, finding positive, negative, and null associations between the two variables. Notably, several of the studies that found no relationship between resilience and cortisol used a single morning saliva or plasma sample as their assessment of HPA axis activity.

Despite limitations such as the great variability of the instruments and methods used by the studies to measure both resilience and cortisol, together with their high heterogeneity and small sample sizes, the evidence found in this systematic review points to the potential of resilience as a modifiable key factor to modulate the physiological response to stress. Therefore, further exploration of the interaction between the two variables is necessary for the eventual development of future interventions aimed at promoting resilience as an essential component of health prevention.

1 | INTRODUCTION

Resilience as a broad and multifactorial phenomenon represents a set of personal resources that allow the individual to cope successfully with adversity (Fletcher & Sarkar, 2013). Metaphorically defined as the tendency to "bend but not break" (Karatsoreos & McEwen, 2013), it refers to the ability to maintain or regain psychophysiological equilibrium during or after exposure to stressful life events (Bonanno et al., 2011). Because of its increasing relationship to positive health outcomes, resilience has been gaining attention over the last few years. Specifically, literature has documented greater levels of mental and physical quality of life (Moore et al., 2015), higher self-efficacy (Schueler et al., 2021) and self-esteem (Joy et al., 2023), and fewer anxiety and depressive symptoms (Zhang et al., 2023) among individuals displaying higher resilience levels. However, pathological emotional states, such as negative affect and anxiety that often emerge in response to repeated stress have been observed in less resilient subjects; these states, in turn, have been linked to detrimental physiological processes including dysregulated circulating cortisol (Zapater-Fajarí et al., 2021; Zautra et al., 2010).

Cortisol, the glucocorticoid hormonal end-product of the hypothalamic–pituitary axis (HPA), is one of the major hormonal regulators of the physiological response to stress. Upon perception of an acute psychological or physiological threat, cortisol secretion is initiated through a cascade of hormones in the HPA axis. The first link in this cascade begins in the paraventricular nucleus of the hypothalamus, which releases corticotropin-releasing factor (CRF) into the pituitary portal circulation. CRF then targets the anterior pituitary gland triggering the production of the adrenocorticotropin hormone (ACTH) and its release into the circulation, which after traveling through the bloodstream stimulates the production of cortisol by the adrenal glands. From this moment on, the availability of cortisol generates a multitude of downstream effects on different bodily functions, including metabolic, immune, cardiovascular, and gastrointestinal functions, all of which are intended to help the organism cope with the impending challenge (Oakley & Cidlowski, 2013). In addition to its response to an acute stressor, cortisol secretion is also subject to diurnal oscillations controlled by the central circadian clock (Dickmeis, 2009). This circadian pattern is characterized by a marked increase in its levels within approximately 30 min after waking (i.e., cortisol awakening response, CAR) (Stalder et al., 2016) followed by a subsequent decrease throughout the day, until it reaches its lowest point at bedtime (i.e., diurnal cortisol slope, DS) (Adam et al., 2017).

1.1 | Regulatory mechanisms of cortisol secretion

Cortisol secretion in the HPA axis is regulated through a negative feedback loop in which cortisol release inhibits ACTH secretion from the pituitary gland and with it, its further suppression (Elder et al., 2014). Specifically, glucocorticoid feedback has been shown to be a key mechanism that enables the rapid activation of the HPA axis in response to acute stress and its subsequent return to pre-stress conditions. However, it is known that the chronic activation of stress response systems can lead to methylation changes in glucocorticoid receptor (GR) genes, resulting in the dysregulation of feedback loops. Such dysregulation typically leads to excessive concentrations of cortisol in cerebrospinal fluid, plasma, and saliva (Bellavance & Rivest, 2014; Ryan & Ryznar, 2022). Moreover, repeated activation can also result in HPA habituation, negative feedback hypersensitivity of up-regulated GR receptors, and blunted responses to stress, ultimately giving rise to lower cortisol levels or a flattened diurnal cortisol slope across the day (Holochwost et al., 2021; Nishimi et al., 2022). Cortisol dysregulation, in turn, has been proposed as a risk factor for the development of several illnesses, including depression, type 2 diabetes, and Alzheimer's disease (Ennis et al., 2017; Joseph & Golden, 2017).

1.2 | Current status of the relationship between cortisol and resilience

Over the last decade, interest in linking resilience to putative biomarkers has grown and several studies have hypothesized that resilient individuals would have better-regulated cortisol levels than their non-resilient counterparts (Nishimi et al., 2022; Petros et al., 2013). Thus, resilience has been suggested to reduce alterations in daily cortisol patterns, acting as a modulator of the association between diurnal cortisol and health and, through this, enhancing adaptation (Gaffey et al., 2016). With that in mind, several studies have measured both self-reported resilience and cortisol levels, among which inversely significant associations between the two variables have been identified (Costa de Robert et al., 2010; Krisor et al., 2015; Ruiz-Robledillo et al., 2014; Sun et al., 2014). However, these investigations used a wide range of different resilience scales (Campbell-Sills & Stein, 2007; Connor & Davidson, 2003; Sinclair & Wallston, 2004; Tang & Zhang, 2009) or cortisol measurement matrices, such as hair, serum, saliva or urine (Costa de Robert et al., 2010; Krisor et al., 2015; Ruiz-Robledillo et al., 2014; Sun et al., 2014), and a variety of strategies

for quantifying this hormone, including 24-h integrated cortisol levels, measurement of the cortisol awakening response (CAR) or analysis of mean net serum cortisol levels at a single time point (Costa de Robert et al., 2010; Krisor et al., 2015; Ruiz-Robledillo et al., 2014; Sun et al., 2014).

1.3 | Short and long-term cortisol estimates

It is important to note that, depending on when they are taken or what specific measurement parameters are used, cortisol samples may represent different underlying physiological mechanisms of HPA functioning (Dobler et al., 2019; Epstein et al., 2021; Jiang et al., 2019; Short et al., 2016). For example, saliva, blood, and urine matrices provide estimates of cortisol circadian rhythms, acutely circulating cortisol levels, and basal cortisol production for periods of usually less than 24 h (Jiang et al., 2019; Stalder & Kirschbaum, 2012). With respect to cortisol circadian rhythms, deviations from a typical CAR pattern and flatter diurnal cortisol slopes (DS) have been associated with non-adaptive neuroendocrine processes and poorer physical and mental health outcomes (Adam et al., 2017; Short et al., 2016). On the other hand, circulating cortisol levels resulting from acute stress reflect the activation of the phasic (reactive) component of the HPA response, which is usually triggered by stimuli of an unexpected and uncontrollable nature (Dickerson & Kemeny, 2004). The phasic cortisol response is characterized by a marked initial increase (reactivity) of this hormone within 20 min of perceiving a stressor, followed by its continued decline (recovery) after about 70 min (Engert et al., 2011). In contrast, basal cortisol production, which can be estimated using a variety of measures, including single saliva or blood samples, area under the curve (AUC) calculations indicative of total daily cortisol production, or 12- or 24-h integrated urine samples, reflects the tonic component of the HPA response, which can only be measured under non-stress conditions (Dobler et al., 2019; Jiang et al., 2019).

For their part, hair cortisol measures provide retrospective estimates of integrated basal cortisol production over periods ranging from one to several months, a time interval difficult to encompass using any of the methods described above. Although there is some inter-individual variation in the rate of scalp hair growth, it is generally accepted that each centimeter of hair taken from the posterior vertex region of the scalp reflects the mean cortisol levels of the previous month (Stalder & Kirschbaum, 2012). Unlike 12- or 24-h integrated urinary cortisol, hair cortisol is thought to reflect the long-term tonic activity of the HPA axis, which is why it is considered a more reliable and valid indicators of chronic physiological stress (Russell et al., 2012).

Taking into account that each cortisol measurement targets a specific time period (short or long-term) as well as a differentiated component of the HPA output (diurnal, phasic, or tonic), its choice should suit each type of research question, with saliva, blood, and urine matrices being more suitable for the analysis of short-term cortisol production as opposed to hair, which allows the estimation of long-term cortisol production.

1.4 | Rationale and aim of the study

Given the emerging evidence pointing to resilience as a possible attenuator of the deleterious effects of the physiological response to stress through cortisol (Gaffey et al., 2016), discerning the conditions under which the relationship between the two variables occurs is of particular importance. It is therefore necessary to summarize the current state of the art in order to identify and differentiate the currently applied resilience and cortisol measurement methods in an attempt to guide future research toward more standardized and comparable study designs. Thus, the aim of the present study is to carry out a systematic review of the literature to gather evidence on the relationship between psychological resilience and cortisol levels in adult humans.

2 | METHODS

Each step of the following systematic review was informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to ensure comprehensive reporting of the evidence-based minimum reporting items (Liberati et al., 2009).

2.1 | Search strategy

An extensive systematic search of the extant published literature on the relationship between psychological resilience and cortisol was conducted in the Pubmed and Web of Science electronic databases, from inception up until January 11, 2022. Our search terms comprised the following keyword combinations: resilienc* AND cortisol. Both published peer-reviewed original manuscripts and in-press manuscripts were deemed eligible for inclusion. We also hand-searched the reference list of all eligible articles in an attempt to identify further studies. Gray literature was not searched. Selected articles were then

exported to the Mendeley Reference Manager for management.

2.2 | Eligibility criteria

Studies were deemed eligible for initial review if they met the following criteria: (1) participants were adults aged 18 years or older; (2) participants' psychological resilience and cortisol were examined using quantitative procedures; (3) studies assessed the link between resilience and cortisol; and (4) studies were original articles published in English or Spanish.

Although no restrictions were imposed in terms of year publication, we did exclude quantitative works that (1) were not conducted with humans; (2) only mentioned resilience or cortisol, without objectively assessing them; (3) involved a qualitative examination of participants' resilience; (4) were not published in English or Spanish; and (5) were review articles, books or chapters, commentaries, protocols, editorials, poster abstracts, case reports or dissertations.

2.3 | Study selection

A total of 1256 articles were identified in our initial database search (Figure 1: PRISMA flowchart). Titles, abstracts, and full-text articles were assessed independently by three researchers (author AMV, author JPT, and author IAP), following a screening procedure that was agreed upon in advance.

After the initial removal of duplicates (412 articles), 763 of the remaining records were identified as non-relevant based on a review of titles and abstracts and were excluded because they: did not measure resilience and/or cortisol ($n = 323$); did not follow a quantitative design ($n = 4$); did not use adult participants ($n = 57$); were not conducted with humans ($n = 141$); were published in a language other than English or Spanish ($n = 8$); or were theoretical reviews, book chapters, protocols abstracts or conference papers ($n = 227$). In addition, 3 more articles that turned out to be duplicates were excluded at this stage. Next, a second-stage screening process was conducted independently by AMV, JPT, and IAP with the remaining potentially relevant 81 articles to ensure they met the inclusion criteria. This resulted in the exclusion of 46 additional articles that did not measure the relationship between cortisol and resilience ($n = 38$); did not provide the full resilience scale ($n = 1$); or for which the full texts were not available ($n = 7$). Finally, the authors reviewed each of the 35 articles that met the study criteria. Any possible discrepancies concerning the inclusion of a study were resolved through consensus-based discussion. The data extracted from the eligible articles included study design, subject characteristics, resilience measurement scale, cortisol measurement methodology, and key research findings.

3 | RESULTS

3.1 | Research design of the reviewed studies

A total of 35 studies met the inclusion criteria and were included in the final review (Tables 1 and 2). All the articles followed a quantitative methodology. Most were written in English ($n = 35$), with one written in Spanish, and were conducted in Europe ($n = 16$), North America ($n = 6$), South America ($n = 2$), Asia ($n = 7$), Oceania ($n = 3$) and Africa ($n = 1$).

Most ($n = 21$) had a cross-sectional design, with the remaining studies having either an intervention ($n = 9$) or a longitudinal design ($n = 5$).

3.2 | Study participants

The sample sizes of the reviewed studies ranged from 28 to 800 participants, and the average age ranged from 20.52 to 64.24 years. Participants were recruited from a variety of different settings, specifically hospitals or private health centers ($n = 10$), youth residential care institutions ($n = 1$), universities ($n = 10$), army special forces ($n = 1$), workplaces and associations ($n = 5$), and newspapers and internet websites ($n = 5$). Three studies did not report information about the recruitment process. Four studies focused on the female population, another four on the male population, and the remaining articles included participants of both sexes.

3.3 | Measures of resilience

Authors used various measures to quantify psychological resilience. The most frequently used were the different versions of the Connor-Davidson Resilience Scale (CD-RISC; $n = 15$), with eight studies including the original 25-item version of the CD-RISC (Connor & Davidson, 2003) and six the reduced 10-item version (Campbell-Sills & Stein, 2007). The second most commonly used scale was the 6-item Brief Resilience Scale (BRS, Smith et al., 2008) ($n = 7$), and one study employed both the BRS and the CD-RISC-25 simultaneously. Instruments used by the remaining studies included the

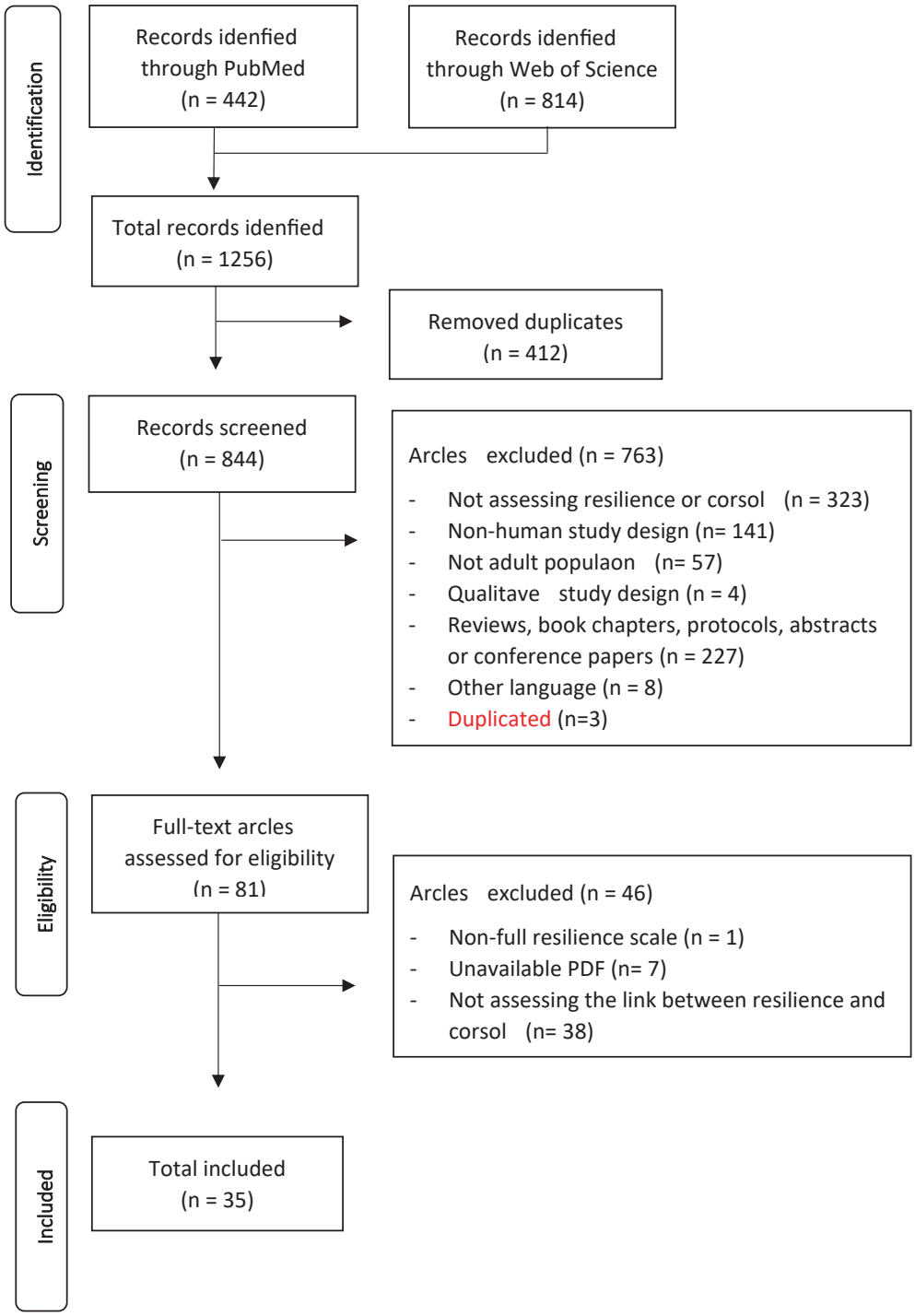

FIGURE 1 PRISMA flowchart of study selection.

complete and reduced versions of the Resilience Scale-25 (RS-13 and RS-25: Wagnild & Young, 1993) ($n = 6$), the Brief Resilient Coping Scale (BRCS; Sinclair & Wallston, 2004) ($n = 2$), the Ego Resiliency Scale (Block & Kremen, 1996) ($n = 1$), the Adult Resilience Scale (RSA; Friborg et al., 2003) ($n = 1$), the Defense Style Questionnaire (Bond, 1986) ($n = 1$), the Military Personnel Mental Resilience Scale (Tang & Zhang, 2009) (n = 1), and the reduced version of the Sense of Coherence Scale (Antonovsky, 1993) ($n = 1$). See Table 3 for a more detailed description of the resilience measures most commonly used by the studies.

3.4 | Cortisol measures

The methods used to determine participants' cortisol levels varied across studies, with saliva, blood, or urine samples being used as short-term cortisol assessment measures and hair as a marker for long-term integrated

TABLE 1 Short-term cortisol production associated with psychological resilience.

Cortisol parameters	Authors (year)	Study design (sample size)	1. Population 2. Age in years (SD) 3. Gender	Scale to assess resilience	Cortisol measurement 1. Common source of bioespecimen 2. Measure 3. Number of measures/ time points 4. Collection protocol	Results
Diurnal cortisol response	Lai et al., 2020	Cross-sectional ($N = 49$)	1. Chinese undergraduate university students of Psychology 2. 20.92 years (SD = 1.94) 3. 57.1% female	BRS	1. Saliva 2. DS and CAR 3. 6 time points over 3 consecutive weekdays 4. T0 = Immediately after waking; T1 = 30 min after T0; T2 = 3 h after T0; T3 = 6 h after T0; T4 = 12 h after T0; T5 = at bedtime	• Positive association between resilience with both larger CAR and steeper DS.
	O'Connor et al., 2021	Cross-sectional ($N = 142$)	1. British adults with a history of suicidal ideation or attempt ($n = 95$) and without suicide risk history ($n = 47$) 2. 27.74 years (SD = 9.27) 68.1% female	BRS	1. Saliva 2. CAR 3. 4 time points in 7 consecutive days. 4. T0 = immediately upon waking; T1 = 15 min after awakening; T2 = 30 min after awakening; T3 = 45 min after waking	• Positive association between resilience and CAR. Individuals with lower levels of resilience exhibited lower total CAR.
	Ruiz-Robledillo et al., 2014	Cross-sectional ($N = 67$)	1. Spanish caregivers (parents) of people with an autism spectrum disorder diagnosis 2. 45.46 years (SD = 6.56) 3. 3. 59.7% female	BRCS	1. Saliva 2. CAR, AUCgCAR and AUCiCAR 3. 4 time points in two consecutive days 4. T0 = at waking up; T1 = 30 min after awakening; T2 = 45 min after awakening; T3 = 60 min after awakening	• Negative association between resilience and both CAR and AUCgCAR. Caregivers with higher resilience showed lower CAR and AUCgCAR.

TABLE 1 (Continued)

Cortisol parameters	Authors (year)	Study design (sample size)	1. Population 2. Age in years (SD) 3. Gender	Scale to assess resilience	Cortisol measurement 1. Common source of bioespecimen 2. Measure 3. Number of measures/ time points 4. Collection protocol	Results
Basal cortisol response (tonic)	Costa de Robert et al., 2010	Cross-sectional ($N = 53$)	1. Normotensive or hypertensive patients in periodic health check-ups from Argentina 2. Males = 41 years (SD = 12.2); Females = 43 years (SD = 09.1) 3. 39.6% female	CD-RISC-25	1. Urine 2. 24 h integrated mean net urine calculation 3. 1 single time point 4. Total urine collection for 24 h	• Negative association between resilience and basal 24 h urine cortisol response. Lower resilience and higher basal 24 h urine cortisol levels were observed in hypertensive patients, but not in normotensive patients.
	Farina et al., 2019	Cross-sectional ($N = 800$)	1. Active duty, male, U.S. Army Soldiers 2. No data 3. 0% female	CD-RISC −25	1. Serum 2. Mean net serum cortisol 3. 1 single time point 4. 1 h upon awakening in the morning, between 4:30 and 6:30 a.m.	• Positive correlation between resilience and basal morning serum cortisol.
	Fazeli et al., 2020	Cross-sectional ($N = 171$)	1. Older seropositive (HIV +) ($n = 96$) and seronegative (HIV-) people ($n = 75$) from U.S. 2. HIV+: 55.81 years (SD = 5.06) HIV-: 60.61 years (SD = 7.37) 3. HIV+: 32% female; HIV-: 55% female	CD-RICS-10	1. Serum 2. Mean net serum cortisol 3. 1 single time point 4. In the morning at approximately 9 a.m.	• No significant correlation between resilience and basal morning serum cortisol in either HIV+ or HIV- people.
	Krisor et al., 2015	Cross-sectional ($N = 53$)	1. German parents in active employment caring for children up to the age of six. 2. 33 years (SD = 5.2). 3. 54% female.	Brief version of RS-25	1. Saliva. 2. Mean net salivary cortisol. 3. 3 time points during daytime. 4. T0 = 30 min after awakening; T1 = at noon; T2 = just before bedtime.	• Negative correlation between resilience and basal daytime salivary cortisol.

(Continues)

TABLE 1 (Continued)

Cortisol parameters	Authors (year)	Study design (sample size)	1. Population 2. Age in years (SD) 3. Gender	Scale to assess resilience	Cortisol measurement 1. Common source of bioespecimen 2. Measure 3. Number of measures/ time points 4. Collection protocol	Results
	Lai et al., 2020	Cross-sectional ($N = 49$)	1. Chinese undergraduate university students of Psychology. 2. 20.92 years (SD = 1.94). 3. 57.1% female.	BRS	1. Saliva 2. AUCg. 3. 6 time points over 3 consecutive weekdays. 4. T0 = immediately after waking; T1 = 30 min after T0; T2 = 3 h after T0; T3 = 6 h after T0; T4 = 12 h after T0; T5 = at bedtime	• A trend non-significant positive association between resilience and basal cortisol AUCg response.
	Lim et al., 2018	Cross- sectional ($N = 57$)	1. 24 bank clerks working in a face-to-face customer service and 33 bank clerks working without face-to-face customer service from Korea. 2. 37.26 years (SD = 7.36). 3. 38.6% female.	Ego-Resiliency Scale	1. Saliva. 2. Mean net salivary cortisol. 3. 1 single time point. 4. At 6 pm. on a working day.	• No significant correlation between resilience and basal evening salivary cortisol.
	Mizuno et al., 2016	Cross-sectional ($N = 180$)	1. Japanese adults with a diagnosis of schizophrenia or bipolar disorder, and healthy controls. 2. Schizophrenia = 45.9 (SD = 10.0); Bipolar = 50.2 (SD = 13.8); Control = 41.0 (SD = 17.6). 3. Schizophrenia = 64.3% female; Bipolar = 53.3% female; Control = 50% female.	RS-25	1. Plasma. 2. Mean net plasma cortisol. 3. 1 single time point. 4. Patients = during regular outpatient visits; Controls = between 10 and 11 a.m.	• No significant correlation between resilience and basal plasma cortisol.

TABLE 1 (Continued)

Cortisol parameters	Authors (year)	Study design (sample size)	1. Population 2. Age in years (SD) 3. Gender	Scale to assess resilience	Cortisol measurement 1. Common source of bioespecimen 2. Measure 3. Number of measures/ time points 4. Collection protocol	Results
	Petros et al., 2013	Cross-sectional ($N = 32$)	1. Healthy non-clinical British adults (%74 Caucasian). 2. 30 years (SD = 10.9). 3. 62.5% female.	CD-RISC-25	1. Saliva. 2. Mean net salivary cortisol. 3. 1 single time point. 4. 45 s immediately upon awakening.	• No correlation between resilience and basal morning salivary cortisol.
	Ramiro-Cortijo et al., 2021	Longitudinal: T0-T2 ($N = 133$)	1. Healthy Spanish pregnant women. 2. 35 years. 3. 100% female.	RS-25	1. Plasma. 2. Mean net plasma cortisol. 3. 1 measurement (at T0) of a single time point. 4. T0 = at 9–11 weeks of gestation from 8:00 to 9:00 a.m.	• No significant correlation between resilience and basal morning plasma cortisol in either the first trimester of pregnancy (T0) or the third trimester of pregnancy (T2).
	Rhoden et al., 2021	Longitudinal: T0-T1 ($N = 53$)	1. Brazilian nurses 2. No data 3. 75.5% female	RS-25	1. Saliva 2. Mean net salivary cortisol for each time point 3. 2 measurements (at T0 and at T1), consisting of 3 time points each 4. T0 = before the Hospital Accreditation maintenance assessment; T1 = 60 days after the audit visit. 1st time point = at waking up; 2nd time point = one h after starting work; 3rd time point = one h before ending work	• No significant correlation between resilience and basal salivary cortisol at either T0 or T1 at any of the three time points at which the latter was measured.
	Sharpley et al., 2018	Cross-sectional ($N = 93$)	1. Australian prostate cancer patients 2. 67.9 years (SD = 6.37) 3. 0% female	CD-RISC-25	1. Saliva 2. Mean net salivary cortisol 3. 1 single time point 4. Between 30 and 45 min after awaking	• No significant correlations between resilience and basal morning salivary cortisol. No significant differences

(Continues)

TABLE 1 (Continued)

Cortisol parameters	Authors (year)	Study design (sample size)	1. Population 2. Age in years (SD) 3. Gender	Scale to assess resilience	Cortisol measurement 1. Common source of bioespecimen 2. Measure 3. Number of measures/ time points 4. Collection protocol	Results
						between high- and low-resilience participants in basal morning salivary cortisol.
	Simeon et al., 2007	Intervention: TSST and DST ($N = 54$)	1. Healthy adults from U.S 2. 33,2 years (SD = 11.0) 3. 46.3% female	Defense Style Questionnaire	1. Urine 2. 24 h integrated mean net urine calculation 3. 1 single time point 4. Total urine collection for 24 h	• Positive correlation between resilience and 24 h basal urinary cortisol response.
Acute cortisol response (phasic)	Black et al., 2017	Intervention: acute psychological stress task ($N = 31$)	1. British manual workers aged +50 2. 54.9 (3.78) 3. 41.9% female	BRS	1. Saliva 2. Acute response: mean net salivary cortisol change with respect to baseline 3. 4 time points before and after the stress task 4. T0 = at 10 minutes into baseline; T1 = 1 min of the end of the stress task at the start of recovery; T2 = 10 min following stress task; T3 = 20 min following stress task	• No significant associations between resilience and acute salivary cortisol response.
	DiMenichi et al., 2018	Intervention: Failure versus Control Writing manipulation + TSST ($N = 102$)	1. American general population, mostly university students 2. 24.09 years (SD = 7.36) 3. 54% female	CD-RISC-25	1. Saliva 2. Acute response: AUCi 3. 6 time points points before and after the stress task 4. T0 = baseline measurement; T1 = 15 min elapsed since T0 (20–25 min since arrival); T2 = 35 min	• A trend positive correlation between resilience and acute salivary cortisol response only among individuals undergoing the TSST.

TABLE 1 (Continued)

Cortisol parameters	Authors (year)	Study design (sample size)	1. Population 2. Age in years (SD) 3. Gender	Scale to assess resilience	Cortisol measurement 1. Common source of bioespecimen 2. Measure 3. Number of measures/ time points 4. Collection protocol	Results
					elapsed since T0, after TSST; T3 = 55 min elapsed since T0, after 1/2 SART task; T4 = 70 min elapsed, after complete SART task; T5 = 85 min elapsed, at the conclusion of the survey battery.	
	García-León, Pérez-Mármol, et al., 2019	Intervention: TSST ($N = 80$)	1. Spanish healthy undergraduate university students 2. 21.14 years (SD = 4.17) 3. 65% female	CD–RISC10	1. Saliva 2. Acute response: AUCi 3. 4 time points before and after the stress task 4. T0 = after the explanation of the TSST; T1 = upon completion of the three tasks; T2 and T3 = 10 and 20 min after the end of the TSST	• No significant differences in acute salivary cortisol response during TSST between high and low resilient participants.
	Hundertmark et al., 2019	Cross-sectional ($N = 60$)	1. German active tutors of Medical Faculty 2. 22.8 years (SD = 2.6) 3. 3.3% female	Brief version of the RS-25 (RS-13)	1. Saliva 2. Acute response and recovery: mean net salivary cortisol change with respect to baseline before, immediately after and in the recovery phase of a peer-led tutorial course session 3. 3–4 saliva samples on the late afternoon and evening of a rest day for baseline +3 time points in three consequently days	• No significant correlation between resilience and acute salivary cortisol response or recovery.

(Continues)

TABLE 1 (Continued)

Cortisol parameters	Authors (year)	Study design (sample size)	1. Population 2. Age in years (SD) 3. Gender	Scale to assess resilience	Cortisol measurement 1. Common source of bioespecimen 2. Measure 3. Number of measures/ time points 4. Collection protocol	Results
					4. T1 = 30 min before course session; T2 = in the end of course session; T3 = in the end of recovery phase	
	Lau et al., 2021	Intervention: TSST ($N = 107$)	1. Chinese university students 2. 21.02 years (SD = 0.23) 3. 48.6% female	CD-RISC-25	1. Saliva 2. Acute response: mean net salivary cortisol change before, during and after TSST 3. 5 time points 4. T0 = at baseline; T1 = after TSST; T2 = 5 min after TSST; T3 = 10 min after TSST; T4 = 20 min after TSST	• Negative association between acute salivary Cortisol/DHEA ratio response at baseline (T0) and 5 min after TSST (T2) with resilience.
	Mikolajczak et al., 2008	Intervention: TSST ($N = 28$)	1. Non-smoker Belgian male students 2. 20.86 years (SD = 2.38) 3. 0% female	Adult Resilience Scale (RSA)	1. Saliva 2. Acute response and recovery: anticipatory response (baseline cortisol: mean of T0 and T1), reactivity (AUCi from baseline to peak), recovery (recovery slope: between T3 and T7) and AUCg (integrated responses) 3. 8 time points 4. T0 = 2–4 min; T1 = 21-23 min (after relaxation time); T2 = 48-50 min (after TSST), T3 = 54-60 min; T4 = 70-72 min;	• Negative association between resilience and anticipatory acute salivary cortisol response. No significant differences between highly or less resilient peers in either reactivity or recovery responses.

TABLE 1 (Continued)

Cortisol parameters	Authors (year)	Study design (sample size)	1. Population 2. Age in years (SD) 3. Gender	Scale to assess resilience	Cortisol measurement 1. Common source of bioespecimen 2. Measure 3. Number of measures/ time points 4. Collection protocol	Results
					T5 = 81-83 min; T6 = 96-98 min; T7 = 113-115 min (after debriefing)	
	Park et al., 2018	Cross-sectional ($N = 91$)	1. Patients with Irritable bowel syndrome (IBS; $n = 37$) and healthy controls (HC; $n = 54$) from U.S. 2. IBS = 28.96 years (SD = 10.78); HC = 27.59 years (SD = 9.24) 3. 62.6% female	CD-RISC-25 and BRS	1. Serum 2. Acute response and recovery: rise slope (AUCi from baseline to peak); decline slope (from peak to the lowest value after the peak) 3. 7 time points 4. T0 = baseline at 9 am; T1-T6: 30, 60, 90, 120, 150, and 180 min. after ACTH administration.	• HC group: positive association between resilience and both the acute serum cortisol response and recovery to ACTH stimulation. • IBS group: negative association between resilience and both the acute serum cortisol response and recovery to ACTH stimulation.
	Ruiz-Robledillo et al., 2017	Intervention: Psychosocial stressor ($N = 40$)	1. Spanish caregivers (parents) of people with an autism spectrum disorder diagnosis 2. 45.77 years (SD = 6.90) 3. 60% female	BRCS	1. Saliva 2. Acute response: total AUCg, stressor AUCg (from T0 to T4), total AUCi and stressor AUCi (from T0 to T4); 3. 10 time points. 4. T0 = upon arrival at the laboratory (at 4 p.m.; T1 = after a habituation period; T2 = after psychological questionnaires; T3 = between the second and third tasks of an acute psychosocial stress task; T4 = immediately after completing the	• Negative association between resilience and both the total AUCg and stressor AUCg. Trait resilience was a significant predictor of stressor AUCg, but not of the total AUCg, total AUCi nor stressor AUCi.

(Continues)

TABLE 1 (Continued)

Cortisol parameters	Authors (year)	Study design (sample size)	1. Population 2. Age in years (SD) 3. Gender	Scale to assess resilience	Cortisol measurement 1. Common source of bioespecimen 2. Measure 3. Number of measures/ time points 4. Collection protocol	Results
					stress task; T5-T9: 10, 20, 30, 45, and 60 min after the end of the stress task.	
	Simeon et al., 2007	Intervention: TSST and DST ($N = 54$)	1. Healthy adults from U.S 2. 33,2 years (SD = 11.0) 3. 46.3% female	Defense Style Questionnaire	1. Plasma 2. Acute response: hourly serial plasma cortisol from 8 a.m. to 11 p.m. averaged over 16 time points and mean net plasma cortisol response to DST and TSST. 3. 16 time points 4. Hourly serial plasma cortisol from 8 a.m. to 11 pm (T0-T15)	• No significant correlation between resilience and acute plasma cortisol response to both DST and TSST.
	Sun et al., 2014	Intervention: sleep deprivation ($N = 160$)	1. Chinese servicemen of a military unit. 2. 20.52 years (SD = 1.81). 3. 0% female.	Military Personnel Mental Resilience Scale	1. Serum. 2. Acute response: mean net serum cortisol before and after 24 h sleep deprivation intervention 3. 2 time points 4. T0 = day 1 8a.m, before sleep deprivation; T1 = day 2 8a.m, after sleep deprivation	• Negative relationship between resilience and acute serum cortisol response. The difference values of cortisol between T1 and T2 of the lower resilience group were significantly greater than those of the higher resilience group. Willpower, one of the 6 subscales of the Military Personnel Mental Resilience Scale, negatively predicted the increases of serum cortisol induced by sleep deprivation.

TABLE 1 (Continued)

Cortisol parameters	Authors (year)	Study design (sample size)	1. Population 2. Age in years (SD) 3. Gender	Scale to assess resilience	Cortisol measurement 1. Common source of bioespecimen 2. Measure 3. Number of measures/ time points 4. Collection protocol	Results
	Zapater-Fajari et al., 2021	Intervention: TSST ($N = 66$)	1. Spanish healthy older adults 2. 64.24 years (SD = 0.573) 3. 46.9% female	CD-RISC-10	1. Saliva 2. Acute response: total AUCi 3. 7 time points 4. T0-T2 = 55, 25 and 2 min before the TSST; T3 = during the TSST; T4-T6 = 7, 20 and 30 min after the end of TSST	• No significant correlation between resilience and acute salivary cortisol response.

cortisol secretion. In terms of frequency, the most common biological matrix sampled by the studies was saliva ($n = 17$), followed by hair ($n = 12$), serum ($n = 4$), plasma ($n = 3$), and, finally, urine ($n = 2$).

Using the sampling source chosen to determine the nature of the stress experienced by study participants (acute vs. chronic) (Stalder & Kirschbaum, 2012) as our main reference, we have grouped the results of the studies in accordance with the short- or long-term secretion period covered by the selected cortisol matrices. We have also classified cortisol responses in accordance with the differentiated diurnal, phasic (acute), and tonic (basal) components of the HPA output to which they refer (Dobler et al., 2019; Epstein et al., 2021; Jiang et al., 2019; Short et al., 2016) (see Tables 1 and 2).

3.5 | Synthesis of the findings

3.5.1 | Relationship between resilience and short-term cortisol production

Resilience and diurnal cortisol response

Lai et al., 2020 found both a stronger CAR and a steeper diurnal cortisol slopes (DS) among undergraduate students with higher levels of resilience. Similarly, O'Connor et al., 2021 observed a positive association between resilience and cortisol awakening response in adults with a history of suicidal ideation or attempt, finding lower levels of the former among those with a weaker total cortisol awakening response. In contrast, Ruiz-Robledillo et al., 2014 observed a weaker cortisol awakening response, and a smaller area under the curve with respect to ground (AUCg) derived from cortisol awakening response (AUCgCAR), among highly resilient caregivers of people with an autism spectrum disorder diagnosis.

Resilience and acute cortisol response

Resilience was significantly associated with acute cortisol response and/or recovery from momentary stressors in six out of the 11 studies that reported on this relationship, with the nature of the association between these two variables being primarily negative (Lau et al., 2021; Mikolajczak et al., 2008; Ruiz-Robledillo et al., 2017; Sun et al., 2014), but also, in some cases, positive (DiMenichi et al., 2018) or mixed (Park et al., 2018).

Similarly, Lau et al., 2021 found an increased acute salivary cortisol/ dehydroepiandrosterone (DHEA) ratio response in low resilience university students who underwent a standardized acute psychosocial stress test (Trier Social Stress Test, TSST), both at baseline (T0) and during the first 5 min post-test. Similar results were reported among non-smoker male students by Mikolajczak et al.

TABLE 2 Long-term cortisol production (tonic) associated with psychological resilience.

Authors (year)	Study design (sample size)	1. Population 2. Age in years (SD) 3. Gender	Scale to assess resilience	Cortisol measurement 1. Common source of bioespecimen 2. Measure 3. Number of measures/time points 4. Length; Collection protocol	Results
Alhalal & Falatah, 2020	Cross-sectional ($N = 156$)	Saudi women from heath care settings 32.2 years (SD = 7.9) 100% female	CD-RISC-25	Hair Mean net hair cortisol 1 single time point 6 cm	Negative correlation between resilience and hair cortisol. Resilience (along with intimate partner violence in the model) also acted as a significant predictor of lower hair cortisol concentrations.
Arco Garcia et al., 2020	Cross-sectional ($N = 347$)	1. Spanish healthy adults 2. 33.39 years (SD = 12.63) 3. 66.3% female	CD–RISC10	1. Hair 2. Mean net hair cortisol 3. 1 single time point 4. 3 cm	• No significant correlation between resilience and hair cortisol. Resilience did not predict hair cortisol.
Burgin et al., 2020	Cross-sectional ($N = 134$)	1. Swiss professional caregivers in youth residential care institutions 2. 35.20 years (SD = 9.54) 3. 64.2% female	Short version of the Sense of Coherence Scale	1. Hair 2. Mean net hair cortisol 3. 1 single time point 4. 1.5 cm	• No significant correlation between resilience and hair cortisol, but a negative association between resilience and Cortisol/DHEA ratio.
Chen et al., 2021	Cross-sectional ($N = 80$)	1. Chinese people with and without HIV 2. Patients with HIV: 37 years; controls: 39 years 3. Patients with HIV: 45% female; controls: 45% female	CD-RISC-10	1. Hair 2. Mean net hair cortisol 3. 1 single time point 4. 1 cm	• No significant correlation between resilience and hair cortisol.
Engert et al., 2021	Longitudinal: T0-T2 ($N = 80$)	1. German adult volunteers 2. 35.65 years (SD = 11.49) 3. 90% female	RS-25 and BRS	1. Hair 2. Mean net hair cortisol 3. 1 measurement (at T2) of a single time point 4. 1 cm; T2 = after the first lockdown period of the Covid-19 pandemic	• No significant relationship between resilience and hair cortisol; neither baseline values (T0) nor change in resilience (T1) predicted cortisol and cortisone levels at T2.

TABLE 2 (Continued)

Authors (year)	Study design (sample size)	1. Population 2. Age in years (SD) 3. Gender	Scale to assess resilience	Cortisol measurement 1. Common source of bioespecimen 2. Measure 3. Number of measures/time points 4. Length; Collection protocol	Results
García-León, Caparros-Gonzalez, et al., 2019	Longitudinal: T0-T1 ($N = 151$)	1. Spanish pregnant women in the third trimester of pregnancy. 2. Low resilience group ($n = 55$): 33.04 years (SD = 4.10); High resilience group (n = 97): 33 years (SD = 4.62) 3. 100% female	CD–RISC10	1. Hair 2. Mean net hair cortisol 3. 2 measurements (at T0 and at T1), each of a single time point 4. 3 cm; T0 = before delivery, at the end 3rd trimester of pregnancy; T1 = after delivery	• Negative correlation between resilience and hair cortisol only at T0. Significant differences between participants belonging to the high and low resilience groups in hair cortisol at T0, specifically, the low resilience group of women showed higher hair cortisol concentration compared to the high resilience group. • No significant differences between women belonging to the high and low resilience groups in hair cortisol at T1.
García-León, Pérez-Mármol, et al., 2019	Intervention: TSST ($N = 80$)	1. Spanish healthy undergraduate university students 2. 21.14 years (SD = 4.17) 3. 65% female	CD–RISC10	1. Hair 2. Mean net hair cortisol 3. 1 single time point 4. 3 cm, 20 min after TSST	• Negative correlation between trait resilience and hair cortisol. No significant differences in acute salivary cortisol response during TSST between high and low resilient participants.
Lehrer et al., 2019	Cross-sectional ($N = 228$)	1. Community-dwelling adults from U.S. 2. 45.29 years (SD = 14) 3. 68% female	BRS	1. Hair 2. Mean net hair cortisol 3. 1 single time point 4. 3 cm	• No significant correlation between resilience and hair cortisol.
Lines et al., 2020	Cross-sectional ($N = 140$)	1. Australian undergraduate students 2. 21.68 years (SD = 4.88) 3. 70.7% female	BRS	1. Hair 2. Mean net hair cortisol 3. 1 single time point 4. 1.5 cm	• Negative correlation between resilience and hair cortisol.

(Continues)

TABLE 2 (Continued)

Authors (year)	Study design (sample size)	1. Population 2. Age in years (SD) 3. Gender	Scale to assess resilience	Cortisol measurement 1. Common source of bioespecimen 2. Measure 3. Number of measures/time points 4. Length; Collection protocol	Results
Lines et al., 2021	Longitudinal: T0-T2 ($N = 52$)	1. Australian undergraduate students 2. 21.94 years (SD = 4.57) 3. 78.8% female	BRS	1. Hair 2. Mean net hair cortisol 3. 3 measurements, each of a single time point (at T0, at T1 and at T2) 4. 2 cm; T0 = before examination period; T1 = immediately before examination period (8 weeks after T0); T2 = after examination period (8 weeks after T1)	• No significant correlation between resilience and hair cortisol at T0 and T1, but positive correlation at T2.
Ullmann et al., 2016	Cross-sectional ($N = 40$)	1. German healthy students 2. 24,08 years 3. 55% female	Brief version of the RS-25	1. Hair 2. Mean net hair cortisol 3. 1 single time point 4. 3 cm	• No significant correlations between resilience and hair cortisol.
van den Heuvel et al., 2020	Cross-sectional ($N = 164$)	1. Mixed ancestry colored ethnic group from South Africa. 2. 48.5 years 3. 100% female	CD-RISC-25	1. Hair 2. Mean net hair cortisol 3. 1 single time point 4. 3 cm	• Negative association between resilience and hair cortisol, but only in those who had not completed secondary education.

(2008) who found a lower anticipatory acute salivary cortisol response after TSST among more resilient individuals than among their less resilient counterparts. However, this did not lead to the former displaying lower HPA reactivity or faster HPA recovery after TSST. In a study with caregivers of people with an autism spectrum disorder diagnosis, Ruiz-Robledillo et al., 2017 found a lower total and specific stressor-related salivary cortisol area under the curve with respect to the ground (AUCg) after TSST among more resilient than among less resilient caregivers. Similarly, Sun et al. (2014) found that serum cortisol increases induced by a sleep deprivation intervention in a group of servicemen were significantly greater in the less resilient subgroup than among their more resilient peers and that willpower, a subscale of the resilience scale, negatively predicted these increases.

Despite the negative associations found by the authors mentioned above, other studies report opposite results. For example, in a study aimed at determining the influence of expressive writing on acute stress elicited by TSST, DiMenichi et al., 2018 found a positive correlation between resilience and the cortisol area under the curve with respect to increase (AUCi) in adults undergoing the TSST. Similarly, Park et al., 2018 found that less resilient controls had a weaker serum cortisol response to adrenocorticotropic hormone (ACTH) stimulation and a slower recovery to baseline than their more resilient counterparts. However, these authors reported opposite results among patients with irritable bowel syndrome, observing a stronger serum cortisol response to ACTH stimulation and a faster recovery to baseline among less resilient patients than among highly resilient ones.

One of the five studies that found no significant relationship between the two variables was that conducted by Hundertmark et al. (2019) which aimed to analyze the influence of a structured peer-led tutorial course on the psychophysiological response to stress of near-peer tutors of medical students. The authors found no significant relationship between acute cortisol responses or recovery following tutorial sessions and resilience levels. For their part, García-León, Pérez-Mármol, et al. (2019), Black et al. (2017), Simeon et al. (2007), and Zapater-Fajarí et al. (2021), whose studies sought to analyze the effect of TSST on acute salivary cortisol response of adult participants, found no significant relationship between cortisol responses to acute stress and resilience levels.

Resilience and basal cortisol levels

Resilience was found to be significantly associated with basal cortisol levels in five out of the 12 studies that reported on this relationship, with the nature of the association between the two variables being both negative (Costa de Robert et al., 2010; Krisor et al., 2015) and positive (Farina et al., 2019; Lai et al., 2020; Simeon et al., 2007).

With respect to the first group, Krisor et al., 2015 found lower levels of integrated daytime basal salivary cortisol and higher levels of resilience among parents in active employment caring for children up to the age of six. Likewise, in a study conducted with hypertensive and normotensive patients during periodic clinical health check-ups, Costa de Robert et al., 2010 found that only the first group had significantly lower resilience and higher baseline 24 h urine cortisol levels. These results contradict those reported by Simeon et al. (2007), who observed significantly higher baseline 24 h urine cortisol levels among highly resilient healthy individuals. Basal morning serum cortisol levels were also found to be positively associated with resilience in the study conducted by Farina et al. (2019) with active-duty army soldiers, with higher morning cortisol concentrations being observed among more resilient subjects. Similar findings were reported by Lai et al. (2020), who observed a positive (although not significant) correlation between resilience and cortisol area under the curve with respect to the ground (AUCg) response in a group of undergraduate students.

One of the remaining seven studies that failed to find a significant relationship between the two variables was that conducted by Rhoden et al. (Rhoden & Stumm, 2021), who longitudinally evaluated a group of nurses before and after a Hospital Accreditation maintenance assessment, finding no significant correlations between resilience and basal salivary cortisol at any of the three-time points at which the latter was analyzed (at waking up, 1 h after starting work, and 1 h before finishing work). In contrast, the other six studies that also reported non-significant associations between these two variables analyzed basal cortisol levels at a single time point (either early morning or in the evening) through saliva samples (Lim et al., 2018; Petros et al., 2013; Sharpley et al., 2018) or plasma or serum (Fazeli et al., 2020; Mizuno et al., 2016; Ramiro-Cortijo et al., 2021).

3.5.2 | Relationship between resilience and long-term cortisol production

Resilience was found to be significantly associated with long-term integrated (i.e., hair) cortisol secretion in seven out of the 12 studies that reported on this relationship, with the nature of the association between these two variables being mainly negative (Alhalal & Falatah, 2020; Burgin et al., 2020; García-León, Caparros-Gonzalez, et al., 2019; García-León, Pérez-Mármol, et al., 2019; Lines et al., 2020; van den Heuvel et al., 2020) but also, in one case, positive (Lines et al., 2021).

In contrast to Lines et al. (2021) who, despite observing no significant correlations between resilience and hair cortisol levels among undergraduate students before and immediately following an examination period, nevertheless found that the two variables correlated positively with each other 8 weeks later, the results of the remaining six studies pointed in the opposite direction. In relation to university students, both García-León, Pérez-Mármol, et al. (2019) and Lines et al. (2020) found lower levels of resilience among participants with elevated hair cortisol concentrations. Similar findings were reported by Alhalal and Falatah (2020) and Van den Heuvel et al. (2020) among Saudi and South African women, respectively, with results revealing significantly higher levels of resilience among those with lower hair cortisol values. For their part, in a longitudinal study aimed at identifying biopsychosocial differences among pregnant women before and after delivery, (García-León, Caparros-Gonzalez, et al., 2019) found a negative correlation between resilience and hair cortisol before (although not after) participants gave birth, specifically at the end of their third trimester of pregnancy. Moreover, these authors also found that the low-resilience group of pregnant women had higher cortisol concentrations than the high-resilience group. Finally, while the correlation between resilience and hair cortisol did not reach statistical significance in the study conducted by Burgin et al. (2020) with a sample of professional caregivers from residential care institutions, the association between resilience and the cortisol/DHEA ratio did, with this relationship being an inverse one.

TABLE 3 Description of the most commonly used Resilience Measures in the studies.

Name	Author(s)	Mode of completion	Number of dimensions/ factors (items)	Purpose
The Connor-Davidson Resilience Scale (CD-RISC)	Connor and Davidson (2003)	Self-report	5 (25); Personal competence, Trust/Tolerance/Strengthening effects of stress, Acceptance of change and secure relationships, Control and Spiritual Influences.	Designed to measure the ability to cope with stress in clinical settings. Resilience is a multidimensional construct that reflects the subject's capacity to identify available resources to manage stress.
The Connor-Davidson Resilience Scale (CD-RISC)	Campbell-Sills and Stein (2007)	Self-report	1 (10)	A short version of the 25-item CD-RISC. Designed to measure the ability to cope with stress in clinical settings.
The Brief Resilience Scale (BRS)	Smith et al. (2008)	Self-report	1 (6)	Designed to measure the individual's perceived ability to recover from stress, it assesses resilience as a unitary construct. Resilience is viewed as an individual's disposition to bounce back from stress.
The Resilience Scale (RS)	Wagnild and Young (1993)	Self-report	2 (25); Acceptance of self and life and Personal competence.	Developed to identify the degree of an individual's perceived competence and self-acceptance. Resilience is regarded as a positive construct that enhances individual adaptation.
The Brief Resilient Coping Scale (BRCS)	Sinclair and Wallston (2004)	Self-report	1 (4)	Designed to identify highly adaptive stress-coping tendencies in clinical practice. Resilience is understood as a set of adaptive coping resources to stress.

Null findings regarding the relationship between resilience and hair cortisol were reported by five studies, four of which were conducted with healthy adults with no diagnosed psychiatric or physical pathologies (Arco Garcia et al., 2020; Engert et al., 2021; Lehrer et al., 2019; Ullmann et al., 2016). The study by Chen et al. (2021), which included people with and without human immunodeficiency virus (HIV), found a positive, but not significant, relationship between the two variables.

4 | DISCUSSION

In the systematic review presented here, we synthesize evidence from 35 cross-sectional, longitudinal, and intervention studies, all of which were quantitative in nature, with the aim of providing evidence on the relationship between resilience and cortisol in human adults. Specifically, we summarize the extant evidence obtained using any of the current methods for cortisol collection in relation to psychological resilience, mainly blood, urine, hair, and saliva sampling. It should be noted that the variety of measurements and time points employed for both the recording and sampling of cortisol, as well as the lack of consistency in the questionnaires used to measure resilience and the discrepancy between the results obtained by the different authors, prevented us from pooling the data from the studies into a meta-analysis.

On balance, we observed that (1) the selected studies were largely conducted with representative samples of European and Caucasian populations ($N = 22$ out of 35); (2) saliva and hair were the most common biological

matrices used for cortisol detection ($N = 15$ and 12 out of 35, respectively); (3) the different versions of the CD-RISC scale were the most widely used instruments for assessing participants' resilience ($N = 15$), followed by the BRS scale ($N = 8$); and (4) the majority of eligible studies reported statistically significant associations between psychological resilience and cortisol ($N = 19$ out of 35).

It is important to note the high degree of heterogeneity in the population included in the studies, with participants coming from different backgrounds (e.g., patients from healthcare settings, undergraduate university students, and professional caregivers) and age ranges, and of both sexes. This last aspect is particularly significant, since there is strong evidence of sex-specific behavioral and physiological responses to stress (Bangasser & Wicks, 2017), with some authors, for instance, reporting evidence indicating that the hypothalamic–pituitary–adrenal (HPA) axis operates in a sex-dependent manner (Barel et al., 2018; Goel et al., 2014; Heck & Handa, 2019). It is also worth mentioning that, of the four studies carried out exclusively with women, three measured long-term cortisol production in hair, and all of them found a negative correlation between resilience as measured by the CD-RISC scale and hair cortisol levels (Alhalal & Falatah, 2020; García-León, Caparros-Gonzalez, et al., 2019; van den Heuvel et al., 2020). Given that no studies to date have examined hair cortisol levels and resilience exclusively among men, it has yet to be determined whether the results would be similar among this population. Notably, all eight studies that found no significant relationship between the core variables were carried out with a mixed-sex population, of which 4 controlled for sex (Arco Garcia et al., 2020; Lehrer et al., 2019; Lines et al., 2020; Lines et al., 2021), 3 controlled for gender (Burgin et al., 2020; Chen et al., 2021; Ullmann et al., 2016), and 1 study controlled for neither sex nor gender (Engert et al., 2021). Current evidence suggests that gender roles (i.e., masculine, feminine, androgynous, and undifferentiated) are significantly associated with cortisol habituation to repeated acute stress (Manigault et al., 2021), suggesting that failure to account for sex and gender differences may result in significant effects being overlooked. This, together with the small sample size of many of the studies and the fact that several of them did not include sex-, gender- and age-matched controls, may limit the generalizability of our conclusions.

Additionally, it is worth mentioning that the method used to measure cortisol may also have influenced the findings presented here. In this regard, it should be remembered that six of the seven studies that found no relationship between resilience and tonic basal short-term cortisol levels used a single morning saliva or plasma sample to assess HPA axis activity (Fazeli et al., 2020; Lim et al., 2018; Mizuno et al., 2016; Petros et al., 2013; Ramiro-Cortijo et al., 2021; Sharpley et al., 2018). This methodological approach may have increased the likelihood of a false negative, since high day-to-day variability has been reported in salivary or plasma cortisol levels (El-Farhan et al., 2017; Matsuda et al., 2012).

Particularly, we believe that the variability of the results may be reflecting the complexity of the relationship between stress and HPA axis functioning, given that the latter may be heavily influenced by aspects such as the subject's personal attributes (i.e., their psychological functioning and the principal emotions elicited by the stressor) and the characteristics of the stressor itself (i.e., threat features and time elapsed since stressor onset) (Miller et al., 2007). In this sense, we were struck by the fact that many of the studies included in the review did not control for the effect of possible psychiatric alterations among participants, since this is a key factor that has been shown to be associated with sex-specific changes in cortisol stress reactivity (Zorn et al., 2017). Furthermore, the nature of the threat to which participants were exposed varied considerably across studies, with some stressors being more psychosocial in nature (e.g., TSST, work-family related conflicts, or caregiving stress) and others more physical (e.g., sleep deprivation or exposure to various viral, metabolic or cancer diseases). This may possibly have led to different HPA activity patterns, since different threats are associated with different adaptive requirements that cortisol helps to sustain metabolically (Kemeny, 2003; Miller et al., 2007; Weiner, 1992). What's more, the multiple roles that cortisol plays in the body, both as a supporter and regulator of several physiological processes including gluconeogenesis, lipolysis, vascular reactivity as well as inflammatory, immune, and central nervous system functions (Halpern et al., 2012), may have hindered the control of potential stress-sensitive physiological confounders in this analysis and, therefore, be one of the reasons for a lack of consistency in its relationship to resilience. We also believe that this variability may be the result of the inconsistency in the resilience scales used (which raises questions about the extent to which researchers are measuring the same or different components of the construct) and the different methods of collecting cortisol. Regarding the latter, although most studies used biological matrices that reflected acute cortisol levels during the 24 h preceding their collection (saliva, blood, and urine) ($N = 23$ out of 35), many others utilized hair samples, which reflected long-term cortisol levels in the 1–6 months prior to collection ($N = 12$ out of 35). The fact that the timing of the

stress experienced is a key element that determines whether cortisol levels are higher or lower over time (Chrousos, 2009; Miller et al., 2007) and that the aforementioned methods capture vastly different time scales, makes it difficult to draw valid comparisons between the results reported. Consequently, since the influence of these factors precludes any further evidence being obtained regarding the effect of cortisol on resilience or vice versa, future studies should take them into account when continuing to analyze the relationship between these two variables. Also, future research may benefit from synchronizing the time depth of cortisol measurements with the resilience scales used and should consider designing longitudinal studies to explore the development of resilience in tandem with cortisol levels.

Despite the high degree of methodological variability found among the studies included in the present review, we should highlight the fact that, unlike the cross-sectional and longitudinal studies, which only found significant associations between resilience and cortisol in an approximate proportion of 40%–50%, the majority of the intervention studies reported significant associations between these two variables (7 out of 9: Dimenichi et al., 2018; García-León, Pérez-Mármol, et al., 2019; Lau et al., 2021; Mikolajczak et al., 2008; Ruiz-Robledillo et al., 2017; Simeon et al., 2007; Sun et al., 2014). Even though some differed in terms of the directionality of the relationship observed, this finding serves to highlight the potential of resilience as a modifiable key factor for modulating the stress response, as indeed has been suggested recently by different studies (Bergquist et al., 2021; Harvanek et al., 2021). Specifically, Harvanek et al. (Harvanek et al., 2021) have suggested that, among others, psychological resilience factors may moderate the deleterious effects of cumulative stress on epigenetic aging in healthy adults, thereby emphasizing the usefulness of preventive interventions aimed at fostering resilience and reducing stress in order to improve quality of life. Several resilience training interventions have been conducted to date, mainly focusing on strengthening resilience or diverse psychosocial factors associated with resilience, such as active coping, positive reappraisal, and self-efficacy, using different approaches such as problem-solving therapy, relaxation, and mindfulness-based training or some elements of positive psychology (Blessin et al., 2022; Chmitorz et al., 2018; Kunzler et al., 2020, 2022). These interventions have been shown to be effective in improving mental health outcomes, including quality of life and perceived stress or distress in different populations (Blessin et al., 2022; Chmitorz et al., 2018). Surprisingly, to the best of our knowledge, only one study to date has analyzed participants' cortisol levels following a resilience-related intervention. In that study, Arch et al. (2014) explored whether a brief training course in self-compassion (a widely recognized resilience factor) moderated, among other variables, salivary cortisol responses to the TSST among female undergraduates, finding no significant differences between participants who engaged in the intervention and the control groups. However, the authors did not control for participants' previous experience with contemplative practices or the presence of possible psychiatric disorders at the time of recruitment, which may have conditioned their results. There is, therefore, a need for further research into resilience-enhancing interventions, in order to examine their effects on participants' cortisol levels as a physiological response to stress. Nevertheless, it is important to remember that, due to the lack of clear directionality of the results found by the studies included in this review, the relationship between resilience and cortisol still needs to be further specified. In particular, the impossibility to discern the sense of the interaction between the two variables suggests the existence of third variables not taken into account in the present paper that might be modulating this relationship. In this respect, in the study by Zapater-Fajarí et al. (2021) aimed at analyzing the influence of resilience and different coping strategies in dealing with stressful situations, the authors found that active coping strategies mediated the relationship between psychological resilience and cortisol reactivity in a sample of 66 healthy older adults exposed to a TSST, thus suggesting the idea that resilient individuals who use active coping strategies might have a more adaptive response to stress. These results point to active coping strategies as one of the mechanisms through which resilient individuals bounce back from stressful life experiences. For this reason, further studies aimed at investigating resilience as well as those third variables through which it might be operating as promoters of a more adaptive response to stress are crucial to better understand the mechanisms underlying interindividual variations in stress regulation (Wu et al., 2013).

In our study, we observed that the most widely used scales for measuring resilience were the short and original versions of the CD-RISC scale (Campbell-Sills & Stein, 2007; Connor & Davidson, 2003) and the BRS scale (Smith et al., 2008). Previous research suggests that, of all existing resilience scales, these are two of those with the best psychometric ratings (Windle et al., 2011), we therefore recommend their use in future studies in order to facilitate the comparison of results. However, recent evidence suggests that although the CD-RISC views resilience as a multidimensional concept and focuses on identifying available resources that help individuals adapt to disturbances, the BRS conceptualizes it in a unidimensional manner, viewing it as one's intrinsic

capacity to recover from adversity (Ye et al., 2022). Thus, since the two scales capture different aspects of resilience, the choice of which to use should depend on the extent to which they fit the research purpose being pursued in each case. For its part, the most commonly used method for measuring cortisol was saliva, followed by hair. Although both methods can be considered non-invasive, valid, and well-established for the analysis of this hormone, salivary cortisol only provides situational information about short-term stress(if not taken longitudinally), which is why an increasing number of authors are opting for the use of hair samples that allow them to quantify the long-term cumulative release of cortisol (Cruickshank et al., 2021; Herane-Vives et al., 2020). In this regard, it is worth noting that, because of the time scale depicted and the fact that it is not as influenced by situational factors (Stalder & Kirschbaum, 2012), hair would represent the overall phenotype of the stress response rather than the acute response to stress, making it a suitable measure for assessing long-term chronic stress. Although previous evidence suggests a positive correlation between hair and saliva samples that tends to strengthen as the number and days of saliva sampling increases (Stalder & Kirschbaum, 2012), the contradictory findings found regarding the consistency between the two measures (Zhang et al., 2018) indicate that there is a need for more studies to include data from both biological matrices to gain a deeper understanding of the optimal conditions required for their association.

The systematic review presented here has certain limitations that should not be overlooked. The first one concerns possible bias resulting from the high degree of variability observed in terms of sample sizes, study designs, age ranges, resilience assessment tools, and cortisol analysis methods. In this regard, the heterogeneity of the scales and measures used by the different studies precluded any meaningful comparison between resilience and cortisol means. Second, most of the studies included in the review used representative samples of Caucasian populations. Previous research has shown that cortisol specimens may differ significantly across ethnic groups (Abell et al., 2016; Schreier et al., 2016), due primarily to physiological factors, socio-environmental influences, and hair maintenance practices (van den Heuvel et al., 2020). This finding points to the need for future studies to include data from diverse populations in order to improve our interpretation of the results and ensure their generalizability. Finally, most of the evidence in the present systematic review was derived from cross-sectional studies, which precludes any inferences regarding causality and/or directionality.

Despite these limitations, however, our study is the first to systematically review associations between psychological resilience and cortisol in human adults. Although based on studies with a large degree of methodological variability, it nevertheless directs attention toward the significant relationship that appears to exist between resilience and cortisol. It also reveals that the most commonly used resilience scale was the CD-RISC, followed by the BRS, which, in view of their remarkable psychometric qualities, we consider to be the most recommendable for use in order to facilitate the comparison of resilience results obtained by future studies On the other hand, while the most frequently used method for measuring cortisol was saliva, followed by hair, we believe that hair (or longitudinal saliva sampling) would better inform future resilience studies as it provides greater insight into the phenotype of this hormone. Because cortisol intrinsically responds to stress and rises consequently to return the body to homeostasis, studies on the dysregulation of the system would be better served by a longitudinal measurement. Although the heterogeneity of the studies prevented us from establishing any definite direction toward which the results pointed, the evidence found in the present systematic review suggests a significant relationship between resilience and cortisol, which is why further studies are required to gain a clearer picture of the precise mechanisms and possible third variables that could fully explain this association. Since psychological resilience is already considered a key protective factor for health and well-being (Chmitorz et al., 2018; Dulin et al., 2018), analyzing its possible interactions with cortisol as an end product of the HPA-axis would improve our understanding of its effect at the physiological level. Our results are of practical importance since they provide tentative insight into the importance of considering resilience as a possible modulating factor of the physiological response to stress. Hence, an opportunity exists for scientists to explore the interactions between these two variables in the potential development of future interventions aimed at fostering resilience as an essential component of health promotion.

AUTHOR CONTRIBUTIONS

Ibane Aizpurua-Perez contributed to conception, design, acquisition, data analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be held accountable for all aspects of work ensuring integrity and accuracy.

Amaia Arregi contributed to conception, design, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be held accountable for all aspects of work ensuring integrity and accuracy.

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Arian Martinez-Villar contributed to conception, design, acquisition, data analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be held accountable for all aspects of work ensuring integrity and accuracy.

Joana Perez-Tejada contributed to conception, design, acquisition, data analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be held accountable for all aspects of work ensuring integrity and accuracy.

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CONFLICT OF INTEREST STATEMENT

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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3. Study #3

Aizpurua-Perez, I., Arregi, A., Gonzalez, D., Macia, P., Ugartemendia, G., Labaka, A., Zabalza, N., & Perez-Tejada, J. (2023b). Resilience in Newly Diagnosed Breast Cancer Women: The Predictive Role of Diurnal Cortisol and Social Support. *Biological Research for Nursing*, *26*(1), 68–77. https://doi.org/10.1177/10998004231190074

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Abstract

Background: Breast cancer is currently the most prevalent malignancy among women. Psychological resilience is an important factor that diminishes the stress-related emotional and psychosocial disturbances triggered when receiving the diagnosis. Furthermore, resilience appears to be associated with cortisol, the hormonal end-product of the hypothalamic-pituitary-adrenal axis; however, further studies are needed due to the mixed results reported. Thus, we aim to examine the predictive role of social support and cortisol in resilience among breast cancer patients. **Methods:** A total of 132 women with primary breast cancer completed the Medical Outcomes Study-Social Support Survey (MOS-SSS) and the Resilience Scale (RS-14) and provided four salivary samples for the estimation of participants' total daily cortisol production, for which the formula of the area under the curve with respect to the ground (AUCg) was applied. Moderation analyses were performed to study the influence of social support and AUCg on psychological resilience levels. **Results:** The regression analyses showed a direct significant effect for the emotional support subscale of MOS-SSS on resilience and the interaction between emotional support and AUCg was also found to be statistically significant. Specifically, the conditional effect of emotional support on resilience was found to be significant at middle (M = 3.08; $p < .05$) and low levels (M = .59; $p < .001$) of AUCg. **Conclusions:** Our results suggest that newly diagnosed breast cancer women with middle and low diurnal cortisol profiles may benefit more from emotional support based-interventions while women with high diurnal cortisol may need more individualized therapies.

Keywords

breast cancer, diurnal cortisol, emotional support, resilience, social support

Introduction

Breast cancer is currently the world's most prevalent malignancy among women, with approximately 2.3 million new cases identified in 2020 that are expected to more than double by 2030 (Cerezo et al., 2022; World Health Organization, 2021). The diagnosis of breast cancer is a potentially stressful life event that can significantly deteriorate patients' health due to its implications and consequences in areas such as physical, psychological, social, economic, and spiritual (Aizpurua-Perez & Perez-Tejada, 2020). Specifically, the scientific literature points to anxiety and depression as highly prevalent emotional problems during the year following diagnosis and throughout the course of the disease (Hernández Blázquez & Cruzado, 2016; Seib et al., 2018) with important repercussions on the patients' adjustment as they can worsen their disease prognosis and reduce their life satisfaction (Seib et al., 2018). Interestingly, while for some women coping with disease-related demands is a particularly challenging process, many others adapt much more effectively (Macía et al., 2020; Montiel et al., 2016). Psychological resilience has been identified as an important variable in explaining these differences (Mikolajczak et al., 2008).

Resilience is understood as the ability to cope successfully with stressful life events despite the adverse and traumatic

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nature of the faced circumstances (Bonanno, 2012). In cancer patients, resilience refers to an interactive and dynamic process characterized by effective adaptation to disease-related adversity (Eicher et al., 2015). Thus, highly resilient cancer patients are characterized by individual protective attributes encompassing cognitive flexibility, positive affect, an active coping style, and/or acceptance of adverse events, leading to more adaptive outcomes when facing disease-related challenges (Aizpurua-Perez & Perez-Tejada, 2020; Deshields et al., 2016; Macía et al., 2022). Conversely, less resilient breast cancer patients usually exhibit a more pessimistic outlook on life, decreased physical functioning, and more severe treatment-related side effects (Ristevska-Dimitrovska et al., 2015).

Among the various protective factors thought to influence resilience, social support stands out as one of the most relevant (Zhang et al., 2017). Social support is defined as the perception of the availability of supportive resources in the environment, such as emotional, affective, or instrumental resources (Sherbourne & Stewart, 1991), which has been found to play a protective role in coping with traumatic or negative life experiences (Migerode et al., 2012; Somasundaram & Devamani, 2016). Moreover, scientific research provides evidence of the positive effects of social support in alleviating the negative effects of stressful circumstances experienced during oncological processes, including breast cancer populations (Kim et al., 2010; Kroenke et al., 2013). Interventions based on increasing awareness of social support in breast cancer patients have demonstrated significant effectiveness in improving their emotional well-being. In fact, perceptions of quality social support have been shown to decrease levels of depression, boost self-esteem, and favor ways of coping with the disease (Fong et al., 2017; Huang & Hsu, 2013; Kim et al., 2010). Breast cancer patients with more perceived social support are more able to cope better with the disease burden and return to their lives faster (Çakir et al., 2021). Nevertheless, the large methodological variability of studies measuring social support and resilience in breast cancer patients makes it difficult to draw firm conclusions about the association between social support and resilience at diagnosis before the initiation of treatment (Aizpurua-Perez & Perez-Tejada, 2020; Huang & Hsu, 2013; Zhang et al., 2017).

In contrast to the large number of studies aimed at examining the psychosocial correlates of resilience, only a few have investigated its biological correlates, and specifically its relationship with cortisol, the hormonal end-product of the hypothalamic-pituitary-adrenal (HPA) axis (Lai et al., 2020). As for the latter, dysregulation of the diurnal cortisol secretion is associated with various pathological disorders such as depression, post-traumatic stress and/or anxiety, cardiovascular diseases, and even breast cancer mortality (Labonté et al., 2014; Speer et al., 2019; Doane et al., 2013; Kumari et al., 2011). In particular, dysregulation of the cortisol-awaking response (CAR) has been found to be related to psychological distress in breast cancer patients (Perez-Tejada et al., 2019). With respect to the relationship between resilience and cortisol, during the last few years some studies have found positive (Lai et al., 2020; Lines et al., 2021), negative (Krisor et al., 2015; Burgin et al., 2020) and null (Ramiro-Cortijo et al., 2021; Sharpley et al., 2018) associations between the two variables in different populations, making it difficult to derive clear conclusions about the nature of their relation from these mixed results. Furthermore, only one of these studies was conducted in cancer patients (Sharpley et al., 2018); after analyzing the basal salivary cortisol response of prostate cancer patients no significant associations between the two variables was found. This coupled with the robust evidence for sex-specific behavioral and physiological responses to stress (Bangasser & Wicks, 2017), as well as studies reporting evidence suggesting that the HPA axis functions in a sex-dependent manner (Barel et al., 2018; Goel et al., 2014; Heck & Handa, 2019), indicate that studies aimed at examining. Bidirectional influences between resilience and cortisol in women with breast cancer are necessary.

Given the large number of studies demonstrating a positive association between resilience and social support (Cai et al., 2017; Çakir et al., 2021), and the close association between diurnal cortisol rhythms and health outcomes (Caulfield & Cavigelli, 2020), it is plausible that resilience is shaped by the same diurnal cortisol rhythm related with better health. The main objective of the present study is to examine the predictive role of social support and cortisol in explaining psychological resilience among newly diagnosed breast cancer patients.

Methods

A descriptive cross-sectional design was used to study the influence of cortisol and social support on resilience among women with breast cancer. Participants were 132 women newly diagnosed with breast cancer recruited from a hospital located in the Basque Country (Spain). The sample focused on those women who received their cancer diagnosis for the first time, due to the possible influence on the psychological state that a previous diagnosis of cancer could have. Therefore, the inclusion criteria for this study were: (1) non-pregnant women aged 18–70 years; (2) cancer diagnosis for the first time within the last 2 months; and (3) no history of a known mental disorder. The exclusion criteria were women with metastases. Women who met the inclusion criteria were informed about the study procedures and those who agreed to participate were given a detailed informed consent with sufficient time for their consideration. All procedures performed in this study were in accordance with the relevant national legislation and were approved by the corresponding Ethics Committee.

Procedure for Salivary Cortisol Collection

After participants signed the informed consent they were provided with four tubes for saliva collection; they were asked

to collect saliva at four different times on a single day: upon awakening, 30 minutes after awakening, at 1:00–1:30 pm, and at 8:00–8:30 pm. In order to ensure that saliva sampling was free of contamination from particulate matter or other interfering substances, thus diminishing the possibility of sampling error, participants were instructed to abstain from eating, drinking, or brushing teeth 30 min before sample collection. After the cortisol self-collection, participants were required to store the saliva samples at 4°C in their home freezers and deliver them the next day to the researchers together with the completed questionnaires.

Psychological and Physiological Variables

The psychological measures included the Medical Outcomes Study-Social Support Survey (MOS-SSS) and the Resilience Scale Short version (RS-14). The MOS-SSS (Sherbourne & Stewart, 1991) is a self-administered multidimensional measure of social support that assesses the availability of different types of support through 19 5-point Likert items (ranging from: 'never' = 1 to 'all of the time' = 5). In the Spanish adaptation of this questionnaire in the oncology population, the factor structure of the MOS-SSS was grouped into 3 factors: (a) emotional/informational support and positive social interaction, (b) affective support, and (c) instrumental support (Costa Requena et al., 2007). To obtain the total scale score, the addition of all the items is necessary (range 19–95). The Cronbach's Alpha coefficient of total scale in this study was .95.

The RS-14, a short 14-item Spanish version of Wagnild and Young's (1993) resilience scale was used to identify the level of resilience of the participants (Sánchez-Teruel and Robles-Bello, 2015), understood as the degree of perceived competence and self-acceptance. Each of the 14 items has a 7-point Likert-type response graded from '1' (strongly disagree) to '7' (strongly agree), with a total score range from 14 to 98. In particular, scores under 65 indicate low resilience, those between 65 and 81 reflect moderate resilience, and scores above 81 indicate high levels of resilience (Mirosevic et al., 2019). The reliability coefficient of psychological resilience in the present study was .90.

The saliva was centrifuged at 3000 rpm for 15 min to remove mucins and frozen at −80°C until enough samples were collected to be analyzed in batches. An enzyme immunoassay kit (Salimetrics, Stratech Scientific, UK) was used to determine cortisol levels, and plates were read at 450 nm using a Synergy™ HT plate reader (Bio-Tek Instruments, Inc, Winooski, VT, USA). The assay sensitivity of cortisol was .007 µg/dL, and the average intra and inter-assay variation coefficients were 1.8%, and 1.97%, respectively. Finally, the area under the curve with respect to the ground (AUCg) was calculated for the determination of participants' total diurnal cortisol production based on the cortisol data time points.

Statistical Aanalysis

To test possible associations between the different variables studied, Spearman correlation coefficient was used. Regression analyses were carried out to study the influence of AUCg, social support subscales, and their interactions on resilience, with the following variables included as controls: type of initial oncologic treatment (chemotherapy or surgery), type of surgery, and use of psychotropic drugs. To assess significant interactions, moderation analyses with the Johnson–Neyman technique were used (Hayes, 2013). All statistical analyses were conducted using the SPSS 26.0 statistical package.

Results

The demographic and clinical characteristics of the sample and study variables are presented in Table 1. The mean age of the 132 women who participated in this study was 54.51 (SD = 8.29) years and the majority were married (n = 106; 80.3%) and living with their partners and children (n = 69; 54.8%). Nearly half of the patients reported being actively employed after receiving the news of the diagnosis and the use of anxiolytics and antidepressants was stated by 12.2%. In terms of disease severity (stage I-III), most of the participants were at stage II (n = 70; 53%) and received surgery as initial treatment (n = 93; 70.5%), which in the majority of cases turned out to be conservative (n = 124; 93.9%). The mean scores for the resilience and social support scales and the mean values for the AUCg were 73.93 (SD = 14.14), 13.67 (SD = 1.91), and 3.09 (SD = 2.48), respectively.

Correlation Analyses

Spearman correlations were computed to assess associations among resilience, general score, and subscales of social support and AUCg. As shown in Table 2, resilience was found to be positively correlated with both the general score (r = .38, p < .001) and the subscales of social support: affective, emotional and instrumental support (r = .31, p < .001; r = .39, p < .001; r = .29, p < .001, respectively).

Effects of the Interaction Between Psychological Variables and AUCg on Resilience

The general regression model obtained for resilience was found to be significant (R^2 = .283, $F_{(10, 117)}$ = 4,6091, p < .001). A direct statistically significant effect was found for the emotional support subscale of the MOS-SSS and the interaction between emotional support and AUCg was also found to be statistically significant (Table 3). Specifically, the conditional effect of emotional support on resilience was found to be statistically significant at middle (M = 3.08; p < .05) and low (M = .59; p < .001) levels of AUCg. Thus, the relationship between emotional support and resilience turned out to be positive only when AUCg was on average or one

Table 1. Demographic and Clinical Characteristics of the Sample and Descriptive Data for Psychological and Biological Variables.

Characteristics	*N* = 132
Age (mean; SD)	54.51 (8.29)
Marital status (*N*; %)	
Single	10 (7.6)
Married	106 (80.3)
Divorced	12 (9.1)
Widow	4 (3)
Household composition (*N*; %)	
Single	14 (11.1)
Partner	32 (25.4)
Children	6 (4.8)
Partner and children	69 (54.8)
Son or daughter and grandchildren	1 (.8)
Son or daughter and son or daughter-in-law	1 (.8)
Son or daughter, son or daughter-in-law and grandchildren	1 (.8)
Parents	1 (.8)
Religious community	1 (.8)
Employment situation (*N*; %)	
Employed	59 (46.5)
Housewife	13 (10.2)
Unemployed	12 (9.4)
On leave	26 (20.5)
Retired	17 (13.4)
Consumption of anxiolytics and antidepressants (*N*; %)	16 (12.2)
Stage of disease (*N*; %)	
Stage I	23 (17.5)
Stage II	70 (53)
Stage III	39 (29.5)
Initial treatment (*N*; %)	
Surgery	93 (70.5)
Neoadjuvant chemotherapy	39 (29.5)
Surgery procedure type (*N*; %)	
Lumpectomy	124 (93.9)
Mastectomy	8 (6.1)
Resilience (mean; SD)	73.93 (14.14)
General social support score (mean; SD)	13.67 (1.91)
Affective support	4.71 (.64)
Emotional support	4.40 (.73)
Instrumental support	4.56 (.71)
AUCg (mean; SD)	3.09 (2.48)

Note. AUCg = area under the curve with respect to the ground.

Table 2. Spearman Correlations Between Resilience, General Score, and Subscales of Social Support and AUCg.

	Resilience	Social Support	Affective Support	Emotional Support	Instrumental Support
AUCg	−.158	−.098	−.069	−.055	−.162
Resilience		.375**	.312**	.390**	.288**
Social support			.752**	.913**	.807**
Affective support				.654**	.553**
Emotional support					.562**

Note. **level of significance $p \leq .001$.

Table 3. Regression Analysis for Resilience.

	Unstandardized			Standardized	
Variable	B	SE	B [95% CI]	β	p
Anxiolytics and antidepressants	.742	.257	[.233, 1.251]	.241	.005*
Initial treatment	.106	.175	[−.239, .452]	.049	.544
Surgery procedure type	.508	.341	[−1.68, 1.183]	.124	.139
AUCg	.412	.358	[−.297, 1.121]	1.029	.252
Affective support	−.553	.437	[−1.418, .311]	−.363	.208
Emotional support	**1.240**	**.405**	**[.438, 2.043]**	**.909**	**.003***
Instrumental support	.155	.315	[−.468, .778]	.112	.624
Affective support X AUCg	.126	.101	[−.074, .325]	1.524	.214
Emotional support X AUCg	**−.244**	**.121**	**[−.483, −.004]**	**−2.757**	**.046***
Instrumental support X AUCg	.007	.083	[−.158, .171]	.071	.938

Total model *Adjusted* R^2 = .221, F [10,117] = 4.609, p = <.001. *Note.* SE = Standard Error; CI = Confidence Interval; *p < .05.

standard deviation below average (i.e., mean or -1*SD*), resulting in higher levels of resilience at greater levels of emotional support. The visual plot of the interaction is shown in Figures 1 and 2.

Discussion

Our results indicate that the resilience of newly diagnosed breast cancer patients is partially influenced by social support and diurnal cortisol secretion (AUCg), explaining 28% of the variance. The overall punctuation of the social support scale as well as each of its subscales, namely affective, emotional, and instrumental support, were revealed to positively correlate with resilience. According to a systematic review that supported this finding, patients with breast cancer who perceived higher availability of social support were more likely to display greater levels of resilience (Aizpurua-Perez & Perez-Tejada, 2020), although some other authors reported that social support has a lower impact on resilience when patients are in the moment of the diagnosis (Gálvez-Hernández et al., 2018; Wu et al., 2016). This difference might be the result of important factors that were not previously considered, such as cortisol. In this sense, this is the first study to our knowledge, that measures resilience and cortisol along with social support simultaneously in breast cancer patients, and the results point out the moderating role of AUCg in resilience. Specifically, the correlation analysis showed a negative trend between AUCg and resilience. This finding is in line with studies hypothesizing that resilient individuals may have better regulated cortisol levels than their non-resilient homologs (Nishimi et al., 2022; Petros et al., 2013). Thus, evidence suggests that psychological resilience acts as an attenuator of the deleterious effects of the physiological response to stress by reducing alterations in daily cortisol patterns, serving as a modulator of the link between diurnal cortisol and health and, thereby, improving adaptation (Gaffey et al., 2016). Proof of the latter is the study by Ruiz-Robledillo et al. (2017), which found that higher resilience levels were related to low AUCg in caregivers of children with autism. Moreover, our regression analysis showed a significant interaction between AUCg and emotional support when explaining resilience. Specifically, middle and low levels of AUCg strengthen the positive contribution of emotional support to resilience, while no interaction was found in patients with high levels of AUCg. With regard to the former group, it can be inferred that social support act as a protective factor that promotes adaptation to the shocking diagnosis of breast cancer in low and middle AUCg women and that, in turn, these patients may be especially prone to benefit from interventions of emotional peer support during the cancer process. Hence, AUCg also showed its mediator role in the relationship between emotional intelligence constructs and self-perceived general health in caregivers of people with autism spectrum (Ruiz-Robledillo & Moya-Albiol, 2014), and Sladek et al. (2017) reported that a coping style characterized by greater use of social support predicted flatter average diurnal cortisol slope for young women with attentional avoidance. With regard to the latter group of women, those with high levels of AUCg may need more personalized psychological support to cope with a breast cancer diagnosis, given that it seems that their standard emotional support is not enough to stimulate resilience. This constitutes a challenge in as much as resilience capacity at diagnosis and first stages of the cancer progress can condition posterior health outcomes. According to Tu et al. (2020), trait resilience significantly predicted high levels of perceived growth and health-related quality of life in breast cancer patients. Kourou et al. (2021) also identified low resilience as a heavy predictor of depression in a sample of 609 women recently diagnosed with breast cancer, and Mohlin et al. (2020) showed that higher levels of psychological resilience were significantly related to increased levels of health-related quality of life in women with newly diagnosed breast cancer. These last authors assert that assessment of resilience at the time of breast cancer diagnosis might enable early detection of women in need of more intense psychosocial support.

Similar to the direction of low resilience scores, high AUCg levels have been related to poorer outcomes in different health contexts. For instance, pre-pandemic AUCg was

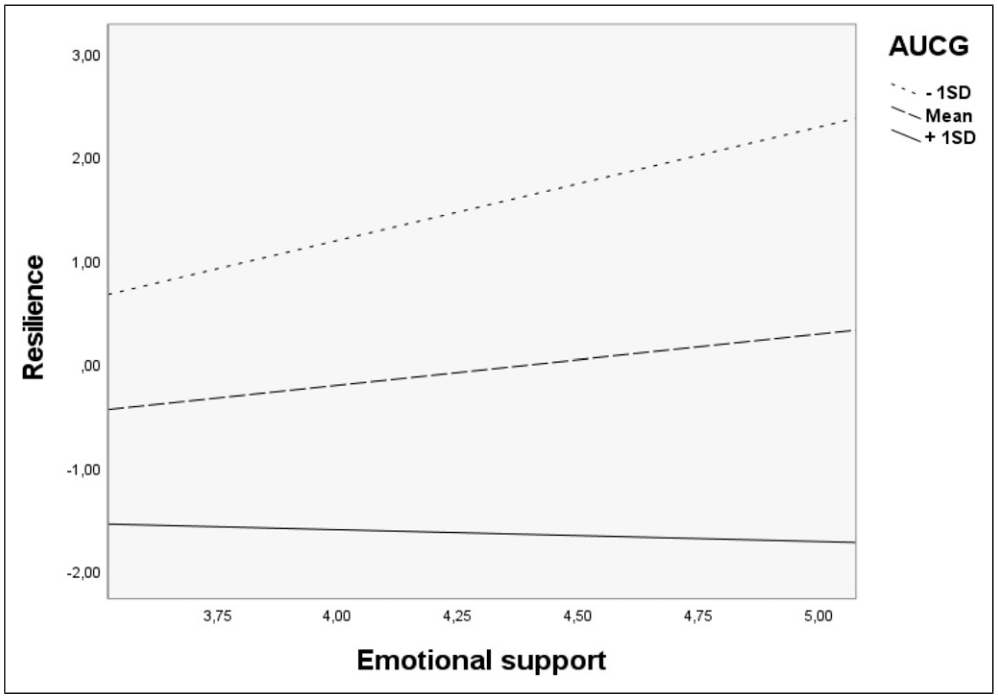

Figure 1. Moderating effect of AUCg on the relationship between emotional support and resilience.

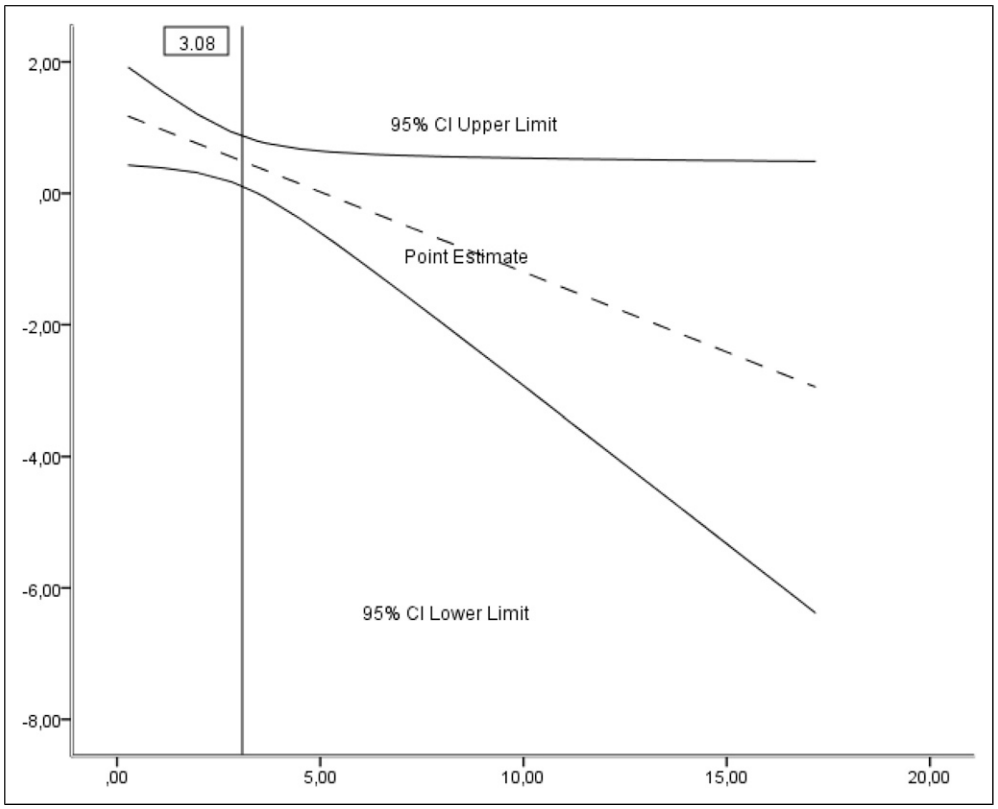

Figure 2. Floodlight analysis graph of the conditional effect of emotional support on resilience as a function of AUCg: the effect of emotional support on resilience is only statistically significant at medium (mean) levels (cutoff point $M = 3.08$; $p < .05$; 95%CI) of AUCg, including low (-1SD) levels of AUCg ($M = .59$; $p < .001$; 95%CI).

associated with depression, anxiety levels, and total perceived stress levels reported during confinement in young adults (Baliyan et al., 2021) and AUCg also correlated with anxiety scores in patients with coronary heart disease (Merswolken et al., 2013). Fortunately, neither psychological resilience nor AUCg levels are static or non-regulable factors, and emotional support has shown to have predictive value towards resilience in its own right for our regression model. In this regard, Di Giacomo et al. (2018) found a positive impact on psychological resilience and distress following the emotional patient-oriented support psychotherapy intervention in young breast cancer women. Additionally, Aguilar-Raab et al. (2021) reported that a 3-month mindfulness based group-intervention decreased AUCg levels from pre to post-compared to controls in healthy subjects.

The present study has certain limitations that should not be overlooked. The first one concerns possible bias resulting from the inclusion of a representative sample of Caucasian population, which reduces cross-cultural reproducibility. The second limitation refers to the cross-sectional design of the study, which precludes any inference about the causality and/or directionality of the results as well as the evaluation of the evolution of the variables during the cancer continuum. Finally, we consider that our sample size could limit the generalizability of the results. It would therefore be advisable for future research to expand the sample size in order to explore whether the significance and effect of the size of the results increase.

Clinical Implications

Promoting resilience following a diagnosis of breast cancer is necessary for successful adaptation to illness, and the results presented in this paper highlight the need for personalized care delivery programs targeted at women who have different psychobiological profiles. According to our regression analysis and in line with other authors (Zhang et al., 2017), emotional support plays a fostering role in resilience, suggesting that peer support programs aimed at newly diagnosed breast cancer patients can mitigate the detrimental psychological consequences of the cancer process. However, standard social support programs may not be enough to meet the needs of all breast cancer patients because high diary cortisol secretion seems to hinder the beneficial effect of emotional support on resilience. Therefore, assessing resilience and AUCg levels at diagnosis can be crucial in order to identify those women who would be better assisted with individualized psychotherapy interventions. An individualized approach should not only be aimed at preventing the onset of distress and maladaptive situations, but also at reinforcing adjustment for optimal health under the circumstances.

In conclusion, the explanatory role of social support and AUCg in resilience indicates that certain psychobiological profile influences the vulnerability of women when facing their new reality. On the one hand, women with high AUCg levels may be especially vulnerable to the detrimental effect of receiving a breast cancer diagnosis and may be, in turn, more likely to develop stress-related disorders. On the other hand, women with low and middle levels of AUCg may exploit the beneficial effect that provides emotional support sources on them. Overall, these results provide a framework for assessing psychobiological indicators and detecting vulnerable newly diagnosed breast cancer patients before the onset of maladaptive situations or stress-related disorders.

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Author Contributions

Ms has 3 tables and 2 figures Aizpurua-Perez, I. contributed to conception and design contributed to acquisition, analysis, and interpretation drafted manuscript critically revised manuscript gave final approval agrees to be accountable for all aspects of work ensuring integrity and accuracy Arregi, A. contributed to conception and design contributed to acquisition and interpretation critically revised manuscript gave final approval agrees to be accountable for all aspects of work ensuring integrity and accuracy Gonzalez, D. contributed to conception and design contributed to acquisition critically revised manuscript gave final approval agrees to be accountable for all aspects of work ensuring integrity and accuracy Macía, P. contributed to conception and design contributed to interpretation drafted manuscript critically revised manuscript gave final approval agrees to be accountable for all aspects of work ensuring integrity and accuracy Ugartemendia, G. contributed to conception and design contributed to acquisition critically revised manuscript gave final approval agrees to be accountable for all aspects of work ensuring integrity and accuracy Labaka, A. contributed to conception and design contributed to interpretation drafted manuscript critically revised manuscript gave final approval agrees to be accountable for all aspects of work ensuring integrity and accuracy Zabalza, N. contributed to acquisition critically revised manuscript gave final approval agrees to be accountable for all aspects of work ensuring integrity and accuracy Perez-Tejada, J. contributed to conception and design contributed to acquisition, analysis, and interpretation drafted manuscript critically revised manuscript gave final approval agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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4. Study #4

Aizpurua-Perez, I., Arregi, A., Gonzalez, D., Urruticoechea, A., Labaka, A., Minguez, X., Ugartemendia, G., Pascual-Sagastizabal, E., Echeverria, R., & Perez-Tejada, J. (under review). Elkar-laguntza study, a randomized controlled trial on the effectiveness of a one-to-one peer support intervention on resilience, social support, and salivary cortisol in recently diagnosed women with breast cancer.

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        - Quartile: Q1
        - Rank: 20/123

TITLE: Elkar-laguntza study, a randomized controlled trial on the effectiveness of a one-to-one peer support intervention on resilience, social support, and salivary cortisol in recently diagnosed women with breast cancer

ABSTRACT:

Background: Coping with the demands associated with breast cancer diagnosis and treatment is a complicated process for some women, while many others adapt much more effectively, developing psychological resilience. Peer support may be one way to promote resilience and thus adaptation to illness, but studies on its effectiveness have yielded conflicting results.

Purpose: The present randomized controlled trial aimed to study the effectiveness of a one-to-one peer support intervention on psychological resilience, social support, and salivary cortisol among breast cancer patients.

Methods: 121 newly diagnosed patients at XXX Hospital were randomly assigned to Intervention Groups I or II or Control Groups I or II. IG1 and IG2 received 8 or 6 biweekly face-to-face social support sessions, respectively. CG only received usual care. Resilience, social support, and salivary cortisol were assessed at baseline (T1) and at the end of the intervention (T2).

Results: We found a significant decrease in resilience levels in CG2 from T1 to T2 and a nonsignificant but moderate-effect increase from T1 to T2 in IG1 who received the social support intervention. Furthermore, regression analysis showed that, while the increase in resilience score of IG1 was determined by the change in cortisol, affective support, and emotional support, however, these factors did not explain the reduction in resilience of participants belonging to CG2.

Conclusion: The present study suggests that peer support can exert a protective psychological influence on women diagnosed with breast cancer, and further indicates an exciting avenue for future intervention development in the breast cancer care continuum.

Keywords: breast cancer, peer support, resilience, salivary cortisol, social support.

Trial registration: ClinicalTrials.gov NCT05077371.

INTRODUCTION

Breast cancer, the main malignant tumor among women, has a direct impact on health and quality of life, due to its consequences in the physical and psychosocial spheres, among others. The diagnosis and treatment of this pathology disrupt almost all aspects of the patient's life, which can lead to several long-term negative emotional outcomes. Thus, approximately one-third of breast cancer patients present anxiety and/or mood spectrum disorders at some point during their oncologic process (Naik *et al.*, 2020). However, these findings also reflect that, although the oncologic process entails great personal suffering, many breast cancer patients present good psychological adjustment, suggesting that they can adapt and cope well with this situation, leading to improved resilience (Stanton and Bower, 2015; Padilla-Ruiz *et al.*, 2019).

Resilience refers to the individual's ability to successfully maintain or recover from the negative effects of stressful life events, such as a cancer diagnosis, by relatively stabilizing psychological and physical functioning (Bonanno, Westphal and Mancini, 2011). In women with breast cancer, resilience seems to be a protective factor that promotes adaptation to the disease process, enabling the former to extract positive aspects from their experience and face obstacles by responding constructively to challenges,

thereby turning them into opportunities for progress (Zayas *et al.*, 2018; Sisto *et al.*, 2019; Yi *et al.*, 2020). There is evidence showing that more resilient patients tend to score higher on general health outcomes, such as emotional well-being and quality of life within the breast cancer care continuum (Aizpurua-Perez and Perez-Tejada, 2020). Hence, resilience can be considered a dynamic mechanism that moderates the negative effect of stress or adverse situations, helping breast cancer patients not only to manage cancer-related distress (Zhang *et al.*, 2017), but also to identify and accept changes resulting from the oncologic process while promoting healthier physical and psychosocial states (Kim *et al.*, 2019).

Beyond psychological perspectives on resilience, biological components of resilience include genetic and psychophysiological factors (Oken, Chamine and Wakeland, 2015; Rakesh *et al.*, 2019). Thus, resilience has been suggested as a key modifiable factor in modulating the physiological response to stress through cortisol (Bergquist *et al.*, 2021; Harvanek *et al.*, 2021). Despite the lack of consistency resulting from the high variability of the resilience assessment tools and cortisol analysis methods used by the studies, data point to the existence of an inverse relationship between cortisol and resilience (Ruiz-Robledillo *et al.*, 2014; Sun *et al.*, 2014; Krisor, Diebig and Rowold, 2015). In particular, it has been hypothesized that resilient individuals would have better-regulated cortisol levels than their non-resilient counterparts (Petros, Opacka-Juffry and Huber, 2013; Nishimi *et al.*, 2022). Thus, some authors have argued that resilience could contribute to reducing alterations in day-to-day cortisol patterns, modulating the association between diurnal cortisol and health, and, through this, fostering adaptation (Gaffey *et al.*, 2016).

Social support, for its part, has been identified as an important factor in alleviating the negative impact of cancer-related stress and enhancing patients' ability to accept adversity giving it a positive meaning (Leung, Pachana and McLaughlin, 2014; Huang *et*

al., 2019; Aizpurua-Perez and Perez-Tejada, 2020). Although there is no single definition of social support, it generally refers to an individual´s subjective assessment of psychological and physical resources provided by social interactions. In breast cancer patients, social support plays a critical role in improving psychological well-being and resilience (Ye *et al.*, 2018; Huang *et al.*, 2019). Specifically, those patients with higher levels of perceived social support have been found to present less anxious-depressive symptomatology and to be able to return to their lives more quickly (Huang and Hsu, 2013; Kroenke *et al.*, 2013). In addition, social support serves as a mediator between psychological resilience and quality of life, particularly in maintaining physical and mental well-being (Ruiz-Rodriguez *et al.*, 2022; Zhou *et al.*, 2022). It is therefore through its buffering and protective role that social support helps patients to focus on the positive aspects and potential benefits of the cancer process and to cope with it effectively (Ma, Wan and Chen, 2022).

Given the modifiable nature of resilience over time, resilience-enhancing interventions are being considered a promising strategy to reduce the negative impact of stressful situations and thus mitigate psychological distress, shifting from an illness-centered to a health-centered approach (Kalisch *et al.*, 2017). In this regard, interventions focusing on social interaction, such as peer support, are being implemented to promote resilience (Chmitorz *et al.*, 2018). Peer support refers to the support provided or exchanged by people who have faced similar challenges, and, unlike professional help, it is based on a non-hierarchical relationship through which individuals with the same problem come together to exchange information, share experiences, and encourage or help each other to overcome difficulties (Munce *et al.*, 2017; Park *et al.*, 2019). Because of their genuine and experiential knowledge (Kirkegaard, 2022), peers are able to uniquely understand the challenges the others are facing, thus engaging in authentic emotional mutually

exchanging relationships with them. Through the use of active listening and empathy, peers can provide patients with a safe space that facilitates the communication of practical and emotional concerns and promotes adaptive coping with distressing emotions (Pistrang *et al.*, 2013), in addition to connecting them with clinical and community resources. Specifically, in cancer patients, peer support interventions are designed primarily to supplement, and not replace, professionally delivered psychological support (Zhang, Li and Hu, 2022), as they alone may not be sufficient to cover the psychological and emotional needs of patients throughout the oncological process.

In recent decades, research conducted with these types of programs has considerably grown showing significant improvements in cancer patients' quality of life, depression, anxiety, and self-efficacy (Zhang, Li and Hu, 2022). Among the different modalities of peer support (one-to-one vs group), research suggests that the one-to-one modality, in addition to being an easier option for patients to establish a more harmonious relationship with their peers, improves psychological outcomes in people with a wide range of risk factors and diagnoses (Hoey *et al.*, 2008; Meyer, Coroiu and Korner, 2015; Ramchand *et al.*, 2017). Likewise, among the different formats for conducting peer support, mixed formats, which include modalities such as face-to-face and telephone, have been found to optimize outcomes by utilizing the benefits of nonverbal language along with the flexibility of the telephone (Zhang, Li and Hu, 2022). However, despite the positive psychological results found in these investigations, the considerable heterogeneity in the forms of application of peer intervention and the mixed findings found from studies suggest that well-designed RCTs with larger sample sizes are necessary to evaluate the benefits of this type of intervention in cancer patients (Hu *et al.*, 2019; Zhang, Li and Hu, 2022). Moreover, the fact that, to our knowledge, only the psychological influences of these programs have been studied in cancer patients, makes further research identifying

the biological processes underlying the efficacy of these interventions necessary for their possible generalization.

The present research aimed to study the influences of a one-to-one peer support intervention on both psychosocial and physiological variables among women newly diagnosed with breast cancer in Spain. Specifically, the effect of the intervention on the psychological resilience, social support, and salivary cortisol of the participants was examined.

METHODS

1. Study Design

A randomized controlled trial (RCT) design was used to evaluate the effects of a one-to-one peer support intervention on certain biopsychosocial variables in a sample of breast cancer patients from Xxxxx (Xxxxx) (National Institutes of Health Clinical Trial NCT05077371). CONSORT reporting guidelines were followed in this study.

2. Participants

Participants were 121 women newly diagnosed with breast cancer (M_{age} = 54.29 ± 8.47, range = 33-70 years) recruited between June 2019 and August 2022 from the Xxxxxx Hospital (Xxxx) by two study researchers (JPT and IAP) following consultations for communication of diagnosis and initial treatment (surgery or neoadjuvant chemotherapy) (see Figure 1). Patients whose primary treatment was surgery (n = 84) were recruited during the 2 weeks prior to undergoing surgery, whereas patients who were prescribed neoadjuvant chemotherapy (n = 37) were recruited either during the 2 weeks prior to the start of treatment or once they had received the first chemotherapy session, due to

circumstances beyond the control of the study design related to the operation of the hospital. Potentially eligible participants (N = 247; see Figure 1) were approached and informed about the study through individual sessions with a researcher, in which the study was described as an opportunity to talk about their worries and concerns with someone who had faced a similar experience. The inclusion criteria for the study were (1) women aged 30-70 years with stage I-III breast cancer, (2) within 2 months after diagnosis of breast cancer, (3) without a diagnosis of major psychiatric condition or mental disorder (according to DSM-V criteria; American Psychiatric Association, 2013), and (4) able to communicate and read in Spanish. The exclusion criteria were (1) diagnosis of prior cancer (except minor skin cancer) and (2) metastasis. These criteria were set with the objective of creating a reasonably homogeneous sample of individuals with similar clinical characteristics and medical treatments, able to understand the evaluation materials and assiduously participate in the intervention sessions. Women who met the inclusion criteria and were willing to participate in the study were given written informed consent with sufficient time for consideration. After the signature of the informed consent, participants were administered a battery of psychosocial self-report measures (psychosocial questionnaires and sociodemographic questions created ad hoc) and 4 salivary cortisol samples, which they were asked to collect at four different times on the same day they had to fill out the questionnaires (upon awakening, 30 minutes after awakening, at 1:00-1:30 pm, and 8:00-8:30 pm; 1 single day). Participants were also instructed to abstain from eating, drinking, or brushing teeth 30 min before sample collection and to store the saliva samples at 4°C in their home freezers. Appointments were then made with the participants at the hospital for baseline collection of questionnaires and saliva samples (Time 1; T1), and the same procedure was repeated 12- to 16-weeks later, after completion of the intervention (Time 2; T2).

3. Volunteers/Support partners

Volunteers were 14 disease-free breast cancer survivors (M_{age} = 54.07 ± 8.82, range = 40-68 years) recruited from the Xxxxx Hospital and the Axxxx Pxxxx Program of the territorial health care system by their oncologist and nurses, as well as from one breast cancer association through public talks and informative letters sent between June 2017 and November 2017. The inclusion criteria for the volunteers were (1) women aged at least 18 years, (2) with completed cancer treatment at least 1 year prior to recruitment (surgery, chemotherapy, and/or radiation therapy), and (3) without a diagnosis of major psychiatric condition or mental disorder (according to DSM-V criteria; American Psychiatric Association, 2013). The exclusion criteria were: (a) women with metastasis. Interested women contacted one of the study researchers (JPT), who checked their eligibility and subjected them to a semi-structured individual psychological interview to assess their adequate mental and physical recovery, and verify that participation in the program had the least psychological impact on them. Thus, during the individual psychological interview, women were asked to complete a battery of psychological measures, which are detailed in Table 1.

The selected volunteers then participated in a Psychoeducational and Emotional Intelligence (IE)-based training program under the supervision of the study researchers aimed at providing them with tools to facilitate proper management of sessions and patient follow-up. The training program involved six 1-day workshops (each of 3 hours, 18 hours in total) by two professors from the University of XXXX over a period of 3 months. All programs included a variety of lectures, role-playing activities, and group discussions. The main topics included diagnosis and treatment of breast cancer, healthy habits, self-awareness, self-regulation, motivation, empathy, communication skills, as

well as emotional expression and regulation. Volunteers were also informed of the importance of maintaining confidentiality of patient information.

During the research period, women attended sixteen quarterly 1-day supervision meetings (each of 3 hours, 48 hours in total) by two study researchers (JPT and IAP) in order to evaluate the intervention, identify training needs and possible problems encountered during the sessions and explore appropriate solutions to the problems. These sessions also sought to strengthen group cohesion and emotional bonds among the volunteers through the creation of spaces in which they could share their personal experiences and emotions triggered by accompanying the patients. During these meetings, volunteers were advised to keep a record of the challenges and difficulties encountered during the sessions with the patients for later review.

4. Procedure

All procedures performed in this study were in accordance with the relevant national legislation and were approved by the corresponding Ethics Committee (registration number PI2018068). No compensation was offered for participation in the study. Participants completed a first assessment on recruitment (T1) and then were randomly assigned to the intervention (1) or control (2) conditions, where the concrete assignment to each of the two intervention groups [Intervention Group I (IG1); Intervention Group II (IG2)] or control groups [Control Group I (CG1); Control Group II (CG2)] depended on their type of medical treatment (see explanation in the paragraph below). Thus, participants were blinded to condition assignment until the completion of the first assessment (T1), when they were informed of their belonging to each of the intervention or control conditions. With respect to the randomization method, the balanced block randomization method was used to allocate participants to each of the conditions (Efird, 2011). Briefly, the allocation sequence was arbitrarily determined in a 1:1 ratio (x2),

resulting in a total of four groups (IG1 and CG1; IG2 and CG2). The order was rearranged by random assignment by one of the researchers (JPT) using a computer program (Microsoft Excel, versión 2016).

Participants assigned to the intervention condition were assigned to either Intervention Group I (IG1) or Intervention Group II (IG2) depending on the type of medical treatment they were to receive. Specifically, IG1 (n=27) consisted of patients who were prescribed a chemotherapy treatment (adjuvant or neoadjuvant), while IG2 (n=32) consisted of patients who, without receiving chemotherapy, had a shorter adjuvant radiotherapy treatment. Similarly, participants assigned to the control condition were assigned to Control Group I (CG1) or Control Group II (CG2) according to their medical treatment, with the former consisting of patients receiving chemotherapy (adjuvant or neoadjuvant) (n=32) and the latter of patients with shorter adjuvant radiotherapy treatment (n=30).

The intervention occurred over a 16-week period in IG1, while it lasted a total of 12-weeks in IG2 (Figure 1), the length of which was determined by the duration of the participants' medical treatment (16 weeks for patients with adjuvant or neoadjuvant chemotherapy vs. 12-weeks for patients without chemotherapy and with adjuvant radiotherapy). In both cases, it began during the first week following the completion of the first assessment. Women in the control group received treatment as usual. A second assessment (T2) was performed at the end of the intervention, which took place 16 weeks after T1 in IG1 and CG1, and 12 weeks after T1 in IG2 and CG2. Thus, the follow-up period spanned 4 and 3 months for the IG1-CG1 and IG2-CG2 groups, respectively, after randomization.

4.1 Intervention

The one-to-one peer support program “Xxxxx Xxxxxxxx” aimed at offering women newly diagnosed with breast cancer the possibility to express their concerns, ask questions, and receive social support from survivors who overcame the same difficulty. Building on the literature on peer support (Simoni *et al.*, 2011; Jablotschkin *et al.*, 2022; Ziegler *et al.*, 2022) and particularly on social comparison theory (Mussweiler, 2003; Gerber, Wheeler and Suls, 2018; Corcoran *et al.*, 2020), the program was based on the idea that sharing personal experiences to individuals who have gone through the same difficulties not only normalizes patients' experience but also favors their psychological adjustment.

The intervention consisted of 6 or 8 face-to-face, telephone, or virtual biweekly social support sessions involving one patient and one volunteer. The total number of sessions received by each participant depended on the duration of their medical treatment, providing 8 sessions in patients who received chemotherapy (participants belonging to IG1), and 6 in those having a shorter radiotherapy treatment (patients belonging to IG2). On the other hand, the frequency and number of sessions established were intended to allow sufficient time for the peer-to-peer bonding to develop, while setting a frame of reference to limit the commitment required of volunteers. No minimum or maximum time was established for the duration of the meetings. The modality of the sessions (face-to-face, telephone, or virtual) was left to the choice of the patients, with emphasis on the importance of the former being held in places that offered a relaxed atmosphere necessary for the two women to carry on a private conversation. No formal rules were included to define the topics to be discussed during the sessions so that each dyad decided the focus and direction of their interactions. The intervention focused on creating a supportive, respectful, and caring environment that encouraged patients the free expression of their emotions, feelings, and thoughts.

Matches between patients and volunteers were conducted by two members of the research team (JPT and IAP) who attended all training and quarterly supervision meetings (in addition to the individual interviews conducted by JPT), so they were sufficiently familiar with the study volunteers. Matching was mainly carried out based on diagnosis and medical treatment, age, and family status of the patients, in addition to considering characteristics related to their personality. Before the first program session, each patient was offered basic information about the other (e.g., age, tumor type, and treatment received) by requesting their permission beforehand to ensure confidentiality. Patients were also informed that they could request a change at any time during the program should they not feel comfortable with the assigned volunteer. Finally, since there is evidence that providing support to more than one patient can compensate for a poor relationship with another patient (Moulton *et al.*, 2013), volunteers accompanied 2 or 3 patients at the same time on several occasions.

After each of the program sessions, each volunteer participated in an individual telephone supervision session with one of the two research psychologists (JPT and IAP) to talk about her emotions and impressions after the meeting with the patient. The psychological supervision of the volunteers constituted a fundamental part of the intervention that sought to protect them from retraumatization and the appearance of anxiety and depressive symptoms that may occur when accompanying someone who has been recently diagnosed (Giese-Davis *et al.*, 2006). During these supervision calls, the volunteers were also asked about the modality and duration of the sessions with the patients for subsequent data recording.

4.2 Control group

Women in the control group received treatment as usual and were informed of the psycho-oncology services offered by the hospital, emphasizing the importance of contacting these

professionals whenever necessary. For ethical reasons, control group members were not discouraged from seeking peer support if needed.

5. Psychological and Physiological Variables Psychosocial variables

5.1 Resilience

The Spanish version of the Wagnild Resilience Scale of 14 items (RS-14) was used to assess the level of individual resilience of participants (Sánchez-Teruel and Robles-Bello, 2015). Each of the 14 items is scored on a 7-point Likert-type response graded from '1' (strongly disagree) to '7' (strongly agree) and provides a total score range from 14 to 98. Specifically, scores below 65 indicate low resilience, those between 65 and 81 indicate moderate resilience, and scores above 81 reflect high levels of resilience (Miroševič, Klemenc-Ketiš and Selič, 2019). The reliability coefficient of psychological resilience was 0.895.

5.2 Social Support

The Medical Outcomes Study–Social Support Survey (MOS-SSS) (Sherbourne and Stewart, 1991) is a self-administered rating scale developed for the measurement of the perceived availability of social support through 19 5-point Likert items (ranging from: 'never' = 1 to 'all of the time' = 5). In the Spanish adaptation of the questionnaire with cancer outpatients, this construct was grouped into the following 3 factors: a) emotional/informational support and positive social interaction; b) affective support, and c) instrumental support (Costa Requena, Salamero and Gil, 2007). The sum of all the items included in the scale is necessary to obtain the total score of the scale (range 19-95). The Cronbach´s Alpha coefficient of the total scale was 0.950.

5.3 Salivary Cortisol

Saliva samples were centrifuged at 3000 rpm for 15 min to remove mucins and frozen at -80ºC until enough samples were collected to be analyzed in batches. On the day of the assay, saliva samples were thawed, vortexed, and assayed using the Salimetrics high-sensitivity enzyme immunoassay kit (Stratech Scientific, UK) to determine cortisol levels, and plates were read at 450 nm using a Synergy™ HT plate reader (Bio-Tek Instruments, Inc., Winooski, VE, USA). The assay sensitivity of cortisol was 0.007 μg/ dL, and the average intra and inter-assay variation coefficients were 1.8%, and 1.97%, respectively. The area under the curve with respect to the ground (AUCg) was calculated to determine the total diurnal cortisol production of each participant based on the cortisol data time points.

6. Statistical Analyses

Data were analyzed using SPSS statistics version 28. Data were first screened for outliers and assumptions of normality. In the case of variables that did not follow a normal distribution, the Bloom transformation was applied, which is one of the best transformations for dealing with asymmetric distributions (Rodríguez and Díaz, 2008). ANOVA was used to test for group variations within each study assessment (T1, T2), with repeated measures ANOVA specifically used to study the possible differential change by group in resilience during the transition from T1 to T2. A-priori sample size is calculated with G*Power for repeated-measures ANOVA with within-between interaction effects and an effect size specification as recommended by Cohen (1988). To determine whether changes in cortisol and social support from T1 to T2 were predictive of possible changes in resilience, a Multiple Linear Regression analysis was carried out.

RESULTS

Participants

The baseline demographic and clinical characteristics of the participants by condition and type of medical treatment are presented in Table 2. Briefly, our study sample consisted of 121 patients, who were predominantly middle-aged (mean 54.29 years (range 33-70 years) and with stage II (52.9%) disease. Among patients who received surgery over the study period (n = 84), most were found to have received conservative surgery (95.23%). The use of anxiolytics and antidepressants was identified in approximately one-tenth of the patients, with a total of 14 patients (out of 121) reporting their use at the time of diagnosis. No significant baseline differences were observed with respect to age, stage, primary treatment, type of surgery, and consumption of anxiolytics and antidepressants among patients in the IG1, CG1, IG2, and CG2 groups.

Differences by each group within each evaluation

Table 3 and Table 4 show the descriptive statistics of dependent and predictor variables along with the results of the ANOVA analysis for each of the groups, which show that there are no statistically significant differences regarding resilience, cortisol, affective support, instrumental support, and emotional support between the IG1, CG1, IG2 and CG2 groups at T1 and T2.

Differences by each evaluation within each group

On the other hand, ANOVA analyses also revealed that there were no statistical differences were found between groups in resilience at T1 ($F_{(3,116)}$=1.585, p=0.197, , ω_P^2= 0.014) and T2 ($F_{(3,117)}$=1.064, p=0.367; ω_P^2= 0.001), cortisol levels at T1 ($F_{(3,114)}$=0.912, p=0.438; ω_P^2= -0.002) and T2 ($F_{(3,111)}$=0.111, p=0.953, ω_P^2= 0.025),

affective support at T1 (F(3,121)=0.374, p=0.772, ωP2= -0.016) and T2 (F(3,121)=1.847, p=0.142, ωP2= 0.021), emotional support at T1 (F(3,121)=0.509, p=0.677; ωP2= -0.012) and T2 (F(3,121)=1.192, p=0.316; ω_P^2= 0.005), and, instrumental support at T1 ($F_{(3,121)}$=0.886, p=0.451; ω_P^2= -0.002) and T2 ($F_{(3,121)}$=0.622, p=0.602, ω_P^2= -0.010).

Changes in resilience levels: the role of cortisol levels and social support

A mixed ANOVA analysis was performed with the aim of identifying possible differences in resilience between the two periods studied (T1 and T2) in each of the groups IG1, CG1, IG2, and CG2. Thus, the results of the mixed ANOVA test revealed a statistically significant interaction effect ($F_{(1,116)}$=3.368; p= 0.021; ω_P^2= 0.047) (Figure 2).

In order to study this interaction a pairwise comparison between evaluations for each group was done. The differences between T1 and T2 were only statistically significant for CG2 ($F_{(1, 29)}$=9.317; p=0.003; dDc=0.88). However, the effect size analysis showed that the difference between T1 and T2 in IG1 was moderate ($F_{(1,25)}$=1.362; p=0.246; dDc= 0.47), so we decided to study this change.

Finally, two regression analyses were carried out, one for CG2 and, another one for IG1, in order to determine which variable (change in cortisol, change in affective support, change in emotional support, and/or change in instrumental support) predicted their resilience change score.

For CG2, the model was not significant (R^2= 0.184; $F_{[4, 25]}$= 1.184, p= 0.346) and revealed that neither change in cortisol (β = -.063, p = .758), nor change in affective support (β = .586, p = .094), change in emotional support (β = -.171, p = .595) or change in instrumental support (β = -,282, p = .228) explained the drop in participants' resilience levels between T1 and T2 (Table 5).

For IG1, however, the model was found to be significant (R2 = 0.548; F[4, 18] = 4.238, p = 0.019) and revealed statistically significant main effects for change in cortisol, change in affective support and change in emotional support between T1 and T2 Specifically, women with smaller increases in cortisol and larger reductions in affective support between T1 and T2 had greater improvements in resilience between the two assessments (β = -.658, p = .010 and β = -.997, p = .014, respectively). Likewise, women with higher increases in emotional support between T1 and T2 were those with greater gains in resilience between the two periods studied (β = .935, p = .008).

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the effects of a one-to-one peer-support intervention on both psychosocial and physiological variables among women newly diagnosed with breast cancer. Specifically, we studied the influence of the intervention on psychological resilience, social support, and salivary cortisol, finding significant changes in participants' psychological resilience from the time of diagnosis to the completion of the peer-support program. We found a significant decrease in the resilience levels of study participants belonging to Control Group 2 (CG2: control condition + no chemotherapy) at the 12-week time interval from diagnosis, and a non-significant but moderate-effect increase in the resilience of those women belonging to Intervention Group 1 (IG1: intervention condition + chemotherapy) who received the 16-week intervention. Certain factors should be considered when interpreting the different patterns of change found in each group. Current evidence suggests that chemotherapy contributes significantly to a pronounced deterioration in the well-being of cancer patients because of the impact of side effects on the physical and emotional dimensions of their quality of life (Hwang, Chang and Park, 2013; Zhao *et al.*, 2022). In the study by Veličković *et al.* (2022), the authors found

steeper decline in the health-related quality of life of breast cancer patients who received chemotherapy in the year following diagnosis compared to their peers who did not, further noting that psychological resilience was strongly associated with their quality of life. However, other authors argue that adverse situations generated by chemotherapy treatment can stimulate transformative processes of psychological resilience in breast cancer patients. In this regard, Padilla-Ruiz *et al.* (2019) found lower CD-RISC resilience scores in a sample of breast cancer survivors who did not receive chemotherapy at 6 years post-diagnosis compared with those who did. Although the design of the latter was cross-sectional and did not measure the trajectory of resilience since diagnosis, its findings suggest that the demands and difficulties associated with chemotherapy may also foster the development of resilience in women with breast cancer. Nevertheless, it is noteworthy that, in addition to finding higher levels of resilience in IG1 from the first assessment (T1) to the completion of the second assessment (T2), our results also identified significantly lower levels of resilience in CG2 at T2 compared to T1 despite that group not undergoing chemotherapy. This fact points to the health-protective and resilience-promoting role that the peer-support intervention may have played in participants and suggests that sharing personal experiences with people who have undergone the same difficulties can not only demystify and normalize patients' experience but also promotes their psychological adjustment to oncological challenges, as has been suggested in previous studies (Pistrang *et al.*, 2013; Zhang, Li and Hu, 2022). At the same time, our findings further suggest that the lack of opportunities to engage in emotional relationships founded on mutual exchange during the treatment continuum may not only fail to enhance but also hinder the development of patients' resilience. This may be in part because, as suggested by Taleghani *et al.* (2022), current basic oncology care still maintains paternalistic attitudes such as ignoring or overriding the legitimacy of patients' feelings, preferences, or actions,

posing significant barriers to the promotion of their emotional growth and well-being. Furthermore, there is evidence that a lack of patient-centered messages from support providers can lead to negative emotional outcomes and unfavorable relational ramifications for women with breast cancer who expect to be accompanied during their disease process (Ray and Veluscek, 2018).

The results of the regression analysis revealed that the increase in resilience shown by women belonging to IG1 between the two assessments was partially explained by the change experienced in both their emotional support (β = .935, p= .008) and affective support (β = -.997, p= .014). Specifically, patients who experienced larger increases in emotional support as well as steeper declines in affective support between T1 and T2 had stronger improvements in their levels of resilience. On the one hand, the positive relationship found between the change in emotional support and the improvement of the latter suggests that the peer support intervention may have promoted participants' resilience by enhancing their perception of emotional support. Thus, we consider that the intervention contributed to greater satisfaction of their emotional needs as a consequence of receiving empathic understanding, exposure to informative guidelines, and the emotional bond generated with peers, in addition to the communication of practical and emotional concerns related to their disease. Moreover, in the Spanish validation of the MOS-SSS scale used in the present investigation (Costa Requena, Salamero and Gil, 2007), the authors of the study indicated that the emotional support subscale of this questionnaire refers precisely to empathic understanding and to the possibility of obtaining informative advice and guidance from others, which confirms that the social support received through the peer support intervention is of an emotional nature. The results found in the present investigation seem to be in line with those found by Gümüs and Cam (2008), who after applying a 7-session emotional support-focused nursing

intervention found increased scores on the Psychosocial Adjustment to Illness Scale at a 6-month follow-up assessment in newly diagnosed breast cancer patients. In addition to this, other studies have also pointed to social support as a decisive factor for the improvement of resilience in women with breast cancer. For instance, Zhang et al. (2017) identified higher levels of resilience among patients with higher social support scores and observed that social support played a partial mediating role in the relationship between resilience and quality of life. Along the same lines, Ye *et al.* (2016) found higher levels of social support and resilience at the 6-month follow-up of a multidisciplinary mentorship-based Be Resilient to Breast Cancer program delivered after breast surgery. All of these data together with our results indicate that women with breast cancer benefit from interventions based on the provision of emotional support and that such support in turn is related to better resilience.

On the other hand, the inverse association identified in our study between the change in affective support, which according to Costa Requena, Salamero and Gil (2007) involves real demonstrations of love or affection by the individual's inner social circle, and the improvements in resilience, points to the reduction in the perception of affective support as one of the mechanisms through which the peer support intervention may have promoted the resilience of participants belonging to IG1. Thus, we believe that one of the reasons why greater decreases in perceived affective support from out-of-hospital resources such as family or friendship networks have contributed to the improvement of participants' resilience is due to the particular characteristics of its demonstrations. The diagnosis of breast cancer often represents a highly distressing experience that can alter the normal course of the patient's life. When coping with this situation, women usually turn to their intimate networks for support, affection, and/or understanding, which can promote positive affect and prevent the development of negative emotions in the former

(Yang *et al.*, 2022). However, either intentionally or unintentionally, immediate surroundings may sometimes behave in unhelpful and/or unsupportive manners, adopting overprotective or overly critical attitudes, or minimizing the patient's concerns ((Peters-Golden, 1982; Woźniak and Iżycki, 2014; Manne *et al.*, 2019), which can hinder the latter's ability to adjust to the disease process. The patients in our study may have experienced the affective support received from their surroundings as non-beneficial, possibly by assigning negative attributions to it, thus leading them to actively seek less affective exchanges with the latter. In addition, we suspect that the application of the intervention, and with it, the greater satisfaction of their emotional needs through the emotional bond generated with peers, may also have prompted patients to make less use of close support networks to meet their needs. This indicates that a better understanding of the conditions through which affective support can influence resilience is needed in order to optimize the adaptation of women with breast cancer during the treatment continuum.

The results of the regression analysis also revealed that, in contrast to IG1, neither the change in emotional support (β = -.171, p= .595) nor the change in affective support (β = ,586, p= .094) nor the change in instrumental support (β = -.282, p= .228) explained significantly the decrease in the resilience scores of CG2. This, in our opinion, points to the existence of third variables not taken into account in the present study that could partially explain the reduction in resilience observed in participants who, in addition to not undergoing chemotherapy, did not receive the peer support intervention. In this respect, in the study by Hsu *et al.* (2021), the authors found that the perceived social support of a sample of breast cancer patients in active treatment did not directly influence their resilience and, instead, affected it indirectly through hope, understood as the positive expectation of a good future that confers meaning to the cancer experience. Specifically,

hope turned out to have a full mediating role between the two variables, with increasing levels of the former being the way in which social support positively influenced participants' resilience. These results suggest that diminished hope may be one of the mechanisms through which changes in social support may be associated with the reductions in resilience observed in patients belonging to CG2. However, the fact that approximately 10% of patients in the study by Hsu *et al.* (2021) received chemotherapy, in addition to its cross-sectional design, indicates the need for future research to collect longitudinal data on the relationship between resilience and social support considering the distinctive influences of various breast cancer treatments.

Besides finding out the individual contribution of the change elicited by each subtype of social support on resilience, our study also wanted to ascertain whether the latter is influenced by the change in participants' levels of cortisol, the hormonal end-product of the hypothalamic-pituitary-adrenal (HPA) axis. The results of our regression analysis revealed that, unlike CG2 participants, the increase in resilience shown by women in IG1 between the two assessments was also partially explained by the change experienced in their levels of cortisol (β = -.658, p= .010). Specifically, larger increases in cortisol between T1 and T2 were found to be negatively associated with increases in resilience. These findings are in line with previous studies pointing to the existence of an inverse relationship between cortisol and resilience (Ruiz-Robledillo *et al.*, 2014; Sun *et al.*, 2014; Krisor, Diebig and Rowold, 2015) and further suggest that peer support interventions might contribute to improved resilience by influencing their physiological response to stress. Albeit limited, there is evidence that social support-based interventions may contribute to improved evening serum cortisol (Webster *et al.*, 2016) and diurnal salivary cortisol responses (Hsiao *et al.*, 2016) among breast cancer patients. Moreover, in the only study that, to our knowledge, has studied the relationship between

resilience, cortisol, and social support in women with breast cancer (Aizpurua-Perez, Arregi, Gonzalez, *et al.*, 2023b), our research group found that cortisol acted as a significant moderator between emotional support and resilience, identifying that the positive relationship between emotional support and resilience only held in patients with low and medium (as opposed to high) cortisol levels. These results, together with the current findings, strongly imply that the peer support intervention's positive effect on resilience is modulated by diurnal cortisol levels in breast cancer patients. Additionally, the lack of significant effect found for the change in cortisol on the reduction of resilience experienced by participants belonging to CG2 (β = -.063, p= .758) lends support to the findings of Gundogmus *et al.* (2022), which being so far the sole study analyzing the relationship between resilience and cortisol in breast cancer patients (of whom 70.4% received chemotherapy), identified an absence of correlation between the two variables by measuring participants' one-point morning serum cortisol postoperatively. However, the scarce evidence in the literature describing the relationship between these two variables, which as we were able to verify in a recent systematic review published by our group (Aizpurua-Perez, Arregi, Labaka, *et al.*, 2023a) has been described in cancer patients by an additional study that did not identify a relationship between both variables (Sharpley *et al.*, 2018), warrants further studies in this population aimed at examining the bidirectional influences between resilience and cortisol while accounting for the effects of chemotherapy treatment. There is a large body of evidence showing that cortisol is highly influenced by factors such as chemotherapy in women with breast cancer. In this regard, Limberaki *et al.* (2011) found that serum cortisol levels increased during chemotherapy in oncology patients, and Ramírez-Expósito *et al.* (2021) showed that women with breast cancer treated with neoadjuvant chemotherapy had higher serum cortisol levels within a week after the completion of treatment compared to their peers

who did not receive chemotherapy. Moreover, in breast cancer survivors Cirulli *et al.* (2015) observed that women's cortisol levels also augmented throughout the first year post-chemotherapy, while Lambert *et al.* (2020) found lower absolute post-treatment salivary cortisol levels in those survivors who received chemotherapy than in those who did not. In addition to the inconclusiveness of these results, we believe that the limited number of studies identified, the different cortisol collection methods employed by the investigations (saliva vs. serum), the different underlying physiological mechanisms of hypothalamic-pituitary-axis (HPA) functioning represented by each sample (diurnal vs. tonic cortisol response) and the variability related to stage and/or time since diagnosis of the included participants limits the interpretability of the data. Given that the present investigation is the first to analyze the influences of a one-to-one peer support program on the salivary cortisol of breast cancer patients, more research is needed to extrapolate clear conclusions about the effects of such programs on the physiological stress response of the latter.

Clinical implications

Breast cancer diagnosis and treatment involve personal and environmental imbalances that can impair a woman's ability to respond to the disease and adapt to her new situation. Our results suggest that emotional support received from a peer who has experienced the same situation has the potential to promote the psychological resilience of women with breast cancer, thus facilitating their psychological adaptation to the oncologic process. Specifically, our findings point to change in emotional support, affective support, and cortisol as the mechanisms through which the peer support intervention may have improved the resilience of participants. What's more, we observed that a lack of opportunities to engage in mutual-exchange emotional relationships during treatment may hinder the development of patients' resilience. Although social support and cortisol

were not found to explain the vulnerability of these women to states of diminished resilience, we believe they may benefit from the timely administration of peer support. This is especially salient because in addition to being associated with improved quality of life (Veličković *et al.*, 2022), resilience has also been found to mitigate the effects of stress on inflammation-associated depressive symptoms in breast cancer patients (Manigault *et al.*, 2022).

Among the limitations of this study, we highlight the fact that our participants were mostly Caucasian and of medium socio-economic status, so results cannot be extrapolated to other populations. In addition, factors such as individual inflammatory response or tolerance to chemotherapy could have influenced cortisol levels in women.

In conclusion, our results indicate that our one-to-one peer support program has the potential to increase the resilience levels of women with breast cancer undergoing chemotherapy treatment, whereas its non-administration in patients without chemotherapy may hinder the development of resilience. Furthermore, it was observed that unlike the latter, changes in cortisol, affective support, and emotional support significantly explained the improvement in resilience observed in patients undergoing chemotherapy treatment who received the peer support program. The fact that neither the change in cortisol nor the change in any of the social support subscales explained the reduction in resilience of participants without chemotherapy who did not receive the intervention suggests the existence of third variables not considered in this study that could be accounting for this variance. Thus, we believe it is important in the clinical setting to assess cortisol, emotional, and affective-support changes in order to identify women who are at risk for decreased resilience and negative health effects associated with the diagnosis. The present study suggests that peer support can exert a protective

psychological influence on women diagnosed with breast cancer, and further indicates an exciting avenue for future intervention development in the breast cancer care continuum.

CRediT authorship contribution statement

Ibane Aizpurua-Perez: Conceptualization, Methodology, Data curation, Formal Analysis, Investigation, Visualization, Writing – original draft, Final Approval of the paper. Co-authors: **Amaia Arregi**: Validation, Writing – review & editing, Final Approval of the paper; **David Gonzalez**: Conceptualization, Investigation, Writing – review & editing, Final approval of the paper; **Ander Urruticoechea**: Validation, Project administration, Writing – review & editing, Final approval of the paper; **Ainitze Labaka**: Validation, Writing – original draft, Final approval of the paper; **Xavier Minguez**: Validation, Writing – original draft, Final approval of the paper; **Gurutze Ugartemendia**: Validation, Investigation, Writing – review & editing, Final approval of the paper; **Eider Pascual:** Validation, Formal analysis, Writing – original draft, Final approval of the paper; **Raquel Echeverria:** Validation, Investigation, Writing – review & editing, Final approval of the paper; **Joana Perez-Tejada**; Conceptualization, Methodology, Data Curation, Formal Analysis, Investigation, Visualization, Writing – original draft, Final approval of the paper.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Table 1. Psychological variables assessed in the initial interview of the volunteers prior to their participation in the study.

Variable	Measures
Personality	The Big-5 Inventory (BFI) (John et al, 1991; Benet-Martínez & John, 1998)
Coping	Brief Coping Orientation to Problems Experienced Questionnaire (COPE-28) (Carver, 1997; Morán, Landero & González, 2010)
Anxiety and Depressive Symptoms	Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983; López-Roig et al., 2000)
Resilience	Brief Resilience Scale (RS-14) (Wagnild & Young, 1993; Sánchez-Teruel & Robles-Bello, 2014)
Emotional Regulation	Emotion Regulation Questionnaire (ERQ) (Gross & John; 2003; Cabello et al., 2013)

Table 2. Baseline Medical and Demographic Variables by Condition and Medical Treatment

Variable	IG1 (n = 26)	CG1 (n = 33)	Test Statistic	*p*	IG2 (n = 32)	CG2 (n = 30)	Test Statistic	*p*
Age at Diagnosis (years) (mean, SD)	52.88 (8.60)	51,06 (10,41)	$t(56) = 0.715$	0.477	56.65 (7.53)	56.53 (5.40)	$t(56) = 0.067$	0.947
Stage at Diagnosis (n, %)			$X^2(2) = 0.172$	0.918			$X^2(2) = 1.217$	0.544
I	2 (7.7%)	2 (6.1%)			8 (25%)	11 (36.7%)		
II	15 (57.7%)	18 (54.5%)			18 (56.3%)	13 (43.3%)		
III	9 (34.6%)	13 (39.4%)			6 (18.8%)	6 (20%)		
Primary Treatment			$X^2(1) = 0.845$	0.358			-	
Surgery	8 (30.8%)	14 (42.4%)			32 (100%)	30 (100%)		
Chemotherapy	18 (69.2%)	19 (57.6%)			0 (0%)	0 (0%)		
Surgery Type (n, %)			$X^2(1) = 3.154$	0.076			-	
Lumpectomy	5 (62.5%)	13 (92.85%)			32 (100%)	30 (100%)		
Mastectomy	3 (37.5%)	1 (7.14%)			0 (0%)	0 (0%)		
Consumption of anxiolytics and antidepressants (n, %)	1 (3.8%)	4 (12.1%)	$X^2(1) = 1.284$	0.257	4 (12.5%)	5 (16.7%)	$X^2(1) = 0.172$	0.679

$p<0.05$*

Table 3. Descriptive and ANOVA analysis for patients with chemotherapy treatment (by intervention within each assessment)

	Assessment I (T1)			Assessment II (T2)		
	Intervention group I (IG1; n = 26)	Control group I (CG1; n = 33)	F (by group within each assessment)	Intervention group I (IG1; n = 26)	Control group I (CG1) (CG1; n = 33)	F (by group within each assessment)
	Mean (SD); range	Mean (SD); range		Mean (SD); range	Mean (SD); range	
Resilience	71.60 (16.33); 31-96	78.03 (8.35), 59-90	F(1,57)=3-769; p=0.057; d=0.495	73.98 (12.11); 53-98	77.52 (12.55), 50-94	F(1,58)=1.190; p=0.280; d=0.287
Cortisol	2.31 (0.90), 0.62-3.94	2.91 (1.79), 0.92-7.42	F(1,54)=2223; p=0.142; d=0.423	2.75 (1.95), 0.69-8.17	2.63 (1.55), 0.62-7.07	F(1,51)=0.062; p=0.804; d=0.068
Affective Support	4.65 (0.52), 3-5	4.66 (0.96), 0-5	F(1,58)=0.000; p=0.990; d=0.012	4.60 (0.70), 2-5	4.82 (0.40), 3-5	F(1,58)=2.192; p=0.144; d=0.385
Instrumental Support	4.44 (0.60), 3-5	4.47 (1.40), 4-5	F(1,58)=0.014; p=0.906; d=0.027	4.54 (0.48), 3-5	4.69 (0.63), 2-5	F(1,58)=1.009; p=0.319; d=0.267
Emotional Support	4.31 (0.75), 2-5	4.39 (0.96), 0-5	F(1,58)=0.105; p=0.747; d=0.092	4.39 (0.73), 2-5	4.47 (0.44),4-5	F(1,58)=0.316; p=0.576; d=0.133

* All analyses were computed using a 95% confidence interval (alpha = 0.05).

Table 4. Descriptive and ANOVA analysis for patients without chemotherapy treatment (by intervention within each assessment)

	Assessment I (T1)			Assessment II (T2)		
	Intervention group II (IG2; n = 32)	Control group II (CG2; n = 30)	F (by group within each assessment)	Intervention group II (IG2; n = 32)	Control group II (CG2; n = 30)	F (by group within each assessment)
	Mean (SD); range	Mean (SD); range		Mean (SD); range	Mean (SD); range	
Resilience	74.12 (13.23), 48-94	76.88 (10.52), 44-97	F(1,61)=0.823; p=0.368; d=0.231	74.43 (15.45), 34-96	71.08 (16.5), 25-98	F(1,61)=0.682; p=0.412; d=0.209
Cortisol	2.79 (1.70), 0.29-7.5	2.94 (1.51), 0.98-7.63	F(1,58)=0.130; p=0.720; d=0.093	2.70 (1.51), 0.88-6.98	2.51 (1.36), 0.22-5.91	F(1,58)=0.251; p=0.619; d=0.132
Affective Support	4.68 (0.66). 2-5	4.81 (0.31), 4-5	F(1,61)=1.026; p=0.315; d=0.252	4.47 (0.83), 2-5	4.71 (0.48), 3-5	F(1,61)=1.955; p=0.167; d=0.353
Instrumental Support	4.68 (0.64), 2-5	4.67 (0.45), 3-5	F(1,61)=0.008; p=0.927; d=0.018	4.51 (0.71), 2-5	4.47 (0.88), 1-5	F(1,61)=0.041; p=0.840; d=0.050
Emotional Support	4.33 (0.68), 2-5	4.53 (0.47), 3-5	F(1,61)=1.738; p=0.192; d=0.342	4.18 (0.80), 2-5	4.39 (0.58), 3-5	F(1,61)=1.362; p=0.248; d=0.300

* All analyses were computed using a 95% confidence interval (alpha = 0.05).

Table 5. Regression analysis for change in resilience in Control Group II (CG2).

Variable	Unstandardized			Standardized	
	B	SE	B [95% CI]	*β*	*p*
Change in cortisol	-,267	,854	[-2,04, 1,51]	-,063	.758
Change in affective support	9,176	5,223	[-1,69, 20,04]	,586	.094
Change in instrumental support	-5,268	4,247	[-14,10, 3,56]	-,282	.228
Change in emotional support	-2,902	5,382	[-14,09, 8,29]	-,171	.595
Total Model $R^2 = .184$, F [4,25] = 1.184, $p = .346$					

p<0.05*

Table 6. Regression analysis for change in resilience in Intervention Group I (IG1).

Variable	Unstandardized			Standardized	
	B	SE	B [95% CI]	*β*	*p*
Constant	-1,741	1,509	[-4,978, 1,496]		,268
Change in cortisol	-2,276	,763	[-3,912, -0,641]	-,658	**,010***
Change in affective support	-8,826	3,150	[-15,58, -2,069]	-,997	**,014***
Change in instrumental support	,694	3,376	[-6,54, 7,935]	,048	,840
Change in emotional support	7,898	2,539	[2,45, 13,34]	,935	**,008***
Total Model $R^2 = .548$, F [4,18] = 4.238, $p = .019$					

p<0.05*

Figure 1. Experimental design and CONSORT flow diagram of participation. T = Time; IG1 = Intervention Group I; IG2 = Intervention Group II; CG1 = Control Group I; CG2 = Control Group II.

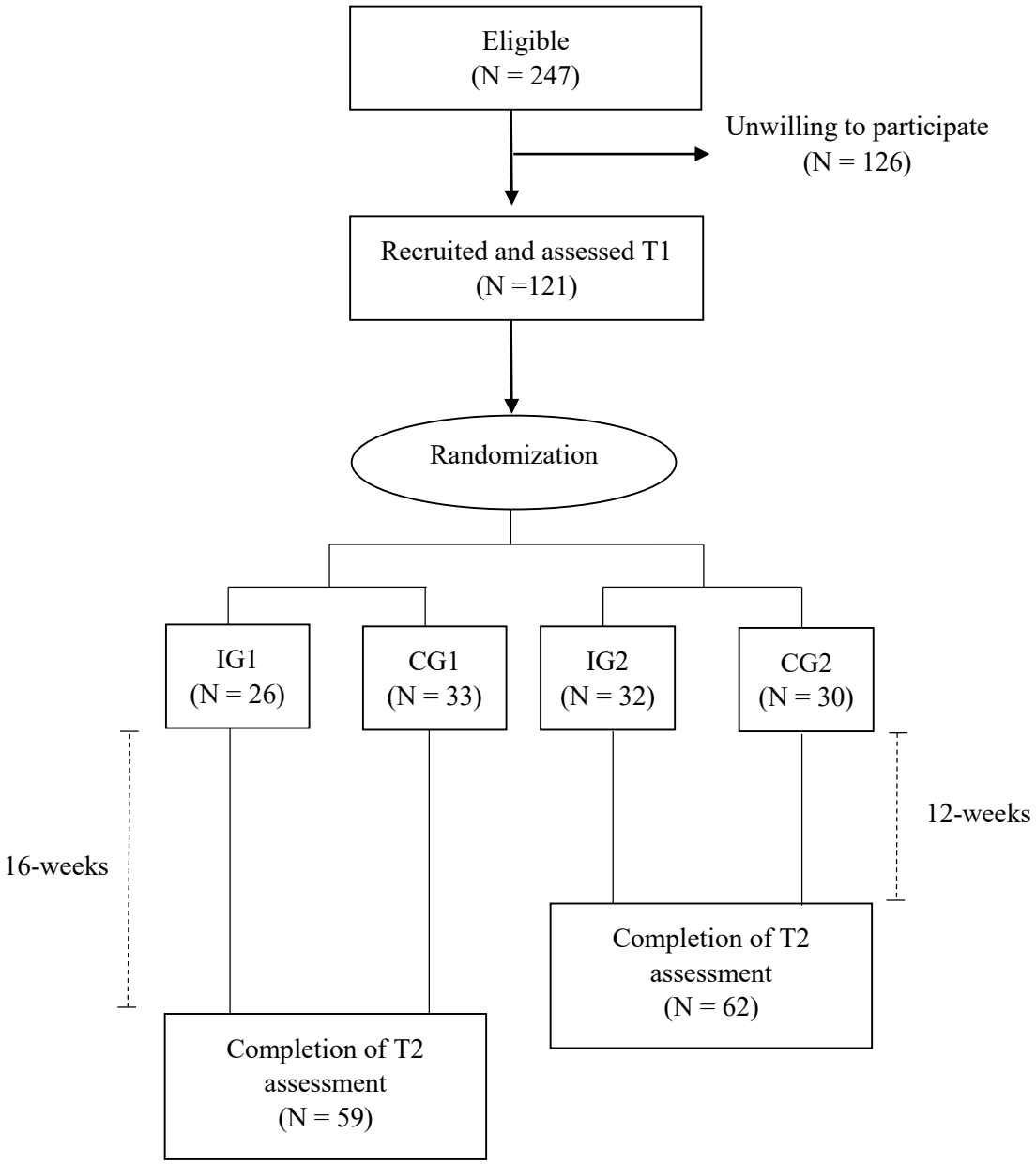
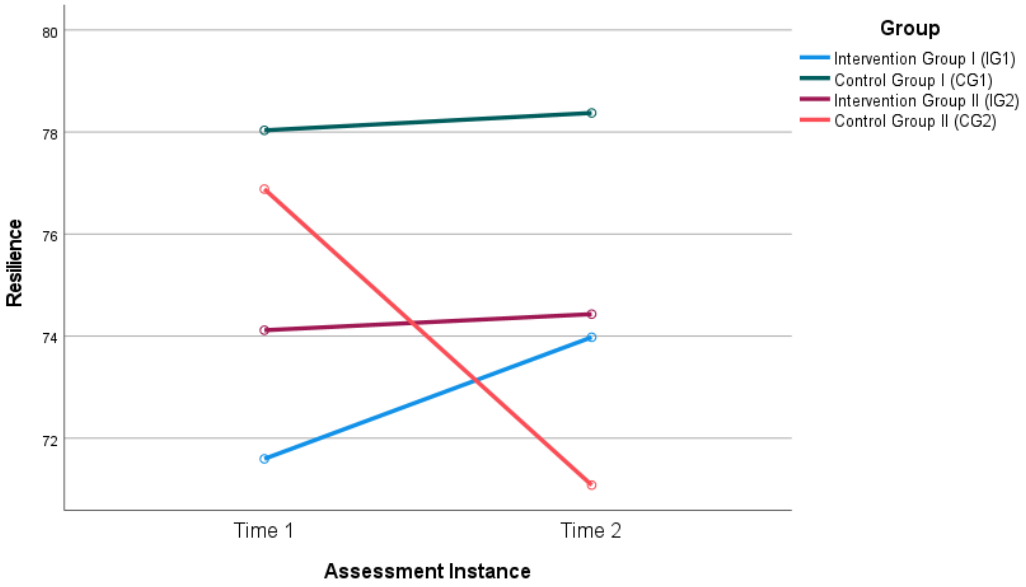


Figure 2. Differences in resilience score means at assessment 1 (T1) and assessment 2 (T2) between groups.



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