PRINCIPLES AND PRACTICE OF CLINICAL RESEARCH
A Global Journal of Clinical Research

Curcumin for Aromatase Inhibitor-Induced Joint Pain in Breast Cancer Survivors - The CurPain Trial: A Randomized, Double-Blind, Phase III, Multicenter Clinical Trial

Michaela Apostolou[1], Tina Mery[2], Ivan Aivasovsky[3], Milena Akamatsu[4], Marianna Daibes[5], Winifer Araujo[6], Maria Burgos[7], Victor Capellan[8], Fabiana Cerulli[9], Vitor Costa[10], Wilson Fandino[11], Igor Farias[12], Vivian Gagliardi[13], Maria Gomez[14], David Guardamino[15], Andreina Guzman[16], Karla Loss[17], Sabah Mohamed[18], Veronica Montero[19], Javier Obeso[20], Alicia Rosell[21], Jorge Sakon[9], Erik Simon[22], Rene Tovar[23], Samuel Afonseca[24], Katarzyna Kresse-Walczak[25*]

[1] Department of Obstetrics and Gynecology, Hospital Chemnitz, Chemnitz, Germany; [2] Children's Hospital Chemnitz, Chemnitz, Germany; [3] Beth Israel Deaconess Medical Center, Cardiology Department - Harvard Medical School, Boston, USA; [4] Instituto Butantan, São Paulo, SP, Brazil; [5] Clínica Cláudio Domênico, Rio de Janeiro, RJ, Brazil; [6] Universidad Autónoma de Santo Domingo, Santo Domingo, Dominican Republic; [7] Tecnoquimicas, Cali, Colombia; [8] Grupo Yunen, Santo Domingo, Dominican Republic; [9] Hospital Alemão Oswaldo Cruz, São Paulo-SP, Brazil; [10] Samaritano Paulista Hospital, São Paulo-SP, Brazil; [11] St Thomas' Hospital, London, United Kingdom; [12] AC Camargo Cancer Center, São Paulo-SP, Brazil; [13] Hospital Israelita Albert Einstein, São Paulo, SP, Brazil; [14] Pontificia Universidad Catolica Madre y Maestra (PUCMM), Santiago, Dominican Republic; [15] Beth Israel Deaconess Medical Center, Gastroenterology Department - Harvard Medical School, Boston, USA; [16] Dominican Red Cross, Santo Domingo, Dominican Republic; [17] Children's Hospital Los Angeles, Los Angeles, USA; [18] Hamad Medical Corporation, Doha, Qatar; [19] University of Southern California, Institute of Urology, Keck School of Medicine, Los Angeles, CA, USA; [20] Plataforma INVEST Medicina UANL - KER Unit Mayo Clinic (KER Unit Mexico), Monterrey, N.L., Mexico; [21] Hospital de Pediatría Juan P. Garrahan, CABA, Argentina; [22] University Hospital Dresden - Neurology Department, Dresden, Germany; [23] University of San Martin de Porres, Lima, Peru; [24] Grupo de Oncologia da Bahia, Feira de Santana, Bahia, Brazil; [25] Department of Prosthetic Dentistry, Carl Gustav Carus Faculty of Medicine, Technische Universität Dresden, Dresden, Germany.

Abstract

Introduction: *Adjuvant treatment with aromatase inhibitors (AIs) is extremely important in hormone-positive breast cancer survivors, reducing the early recurrence of the disease. Arthralgia and musculoskeletal symptoms resulting from AIs-toxicity can be observed in approximately one-third of the treated patients and are the leading cause of AIs-treatment discontinuation. However, there is no sufficient standard treatment. Analgesic and anti-inflammatory effects of curcumin in chronic joint pain are reported. This study protocol will determine whether curcumin supplementation reduces joint pain in breast cancer survivors under AIs therapy.*

Methods: *This study protocol is a phase III, randomized, blinded, placebo-controlled, multicentric, parallel arm design. The study population targets post-menopause women with stage I, luminal, unilateral, non-metastatic, receptor-positive breast cancer after breast-conserving surgery healed per primary intention. 160 participants will be enrolled. Daily curcumin supplementation (500 mg thrice daily) for twelve weeks is planned. Brief Pain Inventory-Worst Pain (Δ BPI-WP) will assess joint pain change after twelve weeks of follow-up as the primary outcome. Secondary outcomes include Quality of Life assessed by Functional Assessment of Cancer Therapy-Breast, further Brief Pain Inventory-Short Form items, Patient Health Questionnaire-8, and Quantitative Analgesic Questionnaire at six and twelve weeks.*

Discussion: *We present a randomized clinical trial to provide scientific evidence that supports the efficacy of curcumin supplementation on joint pain alleviation, pain-relieving medication reduction, and AIs-treatment adherence improvement in a predefined breast cancer survivor population.*

*Corresponding author: katarzyna.kresse@ukdd.de
Received: March 13, 2023 **Accepted:** June 26, 2023
Published: September 3, 2023
Editor: Felipe Fregni **Reviewers:** Siham Shweiki, Gabriel Vallejos

Keywords: curcumin, pain, breast cancer, aromatase inhibitors
DOI: http://dx.doi.org/10.21801/ppcrj.2023.92.10

Introduction

Adjuvant treatment with aromatase inhibitors (AIs) is effectively used in postmenopausal women with early-stage, receptor-positive breast cancer to reduce recurrence and mortality (Early Breast Cancer Trialists' Collaborative Group, 2005; Winer et al., 2002).

Although effective, AIs show toxicity issues especially related to musculoskeletal symptoms. AIs-induced arthralgia is observed in up to 73% of patients receiving the treatment, starting around six weeks after the introduction of AIs and reaching a peak around six months (Henry et al., 2012). About 32% of patients undergoing AIs therapy discontinue the treatment prematurely due to perceived adverse effects. The treatment discontinuation can lead to cancer relapse in up to 24% of patients (Henry et al., 2012).

Besides discontinuation, the use of pain-relieving medications, such as anti-inflammatory drugs and opiates, is necessary for at least 50% of those patients who have known cardiovascular, renal, and gastrointestinal adverse effects for both short-term and long-term use (Benyamin et al., 2008; Crew et al., 2007; Fine, 2013). Nevertheless, there is no standard treatment.

Finding alternative therapies for pain relief with lower adverse effects and an affordable profile is critical for effective treatment, adherence, and patient quality of life for breast cancer survivors (Costa et al., 2017; Henry et al., 2012; Osterberg & Blaschke, 2005).

Curcumin, a natural component obtained from the rhizome of turmeric (Curcuma longa), has been historically used in traditional Asian medicine. The safety profile of curcumin is well-documented (Daily et al., 2016). Its analgesic property has been subjected to research, with some studies suggesting an anti-inflammatory effect and activity through opioid receptors (Aggarwal et al., 2005; Amandusson et al., 1999; Prasad & Aggarwal, 2011). Moreover, a recent meta-analysis showed that curcumin can alleviate chronic knee pain related to osteoarthritis (Zeng et al., 2021). Studies found Curcuma extract dosages between 1000-1500 mg divided into 2 to 3 doses to be effective for joint arthritis (Daily et al., 2016). Differences in pain score due to curcumin use reported in the literature range from 0.25 to 2.8, being 0.25 stated as nonsignificant (Hershman et al., 2015, 2018; Martínez et al., 2019). However, there is not enough data to support the use of curcumin in AI-induced arthralgia.

This study protocol aims to determine if daily curcumin supplementation can reduce AIs-related joint pain in postmenopausal breast cancer survivors after breast-conserving surgery (BCS).

Materials and Methods

Trial Design

The CurPain study is a randomized, controlled, triple-blinded, multicenter trial using a two-arm parallel group design. The intervention group uses curcumin extract capsules (CEC) 500 mg thrice daily, and the control group uses a placebo. Ethical approval will be obtained from ethical committees in all centers. The trial will be registered at Clinicaltrials.gov.

Subject Enrollment/Study Setting

We anticipate that patients will be primarily recruited from tertiary healthcare academic hospitals in Boston and São Paulo, already enrolled in a Gynecologic-Oncology Program. We also plan to advertise this trial using flyers posted in outpatient specialist clinics, public posting boards, and in various media, including the internet (i.e. Google Ads) and newspapers. Given that cancer-related pain is multifactorial, we have included two countries (Brazil and the United States), three centers in each country. Brazil and the United States have differences in their healthcare systems, health indicators, stage of country development, and ethnical and cultural diversity that will ensure the benefits of including both countries as a reliable external validation for the trial (Coronado et al., 2020; Martins, 2018).

Randomization/Allocation concealment

All consented patients who fulfill inclusion criteria will be randomized. Randomization will be generated by a web-based system (Trans European Network for Clinical Trials Services, TENALEA) by a blinded statistician. The system will use permuted block stratified randomization with blocks of four and six. The stratified randomization blocks will be according to the site (Brazil and the United States of America) and the Pain Catastrophizing Scale (PCS). A unique code will be generated and concealed to staff members and participants to ensure allocation concealment. Only pharmaceutical staff responsible for preparing curcumin capsules or placebos can access the randomization list.

Blinding

Participants, investigators, and statisticians will be blinded in this study. The CEC and placebo will be prepared in identical capsules (color, smell, and taste) provided by the laboratory. The CEC will contain 500 mg content per pill. All the participants

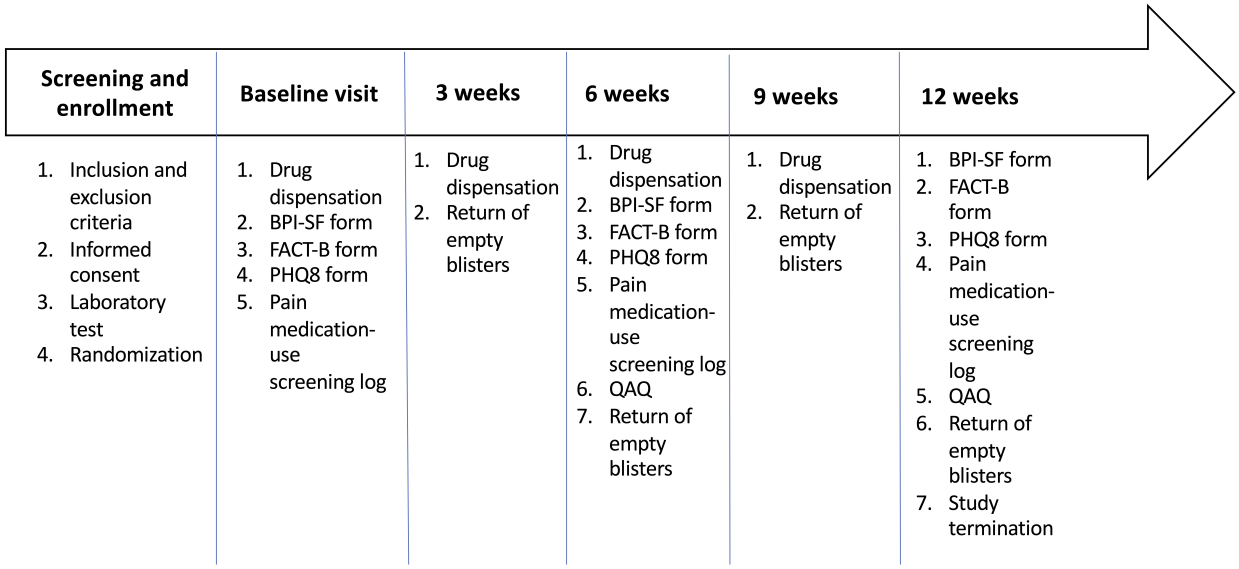

Figure 1: *Graphic timeline of the project.*

will receive the information on their allocation when the research data is published.

Emergency Unblinding

Curcumin has a well-documented safety profile; however, to maintain its quality and legitimacy, code breaks will occur in exceptional circumstances when knowledge of the actual treatment is critical for further patient management (serious allergic reaction, life-threatening bleeding, severe hypoglycemia symptoms). Investigators have to discuss the management of this subject with the advisor if unblinding is necessary.

Eligibility Criteria

Patients will be included according to the following criteria: post-menopausal women who recovered from the confirmed diagnosed breast cancer (stage I), histologically positive for estrogen receptor and/or progesterone receptor, negative human epidermal growth factor receptor-2 (HER2). Also, they must have completed BCS at least eight weeks ago and had AI-induced arthralgia symptoms that started or worsened after the AI therapy with anastrozole, letrozole, or exemestane. They must have a Brief Pain Inventory-Worst Pain (BPI-WP) score ≥ 4 at screening, a Zubrod performance status of 0 to two, and be adherent to the AI for at least four weeks and plans to continue for at least twelve weeks. Subjects will be excluded if they have evidence of inflammatory rheumatic disease or other severe painful disorders that might confound assessment. Subjects will also be excluded if they are using opioids, corticosteroids, serotonin-noradrenaline reuptake inhibitors, anticoagulation therapy, tamoxifen, or receiving acupuncture. Furthermore, subjects would also be excluded if they had clinically significant or unstable medical or psychological conditions. Besides that, it is important to ask for exclude patients who have an allergy to curcumin or its derivatives.

Recruitment Strategy

A research team will contact the health centers with extensive breast cancer treatment experience in Brazil and USA by phone, letter, email, and/or virtual meeting. After agreeing to participate, oncologists will identify potential participants according to inclusion/exclusion criteria and ask if they are interested in enrolling in the trial. To this eligible population, a leaflet will be given by the patient oncologist with a research summary and the main objectives of the study protocol. In addition, patients will have access to further trial explanations on the study protocol web page. If the patient wants to be included in the trial, she can contact the study team by email or phone to inform them of her interest.

Timeline

Patients will be checked for inclusion and exclusion criteria during the screening visit. If they meet the criteria, informed consent will be applied. The patient will then be randomized. In the baseline visit, patients will receive the study pills and Brief

Pain Inventory-short form (BPI-SF), Functional Assessment of Cancer Therapy - Breast (FACT-B), Patient Health Questionnaire (PHQ-8), and PCS forms will be applied (Figure 1). A "5-day window", defined as five days before and five days after the time point for these visits, will be available. The study will be terminated after twelve weeks.

Adherence

The treatment will be provided in a complete pill count every three weeks. Patients will keep their blisters as proof of use and deliver them to the pharmacist every three weeks for a refill. Moreover, they must record the pills and analgesics intake in a diary. Patients will get a weekly call from the research team to address adverse effects and encourage treatment adherence and feedback on pill intake.

Interventions

The interventions will be administered at least eight weeks after BCS and, if indicated, postoperative radiotherapy. This period was explicitly chosen not only to collide with venous thromboembolism prophylaxis that is administered for up to six weeks after BCS as curcumin supplementation may have blood thinning (antiplatelet) effects but also because AIs adverse effects often begin after six weeks. As our population is classified by obtaining more than four points on the BPI-WP scale, we expect they are already in need and effectively taking daily pain management medications. Participants will receive medication diaries. The experimental group will receive CEC containing turmeric rhizome extract powder (95% curcumin - Curcuma longa L.). CEC will be administered in outpatient settings for twelve weeks in doses of 500 mg 3 times daily every eight h, postprandial, to increase the solubility and bioavailability of curcumin. These doses were defined based on previous trials and present a high safety profile (Daily et al., 2016).

The control group will receive identical placebo capsules in the same setting to match the experimental group and avoid accidental unblinding.

Modification/discontinuation

Curcumin is well-tolerated when taken orally. Previous human trials have reported no toxicity at daily doses up to 8000 mg (Kanai et al., 2011). Most common adverse effects of curcumin are gastrointestinal (around 16%) such as diarrhea, constipation, abdominal distension, and others. Hepatobiliary adverse events (7%) make the second largest group of adverse effects of curcumin (Giordano & Tommonaro, 2019). Allergic skin reactions such as pitting edema and itching are uncommon. The patients need to be specifically aware of the anticlotting effects of curcumin (Lao et al., 2006). All of the mentioned above needs to be reported as adverse events and are reasons for the potential discontinuation of the intervention.

Outcomes

The BPI-SF questionnaire will be provided in Portuguese and English to measure the intensity of joint pain. The BPI-SF is a pain assessment tool for cancer patients and has been validated in the Brazilian population (Ferreira et al., 2011). Pain severity will be measured from 0 to 10 in a questionnaire applied at the beginning, at six and twelve weeks (Cleeland, 2009). The difference between BPI-WP at baseline and twelve weeks (Δ BPI-WP) will be used as the primary outcome.

The secondary outcomes are ΔBPI-WP at six weeks, further BPI-SF items, and quality of life assessed via FACT-B, PHQ-8, and QAQ.

The FACT-B is a validated questionnaire measuring physical, social/family, emotional, and functional well-being (Brady et al., 1997). To assess the prevalence of depression and its severity, the standardized and validated PHQ-8 will be used (Kroenke et al., 2009). PCS will be used to measure the tendency to magnify the pain stimuli (Franchignoni et al., 2022).

The patient will document their intake of analgesics and curcumin in their diet in their Pain Medication/Diet Diary, including the name, dosage, amount, date, and time of each intake. It will be assessed by the Quantitative Analgesic Questionnaire (QAQ) at six and twelve weeks of the trial (Robinson-Papp et al., 2015). QAQ scores are calculated from the questionnaire and categorized into three groups for total analgesic intake: group A = 0 to 3 points, group B = 4 to 7 points, and Group C $\geq$7 points (Svarstad et al., 1999).

Data Management

To record, manage, and analyze the study data, we will use the database in the Research Electronic Data Capture (REDCap) software, which allows the complete recording and analysis of the data obtained, ensuring its quality and security. Data quality and integrity will be maintained through checks at data entry and before input into the database. A database manual will be created to unify data collection.

The database will be destroyed after ten years of

trial termination. A Data User Agreement will be developed to establish the protocol for sharing data with collaborators.

Data Monitoring

The Data Monitoring Committee (DMC) will be implemented to monitor the data and assess the safety of participants in the trial. The DMC will meet at the start of the study, the first month, and every three months after the beginning of the study. If there are urgent safety issues, the DMC will contact the study team by phone and email.

Sample Size Calculation

The alpha level was set at 0.05, and the calculation was conducted for 80% power. The sample size calculation was performed using STATA software (Version 17).

Assuming a mean BPI-WP difference in the placebo group of 1.5 and a mean BPI-WP difference in the intervention group of 2, a standard deviation of 1, and a 25% dropout rate, the sample size needed is 160 participants, 80 per group. We assume the difference between the placebo and intervention group of 0.5 as conservative.

Statistical Analysis for primary and secondary outcomes

Demographic, clinical, and outcome variables will be described using means and standard deviation or median and interquartile range for continuous variables based on the normality assumption. For categorical variables, frequencies and proportions will be used. The analysis will be performed in STATA software version 17 using the Intention to Treat (ITT) approach.

For the primary analysis, the intervention group will be compared with the placebo group by the mean BPI-WP score change (Δ BPI-WP) between baseline and twelve weeks. Statistical analysis of the primary outcome will be performed through a linear regression if data follows linearity, homoscedasticity, and normality of residuals assumptions, or Mann-Whitney in the opposite case. Determination of mean differences and 95% confidence interval will be calculated in case of the use of linear regression.

The analysis of secondary outcomes as Δ BPI-WP at six weeks, further BPI-SF items, FACT-B, PHQ-8, and QAQ change will compare the intervention and placebo groups using linear regression or the Mann-Whitney test depending on the data characteristics. Fisher exact test will test the proportions of responders and non-responders in each group. Responders are defined as participants with a 2-point decrease in BPI-WP after twelve weeks of treatment; this is considered clinically relevant from an individual perspective. Multivariable linear regression adjusted for the study site and PCS will assess the BPI-WP change at twelve weeks between groups.

Missing Data

Due to the necessary long-term intake of the supplement over a period of twelve weeks, an increased probability of discontinuous intake is anticipated and assumed in the present protocol based on previous comparable studies with a combined dropout-, and nonadherence rate of around 25% (Hershman et al., 2015). All reasons for withdrawal and dropout will be reported and compared according to intervention and control groups. Missing data will be addressed using the Last Observation Carried Forward. The effect of the lost data on the results will be quantified by sensitivity analysis, where the complete case scenario will be compared with the imputed missing data. The study team will call participants that lost the follow-up to ask about their motivation to drop out.

Discussion

This protocol is a phase III, multicenter, randomized, placebo-controlled, triple-blinded study planned to investigate the effect of curcumin in pain level change on AIs-induced arthralgia in postmenopausal women with early-stage, receptor-positive breast cancer after BCS. The use of AIs in breast cancer survivors has been demonstrated to increase arthralgias, reducing the quality of life and treatment adherence and consequently increasing the risk of breast cancer recurrence in this set of patients (Henry et al., 2012).

This randomized clinical trial will compare the effectiveness of curcumin in reducing joint pain with placebo in the study population, which can impact the unpleasant sensory and emotional experience often caused by cancer treatment (Sun et al., 2018; Zeng et al., 2021). The target population included in this protocol is homogeneous of a postmenopausal woman with stage I luminal breast cancer diagnosis after BCS and under AIs treatment presenting significant joint pain before enrollment which increases the chance of detecting the effect of curcumin as a pain reduction treatment. Although AIs are recommended for premenopausal women or more advanced stages of the disease, chemotherapy use in this population is more frequent. Using taxanes, the most common drug (paclitaxel and docetaxel), brings a confounding

factor to neuropathic pain. The stratified block randomization will balance important covariates such as PCS and study center. Pain level is a subjective outcome that can negatively impact pain-related results. Analyzing a patient's mindset using PCS is one of the most important psychosocial predictors of pain, distress, and disability. In this scenario, as cross-cultural differences can influence pain, we chose two countries to participate in this study to increase external validity.

We expect the changes to be significant with our intervention, and comparing the intervention group with a control group enables us to see even small changes on the scale. Our sample size calculation is sufficient enough to find differences. Additionally, it is feasible during a multicenter trial.

Currently, there are no published studies that have utilized curcumin as a treatment for joint pain resulting from the use of an aromatase inhibitor. Conducting such a study can provide valuable insights for managing this specific population, either confirming or refuting the null hypothesis. As a limitation of the present study protocol, the slight difference of 0.5 in Δ BPI-WP between the groups can be seen critically. A change of 2 points in BPI-WP is accepted as clinically relevant for an individual (Hershman et al., 2015, 2018). Nevertheless, till now, there is no predefined value regarding the significant difference between treatment groups for Δ BPI-WP. Analysis of existing literature concludes that 0.5 is potentially clinically relevant (Hershman et al., 2015, 2018; Martínez et al., 2019). This study can provide further results to confirm this assumption. Moreover, conducting this trial as a multicenter trial can also have some limitations. The inclusion criteria, showing the trial and results, depend on each physician of the different centers, as curcumin is a dietary supplementation, not a drug. Plant extracts are not subjected to medical control as drugs. Standardization of curcumin can be difficult due to its chemical composition, growing conditions, preparation methods, and differences in the manufacturers (Funk & Schneider, 2021).

This study addresses a significant problem among targeted populations with insufficient standard therapy available. The findings of this study can be crucial for the therapy of AIs induced joint pain in this population using natural good-tolerated compounds such as curcumin.

Abbreviations

AIs: Aromatase Inhibitors
BCS: Breast-Conserving Surgery
BPI-WP: Brief Pain Inventory-worst pain
BPI-SF: Brief Pain Inventory-short form
CEC: Curcumin Extract Capsules
DMC: Data Monitoring Committee
FACT-B: Functional Assessment of Cancer Therapy - Breast
FDA: Food and Drug Administration
FSH: Follicle-Stimulating Hormone
HER2: Human Epidermal Growth Factor Receptor-2
ITT: Intention to Treat
NSAIDs: Non-Steroidal Anti-Inflammatory Drugs
LH: Luteinizing Hormone
PCS: Pain Catastrophizing Scale
PHQ-8: Patient Health Questionnaire
PI: Principal Investigator
QAQ: Quantitative Analgesic Questionnaire

Author Contributions

M.A. and T.M. have contributed equally to this work as first authors, S.A. and K.K-W. have contributed equally to this work as last authors, conceptualization all authors; writing—original draft preparation all authors; writing—review and editing, K.L., W.F., K.K-W.; visualization, V.G.; supervision, K.L., W.F. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Acknowledgments

The authors would like to acknowledge PPCR Team, especially Roberto Paz Manrique for support in developing this project.

Conflicts of Interest

The authors declare no conflict of interest.

References

- Aggarwal, B. B., Shishodia, S., Takada, Y., Banerjee, S., Newman, R. A., Bueso-Ramos, C. E., & Price, J. E. (2005). Curcumin Suppresses the Paclitaxel-Induced Nuclear Factor-κB Pathway in Breast Cancer Cells and Inhibits Lung Metastasis of Human Breast Cancer in Nude Mice. Clinical Cancer Research, 11(20), 7490–7498. https://doi.org/10.1158/1078-0432.CCR-05-1192
- Amandusson, Å., Hallbeck, M., Hallbeck, A.-L., Hermanson, O., & Blomqvist, A. (1999). Estrogen-induced alterations of spinal cord enkephalin gene expression. PAIN, 83(2), 243. https://doi.org/10.1016/S0304-3959(99)00109-8

- Benyamin, R., Trescot, A. M., Datta, S., Buenaventura, R. M., Adlaka, R., Sehgal, N., Glaser, S. E., & Vallejo, R. (2008). Opioid complications and side effects. Pain physician, 11(2S), S105.
- Brady, M. J., Cella, D. F., Mo, F., Bonomi, A. E., Tulsky, D. S., Lloyd, S. R., Deasy, S., Cobleigh, M., & Shiomoto, G. (1997). Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. Journal of clinical oncology, 15(3), 974–986.
- Chlebowski, R. T., Col, N., Winer, E. P., Collyar, D. E., Cummings, S. R., Vogel III, V. G., Burstein, H. J., Eisen, A., Lipkus, I., & Pfister, D. G. (2002). American Society of Clinical Oncology technology assessment of pharmacologic interventions for breast cancer risk reduction including tamoxifen, raloxifene, and aromatase inhibition. Journal of Clinical Oncology, 20(15), 3328–3343.
- Cleeland, C. S. (2009). The brief pain inventory user guide. Houston, TX: The University of Texas MD Anderson Cancer Center, 1–11.
- Coronado, F., Beck, A. J., Shah, G., Young, J. L., Sellers, K., & Leider, J. P. (2020). Understanding the dynamics of diversity in the public health workforce. Journal of public health management and practice: JPHMP, 26(4), 389.
- Costa, W. A., Monteiro, M. N., Queiroz, J. F., & Gonçalves, A. K. (2017). Pain and quality of life in breast cancer patients. Clinics, 72, 758–763.
- Crew, K. D., Greenlee, H., Capodice, J., Raptis, G., Brafman, L., Fuentes, D., Sierra, A., & Hershman, D. L. (2007). Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. Journal of Clinical Oncology, 25(25), 3877–3883.
- Daily, J. W., Yang, M., & Park, S. (2016). Efficacy of Turmeric Extracts and Curcumin for Alleviating the Symptoms of Joint Arthritis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Journal of Medicinal Food, 19(8), 717–729. https://doi.org/10.1089/jmf.2016.3705
- Early Breast Cancer Trialists' Collaborative Group. (2005). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomized trials. The Lancet, 365(9472), 1687–1717.
- Ferreira, K. A., Teixeira, M. J., Mendonza, T. R., & Cleeland, C. S. (2011). Validation of brief pain inventory to Brazilian patients with pain. Supportive Care in Cancer, 19, 505–511.
- Fine, M. (2013). Quantifying the impact of NSAID-associated adverse events. The American Journal of Managed Care, 19(14 Suppl), s267-72.
- Franchignoni, F., Giordano, A., Ferriero, G., & Monticone, M. (2022). Measurement precision of the Pain Catastrophizing Scale and its short forms in chronic low back pain. Scientific Reports, 12(1), 12042. https://doi.org/10.1038/s41598-022-15522-x
- Funk, J. L., & Schneider, C. (2021). Perspective on improving the relevance, rigor, and reproducibility of botanical clinical trials: Lessons learned from turmeric trials. Frontiers in Nutrition, 1001.
- Giordano, A., & Tommonaro, G. (2019). Curcumin and cancer. Nutrients, 11(10), 2376.
- Henry, N. L., Azzouz, F., Desta, Z., Li, L., Nguyen, A. T., Lemler, S., Hayden, J., Tarpinian, K., Yakim, E., & Flockhart, D. A. (2012). Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer. Journal of Clinical Oncology, 30(9), 936.
- Hershman, D. L., Unger, J. M., Crew, K. D., Awad, D., Dakhil, S. R., Gralow, J., Greenlee, H., Lew, D. L., Minasian, L. M., & Till, C. (2015). Randomized multicenter placebo-controlled trial of omega-3 fatty acids for the control of aromatase inhibitor–induced musculoskeletal pain: SWOG S0927. Journal of clinical oncology, 33(17), 1910.
- Hershman, D. L., Unger, J. M., Greenlee, H., Capodice, J. L., Lew, D. L., Darke, A. K., Kengla, A. T., Melnik, M. K., Jorgensen, C. W., & Kreisle, W. H. (2018). Effect of acupuncture vs sham acupuncture or waitlist control on joint pain related to aromatase inhibitors among women with early-stage breast cancer: A randomized clinical trial. Jama, 320(2), 167–176.
- Kanai, M., Yoshimura, K., Asada, M., Imaizumi, A., Suzuki, C., Matsumoto, S., Nishimura, T., Mori, Y., Masui, T., & Kawaguchi, Y. (2011). A phase I/II study of gemcitabine-based chemotherapy plus curcumin for patients with gemcitabine-resistant pancreatic cancer. Cancer chemotherapy and pharmacology, 68, 157–164.
- Kroenke, K., Strine, T. W., Spitzer, R. L., Williams, J. B. W., Berry, J. T., & Mokdad, A. H. (2009). The PHQ-8 as a measure of current depression in the general population. Journal of Affective Disorders, 114(1), 163–173. https://doi.org/10.1016/j.jad.2008.06.026
- Lao, C. D., Ruffin, M. T., Normolle, D., Heath, D. D., Murray, S. I., Bailey, J. M., Boggs, M. E., Crowell, J., Rock, C. L., & Brenner, D. E. (2006). Dose escalation of a curcuminoid formulation. BMC complementary and alternative medicine, 6(1), 1–4.
- Martínez, N., Herrera, M., Frías, L., Provencio,

M., Pérez-Carrión, R., Díaz, V., Morse, M., & Crespo, M. C. (2019). A combination of hydroxytyrosol, omega-3 fatty acids and curcumin improves pain and inflammation among early stage breast cancer patients receiving adjuvant hormonal therapy: Results of a pilot study. Clinical and Translational Oncology, 21, 489–498.

- Martins, A. A. (2018). People or Profit: A Comparison of Health Care in Brazil and the United States. Health Care Ethics USA.
- McCann, D. J., Petry, N. M., Bresell, A., Isacsson, E., Wilson, E., & Alexander, R. C. (2015). Medication nonadherence,"professional subjects," and apparent placebo responders: Overlapping challenges for medications development. Journal of clinical psychopharmacology, 35(5), 566.
- Osterberg, L., & Blaschke, T. (2005). Adherence to medication. New England journal of medicine, 353(5), 487–497.
- Prasad, S., & Aggarwal, B. B. (2011). Turmeric, the Golden Spice. In Herbal Medicine: Biomolecular and Clinical Aspects. 2nd edition. CRC Press/Taylor & Francis. https://www.ncbi.nlm.nih.gov/books/NBK92752/
- Robinson-Papp, J., George, M. C., Wongmek, A., Nmashie, A., Merlin, J. S., Ali, Y., Epstein, L., Green, M., Serban, S., & Sheth, P. (2015). The quantitative analgesic questionnaire: A tool to capture patient-reported chronic pain medication use. Journal of pain and symptom management, 50(3), 381–386.
- Sun, J., Chen, F., Braun, C., Zhou, Y.-Q., Rittner, H., Tian, Y.-K., Cai, X.-Y., & Ye, D.-W. (2018). Role of curcumin in the management of pathological pain. Phytomedicine, 48, 129–140.
- Svarstad, B. L., Chewning, B. A., Sleath, B. L., & Claesson, C. (1999). The Brief Medication Questionnaire: A tool for screening patient adherence and barriers to adherence. Patient education and counseling, 37(2), 113–124.
- Winer, E. P., Hudis, C., Burstein, H. J., Chlebowski, R. T., Ingle, J. N., Edge, S. B., Mamounas, E. P., Gralow, J., Goldstein, L. J., & Pritchard, K. I. (2002). American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for women with hormone receptor–positive breast cancer: Status report 2002. Journal of Clinical Oncology, 20(15), 3317–3327.
- Zeng, L., Yu, G., Hao, W., Yang, K., & Chen, H. (2021). The efficacy and safety of Curcuma longa extract and curcumin supplements on osteoarthritis: A systematic review and meta-analysis. Bioscience reports, 41(6).