Meta-Analysis

Long-Term Effectiveness of Dietary Interventions on Inflammatory Biomarkers in Women with Breast Cancer: A Systematic Review and Meta-Analysis

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Context: *Improving the prognosis of breast cancer remains a challenge despite the reduction in its mortality rates. Inflammatory parameters have been suggested as prognostic biomarkers of cancer. A healthy diet could potentially modify these factors; however, to date, findings have been inconclusive.*

Objective: *This review was conducted to estimate the strength of the association between healthy dietary interventions and inflammatory markers in women with breast cancer after a minimum 6-month follow-up.*

Data Sources: *The following literature databases were searched: MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library.*

Data Extraction: *Clinical trials that compared the effect of dietary interventions on the inflammatory profile of patients with breast cancer were selected. Quality was assessed using the Cochrane Collaboration risk-of-bias tool. Two researchers independently selected and evaluated the quality of the studies based on eligibility criteria.*

Data Analysis: *Mean differences between intervention groups and their 95% CIs were calculated using a random-effects model. The presence of heterogeneity was analyzed with Cochran's Q test, and I^2 was estimated. Funnel plots and Egger's test were used to assess publication bias.*

Results: *A total of 11 trials were included in the meta-analysis. Adherence to a healthy diet significantly decreased C-reactive protein (CRP) levels compared with the control group (standard mean difference = –0.17; 95% CI –0.32 to –0.02; I^2 = 0.00%). This result was maintained in the interventions focused on weight loss, including only patients with overweight, those incorporating physical activity, when follow-up was restricted to 6 months, and with interventions lasting at least 6 months.*

https://doi.org/10.1093/nutrit/nuaf137

Conclusion: *Adhering to a healthy diet could decrease levels of CRP in women with breast cancer. The additional goals of weight loss in patients with overweight, the promotion of physical activity, and the duration of the dietary intervention may be relevant aspects when planning strategies for these patients.*
Systematic Review Registration: *PROSPERO registration No. CRD42023402084.*
Key words: breast cancer; inflammation; dietary interventions; weight loss; meta-analysis.

INTRODUCTION

Breast cancer is the fourth most common cause of cancer death for men and women. Among women specifically, it accounts for 15.4% of all cancer deaths and is the leading cause of cancer-related mortality.[1] Nevertheless, recent advances in treatments and improved early detection have resulted in a 43% reduction in breast cancer deaths in developed countries over the past 30 years.[2] The 5-year survival rates of patients, which range from 85% to 90% in high-income countries, reflect this progress.[3] This situation poses new challenges in the evolution of breast cancer in women with this pathology, including short- to medium-term complications from treatments, relapses, and the appearance of second primary tumors.[4,5]

Modifiable prognostic factors, such as chronic inflammation and inflammatory markers, have been identified as important in the initiation, progression, and relapse of breast cancer.[6,7] Some pro-inflammatory markers are associated with the occurrence of metastases and lower survival rates, including interleukin-1 (IL-1), IL-6, and IL-8; C-reactive protein (CRP); and tumor necrosis factor- α (TNF-α).[8–12] Therefore, the identification of effective strategies that induce changes in the inflammatory profile would allow us to analyze the evolution of breast cancer in women in the short to medium term.

There is evidence that adherence to a healthy dietary pattern and/or a weight-loss diet improves the inflammatory profile in people with obesity or at high risk of cardiovascular disease.[13–16] Of note, the Prevención con Dieta Mediterránea (PREDIMED) randomized clinical trial, consisting of a dietary intervention fostering adherence to the Mediterranean diet, found a reduction in CRP, IL-6, and TNF-α levels after 3 and 5 years of follow-up in people at high risk of cardiovascular disease.[17] Specifically in breast cancer, the association between overweight and/or obesity and an unfavorable breast cancer prognosis in postmenopausal women could be due to the increase of proinflammatory markers.[18] Therefore, following a healthy diet, involving an increased intake of vegetables/fruits and losing weight, could be a valuable goal to improve the inflammatory profile and, thus, the evolution of breast cancer in these patients.

To date, systematic reviews conducted on interventions to induce changes in inflammatory biomarkers among patients with breast cancer have exclusively focused on the effect of weight loss and/or have assessed only 1 inflammatory biomarker as an outcome. The systematic review by Reeves et al[19] and the meta-analysis of Wang et al[20] explored the general benefits of weight loss programs on CRP levels. Despite the studies included in the systematic review, they did not find significant results.[19] The subsequent Wang et al[20] meta-analysis identified a significant improvement in this parameter among women in the intervention groups compared with those in the control groups. Bruinsma et al conducted a meta-analysis to analyze the effect of weight loss through diet, exercise, or both on inflammatory markers.[21] They found significant results for leptin levels in the groups that only promoted exercise, compared with the control groups.

Considering these findings, we aimed to synthesize existing evidence on the relationship between following a healthy diet and changes in inflammatory biomarkers in patients with breast cancer after at least 6 months of follow-up. The possible differences in results due to additional weight-loss goals and promotion of physical activity, follow-up time, and intervention duration were also analyzed.

METHODOLOGY

Design

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[22] The protocol is registered on the PROSPERO platform (registration no. CRD42023402084). No ethical approval was required, because of the study design.

Selection Criteria

The research question for selecting final articles was formulated according to the PICOS/T structure (Table 1). The inclusion criteria were (1) studies that included

Table 1. PICOS/T Criteria for Inclusion and Exclusion of Studies

Parameter	Criterion
Research question	What is the effect of a healthy diet, with or without a weight loss goal, on the inflammatory profile of women with breast cancer after at least 6 mo from the start of the intervention?
P	Women with breast cancer
I	A healthy dietary intervention with or without a weight loss goal
C	Standard care, basic recommendations, information leaflets, unhealthy dietary patterns, other dietary patterns
O	Inflammatory profile
S	Clinical trials
T	At least 6 mo of follow-up

women with breast cancer who were older than 18 years and at any stage of the disease; (2) clinical trials; (3) studies comparing the effect of a healthy diet on the inflammatory profile of women with breast cancer with the effect produced in whose did not follow a healthy diet, received standard care, or another dietary intervention; (4) studies with a minimum follow-up period of 6 months from the start of the intervention or observation; (5) studies published in Spanish, English, French, Portuguese, Italian, German, or Arabic; and (6) for the inclusion in the meta-analysis, studies that reported or allowed the calculation of the mean change in serum or plasma levels of selected inflammatory biomarkers (namely, interleukins, tumor necrosis factors, CRP) in the comparison groups. Note that a woman was considered to have breast cancer if she had received any intervention or treatment, regardless of its duration, and a healthy diet was considered to be any dietary recommendation with recognized evidence of benefit for women with breast cancer, with no restrictions on the specific form of the intervention.

The exclusion criteria were (1) animal or in vitro studies; (2) studies with a case-control or cross-sectional design, narrative reviews, systematic reviews, systematic reviews with meta-analyses, and umbrella reviews; (3) letters to the editor, case studies, conference abstracts; and (4) studies that evaluated inflammatory markers through fingerstick.

Information Sources and Search Strategy

The following electronic health sciences databases were used for the literature searches: MEDLINE (via PubMed), Embase, Scopus, Web of Science, and Cochrane Library. No restrictions were applied, except in the Cochrane Library, where the search was restricted to clinical trials.

The Thesaurus of Health Sciences Descriptors and Medical Subject Headings tools were used to define the search terms and their synonyms. The full strategy using the Boolean operators is shown in **Table S1**. This strategy was adapted to the characteristics of each electronic platform. The searches were carried out on April 1, 2023, and were updated on August 10, 2023. An alert system was set up from this date in each of the electronic platforms that could lead to the inclusion of a potential study. A manual search was also conducted of the references of the articles selected for this review.

Article Selection and Data Extraction

Article selection was performed by 2 reviewers (C.G.-P.T. and M.A.C.-H.). Agreement between reviewers was measured by Cohen's κ coefficient: $\kappa < 0$ indicates poor agreement; κ values from 0.00 to 0.20 indicate slight agreement; 0.21-0.40, fair; 0.41-0.60, moderate; 0.61-0.80, substantial; and 0.81-1.00, almost perfect agreement.[23] Disagreements were resolved by a third reviewer (R.B.-R.). The selection process began with removing all duplicates, followed by an initial screening based on article titles and abstracts to identify studies that potentially met the inclusion criteria. Subsequently, a full-text reading of the identified articles was conducted. If data were not available to be included in the meta-analysis, the article's authors were contacted by email.

Two independent reviewers (C.G.-P.T. and I.I.P.) completed the data extraction for all included studies, and any discrepancies were resolved by a third reviewer (J.J.J.-M.). The following information was extracted for each study: (1) author, year of publication, and country; (2) study design; (3) sample size (total, exposure/intervention group, and comparison/control group); (4) eligibility criteria; (5) participant characteristics; (6) intervention and follow-up duration; (7) instrument used for the assessment of the dietary information; (8) dietary characteristics; (9) description of physical activity intervention (if applicable); (10) inflammatory markers; (11) main results (namely, mean, geometric mean, least squared mean and median); and (12) adjustment variables.

Assessment of the Risk of Bias

Two authors (C.G.-P.T. and I.I.P.) assessed the risk of bias of the articles independently. The weighted κ coefficient was calculated to assess inter-reliability between reviewers.[24] Disagreements throughout the process

were discussed with a third reviewer (J.J.J.-M.) until consensus was reached.

The tool used for randomized clinical trials was the latest version of the Cochrane Collaboration risk-of-bias tool.[25] It assesses the risk of bias with 7 domains, whereby the study is categorized as having a low risk of bias when all domains are categorized as low risk, high risk when any domain is categorized as high risk, and unclear risk of bias when 1 or more domains are classified as unclear risk. The 7 domains are (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessors, (5) incomplete outcome data, (6) selective reporting, and (7) other sources of bias. Domain 3 was not considered because blinding of participants and personnel was not feasible due to the nature of the intervention.

Statistical Analysis

When at least 4 studies were available for each inflammatory biomarker, a meta-analysis was performed using a random-effect model. Sample size, mean change (change from baseline), and SD in the inflammatory biomarker by group (intervention or control) were used for the analysis. If medians and interquartile range were reported, means and SDs were estimated using the equation of Wan et al.[26] As complementary analyses, studies without these data were included in the meta-analyses; we calculated estimated data following the instructions from *Cochrane Handbook for Systematic Reviews of Interventions*.[27](p6) A detailed study was necessary to conduct this estimation. If there were more than 1 study with detailed data, we selected the 1 with the lowest risk of bias. When 2 studies could be selected as a reference, 2 additional meta-analyses were performed.

For the CRP biomarker, differences in mean change were calculated as standardized mean differences (SMDs) and expressed as Hedges's g and 95% CI, due to the different measurement units used in the included studies. According to Hedges' g, SMD values of 0.0 to ≤0.5 indicate small effects, of 0.51-0.79 indicate moderate effects, and ≥0.8 indicate large effects.[28] Mean differences (MDs) and 95% CIs were used for the remaining biomarkers. Harrigan et al reported a missing value for the IL-6 data, but the group was not specified.[29] Two meta-analyses were conducted in which we considered the missing data in each intervention group. Meta-regressions were not performed, due to an insufficient number of studies.[30]

The Cochran *Q* test was used to assess the heterogeneity of results between the studies. The I^2 statistic was estimated, and values were considered as follows: low heterogeneity for values between 25% and 50%, moderate for 50%-75%, and high for values higher than 75%.[31] Subgroup analyses by menopausal status (pre- or postmenopausal), physical activity (yes/no), dietary intervention (focus or not on weight loss), follow-up time (6 or 12 months), and intervention time (≤6 weeks or ≥6 months) were performed to explore potential sources of heterogeneity or its possible outcome effects. Forest plots were used to examine the overall effect. The presence of publication bias was also assessed using funnel plots and the Egger's test.

All statistical analyses were conducted using Stata 18.0 (Stata Corp) and RStudio 2023.09.1 + 494. Statistical tests were 2-sided, with statistical significance evaluated at *P* values <.05, except for the Egger's test, for which *P* values were established at <.1.[32]

RESULTS

The search strategy across different databases initially identified a total of 2858 articles. After removing duplicates, the preliminary screening based on titles and abstracts excluded 1381 articles. The remaining 89 articles were read in full, and 9 studies met the inclusion criteria. Three articles were retrieved from the manual search,[33–35] resulting in a total of 12 included articles. The reasons for the exclusion of each study at the full-text stage are shown in **Table S2**. One study was excluded from the meta-analyses because the necessary data for analysis were not available after contacting the authors.[36] The agreement between reviewers in the search process was substantial, with a κ index of 0.75 (95% CI, 0.67-0.83). Detailed information about the selection process can be found in **Figure 1**.

Characteristics of the Selected Studies

The main characteristics of each included study are listed in Table 2.[29–40] All the included studies were randomized clinical trials. The articles were published between 2008 and 2020. Except for two 3-arm trials and 1 randomized crossover trial,[29,36,37] the studies consisted of 2 arms. The trials were conducted in the United States ($n = 7$) and Europe ($n = 4$); 1 article did not report the trial location.[35] The total sample size was 1101 women with breast cancer, of whom 602 were assigned to the intervention group and 499 to the control group. The study with the largest sample size was the study by Patterson et al, conducted with 333 women.[34] Of the selected studies, 8 included both premenopausal and postmenopausal women,[29–31,35,38,42–44] 3 included only postmenopausal women,[31,39,44] and 1 only included premenopausal women.[34] Seven trials described the stage of breast cancer, among which stages I and II were the most frequent.[29,31,32,34,35,38,44]

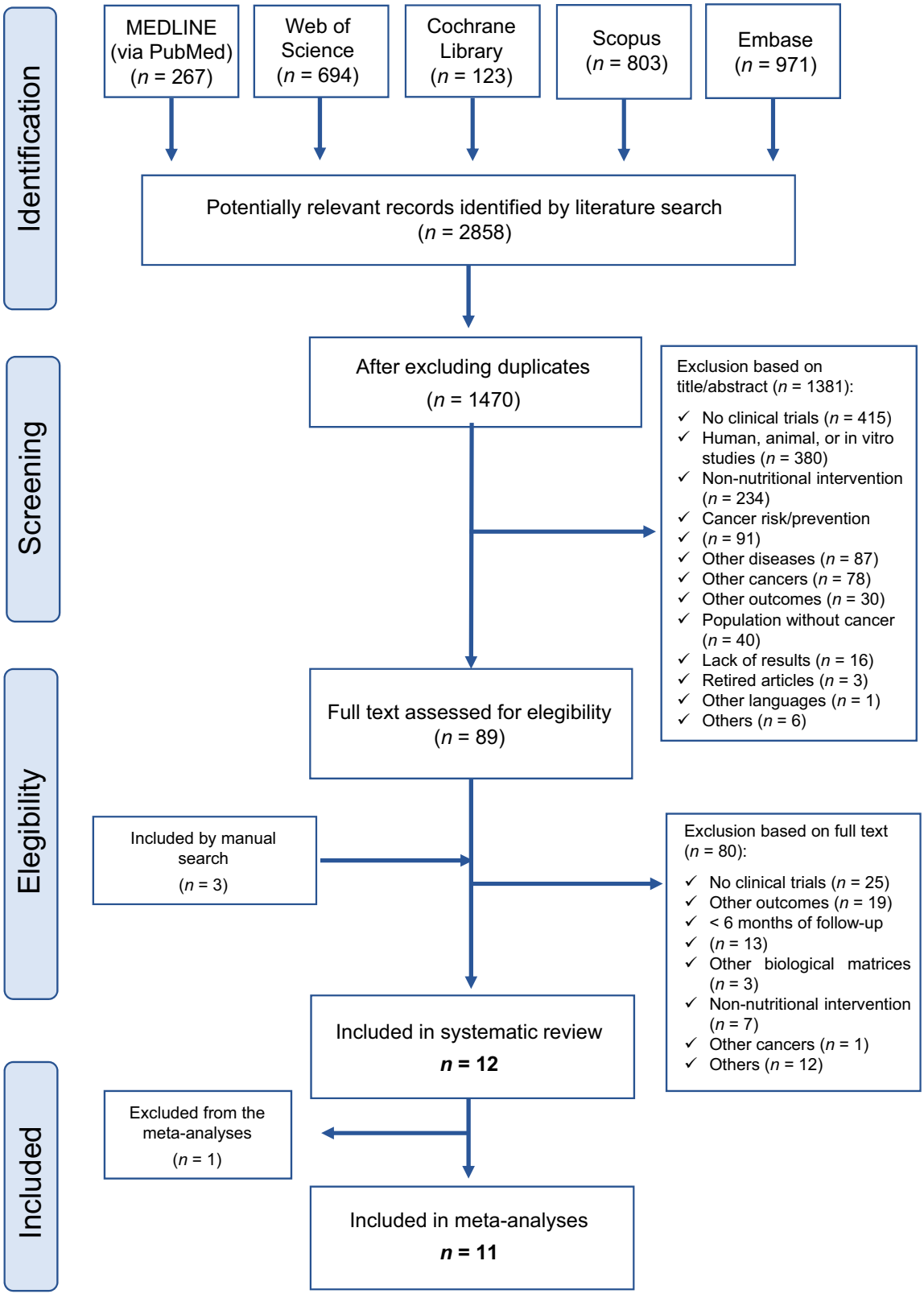


Figure 1. Flowchart of the Selection Process

Nine of the 11 trials included women with a specific body mass index (BMI), ranging from 18.5 kg m^{-2} to 40 kg m^{-2}.[29–33,35,36,39,44]

Women who had breast cancer were recruited at different times, ranging from new diagnosis[33] up to 10 years after diagnosis.[31] The majority of participants

Table 2. Main Characteristics of the Included Clinical Trials

First author (country)	Design		Sample size	Eligibility criteria	Participant characteristics	Time	Assessment dietary information	Dietary intervention	Physical activity	Inflammatory biomarkers
Demark-Wahnefried et al (2008)[37] (United States)	3-arm RCT	90	I1: $n = 32$; completed $n = 29$ I2: $n = 29$; completed $n = 26$ C: $n = 29$; completed $n = 27$	Premenopausal women with BC stage 1, 2, or 3A and candidate to receive chemotherapy	Mean age (SD): 41.8 y (5.6) Mean BMI (SD): 25.8 kg m^{-2} (6.1) Stage, %: 1, 33; 2A, 38; 2B, 21; 3A, 8 Ethnicity, %: White, 85; Black, 12; other ethnicity. 3	IT: 6 mo FT: 6 mo	Diet History Questionnaire	I1: Ca + ≥5 fruit and vegetable per day + fat ≤20% + 14 telephone calls I2: Ca + 14 telephone calls C: Ca + 14 telephone calls	I1: aerobic exercise ≥30 min ≥3 times weekly + strength exercises on the other days I2: aerobic exercise ≥30 min ≥3 times weekly + strength exercises on the other days C: No	CRP, IL-1β, TNFR2
Thomson et al (2010)[38] (United States)	RCT	43	I: $n = 21$; completed $n = 19$ C: 22, completed 21	Postmenopausal women, aged 50-60 y with invasive BC, stage 1 or 2, ER^+ Treatment completed <4 y BMI between >25 kg m^{-2} and <35 kg m^{-2}	Mean age (SD): 56.2 y (9.4) Mean BMI (SD): 31.8 kg m^{-2} (12.3) Mean years since diagnosis (SD): 3.7 (3.4) Stage, %: 1, 35; 2, 57.5; 3, 7.5 Race, %: White 82.5; other race, 17.5	IT: 6 wk FT: 6 mo	Arizona FFQ	I: 0.45-0.68 kg weight loss weekly; modified, reduced CH <30 g d^{-1} first 2 wk; maintain 6 mo: 35% CH, 35%-40% monounsaturated fat and 25%-30% protein C: 0.45-0.68 kg weight loss weekly, low-fat diet. 55%-60% CH, 25% fat, and 15%-20% protein	No	hsCRP
Greenlee et al (2013)[36] (United States)[a]	RCT	42	ImA: $n = 22$; completed $n = 21$ WCA: $n = 20$; completed, $n = 17$	BC stages 0-3A Treatment completed >6 mo BMI ≥25 kg m^{-2} African or Hispanic descent Sedentary	ImA: mean age (SD): 52.6 y (8.0) Mean BMI (SD): 33.4 kg m^{-2} (6.6) Mean years since diagnosis (SD): 3.5 (2.1) Postmenopausal, 77.3% BC stage, %:ductal in situ, 9.1; 1, 50; 2, 27.3; 3, 13.6 Race/ethnicity, %: African, 22.7; Hispanic, 77.2 WCA: mean age (SD): 48.6 y (9.6) Mean BMI (SD): 32.9 kg m^{-2} (5.2) Mean years since diagnosis (SD): 4.7 (3.2)	IT: 6 wk FT: 6 and 12 mo	Baseline visit: FFQ Follow-up visit: Spanish version of Block Questionnaire	ImA: weight loss, 1200 kcal d^{-1} 1–2 wk, 1600 kcal d^{-1} the rest. 45% proteins, 30% CH, and 25% fats + 6 group sessions spread over 6 wk WCA: Wait 6 mo and receive the same intervention as the ImA	ImA: for 6 mo, 3 d wk^{-1} at a fitness center; supervised classes; 25 min of strength + aerobic exercise and 5 min of stretching + cool down	hsCRP

(continued)

Table 2. Continued

First author (country)	Design	Sample size	Eligibility criteria	Participant characteristics	Time	Assessment dietary information	Dietary intervention	Physical activity	Inflammatory biomarkers
				Postmenopausal, 85.0% BC stage, %: ductal in situ, 10.0; 1, 35.0; 2, 40.0; 3, 15.0 Race/ethnicity, %: African, 20.0; Hispanic, 80.0					
Scott et al (2013)[33] (United Kingdom)[b]	RCT	85	I: $n = 44$; completed $n = 41$	BC stage 1, 2, or 3 Treatment completed 3-18 mo ago BMI >25 kg m^{-2}	I: Mean age (SD): 55.8 y (10.0) Mean BMI (SD): 29.7 kg m^{-2} (3.5) Mean no. mo post-treatment (SD): 9 (5.5). White ethnicity, 98%	IT: 6 mo FT: 6 mo	3-d diet diaries	I: hypocaloric diet, reduction 600 kcal d^{-1}, weight loss 0.5 kg wk^{-1} + written information + weekly nutritional education seminars	I: 3 d wk^{-1}, supervised classes: 30 min aerobic exercise and 10–15 min stretching	hsCRP
			C: $n = 41$; completed $n = 38$		C: Mean age (SD): 55.3 y (8.8) Mean BMI (SD): 31.1 kg m^{-2} (5.7) Mean no. mo post treatment (SD): 7.1 (4.4) White ethnicity, 100%			C: healthy eating booklet (*Eat Well*)	C: No	IL-6, TNF-α
Giallauria et al (2014)[40] (Italy)	RCT	94	I: $n = 61$	Aged 35–70 y Diagnosed with BC <5 y, no evidence of recurrence	I: Mean age (SD): 53.5 y (8.6) Mean BMI (SD): 28.01 kg m^{-2} (5.52)	IT: 12 mo FT: 12 mo	N/A	I: Sessions on macrobiotic MedDiet	I: 3 wk^{-1} first 3 mo; 1 wk^{-1} the remainder of months. 30 min cycle/treadmill, 5 min warming, 5 min cool down	hsCRP, IL-6
			C: $n = 33$		C: Mean age (SD): 52.3 y (7) Mean BMI (SD): 26.57 kg m^{-2} (4.6)			C: Recommendations for the prevention of cancer of the WCRF/IARC	C: No	
Harrigan et al (2016)[29] (United States)	3-arm RCT	100	I1: $n = 33$; completed $n = 30$	BC <5 y, stage 0, 1, 2, or 3 Treatment completed >3 mo ago BMI ≥25 kg m^{-2}	Mean age (SD): 59 y (7.5) Mean BMI (SD): 33.1 kg m^{-2} (6.6) Mean years since diagnosis (SD): 2.9 (2.1) Postmenopausal, 82% Stage, %: 0, 15; 1, 51%; 2, 24; 3, 7; unknown, 3 Non-Hispanic White, 91%	IT: 6 mo FT: 6 mo	FFQ	I1: in-person Energy deficit 500 kcal d^{-1} Counseling session 1 wk^{-1} first month, 1/2 wk second and third mo, and 1 mo^{-1} the rest	I1: 150 min wk^{-1} moderate/intense exercise + 10 000 steps d^{-1} with pedometer	IL-6, TNF-α, CRP
			I2: $n = 34$; completed $n = 24$					I2: telephone; energy deficit 500 kcal d^{-1} Counseling session 1 wk^{-1} first month, 1/2 wk second and third mo, and 1 mo the rest	I1: 150 min wk^{-1} moderate/intense exercise + 10 000 steps d^{-1} with pedometer	

(continued)

Table 2. Continued

First author (country)	Design		Sample size	Eligibility criteria	Participant characteristics	Time	Assessment dietary information	Dietary intervention	Physical activity	Inflammatory biomarkers
			C: $n = 33$; completed $n = 31$					C: brochures of American Institute for Cancer Research nutrition and physical activity + 2 weight maintenance sessions	C: No	
Greenlee et al (2016)[41] (United States)	RCT	70	I: $n = 34$; completed $n = 29$	Spanish speakers with BC stage 0, 1, 2, or 3 Treatment completed >3 mo ago without evidence of metastasis	I: Mean age (SD): 55.1 y (9.1) Mean years since diagnosis (SD): 3.6 (2.4) Postmenopausal, 67.6.% Stage, %: ductal in situ, 35.3; 1, 32.4; 2, 14.7; 3, 11.8; locally advanced, 5.9. Race, %: Black, 20.6; White, 41.2; Native American, 5.9; and mixed race, 14.7	IT: 12 wk FT: 12 mo	24-h recall (1 in-person and 2 by telephone call)	I: 9 sessions per 24 h for 12 wk + increase fruit and vegetable consumption + decreased fat consumption	No	IL-1α, IL-6, IL-8, IL-10, TNF-α, hsCRP
			C: $n = 36$; completed $n = 29$		C: Mean age (SD): 58.0 y (10.1) Mean years since diagnosis (SD): 3.1 (3) Postmenopausal, 72.2% Stage, %: ductal in situ, 22.2; 1, 44.4; 2, 25; 3, 2.8; locally advanced, 2.8 Race, %: Black, 30.6; White, 38.9; and mixed race, 16.7			C: Standard information dietary recommendations for BC survivors		
Patterson et al (2018)[34] (United States)	RCT 2 × 2	333	I: $n = 166$; completed $n = 154$	Postmenopausal, operable BC stage 1A-3C <10 y Radio- or chemotherapy treatment completed BMI ≥25 kg m^{-2}	Mean age (SD): 62.6 y (6.9) Mean BMI (SD): 31.1 kg m^{-2} (5.0) Years since diagnosis (SD): 2.7 (2.0) Stage, %: 1, 48.4; 2, 24.8; 3, 16.8 Race, %: White, 83.5; Black or African American, 3.6; Asian, 1.8; and mixed or other race, 1.1 Ethnicity, %: non-Hispanic, 88.6; Hispanic, 11.4	IT: 6 mo FT: 6 mo	N/A	I: Telephone 7% weight loss, reduction of 500-100 kcal d^{-1} 12 motivational interview calls	I: 300 min wk^{-1} moderate to intense physical exercise	hsCRP
			C: $n = 167$; completed $n = 159$					C: US Dietary Guidelines for Americans, 2010	C: No	
Sturgeon et al (2018)[42] (United States)	RCT	35	I: $n = 19$; completed $n = 16$	Postmenopausal women aged 18-55 y BRCA1/2^{+},	I: mean age (SD): 45.1 y (4.0)	IT: 12 mo FT: 12 mo	Self-reported 3-d dietary records	I: online intervention to improve habits, new nutritional	I: 160 min wk^{-1}: 3 resistance days +	IL-1β, IL-6, IL-8, TNF-α

(continued)

Table 2. Continued

First author (country)	Design		Sample size	Eligibility criteria	Participant characteristics	Time	Assessment dietary information	Dietary intervention	Physical activity	Inflammatory biomarkers
				prophylactic oophorectomy, <2 study initiations, and age at surgery ≤45 y; BMI ≥23 kg m^{-2}	Mean BMI (SD): 30.2 kg m^{-2} (4.6) White race, 100% Non-Hispanic ethnicity, 100%			habit every 2 wk + daily health-related reading material	2 aerobic days + 1 active recovery	
			C: $n = 16$		C: Mean age (SD): 47.2 y (3.8) Mean BMI (SD): 29.6 kg m^{-2} (5.1) White race, 100% Ethnicity, %: Hispanic, 13; non-Hispanic, 87			C: Maintain usual daily activities	C: No	
Vasson et al (2020)[43] (France)	RCT	113	I: $n = 57$; completed $n = 55$	Nonmetastatic invasive BC Treatment completed <9 mo BMI between >18.5 kg m^{-2} and <40 kg m^{-2}	I: Mean age (SD): 52.0 y (7.2) Mean BMI (SD): 25.4 kg m^{-2} (4.6) Postmenopausal, 58%	IT: 2 wk (intensive) and 3 y (mild, every 6-mo dietitian visit) FT: 12 mo	Self-reported 3-d dietary records	I: dietary meals with adapted menus + dietary education + caloric intake 1700-2000 kcal d^{-1}, for 2 wk Every 6 mo, dietitian visit	I: 120 min d^{-1}: resistance exercises + strength + flexibility/stretching	CRP
			C: $n = 56$ completed $n = 49$		C: Mean age (SD): 51.9 y (10.6) Mean BMI (SD): 25.5 kg m^{-2} (4.4) Postmenopausal, 63%			C: For 3 y, a dietitian visits every 6 mo	C: No	
Santa-María et al (2020)[35] (N/A)	RCT	96	I: $n = 50$; completed $n = 45$	BC stage 0, 1, 2, or 3 with treatment completed. BMI ≥23 kg m^{-2} Weight ≤ 182 kg	I: median age (range): 53 y (33-71) Mean BMI (range): 32 kg m^{-2} (26.9-49.2) Postmenopausal, 74% Race, %: White, 82; Black, 18 Non-Hispanic ethnicity, 100%	IT: 6 mo[c] FT: 6 mo	N/A	I: minimum 5% active weight loss + DASH dietary pattern	I: ≥300 min wk^{-1} moderate physical activity ≥10 min	IL-1β, IL-6, IL-8, TNF-α, hsCRP
			C: $n = 46$; completed $n = 42$		C: I: median age (range): 55 y (30-73) Mean BMI (range): 32 kg m^{-2} (29.8-45.3) Postmenopausal, 74% Race, %: White, 72; Black, 22; other race, 6. Non-Hispanic ethnicity, 98%; Hispanic 2%			C: standard medical care + 1-time coaching session	C: No	

[a]Crossover randomized control trial.
[b]Results are derived from the same study.
[c]Duration of the intervention was of 12 months, but biomarkers were only analyzed at 6 months.
Abbreviations: BC, breast cancer; BMI, body mass index; C, control group; Ca, calcium; CH, carbohydrates; CH, carbohydrates; CRP, C-reactive protein; DASH, dietary approaches to stop hypertension; FFQ, food frequency questionnaire; FT, follow-up time; hsCRP, high sensitivity C-reactive protein; I, intervention group; I1, intervention group 1; I2, intervention group 2; IARC, International Agency for Cancer Research; IL, interleukin; ImA, immediate arm; IT, intervention time; MedDiet, Mediterranean diet ;N/A, not available ; N/A, not available; RCT, randomized control trial; TNF, tumor necrosis factor; TNFR2, tumor necrosis factor receptor-2; WCA, waitlist control arm;WCRF, Word Cancer Research Fund.

were White, with 1 study including only women of Hispanic or African descent.[35] In 6 of the 11 studies, the intervention lasted for at least 6 months,[29–32,34] but there was considerable variability in the intervention duration (from 2 weeks to 12 months). Seven articles assessed the effect on inflammatory biomarkers at 6 months,[29–32,34,36,44] and 4 assessed them at 12 months.[35,37–39] Greenlee et al evaluated them at both 6 and 12 months.[33]

Two trials focused on adherence to a specific dietary pattern, the Mediterranean diet, and the Dietary Approaches to Stop Hypertension (DASH) diet,[32,37] and 3 studies promoted modification of dietary change by increasing vegetable consumption[39] or vegetable and fruit consumption while reducing fat intake.[34,39] Seven trials focused on weight-loss interventions using different strategies, which mainly were based on restricting energy intake[29–32,35,36] and/or limiting fat consumption.[33,44] Nine of them promoted physical activity.[29–31,33–37,39]

Results of Inflammatory Markers

The main results of different inflammatory markers are summarized in Table 3.[29–43] CRP and IL-6 were the most frequently studied biomarkers, in 9 and 5 clinical trials, respectively.

C-reactive Protein. The meta-analysis included 6 of 10 studies that examined CRP.[29–32,38,44] There was a significant small difference in the reduction of CRP level in favor of the intervention group compared with the control group, with homogeneity in results (SMD = –0.17; 95% CI, –0.32 to –0.02; $I^2 = 0.00\%$) (Figure 2).

The results of the stratified analysis were maintained for the interventions focused on weight loss, those incorporating physical activity, when the follow-up lasted at least 6 months, and with interventions lasting at least 6 months. The results in the other strata (ie, intervention focused on healthy diet, without physical activity, 12 months of follow-up, and ≤6 weeks of intervention) could not be evaluated, because they lacked the minimum number of articles (**Table S4**). With the inclusion of studies with estimated data ($n = 3$), [37,40,43] the changes between groups in the overall analysis did not differ, but there was moderate heterogeneity (SMD = –0.07; 95% CI, –0.27 to 0.13; $I^2 = 54.40\%$) (**Figure S1**).

Interleukin-6. The 4 studies that evaluated the impact of a nutritional intervention on IL-6 levels were included in the meta-analysis.[29,35,41,42] There were no significant results in the differences of mean change between groups, with homogeneity of results (MD = 0.07 pg mL^{-1}; 95% CI, –0.31 to 0.44; $I^2 = 0.00\%$) (Figure 3). No relevant changes were found in the analysis when including the studies with imputed data (**Figure S2**) or considering the missing data of this parameter in the control group ($n = 64$ and $n = 32$ for the control and intervention groups, respectively) instead of the intervention group ($n = 63$ and $n = 33$ for control and intervention groups, respectively) in the study by Harrigan et al.[29] The effect of the dietary pattern, physical activity, follow-up, or intervention time could not be assessed, due to the low number of articles.

Tumor Necrosis Factor-α. Four studies assessed TNF-α and provided suitable results for inclusion in the meta-analysis.[29,35,41,42] No significant differences in mean change were observed between groups, with homogeneity in results (MD = –0.04 pg mL^{-1}; 95% CI, –0.20 to 0.12; $I^2 = 0.00\%$) (Figure 4). All randomized clinical trials promoted physical activity and enrolled women with a pre-established BMI of ≥25 kg m^{-2} or ≥23 kg m^{-2}, except for the study by Harrigan et al,[29] which did not promote physical activity and included women with breast cancer regardless of BMI. All the studies excluded women with stage IV breast cancer, with the exception of the Sturgeon et al study.[42] No change in results was found when 1 article with estimated data[39] was included (**Figures S3 and S4**). The limited number of included studies did not allow for a stratified analysis.

Interleukin-1β. Three of the 11 studies reported data on IL-1β.[35,37,42] All the interventions emphasized the promotion of physical activity. One study was conducted with postmenopausal women with 12 months of follow-up.[42] The others had 6 months of follow-up. One study included only premenopausal women,[37] and the other did not specify the menopausal status.[35] No significant difference was found from baseline to follow-up between arms in any of the 3 studies.

Interleukin-8. Three studies evaluated the effect of the intervention on IL-8[35,41,42] without significant findings. Two of them focused on promoting a healthy diet and showed results at 12 months of follow-up,[41,42] whereas the other study promoted weight loss and presented results at 6 months of follow-up.[35]

Other Inflammatory Markers. Only 1 study was found for each of the following inflammatory biomarkers: IL-1α, IL-10, and TNF receptor-2.[37,41] None of them focused the intervention on weight loss. Although no significant results were reported for these studies, there were reductions in the values of IL-1α and IL-10 in intervention and control groups, with higher reductions in the intervention groups. In the 3-arm study, which

Table 3. Main Results by Biomarkers of the Included Clinical Trials

Inflammatory biomarker	Reference	Group	Baseline sample size	Baseline, mean (SD)	Follow-up, mean (SD)	Change, mean (SD)	Adjustment variables
CRP	Demark-Wahnefried et al (2008) [34] [a]	I	32	0.017 (0.032) ng mL^{-1}	0.02 (0.056) ng mL^{-1}	N/A	Physical activity, age, BMI, and stage
			29	0.016 (0.018) ng mL^{-1}	0.008 (0.007) ng mL^{-1}	N/A	
		C	29	0.016 (0.026) ng mL^{-1}	0.026 (0.072) ng mL^{-1}	N/A	
	Harrigan et al (2016)[29] [b]	I	67	3.5 (0.54)[c] mg L^{-1}	**2.62 (0.33)[c] mg L^{-1}**	**–1.05 (0.29)[c] mg L^{-1}**	No
		C	33	4.77 (1.08)[c] mg L^{-1}	**4.38 (0.95)[c] mg L^{-1}**	**–0.6 (0.41)[c] mg L^{-1}**	
	Vasson et al (2020)[43]	I	57	2.1 (2.3) mg L^{-1}	2.1 (2.5) mg L^{-1}	N/A	No
		C	56	3 (4.5) mg L^{-1}	2.7 (3.8) mg L^{-1}	N/A	
hsCRP	Thomson et al (2010)[38]	I	21	5.9 (7.0) mg L^{-1}	N/A	–0.4 (1.7) mg L^{-1}	No
		C	22	4.4 (2.9) mg L^{-1}	N/A	–0.4 (1.6) mg L^{-1}	
	Greenlee et al (2013)[36] [d]	<2%	N/A	N/A	N/A	21.1 (120.2) mg L^{-1}	No
		≥2%	N/A	N/A	N/A	26.8 (137.5) mg L^{-1}	
hsCRP	Scott et al (2013)[33]	I	44	1.37 (0.64, 2.53)[e] mg L^{-1}	1.52 (0.78, 3.37)[e] mg L^{-1}	0.1 (–0.36, 0.63)[e] mg L^{-1}	Chemotherapy, tamoxifen, aromatase inhibitors, use of hormonal therapy
		C	41	2.12 (0.67, 5.22)[e] mg L^{-1}	2.18 (0.82, 6.17)[e] mg L^{-1}	0.03 (–0.43, 0.70)[e] mg L^{-1}	
	Giallauria et al (2014)[40]	I	64	1.3 (1.7) mg dL^{-1}	1[f]: 1.63[g] (1.76) mg dL^{-1} 2[f]: 1.67[g] (1.89) mg dL^{-1} 3[f]: 0.99[g] (1.05) mg dL^{-1}	N/A	No
		C	33	0.9 (1.1) mg dL^{-1}	0.78 (1.12) mg dL^{-1}	N/A	
	Greenlee et al (2016)[41]	I	34	4.4 (8.3) mg L^{-1}	4.0 (7.6) mg L^{-1}	2.0 (5.0) mg L^{-1}	Menopausal status, use of hormonal therapy
		C	33	3.7 (3.5) mg L^{-1}	3.5 (3.0) mg L^{-1}	–0.2 (1.6) mg L^{-1}	
	Patterson et al (2018)[34]	I	166	3.05 (2.57-3.61)[h] mg L^{-1}	2.61 (2.19-3.1)[h] mg L^{-1}	–0.44 (–0.84 to –0.04)[d] mg L^{-1}	No
		C	167	3.35 (2.82-3.97)[h] mg L^{-1}	3.28 (2.76-3.9)[h] mg L^{-1}	–0.07 (–0.52 to 0.39)[h] mg L^{-1}	
	Santa-María et al (2020)[35]	I	50	N/A	N/A	0.1 (2.6) mg dL^{-1}	No
		C	46	N/A	N/A	2.9 (10.6) mg dL^{-1}	
TNF-α (pg mL^{-1})	Saxton et al (2014)[39]	I	44	0.889 (0.779, 0.999)[i]	0.916 (0.767, 1.065)[i]	N/A	Chemotherapy, tamoxifen, aromatase inhibitors, no hormone therapy
		C	41	1.058 (0.895, 1.221)[i]	0.992 (0.870, 1.114)[i]	N/A	
	Harrigan et al (2016)[29] [j]	I	67	1.86 (0.08)[k]	1.8 (0.1)[k]	–0.06 (0.05)[k]	No
		C	33	1.67 (0.08)[k]	1.61 (0.08)[k]	–0.06 (0.18)[k]	
	Greenlee et al (2016)[41]	I	34	12.5 (7.7)	11.7 (7.3)	–0.5 (6.1)	Menopausal status, use of hormonal therapy
		C	33	12.3 (5.5)	11.9 (4.5)	0.2 (2.6)	
	Sturgeon et al (2018)[42]	I	19	2.4 (1.18)	2.16 (0.85)	–0.3 (0.12)[l]	No
		C	16	2.18 (0.52)	2.08 (0,43)	–0.11 (0.13)[l]	
	Santa-María et al (2020)[35]	I	50	N/A	N/A	0.62 (2.63)	No
		C	46	N/A	N/A	0.31 (7.73)	
IL-6 (pg mL^{-1})	Saxton et al (2014)[39]	I	44	1.599 (1.259, 1.906)[i]	1.692 (1.377, 2.007)[i]	N/A	Chemotherapy, tamoxifen, aromatase inhibitors, no hormone therapy
		C	41	1.755 (1.456, 2.054)[i]	1.942 (1.602, 2.282)[i]	N/A	
	Giallauria et al (2014)[40]	I	64	1.3 (1.3)	1[f]: 1.23[g] (0.81) 2[f]: 1.78[g] (2.34) 3[f]: 0.95[g] (0.66)	N/A	No
		C	33	1.4 (1.4)	1.66 (1.68)	N/A	
		I	67	1.89 (0.15)[k]	2.16 (0.22)[k]	0.14 (0.13)[k]	No

(continued)

Table 3. Continued

Inflammatory biomarker	Reference	Group	Baseline sample size	Baseline, mean (SD)	Follow-up, mean (SD)	Change, mean (SD)	Adjustment variables
	Harrigan et al (2016)[29] [j]	C	33	2.29 (0.33)[k]	2.23 (0.34)[k]	−0.02 (0.18)[k]	
	Greenlee et al (2016)[41]	I	34	10.3 (30.1)	8.3 (18.9)	2.1 (10.1)	Menopausal status, use of hormonal therapy
		C	33	12.0 (39.1)	16.6 (64.3)	3.8 (20.3)	
	Sturgeon et al (2018)[42]	I	19	1.01 (0.9)	0.78 (0.57)	−0.24 (0.25)[l]	No
		C	16	1.43 (1.59)	1.36 (1.01)	−0.06 (0.27)[l]	
IL-6 (pg mL^{-1})	Santa-María et al (2020)[35]	I	50	N/A	N/A	9.7 (57)	No
		C	46	N/A	N/A	60 (370.8)	
IL-1β (pg mL^{-1})	Demark-Wahnefried et al (2008)[37] [a]	I	32	1.5 (3.2)	0.5 (1.4)	N/A	No
			29	1.4 (3.2)	0.7 (2.3)	N/A	
		C	29	0.3 (1.2)	0.2 (0.6)	N/A	
	Sturgeon et al (2018)[42]	I	19	0.25 (0.62)	0.11 (0.04)	−0.14 (0.10)[l]	No
		C	16	0.13 (0.06)	0.09 (0.04)	−0.04 (0.11)[l]	
	Santa-María et al (2020)[35]	I	50	N/A	N/A	4.1 (22.4)	No
		C	46	N/A	N/A	10.1 (62.4)	
IL-8 (pg mL^{-1})	Greenlee et al (2016)[41]	I	34	8.3 (7.6)	7.2 (5.5)	0.1 (3.5)	Menopausal status, use of hormonal therapy
		C	33	7.8 (4.5)	7.5 (3.9)	0.5 (3.4)	
IL-8 (pg/mL)	Sturgeon et al (2018)[42]	I	19	5.08 (1.07)	5.07 (1.49)	0.07 (0.36)[l]	No
		C	16	5.34 (1.96)	4.56 (1.2)	−0.78 (0.38)[l]	
	Santa-María et al (2020)[35]	I	50	N/A	N/A	222.9 (905.2)	No
		C	46	N/A	N/A	121.3 (601.6)	

[a]Three-arm clinical trial.
[b]Three-arm clinical trial, combining the intervention groups to evaluate inflammatory markers.
[c]Mean (SE).
[d]Shows values based on percent weight loss at 6 months. Significant differences between groups are shown in bold ($P < .05$).
[e]Median (interquartile range).
[f]Stratification according to the level of adhesion to the exercise intervention (3 = highest).
[g]Stratification of results based on adherence to physical activity.
[h]Geometric mean and 95% CI.
[i]Median (semi-interquartile range).
[j]Three-arm clinical trial, combining the intervention groups to evaluate inflammatory markers.
[k]Mean (SE).
[l]Least squares mean (SE).
Abbreviations: BMI, body mass index; C, control group; CRP, C-reactive protein; hsCRP, high-sensitivity C-reactive protein; I, intervention group; IL, interleukin; N/A, not available.

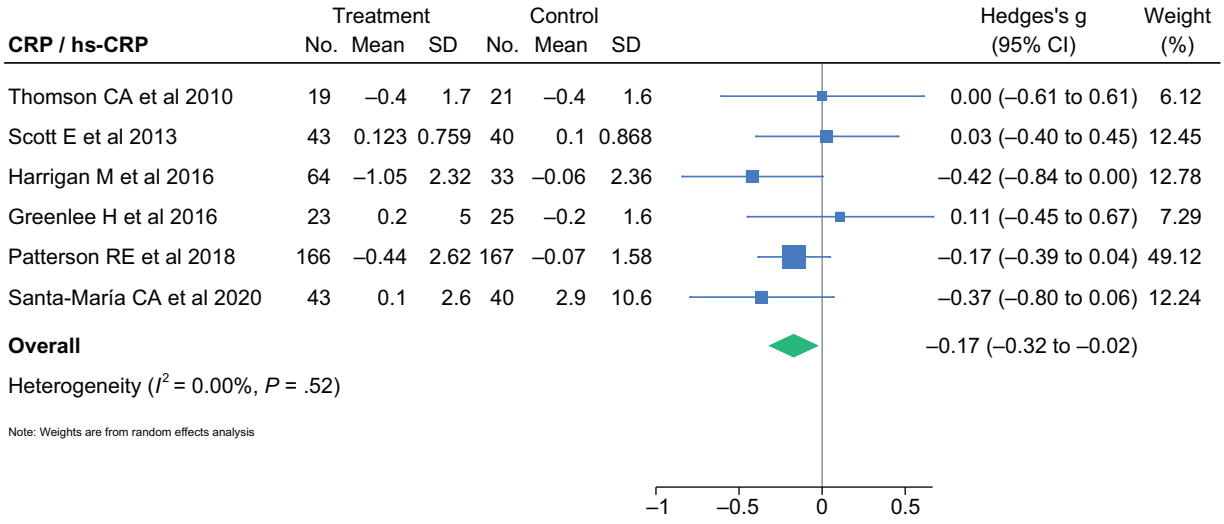


Figure 2. Pooled Estimate of Differences of Mean Change (Hedges's g) with 95% CI between Intervention and Control Group in C-Reactive Protein (CRP).

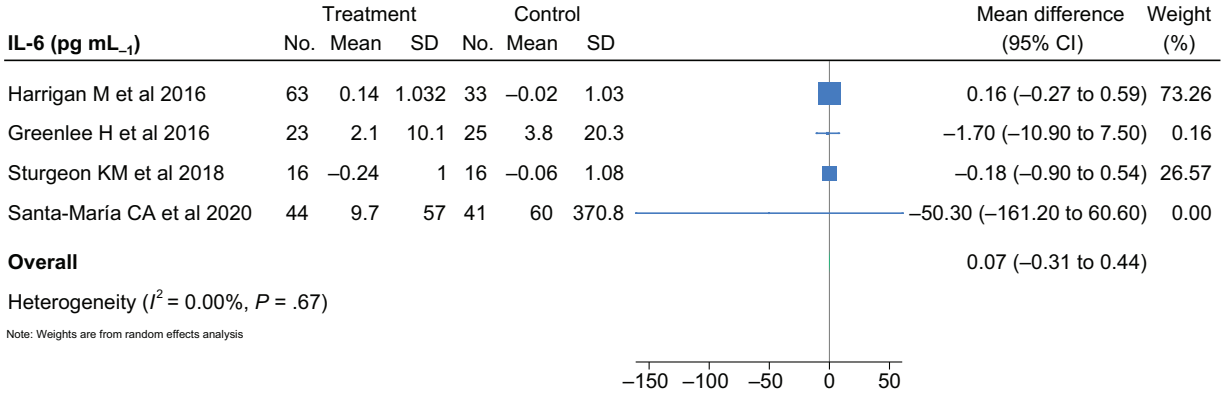


Figure 3. Pooled Estimate of Mean Differences with 95% CI of Change Differences in Interleukin-6 (IL-6) Between Intervention and Control Groups

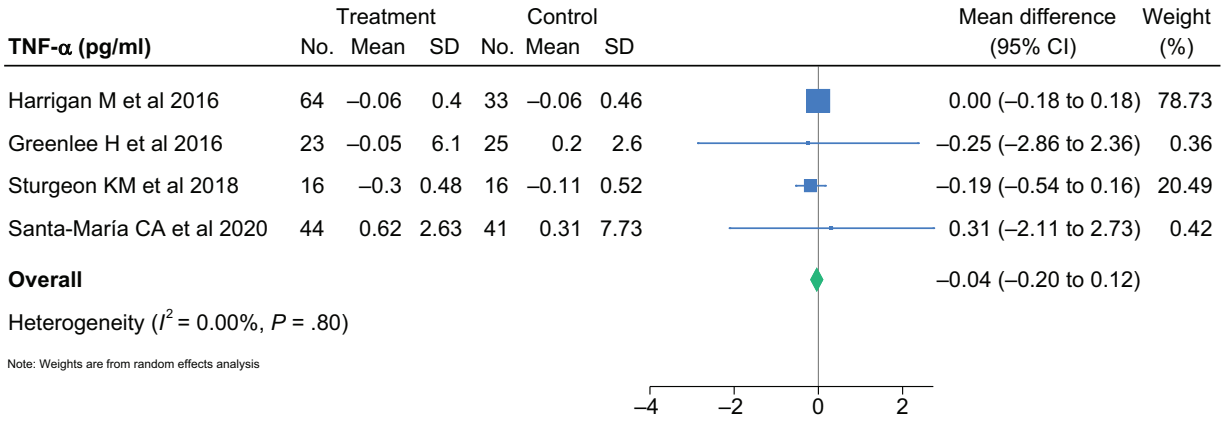


Figure 4. Pooled Estimate of Differences in Tumor Necrosis Factor-α (TNF)-α of Mean Change with 95% CI Between Intervention and Control Groups

promoted physical activity among premenopausal women, a nonsignificant decrease in TNF receptor-2 levels was observed in both intervention groups, and there was a nonsignificant increase in the control group.[37]

Risk of Bias of the Included Articles

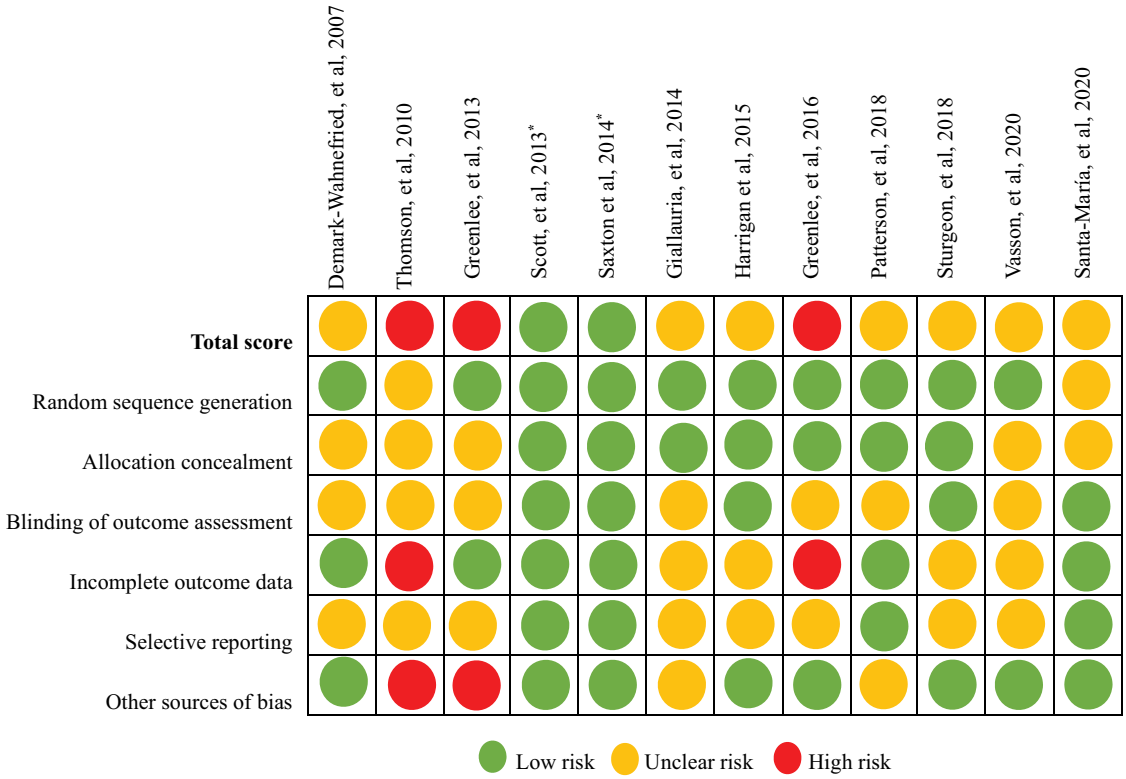
Figure 5 summarizes the score obtained for each domain from each study. The agreement among reviewers was moderate: weighted κ index 0.59 (95% CI, 0.44-0.75). Three studies had a high risk of bias,[36,41,38] 2 had a low risk of bias,[33,39] and the rest had an unclear risk of bias.[29,34,35,37,38,40,43] Regarding the random sequence generation domain, all studies had a low risk of bias except 2, which could not be evaluated in this domain because they did not clearly explain their methodology.[35,38] The domain with the worst score was the incomplete reporting of outcome data, with 2 studies at high risk of bias,[38,39,41] 4 at unclear risk of bias,[29,40,42,43] and 6 at low risk of bias.[33–37, 39] Of note, the selective reporting outcome also had a poor score, with only 4 articles having a low risk of bias,[33–37,39] mainly because the protocol could not be found or numeric results for some biomarkers were not reported.

Publication Bias

Figure 6 depicts the funnel plot of the included studies analyzing CRP, IL-6, and TNF-α. Upon visual inspection and as indicated by Egger's test, it appears unlikely that there was publication bias for CRP ($P = .653$) and TNF-α ($P = .822$). Although asymmetry was observed in the lowest part of the funnel plot for IL-6, the Egger's test indicated no evidence of publication bias ($P = .285$).

DISCUSSION

Our aim for this systematic review and meta-analysis was to analyze the effect of healthy dietary interventions on inflammatory biomarkers in women with breast cancer. The main findings were homogeneous and showed that healthy diets based on increased vegetable and fruit consumption and/or limited fat consumption may diminish the levels of CRP. This result was maintained when the



* Both studies are derived from the same clinical trial

The item "blinding of participants and personnel" is not applicable in this systematic review (see the full description in Methodology section).

Figure 5. Evaluation of the Risk of Bias in the Included Randomized Clinical Trials

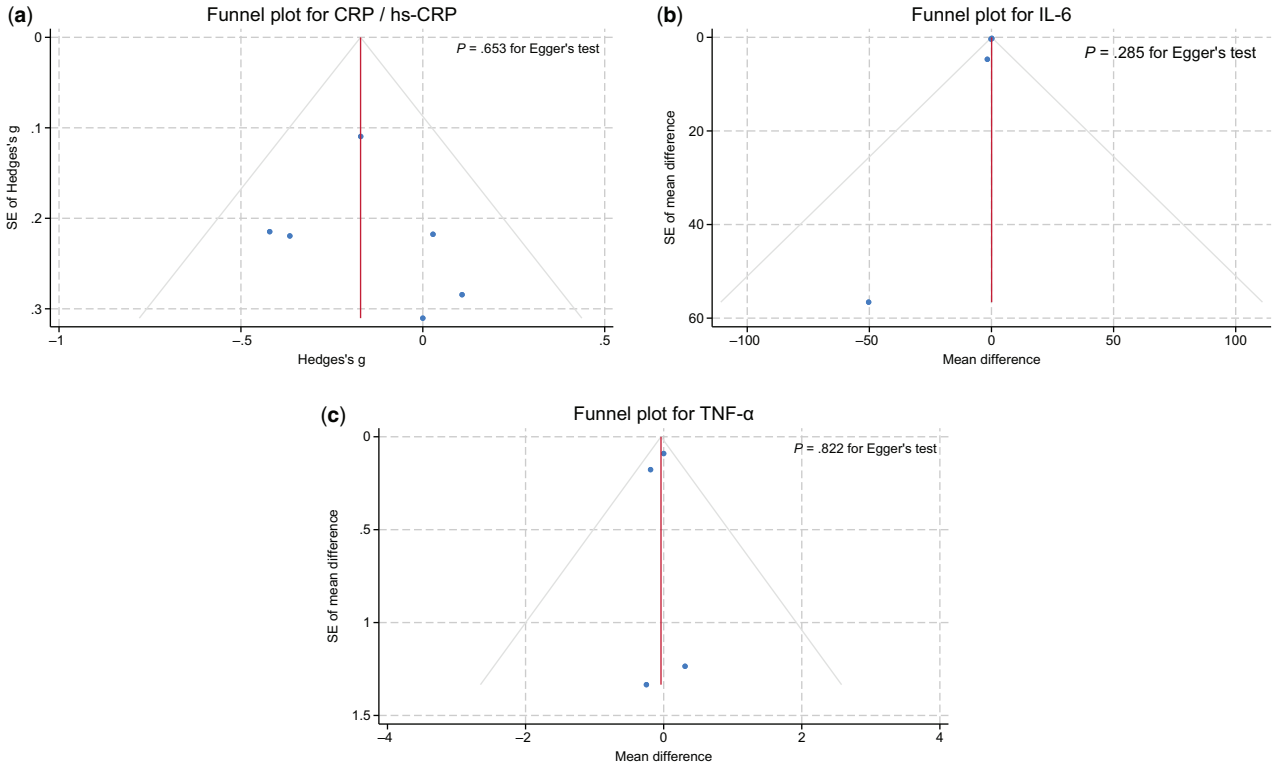


Figure 6. Funnel Plots to Detect Publication Bias of the Inflammatory Biomarkers: (a) Protein C-Reactive (CRP); (b) Interleukin-6 (IL-6); (c) Tumor Necrosis Factor-α (TNF-α)

interventions added a weight loss or physical activity goal. The follow-up time or the intervention duration could be relevant aspects to consider. There was no effect on IL-6 or TNF-α, and inconclusive results for other inflammatory parameters, due to a lack of studies.

Most of the studies included in this systematic review and meta-analysis were classified as having an unclear risk of bias, which could have implications for the results. On the 1 hand, the incomplete outcome data domain was the most impaired for these studies. Of note, our approach included data estimations from those articles with unavailable necessary information. However, when these articles were included in the meta-analyses, the results were similar, but the heterogeneity was increased. On the other hand, blinding participants was not feasible in the selected studies due to the nature of the intervention, so this item was not included in the assessment of bias in the trials. This lack of blinding may have led to reporting bias, whereby participants may have overestimated their adherence to the dietary intervention. Nevertheless, the potential effect of this bias on the reliability of the findings would be minimized by the objective assessment of the outcomes. In addition, only 2 trials used a self-reported dietary intake,[42,43] and these studies were not included in the meta-analysis of the main result of this article (ie, CRP outcome).

The role of chronic inflammation in the development or progression of cancer is widely recognized.[7,45] Elevated levels of CRP in women with breast cancer have been suggested as a possible poorer prognostic marker, either among patients with breast cancer overall,[44,46,47] among patients with nonmetastatic breast cancer,[48,49] or among those with estrogen and progesterone receptor–negative tumors.[49] However, there has been no consensus on the relationship between a healthy diet and inflammation in previous studies. Although the difference in the CRP reduction observed in this study was modest, the previously reported association of this parameter with clinical outcomes such as survival suggests it could have potential clinical relevance. Our findings are in line with the meta-analysis by Wang et al[20] but in contrast with another meta-analysis that found statistically nonsignificant effects in CRP[21] when the types of interventions used in the included studies were similar to those described in this study. Nevertheless, their study[21] did not resolve the heterogeneity in the results and did not consider aspects such as the duration of the intervention. Thus, although the effect of shorter interventions could not be adequately assessed, the duration of the nutritional intervention may be a key aspect and may need to last for at least 6 months to affect CRP levels.

In terms of the type of dietary intervention, the results for CRP were maintained in interventions

focused on weight loss with the establishment of a restricted energy intake. All studies that focused on weight loss selected women with a prespecified BMI, mostly above 25 kg m^{-2}. A common characteristic of these participants is that they tend to lose weight more quickly[50] and often have a strong but specific motivation to do so.[51,52] People with overweight or obesity often have higher levels of inflammatory biomarkers because adipose cells constantly release proinflammatory mediators that trigger inflammatory cascades.[53–56] Therefore, they may benefit most from calorie-restricted dietary interventions. Thus, specific characteristics of patients with breast cancer may be relevant for the design of the type of intervention, in addition to its duration.

The promotion of exercise has emerged as a possible significant factor influencing inflammatory biomarkers in patients with breast cancer.[57–59] In this study, the results in this stratum were similar to the overall results for CRP; however, the evaluation of the results of the trials without physical activity was not possible. Considering the general benefits of physical activity,[60,61] the promotion of this lifestyle could be included in the interventions. Nevertheless, it would have to be evaluated if adding extra interventions may result in reduced or less prolonged adherence to a healthy dietary intervention, as has been described.[62,63] Moreover, the complexity of the inflammatory response, which is influenced by various factors, such as the duration, intensity, and type of exercise, as well as the clinical characteristics of patients,[60] should be considered for future studies.

No significant result was found for IL-6 or TNF-α. It has been reported that these parameters correlated with clinical breast cancer stage.[9] The studies included in the meta-analysis included patients with stages 0 to 3,[29,35,39,41] and that could have made it difficult to detect differences, if they existed, between interventions. Our meta-analysis did not stratify on the basis of the stage of the disease in order to analyze its potential contribution. On the other hand, elevated blood levels of IL-6 have been associated with an unfavorable prognosis in patients with metastatic breast cancer, suggesting its contribution to the proinflammatory environment that drives tumor progression,[64,65] as well as in stages 2 and 3 ductal carcinomas.[9] In contrast, elevated IL-6 levels seem to be associated with a more favorable prognosis in earlier stages of the disease in in vitro studies.[66] Similarly, the role of TNF-α, depending on its levels, in the regulation of both induction and protection in breast cancer has been described.[11]

The limited or inconclusive information found about IL-1β, IL-8, or other inflammatory parameters highlights unexplored areas of knowledge that could be critical for a comprehensive understanding of the impact of diet on the inflammatory response in patients with breast cancer. Furthermore, this gap underscores the importance of initiating research on interleukins, such as IL-25, whose role in breast cancer is not yet fully understood; perhaps these may act therapeutically in combination with other therapies and serve as a biomarker for breast cancer diagnosis and prognosis.[67]

This systematic review and meta-analysis have some limitations: (1) no conclusions could be drawn for relevant socio-demographic characteristics of women with breast cancer or clinical aspects such as menopausal status, the stage of the disease, or the tumor subtype, due to the lack of identified studies; (2) the interrelationship between inflammatory parameters could not be addressed (eg, it has been described that IL-6-can induce the production of CRP[68]); (3) fewer than 10 studies were included to evaluate the publication bias, compromising the robustness of the Egger test,[69] so the existence of this bias should not be entirely discarded; (4) the precision of the results of meta-analysis could be compromised because none of the included studies had the primary objective of measuring inflammatory parameters (sample size calculations were not designed to detect statistical differences in this outcome between the intervention and control groups); and (5) this review was restricted to 3 key biomarkers (CRP, IL-6, and TNF-α) due to the scarcity of data on other inflammatory parameters in the included trials. Although these biomarkers are well-established indicators of systemic inflammation, their exclusive use may overlook other relevant pathways modulated by diet.

We highlight the following strengths: (1) the inclusion of all kinds of dietary interventions in the selection criteria allowed us to assess the impact of the differential aspects of these interventions, including the duration of the intervention or the additional goals of weight loss or physical activity; (2) the search for studies was made without restriction of publication date in 5 important electronic databases to minimize the selection bias; (3) supplementary analyses, including more studies with estimated data, were done to confirm the results found; and (4) a wide range of biomarkers was included, providing a comprehensive view of the effects of the dietary interventions and inflammation in women with breast cancer.

CONCLUSION

In conclusion, this systematic review and meta-analysis showed an association between following a healthy diet and a decrease in CRP levels. Weight-loss goals for patients with breast cancer with overweight, promoting physical activity, or duration of the intervention should

be considered when designing dietary interventions. For future studies, the interrelation of the inflammatory parameters and socio-demographic and clinically relevant aspects of breast cancer, such as the stage, should be considered. These would provide a more comprehensive and specific understanding of the impact that adherence to a healthy diet may have and contribute to a more precise and personalized approach to the treatment of patients with breast cancer.

Acknowledgments

This study will form part of C.G.-P.T.'s doctoral thesis in the context of the Clinical Medicine and Public Health Program of the University of Granada (Spain). The authors thank the Universidad de Malaga/Consorcio de Bibliotecas Universitarias de Andalucía for funding the Open Access fees for the publication.

Author Contributions. C.G.-P.T., C.M.-B., J.J.J.-M., and R.B.-R. designed the research; C.G.-P.T., M.A.C.-H., and R.B.-R. performed the systematic literature search and identified the studies meeting the inclusion criteria; C.G.-P.T. and I.I.P. extracted data from the included studies; C.G.-P.T., I.I.P., and J.J.J.-M. assessed the risk of bias of the included studies; C.M.-B. and R.B.-R. performed the statistical analysis; C.G.-P.T. and R.B.-R. wrote the paper; E.T., T.D.-S., and J.J.J.-M. assisted in the interpretation of the results and the revision of the manuscript. All authors had primary responsibility for the final content and read and approved the final manuscript.

Supplementary Material

Supplementary Material is available at *Nutrition Reviews* online.

Funding. This study has been funded by the Consejería de Salud, Junta de Andalucia (grant PI-0254-2019) and Instituto de Salud Carlos III (grants PI18/01683, PI22/01690, PI18/00631, PI22/00828, PI18/00827, PI22/01766) and cofunded by the European Union. C.G.-P.T. received funding from the Consejería de Transformación Económica, Industria, Conocimiento y Universidades of the Junta de Andalucía for the grant received (grant PREDOC_00551).

Conflicts of Interest

None declared.

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