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NUTRITIONAL STATUS OF SELENIUM IN BREAST CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

ESTADO NUTRICIONAL DO SELÊNIO NO CÂNCER DE MAMA: UMA REVISÃO SISTEMÁTICA E META-ANÁLISE

ESTADO NUTRICIONAL DEL SELENIO EN EL CÁNCER DE MAMA: UNA REVISIÓN SISTEMÁTICA Y UN METANÁLISIS

Diana Stefany Cardoso de Araújo[1], Larissa Layana Cardoso de Sousa[2], Thaís Rodrigues Nogueira[3], Thayanne Gabryelle Visgueira de Sousa[4], Dallyla Jennifer Morais de Sousa[5], Emyle Horrana Serafim de Oliveira[6], Bianca Mickaela Santos Chaves[7], Sarah Ângelo Diniz Melo[8], Dilina do Nascimento Marreiro[9], Betania de Jesus e Silva de Almendra Freitas[10]

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ABSTRACT

Selenium is an essential micronutrient, with antioxidant action and role in cellular defense, and the selenium nutritional status in women with breast cancer has aroused increasing scientific interest. This systematic review and meta-analysis evaluated the nutritional status of selenium in women with and without breast cancer. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study sought to answer the guiding question: “Does the nutritional status related to selenium in women with breast cancer present changes compared to that of women without breast cancer?”. The search took place in PubMed, Web of Science and Embase. Studies that evaluated the nutritional status of selenium in women with breast cancer, compared to women without the disease, were included. Twenty-six articles were identified as eligible. Dietary selenium levels were reduced in women with breast cancer compared to the control group. Reduced concentrations of the mineral in serum, hair and nails were found in women with breast cancer. There were divergent results regarding the activity of the glutathione peroxidase enzyme. The results show compromised nutritional status related to selenium in women with breast cancer; however, the results of the studies are still controversial. This can be justified by the complex metabolism of the nutrient, which may be influenced by physiological changes associated with breast cancer.

KEYWORDS: Selenium. Breast neoplasms. Nutritional Status. Micronutrients. Women.

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RESUMO
O selênio é um micronutriente essencial, com ação antioxidante e papel na defesa celular, e o estado nutricional desse elemento em mulheres com câncer de mama tem despertado crescente interesse científico. Esta revisão sistemática e meta-análise avaliaram o estado nutricional de selênio em mulheres com e sem câncer de mama. A revisão foi conduzida de acordo com as diretrizes PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). O estudo buscou responder à seguinte questão norteadora: "O estado nutricional relacionado ao selênio em mulheres com câncer de mama apresenta alterações em comparação ao de mulheres sem a doença?". A busca foi realizada nas bases de dados PubMed, Web of Science e Embase. Foram incluídos estudos que avaliaram o estado nutricional de selênio em mulheres com câncer de mama, em comparação com mulheres sem a doença. Vinte e seis artigos foram considerados elegíveis. Os níveis de selênio na dieta estavam reduzidos em mulheres com câncer de mama, em comparação com o grupo controle. Concentrações reduzidas do mineral foram encontradas no soro sanguíneo, cabelo e unhas de mulheres com câncer de mama. Os resultados em relação à atividade da enzima glutationa peroxidase foram divergentes. Os achados demonstram um estado nutricional comprometido em relação ao selênio em mulheres com câncer de mama; contudo, os resultados ainda são controversos. Isso pode ser justificado pelo complexo metabolismo do nutriente, que pode ser influenciado por alterações fisiológicas associadas ao câncer de mama.

PALAVRAS-CHAVE: Selênio. Neoplasias da mama. Estado Nutricional. Micronutrientes. Mulheres.

RESUMEN
El selenio es un micronutriente esencial con acción antioxidante y función en la defensa celular. El estado nutricional del selenio en mujeres con cáncer de mama ha despertado un creciente interés científico. Esta revisión sistemática y metaanálisis evaluó el estado nutricional de selenio de mujeres con cáncer de mama en comparación con mujeres sin la enfermedad. La revisión se realizó de acuerdo con las directrices PRISMA (Ítems de Informe Preferidos para Revisiones Sistemáticas y Metaanálisis). El estudio buscó responder a la siguiente pregunta clave: "¿Está alterado el estado nutricional de selenio de las mujeres con cáncer de mama en comparación con las mujeres sin la enfermedad?". La búsqueda se realizó en las bases de datos PubMed, Web of Science y Embase. Se incluyeron estudios que evaluaron el estado nutricional de selenio de mujeres con cáncer de mama en comparación con mujeres sin la enfermedad. Se identificaron veintiséis artículos como elegibles. Los niveles de selenio en la dieta se redujeron en mujeres con cáncer de mama en comparación con el grupo control. Se encontraron concentraciones reducidas del mineral en suero, cabello y uñas en mujeres con cáncer de mama. Se obtuvieron resultados divergentes respecto a la actividad de la enzima glutatión peroxidasa. Los resultados muestran un estado nutricional comprometido relacionado con el selenio en mujeres con cáncer de mama; sin embargo, los resultados de los estudios aún son controvertidos. Esto puede justificarse por el complejo metabolismo del nutriente, que puede verse influido por cambios fisiológicos asociados con el cáncer de mama.

PALABRAS CLAVE: Selenio. Neoplasias de la Mama. Estado Nutricional. Micronutrientes. Mujeres.

1. INTRODUCTION

Breast cancer is a disease characterized by intense changes in the structure and/or function of genetic material, resulting in the uncontrolled multiplication and dissemination of breast cells. This disease is the most common form of cancer among women, being responsible for high mortality rates worldwide (Henry *et al*., 2020; Mendes *et al*., 2019; Inca, 2021).

Several risk factors for this neoplasm have been identified by epidemiological and clinical studies, including age, race, ethnicity, genetic factors and some reproductive aspects, such as early menarche and late menopause, and other factors such as the use of hormone therapy during menopause, smoking, obesity and alcohol consumption (Franco-Marina *et al*., 2015; DeSantis *et al*., 2015; Ahmad, 2019; Grover 2002; Winters *et al*., 2017).

Furthermore, the literature has demonstrated the impact of diet on the development of breast cancer. Therefore, adopting a healthy eating pattern, based on high consumption of fruits, vegetables, whole grains, poultry and fish, and low consumption of red meat, refined foods and sweets, can reduce exposure to risk factors for breast cancer (Ahmad, 2019, De Cicco *et al*., 2019; Mourouti *et al*., 2015).

Selenium is an essential mineral for the human body, whose functions are directly related to the functions of selenoproteins and some mineral metabolism products. The literature reports that this nutrient appears to be involved in several biological processes, including antioxidant defense mechanisms, thyroid hormone metabolism, genomic stability, immunomodulation, fertility and reproduction, neurological function and reducing the risk of chronic non-communicable diseases (Donadio *et al*., 2019; Yoo *et al*., 2010; Wu *et al*., 2015; Cai *et al*., 2016).

Therefore, the protective role of selenium and its compounds in breast cancer has been investigated since 1969, and some studies show that individuals with low selenium concentrations may have a higher incidence of the disease. In this sense, the chemoprotective and chemopreventive mechanisms involving selenium and its compounds stand out, which have the ability to prevent carcinogenesis and cancer progression, respectively. Furthermore, the mineral contributes to reducing DNA damage, attenuating oxidative stress and inflammation through mechanisms involving selenoproteins, improving the immune response, increasing the expression of the tumor suppressor protein p53, inactivating protein C kinase, blocking the cell cycle, inducing apoptosis of cancer cells and inhibiting angiogenesis (Cai *et al*., 2016; Sinha and El-Bayoumy, 2004; Babaknejad *et al*., 2016; Rayman, 2005; Almondes *et al*., 2010).

Given the important functions of selenium in the prevention of breast cancer, several studies have evaluated the nutritional status of the mineral in women with breast cancer to elucidate the influence of the disease on the homeostasis of this element. However, the results are quite controversial, probably due to the different parameters used, variations in selenium concentrations in the soil, as well as variations in the health conditions of the participants. Therefore, carrying out a systematic review of studies already available in the literature is essential to establish the connection between the mineral and the disease. The objective of this study was to analyze the nutritional status of selenium in women with breast cancer.

2. METHODOLOGY

The present systematic review and meta-analysis was carried out following a methodological protocol similar to that proposed by Fontenelle *et al*., (2022), ensuring rigor, transparency and reproducibility to the process.

As described by the authors, the stages of formulating the research question, developing the search strategy, establishing eligibility criteria, selecting studies, standardized data extraction and critical assessment of methodological quality were previously defined. Finally, a meta-analysis of the included studies was performed.

This review was developed with the aim of clarifying whether there are differences in the nutritional status of selenium between women with breast cancer and women without the disease. To this end, the following guiding question was formulated: “Does the nutritional status related to selenium in women with breast cancer present changes when compared to that of women without breast cancer?”. The structure of the question was based on the PECO strategy, considering: Population = women; Exposure = breast cancer; Comparator = control group (women without breast cancer); and Outcome = selenium nutritional status.

The protocol for this review was registered in the International Prospective Registry of Systematic Reviews (PROSPERO) (registration number: CRD42021268203). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used to report this study (Page *et al*., 2020).

Search strategies

The bibliographic survey was carried out in the following electronic databases: PubMed, Web of Science and Embase. The search was carried out without restrictions regarding the period of publication, being filtered into English, Spanish and Portuguese. The initial search took place in August 2021 and, at the end of the review writing process, in March 2025, a new search was carried out to verify the existence of new publications eligible for inclusion in this systematic review.

The descriptors registered in Medical Subject Headings – MeSH Terms were used in the search, including synonyms, combined with Boolean operators “*AND/OR*”. The descriptors used were *Selenium, Selenoprotein, Glutathione Peroxidase, Breast Neoplasm, Breast Carcinoma, Breast Cancer, Mammary Cancer, Malignant Neoplasm of Breast, Malignant Tumor of Breast, Human Mammary Carcinoma and Human Mammary Neoplasm.* As the individual database uses different indexed terms, it was necessary to adapt the search strategy in each of the databases. The search strategies for each database are listed in Table 1.

Table 1. Search strategies

Database	Search strategies
Pubmed	((((((((((Breast Neoplasm) OR (Breast Carcinoma)) OR (Breast Cancer)) OR (Mammary Cancer)) OR (Malignant Neoplasm of Breast)) OR (Malignant Tumor of Breast)) OR (Human Mammary Carcinoma)) OR (Human Mammary Neoplasm)) (breast cancer terms) AND (selenium OR selenoprotein OR glutathione peroxidase)

Web of Science	Breast Neoplasm (All Fields) OR Breast Carcinoma (All Fields) OR Breast Cancer (All Fields) OR Mammary Cancer (All Fields) OR Malignant Neoplasm of Breast (All Fields) OR Malignant Tumor of Breast (All Fields) OR Human Mammary Carcinoma (All Fields) OR Human Mammary Neoplasm (All Fields) AND Selenium (All Fields) OR Selenoprotein (All Fields) OR Glutathione Peroxidase (All Fields)
Embase	('breast neoplasm'/exp OR 'breast neoplasm' OR (('breast'/exp OR breast) AND ('neoplasm'/exp OR neoplasm)) OR (breast AND carcinoma) OR (breast AND cancer) OR (mammary AND cancer) OR (malignant AND neoplasm AND of AND breast) OR (malignant AND tumor AND of AND breast) OR (human AND mammary AND carcinoma) OR (human AND mammary AND neoplasm)) AND selenium OR selenoprotein OR (glutathione AND peroxidase)

Study selection

Two nutrition researchers independently evaluated the articles. Relevant articles were obtained in full and were assessed against the eligibility criteria. Search results in each database were imported into EndNote Web software, where duplicate studies were automatically removed, followed by a manual check to delete remaining duplicates. Subsequently, the studies were independently selected blindly by two reviewers. Disagreements between these reviewers were resolved by consensus, and a third researcher was consulted when this consensus was not possible.

Initially, the titles and abstracts were read to screen the articles and then the full reading was carried out to confirm whether the study actually met the eligibility criteria. After screening and selection of articles, a manual search of the reference list of included articles was carried out to find possible studies that met the eligibility criteria, but had not been retrieved in the search in electronic databases.

The inclusion criteria were as follows: (1) studies including women with breast cancer (case group) and women without breast cancer (control group); (2) who did not undergo surgery to remove the tumor; and (3) studies that evaluated at least one parameter representative of selenium status.

Exclusion criteria were studies with samples consisting of (1) women diagnosed with kidney, liver or heart disease, autoimmune diseases, other types of cancer, diseases that disrupt digestion and absorption in the gastrointestinal tract and other conditions known to affect selenium metabolism in the body, (2) pregnant and lactating women and (3) who take nutritional supplements.

The definition of selenium nutritional status parameters was based on the article by Combs (2015). According to this author, the nutritional status of a nutrient can be understood as a result of its intake, metabolism and retention in the body. Thus, the author presents four components of the

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nutritional status of selenium, that is, dietary intake, tissue concentrations (plasma, erythrocytes, lymphocytes and cells of the oral mucosa), quantity excreted (urine, feces, hair and nails) and functionality (glutathione peroxidase and selenoprotein P).

Data Extraction

Extracted data included information on authorship, year of publication, title, objective, country of research, study design, sample size, division of participants into groups, age, selenium parameters and analysis methods, and main results on selenium status. The extracted data was organized in Microsoft Office Excel spreadsheets and checked by the main reviewer.

Bias risk assessment

Risk of bias was assessed independently by two assessors using the Joanna Briggs Institute (JBI) (Institute TJB, 2014) critical appraisal checklist for cross-sectional studies. Decisions on the scoring system and cut-off points were agreed by all reviewers, as recommended by the JBI reviewers' manual, and studies were classified according to the number of questions answered “yes” as follows: 1) low risk of bias (≥ 6 questions); 2) moderate risk of bias (4-5 questions); and 3) high risk of bias (≤ 3 questions). For the purposes of classifying the risk of bias, the answer “not applicable” was considered as “yes” and the answer “uncertain” was considered as “no”.

Additionally, for the study that looked at dietary selenium, the tool Strengthening the Reporting of Observational Studies in Epidemiology - Nutritional Epidemiology (STROBE-nut) (Lachat *et al*., 2016) was used to verify that the study contains adequate and complete information related to the assessment of dietary intake. This assessment was not used for inclusion purposes; therefore, no study was excluded based on the evaluation result.

Meta-analysis

Regarding quantitative analysis, the mean and standard deviation of selenium levels were collected directly from the articles and organized in Microsoft Office Excel spreadsheets, as well as the sample size of each group analyzed (women with or without breast cancer). Continuous data regarding the following outcomes were analyzed: dietary selenium, capillary selenium, serum selenium, serum GPx and erythrocyte GPx. The Review Manager (RevMan) software from the Cochrane Collaboration was used to perform the meta-analysis (Brasil, 2021). The mean difference (MD) was determined for serum GPx, as the studies used the same measurement unit to measure this outcome. To analyze the others, the standardized mean difference (SMD) was used, as this method is more appropriate when the studies analyzed have different scales or units of measurement (Rubinstein; Keynan, 2014).

Considering that the data were obtained from studies carried out independently and are probably not functionally identical, the random effects model was used. Regarding the statistical method, the inverse of the variance was implemented in all analyses, as it is the simplest method, in addition to being able to be used for all metrics of dichotomous and continuous outcomes. A 95% confidence interval was adopted, and the results were considered statistically significant when $p < 0.05$ (Brasil, 2021).

Heterogeneity between studies was determined using I-square (I^2) statistical tests, chi-square (Chi^2) and tau-square (T^2). To assess the magnitude of heterogeneity, it was considered that an I^2 greater than 50% refers to substantial heterogeneity and, above 75%, considerable heterogeneity (Brasil, 2021; Pereira; Galvão, 2014).

3. RESULTS AND DISCUSSION

Description of screening and selection of articles

The search in the databases retrieved a total of 2941 references. After removing 145 duplicates, the titles and abstracts of the remaining 2796 references were evaluated, resulting in the selection of 151 articles. These articles were read in full to check whether they met the inclusion criteria for this review. The eligibility assessment resulted in the inclusion of 23 articles. In addition, three studies were selected from a manual search of the reference list of articles already included, totaling 26 articles included in this review. The flowchart of the study screening and selection process is shown in Figure 1.

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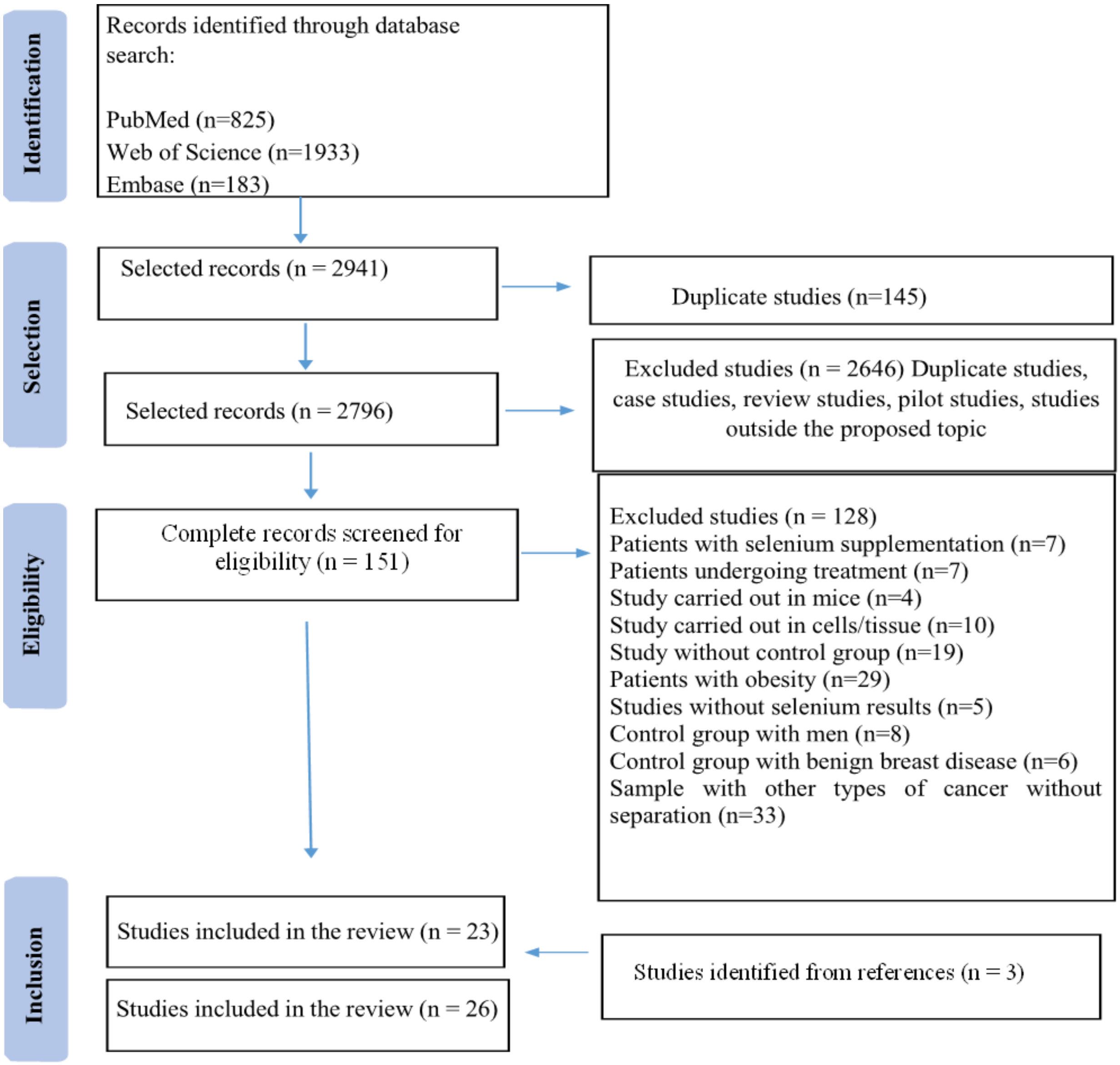
Figure 1. PRISMA flowchart for search and selection of included studies



Characteristics of the included studies

Table 2 shows a description of the studies included in this review. All articles included only female participants, totaling 3454 women with breast cancer, 27839 women without cancer and 92 with benign breast disease. Regarding age group, the average age of women with breast cancer was 49.3 years, without breast cancer was 46.3 years and with benign breast disease was 48.5 years. The research locations varied, totaling 17 countries.

With regard to parameters related to the nutritional status of selenium, 23 articles evaluated only one parameter and three evaluated two or more parameters.

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The parameters analyzed were the activity of the enzyme glutathione peroxidase (n = 12), the concentration of selenium in plasma or serum (n = 10), food intake (n = 3), the concentration of selenium in nails (n = 2) and in hair (n = 3).

Table 2. Simplified description of the studies selected for the systematic review

Authors (year)	Country	Design/Sample	Selenium biomarkers	Main results
Adeoti *et al*. (2015)	Nigeria	Cross-sectional study: -30 patients with breast cancer (47.3±6.8 years) - 30 healthy volunteers (46.5±6.8 years)	Serum selenium	↓ serum selenium concentrations in patientswith breast cancer compared to healthy women ($p<0.01$).
Atukeren *et al.* (2010)	Turkey	Cross-sectional study: -30 patients with breast cancer; median age: 46 years- 20 healthy volunteers	Serum GPx	↓ serum GPx concentrations in patients with breast cancer compared to healthy women ($p<0.001$).
Badid *et al*. (2010)	Algeria	Cross-sectional study: Premenopausal women 38 newly-diagnosed breast cancer women (41±4 years) 50 healthy age matched women (40±5 years)	Erythrocyte GPx activity	Glutathione peroxidase activity were significantly higher in breast cancer patients when comparedwith controls ($p<0.01$).
Basu *et al*. (1989)	Canada	Cross-sectional study: 30 patients with malignant breast tumour (55.2±2.4 years) 29 patients with benign breast disease (59.3±2.6 years) 30 healthy control subjects (53.7±2.4 years)	Serum selenium	No significant difference in serum selenium between groups.
Chaitchik *et al.* (1988)	Israel	Cross-sectional study: 32 patients with breastcancer (59.9 years) 36 healthy controls women(46.8 years)	Serum selenium	The results of the selenium analyses in blood serum show that the weighted mean of the selenium concentration in the group of breast cancer patients is 0.076±0.014 ppm (for 32 cases). This value is significantly lower than the weighted mean of 0.119±0.023 ppm obtained for the group of controls (36 cases).
Choi *et al*. (2018)	Korea	Cross-sectional study: 1st Dataset for DiscoveryCohort: - 150 breast cancer patients (46 median age) - 137 controls without any breast lesions (48 median age)	Serum selenium	↓ serum selenium concentrations in patients with breast cancer compared to healthywomen ($p=0.0241$)
Cihan *et al*. (2011)	Turkey	Hospital-based case control study: 52 patients diagnosed with stage III breast cancer (50.3±8.8 years) 52 healthy volunteers (47.4±10.1 years)	Hair selenium	↓ hair selenium in patients with breast cancer compared to healthywomen ($p<0.05$).

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Gerber *et al*. (1991)	France	Case-control study: 50 breast cancer patients(53.1 ± 9.8 years) 50 healthy control subjects(53.1 ± 8.6 years)	Toenail selenium Serum selenium	There was no significant difference in the selenium levels of the patients and controls.
Goswami *et al*. (2010)	India	Cross-sectional study: 60 cases of carcinoma of the breast (49.2 ± 12.7 years) 60 healthy controls (47.7±11.9 years)	Whole-blood GPx activity	↓ whole-blood GPx activity in patients with breast cancer compared to healthywomen (p<0.001).
Hadi *et al*. (2021)	Iraq	Cross-sectional study: - 90 breast cancer patients (49 median age) 30 newly diagnosed with breast cancer; 60 were already treated with DOXO. - 30 healthy control subjects	GPx activity	GPx mean value in newly diagnosed patients was significantly lower than the control (p = 0.0001), on the other hand the activity of GPx in DOXO treated patients was significantly increased (p < 0.0001); A significant difference in GPx level was recordedbetween control group and patients treated with DOXO (p = 0.0033).
Huang *et al*. (1999)	Taiwan	Cross-sectional study: 35 patients with breast cancer (48.2 ± 12.1 years) 35 healthy controls (44.5 ± 10.2 years)	Serum selenium	No significant difference in serum selenium between groups, but, the mean Se level was lower in stage III as compared to that of the control group (p<0.05).
Kangari *et al*. (2018)	Iran	Cross-sectional study: 38 patients with newly diagnosed breast cancer (40.78±0.847 years) 38 healthy controls women (39.61±0.927 years)	Erythrocyte GPx activity	GPx activity was significantly lower in the breast cancer patients in comparison with the controls (p=0.001).
Piccinini *et al*. (1996)	Italy	Cross-sectional study: 38 patients with breast cancer (58.6 ± 10.3 years) 22 healthy controls women(56.8 ± 11 years)	Hair selenium Plasma selenium	↓ Se hair concentration in patients with breast cancer compared to controls (p<0.01). No significant difference inplasma selenium between groups.
Polat *et al*. (2002)	Turkey	Cross-sectional study: 40 patients with malignant breast tumour (52.7±11.3years) 20 patients with benign breast disease (38±8.3 years) 20 healthy control subjects (48.5±10.2 years)	Erythrocyte GPx activity	Glutathione peroxidase activity were significantly higher in breast cancer patients when compared with healthy controls andbenign disease (p<0.05).

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Rajendra *et al*. (2020)	India	Cross-sectional study: - 30 patients with breast cancer (52 years) - 30 healthy controls women (52 years)	GPx activity	There was no significant difference in the GPx activity of the patients andcontrols (p= 0.609).
Ramírez-Expósito *et al*. (2014)	Spain	Cross-sectional study: 198 women with breast cancer (pre and postmenopausal) (45.2 ± 1.2 years) Premenopausal women without chemotherapy (n=39) and with chemotherapy (n=63); Postmenopausal women without chemotherapy (n=44)and with chemotherapy (n=52). 78 healthy women volunteers (48.5 years) Premenopausal women (n=38); Postmenopausal women (n=40).	Serum GPx activity	GPx activity were significantly lower (p<0.01) with menopause. Women with breast cancer not treated with NC showed significantly lower GPx activity than healthycontrol women (p< 0.01),remaining the significant differences withmenopause. Women with breast cancertreated with NC also showed significantly lower GPx activity than healthy control women (p<0.01),although no differences were found with menopause and NC.
Rao and Kumari (2012)	India	Cross-sectional study: 40 patients with breastcancer (48.5 years) Stage-I (n=10); Stage-II (n=10); Stage-III (n=10);Stage-IV (n=10). 40 healthy controls women (48.5 years)	GPx activity	The activity of GPx was found to be increased significantly in breast cancer patients. GPx activity was elevated significantly from stage -II to Stage -IV breast cancer patients (4% to 25%) whereas no significant change was observed instage I breast cancer patients, when compared to controls.
Ray *et al*. (2000)	India	Case-control study: - 54 breast cancer patients(47.2 ± 10.05 years) 28 premenopausal and 26 postmenopausal. - 42 healthy control subjects (45.6 ± 10.5 years) 23 premenopausal and 19 postmenopausal.	GPx activity	GPx activity showed highly significant elevation in BC patients (p<0.001),irrespective of menopausal status.
Saleh *et al*. (2011)	Kuwait	Cross-sectional study: 50 patients with breast cancer (47.2±11.77 years) 150 healthy controls women (46.9±12.52 years)	Whole blood level of selenium	↓ serum selenium concentration in patients with breast cancer compared to controls (p<0.0001).
Singh *et al*. (2005)	India	Hospital-based case control study: - 160 breast cancer patients (45.29 ± 10.64 years) - 160 controls (40.98 ± 10.32 years)	Serum selenium	There was no significant difference in the selenium levels of the patients and controls.

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Sivakumar *et al*. (2011)	India	Cross-sectional study: 50 patients with breast cancer (45 years) 50 healthy controls women(45 years)	Erythrocyte GPx activity	GPx activity was significantly lower in the breast cancer patients in comparison with the controls ($p<0.001$).
Suzana et al. (2009)	Malaysia	Cross-sectional study: 64 patients with breast cancer (46.7 ± 6.4 years) -127 healthy controls women (47.2 ± 7.4 years)	Selenium Intake Toenail selenium Hair selenium	- The dietary selenium among cases was significantly lower than the controls ($p<0.05$); Selenium in hair did not differ among cases and controls; Selenium status in the nails of controls was significantly higher as compared to cases ($p<0.05$).
Tu *et al*. (2023)	China	Case-control study: 1591 cases of breast cancer (47.79 ± 9,57 years) 1622 controls women (47,73 ± 9,85 years)	Dietary selenium	- The Selenium from plants and Selenium from white meat intake among cases was significantly lower than the controls ($p<0.05$); -Selenium consumption from red meat in cases was significantly higher compared to controls ($p<0.05$).
Wang *et al*. (2025)	China	Case-control study: 410 cases of breast cancer (66 ± 15,22 years) 24.834 controls women (45,8 ± 13,34 years)	Dietary selenium	↓ intake selenium concentration in patients with breast cancer compared to controls ($p<0.01$) Logistic regression analysis showed a strong linear protective association between selenium levels and breast cancer.
Wu *et al*. (2006)	Taiwan	Cross-sectional study: 25 patients with malignant breast tumour 43 patients with benign breast disease 26 healthy control subjects	Serum selenium	↓ serum selenium concentration in patients with breast cancer compared to controls ($p<0.01$).
Yadav *et al*. (2012)	Nepal	Hospital-based case control study: - 69 breast cancer patients (47.5 years) 25 premenopausal and 44 postmenopausal. - 70 healthy control subjects (47.5 years) 25 premenopausal and 45 postmenopausal.	Serum selenium	↓ serum selenium concentration in patients with breast cancer compared to controls ($p<0.01$), irrespective ofmenopausal status.

GPx: Glutathione peroxidase; Se: Selenium; NC: Neoadjuvant Chemotherapy; BC: breast cancer.

The risk of bias assessment showed that 38% of the studies (n=10) completed six or more checklist items (low risk), 54% (n=14) completed four or five items (moderate risk), while 8% (n=2) of studies completed less than four items (high risk). In general, the main points identified as risk of bias were confounding factors not considered in the data analysis, mainly related to the age at menarche, breastfeeding, smoking and the presence or absence of obesity and other diseases that increase the risk of developing cancer and the superficial description of the selenium analysis and the statistical tests applied. Table 3 show a detailed assessment of the risk of bias in the studies included in this review.

Table 3. Assessment of the risk of bias of the studies selected for the systematic review

Study (Year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Risk
Adeoti, M. *et al.* (2015)	S	N	S	*	N	N	S	S	T
Atukeren, P. *et al.* (2010)	S	N	N	*	N	N	S	S	T
Badid, N. *et al.* (2010)	S	S	N	*	S	N	T	S	T
Basu, T. K. *et al.* (1989)	N	N	N	*	S	S	S	S	T
Cihan, Y. B.; Sözen, S.; Öztürk Yildirim, S. (2011)	S	N	N	*	N	N	S	S	T
Chaitchik, S. *et al*. (1988)	N	S	N	*	N	*	S	T	T
Choi, R.; Kim, M. J.; Sohn, I. (2018)	S	S	S	*	S	N	S	S	S
Gerber, M. *et al*. (1991)	N	N	N	*	S	S	S	S	S
Goswami, B. *et al*. (2010)	S	N	S	*	N	S	T	S	N
Hadi, N. A.; Mahmood, R. I.; Al-Saffar, A. Z. (2021)	N	N	N	*	N	*	S	S	T
Huang, Y. L.; Sheu, J. Y.; Lin, T. H. (1999)	S	N	S	*	S	S	S	S	S
Kangari, P.; Zarnoosheh, T. F.; Golchin, A. (2018)	S	S	N	*	S	S	S	S	S
Piccinini, L. *et al*. (1996)	S	N	N	*	N	N	S	S	T
Polat, M. F. *et al*. (2002)	N	N	N	*	N	N	S	S	N
Rajendra C. H.; Kedari G. S. R. (2020)	S	N	S	*	N	*	S	S	S
Ramírez Expósito, M. J.; Sánchez-López, E.; Cueto-Ureña, C. (2014)	S	N	N	*	N	N	S	S	T
Rao, S.; Kumari, D. S. (2012)	N	N	N	*	N	*	S	S	T
Ray, G.; Batra, S.; Shukla, N. K. (2000)	N	N	N	*	N	*	S	S	T
Saleh, F. *et al*. (2011)	N	N	N	*	N	*	S	S	T
Singh, P. *et al*. (2005)	S	S	S	*	N	*	S	S	S
Sivakumar, S.; Niranjali, S. D. (2011)	N	N	S	*	N	*	S	S	T
Suzana, S.; Cham, B. G.; Ahmad, G. R. (2009)	S	S	N	*	N	*	S	S	S
Tu, K. *et al*. (2023)	S	S	S	*	S	T	T	S	S
Wang *et al*. (2025)	S	S	S	*	S	T	S	S	S
Wu, H. I. *et al*. (2006)	N	N	N	*	N	*	S	S	T
Yadav, N. K. *et al*. (2012)	S	N	S	*	N	*	S	S	S

Note: (S) = Green - Yes/low risk of bias; (T) = Yellow - Unclear/moderate risk of bias; (N) = Red - No/high risk of bias); * = Not applicable. Q1. Were the criteria for inclusion in the sample clearly defined? Q2. Were the study subjects and the setting described in detail? Q3. Was the exposure measured in a valid and reliable way? Q4. Were objective, standard criteria used for measurement of the condition? Q5. Were confounding factors identified? Q6. Were strategies to deal with confounding factors stated? Q7. Were the outcomes measured in a valid and reliable way? Q8. Was appropriate statistical analysis used?

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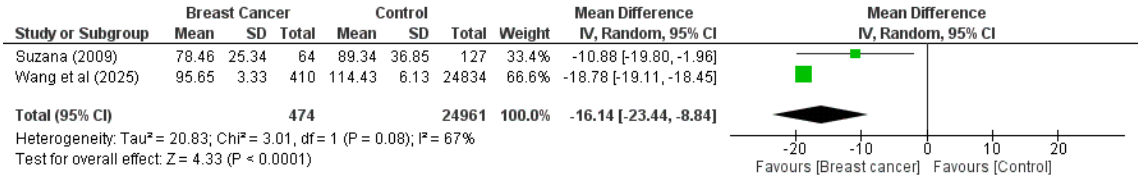
Assessment of selenium nutritional status biomarkers

Two studies with a total of 25435 women were included in the meta-analysis to verify the dietary selenium of women with breast cancer (Figure 2). In the joint analysis, it was observed that there was a significant statistical difference between the groups, where women with breast cancer had reduced intake compared to the control group (*p* <0.0001). The heterogeneity was substantial (I^2 = 67%). It is worth mentioning that the study by Tu *et al*., (2023) was not included in the analysis, as it did not provide data necessary to carry out the statistical treatment.

Figure 2. Dietary selenium in women with and without breast cancer

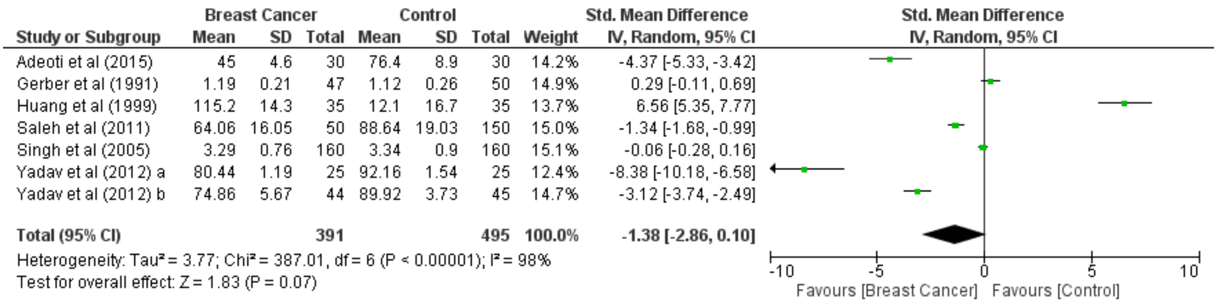


Study or Subgroup	Breast Cancer Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Suzana (2009)	78.46	25.34	64	89.34	36.85	127	33.4%	-10.88 [-19.80, -1.96]
Wang et al (2025)	95.65	3.33	410	114.43	6.13	24834	66.6%	-18.78 [-19.11, -18.45]
Total (95% CI)			**474**			**24961**	**100.0%**	**-16.14 [-23.44, -8.84]**

Heterogeneity: Tau² = 20.83; Chi² = 3.01, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 4.33 (P < 0.0001)

Six studies with a total of 886 women were included in the meta-analysis to check the serum selenium levels of women with breast cancer (Figure 3). In the joint analysis, it was observed that there was no statistically significant difference between the groups (*p* = 0.07). The heterogeneity was considerable (I^2 = 98%). It is worth mentioning that the studies by Basu *et al*., (1989), Chaitchik *et al*., (1988), Choi *et al*., (2018) and Wu *et al*., (2006) were not included in the analysis, as they provided non-specific data on the levels obtained from the mineral.

Figure 3. Serum selenium levels in women with and without breast cancer



Study or Subgroup	Breast Cancer Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Adeoti et al (2015)	45	4.6	30	76.4	8.9	30	14.2%	-4.37 [-5.33, -3.42]
Gerber et al (1991)	1.19	0.21	47	1.12	0.26	50	14.9%	0.29 [-0.11, 0.69]
Huang et al (1999)	115.2	14.3	35	12.1	16.7	35	13.7%	6.56 [5.35, 7.77]
Saleh et al (2011)	64.06	16.05	50	88.64	19.03	150	15.0%	-1.34 [-1.68, -0.99]
Singh et al (2005)	3.29	0.76	160	3.34	0.9	160	15.1%	-0.06 [-0.28, 0.16]
Yadav et al (2012) a	80.44	1.19	25	92.16	1.54	25	12.4%	-8.38 [-10.18, -6.58]
Yadav et al (2012) b	74.86	5.67	44	89.92	3.73	45	14.7%	-3.12 [-3.74, -2.49]
Total (95% CI)			**391**			**495**	**100.0%**	**-1.38 [-2.86, 0.10]**

Heterogeneity: Tau² = 3.77; Chi² = 387.01, df = 6 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.83 (P = 0.07)

Considering that capillary selenium reflects serum concentrations of the mineral over long periods, a meta-analysis of data referring to this outcome was carried out. Three studies with a total of 212 women were included in the analysis (Figure 4), however, it was found that there was no significant statistical difference between the groups either (*p* = 0.08). The heterogeneity was considerable (I^2 = 76%).

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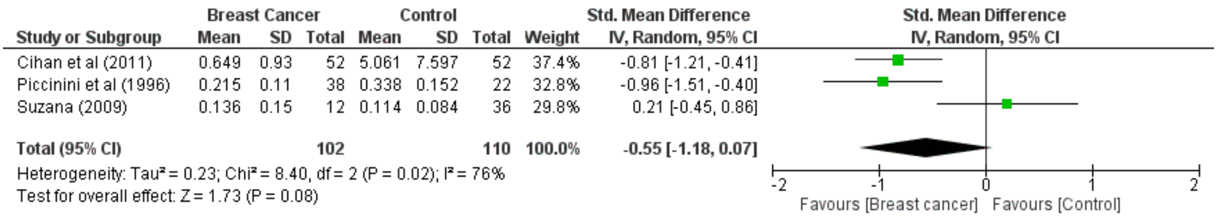
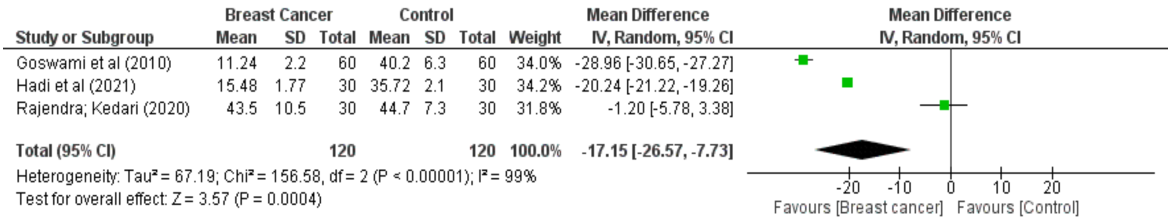
Figure 4. Hair selenium levels in women with and without breast cancer



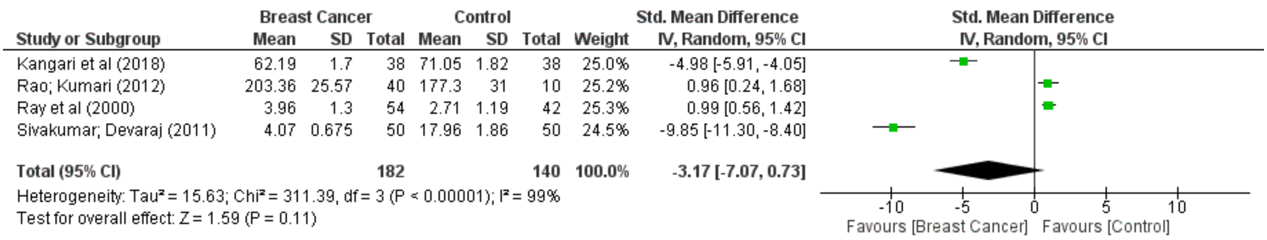
As selenium is the main cofactor of the enzyme Glutathione Peroxidase (GPx), the activity of this enzyme was also analyzed. Three studies with 240 participants were included and the meta-analysis demonstrated that women with breast cancer had significantly lower levels of this enzyme compared to the control group (p = 0.00004) (Figure 5). The heterogeneity was considerable (I^2 = 99%).

Figure 5. Serum GPx levels in women with and without breast cancer



Erythrocyte GPx levels were also analyzed, as they reflect the long-term status of the enzyme. In this analysis, four studies were included with a total of 322 women (Figure 6), however it was found that there was no statistically significant difference between the groups (p = 0.11). The heterogeneity was considerable (I^2 = 99%).

Figure 6. Erythrocyte GPx levels in women with and without breast cancer



The literature highlights some markers, such as analysis of dietary selenium in the diet, blood and tissue concentrations, as well as the excretion of this mineral. Furthermore, the analysis of the concentration or activity of selenoproteins also constitutes a parameter to measure the action of selenium in the body. It is noteworthy that parameters such as dietary selenium, plasma selenium and urinary selenium have high sensitivity, that is, markers that are easily influenced by other endogenous factors, therefore they constitute short-term markers of the mineral. On the other hand, biomarkers such as erythrocyte, capillary and nail selenium constitute long-term biomarkers, better reflecting the nutritional status of selenium present in individuals. (Ashton *et al*., 2009).

In this meta-analysis, selenium parameters researched in at least two studies were evaluated, which analyzed data referring to the mean and standard deviation of the parameters. In this way, we sought to understand the behavior of the mineral in relation to the pathophysiological changes inherent to the disease, considering the cross-sectional design of the included studies.

Dietary selenium

This meta-analysis demonstrated that individuals with breast cancer had lower dietary selenium than that observed in individuals without the disease. This result may reflect a low intake of source foods, such as Brazil nuts, fish such as tuna and salmon, meat such as chicken and liver, as well as vegetables such as broccoli and spinach. However, it is worth highlighting that the intake values for this micronutrient showed substantial heterogeneity between studies, indicating that the estimated effect may not accurately reflect the real situation of this group in terms of compliance with nutritional recommendations for selenium.

In this context, it is highlighted that geographical origin is a determining factor in the variation of selenium content in foods, since there are regions with a high concentration of this mineral in the soil, which can lead to excessive intake and risk of poisoning, while others have low levels, favoring the occurrence of deficiency (Combs, 2015; Institute of Medicine, 2000; Ferreira *et al*., 2002; Flowers *et al*., 2022; Jaworska *et al*., 2012). Furthermore, considering the limitations inherent to dietary assessment, dietary selenium must be interpreted in conjunction with biochemical markers, in order to allow a more accurate assessment of the nutritional status of this micronutrient.

It is noteworthy that adequate dietary selenium is essential for maintaining appropriate tissue concentrations and for the activity of selenoproteins, which play an important role in cancer prevention, as they act to neutralize free radicals in mammary epithelial cells, contributing to the reduction of oxidative damage to DNA (Key *et al*., 2003; Burk and Hill, 2015; Duntas and Benvenga, 2015).

Serum selenium

Plasma and serum selenium levels are the most used parameters to analyze the nutritional status of this element. It is worth mentioning that selenium concentrations in plasma or serum reflect the content of the mineral absorbed after ingestion and are therefore considered a biomarker that reflects the nutritional status of the mineral in an acute form (Combs, 2015).

Regarding the meta-analysis carried out, serum selenium levels were similar between women with and without breast cancer, without significant differences. However, the high heterogeneity for this parameter between studies must be considered, as it suggests the existence of other factors that can influence selenium concentrations, such as the nutritional and metabolic status of the participants, sociodemographic characteristics, stage of the disease, type of oncological treatment, as well as methodological variations between studies (Zakeri *et al*., 2021). Furthermore, increased oxidative stress, observed in chronic diseases such as cancer, may contribute to selenium depletion due to the greater use of this mineral in the synthesis of antioxidant agents, such as glutathione peroxidase (Szwiec *et al*., 2025).

Another important point concerns the influence of geographic region, as studies conducted in regions with low to moderate selenium content in the soil showed a more pronounced reduction of the mineral in the group of individuals with cancer when compared to individuals without this pathology. This result indicates the strong influence of selenium content in the soil on variations in serum concentrations of the mineral in individuals (Flowers *et al*., 2022; Jaworska *et al*., 2012).

Selenium in hair

Assessment of selenium concentrations in hair, as well as nails, reflects the long-term nutritional status of the mineral. Regarding this aspect, it is worth mentioning that these parameters do not present dynamic balance with the circulating quantity of the mineral and correspond to a form of excretion of this nutrient (Combs, 2015).

With regard to hair selenium, the meta-analysis revealed that there was no statistically significant difference between the groups. A similar result was found by Suzana *et al*. (2009), who observed no difference in hair selenium concentrations between women with and without breast cancer. This fact can be justified because changes in hair selenium parameters are better observed in the long term. This is because selenium has gradual effects on the body, and the impacts on hair health can manifest themselves over months or even years (Babaknejad *et al*., 2014).

Glutathione peroxidase enzyme activity

Given that selenium is a component of the amino acid selenocysteine, an essential substrate for the synthesis of a group of proteins called selenoproteins, determining the concentration or activity of these proteins can be used to assess selenium-related nutritional status from a functional perspective (Labunskyy *et al*., 2014; Combs, 2015).

Among the selenoproteins, glutathione peroxidase 1 (GPx1) and glutathione peroxidase 3 (GPx3) stand out, being present in greater quantities in plasma or serum, constituting relevant components of the functional pool of circulating selenium (Renko, 2018). Furthermore, these proteins respond, to some extent, to dietary selenium, and are used as parameters to estimate the recommended intake of the mineral and establish appropriate values for its concentration in plasma or serum (Thomson, 2004; Hurst *et al*., 2013).

In the studies included in this meta-analysis, enzyme activity was evaluated in erythrocytes and serum, corresponding mainly to the GPx1 and GPx3 isoforms, respectively. GPx1 is an intracellular enzyme located in the cytosol, mitochondria, or nucleus, and is considered the most

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abundant selenoprotein in the body. GPx3 is secreted primarily by the kidneys and constitutes the predominant form in plasma. Both play an important antioxidant role, acting in the reduction of hydrogen peroxide, lipid hydroperoxides, and other organic hydroperoxides (Labunskyy *et al*., 2014).

A meta-analysis revealed that women with breast cancer had significantly lower serum GPx levels when compared to women without the disease. This reduction may reflect a greater antioxidant demand associated with breast cancer, a specific condition of increased production of reactive oxygen species (ROS). When the generation of these species exceeds the cellular antioxidant capacity, there may be a decrease in the activity of enzymes such as GPx. In this context, these changes contribute to a pro-oxidant environment and consequently the emergence of oxidative damage to proteins, lipids and DNA (Danesh *et al*., 2022; Rajendra; Kedari, 2020; Hewala; Elsoud, 2019; Salman *et al*., 2020).

However, extremely high statistical heterogeneity was observed between the included studies (I^2 close to 99%), which indicates great variability between individual results. This heterogeneity may be associated with methodological differences between studies, including variations in the laboratory techniques used to determine GPx activity, differences in participants' clinical characteristics, tumor stage, selenium nutritional status and sample size. Therefore, the results should be interpreted with caution, considering that these sources of variability can influence the magnitude of the combined estimates.

Regarding erythrocyte GPx activity, no statistically significant differences were observed between women with and without breast cancer. As erythrocyte GPx reflects long-term enzymatic status, the absence of differences may indicate that acute changes in antioxidant status are more evident in circulating compartments, such as serum, than in long-lived cells, such as erythrocytes. Furthermore, factors such as differences in the stage of the disease, treatments performed and laboratory methods used may contribute to the variability of the results observed (Hecht *et al*., 2016; Ghafoor, 2023; Kangari *et al*., 2018; Ramírez-Expósito *et al*., 2014).

Scientific evidence highlights the role of selenium as a potential therapeutic modulator in breast cancer. Recent studies indicate that selenium supplementation at doses between 200 and 500 µg/day can promote significant benefits, especially in reducing toxicities associated with radiotherapy and chemotherapy. However, the effectiveness of this intervention appears to depend on the patient's baseline selenium status. Individuals with serum deficiency show significant improvements after supplementation, including increased survival and reduced adverse effects such as diarrhea and neuropathy. Conversely, patients with adequate selenium levels do not appear to show significant additional benefits after supplementation (Muecke *et al*., 2010; Yang *et al*., 2023; Yim *et al*., 2026).

These findings can be partially explained by variations in the biological response to selenium, mediated by genetic determinants.

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Polymorphisms in selenoprotein genes, such as GPX1 and SEPP1, have been associated with both the risk of developing breast cancer and the response to supplementation. Furthermore, cancer treatment itself can contribute to the depletion of the body's selenium reserves, intensifying oxidative stress and immunosuppression (Méplan *et al*., 2013; Cheng *et al*., 2025).

Therefore, it becomes evident that there is a need for additional, methodologically robust clinical trials that evaluate the use of selenium supplementation in clinical practice in a stratified manner, considering the prior nutritional status and genetic profile of patients with breast cancer.

This review has several strengths, highlighting the search carried out in three relevant health databases, ensuring broad coverage of the available literature. The methodology applied strictly followed international standards for systematic reviews, including the use of the PRISMA protocol and registration in PROSPERO, which reinforces the transparency and reproducibility of the study. Furthermore, the geographic diversity of the included studies allowed us to observe variations in selenium concentrations associated with soil composition in different regions.

Limitations

However, some limitations were identified. Five potentially relevant studies could not be accessed due to the inability to contact the authors, probably because of the age of the publications. Furthermore, limitations were observed in the detailed characterization of the samples, including the lack of stratification by tumor stage and the restricted assessment of selenium-related parameters, which compromised a more comprehensive analysis of nutritional status. In addition, the meta-analyses showed substantial statistical heterogeneity among the included studies, which may reflect differences in study design, populations, and selenium assessment methods. Finally, the predominance of cross-sectional studies limited the ability to establish causal relationships and made it impossible to assess the temporality of changes in selenium levels in relation to breast cancer.

4. FINAL CONSIDERATIONS

The results contained in the articles selected for this review show compromised nutritional status related to selenium in women with breast cancer, in relation to women without the disease. However, the results of the studies are still quite controversial, which can be attributed to the complex metabolism of the nutrient, as well as the lack of control of some variables that can interfere with the homeostasis of the mineral in the body, such as weight, use of supplements, tumor stage, inflammatory conditions, unreported diseases, among other factors.

Associated with this, the data found shows that there is no single biomarker that best clarifies the nutritional status related to selenium, despite the concentrations of the mineral or selenoproteins in plasma being the most sensitive parameters to identify the status of this nutrient.

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Clinically, this highlights the need for caution when interpreting isolated biomarkers and supports the use of combined measures for a more accurate assessment.

In view of this, the need to carry out more studies, in particular, of a longitudinal nature, is highlighted, which investigate the relationship between the nutritional status of selenium and breast cancer, taking into account two or more biomarkers of the mineral and the tumor staging.

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