Contralateral prophylactic mastectomy

Mastectomia profilática contralateral

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize procedures to assist the reasoning and decision-making of doctors.
The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.

Description of the evidence collection method

This guideline followed the standard of a systematic review with evidence retrieval based on evidence-based medicine (EBM), so that clinical experience is integrated with the ability to critically analyze and apply scientific information rationally, thus improving the quality of medical care.

We used the structured mode of formulating questions synthesized by the acronym PICO, where P stands for patient, i.e. women diagnosed with unilateral breast cancer; I for intervention, i.e. simple or total mastectomy, skin-sparing mastectomy, and nipple-areola complex-sparing mastectomy; C for comparison with women who did not undergo contralateral prophylactic mastectomy, and O for the outcome of reduction of the incidence of breast cancer in the contralateral breast.

Based on the structured question, we identified the descriptors that formed the basis of the search for evidence in the databases: Medline-Pubmed and Cochrane. A total of 424 studies were retrieved, of which five were selected to answer the clinical questions (Annex I).

Clinical question

Is contralateral prophylactic mastectomy (CPM) in women with unilateral breast cancer associated with a decline in the incidence of breast cancer in the contralateral breast?

Grades of recommendation and levels of evidence

- A: Experimental or observational studies of higher consistency.
- B: Experimental or observational studies of lower consistency.
- C: Cases reports / non-controlled studies.
- D: Opinion without critical evaluation, based on consensus, physiological studies or animal models.

Objective

This guideline is intended for physicians and medical students and aims to assess whether contralateral prophylactic mastectomy (CPM) in women with unilateral breast cancer is associated with a decline in the incidence of breast cancer in the contralateral breast.

Introduction

Breast cancer is the neoplastic disease that most affects women in Brazil and the world. In Brazil, for the year 2016, 57,960 new cases were expected.[1]

Women with a history of breast cancer are at increased risk for developing contralateral breast cancer, and this risk is related to a variety of factors, including genetics, family history and characteristics of the primary cancer itself.[2,3]

Although studies have shown the efficacy of adjuvant endocrine therapy to reduce the risk of contralateral breast cancer, a growing proportion of women in the early stages of breast cancer have undergone surgical removal of the non-affected breast through risk reducing mastectomy of the contralateral breast.[4,5] Despite the substantial benefits associated with reducing the risk of breast cancer itself, its risk-benefit ratio is controversial because of the negative impact of surgery on self-image, sexuality and quality of

life, in addition to complications related to the procedure itself.[6] Thus, in order to support decision-making by the indication or not of the contralateral prophylactic mastectomy using robust evidence, a systematic review was carried out to evaluate whether CPM in women with unilateral breast cancer is associated with a decline in the incidence of breast cancer in the unaffected breast.

Data extraction

Data referring to a total of 5,532 patients were analyzed, with 2,700 of these women undergoing contralateral prophylactic mastectomy following a personal history of unilateral breast cancer. The mean age of these patients was 46 (Table 1). With mean follow-up time ranging from 3.5 to 17.3 years, it was observed that the contralateral prophylactic mastectomy was associated with a reduction in the incidence of breast cancer in the contralateral breast with values ranging from 78 to 98% and overall risk reduction of 95% (RR=0.05; 95CI 0.02-0.11) (Table 2).

Regarding data on overall survival, studies have conflicting results, some with increased survival[7] and others not confirming this gain.[8-10] Two studies analyzed the incidence of distant metastasis, with a difference between women treated and not treated with CPM (RR=0.65; 95CI 0.46-0.91) (Table 3).[7,11] (**B**).

Studies have demonstrated that contralateral prophylactic mastectomy is associated with a decline in the incidence of contralateral breast cancer in approximately 95% of women with a personal history of unilateral breast cancer.[12,13] (**B**) Supporting these findings, there was a 95% reduction in the incidence of breast cancer; however, the impact on overall survival or even breast cancer-free survival is uncertain, as evidenced in another systematic review that included observational studies.[13] (**B**)

In a retrospective study that showed an average follow-up of around 17 years, the authors reported a 94% lower incidence of contralateral breast cancer in women with stage I or II breast cancer who had undergone therapeutic mastectomy combined with contralateral prophylactic mastectomy.[7] (**B**) The study, with significant long-term follow-up, showed that contralateral prophylactic mastectomy was also associated with superior overall survival and disease-free survival outcomes, although a difference with respect to the incidence of distant metastases was not found.[7] (**B**) On the other hand, other authors, analyzing women with mutations in BRCA1 and BRCA2 genes previously treated for unilateral invasive breast cancer (stage I–IIIa), did not find an increase in overall survival after adjustment for bilateral prophylactic oophorectomy.[9] (**B**) These authors, with no adjustment for prophylactic oophorectomy, found greater overall survival at 5 years in patients undergoing contralateral prophylactic mastectomy, but attributed these findings to the higher mortality observed in the group of patients kept under surveillance.[9] (**B**)

Supporting these findings, in another retrospective study in which more than 1,000 patients with breast cancer were analyzed, the contralateral prophylactic mastectomy was not associated with greater overall survival.[10] (**B**) With a mean follow-up of 6.8 years, the authors found greater disease-free survival for patients undergoing contralateral prophylactic mastectomy (55% versus 28%,

TABLE 1 Studies selected.

Authors and publication year	Type of study	Age	N/CPM	N/Control	Follow-up time	Endpoints
Peralta et al., 2000	Retrospective cohort	45.5	0/64	36/182	6.2 years for CPM and 6.8 years for the control group	Overall survival, disease-free survival, incidence of cancer in the contralateral breast
van Sprundel et al., 2005	Retrospective cohort	CPM=41.5±0.9 Control=46.7±1.1	1/79	6/69	3.5 years	Overall survival, incidence of cancer in the contralateral breast
Boughey et al., 2010	Retrospective cohort	NA	2/385	31/385	17.3 years	Overall survival, disease-free survival, incidence of cancer in the contralateral breast, distant metastases
Herrinton et al., 2005	Retrospective cohort	CPM=50 Control=58	5/1,072	69/317	5.7 years	Cancer incidence in the contralateral breast; overall survival
King et al., 2011	Retrospective cohort	CPM=44.8 Control=53.2	0/407	14/2,572	4.4 years for CPM and 6.8 years for the control group	Incidence of contralateral breast cancer, distant metastases

Age: years ± standard deviation; N: patients with breast cancer; CPM: contralateral prophylactic mastectomy; Control: not treated with CPM; Follow-up time: years; NA: not available.

TABLE 2 Incidence of breast cancer in the contralateral breast.

Study or subgroup	CPM Events	CPM Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95CI
Boughey et al., 2010	2	385	31	385	25.3%	0.06 [0.02, 0.27]
Herrinton et al., 2005	5	1,072	69	317	44.1%	0.02 [0.01, 0.05]
King et al., 2011	0	407	14	2,572	8.2%	0.22 [0.01, 3.64]
Peralta et al., 2000	0	64	36	182	8.5%	0.04 [0.00, 0.62]
van Sprundel et al., 2005	1	79	6	69	13.9%	0.15 [0.02, 1.18]
Total (95CI)		**2007**		**3,525**	**100.0%**	**0.05 [0.02, 0.11]**
Total events	8		156			

Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 5.15$, df = 4 (p=0.27); $I^2 = 22\%$

Test for overall effect: Z = 7.04 (p<0.00001)

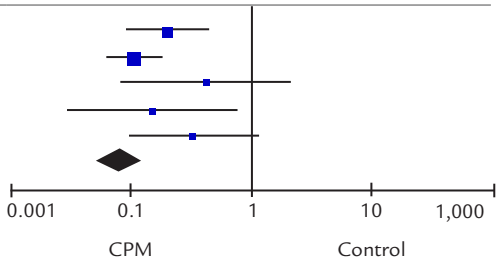
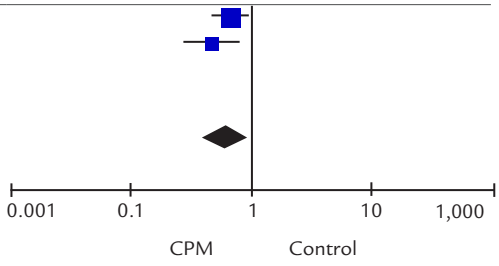


TABLE 3 Incidence of distant metastases.

Study or subgroup	CPM Events	CPM Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95CI
Boughey et al., 2010	60	385	82	385	66.2%	0.73 [0.54, 0.99]
King et al., 2011	15	407	187	2,572	33.8%	0.51 [0.30, 0.85]
Total (95CI)		**792**		**2,957**	**100.0%**	**0.65 [0.46, 0.91]**
Total events	75		269			

Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 1.51$, df = 1 (p=0.22); $I^2 = 34\%$

Test for overall effect: Z = 2.46 (p=0.01)



p=0.01), but did not identify a difference for the rate of overall survival (64% versus 48%, p=0.2).[8] (**B**) Even after adjusting the groups for prognostic factors, they did not find an improvement in the overall survival rate after 15 years of follow-up.[8] (**B**)

The lack of translation to benefit of contralateral breast cancer control, in terms of greater overall survival and disease-free survival, based on a decline in the incidence of breast cancer with the indication of CPM, is not unusual. For many women with early-stage breast cancer, the risk of metastatic disease is greater than that for contralateral breast cancer.[2] (**B**) Therefore, it is possible that the benefits of CPM in terms of disease-free survival are observed only in certain patient subgroups. In fact, another study based on the SEER (Surveillance, Epidemiology and End Results) database showed that, in patients with estrogen receptor-positive breast cancer, the contralateral prophylactic mastectomy was not associated with higher specific survival related to breast cancer.[14] (**B**)

Recommendation

For women who have already been diagnosed with unilateral breast cancer, the contralateral prophylactic mastectomy reduces the incidence of breast cancer in the contralateral breast and distant metastases. With respect to survival (overall or disease-free), the evidence is limited.

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Conflict of interest

The authors state that there is no conflict of interest regarding this review.

Annex I

Structured question

- **P** – Women diagnosed with unilateral breast cancer.
- **I** – Simple or total mastectomy, skin-sparing mastectomy, and nipple-areola complex-sparing mastectomy.
- **C** – Women who did not undergo contralateral prophylactic mastectomy.
- **O** – Reduction of the incidence of breast cancer in the contralateral breast.

Search strategy

- **PubMed-Medline:** (Prophylactic Mastectomy OR Prophylactic Mastectomies OR (Mastectomy AND prevention and control)) AND contralateral.
- **Cochrane:** Prophylactic Mastectomy AND contralateral.

Study selection

Initially selected by the title, then by the abstract, and finally by their full text, the latter being subject to critical evaluation and extraction of results related to the endpoints (Table 1).

Retrieval of relevant articles was conducted through the strategy described in Chart 1 using as primary databases Medline and Cochrane for search completed in April 2017, without restricting the year of publication or language. The process of retrieving articles, as well as evaluating the titles and abstracts obtained, was conducted by two researchers qualified to conduct systematic reviews (W.M.B. and R.S.S.) independently and blindly, following the criteria of inclusion and exclusion according to the PICO components.[15] Then, the selected articles were critically evaluated to decide whether they would be included in the review. Whenever there was disagreement over the selection of studies among the investigators, a third reviewer was consulted (A.S.). To analyze the methodological quality of the included articles, a Cochrane Collaboration tool was used, excluding three domains related to the evaluation of randomized clinical trials (adequate generation of random sequence, concealment of allocation and blinding), not applicable to this review.[16]

Language

We included studies available in Portuguese, English or Spanish.

According to publication

Only full-text studies were considered for critical assessment.

Critical evaluation and strength of evidence

The strength of the evidence from experimental studies was defined taking into account the study design and corresponding bias risks, the results of the analysis (magnitude and precision), relevance and applicability (Oxford).[17]

Articles retrieved

The process of searching, identifying and selecting articles is demonstrated in Figure 1. From the elaborated search strategies, 424 articles were retrieved, of which 32 were selected after reading the title and abstract. Of these studies, five were selected for inclusion in the systematic review and meta-analysis. No randomized clinical trials were retrieved. The main reason for excluding articles was the fact that they were not related to the PICO components. The methodological evaluation of included studies

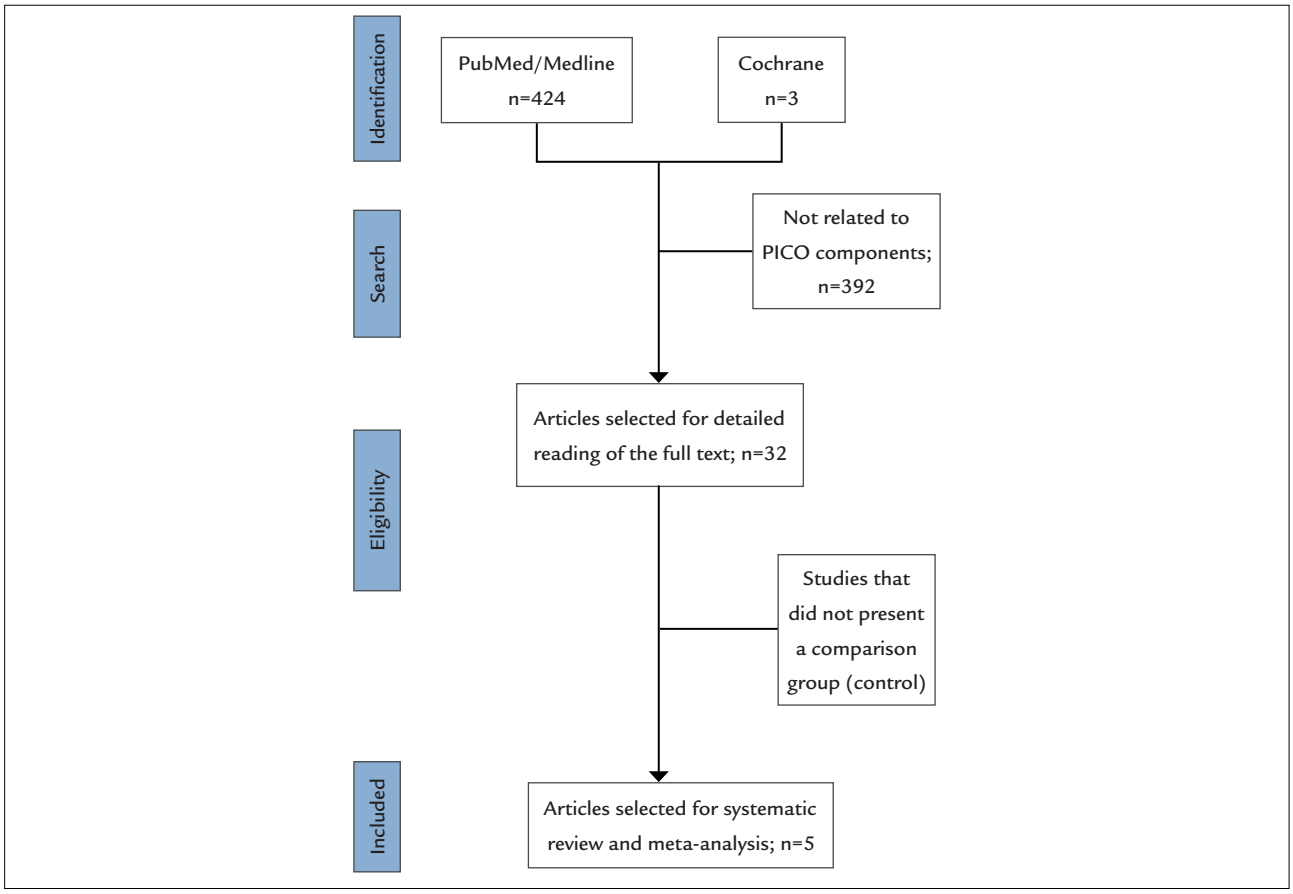

FIGURE 1 Study selection flowchart.

according to the Cochrane Collaboration tool is presented in Figures 2 and 3. Figure 4 shows the evaluation of publication bias using a Funnel plot.

Inclusion and exclusion criteria

In the selection of studies, we included only those that analyzed women diagnosed with unilateral breast cancer and who were subjected to contralateral prophylactic mastectomy, which were compared to a control group comprising women who were not treated with contralateral prophylactic mastectomy, continued to be monitored. The procedures related to prophylactic or reductive mastectomy of the contralateral breast were: simple or total mastectomy, skin-sparing mastectomy, and nipple-areola complex-sparing mastectomy, performed in the breast without clinical or radiological evidence of the presence of malignancy.

Critical appraisal method

Whenever, after applying the inclusion and exclusion criteria, the selected evidence was defined, an appropriate Critical Assessment Checklist was applied.

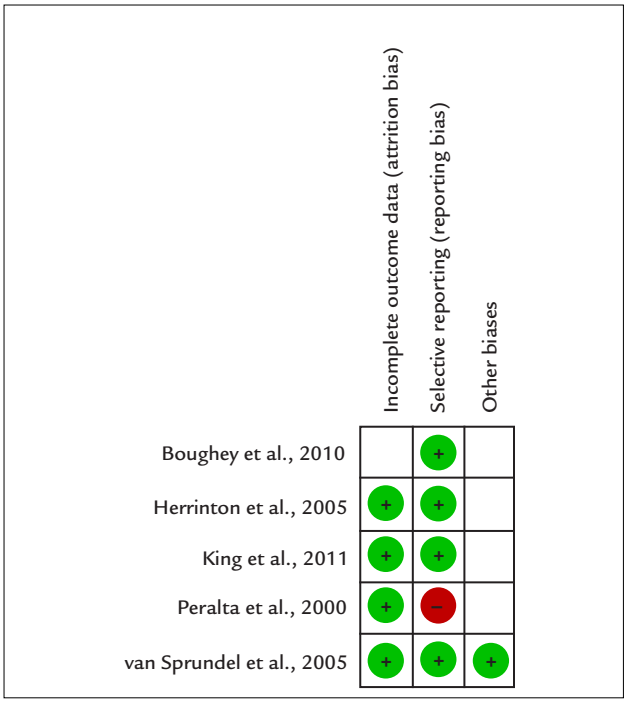

FIGURE 2 Risk of bias, author's judgment and criteria used to judge.

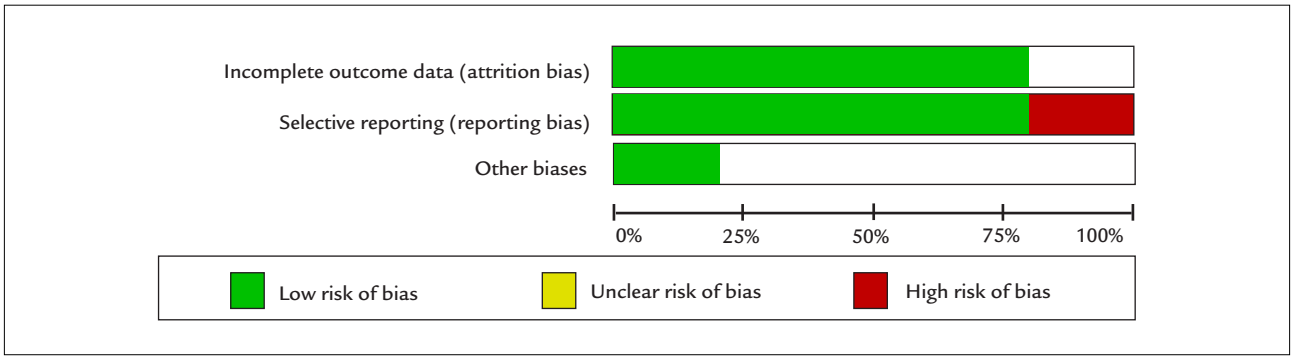

FIGURE 3 Bias risk graph expressed in percentages.

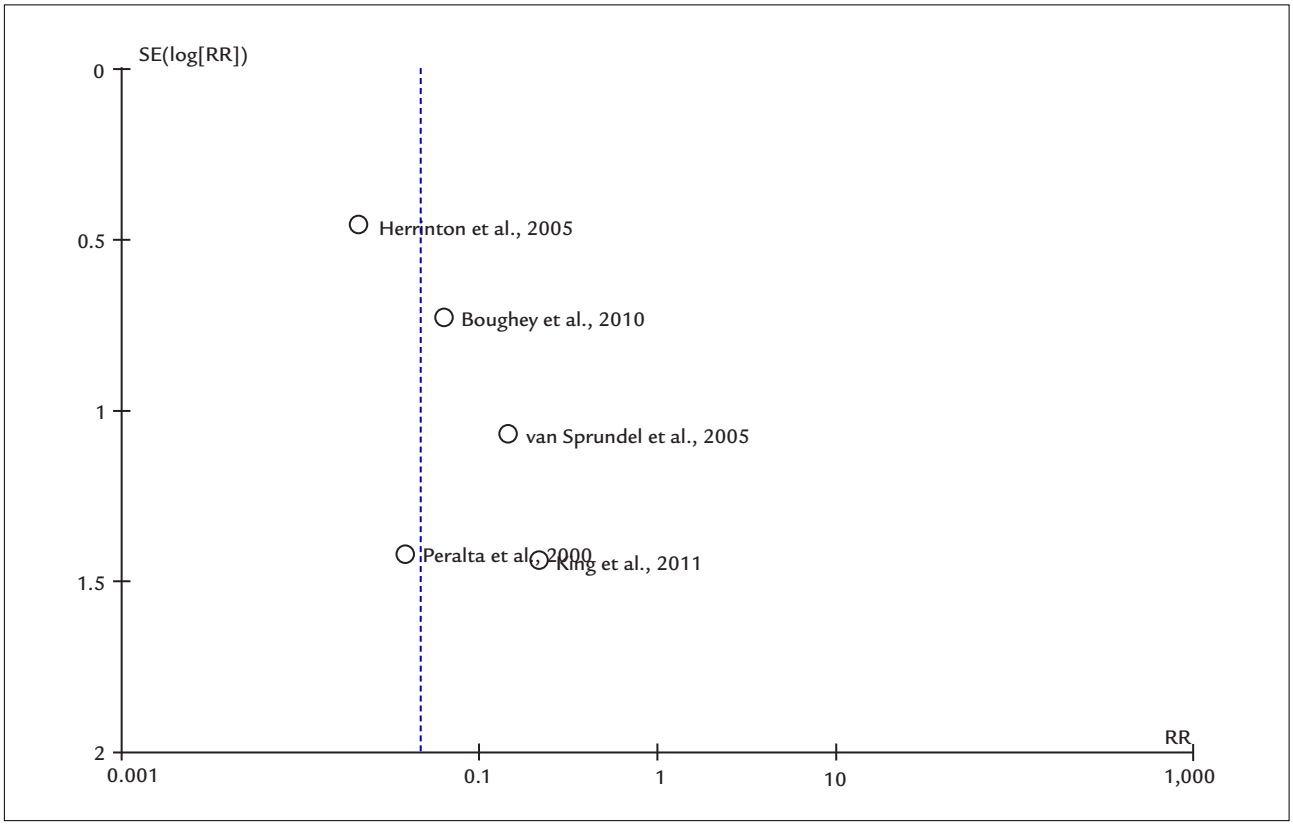

FIGURE 4 Evaluation of publication bias.

Exposure of results

The information obtained from the studies selected for the systematic review was inserted in a table where the following characteristics were described if present in the articles: author's name and year of publication, study design, number of patients who developed breast cancer, number of patients treated or not treated with contralateral prophylactic mastectomy, age, follow-up time and endpoints analyzed (Table 1).

Recommendation

The recommendations will be elaborated by the authors of the review, with the initial characteristic of synthesis of the evidence, and later validated by all the authors who participate in the elaboration of this Guideline.

The grade of recommendation stems directly from the available strength of included studies.