Prophylactic mastectomy versus surveillance for the prevention of breast cancer in women's BRCA carriers

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Citation Honold F, Camus M. Prophylactic mastectomy versus surveillance for the prevention of breast cancer in women's BRCA carriers. *Medwave* 2018 Jul-Ago;18(4):e7160

Doi 10.5867/medwave.2018.04.7160

Fecha de envío 25/1/2018
Fecha de aceptación 23/4/2018
Fecha de publicación 09/7/2018

Origin This article is a product of the Evidence Synthesis Project of Epistemonikos Fundation, in collaboration with Medwave for its publication

Type of review Non-blinded peer review by members of the methodological team of Epistemonikos Evidence Synthesis Project

Potential conflicts of interest The authors do not have relevant interests to declare.

Abstract

Introduction

Women who have mutations in BRCA genes have a high risk of developing breast cancer. Therefore, multiple preventive strategies have been proposed, within which is prophylactic mastectomy. Considering physical and psychological effects of surgery, the controversy is established as to whether the preventive effect exceeds that of active vigilance.

Methods

To answer this question we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified 13 systematic reviews including 50 studies overall. We concluded prophylactic mastectomy is associated with frequent adverse effects, but probably reduces the incidence of breast cancer and decreases mortality, in addition to being associated with high levels of satisfaction.

Problem

Breast cancer has become a relevant public health problem, being one of the leading causes of cancer in women in some countries, and a leading cause of mortality. Mutations in BRCA1 and 2 genes are present in 1 of 300-500 people in the general population and confer 80% lifetime risk of developing breast cancer. Hereditary breast cancer is associated with mutations in the BRCA1 and BRCA2 genes in 40-50% of cases.

With the advancement of technology for genetic diagnosis, the detection of these genes has become more common, opening questions related to which interventions could reduce the incidence of this disease.

Several interventions have been considered, including active surveillance (periodic clinical examination plus imaging tests such as mammography, echotomography or magnetic resonance) and chemoprophylaxis. Prophylactic mastectomy has gained popularity in the last years, but there is a high level of controversy.

Key messages

- Prophylactic mastectomy decreases the risk of developing breast cancer, and the mortality from any cause.
- Prophylactic mastectomy is frequently associated with adverse effects such as: lower sensitivity, pain, tingling, infections, among others.
- Patients who underwent a prophylactic mastectomy might have high levels of satisfaction with their decision and with the cosmetic results of the procedure, and better levels of psychological well-being, but the certainty of this evidence is low.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found 13 systematic reviews[1-13] including two randomized trials[46,55] and 48 observational studies[14-68]. However, the two trials[46],[55] did not include the outcomes selected and analyzed in this article. Only 32 studies[14-45] reported the outcomes of interest. So, this table and the summary in general are based on the latter.
What types of patients were included*	The 32 studies[14-45], included adult women (between 18 and 80 years), with a positive test for BRCA1,BRCA2 or both,who did not have breast cancer before or during prophylactic mastectomy or at the start of surveillance.
What types of interventions were included*	Only seven studies[14-20] compared prophylactic mastectomy versus surveillance. The rest of the studies were based on interviews and questionnaires and only report information on women receiving prophylactic mastectomy. The intervention was any type of mastectomy performed to prevent breast cancer (subcutaneous, wholly or simple, modified radical mastectomy and radical mastectomy). The surveillance included any type of follow-up seeking to prevent breast cancer: annual breast exams, mammography, ultrasound, magnetic resonance and core biopsy, among others.
What types of outcomes were measured	The outcomes, according to how they were grouped in the identified systematic reviews, were: Incidence of breast cancer, mortality (any cause), physical impact after the intervention, satisfaction with the decision of prophylactic mastectomy, satisfaction with cosmetic results, psychosocial well-being, body image, sexuality, impact of mastectomy on relationship, incidence of other cancers, etc.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Summary of Findings

The information on the effects of prophylactic mastectomy compared to surveillance in women carrying a BRCA mutation is based on observational studies that included 6,328 patients[14-45].

Only seven studies reported the incidence of breast cancer after prophylactic mastectomy or surveillance (2791 patients)[14-20] and three studies measured mortality from any cause (1292 patients)[14,18,19]. Ten studies reported information on negative physical impact (2287 patients)[17,21-29], 12 on satisfaction regarding the decision to have a prophylactic mastectomy (1464 patients)[23,27,28,30-38], six on satisfaction regarding the cosmetic aspect of the surgery (1025 patients)[27,30,31,33,39,40] and 13 on psychological well-being of patients undergoing prophylactic mastectomy (1307 patients)[23,26,29,31-34,37,41-45]. It was not possible to reanalyze the data from the primary studies on these last four outcomes, so the information was used as presented by the systematic reviews.

The summary of findings is the following:

- Prophylactic mastectomy prevents breast cancer in women carrying BRCA mutations. The certainty of the evidence is high.
- Prophylactic mastectomy decreases mortality in women carrying BRCA mutations. The certainty of the evidence is high.
- Prophylactic mastectomy probably has a negative physical impact in women carrying BRCA mutations. The certainty of the evidence is moderate.
- Prophylactic mastectomy might decrease depressive symptoms and anxiety in women carrying BRCA mutations, but the certainty of the evidence is low.
- Prophylactic mastectomy might be associated with a high level of satisfaction with the decision in women carrying BRCA mutations, but the certainty of the evidence is low.
- Prophylactic mastectomy might be associated with a high level of satisfaction with the cosmetic outcome in women carrying BRCA mutations, but the certainty of the evidence is low.

Prophylactic mastectomy in women carrying BRCA mutations				
Patients	Women carrying BRCA mutations			
Intervention	Prophylactic bilateral mastectomy			
Comparison	Surveillance			
Outcome	**Absolute effect***		**Relative effect (95% CI)**	**Certainty of evidence (GRADE)**
	WITH surveillance	WITH prophylactic mastectomy		
	Difference: patients per 1000			
Incidence of breast cancer	245 per 1000	12 per 1000	RR 0.05 (0.02 to 0.1)	⊕⊕⊕⊕[1,2] High
	Difference: 233 patients less (Margin of error: 12 less to 8 more)			
Mortality from any cause	92 per 1000	11 per 1000	RR 0.12 (0.04 to 0.36)	⊕⊕⊕⊕[1,2] High
	Difference: 81 patients less (Margin of error: 22 less to 8 more)			
Negative physical impact	Up to 64% of women presented physical adverse effects after prophylactic mastectomy[2,8,9,12]. Among these were: lower sensitivity, pain, tingling, infection, edema, contracture, bruising, failed reconstruction, thrombosis and pulmonary embolism.		---	⊕⊕⊕○[1,3] Moderate
Psychosocial well-being	Anxiety and depressive symptoms decreased after surgery, mainly due to decreased fear of cancer[7,8,12].		---	⊕⊕○○[1,3,4] Low

Satisfaction with the decision	Most women who underwent prophylactic mastectomy not regretted their decision and would recommend it to another woman[7,9,12].	---	⊕⊕◯◯[1,3,4] Low
Satisfaction with cosmetic result	Most women who underwent prophylactic mastectomy were satisfied with the cosmetic results of the surgery[12].	---	⊕⊕◯◯[1,3,4] Low

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
GRADE: Evidence grades of the GRADE Working Group (see later).

*The risk WITH surveillance is based on the risk in the control group of the trials. The risk WITH prophylactic mastectomy (and its margin of error) is calculated from the relative effect (and its margin of error).

[1] Studies are not randomized trials.
[2] We upgraded two levels of certainty of the evidence for the magnitude of the effect (RR <0.2).
[3] We upgraded one level of certainty of the evidence given the effect of high magnitude.
[4] We downgraded one level of certainty since there were studies of moderate and high risk of bias that constituted a significant proportion of patients.

Follow the link to access the interactive version of this table (Interactive Summary of Findings – iSoF)

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

Other considerations for decision-making

To whom this evidence does and does not apply

The evidence presented in this summary is applicable to women with a positive result in a screening test for BRCA gene identification.

It is debatable to apply the results of this article to women with other high-risk factors, such as strong family history of breast cancer. However, in the absence of direct evidence in these cases, this summary could be useful.

It is not applicable to women who have a moderate- or low-risk of breast cancer.

The conclusions of this summary apply to the comparison between prophylactic mastectomy and the usual active surveillance of patients carrying BRCA mutations. Therefore, they do not allow us to state what the benefit is against an optimal surveillance strategy that involves: medical check-ups since the age of 25 with a mammary exam every 6 or 12 months; annual mammograms 10 years before the age of presentation of the first case of family breast cancer or, failing the latter, at age of 30; or annual magnetic resonance study with contrast.

About the outcomes included in this summary

The outcomes included in the summary of findings table are those considered critical for decision-making by the authors of this summary.

The outcomes physical impact, psychological well-being, satisfaction with the decision and satisfaction with the cosmetic result are not comparative with a population under surveillance, so it is not possible to estimate the effect.

Regarding the physical impact outcome, the trials that measured it were based on interviews and questionnaires applied to patients after the surgery.

Regarding the psychosocial well-being outcome, some studies used scales such as: Hospital Anxiety and Depression Scale[41] and CES-D[33,37].

The outcome "satisfaction with the decision" was measured through questionnaires and interviews. According to the included trials, the reduction in cancer risk would help explain the high acceptance of the surgery. In addition, a relationship could be observed between the patient's age and the level of satisfaction, showing that the younger the patient, the lower the level of satisfaction.

The outcome 'satisfaction with the cosmetic result' refers to the expectations that the patients had before the surgery, so it is not necessarily consistent with the optimal result of the surgery. It was noted that this outcome is more dependent on the results of reconstruction and its complications. However, a minority of patients chose not to perform the reconstruction and 100% of these patients had high levels of satisfaction in all the studies.

Balance between benefits and risks, and certainty of the evidence

It is an intervention with clear benefits and could be associated with high levels of satisfaction. Although it probably entails adverse effects, the balance between benefits and risks is favorable.

Resource considerations

One study[69] showed that prophylactic mastectomy would be more costeffective than surveillance in high-risk patients due to a strong family history, but it is unknown whether these patients have BRCA mutations.It is reasonable to believe this could also be costeffective to patients with BRCA tests already performed.

It must be considered that there are costs associated with BRCA gene detection, which are high and are not widely available.

The consequences of performing this type of screening can go beyond changes in clinical management. For example, it can influence health insurance, raising the policies due to the pre-existence of illness.

Therefore, it is reasonable to conduct a formal economic analysis in the places where this intervention is being considered, including the value of the genetic study and the cost of surgery.

What would patients and their doctors think about this intervention?

Faced with the evidence presented in this summary, most patients and clinicians should lean in favor of the intervention. However, it is expected that there will be variability in decision-making because it is an intervention with a strong emotional charge, and there are important preconceived ideas.

It is likely that resource considerations will strongly influence the decision, especially in cases where the intervention is not covered by the health system or the corresponding insurance.

Differences between this summary and other sources

The conclusions of this summary agree with those presented by the different systematic reviews identified.

The conclusions of this summary also agree with the main clinical guidelines. For example, the NCCN guideline (National Comprehensive Cancer Network)[70] recommends prophylactic surgery to women carrying BRCA mutations since it significantly reduces the incidence of breast cancer. Furthermore, it emphasizes providing information about the adverse effects and implications of the surgery. The ESMO guideline also recommends prophylactic mastectomy and ensures it is the most effective intervention in terms of preventing breast cancer in women with mutations in BRCA genes[71].

Could this evidence change in the future?

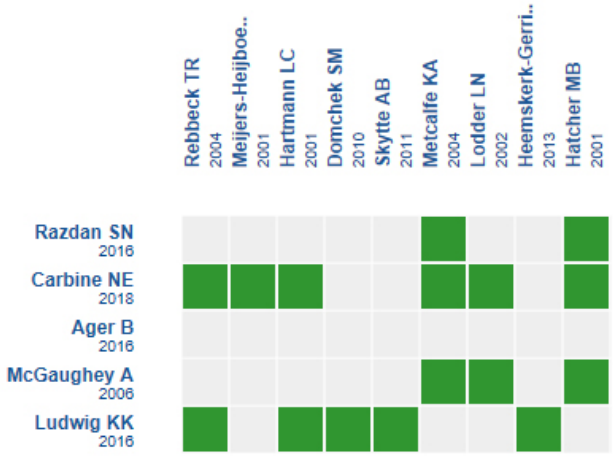
The probability that the conclusions of this summary change with future research is low, due to the certainty of the evidence, especially with regard to the incidence of breast cancer and mortality. However, the probability of future research changing the conclusions about physical morbidity and quality of life is high, given the existing uncertainty.

There are several systematic reviews in progress evaluating various aspects of prophylactic surgery such as: the effectiveness of the intervention [72], the psychosocial impact[73],[74], quality of life after the intervention [75] and the costeffectiveness of the procedure [76].

Regarding clinical trials, only one ongoing trial was identified that intends to measure the decision-making of patients in relation to prophylactic mastectomy [77].

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

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