

## EFFECTIVENESS OF NEW SURGICAL TECHNIQUES, HORMONAL THERAPIES AND IMMUNOTHERAPIES IN REDUCING THE RISK OF OVARIAN CANCER

---

***Bruno Teixeira Marcos Moraes***

Centro Universitário Barão de Mauá -  
CUBM  
Ribeirão Preto -SP  
<https://orcid.org/0000-0003-2763-0398>

***Camila França Rocha***

Centro Universitário Imepac - IMEPAC  
Araguari - MG  
<https://orcid.org/0009-0002-0165-3831>

***Lara Dias Cardoso Ribeiro***

Faculdade de Ciências Médicas de São José  
dos Campos - Humanitas  
São José dos Campos - SP  
<https://orcid.org/0009-0002-1171-4124>

***Luana Sula Sousa dos Reis Araújo***

Universidade Paranaense - UNIPAR  
Umuarama - PR  
<https://orcid.org/0000-0002-3408-1967>

***Isabella Vitória Sousa Soares Tomiazzi***

Centro Universitário Maurício de Nassau de  
Cacoal - UNINASSAU  
Cacoal - RO  
<https://orcid.org/0009-0005-3261-4490>

All content in this magazine is licensed under a Creative Commons Attribution License. Attribution-Non-Commercial-Non-Derivatives 4.0 International (CC BY-NC-ND 4.0).



***Sophia Bermal Oliveira***

Universidade de Santo Amaro - UNISA  
São Paulo - SP  
<https://orcid.org/0009-0006-3960-9616>

***Leticia Almeida de Santis***

Universidade Santo Amaro - UNISA  
São Paulo- SP  
<https://orcid.org/0009-0008-8137-0981>

***Lethicia Costa Pardino***

Faculdade Pitágoras de Medicina de  
Eunápolis  
Eunápolis - BA  
<https://orcid.org/0009-0004-3619-3112>

***Maria Eduarda Gaigher Biazus***

Universidade para o Desenvolvimento do  
Estado e Região do Pantanal - UNIDERP  
Campo Grande- MS  
<https://orcid.org/0009-0002-4864-5855>

***Ana Beatriz Maria Da Costa***

Universidade Cidade de São Paulo - UNICID  
São Paulo - SP  
<https://orcid.org/0009-0002-9349-4005>

***Anna Gabriela da Rocha Pereira***

Centro Universitário Euro Americano -  
UNIEURO  
Brasília - DF  
<https://orcid.org/0009-0008-2462-6338>

***Josenil Bezerra Nascimento Neto***

Universidade Estadual do Piauí - UESPI  
Teresina - PI  
<https://orcid.org/0000-0001-7893-7803>

**Abstract:** OBJECTIVE: To evaluate the effectiveness of new surgical techniques, hormonal therapies and immunotherapies in reducing the risk of ovarian cancer. METHODOLOGY: This is a bibliographic review developed according to the criteria of the PVO strategy. The searches were carried out in the PubMed and SciELO databases. After associating the descriptors used in the researched databases, 14 studies were selected to compose the collection. DISCUSSION: Ovarian cancer is the fifth leading cause of cancer death in women. Patients considered at risk include those who have first-degree relatives affected by ovarian cancer, obesity, smoking, and mutations in the BRCA1 and BRCA2 genes. Prophylactic oophorectomy is a minimally invasive surgical procedure that involves laparoscopic removal of the adnexa and endometrial biopsy. High-grade serous ovarian cancer has a poor prognosis due to the limited effectiveness of currently available chemotherapies. Hormone replacement with estrogen, when properly performed after risk-reducing salpingo-oophorectomy (RRBSO), helps control postmenopausal symptoms. Chemotherapy can induce amenorrhea in 60% to 80% of premenopausal women who receive adjuvant treatment. CONCLUSION: Ovarian cancer requires an approach that provides more information to the population. Chemoprevention, whether natural or synthetic, is an effective alternative, unlike immunotherapy, which has limited and more specific efficacy.

**Keywords:** Ovarian Neoplasms; Oophorectomy; Immunotherapy; Hormone Therapy; Genetic predisposition.

## INTRODUCTION

Ovarian neoplasia is the gynecological cancer with the highest mortality rate in the United States, with approximately 70% of patients affected by the disease in an advanced

stage. Despite being a disease with low prevalence, the incidence is much higher in women with genetic predisposition, especially those with BRCA1 and BRCA2 mutations. The risk of developing cancer for BRCA1 is 39-46% and for BRCA2 is 10-28% at age 70 (LEWIS et al., 2018). However, ovarian cancer often has nonspecific symptoms, such as pelvic/abdominal pain, polyuria, urinary urgency and edema, which makes diagnosis difficult (JAMMAL et al., 2017). Therefore, this type of neoplasm is often identified when it is already in an advanced stage, which highlights the importance of prophylactic measures, especially in patients with a genetic predisposition.

In view of this, it is clear that there are several therapies and surgical techniques to prevent the development of ovarian neoplasia, with oophorectomy being the most indicated currently. Research has shown that this surgery can reduce the risk of developing the disease by up to 80% (LEWIS et al., 2018). However, due to the various effects of the surgery, such as the induction of early menopause accompanied by symptoms such as hot flashes, lack of vaginal lubrication, low libido, among others (JAMMAL et al., 2017), in addition to the impossibility of becoming pregnant naturally, studies have sought new surgical techniques, immunotherapies and hormonal therapies to avoid these consequences, which can considerably affect the quality of life of these women.

Pathogenic mutations in the BRCA gene are linked to an increased risk of hereditary ovarian cancer, which tends to manifest at younger ages, with an average age of 50 years for ovarian cancer caused by mutations in the BRCA1 gene. Due to these risk factors, it is necessary to establish preventive strategies during the reproductive years. If a woman is identified as a BRCA gene mutation carrier, it is essential to implement rigorous

and specialized surveillance to enable early diagnosis, as there is a significant risk of developing ovarian cancer at a younger age (DOREN et al., 2018).

There are risk reduction strategies for breast and ovarian cancer, which include surgery and/or chemoprevention. Risk-reducing salpingo-oophorectomy (RRSO) surgery has been effective in reducing the risk of ovarian cancer by 85-90%. Bilateral salpingectomy has also been proposed as a risk reduction surgery for ovarian cancer, but it is still under study (DOREN et al., 2018). Concerns regarding the risks associated with oophorectomy in premenopausal women, such as osteoporosis, cardiovascular and neurological diseases, as well as an increase in overall mortality, may influence the decision to opt for RRSO (DOREN et al., 2018).

The aim of this literature review is to evaluate the effectiveness of new surgical techniques, hormonal therapies and immunotherapies in reducing the risk of ovarian cancer in genetically predisposed women who opt for prophylactic oophorectomy. The benefits and risks associated with these treatment options will be considered, analyzing the best approach for preventing ovarian cancer in these patients.

## **METHODOLOGY**

This is a bibliographic review developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. The strategy was used for the development of the research through the guiding question: "What is the effectiveness of new surgical techniques, hormonal therapies and immunotherapies in reducing the risk of ovarian cancer in women with genetic predisposition who opt for prophylactic oophorectomy?". In this sense, according to the parameters mentioned above, the population or problem of this

research refers to female patients with genetic predisposition who opt for prophylactic oophorectomy for treatment and prevention of ovarian cancer.

The searches were carried out through searches in the PubMed and SciELO databases.

The following descriptors were used in combination with the Boolean term "AND": Ovarian Neoplasms; Oophorectomy; Genetic predisposition to ovarian neoplasms; immunotherapy; hormone therapy and genetic predisposition. The articles were submitted to the selection criteria: articles in English and Portuguese; published in the period from 2017 to 2022 and that addressed the themes proposed for this research, studies of the type (review, meta-analysis and cohort), available in full. Exclusion criteria were: duplicate articles, available only in summary form, which did not directly address the studied proposal and which did not meet the other inclusion criteria. After associating the descriptors used in the searched databases, a total of 77 articles were found. Of which, 57 articles belonged to the PubMed database and 20 articles to SciELO. After applying the inclusion and exclusion criteria, 12 articles were selected from the PubMed database and 2 articles from SciELO, using a total of 14 studies to compose the collection.

## RESULTS

### PROPHYLACTIC OOPHORECTOMY

According to Ricciardi et al. (2017), currently, ovarian cancer is the fifth leading cause of death from cancer in women, and it is necessary to seek prevention strategies for this disease. Patients considered to be at risk include those who have first-degree relatives affected by ovarian cancer, obesity, smoking, mutations in the BRCA1 and BRCA2 genes. Women carrying these mutations have an approximate risk of 17% and 44% of developing

ovarian cancer, and an average of 65% and 72% of developing breast cancer, respectively (Gaba; Manchanda, 2020). In addition, the use of postmenopausal hormone therapy is also considered a risk factor (CHENG et al., 2020).

For the control and reduction of previous cell and tissue damage, women with these risk factors can undergo different strategies, including intensive screening, since ovarian cancer is usually asymptomatic for a long time, and prophylactic oophorectomy, which reduces the risk of ovarian cancer by more than 95% (RICCIARDI et al., 2017).

Prophylactic oophorectomy is a minimally invasive surgical procedure that involves laparoscopic removal of the adnexa, collection of peritoneal lavage cytology and endometrial biopsy (CHENG et al., 2020). Minimally invasive hysterectomy must only be considered during prophylactic oophorectomy in cases of associated risk of uterine cancer. After prophylactic oophorectomy, follow-up of these patients must continue, including gynecological examination, pelvic ultrasound and CA-125 measurement every 6 months, in addition to breast cancer screening, as is commonly performed (PAFFENHOLZ et al., 2022).

Furthermore, according to Gaba; Manchanda (2020), risk-reducing salpingo-oophorectomy (RRSO) is considered the gold standard for reducing the risk of ovarian cancer, as there is no effective national screening program for this disease. RRSO is generally offered from ages 35-40 for BRCA1 carriers and 40-45 years for BRCA2 carriers. However, there are risks associated with performing the surgery, such as low hormone production, mainly estrogen, which can lead to loss of libido, dyspareunia and vasomotor symptoms (LEWIS et al., 2018).

Women at high risk of tubo-ovarian cancer are advised to consider prophylactic

oophorectomy at age 35 if they are BRCA1 carriers or at age 40 if they are BRCA2 carriers, or at later times after completion of pregnancy. This also applies to women who test negative for BRCA gene mutations but have two or more risk factors, one of which is obligate genetic load. Opportunistic salpingectomy, performed during other benign gynecological surgery, has been recommended as a primary preventive strategy for low-risk women.

Furthermore, as an alternative for patients who do not wish to undergo surgery or who do not meet the criteria, chemoprevention with the use of natural or synthetic agents, as well as oral contraceptives, has been suggested, since these methods have inhibitory effects. In ovulation, reducing the risk of ovarian cancer in carriers of mutations in the BRCA1 and BRCA2 genes (LEWIS et al., 2018). Therefore, it is clear that decision-making regarding the procedure is a complex process, involving conflicting considerations, requiring adequate time for the woman to analyze the numerous informed factors and receive appropriate advice (Gaba; Manchanda, 2020).

## **HORMONE THERAPIES IN PREVENTION**

The surgical procedure has consequences that can be harmful, such as the induction of menopause, which affects the quality of life and reduces the patient's life expectancy. To mitigate these consequences, it is possible to use hormone replacement therapy (HRT). However, there is a debate regarding the safety of using hormones by patients with mutations in the BRCA1 and BRCA2 genes. It is suspected that HRT, especially in BRCA2 mutation carriers, may affect the development of breast cancer, even in patients who have already undergone RRBSO (SILVA et al., 2020).

Although there are fewer studies on the use of HRT in BRCA2 gene mutation carriers,

Vermeulen et al. (2019) indicate that guidelines are against the use of HRT in women with a history of breast cancer. However, they agree with Eleje et al. (2018) when stating that short-term use does not invalidate the protection offered by salpingo-oophorectomy in relation to the future risk of breast cancer in BRCA1/2 mutation carriers, until they reach natural menopause around 50 years of age. In addition, there is evidence to indicate that HRT may have a positive effect on menopausal symptoms, such as hot flashes, in BRCA1/2 mutation carriers after RRBSO. Considering the risks of the procedure in younger women before natural menopause, HRT can be recommended after performing surgery before the age of 50 (Huber et al., 2021).

There is also a consensus between Silva et al. (2020) and Vermeulen et al. (2019) regarding the greater effectiveness of estrogen-only therapy, rather than a combination with progesterone, especially in women who have undergone prophylactic salpingo-oophorectomy and no longer have a uterus. The absence of progesterone can cause endometrial wall thickening in women with a remnant uterus (VERMEULEN et al., 2019). Hormone replacement with estrogen, when properly performed after RRBSO, helps control postmenopausal symptoms and prevents chronic diseases associated with reduced estrogen levels, such as osteoporosis and myocardial infarction (Huber et al., 2021). In addition, improvements are observed in the quality of life of women who undergo hormone replacement therapy after prophylactic salpingo-oophorectomy, such as a reduction in vasomotor symptoms, improvement in sexual function and a decrease in the likelihood of bone diseases (SILVA et al., 2020).

## IMMUNOTHERAPY IN THE TREATMENT AND PREVENTION

High-grade serous ovarian cancer is a cancer with a poor prognosis due to the limited effectiveness of currently available chemotherapies and immunotherapies. For most cases, treatment involves surgical debulking and platinum/taxane-based chemotherapy. However, the outcome of treatment may be transient and resistance to cancer may emerge (PAFFENHOLZ et al., 2021).

According to Morand et al. (2021), ovarian cancer response to immunotherapy is limited. However, studies involving tumor biomarkers increase the likelihood of success with immunotherapy in ovarian cancer. The assessment of targeted treatment-sensitive/resistant subpopulations, based on stratification by tumor biomarkers, may improve the prediction of response to immunotherapy. Studies involving immunostimulating cytokines, tumor antigen vaccines and monoclonal antibodies directed at immunosuppressive ligands expressed by tumor cells increase the anticancer immune response through multiple immunotherapeutic approaches (MORAND et al., 2021).

However, due to ovarian cancer being in a complex immunologic setting, more than one biomarker may be needed for accuracy. Combined therapy seems to be a good option to obtain benefits against cancer, but in-depth studies of the effectiveness and the risk that can be caused are needed (MORAND et al., 2021).

Immunotherapy is one of the new therapeutic strategies under investigation for ovarian cancer. It aims to induce or potentiate active immune responses directed at the tumor and consolidate the antitumor effects of standard therapy, delaying and possibly preventing the progression of the disease.

Antigen-specific active immunotherapy aims to activate the adaptive immune system directed to a specific target antigen through the administration of a molecularly defined antigen-specific vaccine to the patient (PAIJENS et al., 2018).

An antigen is a molecule, usually a protein or polysaccharide, that can stimulate an immune response. Tumor antigens can be subdivided into different categories such as mutated self-proteins, oncogene products (e.g. Her-2/Neu), mutated tumor suppressor genes (e.g. p53) and aberrantly expressed self-proteins (e.g. sperm 17, MAGE-1). Monoclonal antibodies can induce anti-idiotypic antibodies (Ab2), directed mainly against the administered monoclonal antibody, as well as anti-anti-idiotypic antibodies (Ab3), directed to the target antigen (PAIJENS et al., 2018).

Systemic adverse events resulting from immunotherapy can be subdivided into autoimmunity, allergic reactions and other adverse events occurring after immunization (PAIJENS et al., 2018). Additionally, studies have reported local adverse events following local administration of the vaccine, such as inflammatory responses, ulceration, and/or abscesses at the injection site (BERINSTEIN 2012; BERINSTEIN 2013; FREEDMAN 1998; GRIBBEN 2005; PAIJENS et al., 2018).

Chemotherapy can induce amenorrhea in 60% to 80% of premenopausal women who receive adjuvant treatment (Bines 1996; Walshe 2006). Women who become amenorrheic after chemotherapy have better disease-free survival than those who do not, especially in the case of hormone-sensitive disease (Bui et al., 2020).

For women undergoing ovarian ablation in the absence of chemotherapy, a 25% reduction in annual odds of recurrence has been reported, along with a 24% reduction in annual odds of death (BUI et al., 2020).

Therapy-related adverse events include hot

flashes, mood disturbances, reduced bone density, arthralgias, altered sexual function, increased cardiovascular risk, deep vein thrombosis, pulmonary embolism, impaired cognitive function, treatment-related death, and others. significant toxicities reported by studies. These toxicities can be defined according to the World Health Organization (WHO)/National Cancer Institute of Canada (NCIC) toxicity criteria or according to the study in question (BUI et al., 2020).

## CONCLUSION

Ovarian cancer needs an approach that generates more information for the population, considering its initially asymptomatic evolution and its worse prognosis if associated with the presence of risk factors such as first-degree relatives with a history of ovarian cancer,

obesity, smoking mutations in the BRCA 1 and BRCA2 genes. However, it is possible to carry out preventive treatments, which reduce the chances of developing ovarian cancer by up to 95%, such as prophylactic oophorectomy, and RRSO, considered the gold standard. However, as with any surgical procedure, such prophylactic measures may have adverse effects, such as early menopause, loss of libido, among others, and this type of surgery is directed to women over 35 years of age, in order to postpone treatment with hormone replacement therapy, for example. Thus, as an alternative for patients who do not wish to undergo surgery, it was concluded that natural or synthetic chemoprevention is an effective alternative, unlike immunotherapy, which has limited and more specific efficacy.

## REFERENCES

- BUI K.T., et al. Ovarian suppression for adjuvant treatment of hormone receptor-positive early breast cancer. **Cochrane Database of Systematic Reviews**, 2020.
- CHENG, A. et al. Pathological findings following risk-reducing salpingo-oophorectomy in BRCA mutation carriers: A systematic review and meta-analysis. **European Journal of Surgical Oncology**, v. 46, n. 1, p. 139-147, 2020.
- DOREN, A. et al. Gynecological-endocrinological aspects in women carriers of BRCA1/2 gene mutations. **Climacteric**, v. 21, n. 6, p. 529-535, 2018.
- ELEJE, G. U. et al. Salpingo-ooforectomia bilateral com redução de risco em mulheres com mutações BRCA1 ou BRCA2. **Cochrane Database of Systematic Reviews**, n. 8, 2018.
- GABA, F. e MANCHANDA, R. Systematic review of acceptability, cardiovascular, neurological, bone health and HRT outcomes following risk reducing surgery in BRCA carriers. **Best Practice & Research Clinical Obstetrics & Gynaecology**, v. 65, p. 46-65, 2020.
- HUBER, D. et al. Terapia de reposição hormonal em portadores de mutação BRCA e risco de câncer de ovário, endométrio e mama: uma revisão sistemática. **Journal of Cancer Research and Clinical Oncology**, v. 147, n. 7, p. 2035-2045, 2021.
- JAMMAL, M. P. et al. A prevenção do câncer de ovário ainda é uma recomendação de nossos avós? **Revista Brasileira de Ginecologia e Obstetria**, v. 39, p. 676-685, 2017.
- LEWIS, K. E. et al. Recommendations and choices for BRCA mutation carriers at risk for ovarian cancer: a complicated decision. **Cancers**, v. 10, n. 2, p. 57, 2018.
- MORAND, S. et al. Imunoterapia do câncer de ovário e medicina personalizada. **International Journal of Molecular Sciences**, v. 22, n. 12, p. 6532, 2021.

PAFFENHOLZ, S. V. et al. A indução da senescência determina a resposta à quimioterapia e imunoterapia em modelos pré-clínicos de câncer de ovário. **Proceedings of the National Academy of Sciences**, v. 119, n. 5, p. e2117754119, 2022.

PAIJENS, S. T. et al. Imunoterapia ativa antigênica específica para câncer de ovário. **Cochrane Database of Systematic Reviews**, n. 9, 2018.

RICCIARDI, E. et al. Risk-reducing Salpingo–Oophorectomy in Women at Higher Risk of Ovarian and Breast Cancer: A Single Institution Prospective Series. **Anticancer Research**, v. 37, n. 9, p. 5241-5248, 2017.

SILVA F. A. L. et al. Hormone therapy after risk-reducing surgery in patients with BRCA1/BRCA2 mutation: evaluation of potential benefits and safety. **Revista da Associação Médica Brasileira**, v. 66, p. 1134-1138, 2020.

VERMEULEN, R. F M. et al. Segurança da terapia de reposição hormonal após salpingo-ooforectomia redutora de risco: revisão sistemática da literatura e diretrizes. **Climatério**, v. 22, n. 4, p. 352-360, 2019.