REVIEW ARTICLE
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# Should the use of hormones for contraception and during menopause be contraindicated in women with high-penetrance mutations?

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## ABSTRACT

Medical genetics is one of the fields with the greatest advancements in medical knowledge. The discovery of genes that determine greater susceptibility to certain neoplasms has motivated a vast amount aimed at determining the best management of patients with these mutations. The use of hormones, both as contraception and during menopause, for these women is a subject of ongoing debate — given their involvement in the pathophysiology of breast neoplasia. This article, therefore, aims to review the available literature on the topic. Thirteen publications were selected for narrative review. Regarding contraception, individualized assessment of these patients is still paramount in indicating hormonal contraception, with no formal contraindication to its use for patients with high-penetrance mutations. Regarding hormone therapy (HT), there are also no absolute contraindications. Consideration is only given to patients who have not undergone mastectomy. In such cases, HT can be considered for short periods, ideally using micronized progesterone in patients with a uterus.

KEYWORDS: hormone therapy; mutation; contraception.

## INTRODUCTION

The use of hormones for contraception and in the management of menopausal symptoms in women with high-penetrance genetic mutations is a complex decision with significant clinical relevance[1]. High-penetrance genes for breast cancer are those that increase the relative risk of developing the disease phenotype by at least five times during a lifetime. Currently, the National Comprehensive Cancer Network (NCCN) includes the genes BRCA1, BRCA2, TP53, PTEN, CDH1 e PALB2[2].

The safety of using exogenous hormones in women genetically predisposed to cancer is a continuous focus of research. Hormone therapy (HT) and contraceptives act directly on tissues that express hormone receptors and slightly increase breast cancer risk in the general population[2]. In patients with high genetic risk, increased hormone exposure may accelerate the development of neoplasms; therefore, updates regarding their impact on clinical practice must continue to be encouraged.

## METHODOLOGY

A literature review on the topic was conducted using the PubMed, Cochrane, and SciELO databases. No restriction was applied regarding the year of publication. The following search terms were used: "hormone therapy and mutation", "contraception and mutation", "BRCA", "hormone and BRCA", "BRCA hormone therapy", and "menopause".

At the end of the analysis, 13 publications were selected, including nine reviews, three of which included meta-analyses. Among the selected articles, there is also one randomized clinical trial, one prospective cohort study, and two guidelines from international medical entities: the NCCN and the American College of Obstetricians and Gynecologists (ACOG). All selected articles and their respective methodologies are presented in Table 1.

### Contraception in mutated women

Hormonal contraception includes multiple possible routes of administration. Its advantages include high effectiveness and

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control of symptoms of diseases such as endometriosis, premenstrual dysphoric disorder, and polycystic ovary syndrome. Most studies evaluating hormonal exposure have primarily investigated oral contraceptives (COCs) and their association with BRCA1/2, due to their higher prevalence, but recommendations are extended to other genes as well[3].

The impact of hormonal contraceptive use in patients with high-penetrance mutations remains controversial. Some studies suggest an increased risk of breast cancer among COC users, particularly those with BRCA1 mutations and associated with duration of exposure. Bommel et al. reported a small increased risk in a meta-analysis based on studies with moderate heterogeneity. However, its proven protective effect against ovarian cancer highlights the importance of individualized decision-making[4].

Phillips et al.[5] described a slight increase in breast cancer risk compared to non- exposed individuals, although without statistical significance. No association was found between early initiation of use or initiation after the first pregnancy[5]. There was an association with cumulative use for BRCA1. In the same study, the analysis of 191 BRCA2-mutated patients did not report an association between oral contraceptive use and breast cancer risk, even with cumulative exposure.

Regarding the use of contraceptives in patients with the mutation, recommendations from both the NCCN and ACOG are similar, not completely contraindicating their use outright[2,6]. Both emphasize the challenges in interpreting data given the lack of homogeneity in studies and highlight the importance of considering good birth control associated with the reduction in ovarian and endometrial cancer risk with these medications. They also emphasize, as most studies do, that the decision to use oral contraceptives in patients with the mutation should be shared by the patient and the multidisciplinary care team.

Other specific aspects of the scenario should be analyzed, such as comorbidities, previous personal history of thromboembolism or neoplasms, smoking, adherence to medication use, and tolerability of adverse effects.

## Hormone therapy in women with mutations

In climacteric syndrome, the transition from ovulatory cycles to the end of ovarian function can cause symptoms that impact

**Table 1.** Selected articles.

| Author | Study | Year of publication | Type of study |
|---|---|---|---|
| Pederson and Batur[1] | Use of exogenous hormones in those at increased risk for breast cancer: contraceptive and menopausal hormones in gene carriers and other high-risk patients | 2023 | Narrative review |
| Dwyer et al.[2] | NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2024 | 2023 | Clinical guideline |
| Robson[3] | Management of women with breast cancer and pathogenic variants in genes other than BRCA1 or BRCA2 | 2021 | Narrative review |
| Van Bommel et al.[4] | Contraceptives and cancer risks in BRCA1/2 pathogenic variant carriers: a systematic review and meta-analysis | 2023 | Systematic review and meta-analysis |
| Phillips et al.[5] | Hormonal contraception and breast cancer risk for carriers of germline mutations in BRCA1 and BRCA2 | 2024 | Prospective cohort |
| ACOG[6] | Practice Bulletin No 182: Hereditary Breast and Ovarian Cancer Syndrome | 2017 | Clinical guideline |
| Santoro et al.[7] | The menopause transition: signs, symptoms, and management options | 2021 | Narrative review |
| Writing Group for the Women's Health Initiative Investigators[8] | Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from WHI randomized controlled trial | 2002 | Randomized clinical trial |
| De Felice et al.[9] | Bilateral risk-reduction mastectomy in BRCA1 and BRCA2 mutation carriers: a meta-analysis | 2015 | Meta-analysis |
| De Felice et al.[10] | Risk-reducing salpingo-oophorectomy in BRCA1 and BRCA2 mutated patients: An evidence-based approach on what women should know | 2017 | Narrative review |
| Abenhaim et al.[11] | Menopausal hormone therapy formulation and breast cancer risk | 2022 | Narrative review |
| Marchetti et al.[12] | Hormone replacement therapy after prophylactic risk-reducing salpingo-oophorectomy and breast cancer risk in BRCA1 and BRCA2 mutation carriers | 2018 | Meta-analysis |
| Nitschke et al.[13] | Long-term non-cancer risks in people with BRCA mutations following risk-reducing bilateral salpingo-oophorectomy and the role of hormone replacement therapy: A review | 2023 | Narrative review |

quality of life. Genitourinary and vasomotor changes, alopecia, depression, and even memory alterations secondary to hypoestrogenism have been described[7]. In patients with pathogenic variants of high-penetrance genes, these symptoms can be anticipated through prophylactic bilateral salpingo-oophorectomy (SORR), indicated as soon as the family is complete[2].

Among the currently available options, HT (Hormone Therapy) remains the therapy that best controls these symptoms. It can be administered with estrogens (orally or transdermally) and progestogens in combination, in the case of non-hysterectomized patients (in oral combination or via intrauterine devices)[7].

Since 2002, with the publication of the impactful Women's Health Initiative (WHI) study on HT, there has been apprehension about its use, given its association with thromboembolic and oncological risks[8]. Although it is known to be contraindicated for patients with a prior history of breast cancer, recent studies have shown that HT may be considered for use in non-diseased patients carrying high-risk mutations[2].

The effectiveness of prophylactic surgeries in patients with high-risk mutations has been documented for decades. Both risk-reducing mastectomy (RRM) and bilateral salpingo-oophorectomy (SORR) are responsible for reducing the incidence of breast cancer by approximately 95% and 50%, respectively. With this reduction in incidence, there is the safety of administering exogenous hormones without losing the benefit of surgery[9].

C. Marchetti et al. demonstrated, in a meta-analysis, the absence of impact of hormone therapy in mutated patients undergoing risk-reducing surgery in prospective cohorts[10]. In subgroup analysis, the average duration of HT was 3.3 years and there were no differences in the estrogen-only formulation and in the combination of estrogen and progesterone, with a tendency towards less impact in the subgroup where there is only exposure to estrogen (OR=0.62; 95%CI 0.29–1.31). There is a greater tendency to prefer micronized progesterone to synthetic progestins — with a greater relationship to the increased risk of breast cancer (OR=1.28; 95%CI 1.22–1.35)[11].

It is also crucial to consider the particularities involving the BRCA1 (typically related to triple-negative tumors) and BRCA2 (largely associated with hormone receptor-positive lesions) genes. Most studies, in subgroup analysis, involved a larger number of patients with BRCA1 mutations, with scarce data for BRCA2[12]. Thus, although HT is still a viable option for the BRCA2 subgroup, it should be used with great caution due to limited data.

Practicing modern medicine requires recognizing the importance of HT when properly indicated. Promoting quality of life and reducing the risk of bone, cognitive, and cardiovascular diseases should always encourage its use[13]. If contraindicated, treatment should also be guided by an understanding of the greater risk in relation to its benefit in individualizing treatment.

## CONCLUSION

The use of hormones in women with high-penetrance mutations requires a personalized approach. There are no absolute contraindications for the use of COCs. Multidisciplinary evaluations should be performed, balancing the benefits in reducing ovarian cancer risk with the potential implications for breast cancer risk. It is essential to advise patients about the possibility of choosing for non-hormonal methods.

For postmenopausal patients who have undergone prophylactic mastectomy and salpingo-oophorectomy, HT does not present absolute contraindications. However, when only prophylactic salpingo-oophorectomy is performed, HT may be considered for short periods, ideally using micronized progesterone in women with a uterus, until the expected age of natural menopause[13].

Although the cancer risk appears to be higher in BRCA2 mutation carriers compared to BRCA1, robust data are lacking to assess the impact of COC or HT use in carriers of other genetic mutations. These aspects highlight the importance of informed decisions based on the best available evidence and the characteristics of each patient.

## AUTHORS' CONTRIBUTION

VAS: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Visualization, Validation, Writing — original draft, Writing — review & editing. WJAJ: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Supervision, Validation, Visualization, Writing — review & editing. ACA: Software, Resources, Writing — original draft. LMACL: Investigation, Methodology, Visualization, Writing — original draft.

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