Modern Approaches and Future Perspectives on Breast and Ovarian Cancer Prevention Strategies in BRCA1 and BRCA2 Mutation Carriers: A Literature Overview

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Abstract

Introduction and purpose
Individuals with BRCA1 and BRCA2 mutations face significantly heightened likelihood of developing breast and ovarian cancers. Besides some lifestyle recommendations, like maintaining physical activity, healthy BMI, possibly early parenthood and breastfeeding, the management of BRCA1/2 mutation carriers includes gene mutation early-detection, screening, risk-reducing surgeries, and chemoprevention. Various prevention strategies exist, all aimed at monitoring patients and mitigating the cancer risks. However, even with the existence of national and international guidelines to direct prevention efforts, there is no ideal protocol that would be universally applicable for all individuals with mutated BRCA gene. This article aims to delve into the currently available surveillance and preventive strategies and explore the potential future avenues for early detection and risk reduction in BRCA mutation carriers.

Materials and methods
This study is a literature review based on publications on PubMed using key words: BRCA mutation, breast cancer, ovarian cancer, cancer prevention, surveillance, screening

Description of the State of Knowledge
Women identified with BRCA1/BRCA2 mutation are at higher life-time risk of developing breast and ovarian cancer than the general population. Regular screening of breasts and reproductive organs is crucial for managing BRCA germline mutation carriers. There are no
preventive medications registered to diminish the endangerment of malignancy. Surgical interventions, such as prophylactic mastectomy and prophylactic salpingo-oophorectomy are preventive measures that significantly mitigate the likelihood of cancer development.

**Conclusion**
In consideration of the research discussed, it is imperative that contemporary risk-minimizing strategies for individuals with BRCA gene variation should be customized according to the age of mutation identification, reproductive plans, family history of carcinoma occurrence, and the patient's medical background. Relying solely on surveillance methods may not always be sufficient in managing high-risk patients such as BRCA1/2 carriers. Despite the compelling evidence supporting the effectiveness of risk-reducing surgeries for ovarian and breast cancers, some patients harbor reservations about undergoing procedures that undoubtedly entail potential side effects. The pressing need for alternative non-surgical approaches has prompted increased attention to chemoprevention possibilities. Ongoing research endeavors offer hope for advancements and aim to diversify the range of preventive strategies available for BRCA mutation carriers in the future.

**Key words**
BRCA mutation; breast cancer; ovarian cancer; cancer prevention; surveillance; screening

**Introduction**
BRCA1 and BRCA2 are genes crucial for preserving genome stability, as they encode proteins involved in DNA repair and transcription regulation. These genes function as tumor suppressors, restraining tissue growth. However, if particular changes in them occur, such as point mutations, deletions, or loss of expression, the risk of malignancy significantly increases.

[1]
When a harmful variant of BRCA is inherited, the risk of several cancers increases, such as fallopian tube, primary peritoneal, melanoma, pancreatic, prostate, colon cancers and male breast cancer. However, the highest risks are for breast (approximately 72% for BRCA1 and 69% for BRCA2 carriers) and ovarian cancer (44% for BRCA1 and 17% for BRCA2 carriers).

[2] Moreover, when compared to patients without the genetic mutation, individuals who
Inherit a mutated BRCA1/BRCA2 gene often develop cancer at a younger age and are more prone to high-grade tumors with a more aggressive disease progression. [3]

In recent years, significant progress has been made in sequencing platforms, leading to improved accuracy in BRCA testing. As a result, an increasing number of women require recommendations aimed at reducing the risks of mutation-related cancers. Risk-reducing strategies for this group of patients include both noninvasive options such as regular screening and chemopreventive agents, as well as invasive procedures such as bilateral salpingo-oophorectomy and bilateral mastectomy.

**Surveillance**

In the context of breast cancer risk, clinical examination is recommended every 6–12 months from the age of 25 or a decade before the youngest instance of breast cancer within the family, whichever comes first. [4] However, it's essential to note that relying solely on clinical examinations is not sufficient, and incorporating imaging techniques is highly recommended for comprehensive screening.

Magnetic resonance imaging (MRI) is known to be the reliable screening tool for the BRCA mutation carriers, with reported sensitivity of 100% and specificity of 97% for breast cancer. [5] It should be done once a year from the age of 25 or earlier if breast cancer was diagnosed in family member before the age of 30 years. The use of MRI is limited by extended acquisition, the requirement for intravenous administration of contrast agents and relatively high cost. Over the past years, there have been efforts to ascertain whether abbreviated protocols could match the reliability of the standard one, what indeed was confirmed in a prospective observational study. [6] Nevertheless, when considering high-risk patients such as BRCA carriers, there were concerns regarding whether the abbreviated protocol would suffice. Recently, Naranjo et al. proved in their study that the abbreviated protocol, with the incorporation of T2-weighted imaging, demonstrates comparable sensitivity, specificity, and accuracy when compared to the full protocol in the BRCA-positive population. [7]

In addition to MRI, it is advised to initiate annual mammography screenings from the age of 30. The sensitivity of mammography for breast cancer detection is much lower when it comes to BRCA mutation carriers (30%) in comparison to the general population (83%). [8] The reasons for that are higher growth rate of tumors, dense breast tissue related to the younger age of patients and also, malignancies presenting the features of benign lesions more frequently than in the general population, all leading to a false-negative results more often. [9]
Therefore, doubts have been raised about mammography’s additional detection benefits, when MRI is being conducted. Indeed, a study conducted in 2018 [10], demonstrated that mammographic screening does not notably elevate cancer detection rates in BRCA mutation carriers who undergo magnetic resonance imaging examinations. While intensified screening programs, combining both MRI and mammography, remain a universal standard globally, in the future, we might witness MRI becoming the sole recommended imaging tool.

In women under 30 years of age, breast ultrasonography is taken into consideration if MRI is unavailable. It can also be used in addition to mammography at all ages. However, its sensitivity in detection of breast carcinomas is reported to be 33% [5], so screening with ultrasound in patients with BRCA mutation gives no additional benefit when other methods are used.

For ovarian cancer surveillance, the role of imaging has a limited value. It is advised to undergo a prophylactic ovarian operation, however, before the surgical intervention, transvaginal ultrasound with the addition of measures of serum Ca-125 every 6-months may be considered from the age of 30 or 10 years before the earliest ovarian cancer diagnosis in the family. [6] The efficacy of ultrasonographic assessment is limited by an early time of detection, visibility constraints and the operator’s experience. [11]

CA125 is currently regarded as the most dependable biomarker for ovarian cancer, but its sensitivity varies from 50% to 62%, and its specificity ranges from 73% to 77%. [12] In contemporary practice, it is primarily used as a component of multivariate algorithms, such as ROMA, RMI, or OVA1, all aimed at increasing its effectiveness. Nonetheless, there is currently no proven screening protocol that can reliably detect ovarian cancer early enough to significantly reduce the risk of death. [4] However, according to Nebgen et al. an algorithm incorporating CA125 levels alongside transvaginal USG has demonstrated a shift towards detecting earlier-stage cancers in high-risk women. [13]

Meanwhile, researchers are intensively seeking out new strategies. A test named CancerSEEK, developed through research at Johns Hopkins University in Baltimore, has been devised. This blood test has the potential to identify eight cancer types, including ovarian cancer, by evaluating the levels of circulating proteins and mutations in cell-free DNA. Its sensitivity for detecting ovarian cancer was reported to be 98%, with a specificity exceeding 99%. [14]

**Surgical prevention**

Prophylactic bilateral mastectomy remains the most effective strategy for BRCA-associated breast cancer avoidance, as it is proven to be linked with a notable decrease in the occurrence
of breast carcinoma, with estimation up to 90%. [15] According to Bertozzi et al., the most suitable age for BRCA-positive women to undergo prophylactic mastectomy is between 25 and 30 years. [16]

Risk-reducing mastectomy can be done with the nipple-areolar complex removal or with its preservation. Despite the concerns about the remaining tissue being the potential source of tumor cells, recent data suggests no additional risks related with this method. Yao et al. in their review concluded that nipple-sparing mastectomy is associated with low rates of locoregional recurrence and low complication rates in BRCA-positive women. [17] In view of this, the current approach is to preserve the nipple unless there are anatomical or oncological circumstances that prohibit it. Nipple-sparing mastectomy (NSM) is the preferred method given its beneficial impact on psychological and sexual welfare. [18]

Prevailing group of patients undergoing risk-reducing mastectomy request breast reconstruction and as the prophylactic mastectomy becomes more common practice, there has been a corresponding increase in the development of reconstructive methods in recent years. Majority of high-risk patients are provided with classic, implant-based methods. [19] In the past, a two-stage breast reconstruction was commonly performed, but nowadays it is primarily reserved for patients at high risk of postoperative complications. Among the remaining patients, immediate reconstruction, also known as direct-to-implant (DTI) procedure, is favored. [19]

In recent times, there have been advancements in reconstructive techniques using autologous tissues. The assembly of trans rectus abdominis myocutaneous flap (TRAM) is the most frequently employed technique using self-derived materials. For it to be performed, surgeons use a free flap, pedicled flap or a muscle-sparing trans rectus abdominis myocutaneous flap (MS-TRAM). [20] A meta-analysis from 2020 showed that women who underwent reconstruction using their own tissues reported higher satisfaction levels compared to those who opted for implant-based reconstruction [21], thus it is conceivable that in the future, a larger proportion of women will undergo this type of procedure.

Another technique that has emerged relatively recently involves the use of acellular dermal matrices (ADM), which facilitate tissue vascularization and cellular proliferation while integrating with the host's tissues without eliciting an immune response. An analysis conducted in 2020 provided evidence that implementing ADMs in breast reconstruction reduces the complications’ rate. [22]
It is important to note, that numerous factors must be taken into account when selecting the reconstruction method, such as oncological history, tissue condition, medical comorbidities and desirable aesthetic results. While TRAM and ADM-assisted breast reconstructions are not yet a conventional practice, their potential use in the future warrants further analysis. Given the deficiency of dependable screening methods for early detection, in order to prevent ovarian cancer it is universally recommended to do the bilateral salpingo-oophorectomy. According to the National Comprehensive Cancer Network (NCCN) it is best to perform by the age 35 for individuals with BRCA1 mutation and 45 for BRCA2 mutation carriers. [23] Certainly, reproductive intentions must be considered when determining the timing of the reproductive organs’ elimination. Risk-reducing salpingo-oophorectomy (RRSO) involves the comprehensive removal of both ovaries and fallopian tubes up to their connections at the level of the uterine horns, usually through minimally invasive laparoscopic surgery. Research has indicated its effectiveness in reducing the risk of gynecological tumors (including ovarian, fallopian tube, or primary peritoneal cancers) by 85% to 95%. [24] While RRSO remains an international gold standard in high-risk patients, researchers are looking for an alternatives to strike a balance between reducing risk and maintaining quality of life by holding up the side effects of an early menopause. In a recent study, BRCA pathogenic variant carriers were offered a prophylactic salpingectomy with delayed oophorectomy (PSDO). [25] The researchers have indeed proven that the quality of life was better in the salpingectomy group than in the RRSO group. It remains uncertain whether bilateral salpingo-oophorectomy conducted on BRCA pathogenic variant carriers diminishes not only ovarian but also breast cancer risk. Marchetti et al. in their research reported that RRSO reduces the risk of breast cancer by 39% in BRCA1 mutation carriers and by 72% in BRCA2 mutation carriers. [26] On the contrary, a study conducted only a year after by Heemskerk-Gerritsen et al. disclosed that RRSO is not related to breast cancer reduction for patients with BRCA mutations. [27] Therefore, at this time, bilateral salpingo-oophorectomy is not an authorized method for breast danger lessening. One of the newest approaches is simultaneous breast and gynecologic surgery. Recently, a large study about RRSO combined with breast mastectomy was conducted in BRCA 1/2 mutation carriers. [28] This strategy needs more examination but seems promising to be a practical and secure method, diminishing hospital stays and anesthesia usage.
Chemoprevention

Current data validates a 40% to 50% reduction in ovarian cancer risk associated with the usage of oral contraceptives, applicable to both the general population and individuals carrying BRCA mutations. [29] Trabert et al. corroborated these statistics in their study, demonstrating that the ovarian cancer likelihood elevates with a greater lifetime number of ovulatory cycles. [30] Nonetheless, it's essential to recognize that while oral contraceptive use lowers the risk of ovarian cancer, it could potentially elevate the likelihood of breast cancer. In the past, studies examining the impact of oral contraceptives on the risk of breast cancer yielded inconsistent results. While some studies indicated no correlation [31], a recent, large meta-analysis revealed that there is a significant association between the use of oral contraceptives and an elevated risk of breast cancer in BRCA-positive women. [32] However, it is worth to note, that according to Moorman et al. the inverse correlation between oral contraceptive use and ovarian cancer is significantly more robust than the positive correlation with breast cancer. [33]

Another area of research involves PARP inhibitors, which target the enzyme poly (ADP-ribose) polymerase and block the DNA-repairing mechanism within cancer cells. [34] These inhibitors are already approved for ovarian and breast cancers treatment in patients with mutated BRCA genes. [35] Ongoing researches aim to determine whether these agents could potentially serve as preventive medications in BRCA-positive individuals without a history of malignancy.

Compounds explored for reducing breast cancer risk include selective estrogen receptor modulators (SERMs), with tamoxifen being a prime candidate. A meta-analysis revealed that tamoxifen treatment for a first breast cancer decreased the risk of a second breast cancer in individuals with BRCA1 and BRCA2 mutations by 44% [36]. SERMs have not yet been officially validated for primary prevention in BRCA mutation carriers. However, a recent trial has commenced with the aim of determining whether tamoxifen, when combined with appropriate lifestyle measures, could potentially emerge as an effective chemopreventive option for this specific patient population. [37]

There are concerns that the benefits of tamoxifen may be limited to preventing estrogen receptor-positive (ER-positive) breast cancer, whereas approximately 70% of breast cancers in patients with BRCA1 mutation are classified as triple-negative, lacking expression of estrogen, progesterone and HER2 receptors. [38] On the other hand, there is some evidence
suggesting that tamoxifen may be equally effective in preventing breast cancer for both BRCA1 and BRCA2 mutation carriers. [39]

Another avenue of research in chemoprevention involves the RANK system, which has been identified as dysregulated in women with BRCA1 mutation, according to recent findings. [40] Indeed, RANKL is a protein that has been shown to be expressed in the mammary gland during both developmental stages and the formation of tumors. [41] Therefore, the utilization of anti-RANKL monoclonal antibodies, like denosumab, presents a potential novel approach for breast cancer prevention in BRCA mutation carriers.

Summary

Breast cancer surveillance revolves around imaging techniques, with MRI emerging as the most dependable tool, and contemporary screening protocols for women with mutated BRCA1/2 gene are centered on its use. Surgical mastectomy remains recognized as the most effective risk reduction option for breast cancer in BRCA mutation carriers. Advancements in this procedure made in last decade, aim to not only reduce risk but also enhance aesthetic outcomes and minimize psychological distress. Thus, it has become customary, provided there are no medical contraindications, that patients are offered the surgery involving nipple preservation and simultaneous reconstruction with a preferred method. As of now, there are no chemopreventive agents that offer substantial risk reduction for breast cancer. However, promising emerging approaches such as selective estrogen receptor modulators (SERMs) and anti-RANKL monoclonal antibodies are being explored as potential novel prevention strategies that may be applicable for individuals with BRCA mutations in the future.

To this day, no surveillance program provides early enough detection to effectively mitigate ovarian cancer risk for BRCA mutation carriers. Presently, algorithms which combine transvaginal ultrasonography with biomarkers, are utilized for screening. However, there is optimism that in the future, ovarian cancer screening will transition towards DNA sample testing, exemplified by innovations like CancerSEEK. Bilateral salpingo-oophorectomy offers the most substantial reduction of ovarian cancer risk for women with BRCA pathogenic variants. Nevertheless, trials are underway to assess whether the elimination of fallopian tubes and postponing the removal of ovaries could potentially establish a new standard of care. Currently, there is no definitive evidence supporting the effectiveness of any agents in preventing ovarian cancer. Oral contraceptives are the most promising in fulfilling this criterion, but the uncertainty surrounding their impact on breast cancer precludes their recommendation for individuals with BRCA mutations. PARP inhibitors, already approved
for the treatment of ovarian cancer, are intensively studied to evaluate their potential in the high-risk group prevention as well.

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