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Review Article

Risk-Reducing Salpingo-Oophorectomy in Patients at High Risk of Epithelial Ovarian and Fallopian Tube Cancer: A Review Article

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Abstract

Background: Risk-reducing bilateral salpingo-oophorectomy (RRBSO) is a surgical procedure in which the fallopian tubes and ovaries are surgically removed from patients who have a heightened susceptibility to epithelial ovarian carcinoma including those with BRCA1 and BRCA2 mutations. It represents the most efficacious approach to mitigating the risk of these malignancies in high-risk patients and to improve women's overall survival rate. **Aim:** The purpose of this article is to explore Risk-reducing bilateral salpingo-oophorectomy (RRBSO) in patient who are at high risk of epithelial ovarian cancer and fallopian tube cancer. **Materials and Methods:** A web-based literature search was conducted utilizing the advanced features of several databases, including PubMed, Scopus, Embase, Google Scholar, the Directory of Open Access Journals (DOAJ), and Cochrane. The keywords that were used included: Risk-Reducing Salpingo-Oophorectomy (RRBSO), Epithelial Ovarian, Fallopian Tube Cancer.**Conclusion:** Risk-reducing bilateral salpingo-oophorectomy (RRBSO) has been shown to improve the survival rate of women that are at high risk of epithelial ovarian cancer especially in those with BRCA 1 and 2 mutations. It has also been associated with a decreased breast cancer risk in BRCA carriers without a history of the disease. There is a 2% chance that cases at high risk for ovarian cancer will develop primary peritoneal carcinoma; this risk remains even after Risk-reducing bilateral salpingo-oophorectomy. It is recommended that a risk-reducing bilateral salpingo-oophorectomy be performed between the ages of 35 and 40, or as soon as a patient's family is complete. Hormonal replacement therapy is an effective treatment for symptoms following Risk-reducing bilateral salpingo-oophorectomy.

Keywords: Risk-Reducing Salpingo-Oophorectomy (RRBSO), Epithelial Ovarian, Fallopian Tube Cancer.

Introduction

Epithelial ovarian carcinoma (EOC) is considered the most frequent ovarian cancer (OC), which originates in the ovaries, fallopian tubes, or main peritoneum [1]. It is the fifth most common cancer in females in the developed world and the fourth leading reason of cancer-related mortality [2]. Due to a deficiency of non-specific and symptom efficient screening [3], Epithelial ovarian carcinoma (EOC) is often identified at an advanced stage (FIGO stage III or IV), with roughly 30% of cases having malignant ascites at the time of admission. The primary treatment options for ovarian cancer include systemic chemotherapy and cytoreductive surgery. Despite breakthroughs in novel cytotoxic and targeted therapy, the overall survival rate for all ovarian cancer is 40% to 50% after ten years [4]. A history of breast and/or ovarian cancer is a significant risk factor for Epithelial ovarian carcinoma. Hormonal and reproductive variables are the most important risk factors [5].

Risk-reducing bilateral salpingo-oophorectomy (RRBSO) is an essential treatment option for cases with inherited ovarian tumors that are at high risk for Epithelial ovarian carcinoma [6]. Women with a detrimental mutation in the BRCA 1 or BRCA 2 genes are more likely to develop Epithelial ovarian carcinoma in their lifetime [7]. Because some apparent ovarian malignancies begin in the fallopian tubes, the risk-reducing operation involves bilateral removal of both the tubes and the ovaries [8]. Risk-reducing bilateral salpingo-oophorectomy (RRBSO) has been proven to decrease the incidence of ovarian cancer by more than 80% in women carrying the BRCA 1 or BRCA 2 mutation [9]. It is the most effective method of lowering the occurrence and mortality rates associated with cancer in this high-risk population [10].

The average age at diagnosis for ovarian cancer varies depending on the type of mutation. Cases with BRCA1 mutations have a considerable rise in ovarian cancer risk starting at the age of 35, with 2-3% developing ovarian cancer by age 40; the usual age at diagnosis is 50 years [11, 12]. BRCA2 mutation carriers had a 2-3 % incidence of ovarian cancer a decade later, by age 50; the average age at diagnosis is 60 years, which is comparable to the overall population. Expanding on this difference in the anticipated age of ovarian cancer initiation, BRCA2 carriers may prefer to postpone risk-reducing surgery, but they would miss out on the lowered risk of breast cancer provided by salpingo-oophorectomy [13].

As a result, the National Comprehensive Cancer Network (NCCN) recommends that patients with BRCA1 mutations undergo RRBSO between the ages of 35-40, or after they have completed childbearing. Because the development of ovarian cancer in BRCA2 mutation carriers is generally 8 to 10 years later than in BRCA1 mutation carriers, the recommended age for Risk-reducing bilateral salpingo-oophorectomy (RRBSO) is 40-45 [14]; as a result, we must continue our research into RRBSO. The purpose of this article is to explore RRBSO in cases at high risk of epithelial ovarian and fallopian tube cancer.

Materials and Methods:

A web-based literature search was undertaken, with advanced databases such as PubMed, Scopus, Embase, Google Scholar, the Directory of Open Access Journals (DOAJ), and Cochrane. The core MeSH and keywords such as Risk-Reducing Salpingo-Oophorectomy, Epithelial Ovarian, and Fallopian Tube Cancer were utilized. The search covered the most recent full-text review articles published between 2015 and 2024, with an emphasis on English-language articles.

Findings:

Epithelial Ovarian cancer

Prevalence

Ovarian cancer is the fifth most frequent malignancy in women in the developed world and the fourth cause of cancer-related mortality [15]. The lifetime risk of ovarian cancer related death is estimated to be one in 54–75 and one in 100 [15, 16]. Epithelial ovarian cancer accounts for 60% of all ovarian cancers and is further classified as benign, borderline, or malignant. High-grade serous ovarian cancer (HGSOC) accounts for 70% to 80% of malignant epithelial ovarian cancer and typically manifests late with widespread of the disease [17]. Originally postulated to have their source on the ovarian surface, their predominant origin is now understood to be the fallopian tube epithelium. [17].

Genetic variations

Almost all High-grade serous ovarian cancer (HGSOC) tumors contain pathogenic somatic mutations in TP53, as well as NF1, FAT3, RAD51C, RAD51D, CSMD3, RB1, BRIP1, CDK12, GABRA6, and the tumor suppressor genes BRCA1 and BRCA2. The FOXM1 and Notch signaling pathways have also been implicated [18-20]. The genomic instability found in HGSOC stimulates the creation of additional variations, enhances genetic diversity, and results in the formation of genetically different subclones within a tumor [20].

Risk factors

Hereditary breast and ovarian cancers (HBOC) are a significant risk factor for epithelial ovarian cancer. Epithelial ovarian cancer and primary peritoneal cancer (PPC) have traditionally been treated similarly in clinical and research settings [21]. Women with a first-degree relative diagnosed with ovarian

cancer are three times more likely to have the disease [22]. First-degree relatives diagnosed under 50 have a higher relative risk (RR) compared to those over 50. Serous ovarian cancer has a greater relative risk (RR) for first-degree relatives compared to non-serous ovarian cancers [23].

Hormonal and reproductive variables are the most important risk factors. A larger lifetime number of menstrual cycles is linked to an increased risk of epithelial ovarian cancer, implying that ovulation is involved in ovarian carcinogenesis [24]. Pregnancy, nursing, and the oral contraceptive pill all reduce ovulation, and nulliparity is related to increased risk. Hormone replacement treatment (HRT) is associated with a small but long-term risk, as is increasing weight, height, and body mass index [26, 27]. There is no substantial relationship with alcohol and diet [28]. Tobacco use is solely connected with Mucinous ovarian cancer [29]. Endometriosis is linked to 15% to 20% of clear cell and endometrioid ovarian cancer, with a threefold increase in risk [30].

Risk-Reducing Salpingo-Oophorectomy (RRSO)

Risk-reducing salpingo-oophorectomy has been linked to a reduction in epithelial ovarian cancer incidence (about 80%), as well as cancer-specific and overall mortality, and is regarded as the most effective approach for ovarian cancer prevention in this situation [31, 32]. Two large prospective trials found a similar risk decrease and significant reductions in ovarian cancer-specific mortality and all-cause mortality to age 70 years [33, 34].

Prophylactic Ovarian Surgery

Risk-reducing salpingo-oophorectomy is a procedure that removes both ovaries and fallopian tubes, a crucial part of cancer pathogenesis [35]. It is recommended for BRCA mutation carriers due to the lack of cost-effective screening methods for early detection of ovarian cancer, which has a poor prognosis with a 50% 5-year survival rate [36]. The risk of ovarian cancer in the overall female population is 1.3%, increasing to 36-53% in patients with BRCA1, and 10-25% in patients with BRCA2 mutations by the age of 70 [**37**].

BRCA mutation carriers have earlier median ovarian cancer diagnosis compared to the general population, with high-grade serous carcinoma and endometrioid carcinoma being the most common histotypes [38].

A prophylactic salpingo-oophorectomy significantly reduces ovarian cancer risk by over 96%, breast cancer risk by 72%, and overall cancer-specific mortality [33], with occult cancers occurring in 2-10% of patients, primarily localized to the distal fallopian tube [39].

The exact time of when to do the Risk reducing salpingo-oophorectomy is not globally agreed upon, but it is best not to be performed before 35 or childbearing. Delaying intervention until women reach physiological menopause is considered in cases with a high risk of cardiovascular problems or side effects [40]. A recent study offered patients with BRCA mutations the choice between standard Risk reducing salpingo-oophorectomy and delayed oophorectomy [40, 41].

The effectiveness of Risk reducing salpingo-oophorectomy in reducing cancer risk is still ambiguous, but a Risk-reducing salpingectomy combined with delayed oophorectomy is an excellent option for balancing risk reduction and quality of life. However, new ovarian neoplasms can occur after salpingectomy and Risk reducing salpingo-oophorectomy [42]. The efficacy analysis is a long-term balance, with end dates planned beyond 2030. More information is needed before considering this approach [43].

Development of a clinical guide for Risk reducing salpingo-oophorectomy in ovarian cancer

Liu et al. developed a clinical guide to help clinicians understand gene-based ovarian cancer risk and discuss Risk reducing salpingo-oophorectomy, illustrating cumulative lifetime risk and increasing evidence for ovarian cancer risk and benefit (Figure 1) [44]. The *y*-axis represents the estimated cumulative lifetime risk of ovarian cancer. The *x*-axis represents an increasing level of evidence for ovarian cancer risk and benefit from Risk reducing salpingo-oophorectomy with implicated genes plotted accordingly [44].

The population-level lifetime absolute risk of ovarian cancer is 1%-2% [45], with a Risk reducing salpingo-oophorectomy threshold of 2.64% [46]. First-degree relatives with ovarian cancer have a cumulative lifetime risk of 3-4% but are not routinely recommended. New data is needed to better define this risk [47].

Liu et al. provided a range of risks associated with each gene, reflecting uncertainty and potential changes over time. They highlighted areas of controversy and insufficient data, suggesting that the recommended age for Risk reducing salpingo-oophorectomy should be adjusted based on family history [44]

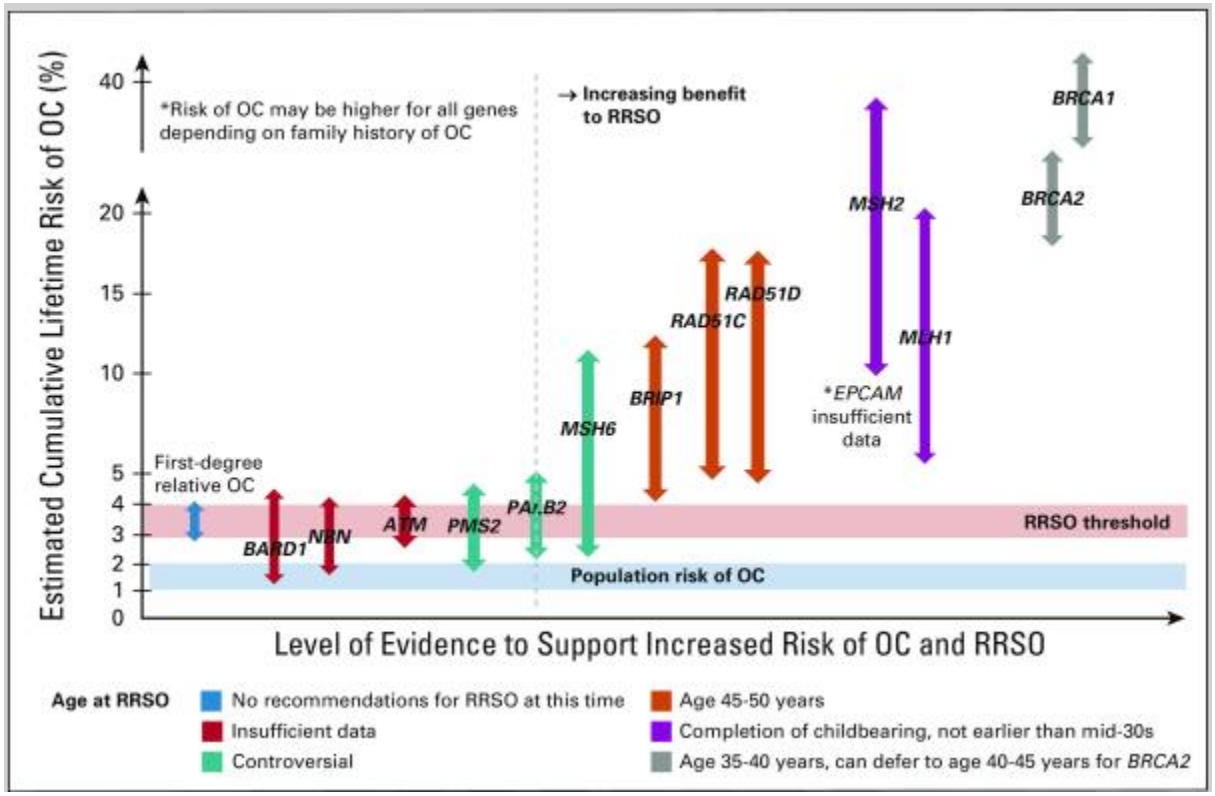

Figure 1: Clinical guide for Risk reducing salpingo-oophorectomy for ovarian cancer by cancer susceptibility gene [44].

Hormonal Replacement Therapy after Risk reducing bilateral salpingo-oophorectomy (RRBSO)

HRT for post- Risk reducing bilateral salpingo-oophorectomy symptoms is beneficial, but not for women at increased risk for breast cancer, as the current standard does not include hysterectomy [48]. The choice of HRT depends on uterus retention, with progesterone and estrogen combined for women with a retained uterus. However, the Women's Health Initiative found a higher risk of premenopausal breast cancer in estrogen-progesterone combination (Prempro) compared to placebo and estrogen alone [49-51]. Limited data from observational studies in mBRCA carriers indicates that HRT is safe after Risk reducing bilateral salpingo-oophorectomy and maintains its protective benefit against breast cancer [49-51].

A study by Madalinska et al. found that HRT only partially alleviates climacteric symptoms after oophorectomy and does not alleviate sexual discomfort in high-risk women [52]. Post-RRBSO women prescribed HRT had fewer vasomotor symptoms but still had higher symptom levels than those without HRT. HRT did not alleviate sexual discomfort, vaginal dryness, and dyspareunia, and decreased libido may persist despite estrogen therapy, as shown in a study involving 34% of oophorectomized women [53].

Morbidity Associated with Risk reducing bilateral salpingo-oophorectomy

mBRCA carriers undergoing Risk reducing bilateral salpingo-oophorectomy and surgical menopause face immediate quality of life (QOL) compromises and long-term health risks from hypoestrogenism, with short-term symptoms and sexual dysfunction well documented [52]. A study of 114 mBRCA carriers found that premenopausal women experiencing hot flashes, night sweats, and sweating worsened one year after RRBSO surgery, comparable to women 2-7 years postmenopausal [53]. A Norwegian study found that women who underwent RRBSO experienced less sexual pleasure, more discomfort, and less frequent sex compared to the general population, indicating a need for improved sexual activity, pleasure, and discomfort measures [54].

Women who undergo RRBSO before menopause face increased risks of obstructive lung disease, hyperlipidemia, cognitive dysfunction, cardiovascular diseases, mental health

issues, and osteoporosis in the long term [55]. Women with coronary heart disease (CHD) are at a higher risk for chronic conditions like diabetes, stroke, and arthritis, with 55.6% of those undergoing bilateral oophorectomy in the Nurse's Health Study [56]. A 24-year follow-up found that bilateral oophorectomy during hysterectomy was related to a higher risk of both fatal and non-fatal coronary heart disease (CHD) [56].

Most of the data on mental health post-oophorectomy and cognitive dysfunction is derived from the Mayo Clinic Cohort Study of Oophorectomy and Aging. Obesity before menopause can increase the risk of cognitive impairment, dementia, depressive symptoms, anxiety, and parkinsonism, with these effects increasing with younger age and independent of surgery indication [57].

Follow-up after Risk-Reducing Surgery

Prophylactic strategies can help reduce the risk of hereditary neoplasm, but their effectiveness is not eliminated, making follow-up vital for high-risk patients post-intervention [58].

A survey of 22 centers found that most agree not to monitor BRCA mutation carriers after risk-reducing surgery. Most centers offer annual clinical breast examinations, but only four provide post-risk reducing salpingo-oophorectomy gynecological surveillance. Further evidence is needed for improved management [59].

It is recommended to continue imaging follow-up with regular ultrasounds and alternating with MRI if the radiologist suggests it [60].

Economic Impact

Preventing new primaries in breast and gynecologic malignancies is crucial for cost-effective treatment, but the choice of prevention varies based on the patient's economic circumstances and country of origin [61].

Prophylactic surgery offers convenience and ease of follow-up for cancer prevention, especially in low-income countries with average life expectancy. However, there's a need for clear guidelines on post-surgery follow-up, necessitating new studies and economic balance considerations [59].

Recent analysis reveals high decision uncertainty in risk-reducing intervention uptake rates, indicating the need for more attention in health economic modeling studies [62].

Conclusion

Risk-reducing bilateral salpingo-oophorectomy (RRBSO) is a treatment that removes both the ovaries and the fallopian tubes in patients who are at high risk of developing EOC, such as those with BRCA1 and BRCA2 mutations. It is the most effective way to lower the risk of these malignancies in patients who are at high risk. Risk reducing bilateral salpingo-oophorectomy has also been linked to a lower risk of breast cancer in BRCA carriers with no past breast cancer. However, it can also cause infertility and early menopause. Cases at high risk for ovarian cancer have a 2% probability of developing primary peritoneal carcinoma, and this risk persists even after RRBSO. Risk reducing bilateral salpingo-oophorectomy is indicated to be performed as soon as childbearing is completed, or by the age of 35-40. Hormonal replacement treatment is effective for treating post-RRBSO symptoms.

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