ISSN: 2576-2842

Review Article

Journal of Gynecology & Reproductive Medicine

Risk-Reducing Salpingectomy And Other Strategies For Prevention Of Ovarian And Tubal Carcinoma

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Submitted: 09 Mar 2023; **Accepted:** 30 Mar 2023; **Published:** 17 Apr 2023

Citation: Adam, S., Badr, M. (2023). Risk-Reducing Salpingectomy And Other Strategies For Prevention Of Ovarian And Tubal Carcinoma. *J Gynecol Reprod Med, 7*(2), 56-67.

Abstract

Objective: *To provide a review of most current evidence and data for risk-reducing strategies used in prevention of ovarian cancer.*

Methods of study selection: *PubMed was used as a search tool for articles with key words focusing on current strategies on prevention of ovarian cancer such as "risk-reducing salpingectomy, "risk-reducing salpingo-oophorectomy, "salpingectomy with delayed oophorectomy". General consensus and society guidelines from leading organizations such as Society of Gynecologic Oncology, American Cancer Society, and American College of Obstetricians and Gynecologists were reviewed and summarized in this review article with supporting evidence and research studies on most current risk-reduction strategies for prevention of ovarian and tubal carcinoma.*

Result: *There is growing evidence that high-grade serous ovarian carcinoma arises in the fallopian tube in the form of serous tubal intraepithelial carcinoma (STIC). Therefore, opportunistic salpingectomy has been increasingly offered at the time of routine benign gynecologic surgery. Risk-reducing bilateral salpingo-oophorectomy has been shown to reduce risk of ovarian cancer up to 90% and offered to women with high hereditary predisposition for ovarian cancer. Risk-reducing salpingectomy with delayed oophorectomy (SDO) has been suggested in younger women to balance the effects of infertility and surgically induced menopause resulting from oophorectomy.*

Conclusion: *Combined oral Contraceptive COCs confer long-term protection against ovarian cancer with reported 20% reduction for every 5 years of use, which have been cited as a confounding factor in most of the published studies. Women who used HRT (estrogen alone or combined estrogen and progesterone) carry 20% higher risk of ovarian cancer compared to never-users. The associated increased risk of cervical and breast cancer with COCs/HTR use, have recently let women prefer the RRSO over COCs for prevention of ovarian cancer.*

Bilateral risk reducing Salpingo-oophorectomy (RRSO) at the age of 40–45 in BRCA1 and 45–50 in BRCA2 mutation carriers is recommended to be the primary approach for risk reduction of ovarian cancer. There is well-supported evidence of lowering the risk of ovarian cancer in high-risk population by 90%. The American college of obstetrics and gynecology committee opinion, recommended opportunistic salpingectomy for the primary prevention of ovarian cancer in a woman already undergoing pelvic surgery for another indication.
Bilateral salpingectomy at the time of cesarean delivery is recommended to replace the tubal ligation as the method of choice for sterilization performed with cesarean delivery.

The novel alternative procedure of Risk-reducing Salpingectomy with delayed risk-reducing oophorectomy (RRSO-RRO) have growing attention as a better alternative to improve the menopause-related morbidity and quality of life.

Keywords: Ovarian Cancer, Risk-Reducing Salpingectomy, Salpingo-Oophorectomy, High-Grade Serous Cancer, Prevention Of Ovarian Cancer.

Introduction

Ovarian cancer is the second most common gynecologic malignancy in the developed world and the leading cause of death in gynecologic malignancies [1]. Subtle clinical presentation of ovarian cancer together with the lack of effective screening tools have led to diagnosis of ovarian cancer at advanced stages with poor prognosis [2]. High-grade serous ovarian carcinoma is thought to start as a microscopic lesion in the fallopian tube that is difficult to detect with current screening strategies.

For women with family history of Lynch syndrome or BRCA1/2 mutations, a thorough pelvic examination in combination with transvaginal ultrasound and blood levels of tumor marker CA125 may be offered, although this strategy has not proven effective in reducing ovarian cancer mortality [3, 4].

Because early screening methods have largely failed to prove mortality benefit in ovarian cancer, prevention remains the best current strategy for mortality reduction. With the new understanding and growing evidence that ovarian and pelvic serous carcinoma originates in the fallopian tubes, risk-reducing strategies such as use of combined oral contraceptives (OCPs), opportunistic salpingectomy, salpingo-oophorectomy or salpingectomy with delayed oophorectomy have been suggested.

Discussion

Etiology of Ovarian Cancer

A growing body of research shows most high-grade serous ovarian carcinomas arise in the fallopian tube in the form of serous tubal intraepithelial carcinoma (STIC) [5-9]. STIC is found in 4-12% of germline BRCA1/2 carriers and in 36-60% of sporadic pelvic serous carcinomas [11-14]. The same TP53 mutations seen in STIC have been found in 92% of pelvic serous carcinomas [15]. Pelvic serous carcinoma cells have also been noted to be more similar to tubal epithelium than ovarian surface epithelium [16]. The process is thought to start by transformation of the benign tubal epithelium into serous tubal intraepithelial cells or invasive tubal carcinoma [11]. The (pre)malignant cells then likely migrate to the ovary and pelvis, resulting in ovarian or peritoneal carcinoma.

Hereditary genetic mutations account for 10% of ovarian cancer cases in the United States [cite source]. Women with Lynch syndrome have an increased 8% risk of developing ovarian cancer by age 70, compared to 0.7% in the general population [22, 24]. Breast cancer risk is estimated to be 65% and 49%, for BRCA 1 and BRCA2 mutation carriers by the age of 70 respectively, and ovarian cancer risk 40% and 18% by the age of 70 for BRCA1 and BRCA2, respectively [17, 18].

Risk-Reducing Strategies For Ovarian Cancer

Oral Contraceptives

Current evidence supports the protective effects of combination oral contraceptives (COCs) in risk reduction of epithelial ovarian cancer. COC use for up to three years has been shown to reduce the risk of ovarian cancer by 50% in both high risk and average risk populations [25, 26]. The protective effect of COCs has been attributed to direct effect of the progestin component. COCs with high potency progestins have demonstrated the highest risk reduction. However, currently there is insufficient data to support recommendation of a progestin-only pills, a levonorgestrel-releasing intrauterine system, or depot medroxyprogesterone acetate for ovarian cancer risk reduction [27, 28].

Current evidence shows COCs decrease overall cancer risk by 12%, with considerable reductions in mortality from ovarian, colorectal, and endometrial cancers [29, 30]. Conversely, COCs have been associated with increased risk of cervical and breast cancer [29, 30].

COCs also confer long-term protection against ovarian cancer with an additional 20% reduction for every 5 years of use [31]. Moreover, the protective effect seen in BRCA1 and BRCA2 carriers can last up to 30 years after discontinuation [32]. COCs are estimated to have prevented 200,000 ovarian cancer cases and 100,000 deaths from the disease to date [32].

Although evidence supports the risk reduction of ovarian cancer with COC use, the reported increased risk of cervical and breast cancer cannot be ignored. In some studies, women were found to prefer risk reducing surgery over COCs because of this risk [32].

Declining Use of Hormone Replacement Therapy (HRT)

Overall incidence of ovarian cancer has been decreasing since 1980s, with an accelerated decline noted in 2000s [33]. There were 19,600 newly diagnosed ovarian cancer cases in 2019, down from 21,000 in 2017 and projected 19,800 in 2022 [1]. Some experts have associated the declining rates of ovarian cancer partly to decreasing use of hormone replacement therapy (HRT) after the Women's Health Initiative (WHI) report in 2002, which linked HRT to significant adverse health outcomes [34] .

Following the WHI report, there was an abrupt decrease in HRT use across the United States with a subsequent decline in breast cancer rates, supporting link between HRT and breast cancer. Later studies also demonstrated a link between HRT and ovarian cancer, attributing the decline in incidence of ovarian cancer in recent years partly to decreasing HRT use [35].

Among postmenopausal HRT users, an increased risk of ovarian cancer is observed with even < 5 years of use [35]. Women who used HRT (estrogen alone or combined estrogen and progesterone) carry 20% higher risk of ovarian cancer compared to never-users. Among recent users, current users, and those who stopped within 5 years, the risk is higher at 40% and the risk is thought to remain high for at least 10 years after discontinuation [36].

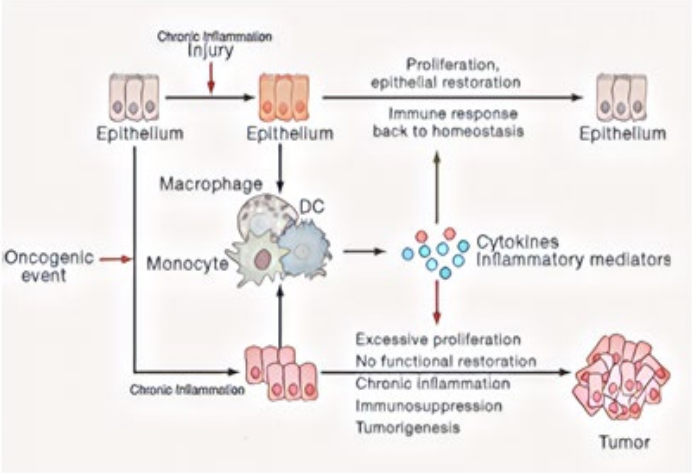
In a recently updated statement, United States Preventive Services Task Force (USPSTF) recommends against the use of HRT for the primary prevention of chronic conditions in postmenopausal wom-

en the observed carcinogenic effect in this age group [37].

Endometriosis and high ovarian cancer association

It has been established that patients with endometriosis had a higher prevalence of epithelial ovarian cancer than the general population, particularly in endometrioid and clear cell types [38]. Endometriosis has been linked to a persistent inflammatory condition that results in cytokine release. These cytokines have a complex mechanism of action that allows them to either induce or suppress their own production. They can also result in uncontrolled mitotic division, growth, and differentiation [38]. According to studies, extraovarian endometriosis undergo the same histologic transition into ovarian cancer due to chronic inflammation.

Around 20% of all cancer cases are preceded by infection, chronic inflammation, or autoimmunity at the same tissue or organ site [39]. Chronic inflammation causes cell injury which increase the production of cytokines and growth factors such as Tumor Necrosis factor (TNF) and epithelial growth factor (EGF) from myeloid cells, macrophages and fibroblasts to activate innate and adaptive sterilizing immunity to get rid of the injured cells and to activate epithelial cell proliferation to close down the barrier dysfunction which allowed translocation of injured cells or to repair inflamed cells. These growth factors serve as anti-death signals, which lead to excessive proliferation of epithelial cells and eventually tumor growth.



In addition to the carcinogenic effect of endometriosis due to chronic inflammation. Endometriosis demonstrates somatically acquired genetic alterations as those found in cancer. Families with genetic abnormalities, such as PTEN, p53, and bcl gene mutations, have been highly associated with ovarian cancer and endometriosis, pointing toward a potential malignant genetic etiology of endometriosis [40]. Endometriosis has been linked to loss of heterozygosity at the 5q, 6q, 9p, 11q, 22q, p16, and p53 loci, indicating loss of tumor suppression genes [41]. Loss of heterogenicity at 10q23.3 also has been linked to endometriosis. Gain of 17q has been shown by fluorescent in situ hybridization tests to include amplification of the proto-oncogene HER-2/neu [42]. The phosphatase domain-encoding PTEN gene has been identified in ovarian clear cell carcinomas and endometrial cysts [43]. PTEN deletion in the background of oncogenic K-ras activation within the OSE results in endometriotic-like precursor lesions that develop into invasive endometrioid ovarian carcinoma within 7-12 weeks in a mouse model of endometrioid ovarian cancer [44].

Nezhat et al 2008, concluded that endometriosis's risk for malignancy has significant therapeutic ramifications, such as the requirement for earlier and more thorough surgical intervention for thorough disease therapy [38].

Opportunistic salpingectomy

Bilateral salpingectomy has been increasingly utilized as a method of risk reduction for ovarian cancer with growing evidence showing fallopian tubes as the potential source and molecular origin of ovarian cancer. Opportunistic salpingectomy is now widely used at the time of routine benign gynecologic surgery, with a 10-fold increase over the past two decades [45, 46].

Bilateral salpingectomy is associated with a 42-65% reduction in ovarian cancer risk [38]. While hysterectomy with bilateral salpingo-oophorectomy confers the highest degree of protection, prophylactic salpingectomy is a feasible option for younger women with a high risk of ovarian cancer, although the benefits of sparing the ovaries must be balanced against the remaining risk of ovarian cancer.

Current evidence shows a significantly lower risk of ovarian cancer among women with past surgical history of salpingectomy [47]. In the published studies a major confounding factor is the long-term use of COCs in women seeking sterilization. The use of COCs is a well-established risk reducing factor for ovarian cancer and may be contributing to the risk-reduction observed in women with history of salpingectomy [41]. However, studies that have eliminated the bias effect of COCs have also demonstrated considerable risk-reduction in ovarian cancer by salpingectomy, further supporting the risk-reducing role of salpingectomy in ovarian cancer [48, 49].

In an initiative undertaken by OVCARE team in British Columbia (BC), resulted in such a remarkable consideration in opportunistic salpingectomy (removal of fallopian at the time of hysterectomy or in lieu of tubal ligation) by gynecologic surgeons in BC [50]. OVCARE Team have started on a long-term study (over 20 years) to discover whether salpingectomy will decrease the incidence of ovarian cancer in BC. In September 2010, OVCARE started an educational initiative & distributed an educational DVD to gynecologist in BC to consider changing their surgical practice to favor tubal resection over tubal ligation and at every hysterectomy. In September 2011, the Society of Gynecologic Oncology of Canada (GOC) supported OVCARE's cancer prevention strategy and encouraged the Gynecologist to discuss the risks and benefits of bilateral salpingectomy with patients undergoing hysterectomy

or requesting permanent sterilization. It is important to mention that OVCARE's Team aren't recommending women have surgery solely to remove their fallopian tubes.

In 2015, the American College of Obstetricians and Gynecologists recommendations supports the Opportunistic salpingectomy is safe and effective procedure for the primary prevention of ovarian cancer in a woman already undergoing pelvic surgery for another indication and it does not affect the ovarian function or as a method of permanent sterilization instead of tubal ligation. The surgeon and patient should discuss the potential benefits of the removal of the fallopian tubes during a hysterectomy in women at population risk of ovarian cancer who are not having an oophorectomy. The ACOG call for more randomized controlled trials to support the validity of this approach for ovarian cancer prevention [51].

Opportunistic bilateral salpingectomy can also be offered at time of Cesarean section in women desiring permanent sterilization, and has increasingly replaced tubal ligation as the method of choice for sterilization due to its superiority in both sterilization and ovarian cancer risk-reduction [52].

Cost effectiveness and higher surgical morbidity such as operative complications, longer operative time and higher blood loss in bilateral salpingectomy compared to tubal ligation need further investigation [53].

Prophylactic Salpingo-Oophorectomy

Risk-reducing salpingo-oophorectomy (RRSO) is associated with up to 96% reduction in risk of ovarian cancer [54, 55].

RRSO is currently recommended for high-risk women with germline BRCA 1 and BRCA 2 mutations by Society of Gynecologic Oncology, and has been shown reduce ovarian cancer in this population by 80% [56]. Mavaddat et al. 2020, found a preventive effect for BRCA2 mutation carriers after 5 years following RRSO. These results may inform counselling and management of carriers with respect to RRSO. RRSO is recommended be offered to germline BRCA1/2 carriers by age of 40 or after childbearing is completed [57].

There are no specific guidelines for women with strong family history of breast cancer who have no identified deleterious BRCA 1/2 genetic mutations. Guidance for these women generally follows the same recommendations as those with BRCA 1/2 mutations with timing of RRSO usually individualized based on age of occurrence of the cancer within the family.

Another major benefit of RRSO, especially in BRCA 1/2 mutation carriers, is the associated risk-reduction in breast cancer up to 56% in BRCA 1 mutation carriers and 46% in BRCA 2 mutation carriers, benefits lasting up to 15 years following RRSO [58].

In counseling patients on benefits of RRSO, it is important to also discuss known risks and adverse effects associated with the removal of ovaries in the tradeoff for cancer risk-reduction, such as vasomotor symptoms, vaginal dryness, dyspareunia as well as other long-term health consequences including reduced bone and cardiac health [59].

Currently RRSO only has proven benefit in women with high-risk genetic predisposition to ovarian cancer and only indicated in this population. Benefits of mortality risk-reduction is generally accepted to outweigh the risks in this group of women, but preservation of ovaries is advised otherwise in average-risk women [58].

Complication rates for RRSO is low, cited between 0.6–5 % for major complications such as conversion to laparotomy, bladder or bowel injury, or need for additional surgery [60-70].

Risk-reducing salpingectomy with delayed oophorectomy (SDO) surgically induced menopause. The SOROCK trial studying-whether removing only the fallopian tubes with the intention of removing the ovaries later can lower the risk of ovarian cancer to the same extent as the current gold standard of care, which is to remove both the ovaries and fallopian tubes.

In 2010, the Ovarian Cancer REsearch team (OVCAR), have recently discovered that the most common type of Ovarian Cancer (high-grade serous carcinoma), actually begin in the lining of the fallopian tube [71]. OVCARE team launched the world's first ovarian cancer prevention campaign. The goal being to reduce the incidence of ovarian cancer by 40% over the next two decades. OVCARE is British Columbia's multi-institutional and multidisciplinary ovarian cancer research group. In this Trial all gynecologic surgeons in BC and Canada were encouraged when operating on women at general population risk for ovarian cancer, they should consider performing bilateral salpingectomy at the time of hysterectomy (even when the ovaries are being preserved); and performing bilateral salpingectomy in place of tubal ligation for sterilization referred to as opportunistic salpingectomy (OS).

Phase II trial at MD Anderson (WISP study), In patients with genetic abnormalities at risk for ovarian cancer, examines how well surgery prevents the disease [72]. In risk-reducing salpingo-oophorectomy (RRSO), the ovaries and fallopian tubes are surgically removed in the same time. Interval salpingectomy with delayed oophorectomy (ISDO). It is unknown if ISDO performs better than RRSO in reducing ovarian cancer risk, enhancing quality of life.

In TUBA-WISP II study "TUBectomy With Delayed Oophorectomy in High Risk Women to Assess the Safety of Prevention", an international prospective multicenter preference trial, the participants can select either the normal salpingo-oophorectomy (RRSO) or the experimental salpingectomy (RRS) with delayed oophorectomy [73]. The primary outcome is high grade cancer or premalignant incidence, and breast cancer incident. the occurrence of non-ovarian pelvic cancer, and MR imaging are the main outcomes.

Conclusion

Combined oral Contraceptive COCs confer long-term protection against ovarian cancer with reported 20% reduction for every 5 years of use, which have been cited as a confounding factor in most of the published studies. Women who used HRT (estrogen alone or combined estrogen and progesterone) carry 20% higher risk of ovarian cancer compared to never-users. The associated increased risk of cervical and breast cancer with COCs/HTR use, have recently let women prefer the RRSO over COCs for prevention of ovarian cancer.

Bilateral risk reducing Salpingo-oophorectomy (RRSO) at the age of 40–45 in BRCA1 and 45–50 in BRCA2 mutation carriers is recommended to be the primary approach for risk reduction of ovarian cancer. There is well-supported evidence of lowering the risk of ovarian cancer in high-risk population by 90%. The American college of obstetrics and gynecology committee opinion (No 77), called for performing Opportunistic salpingectomy for the primary prevention of ovarian cancer in a woman already undergoing pelvic surgery for another indication. Bilateral salpingectomy at the time of cesarean delivery is recommended to replace the tubal ligation as the method of choice for sterilization performed with cesarean delivery.

The novel alternative procedure of Risk-reducing Salpingectomy with delayed risk-reducing oophorectomy (DSO) have growing attention as a better alternative. The main advantage of delaying risk-reducing oophorectomy (RRO) beyond the currently recommended age is the avoidance of premature menopause and improve the menopause-related morbidity and quality of life.

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Trial	Title	Methodology	Result	Conclusion
Harmsen et al, 2015	Ovarian cancer risk after salpingectomy: a nationwide population-based study.	used information from 1973 to 2009 on women who had undergone benign surgery (sterilization, salpingectomy, hysterectomy, and bilateral salpingo-oophorectomy [BSO]; n = 251465) in comparison to the general population (n = 5449119).	Women who had previously undergone a salpingectomy had a statistically significantly lower risk of developing ovarian cancer than the general population (HR = 0.65, 95% CI = 0.52 to 0.81). Additionally, women who had previously undergone hysterectomy (HR = 0.79, 95% CI = 0.70 to 0.88), sterilization (HR = 0.72, 95% CI = 0.64 to 0.81), or hysterectomy with BSO (HR = 0.06, 95% CI = 0.03 to 0.12) had statistically significant risk decreases. In comparison to unilateral salpingectomy, bilateral salpingectomy was linked to a 50% lower incidence of ovarian cancer (HR = 0.35, 95% CI = 0.17 to 0.73, and 0.71, 95% CI = 0.56 åto 0.91, respectively).	Reduced risk of ovarian cancer is connected with salpingectomy on benign grounds. These findings provide credence to the idea that the fallopian tube is the site of significant ovarian cancer development. According to our findings, removing the fallopian tubes on their own or in conjunction with other benign surgeries is a useful way to lower the risk of ovarian cancer in the general population.

Falconer et al, 2015	Ovarian Cancer Risk After Salpingectomy: A Nationwide Population-Based Study	This is a population cohort study, between 1973 and 2009, they examined data on women who had undergone benign surgery before (sterilization, salpingectomy, hysterectomy, and bilateral salpingo-oophorectomy [BSO], hysterectomy; n = 251465) in comparison to the general population (n = 5449119). In a subanalysis, the outcomes of one- and two-sided salpingectomy were taken into account. Each and every statistical test has two sides.	Women who had previously undergone a salpingectomy had a statistically significantly lower risk of developing ovarian cancer than the general population (HR = 0.65, 95% CI = 0.52 to 0.81). Additionally, women who had previously undergone hysterectomy (HR = 0.79, 95% CI = 0.70 to 0.88), sterilization (HR = 0.72, 95% CI = 0.64 to 0.81), or hysterectomy with BSO (HR = 0.06, 95% CI = 0.03 to 0.12) had statistically significant risk decreases. In comparison to unilateral salpingectomy, bilateral salpingectomy was linked to a 50% lower incidence of ovarian cancer (HR = 0.35, 95% CI = 0.17 to 0.73, and 0.71, 95% CI = 0.56 to 0.91, respectively).	Reduced risk of ovarian cancer is connected with salpingectomy on benign grounds. These findings provide credence to the idea that the fallopian tube is the site of significant ovarian cancer development. According to our findings, removing the fallopian tubes on their own or in conjunction with other benign surgeries is a useful way to lower the risk of ovarian cancer in the general population.
Rice et al, 2014.	Tubal ligation, hysterectomy, unilateral oophorectomy, and risk of ovarian cancer in the Nurses' Health Studies	to investigate prospectively whether patient, tumor, and surgical variables affected the relationship between tubal ligation, hysterectomy, and unilateral oophorectomy and ovarian cancer. A cohort of 116,430 US female nurses who were 25–42 years old at baseline and a cohort of 121,700 married US female nurses who were between the ages of 30-55 at baseline. Intervention(s): Through biannual surveys, we gathered information on ovarian cancer incidence and gynecologic operations. We determined hazard ratios (HRs) and 95% confidence intervals (Cis) that were modified for known and speculative risk variables for ovarian cancer. Principal outcome: incident epithelial ovarian cancer	An overall lower incidence of ovarian cancer was linked to tubal ligation (HR, 0.76; 95% CI, 0.64-0.90). The unfavorable correlation was more pronounced for nonserous tumors (HR, 0.57; 95% CI 0.40-0.82) and in surgical patients who were females under the age of 35 (HR, 0.67; 95% CI 0.49-0.90). A lower incidence of ovarian cancer was linked to hysterectomy (HR, 0.80; 95% CI 0.66-0.97), and this association was slightly stronger for nonserous tumors (HR, 0.70; 95% CI 0.49-1.02). Without varying by histologic subtype, unilateral oophorectomy was linked to a 30% reduced risk (HR, 0.70; 95% CI 0.53-0.91).	Our research adds to the body of evidence showing that tubal ligation lowers the incidence of ovarian cancer, especially in cases of nonserous tumors and when done before the age of 35. The larger connections for nonserous tumors and the inverse association with hysterectomy suggest that tubal ligation and hysterectomy have similar .

SOROCk Trial, 2003	Salpingectomy to Salpingo-Oophorectomy for the risk reduction of Ovarian Cancer among BRCA1 carriers [SOROCk]	Comparing the Effects of Two Surgical Procedures in Ovarian Cancer Risk Reduction in Women with BRCA1 Mutations The purpose of the study is to determine whether removing only the fallopian tubes with the intention of removing the ovaries later can lower the risk of ovarian cancer to the same extent as the current gold standard of care, which is to remove both the ovaries and fallopian tubes. Since most "ovarian" malignancies are thought to start in the fallopian tubes, eliminating just the tubes may be just as effective as removing the ovaries and fallopian tubes in preventing the development of ovarian cancer while avoiding surgically induced menopause.	Pending Result	View this study on Beta. ClinicalTrials.gov
OVCARE Team, 2010	bilateral salpingectomy at the time of hysterectomy & sterilization.	OVCARE is British Columbia's multi-institutional and multidisciplinary ovarian cancer research group recommended to all gynecologic surgeons, when operating on women at general population risk for ovarian cancer, they should consider: 1) Performing bilateral salpingectomy at the time of hysterectomy (even when the ovaries are being preserved); and 2) Performing bilateral salpingectomy in place of tubal ligation for sterilization referred to as opportunistic salpingectomy (OS).	Pending	http://www.ovcare.ca/research/tackling_ovarian_cancer_one_histotype_at_a_time/

TUBA study, 2015	Early salpingectomy (TUbectomy) with delayed oophorectomy to improve quality of life as alternative for risk-reducing salpingo-oophorectomy in BRCA1/2 mutation carriers. A multicentre non-randomised trial in 11 Dutch centres for hereditary cancer will be conducted. a prospective non-randomised multicentre study	Patients who have finished childbearing and carry the premenopausal BRCA1/2 mutation without having had ovarian cancer in the past are eligible. Participants can opt for the usual method (RRSO at age 35–40 for BRCA1 or BRCA2) or the alternative strategy (RRS once childbearing is finished and RRO at age 40–45 for BRCA1 or 45–50 for BRCA2)). Menopause-related QoL is the main outcome indicator. Ovarian/breast cancer incidence, surgery-related morbidity, histology, cardiovascular risk factors, and illnesses are secondary outcome indicators.	Pending result	https://bmccancer.biomedcentral.com/articles/10.1186/s12885-015-1597-y
WISP (Women Choosing Surgical Prevention), 2016	Risk-reducing salpingo-oophorectomy (RRSO). versus an interval salpingectomy with delayed oophorectomy (ISDO).	In patients with genetic abnormalities at risk for ovarian cancer, a phase II trial examines how well surgery prevents the disease. The ovaries and fallopian tubes are surgically removed during a procedure called a risk-reducing salpingo-oophorectomy (RRSO). Surgery to remove the fallopian tubes is called an interval salpingectomy with delayed oophorectomy (ISDO). It is unknown if ISDO performs better than RRSO in reducing ovarian cancer risk, enhancing sexual function, and enhancing QoLin patients with genetic mutations.	Pending	clinicaltrials.gov NCT No: NCT02760849

TUBA-WISP II study, 2020	TUBectomy with delayed oophorectomy as Alternative for risk-reducing salpingo-oophorectomy in high-risk Women for prevention of ovarian cancer.	In TUBA-WISP II study, an international prospective multicenter preference trial (DO), Women can select either the normal salpingo-oophorectomy (RRSO) or the experimental salpingectomy (RRS) with delayed oophorectomy . The incidence of high grade serous (ovarian) cancer, the prevalence of (pre)malignant abnormalities in the tubes and ovaries, the occurrence of breast cancer, the occurrence of non-ovarian pelvic cancer, and MR imaging are the main outcomes.	Pending Result	https://ijgc.bmj.com/content/31/Suppl_3/A314.1