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Salpingectomy for the risk reduction of ovarian cancer: is it time for a salpingectomy-alone approach?

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Abstract

Objective: To summarize published evidence supporting current strategies for the prevention of epithelial ovarian cancer in women with a genetic, elevated risk for the development of this disease, as well as the emerging data on the novel salpingectomy with delayed oophorectomy (SDO) strategy. Furthermore, we will explore whether salpingectomy alone is a viable risk-reducing strategy for these women. We will also discuss current national guidelines for risk-reducing surgery based on patients' individual genetic predisposition.

Data Sources: MEDLINE, PubMed, Embase, and the Cochrane Database, with a focus on randomized controlled trials and large prospective, observational studies.

Methods of Study Selection: The key search terms for our review included Medical Subject Headings (MeSH): "salpingectomy", "ovarian cancer", and "risk-reducing surgery".

Tabulation, Integration, and Results: The fallopian tube is now well established as the site of origin for most ovarian cancers, particularly high-grade serous carcinomas. This finding has led to the development of new preventive surgical techniques, such as SDO, which may be associated with fewer side effects. Until the results of ongoing trials are reported and SDO's impact on ovarian cancer risk reduction is established, however, it should not be recommended outside of clinical trials, and bilateral salpingo-oophorectomy remains the treatment of choice for risk-reducing surgery, especially in women at a genetic, high risk for ovarian cancer.

Conclusion: The decision to undergo risk-reducing surgery among women at elevated risk for ovarian cancer should be made after comprehensive consultation and individually based on genetic predisposition, childbearing status, and personal preference.

Precis

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Salpingectomy as an effective strategy for risk reduction in women with a genetic, elevated risk for the development of ovarian cancer.

Keywords

ovarian cancer; salpingectomy; risk reduction; surgery

Introduction

Ovarian cancer is the leading cause of death from gynecologic malignancy in the United States, with an estimated 21,750 newly diagnosed cases and 13,940 deaths expected in 2020 [1]. This high mortality rate is due in large part to the late onset of symptoms and the lack of an effective screening test, which result in an advanced-stage diagnosis for most patients [2]. While an early detection test is lacking, there are effective strategies to decrease risk, and prevention remains an essential strategy to reduce deaths from this disease.

For patients with inherited genetic predispositions to epithelial ovarian cancer (EOC), such as mutations in *BRCA1* or *BRCA2,* risk-reducing salpingo-oophorectomy (RRSO) is recommended as the standard of care. RRSO results in an up to 96% reduction in risk of ovarian cancer development and may also lead to a decreased risk in the development of breast cancer [3–5]. Removal of the ovaries, however, carries significant side effects, specifically loss of fertility and the abrupt onset of premature menopause. As recent pathologic, molecular, and genomic evidence has implicated the fimbriated end of the fallopian tube as the origin of most high-grade serous ovarian cancers (HGSCs), risk-reducing salpingectomy with delayed oophorectomy (SDO), which is associated with fewer side effects, has emerged as a potential novel strategy for these patients. With emerging technologies for fertility preservation and increased provider comfort with hormone replacement therapy (HRT), these high-risk women now have more highly individualized and sometimes multi-step risk-reduction plans, making their cancer treatment decisions much more complex.

In this review, we will evaluate the evidence base supporting current strategies for the prevention of EOC in high- and average-risk women, as well as the emerging data on the novel SDO strategy. Furthermore, we will explore whether salpingectomy *alone* is a viable risk-reducing strategy for these women.

Tubal paradigm and “precursor escape” theory

HGSCs account for approximately two-thirds of all ovarian cancers. They are the most common and among the most lethal ovarian malignancies, making them largely responsible for the poor outcomes associated with this disease [6]. The discovery of *BRCA1* and *BRCA2* susceptibility genes in the mid 1990s and recent improvements in pathologic assessment with Sectioning and Extensively Examining the FIMbriated End (SEE-FIM) of the fallopian tube have allowed investigators to demonstrate that most of these carcinomas arise in the fallopian tube in the form of serous tubal intraepithelial carcinomas (STICs) [7].

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STIC lesions are found in approximately 1-10% of patients at the time of RRSO, of whom 5-10% will later develop a recurrent HGSC [8].

Early-stage HGSCs almost always arise from the fallopian tube, whereas in advanced-stage disease, only 10-60% of cases are associated with a concurrent STIC lesion [9, 10]. This paradoxical finding was the impetus for seeking other potential sites of carcinogenesis, such as the peritoneum or ovarian surface. Recent evidence suggests that early precursors in the fallopian tube contribute to the development of HGSC, which led to the emerging concept of "precursor escape". This second component of the tubal paradigm suggests that cells from non-malignant early serous proliferations (ESPs) shed from the tube undergo subsequent malignant transformation, resulting in sudden widespread peritoneal disease. In support of this theory is the finding that essentially 100% of de novo HGSCs contain TP53 alterations, and ESPs with these mutations are often the only abnormality found in the fallopian tubes of patients with metastatic HGSC. Molecular markers and gene expression profiles of HGSCs demonstrate lineage continuity of specific TP53 mutations between ESPs and concurrent serous carcinomas, further supporting this theory. This dualistic 'tubal hypothesis', which incorporates precursor escape, has become the most supported theory for the pathogenesis of EOC and provides a plausible explanation for the hallmarks of the disease, early peritoneal dissemination and the elusiveness of early detection [11].

First step in prevention: identify risk

Approximately 20% of patients diagnosed with HGSC will harbor a predisposing genetic mutation [6]. *BRCA1/2* mutations are the most common and confer a 20-50% lifetime risk for the development of HGSC [12, 13]. The increasing affordability and throughput of genetic testing with next-generation sequencing (NGS) has led to the discovery of inherited gene alterations that are also implicated in the carcinogenesis of EOC, including mutations in BRCA1- interacting protein C-terminal helicase 1 (*BRIP1*). RAD51 homolog C (*RAD51C*), and *RAD51D* [14]. Life-time risk estimates for pathogenic mutations in these moderate-risk genes range from 5-11% [15]. However, as only 15% of patients with ovarian cancer have pathogenic germline mutations in *BRCA 1/2* [16–18], these moderate-risk genes are of high clinical interest/importance.

Cascade testing, defined by the National Cancer Institute as "the systematic process for identification of individuals at risk for a hereditary condition" [19], has been recommended for all patients with HGSC. If a pathologic variant is identified on initial testing, further testing is recommended for at-risk biologic relatives in a sequential fashion. While this is the current strategy, some researchers have suggested a broader, population-based, or "universal", approach. A recent study published by Manchanda et al. evaluated the cost effectiveness of population-based *BRCA* testing compared with clinical criteria/family history-based testing across several different countries and health care systems. Using a Markov model, the authors concluded that the population-based testing approach compared with the clinical criteria testing approach was extremely cost effective, cost saving, and could prevent tens of thousands of breast and ovarian cancer cases [20].

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The gold standard strategy: salpingo-oophorectomy

RRSO is the current standard of care for the prevention of ovarian cancer in women with an elevated, genetic risk for the development of the disease, with an overall risk reduction of 75-95% [4, 5, 21]. All-cause mortality is significantly decreased in women with *BRCA* mutations who undergo RRSO at the recommended age [3, 5, 22, 23]. Breast and ovarian cancer-specific mortality are also decreased [22].

Current National Comprehensive Cancer Network (NCCN) guidelines recommend that *BRCA1* mutation carriers undergo RRSO between the ages of 35 and 40 and that *BRCA2* mutation carriers undergo RRSO between the ages of 40 and 45, as the age of HGSC onset in the latter group occurs on average several years later [24]. The NCCN suggests that in women with germline mutations in RAD51C, RAD51D and BRIP1, RRSO might be considered between 45 and 50 years of age [24]. Despite these recommendations, only 60-70% of these women undergo RRSO, likely due to concerns about the negative impact of premature menopause [25].

While RRSO has been deemed a safe procedure, with a low risk of intraoperative- and short-term complications [26], the long-term effects are significant. Adverse effects associated with RRSO in premenopausal women include loss of fertility, as well as the sequelae of surgical menopause, including but not limited to vasomotor and urogenital symptoms [27, 28], impaired bone health, elevated risk for cardiovascular disease and metabolic syndrome [29, 30], and decline in sexual interest and activity [31]. HRT is often prescribed to mitigate these symptoms; however, many patients are not candidates for HRT due to a personal history of breast cancer and some providers are reluctant to offer HRT even to an unaffected patient with a *BRCA* mutation due to a paucity of long-term safety data in this setting [32]. Taking into account the increased mortality risk in healthy women without *BRCA* mutations who experience surgical menopause before 45 years of age without estrogen replacement [33], the decision to proceed with RRSO with or without HRT is further complicated. Patients are left with a disappointing choice between risk of lethal malignancy versus risk of decreased quality of life and overall wellness.

Is SDO a better option?

Considering the adverse effects associated with RRSO and insights into the tubal origin of HGSC [7], the SDO strategy has gained traction. This two-stage procedure entails the removal of the fallopian tubes when childbearing is complete (or earlier if assisted reproductive technology is planned) followed by a delayed oophorectomy at a later age. From a technical standpoint, both procedures can be performed in a minimally invasive fashion, with attention to the complete removal of the fimbriated end of the fallopian tube during salpingectomy [34, 35]. During salpingectomy, peritoneal inspection, peritoneal washings for cytology, and SEE-FIM processing of the fallopian tube allow for the evaluation of precursor lesions, such as STIC lesions, or even occult HGSC.

Potential barriers to SDO include the need for 2 separate operations with entailed doubled perioperative risk, uncertain compliance for the delayed oophorectomy, and the need for

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prolonged follow-up [36]. In addition, compared with RRSO, SDO will almost certainly not confer any breast cancer risk reduction in women with hereditary breast and ovarian cancer syndrome [22]. Despite these concerns, preliminary evidence indicates that the majority of women find this approach acceptable [37, 38]. Holman et al. conducted an online patient survey of *BRCA* mutation carriers and found that 34% of eligible high-risk women (n=204) were “definitely interested” in an SDO option, even if the delay in oophorectomy resulted in an increased cancer risk without an RRSO [37]. In another poll of 173 cancer geneticists, genetic counselors, and gynecologic oncologists in the UK, 71% agreed with the tubal hypothesis, 77% supported SDO within a clinical trial setting, and 60% agreed to offer it to high-risk women who declined RRSO [37].

Health care providers and payers may be apprehensive about the potentially associated higher costs of 2 interventions. To address this, Kwon et al. looked at the cost effectiveness of 3 strategies for risk reduction in BRCA carriers: RRSO, bilateral salpingectomy, and SDO [39]. Their findings showed that SDO with salpingectomy at 36 years of age followed by oophorectomy at 42 years of age yielded favorable costs and life expectancy compared with RRSO at 40 years of age.

Oncologic outcomes, quality of life, and patient satisfaction with SDO

Nebgen et al. reported their initial experience with SDO in a pilot study of 43 premenopausal *BRCA1/2* mutation carriers to explore the safety and acceptability of the procedure [38]. Women opted for either RRSO, SDO, or screening based on personal preference. The 43 enrolled women chose the following options: SDO, 19 (44%); RRSO, 12 (28%); and screening only, 12 (28%). Women who underwent SDO had no intraoperative complications, were satisfied with their procedure choice, and had decreased cancer worry and anxiety postoperatively.

Based on these promising results, several prospective, observational trials are currently enrolling patients to further evaluate the impact of SDO over RRSO on efficacy in preventing the development of ovarian cancer and on quality of life. These trials include the Women Choosing Surgical Prevention (WISP) study [US: NCT02760849], the early salpingectomy (TUbectomy) with delayed oophorectomy in *BRCA1/2* mutation carriers (TUBA) study [Netherlands: NCT02321228] [40, 41], the PROTECTOR trial (Preventing Ovarian Cancer through early Excision of Tubes and late Ovarian Removal) (UK: ISRCTN25173360), and most recently, the SOROCk study (A Non-Randomized Prospective Clinical Trial Comparing the Non-Inferiority of Salpingectomy to Salpingo-Oophorectomy to Reduce the Risk of Ovarian Cancer Among *BRCA1* Carriers) (US: NRG-CC008/ NCT04251052).

The WISP trial is a non-randomized phase 2 trial, conducted at multiple centers in the US, that recently reported their preliminary results regarding quality of life [41], which showed that women who selected RRSO (n=99) had significantly worse menopausal symptoms after surgery compared with women who selected SDO (n=91). Specifically, hot flashes, night sweats, vaginal dryness, and weight gain were significantly worse in the RRSO arm. Women in the RRSO group also reported higher levels of regret compared to those choosing SDO

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(P<.009), regardless of whether HRT was used to manage menopausal symptoms. Both groups of women indicated significantly lower distress after surgery, and the women who chose RRSO experienced greater stress mitigation (P<.0006). Preliminary data from the TUBA trial [42], a Dutch multicenter trial, support the findings of the WISP trial, showing significant cancer worry decline in both treatment groups and only low levels of decision regret. Of note, women who selected RRSO without postoperative HRT indicated the highest regret.

Regarding oncologic outcome, the recently opened, non-randomized, prospective SOROCk study is designed to determine whether SDO is inferior to RRSO with regard to risk reduction of EOC development in *BRCA1* mutation carriers. This study, planned to follow 2,262 patients over a 10-year period, may provide the first prospective data regarding the effectiveness of SDO for cancer prevention.

Is salpingectomy-alone a viable option?

High-risk women

Studies have focused on the safety and quality-of-life impact of an *interval salpingectomy* option, with oophorectomy at a later time but within the recommended age range. Pending mature data from the ongoing SDO trials, the degree of protection conferred by a salpingectomy and the optimal timing of the surgical procedures in distinct, high-risk groups are debatable. The maximum (and still theoretical) benefit of a salpingectomy-alone approach would be fully realized if data show that oophorectomy can be safely deferred until after the age of natural menopause, or potentially omitted completely. The SOROCk study will inevitably include some patients who opt to defer oophorectomy beyond the recommended age, possibly providing insight into the benefit of a salpingectomy-alone strategy. Mature data, however, are years away. At this time, there are no data to support salpingectomy alone in high-risk women, and SDO should only be offered in a clinical trial setting. As we await these data, improved strategies to safely and effectively mitigate the side effects of RRSO, including improved access to HRT and reproductive technology, as well as expanded non-hormonal options, are greatly needed.

Average-risk women

The emerging evidence of the tubal origin of EOC has led to support for opportunistic bilateral salpingectomy (OBS) at the time of surgery for benign disease in the general population. In a large, Swedish population-based cohort study using national registries, Falconer et al. evaluated the effect of gynecologic surgery for benign indications on the development of ovarian cancer [43] and showed that bilateral salpingectomy (HR = 0.35; 95% CI, 0.17-0.73) was associated with a significant 65% decreased risk of ovarian cancer. Other observational studies have shown similar results. A statistical model predicted that the widespread adoption of OBS at the time of surgery for benign gynecologic indications would decrease the incidence of HGSC by 40% over the next 20 years [44].

Evidence also indicates a favorable cost-benefit ratio for OBS. Kwon et al. performed a cost-effectiveness study evaluating OBS as a cancer prevention strategy [45]. Hysterectomy/OBS

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was less costly than hysterectomy alone or with bilateral salpingo-oophorectomy, and was also more effective. This held true for women who underwent hysterectomy at any time before 50 years of age. Their simulation estimated that after hysterectomy, 270 women subsequently would be diagnosed with ovarian cancer versus 167 after hysterectomy/OBS (38.1% risk reduction, number needed to treat 273). Bilateral salpingo-oophorectomy would lead to an 88% reduction in ovarian cancer but also an additional 934 deaths from premature menopause without routine use of HRT. Salpingectomy for sterilization was slightly more costly, but more effective compared with tubal ligation, with an incremental cost-effectiveness ratio of $27,278 per year of life gained.

A concern with OBS is its potential detrimental effect on ovarian blood supply, and therefore, impact on ovarian function and onset of menopause. In a multicenter trial by Song et al. [46], 68 patients undergoing laparoscopic hysterectomy for benign indications were randomized to OBS versus no salpingectomy. Although anti-Mullerian hormone (AMH) levels were significantly decreased from preoperative levels in both groups, there was no significant difference between the OBS and no-salpingectomy groups. A similar finding was observed in a study by Morelli et al., which demonstrated similar levels of AMH, follicle-stimulating hormone, and estradiol in patients who underwent hysterectomy with or without OBS, and there were no differences in ovarian function between the groups postoperatively [47].

The safety of OBS with regard to perioperative complications has also been investigated [26]. A population-based retrospective cohort study of 43,931 women in British Columbia from 2008-2011 investigated the outcomes of OBS at the time of hysterectomy or for sterilization [48]. Minimal additional surgical time was required for hysterectomy with salpingectomy (+16 minutes) and bilateral salpingectomy for sterilization (+10 minutes) compared with hysterectomy alone or tubal ligation, respectively. There were no significant differences with regard to risks of hospital readmission or blood transfusions in women who underwent hysterectomy with salpingectomy or salpingectomy for sterilization. Overall, the data overwhelmingly support the incorporation of OBS into gynecologic surgery for benign indications, specifically hysterectomy and sterilization procedures, as a cost effective and safe strategy to reduce the risk of EOC.

Conclusion

The fallopian tube undoubtedly plays a primary role in the pathogenesis of EOC, with recent evidence supporting a dualistic paradigm incorporating the novel concept of precursor escape and salpingectomy, and should remain a focus for surgical innovation in the prevention of this disease. For the general population, clear opportunities have been identified to incorporate OBS into practice, with an acceptable degree of risk and cost. Expanding those opportunities to a greater proportion of patients undergoing concurrent indicated procedures should be explored. For high-risk patients, SDO may offer a reduced risk of ovarian cancer development while delaying the detrimental consequences of premature menopause; however, the degree to which oophorectomy can be postponed beyond the recommended age, or potentially omitted completely, is unknown. RRSO remains the data-driven strategy and should be the cornerstone of counseling for high-risk

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women; however, data from ongoing epidemiologic and prospective trials of salpingectomy are eagerly anticipated and may provide evidence for a future paradigm shift.

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References

[1]. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7–30. [PubMed: 31912902]

[2]. Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening randomized controlled trial. JAMA. 2011;305:2295–2303. [PubMed: 21642681]

[3]. Rebbeck TR, Lynch HT, Neuhausen SL, et al.; Prevention and Observation of Surgical End Points Study Group. Prophylactic Oophorectomy in Carriers of BRCA1 or BRCA2 Mutations. N Engl J Med. 2002;346:1616–1622. [PubMed: 12023993]

[4]. Kauff ND, Domchek SM, Friebel TM, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1-and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. J Clin Oncol. 2008;26:1331–1337. [PubMed: 18268356]

[5]. Kauff ND, Satagopan JM, Robson ME, et al. Risk-Reducing Salpingo-oophorectomy in Women with a BRCA1 or BRCA2 Mutation. N Engl J Med. 2002;346:1609–1615. [PubMed: 12023992]

[6]. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7–30. [PubMed: 31912902]

[7]. Soong TR, Howitt BE, Horowitz N, Nucci MR, Crum CP. The fallopian tube,“precursor escape” and narrowing the knowledge gap to the origins of high-grade serous carcinoma. Gynecol Oncol. 2019;152:426–433. [PubMed: 30503267]

[8]. Meserve EE, Brouwer J, Crum CP. Serous tubal intraepithelial neoplasia: the concept and its application. Mod Pathol. 2017;30:710–721. [PubMed: 28106106]

[9]. Chen F, Gaitskell K, Garcia M, Albukhari A, Tsaltas J, Ahmed A. Serous tubal intraepithelial carcinomas associated with high-grade serous ovarian carcinomas: a systematic review. BJOG. 2017;124:872–878. [PubMed: 28218502]

[10]. Kindelberger DW, Lee Y, Miron A, et al. Intraepithelial Carcinoma of the Fimbria and Pelvic Serous Carcinoma: Evidence for a Causal Relationship. Am J Sung Pathol. 2007;31:161–169.

[11]. Soong TR, Kolin DL, Teschan NJ, Crum CP. Back to the Future? The Fallopian Tube, Precursor Escape and a Dualistic Model of High-Grade Serous Carcinogenesis. Cancers (Basel). 2018; 10:468.

[12]. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017;317:2402–2416. [PubMed: 28632866]

[13]. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003;72:1117–1130. [PubMed: 12677558]

[14]. Norquist BM, Harrell MI, Brady MF, et al. Inherited mutations in women with ovarian carcinoma. JAMA Oncol. 2016;2:482–490. [PubMed: 26720728]

[15]. Jones MR, Kamara D, Karlan BY, Pharoah PD, Gayther SA. Genetic epidemiology of ovarian cancer and prospects for polygenic risk prediction. Gynecol Oncol. 2017;147:705–713. [PubMed: 29054568]

[16]. Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Kwan E, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. Am J Hum Genet. 2001;68:700–710. [PubMed: 11179017]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

[17]. Rebbeck TR, Friebel TM, Friedman E, et al. Mutational spectrum in a worldwide study of 29,700 families with BRCA1 or BRCA2 mutations. Hum Mutat. 2018;39:593–620. [PubMed: 29446198]

[18]. Pal T, Permuth-Wey J, Betts JA, et al. BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. Cancer. 2005;104:2807–2816. [PubMed: 16284991]

[19]. National Cancer Institute. NCI Dictionary of Genetics Terms. https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/cascade-screening. Accessed August 14, 2020.

[20]. Manchanda R, Sun L, Patel S, et al. Economic Evaluation of Population-Based BRCA1/BRCA2 Mutation Testing across Multiple Countries and Health Systems. Cancers (Basel). 2020;12:1929.

[21]. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. J Natl Cancer Inst. 2009;101:80–87. [PubMed: 19141781]

[22]. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA. 2010;304:967–975. [PubMed: 20810374]

[23]. Finch AP, Lubinski J, Møller P, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2014;32:1547–1553. [PubMed: 24567435]

[24]. Daly MB, Pilarski R, Berry M, et al. NCCN guidelines insights: genetic/familial high-risk assessment: breast and ovarian, version 2.2017. J Natl Compr Canc Netw. 2017;15:9–20. [PubMed: 28040716]

[25]. Bradbury AR, Ibe CN, Dignam JJ, et al. Uptake and timing of bilateral prophylactic salpingo-oophorectomy among BRCA1 and BRCA2 mutation carriers. Genet Med. 2008;10:161–166. [PubMed: 18344704]

[26]. Kenkhuis M, de Bock G, Elferink PO, et al. Short-term surgical outcome and safety of risk reducing salpingo-oophorectomy in BRCA1/2 mutation carriers. Maturitas. 2010;66:310–314. [PubMed: 20409655]

[27]. Bachmann GA. Vasomotor flushes in menopausal women. Am J Obstet Gynecol.1999;180:S312–316. [PubMed: 10076170]

[28]. Shifren JL, Nahum R, Mazer NA. Incidence of sexual dysfunction in surgically menopausal women. Menopause. 1998;5:189–190. [PubMed: 9774766]

[29]. Finch A, Narod SA. Quality of life and health status after prophylactic salpingo-oophorectomy in women who carry a BRCA mutation: A review. Maturitas. 2011;70:261–265. [PubMed: 21893388]

[30]. Finch A, Metcalfe K, Chiang J, et al. The impact of prophylactic salpingo-oophorectomy on menopausal symptoms and sexual function in women who carry a BRCA mutation. Psychooncology. 2011;121:163–168.

[31]. Taylor M Psychological consequences of surgical menopause. J Reprod Med. 2001;46:317–324. [PubMed: 11304879]

[32]. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet. 2019;394:1159–1168. [PubMed: 31474332]

[33]. Rocca WA, Grossardt BR, De Andrade M, Malkasian GD, Melton LJ 3rd. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol. 2006;7:821–828. [PubMed: 17012044]

[34]. Wong JWH, Killeen JL, Carney ME. Completeness of salpingectomy intended for ovarian cancer risk reduction. Gynecol Oncol. 2019;155:280–282. [PubMed: 31522838]

[35]. Nebgen DR, Holman LL, Hurteau J, et al. Prophylactic salpingectomy with delayed oophorectomy (PSDO): Feasibility study in women with BRCA mutations. J Clin Oncol. 2016;34:1506.

[36]. Arts-de Jong M, Harmsen MG, Hoogerbrugge N, Massuger LF, Hermens RP, de Hullu JAJ. Risk-reducing salpingectomy with delayed oophorectomy in BRCA1/2 mutation carriers: Patients' and professionals' perspectives. Gynecol Oncol. 2015;136:305–310. [PubMed: 25560807]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

[37]. Holman LL, Friedman S, Daniels MS, Sun CC, Lu KH. Acceptability of prophylactic salpingectomy with delayed oophorectomy as risk-reducing surgery among BRCA mutation carriers. Gynecol Oncol. 2014;133:283–286. [PubMed: 24582866]

[38]. Nebgen DR, Hurteau J, Holman LL, et al. Bilateral salpingectomy with delayed oophorectomy for ovarian cancer risk reduction: A pilot study in women with BRCA1/2 mutations. Gynecol Oncol. 2018;150:79–84. [PubMed: 29735278]

[39]. Kwon JS, Tinker A, Pansegrau G, et al. Prophylactic salpingectomy and delayed oophorectomy as an alternative for BRCA mutation carriers. Obstet Gynecol. 2013;121:14–24. [PubMed: 23232752]

[40]. Harmsen MG, Arts-de Jong M, Hoogerbrugge N, et al. Early salpingectomy (TUbectomy) with delayed oophorectomy to improve quality of life as alternative for risk-reducing salpingo-oophorectomy in BRCA1/2 mutation carriers (TUBA study): a prospective non-randomised multicentre study. BMC Cancer. 2015;15:593. [PubMed: 26286255]

[41]. Lu K, Nebgen D, Norquist B, et al. WISP: A prospective, multi-center trial of salpingectomy with delayed oophorectomy versus risk reducing salpingo-oophorectomy in women at increased risk for hereditary ovarian cancer. Gynecol Oncol. 2019;154(Suppl 1):22 [abstract]. [PubMed: 31109659]

[42]. Steenbeek MP, Harmsen MG, Hermens RPMG, de Hullu JA. Worry and regret in the prospective multicentre TUBA study in BRCA1/2 mutation carriers. Gynecol Oncol. 2019;154(Suppl 1):22 [abstract]. [PubMed: 31109659]

[43]. Falconer H, Yin L, Grønberg H, Altman D. Ovarian cancer risk after salpingectomy: a nationwide population-based study. J Natl Cancer Inst. 2015;107:dju410. [PubMed: 25628372]

[44]. Riman T, Dickman PW, Nilsson S, et al. Risk factors for invasive epithelial ovarian cancer: results from a Swedish case-control study. Am J Epidemiol. 2002;156:363–373. [PubMed: 12181107]

[45]. Kwon JS, McAlpine JN, Hanley GE, et al. Costs and benefits of opportunistic salpingectomy as an ovarian cancer prevention strategy. Obstet Gynecol. 2015;125:338–345. [PubMed: 25568991]

[46]. Song T, Kim MK, Kim M-L, Jung YW, Yun BS, Seong SJ, Kwon S-H. Impact of opportunistic salpingectomy on anti-Müllerian hormone in patients undergoing laparoscopic hysterectomy: a multicentre randomised controlled trial. BJOG. 2017;124:314–320. [PubMed: 27342222]

[47]. Morelli M, Venturella R, Mocciaro R, et al. Prophylactic salpingectomy in premenopausal low-risk women for ovarian cancer: primum non nocere. Gynecol Oncol. 2013;129:448–451. [PubMed: 23558052]

[48]. McAlpine JN, Hanley GE, Woo MM, et al. Opportunistic salpingectomy: uptake, risks, and complications of a regional initiative for ovarian cancer prevention. Am J Obstet Gynecol. 2014;210:471. e1–e11. [PubMed: 24412119]